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The correlation of leukocyte-specific protein 1 (LSP1) rs3817198(T>C) polymorphism with breast cancer

A meta-analysis

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Abstract

Background: Multiple studies have investigated the correlation of single nucleotide polymorphisms (SNPs) in leukocyte-specific protein 1 (LSP1) with susceptibility to breast cancer (BC) and have yielded inconsistent conclusions, particularly rs3817198(T > C). Consequently, we performed a meta-analysis to estimate this relationship more comprehensively.

Methods: Four databases were utilized to locate eligible publications: PubMed, Embase, Web of Science, and China National Knowledge Infrastructure. This meta-analysis included 14 studies, including 22 reports of 33194 cases and 36661 controls. The relationship of rs3817198 polymorphism with breast cancer was estimated using odds ratios (ORs) with 95% confidence intervals (CIs). The LSP1 co-expression network was constructed by STRING, and Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) enrichment analyses were performed using DAVIDE. Download TCGA breast cancer mRNA-seq data and analyze the relationship between LSP1 expression and breast cancer chemotherapy sensitivity.

Results: The results indicated that rs3817198(T > C) was positively correlated to with breast malignancy (dominant model: OR = 1.11, 95%CI = 1.06–1.17; recessive model: OR = 1.10, 95%CI = 1.04–1.15; heterozygous model: OR = 1.09, 95%CI = 1.04–1.15; homozygous model: OR = 1.18, 95%CI = 1.09–1.28; additive model: OR = 1.09, 95%CI = 1.05–1.13), among Caucasians and Asians. However, rs3817198(T > C) may reduce the risk of breast carcinoma in Africans. Rs3817198(T > C) might result in breast carcinoma in individuals with BRCA1 and BRCA2 variants and can contribute to estrogen receptor (ER)-positive breast carcinoma. The expression of LSP1 was inversely correlated with the IC50 of doxorubicin (P = 8.91e–15, Cor = –0.23), 5-fluorouracil (P = 1.18e–22, Cor = –0.29), and cisplatin (P = 1.35e–42, Cor = –0.40).

Conclusion: Our study identified that LSP1 rs3817198 polymorphism might result in breast malignancy, particularly among Caucasians and Asians, but lower breast cancer susceptibility in African populations. The expression of LSP1 was negatively correlated with the IC50 of doxorubicin, 5-fluorouracil, and cisplatin.

Abbreviations: BC = breast cancer, CI = confidence interval, GO = gene ontology, KEGG = Kyoto encyclopedia of genes and genomes, LSP1 = leukocyte-specific protein 1, OR = odds ratio, SNP = single nucleotide polymorphism.

Keywords: breast neoplasms, LSP1, meta-analysis, rs3817198, single nucleotide

1. Introduction

BC still represents the primary cancer-related reason for disease burden in females, and its incidence is increasing yearly and getting younger.[1] Moreover, it has overtaken lung carcinoma as the most epidemic malignancy worldwide, with approximately 2.2 million new cases in 2020, accounting for 11.7% of overall new cancer cases.[2] In developed countries, early-onset breast

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All data generated or analyzed during this study are included in this published article [and its supplementary information files]; The datasets generated during and/or analyzed during the current study are publicly available.

Data for this meta-analysis were extracted from published literature without involving patients. Therefore, ethics committee approval and informed consent were unnecessary.

Supplemental Digital Content is available for this article.

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cancer accounts for 6-10% of all breast cancer cases; this doubles in developing countries, with rates reaching 20%; mortality rates are similar, at 7% and 14% in developed and developing regions, respectively.[3] As an intractable malignancy, BC has various clinical behavioral and biological features that undoubtedly make it challenging for doctors and oncologists to manage BC patients and investigate the relevant mechanisms.[4] An update on breast cancer screening, treatment and mechanistic research is imperative. And BC is a multifactorial disease associated with age, obesity, smoking, lifestyle, and hereditary factors.[5–7] Single nucleotide polymorphisms (SNPs), the most common form of variation in the human genome, can alter the structure of genes to affect downstream products and thus determine the phenotype of the organism.[8] SNPs studies can help researchers find new biomarkers and potential drug targets. Through epidemiological evidence, BC was found to be associated with SNPs.[9,10]

The leukocyte-specific protein 1 (LSP1) gene can encode F-actin bundling protein, which is expressed in hematopoietic cells and endothelial cells to play an essential part in the formation and motility of neutrophils and focal adhesion dynamics required for transendothelial cell migration.[11,12] Most studies identified that LSP1 plays a negative role in cell motility,[11,13–15] but some found the opposite result.[16,17] LSP1 is also involved in leukocyte chemotaxis as a barrier to neutrophil migration out of capillaries via endothelial cells[16,17]; it is co-located to F-actin bundling protein in the filopodia, lamellipodia, and cell cortex during chemotaxis.[17] Furthermore, LSP1 is essential in Fcγ receptor-driven phagocytosis; its downregulation of expression critically decreases the phagocytic activity of macrophages.[18] LSP1 is involved in various diseases. LSP 1 can adjust the number of leukocytes in resting and inflamed peritoneum.[13] It was also found to promote the aggregation of neutrophils into lung tissue in acute lung inflammation.[19] Studies have found that LSP1 is overexpressed with leukemia, lymphoma, and breast cancer.[20]

LSP1 has been identified as a novel locus for a predisposing gene to breast carcinogenesis, according to a genome-wide association study (GWAS) published in Nature.[21] Since then, studies working for the link of LSP1 polymorphisms with breast tumors, especially rs3817198(T > C), have been initiated by various institutions. However, the outcomes of these investigations were inconsistent and even contradictory. Two meta-analyses on rs3817198(T > C) with breast malignancy have been reported, showing which the rs3817198(T > C) variation is linked with breast carcinoma among Caucasians and Asians.[22,23] Some additional relevant studies have since been reported with inconsistent results, studies by Jingxuan Shan et al, Nguyen Thi Ngoc Thanh et al, Zuzana Danková et al, Asuman Özgöz et al, Ying Chen et al, and Taeko Mizoo et al all indicated that rs3817198 was not related to breast cancer.[24–29] Due to the enormous burden of breast cancer on the global healthcare system and the potential value of LSP1 polymorphism studies in breast cancer, we updated previous studies and implemented a comprehensive meta-analysis. This study is important for identifying new biomarkers and potential targets for breast cancer. Co-expression network of LSP1, Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) enrichment analysis were also implemented in order to explore the mechanism of LSP1 in breast cancer.

2. Methods

2.1. Registration information

Platform: PROSPERO

Title: The association between Lsp1 rs3817198(T > C) polymorphism and breast cancer: a meta-analysis

ID: CRD42022300191

View website: https://www.crd.york.ac.uk/prospero/

2.2. Search strategy

To access eligible research, we performed a literature search up to October 2020 in 4 databases (Pubmed, Embase, Web of Science, and NCKI). The search strategy on Pubmed details in Table 1 and strategies for searching the 3 other databases was provided in Supplemental Tables S1 to S3, http://links.lww.com/MD/H847. In addition, a search was conducted on the research square for preprints. We also performed a search according to the references of eligible studies. All the above searches are free of language restrictions. The selection criteria are as follows.

Inclusion criteria: Studies examining the correlation of rs3817198 polymorphism with breast malignancy; case-control studies or cohort studies and included patients in studies were those with pathologically definite breast cancer; studies with complete genotype frequencies.

Exclusion criteria: Repeated papers; non-human trials; in case the authors used the same data in multiple papers, we selected articles that were recently published or with a large volume of relevant data.

Two authors performed the above search and selection process individually, and disagreements would be discussed with a third author until the discrepancies were settled.

2.3. Data extraction

Both authors extracted relevant data from every qualifying report independently: first author, publication year, nation, ethnicity, source of the control group, genotyping method, gene

Table 1

Search strategy for Pubmed.

