Association of Interleukin-10 Polymorphism (rs1800896, rs1800871, and rs1800872) with Breast Cancer Risk: an Updated Meta-Analysis Based on Different Ethnic Groups

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Abstract

Background: There have been various publications stating that IL-10 gene polymorphism is connected with the risk of breast cancer. This study was to further evaluate the association between IL-10 gene polymorphism and breast cancer (BC).

Methods: Articles from PubMed, Web of Knowledge, Embase, CNKI databases, China biomedical (CBM), and Google Scholar before March 29, 2020. The data was analyzed by Revman5.3 and Stata 12.0 software, and the strength of the association was identified using the odds ratio (OR) and the corresponding 95% confidence interval (CI).

Results: A total of 23 studies (7250 cancer cases and 7675 case-free controls) were eligible for the meta-analysis. The results show that IL-10 gene polymorphisms have no association with BC risk in any genetic model of the general population. However, there is significantly correlated with BC risk based on subgroup analysis by ethnicity: rs1800896 polymorphism are significantly associated with the risk of BC in Asian population based on the four models (G vs. A: OR= 0.78, 95% CI=0.65-0.95, $P=0.01$; GG vs. AA: OR=0.51, 95% CI=0.31-0.84, $P=0.007$; GA vs. AA: OR=0.6, 95% CI=0.44-0.81, $P=0.0009$; GG+GA vs. AA: OR=0.6, 95% CI=0.45-0.81, $P=0.0007$); rs1800871 polymorphism has association with BC risk in Caucasian population based on the Heterozygous model (CT vs. TT: OR=1.8, 95% CI =1.03-3.13, $P=0.04$). rs1800872 homozygous model was associated with the BC risk in Asians (AA vs CC: OR=0.74, 95%CI =0.55-0.99, $P=0.04$), and allelic model was associated with BC risk among Asians (A vs C: OR= 0.85, 95% CI =0.74-0.98, $P=0.03$) and among Caucasians (A vs C: OR= 0.65, 95% CI 0.43-0.98, $P=0.04$).

Conclusion: IL-10 gene polymorphism rs1800896 and rs1800872 significantly increased the risk of breast cancer in Asians, while rs1800871 was associated with the risk of breast cancer in Caucasians. Therefore, vulnerable individuals can be identified by genotypic characteristics, and the diseases can be prevented through interventions aimed at high-risk groups.

Background

Breast cancer (BC) is the leading cause of death among women worldwide and accounts for 11.9% of cancers in the world[1]. BC incidence varies widely, ranging from 27/100,000 (Central-East Asia and Africa) to 85–94/100,000 (Australia, North America and Western Europe). Its frequency in France is among the highest in Europe[2]. In Asian countries, the incidence of BC is also rising rapidly [3, 4]. Although genetic, environmental, and lifestyle are associated with BC occurrence, the biological mechanism that causes BC remains unclear.

Inflammation plays a significant role in BC development and is an important part of the BC microenvironment[5]. Interleukin-10 (IL-10) is an important anti-inflammatory and immunomodulatory cytokine found in the human immune response. IL-10 is located on chromosome 1 (1q31-1q32) and is composed of 5 exons and 4 introns[6]. Single nucleotide polymorphism (SNP) is the most common form of genetic variation. In the SNP database (<http://www.ncbi.nlm.nih.gov/snp>), the three promoter SNPs of IL-10, rs1800896 (-1082A/G), rs1800871 (-819T/C) and rs1800872 (-592A/C) is considered to be related to differences in gene transcription levels and is the most widely studied in many diseases [7]. It has been reported that IL-10 gene polymorphism plays an important role in the occurrence and development of cancers such as BC, gastric cancer, colorectal cancer, lung cancer, cervical cancer, and digestive cancer[8–10].

A study in Egypt found that: rs1800896 (-1082A/G) polymorphism is correlated with cancer staging and has association with progression of breast cancer at AA genotype [11]. In the research based on Caucasians, it was found that there was a significant association between IL-10-1082 G/G genotype and the increased risk of BC.[12]. Another study found that the rs1800871 (-819T/C) polymorphism increases the risk of BC in Han Chinese women[13]. A rare allele of rs1800872 (-592A/C) polymorphism may be a potential prognostic indicator of disease-free survival in BC patients[14]. Therefore, the IL-10 gene polymorphism can influence the risk of human BC[15], but these are based on research in different countries and populations. Studies have shown that the relationship between IL-10 gene polymorphism and BC risk is strongly associated with ethnicity[16]. Therefore, in this study, a meta-analysis was used to investigate the relationship between IL-10 rs1800896, rs1800871, and rs1800872 polymorphism and BC risk and aimed to explore the association between IL-10 gene polymorphism and BC risk in different populations in the world.

Methods

This meta-analysis was conducted according to the PRISMA reporting criteria [17].

