REVIEW

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Association of *IL-10 rs1800871* and *rs1800872* Polymorphisms with Breast Cancer Risk: A Systematic Review and Meta-Analysis

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Abstract

Background: The rs1800871 and rs1800872 polymorphisms of interleukin 10 (IL-10) gene has been indicated to be associated with breast cancer (BC) risk, but study results are still debatable. To derive a more precise evaluation, we performed a comprehensive meta-analysis. **Methods:** Multiple electronic databases were searched to identify studies assessing the IL-10 rs1800871 and rs1800872 polymorphisms with BC risk. **Results:** A total of 21 case-control studies with 6054 cases and 6355 controls were included in this met-analysis. There was a significant association between the rs1800871 polymorphism and BC risk (CT vs. TT: OR= 1.17, 95% CI 1.01-1.35, p=0.02; and CC+CT vs. TT: OR= 1.29, 95% CI 1.00-1.66, p=0.04). Moreover, increased BC risks were also associated with the rs1800872 polymorphism (C vs. A: OR= 1.29, 95% CI 1.04-1.60, p=0.01; CC vs. AA: OR= 1.54, 95% CI 1.03-2.30, p=0.03; CC+CA vs. AA: OR= 1.43, 95% CI 1.01-2.01, p=0.03; and CC vs. CA+AA: OR= 1.23, 95% CI 1.01-1.51, p=0.04). A pooling of the studies was also conducted by ethnicity, but failed to show an association of IL-10 rs1800871 and rs1800872 polymorphism with BC risk in Asians and Caucasians. **Conclusions:** Our results are inconsistent with previous meta-analysis suggests that IL-10 rs1800871 and rs1800872 polymorphisms might contribute to BC susceptibility in overall population, but not by ethnicity.

Keywords: Breast cancer- interleukin-10- polymorphism- meta-analysis

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Introduction

Breast cancer (BC) is one of the most common forms of cancer and leading cause of female cancer-related death worldwide (Jafari-Nedooshan et al., 2017; Kamali et al., 2017; Karimi Zarchi et al., 2009). It is estimated that BC contributed to 25 % of all cancer cases in women worldwide (Shiryazdi et al., 2015a; Shiryazdi et al., 2015b; Zhang et al., 2016). The incidence rate of BC has also been increasing rapidly in Asian countries (Han et al., 2017). The etiology of BC is poorly understood (Mahdieh Kamali et al., 2017); although genetic, environmental and lifestyle risk factors have been associated to the incidence of BC. Certain risk factors of BC such as age and lifestyle can change over time. For example, the incidence of BC is estimated to increase with age (Doosti et al., 2016; Forat-Yazdi et al., 2015; Kamali et al., 2017).

Several previous studies have reported that genetic polymorphisms close to or within the Interleukin-10 (IL-10) gene play an important role in the development of cancer such as BCs, gastric cancer, colorectal cancer, lung cancer, cervical cancer, and digestive cancer (Niu et al., 2015). IL-10 has pleiotropic effects in immunoregulation and inflammation, which is produced by Th2 cells, regulatory T cells, and monocytes/ macrophages. IL-10 down-regulates the expression of Th1 cytokines, MHC class II Ags, and co-stimulatory molecules on macrophages. Human IL-10 gene is located on chromosome 1q31-1q32, composed of five exons and spans about 4.7 kb (Namazi et al., 2018; Sheikhpour et al., 2017). The IL-10 promoter is highly polymorphic; however, only promoter region polymorphisms including rs1800871 (-819) and rs1800872 (-592) were extensively investigated as they might alter the activity of IL-10 gene, with associated with MsII and RsaI restriction enzyme (RE) sites, respectively. It has been reported that IL-10 promoter region polymorphisms affect IL-10 gene transcription and translation, resulting in abnormal cell proliferation and cancer development (Niu et al., 2015).

In 2003, Giordani et al., (2003) published the first study describing a significant association between -1082 G>A polymorphism in the IL-10 promoter region and increased risk of BC in Italian populations. Since, several numbers of epidemiological studies have evaluated the association of IL-10 polymorphisms and susceptibility to BC. However, these studies results are inconclusive and inconsistent.