Code	Boolean operator	Search formulations
#1		((((((((((((((“Breast Neoplasms”[Mesh]) OR (Breast Neoplasm[Title/Abstract])) OR (Breast Tumors[Title/Abstract])) OR (Breast Tumor[Title/Abstract])) OR (Breast Cancer[Title/Abstract])) OR (Mammary Cancer[Title/Abstract])) OR (Mammary Cancers[Title/Abstract])) OR (Breast Malignant Neoplasm[Title/Abstract])) OR (Breast Malignant Neoplasms[Title/Abstract])) OR (Breast Malignant Tumor[Title/Abstract])) OR (Breast Malignant Tumors[Title/Abstract])) OR (Human Mammary Carcinomas[Title/Abstract])) OR (Human Mammary Carcinoma[Title/Abstract])) OR (Human Mammary Neoplasm[Title/Abstract])) OR (Human Mammary Neoplasms[Title/Abstract])) OR (Breast Carcinoma[Title/Abstract])) OR (Breast Carcinomas[Title/Abstract])
#2	And	(((Lymphocyte-specific protein 1[Title/Abstract]) OR (LSP1 protein[Title/Abstract])) OR (LSP1[Title/Abstract])) OR (rs3817198[Title/Abstract])
#3	And	((((((((((“polymorphism, single nucleotide”[MeSH]) OR (“Mutation”[Mesh])) OR (“Genetic Variation”[Mesh])) OR (“Alleles”[Mesh])) OR (nucleotide polymorphism single[Title/Abstract])) OR (nucleotide polymorphisms single[Title/Abstract])) OR (polymorphisms single nucleotide[Title/Abstract])) OR (single nucleotide polymorphisms[Title/Abstract])) OR (SNPs[Title/Abstract])) OR (single nucleotide polymorphism[Title/Abstract])) OR (Polymorphism[Title/Abstract])
#4	And	(“Case-Control Studies”[Mesh]) OR (“Cohort Studies”[Mesh])

Search strategy: #1 and #2 and #3 and #4.

frequencies for subjects, and Hardy-Weinberg Equilibrium (HWE) *P* value for control groups. We adopt the χ^2 test for determining the goodness of fit for the HWE in the control groups, and studies will be excluded from this meta-analysis with ineligible controls (the *P* values for HWE were below 0.05). In case of disagreements between 2 authors, they should discuss with a third one until reaching a consensus.

2.4. Quality assessment

Two authors separately assessed the quality of the contained reports using the Newcastle-Ottawa Scale (NOS).[30] The NOS consists of 8 projects divided into 3 categories: selection, comparability, and outcome/exposure. For each item, there is a range of options. Each item passing is granted 1 star, except for the item below comparability, which can be awarded 2 stars—a total of 9 stars, with greater than or equal to 5 stars being defined as qualified. Disagreements between 2 authors were discussed with a third author to produce consistent conclusions.

2.5. Statistical analysis

Statistical power calculation: We calculated the statistical power of the 5 genetic models (dominant: CC + TC vs TT, recessive: CC + TC vs TT, heterozygote: TC vs TT, homozygote: CC vs TT, additive: C vs T) for all studies and each racial subgroup using the statistical software Power and Precision 4.

Quantitative synthesis: We estimated the correlation of Lsp1 rs3817198 polymorphism with breast malignancy using ORs and 95 % CIs in the dominant, recessive, heterozygote, homozygote, and additive models.[31] Gene frequencies for all genotypes were obtained from the included studies.

Heterogeneity analysis: To analyze heterogeneity across studies in each genetic model, we adopted Cochran's *Q* test and I^2-value. Since the statistical strength of the Q-test is low, with a *P* value < .10, indicating the presence of heterogeneity.[32] We used fixed-effects models to combine the data when heterogeneity was absent; Else, random-effects models were considered.[33] I^2 values exceeding 25%, 50%, and 75% would be considered low, medium, and high, respectively.[34] We conducted a meta-regression with covariates of ethnicity, control group source, sample size, genotyping method, and publication year to probe the heterogeneity origins. If the *P* value of the regression of the covariate was less than .05, the covariate was considered as the source of heterogeneity in the meta-analysis, and a subgroup analysis of the variable was required to determine the cause of the heterogeneity further.[35,36]

Subgroup analysis: We would perform subgroup analyses for the corresponding variables based on the meta-regression results. Of course, to further investigate the relationship between each variable and polymorphism in BC, subgroup analysis would be performed as well. We defined 5 subgroups, including ethnicity, sample size, sources of control groups, BRCA gene mutations, and estrogen receptor stratification in breast cancer.

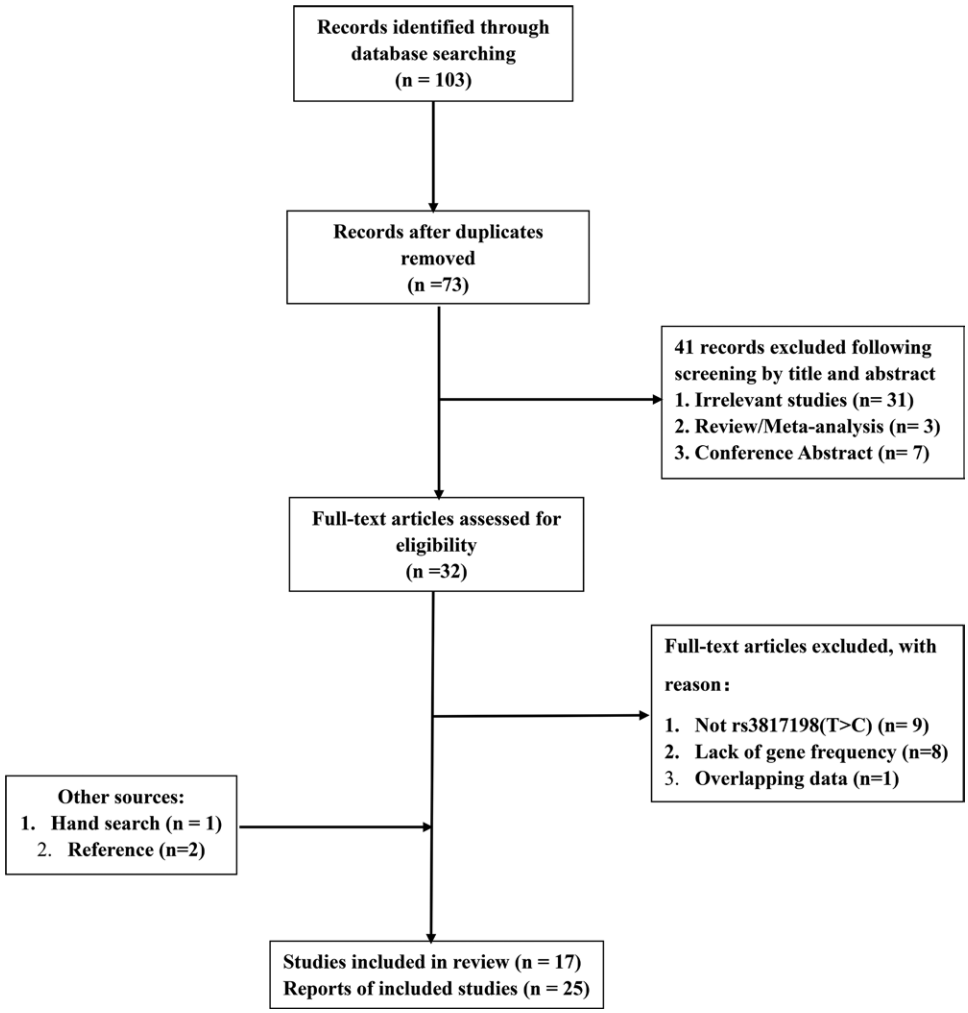

Figure 1. Flow diagram of the choice of eligible reports.

Table 2

Characteristics of the included studies.