Search Strategy

Research articles on the relationship between IL-10 gene polymorphism and BC risk in different databases including PubMed, Web of Knowledge, Embase, CNKI, CBM, VIP, WanFang Data, and Google academic were retrieved with the keywords: Interleukin10/IL-10, 1082A/G/rs1800896, 819T/C/rs1800871, 592A/C/rs1800872, Breast carcinoma/Breast cancer" etc. All eligible studies were searched until March 29, 2020. Take the PubMed database as an example to list the retrieval strategies, as shown in Fig. 1.

Inclusion and exclusion criteria

Inclusion criteria

(1) the case group was clinically diagnosed with BC and the control group was healthy; (2) Case-control studies or cohort studies to evaluate the relationship between IL-10 polymorphism and BC risk; (3) full-text published in English and(or) Chinese; (4) Report the number of cases and controls for each genotype and detailed genotyping data, or knowing the odds ratio (OR) helps to calculate the 95% confidence interval (CI).

Exclusion criteria

(1) Abstracts, reviews, animal studies; (2) Studies of unreported genotypes frequency; (3) Studies on the relationship between IL-10 gene polymorphism and prognosis and other aspects of breast cancer; (4) studies on the obvious imbalance of baseline between the case group and control group; (5) The case and control sources not provided; (6) Repeatedly published literature; and if multiple studies from the same case series are available, the study with the largest number of individuals is used in the analysis.

Data extraction

Two researchers selected the literature according to the inclusion and exclusion criteria, extracted the data, and cross-checked them into a standard data collection form independently. If there are any disputes, we will reach an agreement by discussion or by a third party, and strive to reach a consensus on each project. Data were collected from each article included: the first author, year of publication, study location, type of study, ethnicity (classified as Asian, Caucasian, or mixed descent), total number of cases and controls, genotype frequency, genotype detection method, and the source of control.

Sensitivity analysis

Sensitivity analysis was performed to assess the stability of the results. The Funnel plot, Begg's test, and Egger's test were used to evaluate publication bias. RevMan5.3 and Stata 12.0 software were used for the above statistical analysis [18].

Statistical analysis

The correlation between IL-10 gene polymorphism and BC risk was evaluated by OR and 95% CI as the effect size. 95% CI without 1 and $P < 0.05$ were considered statistically significant. The Z-test determines the significance of the OR value. The effects of heterogeneity were quantified by I^2 and P values. In addition, the I^2 value is used to quantify the degree of heterogeneity, where $I^2 < 25\%$ (low/no heterogeneity), $25-75\%$ (moderate heterogeneity), and $> 75\%$ (large or very heterogeneous). When the $I^2 < 25\%$, the fixed-effect model is adopted; otherwise, the random effect model is adopted.

Results

Search results

We had a total of 78 articles after removing 3 duplicated articles. After layer-by-layer screening, a total of 23 articles finally met the criteria for inclusion in this meta-analysis. Eligible papers were published between 2003 and 2019. The Meta-analysis updates three 2019 case-control studies compared to previous meta-analyses [11, 16, 17].

Data extraction and quality assessment

The 23 eligible articles had a total sample size of 14,925 participants, including 7,250 BC patients and 7,675 healthy controls[11, 16–37]. The samples were involved in three IL-10 polymorphism sites: rs1800896, rs1800871, and rs1800872. There were 17 studies on rs1800896 (3,308 cases and 3,425 controls), 12 studies on rs1800871 (2,530 cases and 2,698 controls), and 13 studies on rs1800872 (4,702 cases and 4,818 controls). The 10 were based on Caucasians and 6 were based on Asians, while the remaining 7 were mixed-race in the 23 criteria studies. Of these studies, the 18 were hospital-based and 5 were population-based. The Newcastle-Ottawa Scale (NOS) was used to assess the quality of the included articles[38]. NOS scores ranged from 0 to 9. We consider the methodological quality of the study to be good if the study score is ≥ 7 . Our data extraction and quality evaluation were independently completed by two authors. Table 1 and Table 2 show the basic characteristics of the included literature, the distribution of polymorphisms at the studied gene sites, allele frequency, and the quality assessment of the included literature.

