Association of IL-8 -251T>A and IL-18 -607C>A polymorphisms with susceptibility to breast cancer – a meta-analysis

Souvislost polymorfizmu IL-8 -251T>A a IL-18 -607C>A s náchylností ke karcinomu prsu – metaanalýza

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Summary

Background: *P*revious studies have evaluated the association of IL-8 -251T>A and IL-18 -607C>A polymorphisms with a risk of breast cancer in different populations, but the results remain inconsistent and inconclusive. Thus, we performed this meta-analysis to explore the associations. ***Methods:*** A comprehensive literature search in PubMed, EMBASE, Web of Science, Scopus, SciELO, SID, and CNKI for all eligible studies published up to October 1, 2020. The pooled odds ratios (ORs) with 95% confidence intervals (CIs) were used to evaluate the intensity of associations. ***Results:*** A total of 12 case-control studies including seven studies with 2,370 cases and 2,314 controls on IL-8 -251T>A, and five studies with 900 cases and 882 controls on IL-18 -607C>A polymorphism were selected. Pooled data showed that IL-8 -251T>A (AT vs. TT: OR= 1.187; 95% CI 1.038–1.356; P = 0.012) and IL-18 -607C>A polymorphisms (A vs. T: OR = 1.205; 95% CI 1.055–1.377; P = 0.006; AA vs. TT: OR = 1.379; 95% CI 1.056–1.802; P = 018; and AA vs. AT+TT: OR = 1.329; 95% CI 1.053–1.678; P = 0.017) were associated with increased risk of breast cancer in overall. Moreover, when the studies were stratified by ethnicity, the IL-8 -251T>A was significantly associated with breast cancer risk in Africans. Publication bias tests provide no evidence of presence of publication bias in a meta-analysis. ***Conclusion:*** This meta-analysis results revealed that the IL-8 -251T>A and IL-18 -607C>A polymorphisms are associated with susceptibility to breast cancer. However, further multicenter studies with larger sample sizes in different ethnicities are required to make a better assessment of these associations.

Key words

breast cancer – interleukin-8 – interleukin-18 – association – meta-analysis

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Souhrn

Východiska: Dříve provedené studie hodnotily souvislost polymorfizmu IL-8 -251T>A a IL-18 -607C>A s rizikem karcinomu prsu v různých populacích, ale výsledky zůstávají nekonzistentní a neprůkazné. Provedli jsme tedy tuto metaanalýzu s cílem prozkoumat souvislosti. ***Metody:*** Komplexní vyhledávání literatury v databázích PubMed, EMBASE, Web of Science, Scopus, SciELO, SID, and CNKI z hlediska všech vhodných studií publikovaných do 1. října 2020. Pro hodnocení intenzity souvislosti byly použity souhrnné poměry šancí (odds ratio – OR) s 95% intervaly spolehlivosti (confidence interval – CI). ***Výsledky:*** Bylo vybráno celkem 12 studií případů a kontrol o polymorfizmu IL-8 -251T>A vč. 7 studií s 2 370 případy a 2 314 kontrolami a 5 studií o polymorfizmu IL-18 -607C>A s 900 případy a 882 kontrolami. Souhrnná data ukázala, že polymorfizmy IL-8 -251T>A (AT vs. TT: OR = 1,187; 95% CI 1,038–1,356; p = 0,012) a IL-18 -607C>A (A vs. T: OR = 1,205; 95% CI 1,055–1,377; p = 0,006; AA vs. TT: OR = 1,379; 95% CI 1,056–1,802; p = 0,018; a AA vs. AT+TT: OR = 1,329; 95% CI 1,053–1,678; p = 0,017) měly obecně souvislost se zvýšeným rizikem karcinomu prsu. Navíc když byly studie stratifikovány podle etnik, u IL-8 -251T>A byla významná souvislost s rizikem karcinomu prsu u Afričanek. Testy publikačního zkreslení u metaanalýzy žádné publikační zkreslení neprokázaly. ***Závěr:*** Tato metaanalýza odhalila, že polymorfizmus IL-8 -251T>A a IL-18 -607C>A je spojen s náchylností ke karcinomu prsu. Pro lepší vyhodnocení těchto asociací je ovšem třeba dalších multicentrických studií s různými etniky.

Klíčová slova

karcinóm prsu – interleukin 8 – interleukin 18 – souvislost – metaanalýza

Introduction

Breast cancer is the most common form of cancer and the leading cause of death in women of all ethnic groups [1,2], especially in case of low- and middle-income developing countries due to screening barriers [3]. In 2018, an estimated 266,000 new cases of breast cancer will be diagnosed with 41,000 cases of deaths, were estimated to occur in women in the United States [4]. In the literature, obesity, hormone replacement therapy, radiation, age, and family history has been described as a pivotal risk factor for breast cancer development [5–8]. Approximately 4% of cases diagnosed with breast cancer in the United States are younger than 40 years and a report by National Cancer Institute showed that the breast cancer incidence rate in women aged 21–54 years was 33.6% of all breast cancer cases [9,10].