Author	Yr	Country	Ethnicity	Control source	Genotype method	Case			Control			HWE*	NOS*
						TT	TC	CC	TT	TC	CC		
Easton	2007	Multi-center	Mixed	Mixed	iPLEX, Taqman	1622	1505	357	2418	1986	458	0.090	7
Antoniou	2009	Multi-center	Caucasian	Mixed	iPLEX, Taqman, Sequencing	2114	2112	555	1940	1810	453	0.316	7
Antoniou	2009	Multi-center	Caucasian	Mixed	iPLEX, Taqman, Sequencing	1283	1375	372	1090	1057	257	0.975	7
Latif	2009	UK	Caucasian	HB	Taqman assays	47	56	17	163	162	41	0.938	6
Latif	2009	UK	Caucasian	HB	Taqman assays	40	54	13	163	162	41	0.938	6
Latif	2009	UK	Caucasian	HB	Taqman assays	327	287	81	163	162	41	0.938	6
Gorodnova	2010	Russian	Caucasian	PB	Real-time PCR	58	61	21	91	69	14	0.856	6
Sloan	2010	US	African	PB	Illumina*	506	224	12	459	175	24	0.168	8
Sloan	2010	US	Caucasian	PB	Illumina*	548	541	139	519	495	103	0.330	8
Campa	2011	Multi-center	Mixed	Mixed	Taqman assays	4131	3382	779	5611	4875	1072	0.780	6
Mulligan	2011	Multi-center	Mixed	Mixed	iPLEX, Taqman	2052	2065	515	1894	1680	422	0.087	7
Mulligan	2011	Multi-center	Mixed	Mixed	iPLEX, Taqman	1289	1371	362	1075	1005	252	0.456	7
Butt	2012	Sweden	Caucasian	PB	MassARRAY, PCR	311	282	76	668	555	107	0.578	8
Shan	2012	Tunisia	Caucasian	PB	Taqman assays	111	96	28	192	147	32	0.611	7
Shan	2012	Tunisia	Caucasian	PB	Taqman assays	172	157	38	192	147	32	0.611	7
Shan	2012	Tunisia	Caucasian	PB	Taqman assays	253	220	58	192	147	32	0.611	7
Shan	2012	Tunisia	Caucasian	PB	Taqman assays	45	45	9	192	147	32	0.611	7
Mizoo	2013	Japan	Asian	PB	Taqman assays	339	120	10	347	107	5	0.280	7
Chen	2016	China	Asian	HB	Taqman assays	85	18	2	272	93	17	0.024	6
Deng	2016	China	Asian	HB	MassARRAY	103	27	6	455	121	7	0.738	6
Nguyen	2018	Vietnam	Asian	PB	Real-time PCR	99	34	11	107	41	9	0.085	6
Danková	2019	Slovakia	Caucasian	HB	Real-time PCR	72	80	18	75	57	14	0.517	6
Li	2019	Chian	Asian	HB	Taqman assay	10	24	71	79	94	209	< 0.001	5
Nourolahzadeh	2020	Iran	Caucasian	HB	Real-time PCR	31	64	5	20	80	0	< 0.001	4
Asuman	2020	Turkey	Caucasian	HB	Multiplex PCR, MALDI-TOF	35	53	13	45	40	15	0.230	6

HB = Hospital-based, HWE*= *P* value for Hardy-Weinberg Equilibrium in controls, Illumina*= Illumina Golden Gate assay, NOS*= Score of the Newcastle-Ottawa Scale, PB = population-based.

Publication bias: We assessed the publication bias of this study using funnel plots, Begg's, and Egger's tests.[37] Asymmetry in funnel plots or the *P* value was below .05 in either test suggested statistically significant. If publication bias was identified, the trim and fill method was applied to assess the influence of publication bias on the results.[38] The asymmetric part of the funnel plot was complemented using the correlation module of STATA 15.0, and then a meta-analysis was performed to compare the complemented results with the previous results, and if the difference was not significant without reversal, the publication bias was acceptable.

Sensitivity analysis: The sensitivity analysis was performed by excluding each study in turns and remerging data to evaluate stability for results. No reversal of the re-combined OR with 95% CI was considered stable for the study results.

The above statistical analyses were performed using stata15.0 software except for statistical power calculation.

2.6. Bioinformatics analysis

Gene co-expression network: STRING (https://string-db.org/), as an online database, allows the construction of gene co-expression visualization networks based on existing high-throughput research data.[39] We constructed a gene co-expression network for LSP1 using STRING. A moderate confident level (0.400) of the lowest interaction rating required for networks was set.

Enrichment analysis: DAVID (https://david.ncifcrf.gov/) serves as a functional commentary tool that lets users understand the biological meaning behind their submitted gene lists.[40] We used it for the Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) enrichment analysis of the co-expression network of LSP1, FDR less than 0.05 was statistically significant. GO analysis includes Biological Process (BP), Cellular Component (CC), and Molecular Function (MF). Visualization was accomplished through Sangerbox, an online free tool (http://www.sangerbox.com/tool).

Prediction of chemosensitivity: Genomics of Drug Sensitivity in Cancer (GDSC, https://www.cancerrxgene.org/) is the largest publicly available pharmacogenomics database.[41] We downloaded TCGA breast cancer mRNA expression data and used GDSC to predict the response to chemotherapy for each TCGA sample. The prediction process was implemented by the R package "pRRophetic." The samples' half-maximal inhibitory concentration (IC50) was assessed by ridge regression. We set all parameters to default values and used the batch effect of combat and tissue type of all tissues; the repeated gene expression was summarized as the mean value. The correlation of IC50 of chemotherapeutic agents with theLSP1 expression level was investigated using Spearman's correlation analysis. The correlation can be graded according to the absolute value of the correlation coefficient Cor, as follows. < 0.10, 0.10 to 0.39, 0.40 to 0.69, 0.70 to 0.89, and 0.90 to 1.00 are defined as negligible correlation, weak correlation, moderate correlation, strong correlation, and very strong correlation, respectively. The "ggstatsplot" package mapped the results. The above analysis methods and R packages were implemented by R program v4.0.3.

3. Results

3.1. Literature search and research characteristics

One hundred three records followed an initial search; 30 duplicate publications were excluded. The titles and abstracts of the remaining 73 records were reviewed and 41 were removed, of which 31 were irrelevant studies, 7 were conference abstracts, 2 were meta-analyses, and 1 was a review. After full-text reading, 18 articles were eliminated, of which 9 studied polymorphisms other than LSP1 rs3817198 (T > C), 8 lacking gene frequencies,

Table 3

Results of the meta-analysis for the association of LSP1 rs3817198 (T > C) polymorphism with breast cancer.