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Possible reasons for this inconsistency might be that single studies did not provide sufficient power and adjustments varied among the included studies by ethnicity, age, lifestyle, and other covariates. Given the important role of IL-10 in the development of BC, we performed this systematic review to evaluate the association of IL-10 rs1800871 and rs1800872 polymorphisms with BC risk from case-control by summarizing it quantitatively with a meta-analytic approach.

Materials and Methods

Publication search and selection criteria

The electronic databases PubMed, EMBASE, Web of Science, China Biological Medicine Database, and China National Knowledge Infrastructure were searched to identifying studies on IL-10 rs1800871 and rs1800872 polymorphisms with BC risk up to September 15, 2018. The following keywords and terms were used: (''breast cancer'' or "breast tumor" or "breast neoplasm" or "breast malignant tumor" or "breast carcinoma'') and (''Interleukin-10'' or ''IL-10'') and (''polymorphism'' or ''SNP'' or ''single nucleotide polymorphism'' or ''variation'' or ''mutation''). In addition, we performed manual reviewing of the reference lists of eligible studies and also previous meta-analyses to find additional studies. The search was limited to human studies and we did not define any minimum number of cases and controls for inclusion, and by the publication year or language.

Inclusion and exclusion Criteria

The following inclusion criteria were used to select literature for the meta-analysis: (1) studies with case-control or cohort design; (2) evaluated the association of the rs1800871 and rs1800872 polymorphisms in the promoter region of IL-10 gene with BC risk; (3) genotypes distributions in the cases and controls were provided, or information that could help calculating an OR with 95% CI. Accordingly, the following were exclusion criteria: (1) studies based on sibling pairs and linkage studies; (2) studies on other polymorphism of IL-10 gene; (3) studies did not report genotype frequencies; (4) not BC research, reviews, abstracts, case reports, commentaries, editorials, proceedings, and animal studies; (5) duplicates or overlapping data.

Data Extraction

Two observers independently extracted data from all eligible studies onto paper data collection forms according to a standard protocol. The collected data from each study comprised the following data: name of the first author, publication year, racial descent (categorized as Asian, Caucasian, or mixed descent), genotyping methods, source of controls, total number of cases and controls as well as numbers of cases and controls for rs1800871 and rs1800872 polymorphisms, minor allele frequency (MAF) in healthy subjects, and evidence of Hardy-Weinberg equilibrium (HWE). If the same data appeared in different studies the results of most recently or large sample size were used. Accordingly, we excluded the studies that were repeated or provided little data from small sample size.

Statistical Analysis

The association between rs1800871 and rs1800872 polymorphisms of IL-10 gene and BC was estimated using the odds ratio (OR) corresponding to a 95% confidence interval (CI). The Z-test was employed to determine the significance of the pooled ORs, and a P-value less than 0.05 was considered statistically significant. The OR and its 95% CI in each comparison were assessed under five genetic models, i.e., allele model (B vs. A), homozygote (BB vs. AA), heterozygote (BA vs. AA), dominant (BB+BA vs. AA), and recessive (BB vs. BA+AA), which a ''A'' denotes a major allele; ''B'' denotes a minor allele. The existence of heterogeneity between studies was ascertained with the chi-square-based Q-test, in which P-value less than 0.05 was considered statistically significant. Moreover, the I2 value was used to quantify the degree of heterogeneity; in which I2<25%, 25–75% and >75% represented low (no heterogeneity), moderate and large or extreme heterogeneity, respectively. Fisher's exact test was used to assess the Hardy–Weinberg equilibrium (HWE) with the significance set at P<0.05. Visual inspection of the asymmetry of funnel plots was carried out to assess potential publication bias. Begg's funnel plots and test were used to statistically estimate publication bias (P<0.05 was taken to indicate significant publication bias). Publication bias was evaluated by Begg's rank correlation test and Egger's linear regression test. If the publication bias tests indicated bias existed, the Duval and Tweedie ''trim and fill'' method was used to adjust the bias. All of the calculations were performed using Comprehensive Meta-Analysis (CMA) version 2.0 (Biostat, USA). Two-sided P-values<0.05 were considered statistically significant.