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

<i>First author</i>	<i>Year</i>	<i>Country</i>	<i>Ethnicity</i>	<i>Genotyping method</i>	<i>SOC</i>	<i>case/control</i>	<i>Study design</i>	<i>SNP No.</i>	<i>NOS score</i>
Gallegos-Arreola	2019	Mexican	Mixed	PCR-RFLP	HB	368/320	CC	3	8
Al-Ankoshy	2019	Iraq	Caucasian	PCR-SSP	HB	70/70	CC	1	8
Zeng	2019	China	Asian	PCR-RFLP	HB	208/215	CC	3	8
Sabet	2017	Egypt	Caucasian	PCR-RFLP	HB	105/50	CC	1,2,3	7
Tian	2017	China	Asian	Mass ARRAY	PB	312/312	CC	1,2,3	7
Maruthi	2017	India	Mixed	PCR-RFLP	HB	285/285	CC	1	7
Atoum	2016	Jordan	Mixed	PCR-RFLP	HB	202/210	CC	1,2,3	7
Alsuhaibani	2016	Egypt	Caucasian	PCR-RFLP	HB	80/80	CC	1	7
Vinod	2015	India	Mixed	ASPCR	HB	125/160	CC	1	8
Li	2014	China	Asian	PCR-SSP	PB	128/128	CC	1,2	7
Wang	2014	China	Asian	PCR-RFLP	HB	474/501	CC	2	8
Pooja	2012	India	Mixed	PCR-RFLP	PB	200/200	CC	1,2,3	7
He	2012	China	Asian	MALDI-TOF MS	HB	347/500	CC	2	7
Kong2010	2010	China	Asian	PCR-RFLP	HB	315/322	CC	1,2,3	7
Pharoah	2007	European	Caucasian	TaqMan	PB	2045/2218	CC	3	8
Gonullu	2007	Turkey	Caucasian	Mass ARRAY	HB	38/24	CC	1,2,3	7
Scola	2006	Italy	Caucasian	PCR-RFLP	HB	84/106	CC	1,2,3	7
Onay	2006	Canada	Mixed	TaqMan	PB	398/372	CC	1	8
Balasu bramanian	2006	UK	Caucasian	TaqMan	HB	497/498	CC	1	7
Guzowski	2005	America	Mixed	DHPLC	HB	50/25	CC	1,2,3	7
Langsenlehner	2005	Australia	Caucasian	TaqMan	PB	500/496	CC	3	8
Abdolrahim	2005	Iran	Caucasian	PCR-RFLP	HB	275/320	CC	1,2,3	8
Smith	2004	UK	Caucasian	ARMS-PCR	HB	144/263	CC	1	8
SOC, source of controls; HB: hospital-based; PB, population-based; CC, case-control; PCR, polymerase chain reaction; RFLP, restriction fragment length polymorphism; DHPLC, denaturing highperformance liquid chromatography; EPIC, European Prospective Investigation of Cancer (a prospective study of diet and cancer being carried out in nine European countries); ASPCR, allele-specific PCR; SNP, single-nucleotide polymorphisms; SNP No.1, - 1082 A > G (rs1800896); 2: - 819 T > C (rs1800871); 3, - 592 A > C (rs1800872). NOS, Newcastle-ottawa scale.									

Table 2
IL-10 Polymorphisms Genotype Distribution and Allele Frequency in Cases and Controls

First author	Cases						Control						MAF
	Case	Control	Genotypes			Alleles		Genotypes			Alleles		
-1082A > G rs1800896			AA	AC	CC	A	C	AA	AC	CC	A	C	
Atoum 2016	202	210	157	29	16	343	61	151	42	17	344	76	0.181
Alsuhaibani2016	80	80	16	47	17	79	81	14	50	16	78	82	0.512
Vinod 2015	125	160	76	31	18	183	67	67	78	15	212	108	0.337
Pooja 2012	200	200	132	60	8	324	76	145	50	5	34	60	0.638
Kong2010	315	322	285	29	1	599	31	285	35	2	605	39	0.061
Gonullu 2007	38	24	13	22	3	48	28	16	7	1	39	9	0.187
Guzowski2005	50	25	10	28	12	48	52	9	12	4	30	20	0.400
Sabet 2017	105	50	15	41	49	71	139	27	21	2	75	25	0.250
Tian 2017	312	312	51	132	129	234	390	27	154	131	208	416	0.666
Abdolrahim-Zadeh 2005	275	320	119	116	40	171	373	146	125	49	417	223	0.348
Scola 2006	84	106	28	40	16	96	72	40	45	21	125	87	0.410
Onay 2006	398	372	90	205	103	385	411	107	194	71	408	336	0.451
Balasu 2006	497	498	121	253	123	499	495	117	260	121	494	502	0.504
Maruthi 2017	285	285	80	146	59	262	308	89	159	37	234	336	0.589
Al-Ankoshy2019	70	70	36	10	24	97	43	16	17	37	44	96	0.690
Smith 2004	144	263	32	58	39	136	122	46	120	57	250	276	0.524
Li2014	128	128	96	30	2	222	34	80	44	4	204	52	0.203
-819T > C (rs1800871)			TT	TC	CC	T	C	TT	TC	CC	T	C	
Atoum 2016	202	210	88	47	67	223	181	93	41	76	227	193	0.459
Wang2014	474	501	90	198	186	378	570	48	219	234	315	687	0.685
Pooja 2012	200	200	54	92	54	200	200	65	78	57	208	192	0.480
Kong2010	315	322	119	135	61	273	257	134	131	57	399	245	0.380
Gonullu 2007	38	24	5	17	16	27	49	4	10	10	18	30	0.625
Guzowski2005	50	25	3	19	28	25	75	1	10	14	12	38	0.760
Sabet 2017	105	50	16	47	42	79	131	26	22	2	74	26	0.260
Tian 2017	312	312	124	141	47	389	235	144	128	40	416	208	0.333
Abdolrahim-Zadeh 2005	275	320	129	120	26	375	172	166	122	32	454	186	0.290
He 2012	347	500	177	141	29	495	199	229	223	44	681	311	0.313