Despite its high prevalence and rapid progress in molecular biology of cancer achieved in the last few decades, the exact mechanism of breast cancer is still poorly understood [11,12]. It is evident that genetic and environmental factors play a role in the development of breast cancer [13,14]. Moreover, there is also a relationship between social environment and breast cancer development and woman cope with a breast cancer diagnosis. Epidemiological studies have demonstrated that single nucleotide polymorphisms (SNPs) in different interleukins might be involved in development of breast cancer [15,16].

Recently, the roles of interleukin 8 (IL-8) and IL-18 have been extensively studied in the development of breast cancer. Human IL-8 enhances the immune system against cancer cells and also modifies the tumor microenvironment facilities [17]. Increasing evidence demonstrates that human IL-8 is considerably expressed in ER-, PR- and HER-2/neu+ breast cancer cells, but highly correlated with invasiveness and metastatic of both ER- and ER+ cells by twofold, indicating the invasion-promoting role of IL-8 [17–20]. IL-8 is associated with growth receptors expressed on the surface of breast cancer cells. However, the mechanisms by which IL-8 contributes to breast cancer progression have remained poorly understood [21]. Moreover, IL-18 may also have role in development of breast cancer. Previous studies revealed that serum levels of IL-18 were higher in advanced than in early stages and higher in metastatic than in non-metastatic breast cancer cases [22]. In the recent decade, several studies have investigated the influence of IL-8 -251T>A and IL-18 -607C>A polymorphisms in breast cancer, but their results remained controversial. Therefore, we performed meta-analyses to evaluate and summarize the contribution of the IL-8 -251T>A and IL-18 -607C>A polymorphisms to breast cancer susceptibility.

Materials and methods

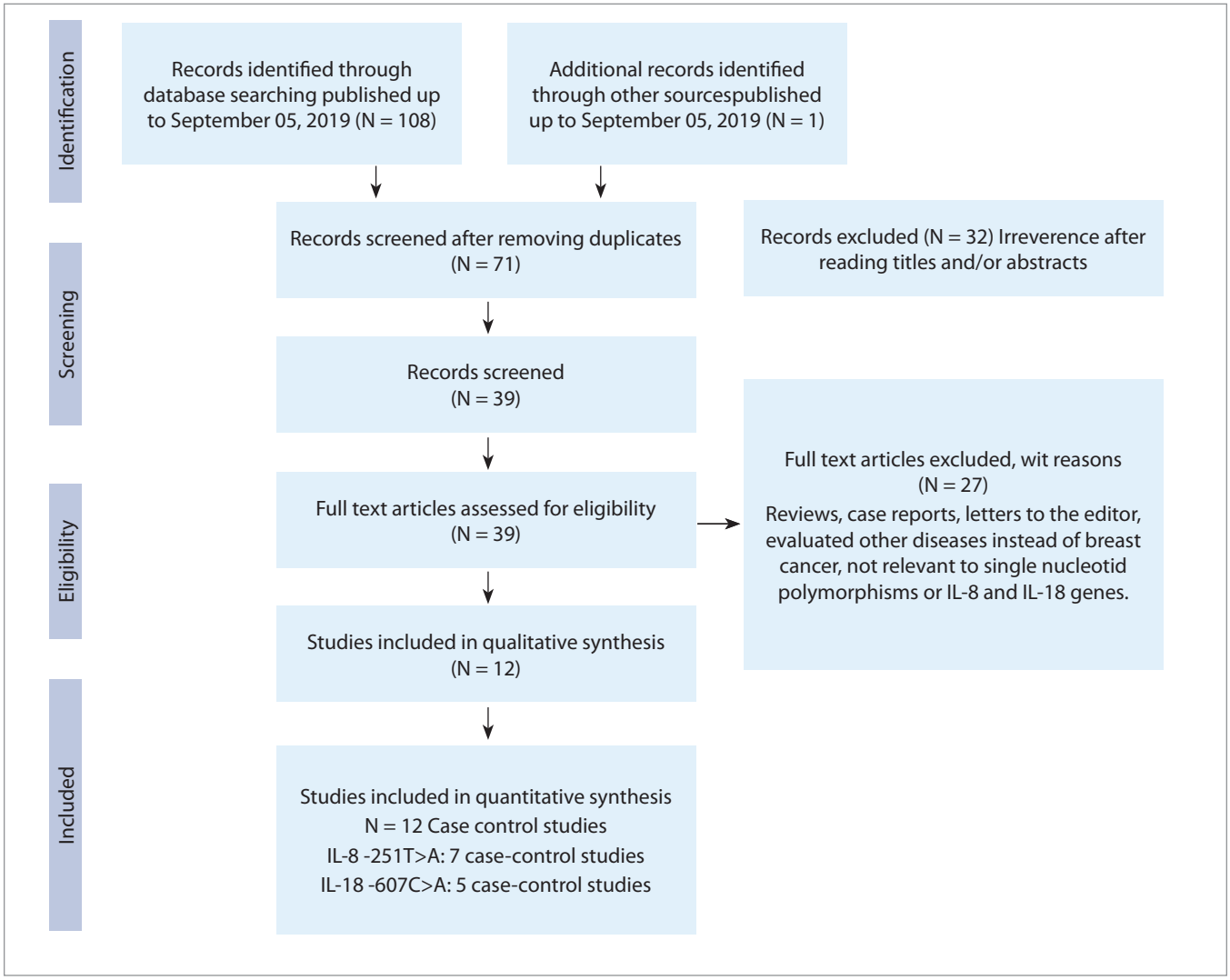
Identification and eligibility of relevant studies