Results

Literature search and study characteristics

A total of 103 articles were identified through the initial search in the different database. Based on the selected criteria, we screened the titles and abstracts of the initial publications and obtained 12 potential articles. After scanning the full texts, three articles were excluded. Finally, a total of 21 case-control studies including ten studies on rs1800871 (with 1,928 cases and 2,069 controls) and eleven studies on rs1800872 polymorphism (with 4126 cases and 4286 controls) were included (Abdolrahim-Zadeh et al., n.d.; Atoum, 2016; Gonullu et al., 2007; Guzowski et al., 2005; He et al., 2012; Kong et al., 2010; Langsenlehner et al., 2005; Pooja et al., 2012; Sabet et al., 2017; Scola et al., 2006; Tianet al., 2017). The characteristics of each study are summarized in Table 1. These included studies were published between 2005 and 2017. The sample size in cases ranged from 38 to 2,045. Of the studies included, eleven case-control studies were on Asians, eight case-control studies on Caucasians, and two case-control studies on Africans (Table 1). The included studies were conducted in Iran, USA, Italy, Turkey, China, India, Jordan, Egypt, Australia and European. Genotyping methods used included PCR-RFLP, DHPLC, Mass Array, MALDI-TOF MS, and TaqMan. Of these, 15 studies were hospital-based (HB) and six on population based

Table 1. Characteristics of the Studies Included in the Meta-Analysis

First Author	Country (Ethnicity)	SOC	Genotyping Method	Case/Control	Cases					Control					MAF	HWE
					Genotypes			Alleles		Genotypes			Alleles			
-819T>C (rs1800871)				1928/2069	TT	TC	CC	T	C	AA	AC	CC	T	C		
Abdolrahim-Zadeh 2005	Iran(Asian)	HB	PCR-RFLP	275/320	129	120	26	375	172	166	122	32	454	186	0.29	0.177
Guzowski 2005	USA(Caucasian)	HB	DHPLC	50/25	3	19	28	25	75	1	10	14	12	38	0.76	0.629
Scola 2006	Italy(Caucasian)	HB	PCR-RFLP	84/106	5	30	49	40	128	12	35	59	59	177	0.721	0.066
Gonullu 2007	Turkey(Caucasian)	HB	Mass ARRAY	38/24	5	17	16	27	49	4	10	10	18	30	0.625	0.586
Kong 2010	China(Asian)	HB	PCR-RFLP	315/322	119	135	61	373	257	134	131	57	399	245	0.38	0.013
He 2012	China(Asian)	HB	MALDI-TOF MS	347/500	177	141	29	495	199	229	223	44	681	311	0.313	0.321
Pooja 2012	India(Asian)	PB	PCR-RFLP	200/200	54	92	54	200	200	65	78	57	208	192	0.48	0.001
Atoum 2016	Jordan(Asian)	HB	PCR-RFLP	202/210	88	47	67	223	181	93	41	76	227	193	0.459	≤0.001
Tian 2017	China(Asian)	PB	Mass ARRAY	312/312	124	141	47	389	235	144	128	40	416	208	0.459	0.174
Sabet 2017	Egypt(African)	HB	PCR-RFLP	105/50	16	47	42	79	131	26	22	2	74	26	0.26	0.31
-592C>A (rs1800872)				4126/4286	AA	AC	CC	A	C	AA	AC	CC	A	C		
Abdolrahim-Zadeh 2005	Iran(Asian)	HB	PCR-RFLP	275/320	27	100	148	154	396	29	132	159	190	450	0.703	0.374
Guzowski 2005	USA(Caucasian)	HB	DHPLC	50/25	3	17	30	23	77	3	10	12	16	34	0.68	0.685
Langsenlehner 2005	Australia(Caucasian)	PB	TaqMan	500/496	21	210	269	252	748	36	199	261	271	721	0.726	0.818
Scola 2006	Italy(Caucasian)	HB	PCR-RFLP	84/106	5	30	49	40	128	12	35	59	59	153	0.721	0.066
Gonullu 2007	Turkey(Caucasian)	HB	Mass ARRAY	38/24	5	17	16	27	49	4	10	10	18	30	0.625	0.586
Pharoah 2007	European(Caucasian)	PB	TaqMan	2045/2218	116	679	1,251	367	3,181	116	764	1,338	9,96	3,440	0.775	0.609
Kong 2010	China(Asian)	HB	PCR-RFLP	315/322	119	135	61	373	257	134	131	57	399	245	0.38	0.013
Pooja 2012	China(Asian)	PB	PCR-RFLP	200/200	45	67	88	157	243	38	84	78	160	240	0.6	0.077
Atoum 2016	Jordan(Asian)	HB	PCR-RFLP	202/210	76	84	42	236	168	79	91	40	249	171	0.407	0.137
Tian 2017	China(Asian)	PB	Mass ARRAY	312/312	131	130	51	392	232	141	127	44	409	215	0.344	0.08
Sabet 2017	Egypt(African)	HB	PCR-RFLP	105/53	4	36	65	42	166	31	16	6	78	28	0.264	0.103