MAFs: minor allele frequencies

First author	Cases						Control						MAF
Scola 2006	84	106	5	30	49	40	128	12	35	59	59	177	0.721
Li2014	128	128	105	22	1	232	23	96	28	4	220	36	0.203
-592C > A (rs1800872)			AA	AC	CC	A	C	AA	AC	CC	A	C	
Gallegos-Arreola2019	368	320	42	154	172	238	498	11	100	209	122	518	0.190
Zeng2019	208	215	10	88	110	108	308	22	95	98	139	291	0.323
Atoum 2016	202	210	76	84	42	236	168	79	91	40	249	171	0.593
Pooja 2012	200	200	45	67	88	157	243	38	84	78	160	240	0.400
Kong2010	315	322	119	135	61	373	257	134	131	57	399	245	0.620
Gonullu 2007	38	24	5	17	16	27	49	4	10	10	18	30	0.375
Guzowski2005	50	25	3	17	30	23	77	3	10	12	16	34	0.320
Langsenlehner2005	500	496	21	210	269	252	748	36	199	261	271	721	0.273
Sabet 2017	105	50	4	36	65	42	166	31	16	6	78	28	0.736
Tian 2017	312	312	131	130	51	392	232	141	127	44	409	215	0.655
Abdolrahim-Zadeh 2005	275	320	27	100	148	154	396	29	132	159	190	450	0.297
Scola 2006	84	106	5	30	49	40	128	12	35	59	59	153	0.278
Pharoah 2007	2045	218	116	679	1251	367	3181	116	764	1338	996	3440	0.225
MAFs: minor allele frequencies													

Meta-analysis results

The association between IL-10 polymorphism (rs1800896, rs1800871, and rs1800872) and BC were shown in Table 3 and Fig. 2–5. Squares and horizontal lines correspond to study-specific OR and 95% CI. The area of a square reflects the weight (inversely proportional to the variance). The diamond represents the sum of OR and 95% CI.

Table 3
The minor allele frequencies of the three IL-10 gene polymorphisms locus

IL10	Minor Allele Frequency(%)								
polymorphic locus	Caucasians			Asians			Mixed-race		
rs1800896(-1082A/G)	18.7%	-	69.0%	6.1%	-	66.6%	18.1%	-	63.8%
	(Turkey)		(Iraq)	(China)		(China)	(India)		(Jordan)
rs1800871(-819T/C)	26.0%	-	72.1%	20.3%	-	65.8%	45.9%	-	76.0%
	(Egypt)		(Italy)	(China)		(China)	(Jordan)		(America)
rs1800872(-592A/C)	22.5%	-	73.6%	32.3%	-	65.5%	19.0%	-	59.3%
	(Eropean)		(Egypt)	(China)		(China)	(Mexiean)		(Jordan)

Table 4
Results of the Association of IL-10 Polymorphisms with BC Risk

Subgroup	Genetic Model	Type of Model	Heterogeneity		Odds Ratio			
			I ² (%)	PH	OR	95% CI	Z test	POR
rs1800896								
Overall	G vs. A	Random	82	< 0.00001	1.06	0.87–1.28	0.56	0.57
	GG vs. AA	Random	71	< 0.00001	1.14	0.81–1.59	0.73	0.46
	GA vs. AA	Random	73	< 0.00001	0.91	0.71–1.17	0.74	0.46
	GG + GA vs. AA	Random	79	< 0.00001	0.99	0.76–1.28	0.11	0.92
	GG vs. GA + AA	Random	53	0.006	1.18	0.94–1.48	1.45	0.15
Ethnicity								
Asian	G vs. A	Fixed	0	0.47	0.78	0.65–0.95	2.49	0.01
	GG vs. AA	Fixed	0	0.97	0.51	0.31–0.84	2.68	0.007
	GA vs. AA	Fixed	24	0.27	0.6	0.44–0.81	3.31	0.0009
	GG + GA vs. AA	Fixed	6	0.34	0.6	0.45–0.81	3.39	0.0007
	GG vs. GA + AA	Fixed	0	0.66	0.94	0.69–1.28	0.39	0.7
Caucasian	G vs. A	Random	0.0089	< 0.00001	1.19	0.83–1.72	0.94	0.35
	GG vs. AA	Random	0.008	0.00001	1.21	0.67–2.16	0.63	0.53
	GA vs. AA	Random	72	0.0008	1.09	0.73–1.62	0.43	0.67
	GG + GA vs. AA	Random	84	< 0.00001	1.19	0.74–1.91	0.7	0.48
	GG vs. GA + AA	Random	70	0.002	1.14	0.75–1.72	0.61	0.55
rs1800871								
Overall	C vs. T	Random	84	< 0.00001	1.11	0.88–1.39	0.87	0.39
	CC vs. TT	Random	75	< 0.00001	1.12	0.75–1.66	0.55	0.58
	CT vs. TT	Random	67	0.0004	1.11	0.85–1.44	0.77	0.44
	CC + CT vs. TT	Random	78	< 0.00001	1.12	0.84–1.50	0.77	0.44
	CC vs. CT + TT	Random	50	0.03	1	0.80–1.25	0.02	0.98
Ethnicity								
Asian	C vs. T	Random	89	< 0.00001	0.94	0.68–1.31	0.35	0.72
	CC vs. TT	Random	79	0.0008	0.81	0.48–1.40	0.74	0.46
	CT vs. TT	Random	76	0.002	0.86	0.61–1.21	0.88	0.38
	CC + CT vs. TT	Random	82	0.0001	0.84	0.58–1.22	0.93	0.35
	CC vs. CT + TT	Random	38	0.17	0.93	0.72–1.20	0.59	0.56
Caucasian	C vs. T	Random	88	< 0.0001	1.57	0.81–3.05	1.33	0.18
	CC vs. TT	Random	84	0.0004	1.11	0.85–1.44	0.77	0.44
	CT vs. TT	Random	45	0.14	1.8	1.03–3.13	2.07	0.04