		Dominant model		Recessive model		Heterozygous model		Homozygous model		Additive model	
		(CC + TC vs TT)		(CC vs TC + TT)		(TC vs TT)		(CC vs TT)		(C vs T)	
Subgroups	**N***	**OR (95%CI)**	***P*/I^2 (%)**	**OR (95%CI)**	***P*/I^2 (%)**	**OR (95%CI)**	***P*/I^2 (%)**	**OR (95%CI)**	***P*/I^2 (%)**	**OR (95%CI)**	***P*/I^2 (%)**
Overall	22	**1.11 (1.06, 1.17)**	.021/41.9	**1.1 (1.04, 1.15)**	.210/19.0	**1.09 (1.04, 1.15)**	.048/36.1	**1.18 (1.09, 1.28)**	.063/33.7	**1.09 (1.05, 1.13)**	.032/39.1
Ethnicity											
Caucasian	14	**1.12 (1.06, 1.18)**	.682/0.0	**1.17 (1.08, 1.27)**	.862/0.0	**1.1 (1.04, 1.16)**	.730/0.0	**1.23 (1.12, 1.34)**	.810/0.0	**1.1 (1.06, 1.15)**	.690/0.0
Asian	3	1.13 (0.91, 1.40)	.788/0.0	**1.96 (1.08, 3.55)**	.370/0.0	1.06 (0.84, 1.33)	.689/0.0	**2.04 (1.12, 3.73)**	.357/2.8	1.18 (0.98, 1.43)	.765/0.0
African	1	1.08 (0.86, 1.35)	–/–	**0.43 (0.22, 0.88)**	–/–	1.16 (0.92, 1.47)	–/–	**0.45 (0.22, 0.92)**	–/–	0.98 (0.81, 1.20)	–/–
Mixed	4	1.08 (0.97, 1.21)	<.001/85.6	1.06 (0.99, 1.13)	.696/0.0	1.08 (0.96, 1.20)	<.001/84.7	1.1 (1.00, 1.21)	.135/46.1	1.06 (0.99,1.14)	.001/81.1
Control source											
PB	10	**1.15 (1.06, 1.25)**	.933/0.0	**1.28 (1.10, 1.49)**	.187/28.0	**1.11 (1.02, 1.22)**	.963/0.0	**1.33 (1.09,1.64)**	.171/29.8	**1.14 (1.07, 1.22)**	.736/0.0
HB	6	1.16 (0.97, 1.39)	.301/174.4	1.14 (0.88, 1.47)	.358/9.2	1.16 (0.94, 1.43)	.211/29.9	1.26 (0.95, 1.67)	.375/6.5	1.11 (0.98, 1.25)	.540/0.0
Mixed	6	**1.09 (1.01, 1.17)**	<.001/78.1	**1.07 (1.02, 1.13)**	.741/0.0	1.08 (1.00, 1.16)	.001/76.0	**1.11 (1.04, 1.20)**	.185/35.5	**1.07 (1.02, 1.12)**	.003/72.7
Sample size											
Large*	10	**1.08 (1.02, 1.15)**	.003/64.5	**1.08 (1.03, 1.14)**	.114/36.8	**1.07 (1.01, 1.14)**	.005/64.1	**1.13 (1.04, 1.24)**	.027/52.1	**1.07 (1.02, 1.11)**	.007/60.5
Small*	12	**1.24 (1.11, 1.38)**	.983/0.0	**1.32 (1.09, 1.60)**	.746/0.0	**1.2 (1.07, 1.34)**	.935/0.0	**1.47 (1.20, 1.80)**	.888/0.0	**1.2 (1.11, 1.31)**	.996/0.0
BRCA mutations											
BRCA 1	3	**1.11 (1.05, 1.18)**	.641/0.0	1.08 (0.98, 1.18)	.791/0.0	**1.1 (1.04, 1.17)**	.622/0.0	**1.13 (1.03, 1.25)**	.767/0.0	**1.08 (1.03, 1.13)**	.706/0.0
BRCA 2	3	**1.15 (1.06, 1.23)**	.750/0.0	**1.14 (1.02, 1.29)**	.940/0.0	**1.13 (1.04, 1.22)**	.683/0.0	**1.22 (1.07, 1.38)**	.966/0.0	**1.11 (1.05, 1.18)**	.902/0.0
ER*											
Positive	2	**1.16 (1.03, 1.31)**	.684/0.0	1.11 (0.92, 1.33)	.414/0.0	**1.15 (1.02, 1.31)**	.881/0.0	1.19 (0.98, 1.45)	.405/0.0	**1.11 (1.02, 1.21)**	.497/0.0
Negative	3	1.08 (0.98, 1.20)	.971/0.0	1.02 (0.86, 1.22)	.058/64.9	1.08 (0.97, 1.21)	.917/0.0	1.07 (0.89, 1.28)	.073/61.9	1.05 (0.97, 1.14)	.576/0.0

Bold text indicates statistically significant results.

N* = The number of reports, Large* = Number of participants in the study is greater than or equal to 1000, Small* = Number of participants in the study < 1000, ER* = Estrogen receptor.

CI = confidence interval, LSP1 = leukocyte-specific protein 1, OR = odds ratio.

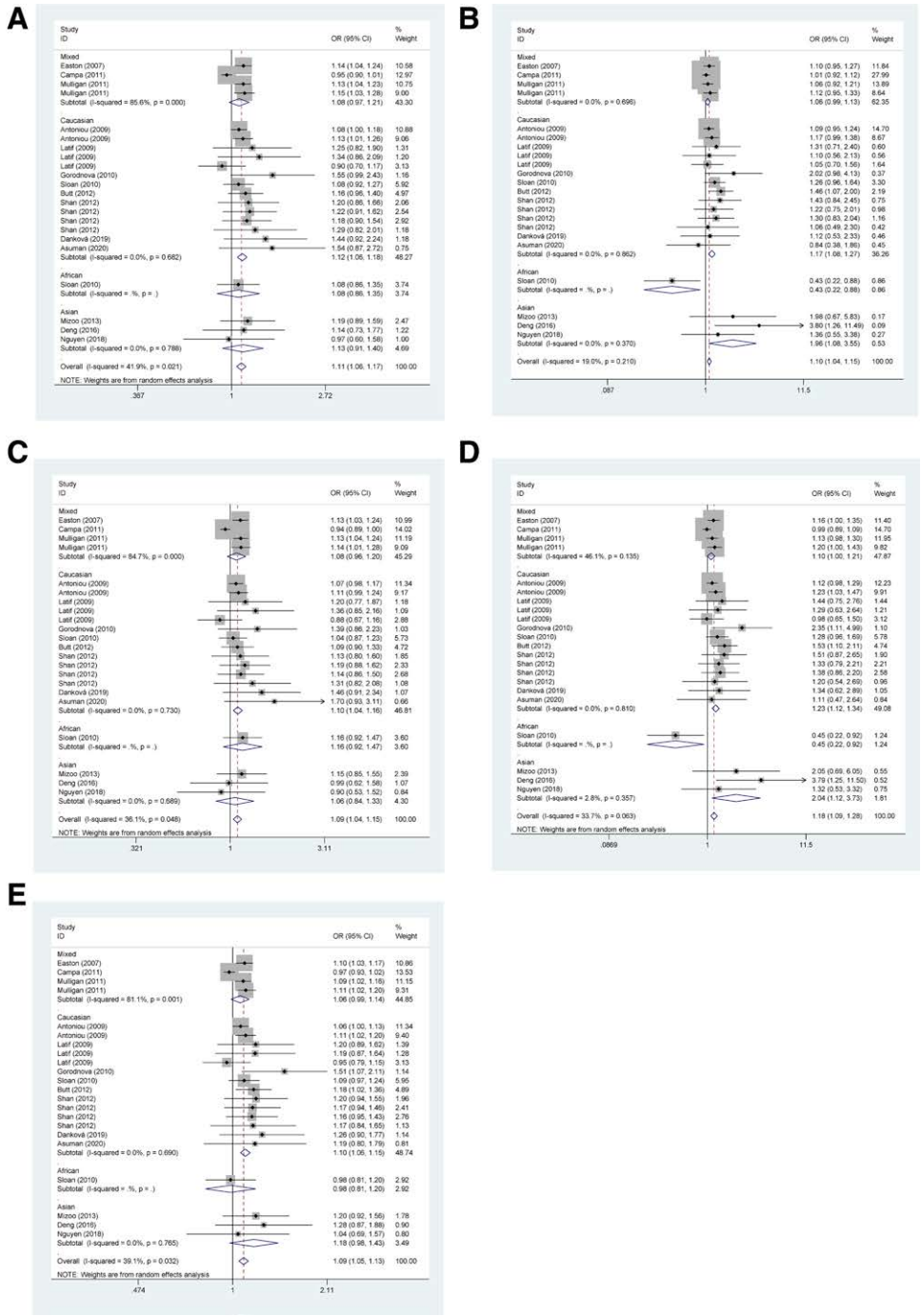

Figure 2. Forest plot of the connection of LSP1 rs3817198 polymorphism with breast cancer risk. (A) dominant model, (B) recessive model, (C) heterozygote model, (D) homozygote model, (E) additive model. LSP1 = leukocyte-specific protein 1.

and 1 using duplicate data; it was worth noting that the base mutation of the LSP rs3817198 polymorphism was T mutated to C, not A mutated to G; therefore, we excluded 3 studies on rs3817198 (G > A) with a total of 71531 subjects.[42–44] We also accessed 3 reports by hand search and reference search.[45–47] The process can be understood more visually in Figure 1. We obtained 17 published articles investigating rs3817198(T > C) and breast cancer.[21,24–29,45–54] We recalculated the P-values of HWE for the control groups and found that the gene frequency distributions of the control group in Ying Chen et al, Zahra Nourolahzadeh et al, and Rui Li et al failed to conform to HWE (*P*-value was below 0.05)[24,47,54]; the 3 trials were eliminated from this meta-analysis. Finally, we included 14 studies with 22 reports covering 33194 cases and 36661 controls.