SOC, source of controls; HB: hospital-based; PB, population-based; RFLP, restriction fragment length polymorphism; DHPLC, denaturing high performance liquid chromatography; MALDI-TOF MS, matrix assisted laser desorption/ionization; MAF, minor allele frequency; HWE, Hardy Weinberg Equilibrium.

(PB). The distributions of genotypes in the controls of the studies were in Hardy-Weinberg equilibrium except for three case-control studies on rs1800871 and one study on rs1800872 (Table 1).

Quantitative Synthesis

rs1800871

A total of 1,928 cases and 2,069 controls were used to evaluate the strength of association between rs1800871 polymorphism and BC. The summaries of meta-analysis results for rs1800871 polymorphism with BC risk are shown in Table 2. There was a significant association between the rs1800871 polymorphism and BC risk under two genetic models, i.e., heterozygote (CT vs. TT: OR= 1.17, 95% CI 1.01-1.35, p=0.02, Figure 1A) and dominant (CC+CT vs. TT: OR= 1.29, 95% CI 1.00-1.66, p=0.04). When further analyzed by ethnicity, there was no significant association of rs1800871 polymorphism with BC in Asians and Caucasians (Table 2).

rs1800872

A total of 4126 cases and 4286 controls were used to evaluate the significant of association between rs1800871 polymorphism and BC. There was a significant association between rs1800872 polymorphism and risk of BC under four genetic models, i.e., allele (C vs. A: OR= 1.29, 95% CI 1.04-1.60, p=0.01), homozygote (CC vs. AA: OR= 1.54, 95% CI 1.03-2.30, p=0.03), dominant (CC+CA vs. AA: OR= 1.43, 95% CI 1.01-2.01, p=0.03, Figure 1B) and recessive (CC vs. CA+AA: OR= 1.23, 95% CI 1.01-1.51,