Subgroup	Genetic Model	Type of Model	Heterogeneity		Odds Ratio			
			I ² (%)	PH	OR	95% CI	Z test	POR
	CC + CT vs. TT	Random	79	0.002	2.13	0.89–5.13	1.69	0.09
	CC vs. CT + TT	Random	78	0.003	1.64	0.69–3.90	1.12	0.26
<i>rs1800872</i>								
Overall	A vs. C	Random	89	< 0.00001	0.82	0.66–1.03	1.7	0.09
	AA vs. CC	Random	83	< 0.00001	0.71	0.46–1.08	1.6	0.11
	AC vs. CC	Random	59	0.004	0.93	0.78–1.11	0.8	0.43
	AA + AC vs. CC	Random	79	0.00001	0.86	0.68–1.08	1.31	0.19
	AA vs. AC + CC	Random	60	0.004	0.95	0.75–1.20	0.44	0.66
Ethnicity								
Asian	A vs. C	Fixed	0	0.54	0.85	0.74–0.98	2.22	0.03
	AA vs. CC	Fixed	23	0.27	0.74	0.55–0.99	2.04	0.04
	AC vs. CC	Fixed	0	0.88	0.88	0.69–1.13	0.96	0.34
	AA + AC vs. CC	Fixed	0	0.81	0.82	0.65–1.04	1.65	0.1
	AA vs. AC + CC	Fixed	25	0.26	0.82	0.66–1.01	1.84	0.07
Caucasian	A vs. C	Random	93	< 0.00001	0.65	0.43–0.98	2.07	0.04
	AA vs. CC	Random	89	< 0.00001	0.43	0.19–1.00	1.96	0.05
	AC vs. CC	Random	48	0.09	0.89	0.72–1.11	1.02	0.31
	AA + AC vs. CC	Random	82	< 0.00001	0.74	0.52–1.05	1.69	0.09
	AA vs. AC + CC	Random	36	0.18	0.87	0.62–1.21	0.84	0.4

Correlation Between rs1800896 polymorphism and BC

The 17 studies were conducted on the association between IL-10 rs1800896 polymorphism and BC, with a total sample size of 6,733 cases, 3,308 patients, and 3,425 healthy controls. Overall population heterogeneity test I² was 82%. The random-effect model results showed that The comparison results of the 5 gene models showed no statistical significance between rs1800896 polymorphism and BC (Table 3). Subgroups by race showed that under the four genetic models (allele G vs. A: OR = 0.78, 95% CI = 0.65–0.95, *P* = 0.01; homozygous GG vs. AA: OR = 0.51, 95% CI = 0.31–0.84, *P* = 0.007; heterozygous GA vs. AA: OR = 0.6, 95% CI = 0.44–0.81, *P* = 0.0009; dominant GG + GA vs. AA: OR = 0.6, 95% CI = 0.45–0.81, *P* = 0.0007) (figure. 2A-D),rs1800896 polymorphism was significantly associated with BC risk in the Asians. This suggests that race is likely to be the source of heterogeneity and the 4 genetic models of rs1800896 polymorphism are significantly associated with the BC risk in Asians.

Correlation between rs1800871 polymorphism and BC

The 12 studies assessed the strength of the association between IL-10 rs1800871 polymorphism and BC in a total of 2,530 patients and 2,698 controls. There was no association between BC risk and rs1800871 polymorphism in any genetic model of the general population. However, when stratified by race, the rs1800871 polymorphism was associated with BC risk in Caucasians in the heterozygous model (CT vs. TT: OR = 1.8, 95% CI = 1.03–3.13, *P* = 0.04) (Fig. 3). This result indicates that Caucasians with the rs1800871 heterozygous model are more likely to develop BC than individuals with other genotypes.