This study was performed according to the Preferred reporting items for systematic reviews and meta-analyses (PRISMA) statement on reporting meta-analysis. We conducted a comprehensive literature on PubMed, EMBASE, Web of Science, Science Citation Index (SCI), Springer Link, CNKI, Wanfang, OVID, SID, EBSCO and Science Direct databases to identify potential studies evaluated the association of IL-8 -251T>A and IL-18 -607C>A polymorphisms with a risk of breast cancer. The search keywords used were as follows: (''Breast Cancer'' OR ''Tumor'' OR ''Cancer'' OR ''Neoplasm'') AND (''Interlukine-8 '' OR ''IL-8'' OR ''-251A>T'' OR ''rs4073'') AND (''Interlukine-18 '' OR ''IL-18'' OR ''-607C>A'' OR ''rs1946518'') AND (''Gene'' OR ''Polymorphism'' OR ''SNPs'' OR ''Mutation'' OR ''Variation'' OR ''Allele''). Then, the references of all retrieved publications and reviews to identify other potential relevant studies were checked manually. The final literature search was updated on October 1, 2020, with no restrictions on publication year or methodological filter. Data for the largest sample set or most recent published articles were included when data from the same set of cases were used more than once within a publication.

Selection criteria

The eligible studies included in the current meta-analysis, must meet all the following criteria:

1) genetic association studies on association of IL-8 -251T>A and IL-18 -607C>A polymorphisms with breast cancer;
2) in human beings;



Scheme 1. Flowchart of literature search and selection process.

3) studies with case-control or cohort design;
4) allele and genotype distribution for both IL-8 -251 T>A and IL-18 -607 C>A polymorphisms provided to estimate the odds ratios (ORs) and 95% confidence intervals (CIs);
5) articles published in English, Chinese, Portuguese and Farsi (with an English abstract).

The studies were excluded if one of the following criteria was fulfilled:
1) studies not about IL-8 -251T>A and IL-18 -607C>A polymorphisms and breast cancer;
2) studies on other polymorphisms at IL-8 and IL-18 genes;
3) animal models, cell lines and *in vitro* studies;
4) no control population;
5) linkage and family-based studies;
6) data unavailable or insufficient for calculating allele and genotypes frequencies;
7) abstracts, posters, case reports, case series, editorials, letters, editorial articles, conference presentations, comments, reviews, meta-analyses;
8) overlapping data or duplicate of previous publication.

Data extraction

The necessary data were carefully extracted by two observers from eligible studies according to the mentioned criteria. Any disagreement between two authors was discussed with the third author until a consensus was achieved. If the data were not presented, the corresponding authors were contacted to request extra information. The following characteristics were collected from each study: last name of first author, year of publication, country of origin, ethnicity of study participants, source of controls (hospital based or population based), genotyping methods, genotypic/allelic distributions for both IL-8 -251T>A and IL-18 -607C>A polymorphisms in cases and controls, the number of cases and control genotypes, minor allele frequency (MAFs) and Hardy-Weinberg equilibrium (HWE) in controls.

Statistical Analysis

The strength of associations of IL-8 -251T>A and IL-18 -607C>A polymorphisms with susceptibility to breast cancer was estimated by ORs with 95%

Tab. 1. Main characteristics of studies included in this meta-analysis.

First author	Country (ethnicity)	Genotyping method	SOC	Case/control	Cases					Controls					MAFs	HWE
					Genotypes			Allele		Genotypes			Allele			
IL-8 -251 T>A					TT	TA	AA	T	A	TT	TA	AA	T	A		
Smith [23]	UK (Caucasian)	ARMS-PCR	PB	119/235	37	63	19	137	101	76	105	54	257	213	0.453	0.131
Snoussi [24]	Tunisia (African)	AS-PCR	PB	308/236	65	157	86	287	329	72	110	54	254	218	0.462	0.338
Vogel [25]	Denmark (Caucasian)	TaqMan	HB	361/361	88	160	113	336	386	78	167	116	323	399	0.553	0.220
Kamali-Sarvestani [26]	Iran (Asian)	ASO-PCR	HB	257/233	64	114	79	242	272	79	106	48	264	202	0.433	0.260
Snoussi [27]	Tunisia (African)	AS-PCR	PB	409/301	84	201	124	369	449	92	138	71	322	280	0.465	0.172
Wang [29]	China (Asian)	PCR-RFLP	HB	474/501	192	231	51	615	333	186	213	102	585	417	0.416	0.005
Zhang 2016 [38]	China (Asian)	PCR-RFLP	HB	442/447	190	174	78	554	330	213	191	43	617	277	0.310	0.984
IL-18 -607 C>A					CC	CA	AA	C	A	CC	CA	AA	C	A		
Khalili-Azad [30]	Iran (Asian)	AS-PCR	PB	200/206	64	103	33	231	169	76	97	33	249	163	0.396	0.825
Taheri 2012 [31]	Iran (Asian)	ARMS-PCR	HB	72/93	29	32	11	90	54	40	45	8	125	61	0.328	0.346
Back 2014 [32]	Brazil (Mixed)	PCR-RFLP	PB	154//118	39	66	49	144	164	43	56	19	142	94	0.398	0.914
Zhao 2017 [33]	China (Asian)	MALDI-TOF	HB	305/305	92	133	80	317	293	100	142	63	342	268	0.439	0.337
Qiao 2018 [34]	China (Asian)	DS	HB	169/160	50	80	39	187	169	41	80	39	162	158	0.494	0.998