Table 2. Results of the Association of IL-10 Polymorphisms with BC Risk

Subgroup	Genetic Model	Type of Model	Heterogeneity		Odds Ratio				Publication Bias	
			I^2 (%)	PH	OR	95% CI	Ztest	POR	PBeggs	PEggers
rs1800871										
Overall	C vs. T	Random	77.57	≤0.001	1.12	0.90-1.40	1.09	0.27	0.72	0.52
	CC vs. TT	Random	57.62	0.01	1.32	0.94-1.84	1.64	0.09	0.59	0.17
	CT vs. TT	Fixed	41.35	0.08	1.17	1.01-1.35	2.19	0.02	0.72	0.19
	CC+CT vs. TT	Random	64.73	0.02	1.29	1.00-1.66	1.98	0.04	0.59	0.2
	CC vs. CT+TT	Fixed	41.09	0.08	1.08	0.92-1.26	0.97	0.33	0.72	0.12
Ethnicity										
Asian	C vs. T	Fixed	5.44	0.38	1.04	0.94-1.15	0.91	0.35	1	0.9
	CC vs. TT	Fixed	0	0.85	1.13	0.93-1.38	1.25	0.2	0.25	0.35
	CT vs. TT	Fixed	26.06	0.23	1.12	0.96-1.30	1.53	0.12	0.7	0.17
	CC+CT vs. TT	Fixed	17.88	0.29	1.1	0.96-1.26	1.42	0.15	0.7	0.28
	CC vs. CT+TT	Fixed	0	0.9	0.99	0.83-1.19	-0.01	0.98	0.7	0.81
Caucasian	C vs. T	Fixed	0	0.44	0.79	0.54-1.14	-1.24	0.21	1	0.19
	CC vs. TT	Fixed	0	0.68	1.15	0.65-3.51	0.97	0.33	0.29	0.05
	CT vs. TT	Fixed	0	0.67	1.55	0.65-3.65	1	0.31	0.29	0.04
	CC+CT vs. TT	Fixed	0	0.66	1.53	0.68-3.44	1.03	0.3	0.29	0.08
	CC vs. CT+TT	Fixed	0	0.97	1.07	0.68-1.67	0.3	0.76	1	0.14
rs1800872										
Overall	C vs. A	Random	85.7	≤0.001	1.29	1.04-1.60	2.36	0.01	0.16	0.1
	CC vs. AA	Random	78.59	≤0.001	1.54	1.03-2.30	2.14	0.03	0.11	0.04
	CA vs. AA	Random	64.94	0.001	1.15	0.87-1.53	1	0.31	0.35	0.1
	CC+CA vs. AA	Random	78.67	≤0.001	1.43	1.01-2.01	2.06	0.03	0.27	0.11
	CC vs. CA+AA	Random	64.98	0.001	1.23	1.01-1.51	2.05	0.04	0.43	0.07
Ethnicity										
Asian	C vs. A	Fixed	0	0.98	1.08	0.97-1.21	1.45	0.45	0.08	0.001
	CC vs. AA	Fixed	0	0.93	1.11	0.88-1.39	0.92	0.35	0.46	0.08
	CA vs. AA	Fixed	0	0.46	0.99	0.82-1.20	-0.03	0.97	0.22	0.02
	CC+CA vs. AA	Fixed	28.09	0.23	1.11	0.95-1.35	1.48	0.13	0.08	0.06
	CC vs. CA+AA	Fixed	0	0.99	1.16	0.97-1.39	1.72	0.08	0.8	0.58
Caucasian	C vs. A	Fixed	0	0.66	1.04	0.95-1.14	1.02	0.3	0.22	0.07
	CC vs. AA	Fixed	34.56	0.19	1.1	0.87-1.39	0.83	0.4	1	0.13
	CA vs. AA	Fixed	0	0.51	1	0.79-1.26	0.03	0.97	0.8	0.06
	CC+CA vs. AA	Fixed	37.7	0.17	1.09	0.87-1.38	0.8	0.41	1	0.14
	CC vs. CA+AA	Fixed	0	0.92	1.04	0.94-1.16	0.83	0.4	0.46	0.21