Table 2 provides a summary of the characteristics of all investigations. Various ethnic groups were recruited, including Caucasians, Asians, and Africans. However, only 1 study was conducted with the African population. Three of these studies examined the effect of rs3817198(T > C) on breast cancer in a population with BRCA gene mutations.[46,48,51] Two publications have reported a link between rs3817198(T > C) and ER-positive breast carcinoma.[51,53] Of the 17 studies initially enrolled, 11

Table 4

***P* values of the meta-regression for LSP1 rs3817198 in dominant, heterozygous, homozygous, and additive models.**

Covariates	N*	Dominant model	Heterozygous model	Homozygous	Additive model
Publication yr	-	0.775	0.811	0.756	0.653
Ethnicity	4	0.894	0.838	0.629	0.886
Source of controls	3	0.394	0.526	0.163	0.188
Genotyping methods	5	0.149	0.215	0.096	0.076
Sample size	2	0.120	0.185	0.245	0.115

LSP1 = leukocyte-specific protein 1, N* = number of dummy variables.

were case-control studies,[21,24–27,29,45,47,49,53,54] 4 were cohort studies,[28,46,51,52] and 2 were nested case-control studies,[48,50] that is why we used NOS for quality assessment (Supplemental Table S4–S5, http://links.lww.com/MD/H848). Only the study by Zahra Nourolahzadeh et al was 4 stars,[47] and it is worth noting that its control group also failed to conform to HWE.

3.2. Meta-analysis findings

After the statistical power calculation, we found high statistical power for all 5 models. For each ethnic group, we found low power in the homozygote model (17%) among Asians and the dominant (18%), homozygote (23%), and additive (5%) models among Africans. Supplemental Table S6, http://links.lww.com/MD/H849 provides the statistical power of all models. Table 3 summarizes the meta-analysis findings on the relationship between LSP1 rs3817198(T > C) and BC, LSP1 rs3817198(T > C) variant is related to an elevated risk for BC (dominant model: OR = 1.11, 95%CI = 1.06–1.17; recessive model: OR = 1.10, 95%CI = 1.04–1.15; heterozygous model: OR = 1.09, 95%CI = 1.04–1.15; homozygous model: OR = 1.18, 95%CI = 1.09–1.28; additive model: OR = 1.09, 95%CI = 1.05–1.13). Subgroup analyses were conducted to estimate further the association of polymorphisms with BC in various subgroups, the results were as follows.

Ethnicity: The forest plots for ethnic subgroup analysis are shown in Figure 2. We noticed that rs3817198(T > C) might contribute to breast carcinoma in Caucasians (dominant model: OR = 1.12, 95%CI = 1.06–1.18; recessive model: OR = 1.17, 95%CI = 1.08–1.27; heterozygous model: OR = 1.10, 95%CI = 1.04–1.16; homozygous model: OR = 1.23, 95%CI = 1.12–1.34; additive model: OR = 1.10, 95%CI = 1.06–1.15) and Asians (recessive model: OR = 1.96, 95%CI = 1.08–3.55; homozygous model: OR = 2.04, 95%CI = 1.12–3.73). But we obtained the opposite outcome in the subgroup of Africans (recessive model: OR = 0.43, 95%CI = 0.22–0.88, homozygous model: OR = 0.45, 95%CI = 0.22–0.92).

Control sources: Population-based studies have connected the rs3817198(T > C) variant with breast cancer (dominant model: OR = 1.15, 95%CI = 1.06–1.25; recessive model: OR = 1.28, 95%CI = 1.10–1.49; heterozygous model: OR = 1.11, 95%CI = 1.02–1.22; homozygous model: OR = 1.33, 95%CI = 1.09–1.64; additive model: OR = 1.14, 95%CI = 1.07–1.22). However, rs3817198 was unrelated to breast cancer in hospital-based studies. In case-control studies of mixed source, rs3817198(T > C) was associated with susceptibility to BC (dominant model: OR = 1.09, 95%CI = 1.01–1.17; recessive model: OR = 1.07, 95%CI = 1.02–1.13; homozygous model: OR = 1.11, 95%CI = 1.04–1.20; additive model: OR = 1.07, 95%CI = 1.02–1.12).

Sample size/BRCA mutations/ER status: Studies with recruitment numbers greater than or equivalent to 1000 are called large sample size studies. Otherwise, they are called small sample size studies. In both large and small sample size groups, breast cancer risk might be elevated by rs3817198(T > C) in each genetic model. Three studies were performed to research the impact of rs3817198(T > C) on breast cancer for persons with BRCA gene mutations[46,48,51]; combining the data, we found that rs3817198(T > C) could cause breast carcinoma in subjects carrying the BRCA1 and BRCA2 variations. In the estrogen receptor subgroup, the SNP might confer a higher chance for ER-positive breast carcinoma in dominant, heterozygous, and additive models.

3.3. Heterogeneity detection

Heterogeneity was found in our study in dominant, heterozygous, homozygous, and additive models. According to Table 3, the I^2 of all 5 gene models was less than 50%, so our work showed low heterogeneity. Meta-regression was employed to probe origins for heterogeneity inside these 4 models, with covariates such as publication year, ethnicity, control sources, genotyping methods, and the number of samples. However, *P* values exceeded .05 for all covariates in each genetic model (Table 4), therefore meaningful results were not found in meta-regression.

In the subgroup analyses, heterogeneity was mainly detected in the mixed groups in ethnicity and control groups sources and studies with large sample sizes. It is noteworthy that these subgroups are multicenter studies. We can infer that the meta-analysis heterogeneity stems from the inconsistency of the recruited populations and the study design of multicenter studies.

3.4. Publication bias

We found that the funnel plots of all genetic models were roughly symmetrical (Fig. 3), and it was hard to determine whether publication bias existed; as a result, Begg's and Egger's tests were utilized to assess it quantitatively. In recessive ($P_{Egger} = 0.038$) and homozygous ($P_{Begg} = 0.042$, $P_{Egger} = 0.001$) models, publication bias was detected. Then, we undertook the trim and fill method. In the analysis of the recessive model, 4 iterations were performed, and 6 studies were trimmed, but the filled ORs and 95% CIs were not reversed; as for the homozygous model, there were 3 iterations, 8 studies were subtracted, and the filled OR with 95% CI also did not invert (Supplemental Table S7, http://links.lww.com/MD/H850). The funnel plots of recessive and homozygous models after trim and fill analysis are shown in Supplemental Figure S1, http://links.lww.com/MD/H851; the ORs and 95% CIs of the 2 models did not alter substantially following trim and fill, and the result did not reverse, indicating that the publication bias was acceptable.

3.5. Sensitivity analysis

The robustness of the outcomes was determined using the leave-one-out approach. After eliminating any single study from the included studies by turns, we recombined the data and found consistent results (Fig. 4). The meta-analysis findings were stable and robust.

3.6. Bioinformatics analysis

Meta-analysis has shown the relationship between LSP1 rs3817198(T > C) polymorphism and BC, and we conducted bioinformatics analysis to explore the mechanism between LSP1 itself and BC.