ARMS – amplification refractory mutation system, AS-PCR – allele-specific polymerase chain reaction, ASO-PCR – allele-specific oligonucleotide polymerase chain reaction, RFLP – restriction fragment length polymorphism, DS – direct sequencing, SOC – source of controls, PB – population-based, HB – hospital-based, MAF – minor allele frequency, HWE – Hardy-Weinberg equilibrium

confidence intervals (95% CIs). The significance of the pooled effect size was examined by the Z-test. The associations were evaluated under all five genetic models, i.e. allele (B vs. A), homozygote (BB vs. AA), heterozygote (BA vs. AA), dominant (BB+BA vs. AA), and recessive (BB vs. BA+AA). To take into account the possibility of between-study heterogeneity, the Cochran's Q test was used, in which $P < 0.10$ indicated a significant heterogeneity. Moreover, I^2 statistic (range of 0–100%) was also employed to qualify the heterogeneity, where a lower value represents non-significant heterogeneity and a higher value represents a high degree of between study heterogeneity. A fixed-effect method (the Mantel-Haenszel method) was applied to calculate the pooled ORs and the corresponding 95% CIs for all genetic models which did not show significant heterogeneity; otherwise a random-effect method (the DerSimonian and Laird method) was adopted. Subgroup analyses were conducted by stratification of ethnicity to identifying potential source of heterogeneity. HWE was tested in control groups of each study by χ^2 test to assess the latent bias resulting from the deviation of the genotype distribution; $P > 0.05$ were considered to have reliable and representative controls. The sensitivity analysis was carried out by omitting one study at a time to determine the underlying effects of each single study on the pooled data. Furthermore, we conducted the sensitivity analyses again to delete those studies deviating from HWE and calculate the pooled ORs for the remainder of the studies. Publication bias was performed by the construction of Begg's funnel plot and Egger's regression analysis. All of the statistical calculations were performed using Comprehensive Meta-Analysis (CMA) software, version 2.0 (Biostat, USA). For all analyses, statistical significance was assumed at $P < 0.05$, unless otherwise stated.

Results

Selected studies characteristics

The selection process of eligible studies is presented in Scheme 1. Initially, 108 studies were obtained through publication search in electronic databases, and one study was identified from other sources. Irrelevant articles were excluded by evaluating the titles and abstracts. Therefore, 76 pub-

lications were deleted for obvious irrelevance. Finally, 12 case-control studies including seven studies [23–29] with 2,370 cases and 2,314 controls on IL-8 -251T>A polymorphism, and 5 studies [30–34] with 900 cases and 882 controls on IL-18 -607C>A polymorphisms were selected to the meta-analysis. Tab. 1 describes principal characteristics of selected studies. All the studies were published between December 2004 and March 2018. The studies have been carried out in UK, Tunisia, Iran, China, and Brazil. Among these studies, eight studies were conducted among Asians, two studies among Caucasians and two studies among Africans. Seven different genotyping methods were used: ARMS-PCR, AS-PCR, TaqMan, ASO-PCR, PCR-RFLP, MALDI-TOF and direct sequencing. The genotype, allele and MAF in each study for both IL-8 -251T>A and IL-18 -607C>A polymorphisms are shown in Tab. 1. Moreover, the distribution of genotypes in the controls was in agreement with HWE for all selected studies, except for one study on IL-8 -251T>A polymorphism (Tab. 1).

Quantitative synthesis

IL-8 -251T>A polymorphism

The association between IL-8 -251T>A polymorphism and breast cancer risk is shown in Tab. 2. Pooled data showed that there was a significant association between IL-8 -251T>A polymorphism and an increased risk of breast cancer under heterozygote model (AT vs. TT: OR = 1.187; 95% CI 1.038–1.356, P = 0.012, Fig. 2A). When stratified analysis by ethnicity, a significant association was found between IL-8 -251T>A polymorphism and breast cancer risk in Africans under all five genetic models, i.e. allele (A vs. T: OR = 1.398; 95% CI 1.174–1.663; P ≤ 0.001), homozygote (AA vs. TT: OR = 2.083; 95% CI 1.529–2.839; P ≤ 0.001), heterozygote (AT vs. TT: OR = 1.411; 95% CI 1.066–1.867; P = 0.016), dominant (AA+AT vs. TT: OR = 1.676, 95% CI 1.295–2.168; P ≤ 0.001), and recessive (AA vs. AT+TT: OR = 1.364; 95% CI 1.055–1.764; P = 0.018), but not in Asians and Caucasians (Tab. 2).