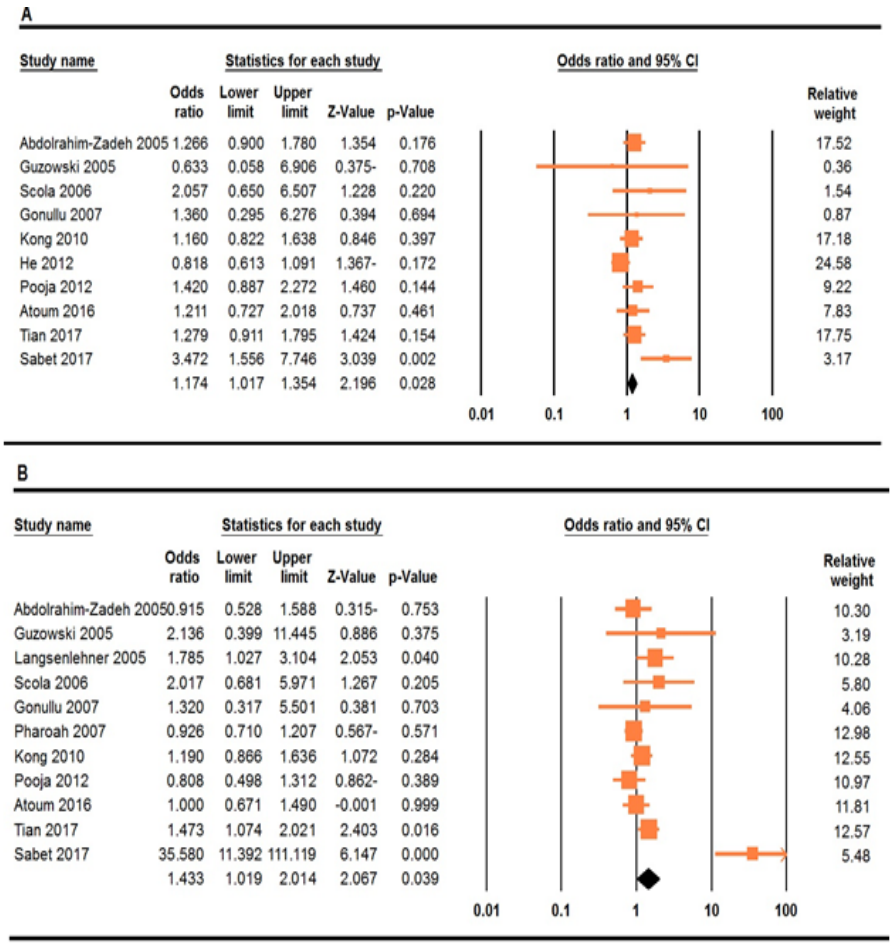

Figure 1. Forest Plots Showed Significant Association of IL-10 rs1800871 and rs1800872 Polymorphisms with BC. A, rs1800871 (heterozygote model: CT vs. TT); B, rs1800872 (dominant model: CC+CA vs. AA).

p=0.04). However, subgroup analyses by ethnicity failed to show an association of IL-10 rs1800872 polymorphism with BC risk in Asians and Caucasians (Table 2).

Heterogeneity test and sensitivity analysis

Between studies heterogeneity was identified in overall estimations under three genetic models for rs1800871 and all five genetics models for rs1800872. Thus, we have performed subgroup analysis by ethnicity, source of control, and genotyping method. The results revealed that ethnicity contributed to the potential source of heterogeneity in the meta-analysis. Moreover, we conducted sensitivity analysis to identify the individual studies influence on the pooled data. However, the results revealed that no individual study affected the pooled OR significantly since no substantial change was found (data not shown).

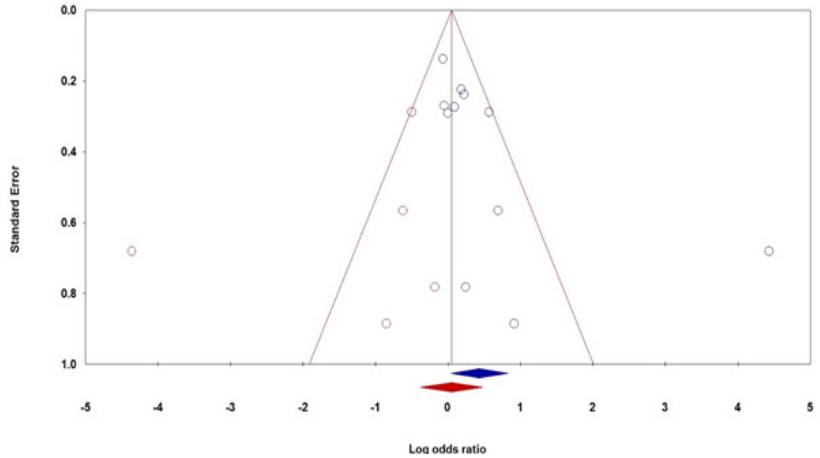

Figure 2. Begg's Funnel Plots of IL-10 rs1800872 Polymorphism and BC Risk for Publication Bias Test under Homozygote Model (CC vs. AA).

Publication bias

We have used Begg's funnel plot and Egger's test to evaluate the publication bias. The shapes of the funnel plots and also Egger's linear regression did not show any evidence of obvious asymmetry under all five genetic models for rs0011080 polymorphism (Table 2). However, Egger's test showed a significant publication bias under the homozygote genetic model homozygote (CC vs. AA: PBeggs = 0.11 and PEggers = 0.04, Figure 2) for rs0011081 polymorphism. Thus, we performed the Duval and Tweedie non-parametric ''trim and fill'' method to adjust for publication bias for rs0011081 polymorphism. However, the outcomes showed that the current meta-analysis with and without ''trim and fill'' did not draw different results, which suggesting that the meta-analysis results were statistically reliable.