Gene co-expression network: The gene co-expression network of LSP1 was visualized by STRING. The co-expression network of LSP1 contained 31 genes (Fig. 5), of which ARHGEF12,[55] ATF2,[56,57] CYLD,[58] DUSP1,[59] IKBKE,[60]

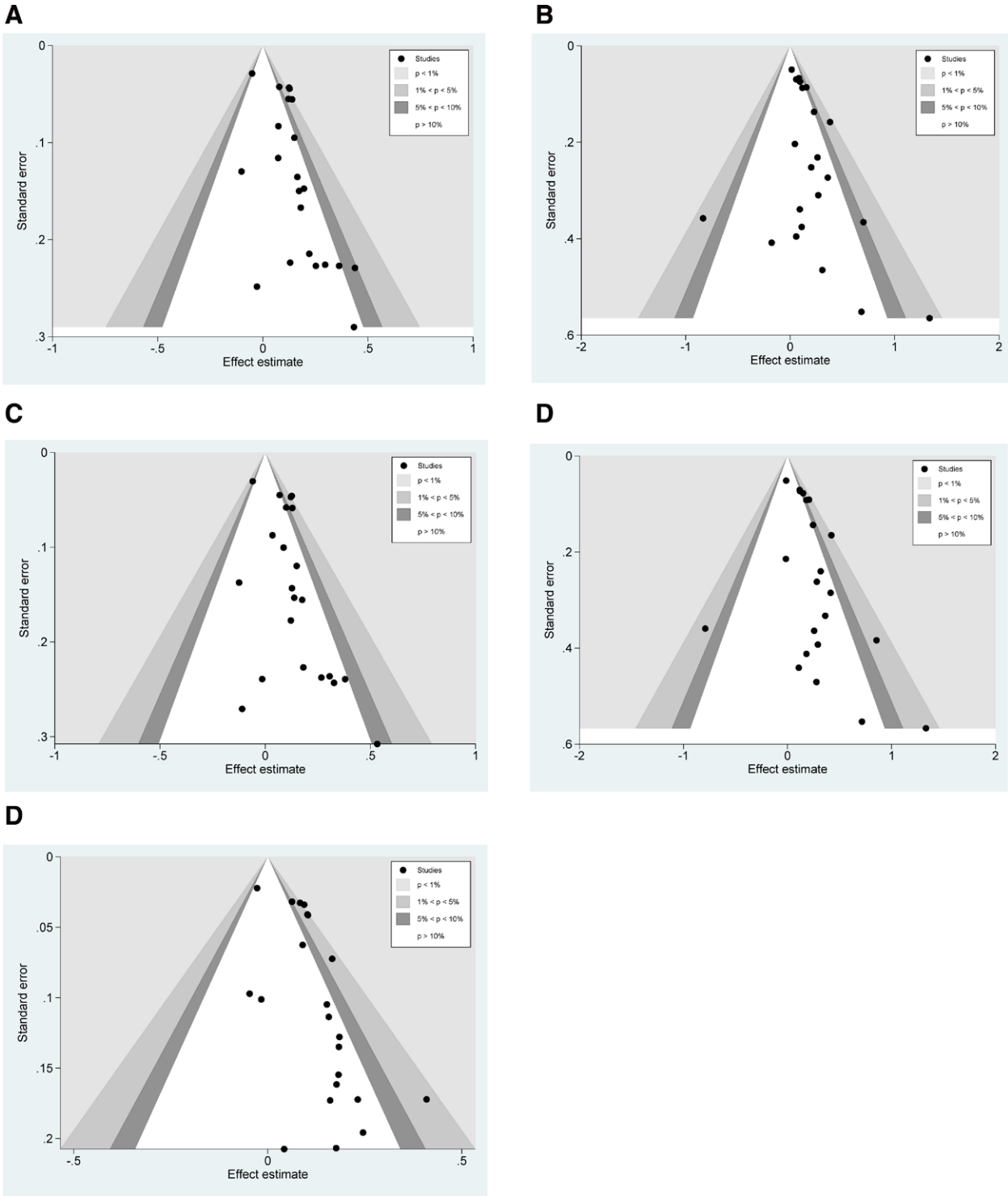

Figure 3. Contour-enhanced funnel plots for 5 genetic models. (A) dominant model, (B) recessive model, (C) heterozygote model, (D) homozygote model, (E) additive model.

KSR1,[61] MAPK11,[62] RHOA,[63] RIPK1,[64] RNF31,[65] TAB1,[66] TP53,[67] TRAF3,[68] and TRAF6[69] were associated with the pathogenesis, progression, and pharmacokinetic mechanisms in breast cancer. And TP53 is a classical anti-oncogene.

Enrichment analysis: We used DAVID for enrichment analysis and obtained 136 GO and 78 KEGG terms. After excluding the terms with FDR > 0.05, 40 GO (BP:21, CC:5, MF:14) terms and 60 KEGG terms were obtained. These statistically significant terms were visualized as shown in Figure 5.

Chemotherapy sensitivity: GDSC was used to assess the relationship between LSP1 expression and the IC50 of chemotherapeutic agents (doxorubicin, 5-fluorouracil, docetaxel, and cisplatin) for BC patients. The lower the IC50 of a drug indicates that it is more effective in suppressing individual tumor cells. As shown in Figure 6, the expression of LSP1 was inversely correlated with the IC50 of doxorubicin (P = 8.91e–15, Cor = –0.23), 5-fluorouracil (P = 1.18e–22, Cor = –0.29), and cisplatin (P = 1.35e–42, Cor = –0.40), which indicates that the higher the expression of LSP1, the

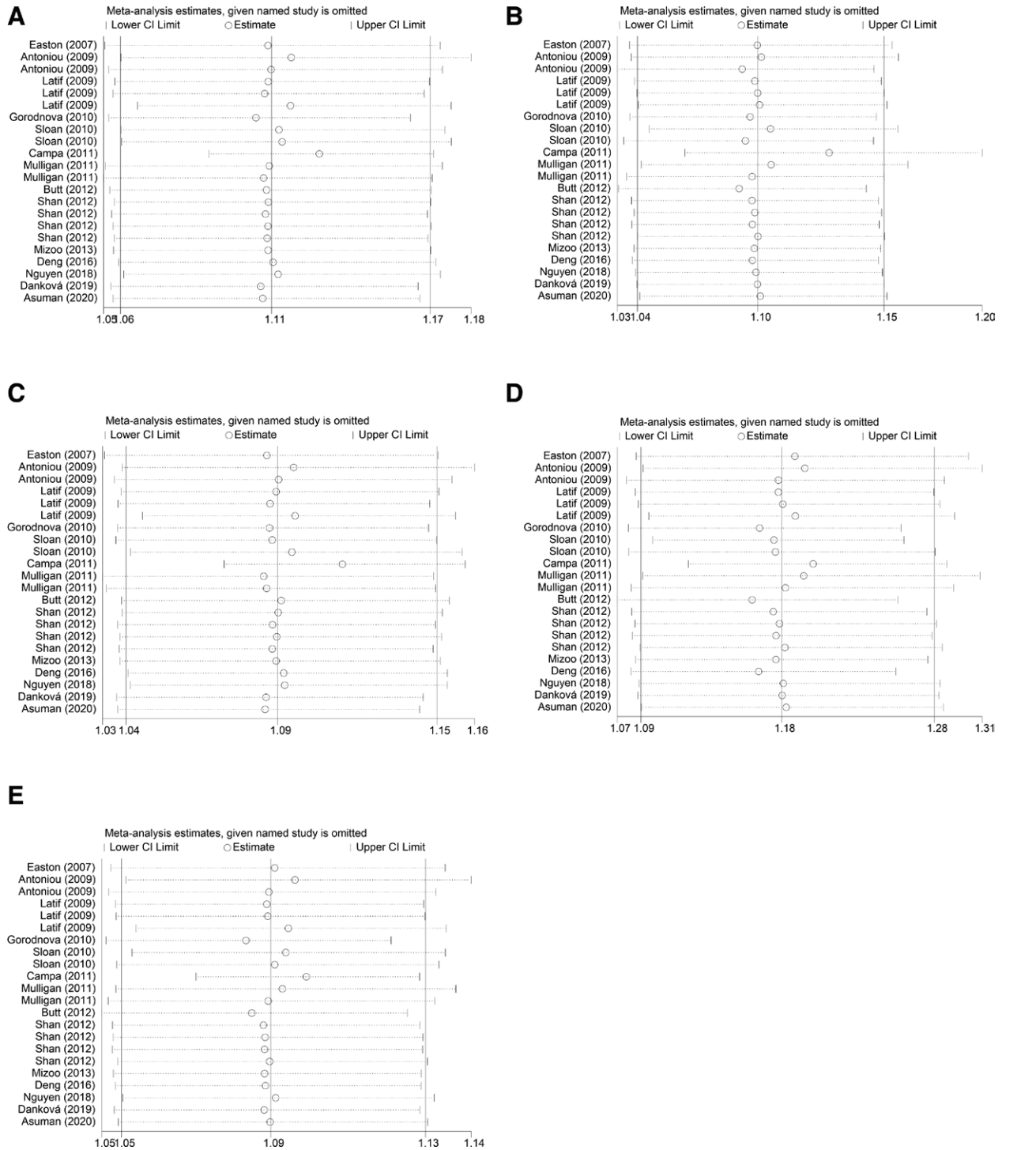

Figure 4. Sensitivity analysis of the connection between LSP1 rs3817198(T > C) and breast cancer in 5 genetic models. The figure indicates the range of ORs and 95% CIs after removing individual studies in turn for recombination. (A) dominant model, (B) recessive model, (C) heterozygote model, (D) homozygote model, (E) additive model. CI = confidence interval, LSP1 = leukocyte-specific protein 1, OR = odds ratio.

better the therapeutic effect of these 3 chemotherapeutic drugs on patients.