IL-18 -607C>A polymorphism

Results of pooled analysis for IL-18 -607C>A polymorphism and breast cancer risk are summarized in detail in Tab. 2. Pooled data showed that the IL-18 -607C>A polymorphism was significantly associated with an increased risk of breast cancer under three genetic models, i.e. allele (A vs. T: OR = 1.205; 95% CI 1.055–1.377; P = 0.006, Fig. 2B), homozygote (AA vs. TT: OR = 1.379; 95% CI 1.056–1.802, P = 018), and recessive (AA vs. AT+TT: OR = 1.329; 95% CI 1.053–1.678; P = 0.017). However, stratified analysis by ethnicity failed to show a significant association between the IL-18 -607C>A polymorphism and breast cancer in Asians (Tab. 2).

Heterogeneity test

In this meta-analysis there was statistical significance between-study heterogeneity for IL-8 -251T>A polymorphism under four genetic models, i.e. allele (A vs. T: I^2 = 83.32; PH ≤ 0.001), homozygote (AA vs. TT: I^2 = 87.78; P_H ≤ 0.001), dominant (AA+AT vs. TT: I^2 = 66.65; P_H = ?) and recessive (AA vs. AT+TT: I^2 = 85.38; P_H ≤ 0.001), models and IL-18 -607 C>A polymorphism under dominant model (AA+AC vs. CC: I^2 = 68.65; P_H = 0.013). Therefore, we conducted subgroup analyses by ethnicity to explain the potential source of heterogeneity. Results showed that the heterogeneity disappeared in the subgroup analysis among Asians, Caucasians and Africans, indicating that ethnicity might be the major source of heterogeneity for IL-8 -251T>A polymorphism (Tab. 2).

Sensitivity analysis

While omitting each individual study any time, sensitivity analysis was applied to detect the influence of each study on the pooled OR by repeating the meta-analysis. Sensitivity analyses results showed that the significance of the pooled data for both for IL-8 -251 T>A and IL-18 -607 C>A polymorphisms was not affected by any single study in the overall population. In addition, when we excluded the studies out of HWE, the statistical significance of the results did not change.

Publication bias

Begg's funnel plot and Egger's test were used to evaluate the publication bias of the literature for IL-8 -251T>A and IL-18 -607C>A polymorphisms. No publication bias was detected with either the Begg's funnel plot or the Egger's tests under all five genetic models in overall and subgroup analysis by ethnicity (Tab. 2). Funnel plots for IL-8 -251T>A polymorphism in allele model and IL-18 -607C>A polymorphism in recessive model were showed in Graphs 3A, B.

Discussion

Human IL-8, also known as neutrophil chemotactic factor, has significant potential as a prognostic and predictive biomarker in various inflammatory conditions and malignancies [35]. It plays a key role in the recruitment of neutrophils and other immune cells to the site of infection [36]. IL-8 is mapped on chromosome 4q13-q21, contains four exons, a proximal promoter region and has a length of 5191 bp [37,38]. Moreover, human IL-18, a member of the IL-1 family, was initially identified as a protein that induces interferon γ (IFNγ) production [39,40]. It is a pro-inflammatory chemokine, plays a key role in the initiation, modulation, and maintenance of the gastrointestinal inflammatory response. Human IL-18 gene is mapped on 11q22.2–22.3, contains six exons and several genetic polymorphisms, especially in the promoter region [41]. A functional polymorphism at position -251 of the IL-8 promoter region has been identified in 2000, which has effect on IL-8 gene expression or secretion [42].

In this study, we evaluated the association of IL-8 -251T>A and IL-18 -607C>A polymorphisms with breast cancer risk based on all available studies. By pooling all eligible studies, we found the IL-8 -251T>A and IL-18 -607C>A polymorphisms are significantly associated with an increased risk of breast cancer in the global population. Previous epidemiological studies have reported that these polymorphisms were associated with an increased risk of breast cancer in different populations such as Chinese, Iranian and Danish. However, subgroup analyses by ethnicity showed lack of association between IL-8 -251T>A and IL-18 -607C>A polymorphisms and a risk of breast cancer in Asians and Cauca-

Tab. 2. Summary of meta-analysis for the association of IL-8 -251T>A and IL-18 -607C>A polymorphisms with breast cancer risk.