Correlation between rs1800872 polymorphism and BC

The 13 studies (4702 cases and 4818 controls) assessed the strength of the association between IL-10 rs1800872 polymorphism and BC. As shown in Table 3, the 5 gene model comparison results all showed the association between IL-10 rs1800872 polymorphism and BC in the general population was not statistically significant. However, after stratification by race, the homozygous model of rs1800872 polymorphism was associated with BC risk in Asians (AA vs. CC: OR = 0.74, 95% CI = 0.55–0.99, $P = 0.04$) (Fig. 4A). Allele model of rs1800872 polymorphism was associated with risk of BC in Asians (A vs. C: OR = 0.85, 95% CI = 0.74–0.98, $P = 0.03$) (figure. 4B) and Caucasians (A vs. C: OR = 0.65, 95% CI = 0.43–0.98, $P = 0.04$) (figure. 4C). In other words, if rs1800872 is an allelic genetic model, the BC risk is much higher in both Asians and Caucasians than in other genotypes.

Publication bias

Funnel plot, Begg's test, and Egger's test were used to evaluate the publication bias (Stata12.0). As shown in Fig. 6, the funnel plot is essentially symmetrical and the P values of Begg's test and Egger test are all greater than 0.05. It is indicated that there is almost no obvious publication bias at the three loci.

Discussion

IL-10, originally known as cytokine synthesis inhibitory factor (CSIF), is a powerful anti-inflammatory cytokine. IL-10 can stimulate the expression of carboxypeptidase B2 (CPB2) in inflammatory BC cells, thus increasing the aggressiveness of the cancer cells [5]. IL-10 is involved in the abnormal proliferation of breast ducts and lobules and stimulates mitotic activity, leading to an increased risk of cancer [24, 39]. Studies on the mechanism have shown that the production of IL-10 may represent a new escape mechanism for breast cancer cells to escape the destruction of the immune system. IL-10 gene silencing down-regulated the expression of PI3K/AKT and Bcl2 genes, and increased the cleavage expression levels of BBC3, Bax, caspase3, and caspase3[40]. IL-10 can also induce tumor progression by inhibiting a large number of cytokines such as IL-1a, IL-1b, TNF-DNA, IL-6, IL-8, IL-12, and IL-18. This shows that IL-10 plays an important role in promoting cancer immune escape. This may be closely related to the fact that IL-10 gene polymorphism can change its transcriptional activity or protein structure. These variants may affect the biological function of IL-10, leading to immune dysfunction, affect the anti-tumor immune response, and ultimately increase susceptibility to BC [24, 41, 42].

Studies have shown that the three most common single nucleotide polymorphisms (SNPs) play an important role in regulating IL-10 activity. They were located at the transcriptional starting point of rs1800896 (-1082A/G), rs1800871 (-819T/C) and rs1800872 (-592A/C) and encoded high (GCC), medium (ACC) or low (ATA) expression of IL-10 respectively[43–45]. Several other polymorphic loci of IL10 (rs1800890, rs6703630, and rs6693899) are also controversial, but there are few relevant studies at present. In recent years, race has been involved in many studies on the relationship between IL-10 gene polymorphism and the risk of BC. For example, the IL-10 gene rs1800872 polymorphism was associated with BC susceptibility in this sample from the Mexican population[16]. Also, there was significant association of mutant allele and genotypes of IL-10 rs1800896 with Indian postmenopausal BC[23]. Since the IL-10 gene polymorphism were associated with the risk of BC, we hypothesized that race is the key to the association between IL-10 polymorphism and BC. This meta-analysis conducted the most comprehensive analysis of the relationship between three IL-10 polymorphisms (rs1800896, rs1800871, and rs1800872) and the BC risk of different races. In a subgroup analysis by ethnicity (Asian and Caucasian/mixed race), the three IL-10 polymorphisms (rs1800896, rs1800871, and rs1800872) were significantly associated with BC. It showed that rs1800896 (allele G vs. A: OR = 0.78, 95% CI = 0.65–0.95, $P = 0.01$; homozygous GG vs. AA: OR = 0.51, 95% CI = 0.31–0.84, $P = 0.007$; heterozygous GA vs. AA: OR = 0.6, 95% CI = 0.44–0.81, $P = 0.0009$; dominant GG + GA vs. AA: OR = 0.6, 95% CI = 0.45–0.81, $P = 0.0007$) were significantly correlated with BC risk in Asia. The rs1800871 heterozygote model (CT vs. TT: OR = 1.8, 95%CI = 1.03–3.13, $P = 0.04$) was associated with BC risk in the Caucasians. The rs1800872 homozygous model (AA vs CC: OR = 0.74, 95% CI = 0.55–0.99, $P = 0.04$) was associated with BC risk in Asians, and the allelic model (A vs. C: OR = 0.85, 95% CI = 0.74–0.98, $P = 0.03$) was associated with BC risk in Asians and Caucasians (A vs C: OR = 0.65, 95%CI 0.43–0.98, $P = 0.04$). It is suggested that the ethnic subgroup of IL-10 gene polymorphism is the key factor affecting the susceptibility to BC.