4. Discussion

This Meta-analysis identified the LSP1 rs3817198(T > C) polymorphism was associated with BC risk and increased the risk for Caucasians and Asians while decreasing the risk for Africans. Numerous clinical studies from 2007 to the present have explored the relationship between this SNP and BC susceptibility. Among the 8 clinical studies in Caucasian populations,[25,28,45–49,52] 4 showed that rs3817198(T > C) polymorphism was associated with BC risk,[47–49,52] with Antoniou et al finding that in BRCA2 mutation carriers, this SNP can lead to an increased risk of BC.[48] In 5 studies on Asians, Li et al and Deng et al found that rs3817198(T > C) polymorphism can increase BC susceptibility,[53,54] and Deng et al's findings were seen in ER-negative patients. However, there was only 1 study on Africans, which showed that rs3817198(T > C) polymorphism reduces the risk of BC in African populations.[45] The

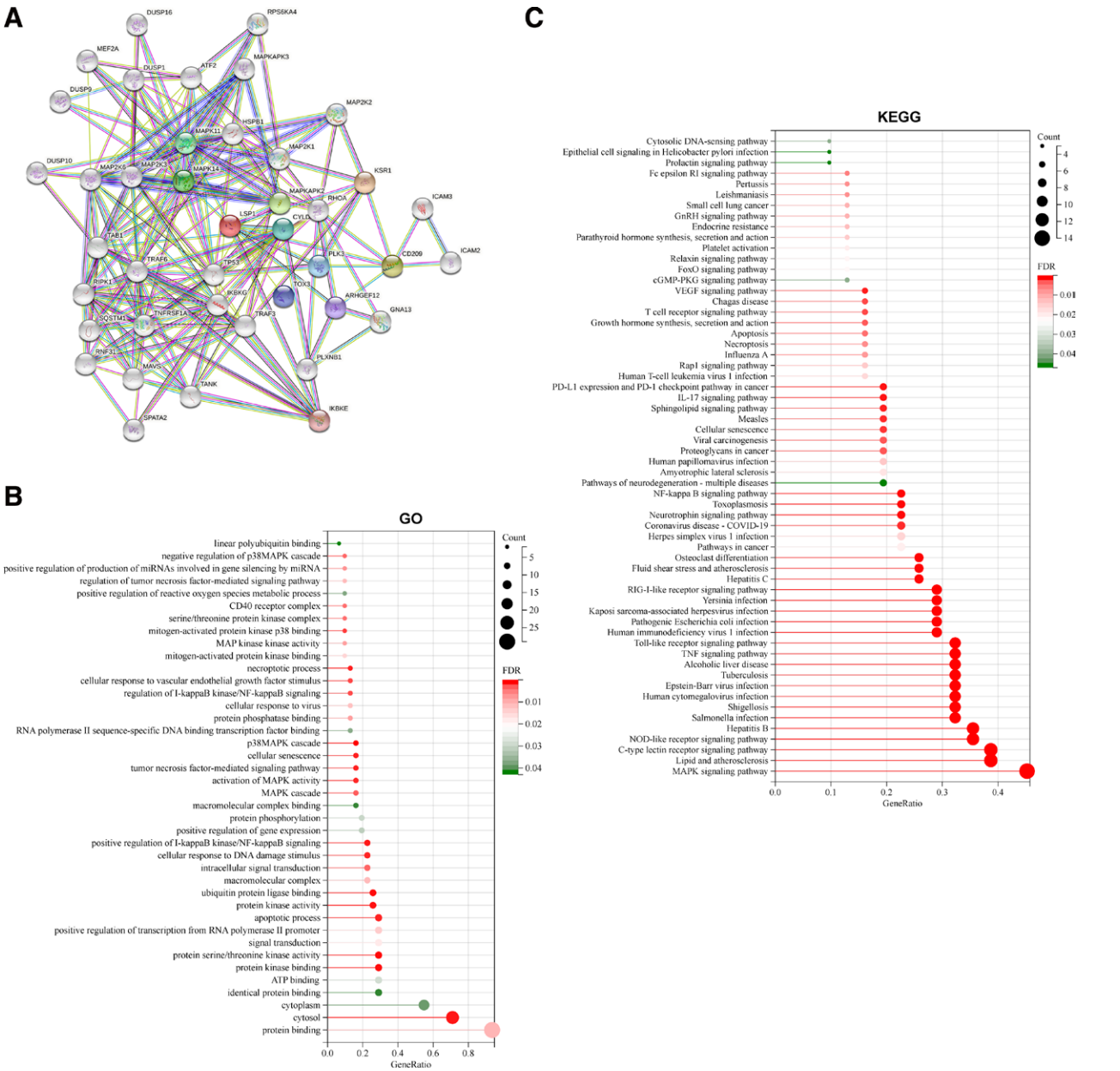

Figure 5. The gene co-expression network of LSP1 and the results of GO and KEGG analysis. (A) Gene co-expression network of LSP1. (B) Results of GO analysis of LSP1 co-expression network. C. Results of KEGG analysis of LSP1 co-expression network. LSP1 = leukocyte-specific protein 1, GO = gene ontology, KEGG = Kyoto encyclopedia of genes and genomes.

above studies shared the same results as our meta-analysis; however some other studies showed that rs3817198(T > C) polymorphism was not associated with BC risk[24–29,45,46,50]; our meta-analysis included all eligible studies, and the large sample size provided a more reliable results.

This meta-analysis incorporated 14 articles with 22 reports with 33194 cases and 36661 controls. Compared to the prior published meta-analyses,[22,23] we excluded 2 studies on rs3817198 (A > G)[42,43] and 3 articles lacking gene frequencies[70–72] and included 8 new publications.[24–29,51,53] Our findings were consistent with Jianzhou Tang et al[23]; because of limitations in the inclusion of studies, Min-Bin Chen et al did not conduct a discussion on Asian populations.[22] Our study showed that rs3817198(T > C) could increase the susceptibility to breast carcinoma for persons with variations in the BRCA1 and BRCA2, congruent with the outcomes of Min-Bin Chen.[22] In addition, we also investigated the stratification of estrogen receptor status and found that this SNP was only related to ER-positive breast carcinoma, which was contrary to the results of the case-control study by Deng et al[53]; this meta-analysis had an enormous amount of data, so the results were more reliable, and there was also a study that reported rs3817198(T > C) was related to ER-positive BC.[73] Our conclusions are more accurate than previous meta-analyses because we excluded some studies rs3817198(A > G)[42–44] and studies with incomplete gene frequencies[70,72,74] and included some newly published studies.[24–26,28,29,47,53,54]

Our study had low heterogeneity, and we performed Meta-regression to investigate the reasons for the heterogeneity. Meta-regression did not yield significant sources of heterogeneity, with all *P* values > .05. According to subgroup analysis, heterogeneity was primarily found in mixed groups of ethnicity and control group sources and in the subgroup with large sample size, all of which came from multicenter studies. The differences in recruitment criteria, population ethnicity, genotyping methods, and experimental design of each research center may account