Subgroup	Genetic model	Type of model	Heterogeneity		Odds ratio				Publication bias	
			I^2 (%)	P_H	OR	95% CI	Z_{test}	P_{OR}	PB_{eggs}	P_{Eggers}
IL-8 -251 T>A										
Overall	A vs. T	random	83.32	≤ 0.001	1.126	0.916–1.384	1.123	0.262	0.548	0.598
	AA vs. TT	random	87.78	≤ 0.001	1.257	0.784–2.074	0.979	0.327	0.763	0.899
	AT vs. TT	fixed	0.00	0.577	1.187	1.038–1.356	2.511	0.012	0.548	0.166
	AA+AT vs. TT	random	66.65	0.006	1.210	0.968–1.513	1.677	0.093	0.763	0.358
	AA vs. AT+TT	random	85.38	≤ 0.001	1.099	0.749–1.611	0.483	0.629	0.763	0.953
Ethnicity										
Asians	A vs. T	random	91.70	≤ 0.001	1.134	0.746–1.722	0.589	0.556	0.296	0.479
	AA vs. TT	random	93.65	≤ 0.001	1.262	0.469–3.393	0.461	0.645	1.000	0.475
	AT vs. TT	fixed	0.00	0.576	1.083	0.906–1.295	0.877	0.380	1.000	0.133
	AA+AT vs. TT	random	69.93	0.036	1.146	0.837–1.570	0.849	0.396	0.296	0.439
	AA vs. AT+TT	random	94.14	≤ 0.001	1.171	0.461–2.977	0.322	0.740	1.000	0.238
Caucasians	A vs. T	fixed	0.00	0.817	0.918	0.772–1.091	–0.975	0.330	NA	NA
	AA vs. TT	fixed	0.00	0.649	0.823	0.585–1.157	–1.122	0.262	NA	NA
	AT vs. TT	fixed	0.00	0.938	1.253	0.939–1.671	1.533	0.125	NA	NA
	AA+AT vs. TT	fixed	0.00	0.475	0.921	0.696–1.219	–0.573	0.567	NA	NA
	AA vs. AT+TT	fixed	34.13	0.218	0.876	0.665–1.154	–0.942	0.346	NA	NA
Africans	A vs. T	fixed	0.00	0.593	1.398	1.174–1.663	3.770	≤ 0.001	NA	NA
	AA vs. TT	fixed	0.00	0.370	2.083	1.529–2.839	4.650	≤ 0.001	NA	NA
	AT vs. TT	fixed	4.14	0.307	1.411	1.066–1.867	2.404	0.016	NA	NA
	AA+AT vs. TT	fixed	0.00	0.889	1.676	1.295–2.168	3.931	≤ 0.001	NA	NA
	AA vs. AT+TT	fixed	0.00	0.773	1.364	1.055–1.764	2.369	0.018	NA	NA
IL-18 -607 C>A										
Overall	A vs. C	fixed	27.52	0.238	1.205	1.055-1.377	2.747	0.006	0.806	0.602
	AA vs. CC	fixed	48.30	0.102	1.379	1.056-1.802	2.357	0.018	0.806	0.604
	AT vs. CC	fixed	0.00	0.705	1.067	0.861-1.321	0.591	0.554	1.000	0.910
	AA+AC vs. CC	random	68.65	0.013	1.009	0.693-1.469	0.046	0.963	0.462	0.324
	AA vs. AC+CC	fixed	44.83	0.123	1.329	1.053-1.678	2.393	0.017	0.462	0.571
Ethnicity										
Asians	A vs. C	fixed	0.00	0.881	1.132	0.980–1.307	1.679	0.093	0.734	0.991
	AA vs. CC	fixed	0.00	0.445	1.211	0.906–1.619	1.291	0.197	1.000	0.864
	AT vs. CC	fixed	0.00	0.656	1.031	0.819–1.299	0.262	0.793	0.734	0.653
	AA+AC vs. CC	fixed	59.22	0.061	0.862	0.690–1.078	–1.300	0.193	0.734	0.544
	AA vs. AC+CC	fixed	0.00	0.456	1.192	0.925–1.536	1.360	0.174	0.734	0.797