Discussion

The current meta-analysis is the most comprehensive meta-analysis of the association of IL-10 rs1800871 and rs1800872 polymorphisms and BC risk. A total of 21 case-control studies with 6,054 cases and 6,355 controls were selected. In the present study, we found a significant association between rs1800871 and rs1800872 polymorphisms of IL-10 gene and BC risk. However, the associations did not statistically significant in subgroup analysis by ethnicity (Asians and Caucasians). Our results were inconsistence with previous meta-analyses on IL-10 rs1800871 and rs1800872 polymorphisms and BC risk. But previous meta-analyses included the limited studies. Thus, the current meta-analysis leads us to draw a conclusion that our results tend to be more precise estimate of the association of IL-10 rs1800871 and rs1800872 polymorphisms and BC risk than those of all previous meta-analyses.

Previously, Yu et al., (2013) in a meta-analysis of six studies (3,032 cases and 3,190 controls) have examined the correlation between IL-10 rs1800872 and BC risk. Their meta-analysis suggests a lack of association between rs1800872 and BC risk. In 2014, Dai et al performed a meta-analysis to evaluate the association of IL-10 rs1800871 and rs1800872 polymorphisms with BC risk. Their meta-analysis was included six studies (1,034 cases and 1,173 controls) on rs1800871 and seven studies (3,637 cases and 3,391 controls) on rs1800872. However, they did not found a significant association between IL-10 rs1800871 and rs1800872 polymorphisms with BC risk in overall and by ethnicity. However, subgroup analysis on ethnicity was based on limited number of studies (Dai et al., 2014). In 2012, Yu et al., (2012) performed a meta-analysis of four studies to assess the association of IL-10 rs1800871 (-819 C>T) polymorphisms with BC risk. However, they results showed that the rs1800871 polymorphism was not significantly associated with BC. Recently, several more studies assessing the association between IL-10 rs1800871 and rs1800872 polymorphisms and BC risk have been published. Therefore, compared to the previous meta-analyses, our meta-analysis involved both the missed studies and the recent published studies, thus markedly minimizing the selection bias. In addition, we have performed subgroup analyses based on ethnicity, source of controls, and genotyping methods, which might help increase the statistical power and get a more reliable results. However, our results based on subgroup by ethnicity were consistent with the previous meta-analyses.

Meta-analysis is a powerful approach that combines similar studies to draw a comprehensive and more reliable conclusion (Abedinzadeh et al., 2015; Sadeghiyeh et al., 2017). However, heterogenetic and publication bias might be distorting a meta-analysis result. The between-study heterogeneity may have several potential causes such as genetic backgrounds of participants, sample size, selection criteria, genotyping methods, source of controls, and lifestyle (Jafari Nedooshan et al., 2017; Mehdinejad et al., 2017; Sobhan et al., 2017). In the current meta-analysis, there was a significant heterogeneity for both rs1800871 and rs1800872 polymorphisms in almost all the genetic models, which the source of heterogeneity in the present analysis should be noted. In subgroup analysis, the between-study heterogeneity among Asians and Caucasians decreased for both rs1800871 and rs1800872 polymorphisms, suggesting ethnicity was most likely source of heterogeneity found in the meta-analysis.

The present meta-analysis was the most comprehensive and has sufficient statistical power to estimate the association of IL-10 rs1800871 and rs1800872 polymorphisms with BC risk. However, it has several limitations that should be acknowledged. First, we have included only published studies to this meta-analysis, no relevant unpublished studies with negative results was identified, which may bias the results of the meta-analysis. Second, the number of cases was limited to establishing a more reliable subgroup analysis by ethnicity, which type-II error could not be dismissed. Therefore, the discrepancy of association among Caucasians should be interpreted carefully. In addition, several number of case-control studies needed to establish whether there is an association between rs1800871 and rs1800872 polymorphisms of IL-10 and BC among Africans. Third, there was a moderate to high heterogeneity in the overall meta-analysis for both IL-10 rs1800871 and rs1800872 polymorphisms. But, subgroup analysis showed that ethnicity contributed heterogeneity between studies. Finally, due to the lack of original data of the majority of eligible studies, we could not be calculated other factors influencing BC, such as age, genetic background, environment, and lifestyle factors, should also be considered.

In conclusion, our meta-analysis suggests that IL-10 rs1800871 and rs1800872 polymorphisms might be the risk factors for BC in overall population, but not by ethnicity in Asians and Caucasians. However, additional larger and ethnically diverse studies are required to further evaluate the association of these polymorphisms with susceptibility to BC.

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