Previously, Dai *et al.*[46], Abedinzadeh *et al.*[47] and Moghimi *et al.* [39] have analyzed the correlation between IL10 polymorphism and breast cancer risk, but their analysis is not comprehensive enough. There are few studies included and the ethnic division is not accurate enough. The quality, quantity and new studies included in the meta-analysis will directly affect the credibility and stability of the results. We used a broad search strategy to capture all relevant information. This meta-analysis conducted a more comprehensive analysis of the relationship between three IL-10 polymorphisms (rs1800896, rs1800871, and rs1800872) and BC risk. 23 studies included in the review span decades (publish between 2004 and 2019). It included the researches both missing and published recently, and ruled out the low quality. So our results more accurately estimate the association between IL-10 polymorphism and BC risk than all previous meta-analysis. In this meta-analysis, the latest, most studies and the quality assessment were good were included. There was no significant publication bias, heterogeneity was small in the subgroups, and the sensitivity analysis results did not change. Therefore, the conclusion of the association between the three IL-10 polymorphisms (rs1800896, rs1800871, and rs1800872) and BC in this meta-analysis is reliable and has certain clinical guidance values. The current meta-analysis is the most comprehensive and has sufficient statistical power to assess the association between IL-10 polymorphism and BC risk.

However, it has several limitations that should be acknowledged. First, due to the limited research on the interaction between these three polymorphic sites and their interaction with the environment, it is impossible to estimate the impact of gene-gene and gene-environment interaction on the results of the study. Secondly, we found that heterogeneity existed in the meta-analysis as indicated by the I^2 values. Despite the usage of a random-effects model in some studies, the heterogeneity remained. It is predictable because other factors that affect BC should be considered, such as staging and grading of tumors, age, genetic background, environment, and lifestyle. However, due to the lack of some qualified original data, we are unable to calculate the impact of these factors on BC. Besides, the variation range of the minimum allele frequency is large due to the differences in the regional environment, living habits, ethnic customs, and age (especially in China), which may have a certain impact on the research results, but these are inestimable. In general, the meta-analysis was performed on 23 articles that addressed the specific research question. Moreover, the influence and sensitivity analyses confirmed the robustness of the main results.

Conclusion

In summary, this meta-analysis provides new ideas for clinical, genetic, and epidemiological studies of breast cancer. Our results show that alleles, homozygotes, heterozygotes, and dominant genotypes of IL-10 rs1800896 are significantly associated with the risk of BC in Asians. The homozygous and allelic patterns of rs1800872 also increase the risk of breast cancer in Asians, while the heterozygous patterns of rs1800871 and rs1800872 increase the risk of breast cancer in Caucasians. IL10 polymorphism may be a key regulator of breast cancer susceptibility. Different ethnic groups can predict breast cancer susceptibility by detecting different IL10 polymorphisms locus. Therefore, vulnerable individuals can be identified by genotypic characteristics, and BC can be prevented through interventions aimed at high-risk groups. However, the etiology of BC is complex, so we strongly recommend further genetic association studies to explore the effects of gene-gene interactions on disease susceptibility. Large-scale multicenter studies can be conducted in the future to further verify the effects of gene-gene and gene-environment interactions on IL-10 polymorphism and BC risk in different environments.

Declarations

Provenance and peer review

Not commissioned, externally peer-reviewed.

Ethics approval and consent to participate

Ethical approval is not applicable.

Consent for publication

Written informed consent for publication was obtained from all participants.

Competing interests

The authors declare no relevant conflict of interest.

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Authors' contributions

Lijun Li participated in the research design. Lijun Li and Jiangang Cao performed data analysis and wrote or contributed to the writing of the manuscript. Lijun Li, Donghua Li, and Wei Xiong interpreted the data and drafted the manuscript. Mengling Cao conceived the idea and supervised the study. All authors read and approved the final manuscript.

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Availability of data and materials

The material of this article is original research. All data in this manuscript are available and transparent for readers.