NA – not applicable

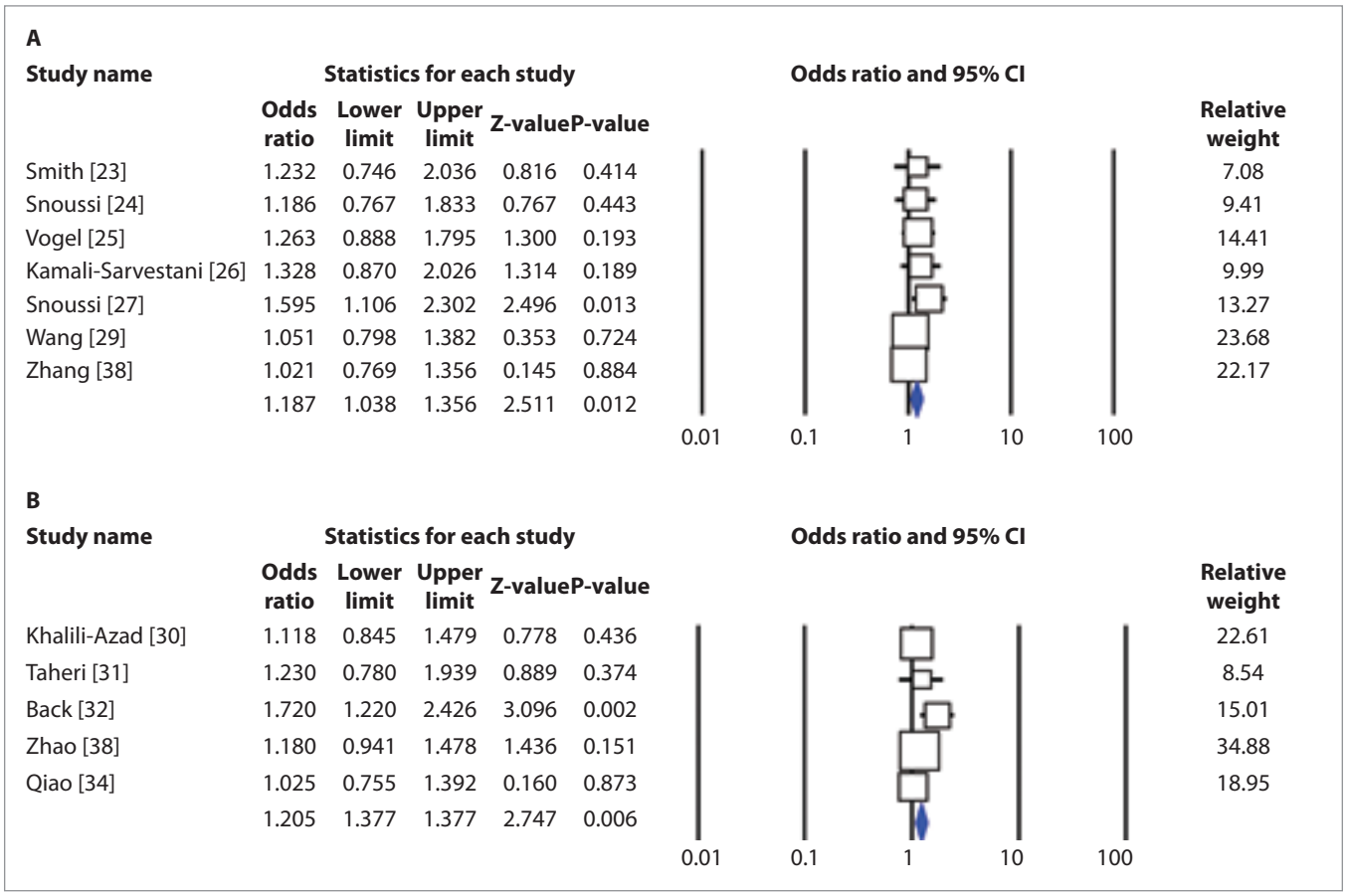
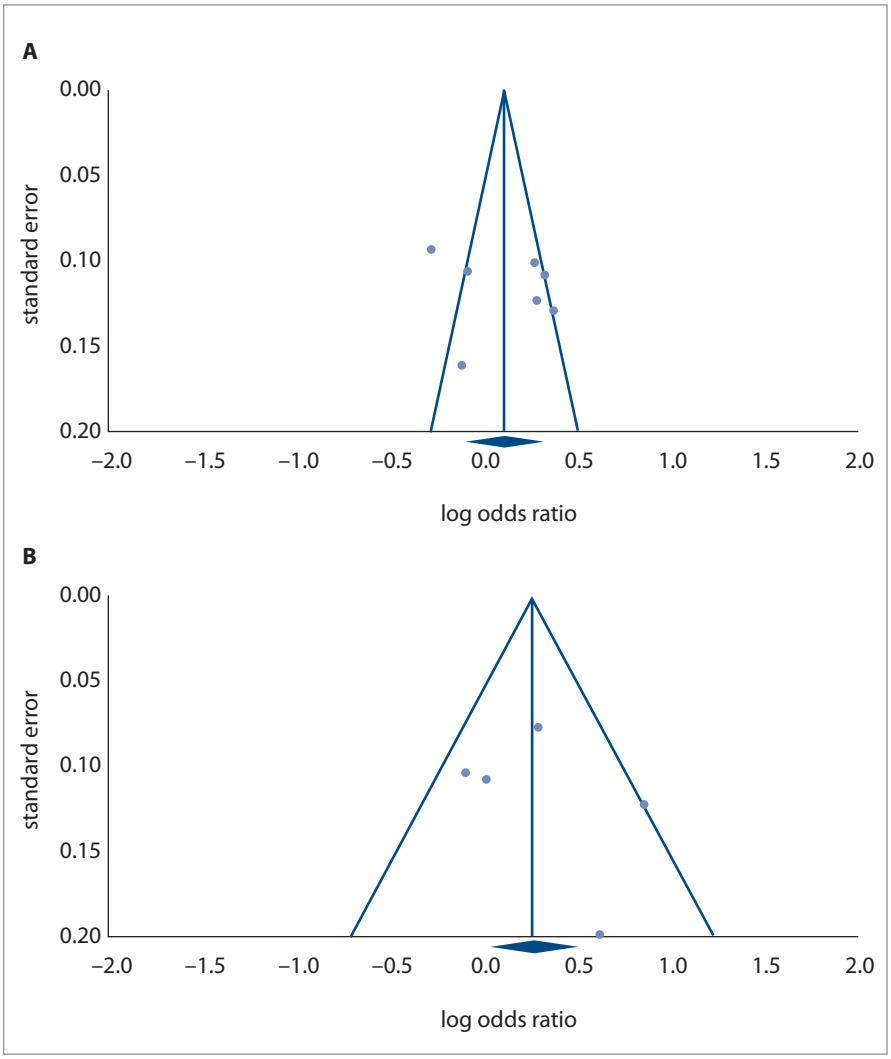


Fig. 1. Forest plot of IL-8 -251T>A and IL-18 -607C>A polymorphisms and risk of breast cancer. A) IL-8 -251T>A (heterozygote model: AT vs. TT); B) IL-18 -607C>A (allele model: A vs. C).