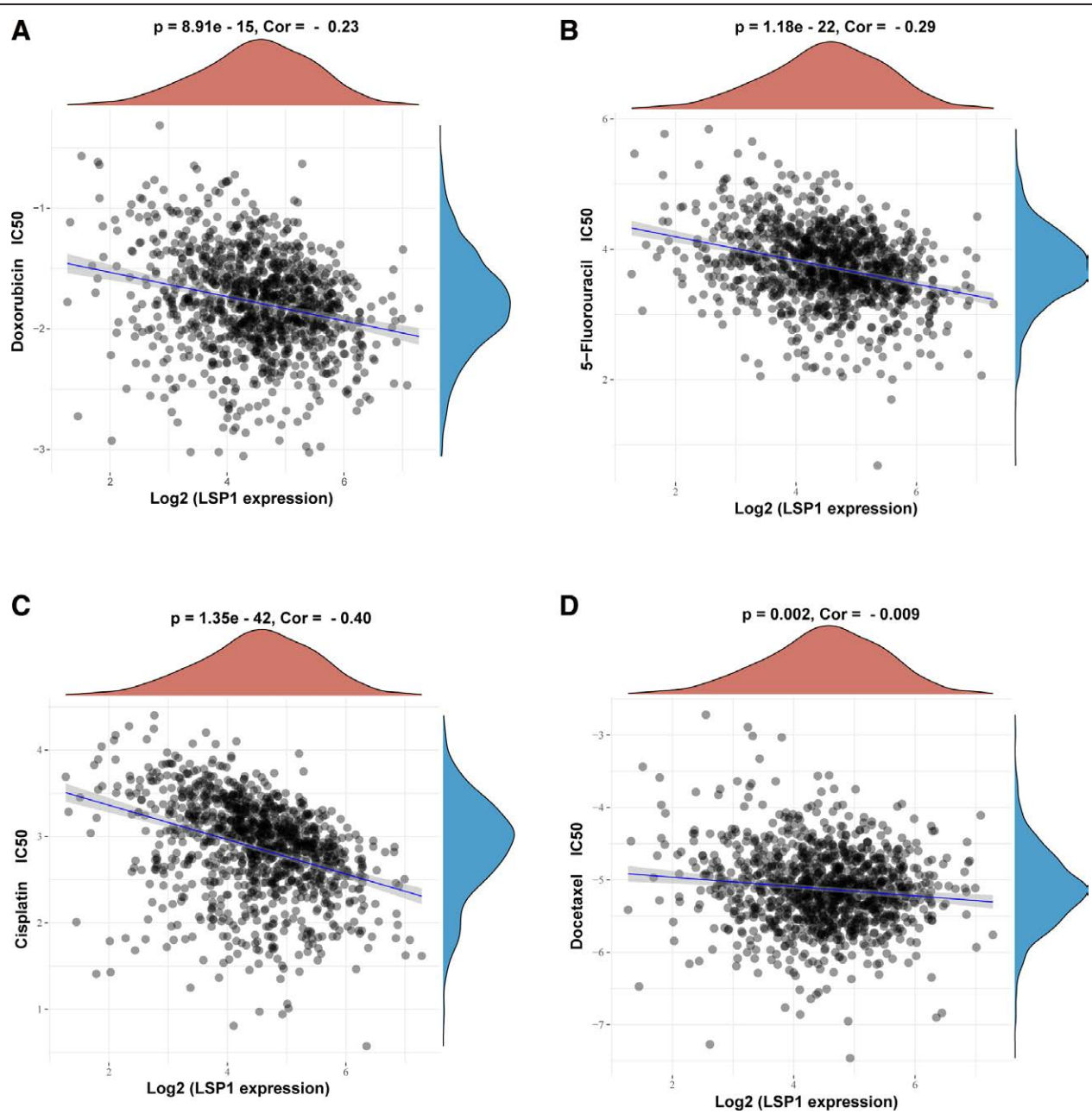

Figure 6. Association of LSP1 expression with the IC50 of doxorubicin (A), 5-fluorouracil (B), cisplatin (C), and docetaxel (D), in breast cancer patients. LSP1 = leukocyte-specific protein 1.

for the heterogeneity of our meta-analysis. Publication bias was found in the recessive and homozygous models via the Begg's and Egger's tests, and the trim and fill method was performed to assess it further; and the results of recessive and homozygous models were consistent with the previous after trim and fill, indicating publication bias is acceptable.

Thirty-one genes, including LSP1, formed the co-expression network, 14 of which are associated with breast cancer[55–69]; TP53 is a classical anti-oncogene. GO analysis showed that the network is associated with protein kinase activity, particularly serine/threonine protein kinases; both kinases have been linked to human tumorigenesis, progression and treatment.[75,76] Through KEGG analysis, we found that this network was highly correlated with the MAPK signaling pathway; this pathway is also hot in oncology research, which regulates cancer cell metabolism and tumor progression and correlates with antitumor drug resistance.[75,77] However, to our knowledge, no basic studies currently exist on LSP1 and this pathway. Doxorubicin, 5-fluorouracil, docetaxel, and cisplatin are common clinical chemotherapeutic agents for BC patients,[78–80] and we found that the expression of LSP1 was most associated with the sensitivity of cisplatin. Cisplatin has also been used in patients with BRCA mutations,[81] and our study also showed that rs3817198(T > C) polymorphism could increase BC susceptibility in individuals with BRCA mutations; whether this SNP can interact with BRCA mutations to influence BC genesis and treatment is also worth noting.

This study analyzed the linkage of LSP1 with breast cancer at 2 dimensions simultaneously: gene polymorphism and the gene itself. The meta-analysis demonstrated that LSP1 rs3817198(T > C) polymorphism was associated with BC risk and that LSP1 might be a potential biomarker for BC diagnosis. Notably, there were studies demonstrating that LSP1 polymorphisms are associated with mammographic density[82–84] and

that mammographic density is a factor in the pathogenesis of BC; however, there were no studies on the mechanisms by which LSP1 polymorphisms and LSP1 expression are associated with mammographic density. In bioinformatic analysis, we found that LSP1 expression in BC correlated with cisplatin sensitivity, and nearly half of the genes in the network were associated with BC and involved in cancer-related mechanisms and pathways. However, to our knowledge, no mechanistic studies of LSP1 in the normal breast or breast cancer have been reported. We believe LSP1 is a highly promising gene in breast cancer research and should not be neglected.

This study has some limitations. First, there was a degree of heterogeneity in our meta-analysis due to the different recruitment populations and experimental settings of the included multicenter studies. Second, only 1 study was reported on Africans, and its statistical power was low in the dominant, heterozygote and additive models, which led to a risk of bias and a lack of confidence in the results. Third, the original studies did not give gene frequencies for tumor subtypes, age, smoking status, BMI, etc, and we could not construct genetic models; therefore, our meta-analysis could not perform a more detailed stratified analysis. Fourth, due to the lack of gene mutation data in the public database, there is no corresponding high-throughput data to validate the conclusions of our meta-analysis. Fifth, due to the limitations of the GDSC database, we can only predict the sensitivity of the drugs in that database and cannot predict other essential chemotherapeutic drugs. Finally, the part of bioinformatics analysis is a retrospective study and needs to be cross-supported with relevant prospective studies.

Overall, our meta-analysis demonstrated that LSP1 rs3817198(T > C) polymorphism is related to a rising risk of BC, particularly among Caucasians and Asians, but reduces BC susceptibility among Africans. LSP1 might affect the sensitivity of cisplatin in BC treatment. In future studies, the increased sample count is still necessary to further validate this finding by examining the relationship of gene-gene and gene-environment interactions on breast carcinoma susceptibility through various rigorous matching of controls and cases. Meanwhile, the mechanism of LSP1 involvement in BC also needs to be considered.

Author contributions

Yingliang Li is the guarantor of this article. Jian Chen, Qiang Xiao, Xudong Li are the co-first author. And all authors have reviewed the final manuscript.
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Visualization: Xiaozhou Long, Xudong Li.
Writing – original draft: Jian Chen.
Writing – review & editing: Yingliang Li, Jian Chen, Qiang Xiao.

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