sians. This difference is a common finding in a meta-analysis and could be explained by two reasons. First, because of the complex nature of breast cancer, it is unlikely that a single nucleotide polymorphism in IL-8 and IL-18 genes would be associated with an increased risk of breast cancer, without an interaction from other polymorphic susceptibility genes. Second, other factors, such as age, hormone therapy, family history, life style and different environmental exposure can also influence the development of breast cancer. In 2014, Wang et al evaluated the association between IL-8 -251T>A polymorphism and breast cancer risk in a meta-analysis of five case-control studies [15]. Their results showed that IL-8 -251T>A polymorphism was significantly associated with an increased risk of breast cancer under four genetic models, i.e. allele (A vs. T, OR = 1.21; 95% CI 1.01–1.45), heterozygote (AT vs. TT, OR = 1.28; 95% CI 1.07–1.53), dominant (AA+TT vs. TT: OR = 1.34, 95% CI 1.03–1.74) and recessive (AA vs. AT+TT: OR = 1.25; 95% CI 1.05–1.49). In 2015, Li et al have examined the association of IL-18 -607C>A polymorphism with risk of breast cancer in a meta-analysis of three case-control studies [43]. They have found that IL-18 -607C>A polymorphism was significantly associated with an increased risk of breast cancer under three genetic models, i.e. allele (A vs. C: OR =1.33; 95% CI 1.00–1.75; P_H = 0.155), homozygote (AA vs. CC: OR = 1.80; 95% CI 1.02–3.21, P_H = 0.162) and dominant (AA+CA vs. CC: OR = 1.33; 95% CI 1.00–1.78; P_H = 0.546). Considering that the samples of breast cancer cases and controls in the previous meta-analyses were quite small, their results might not have enough statistical power. Moreover, their estimates were not adjusted OR values such as ethnicity, which might be caused to inaccurate results. Therefore, our meta-analysis gave strong evidence of an association of IL-8 -251T>A and IL-18 -607C>A polymorphisms with a risk of breast cancer in global population and by ethnicity.

Between-study heterogeneity significantly affects a meta-analysis result. Several factors such as diversity in study populations, study design, sample size, source of controls, genotyping method, and WHE might contribute to potential sources of heterogeneity [44–46]. There was a significant heterogeneity in this meta-analysis mostly for IL-8 -251T>A polymorphism. Thus, due to the significant heterogeneity, we applied the random-effects model to calculate the pooled ORs, which could provide stable results. Subgroup analyses by ethnicity showed that the heterogeneity significantly decreased in Asians, Caucasians and Africans, indicating that ethnicity might be the major source of heterogeneity for IL-8 -251T>A polymorphism.



Graph 1. Begg's funnel plot of the Egger test for publication bias of the IL-8 -251T>A and IL-18 -607C>A polymorphisms and risk of breast cancer. A) IL-8 -251T>A (allele model: A vs. T); B) IL-18 -607C>A (recessive model: AA vs. AC+CC).

We did not observe any publication bias in both IL-8 -251T>A and IL-18 -607C>A polymorphisms, demonstrating that the results of this meta-analysis are stable. However, it is important to note the limitations of our meta-analysis. First, although an increased risk of breast cancer was observed to be associated with IL-8 -251T>A and IL-18 -607C>A polymorphisms; the sample size for both polymorphisms was not large enough to provide enough statistical power. Second, in the current meta-analysis studies from Caucasians, Asians, Africans and mixed populations were involved, although the number of studies was relatively small and results might not have enough statistical power to obtain the association of IL-8 -251T>A and IL-18 -607C>A polymorphisms with breast cancer. Third, only published studies in English were included; it is possible that some relevant published or unpublished studies with null results were missed, which might have biased the results and causing a language bias. Fourth, several important confounding factors, such as age, smoking, drinking, family history of breast cancer, environmental exposures and lifestyle, were not considered for stratification analysis because relevant data was insufficient in the primary reports. Finally, the lack of original data in the eligible studies limited the evaluation of the effects of gene-gene and gene-environment interactions on IL-8 -251T>A and IL-18 -607C>A polymorphisms and breast cancer risk.

Conclusion

Our results showed that IL-8 -251T>A and IL-18 -607C>A polymorphisms are significantly associated with increased susceptibility to breast cancer. Our findings also indicate that the IL-8 -251T>A polymorphism also plays an important role in the development of breast cancer in Africans. Future studies with large sample sizes and more ethnic groups are needed to confirm our findings. Moreover, IL-8 -251T>A, IL-18 -607C>A polymorphisms, other interleukin polymorphisms and gene-gene interactions should also be considered in future studies.

Ethical approval and consent to participate

The ethical approval was not required for this study, as it is a systematic review and meta-analysis.

Availability of data and material

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Authors Contribution

Conceived and designed the study and experiments: MF, FA and SAD
Performed the experiments: HN and MKZ
Analyzed the data: SHS, SK and HN
Contributed reagents/materials/analysis tools: MZS, SAD and FA
Wrote the paper: MF, SAD and HN
All authors have read and approved the manuscript.

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