References

1. Anastasiadi Z, Lianos GD, Ignatiadou E, Harissis HV, Mitsis M. Breast cancer in young women: an overview. *Updates Surg.* 2017;69:313–7.
2. Sancho-Garnier H, Colonna M. [Breast cancer epidemiology]. *Presse Med.* 2019;48:1076–84.
3. Oblak T, Zadnik V, Krajc M, Lokar K, Zgajnar J. **Breast cancer risk based on adapted IBIS prediction model in Slovenian women aged 40–49 years - could it be better?** *Radiol Oncol* 2020.
4. Mubarik S, Wang F, Fawad M, Wang Y, Ahmad I, Yu C. Trends and Projections in Breast Cancer Mortality among four Asian countries (1990–2017): Evidence from five Stochastic Mortality Models. *Sci Rep.* 2020;10:5480.
5. Mohamed HT, El-Husseiny N, El-Ghonaimy EA, Ibrahim SA, Bazzi ZA, Cavallo-Medved D, Boffa MB, El-Shinawi M, Mohamed MM. IL-10 correlates with the expression of carboxypeptidase B2 and lymphovascular invasion in inflammatory breast cancer: The potential role of tumor infiltrated macrophages. *Curr Probl Cancer.* 2018;42:215–30.
6. Roh JW, Kim MH, Seo SS, Kim SH, Kim JW, Park NH, Song YS, Park SY, Kang SB, Lee HP. Interleukin-10 promoter polymorphisms and cervical cancer risk in Korean women. *Cancer Lett.* 2002;184:57–63.
7. Howell WM, Rose-Zerilli MJ. Cytokine gene polymorphisms, cancer susceptibility, and prognosis. *J Nutr.* 2007;137:194S–199S.
8. Chen L, Shi Y, Zhu X, Guo W, Zhang M, Che Y, Tang L, Yang X, You Q, Liu Z. IL10 secreted by cancer-associated macrophages regulates proliferation and invasion in gastric cancer cells via cMet/STAT3 signaling. *Oncol Rep.* 2019;42:595–604.
9. Zhao Y, Chen S, Shen F, Long D, Yu T, Wu M, Lin X. In vitro neutralization of autocrine IL10 affects Op18/stathmin signaling in nonsmall cell lung cancer cells. *Oncol Rep.* 2019;41:501–11.
10. Bhattacharjee HK, Bansal VK, Nepal B, Srivastava S, Dinda AK, Misra MC. Is Interleukin 10 (IL10) Expression in Breast Cancer a Marker of Poor Prognosis? *Indian J Surg Oncol.* 2016;7:320–5.
11. Azher A, Al-Ankoshy M, Hamid A, Dawood Alatbee A. **The impact of IL-10 gene polymorphism on progressive Breast cancer.** 2019.
12. Zhu Z, Liu JB, Liu X, Qian L. Association of interleukin 10 rs1800896 polymorphism with susceptibility to breast cancer: a meta-analysis. *J Int Med Res.* 2020;48:300060520904863.

13. Li M, Yue C, Zuo X, Jin G, Wang G, Guo H, Wu F, Huang S, Zhao X. The effect of interleukin 10 polymorphisms on breast cancer susceptibility in Han women in Shaanxi Province. *PLoS One*. 2020;15:e0232174.
14. Gerger A, Renner W, Langsenlehner T, Hofmann G, Knechtel G, Szkandera J, Samonigg H, Krippel P, Langsenlehner U. Association of interleukin-10 gene variation with breast cancer prognosis. *Breast Cancer Res Treat*. 2010;119:701–5.
15. Setrerrahmane S, Xu H. Tumor-related interleukins: old validated targets for new anti-cancer drug development. *Mol Cancer*. 2017;16:153.
16. Patricia Gallegos-Arreola M, Zuniga Gonzalez GM, Figuera LE, Puebla Perez AM, Delgado Saucedo JI. Association of the IL-10 gene rs1800872 (-592 C > A) polymorphism with breast cancer in a Mexican population. *J BUON*. 2019;24:2369–76.
17. Fanyu Z, Wenhui I, Shan Z, Wei T, xiaofen Z. Qiu jin z: **Association of interleukin-10 gene polymorphism with susceptibility of breast cancer in Chinese women of Guangxi province**. *Guo ji mian yi xue za zhi*. 2019;042:464–7.
18. Goske M, Ramachander VR, Sureka K, Jahan P. **Association of IL10 Gene Polymorphisms (Rs 1800896, Rs1800872) in Breast Cancer Patients**. *International Journal Of Medical Science And Clinical Invention* 2017.
19. Atoum MF. ACC interleukin-10 gene promoter haplotype as a breast cancer risk factor predictor among Jordanian females. *Onco Targets Ther*. 2016;9:3353–7.
20. AlSuhaibani ES, Kizilbash NA, Malik S, Dasti JI, Al Beladi F, El-Morshedi N. **Polymorphisms in promoter regions of IL-6 and IL-10 genes in breast cancer: a case-control study**. *Genet Mol Res* 2016, 15.
21. Vinod C, Jyothy A, Vijay Kumar M, Raman RR, Nallari P, Venkateshwari A. A Common SNP of IL-10 (-1082A/G) is Associated With Increased Risk of Premenopausal Breast Cancer in South Indian Women. *Iran J Cancer Prev*. 2015;8:e3434.
22. Wang Z, Liu QL, Sun W, Yang CJ, Tang L, Zhang X, Zhong XM. Genetic polymorphisms in inflammatory response genes and their associations with breast cancer risk. *Croat Med J*. 2014;55:638–46.
23. Pooja S, Chaudhary P, Nayak LV, Rajender S, Saini KS, Deol D, Kumar S, Bid HK, Konwar R. Polymorphic variations in IL-1beta, IL-6 and IL-10 genes, their circulating serum levels and breast cancer risk in Indian women. *Cytokine*. 2012;60:122–8.
24. Kong F, Liu J, Liu Y, Song B, Wang H, Liu W. Association of interleukin-10 gene polymorphisms with breast cancer in a Chinese population. *J Exp Clin Cancer Res*. 2010;29:72.
25. Gonullu G, Basturk B, Evrensel T, Oral B, Gozkaman A, Manavoglu O. Association of breast cancer and cytokine gene polymorphism in Turkish women. *Saudi Med J*. 2007;28:1728–33.
26. Guzowski D, Chandrasekaran A, Gawel C, Palma J, Koenig J, Wang XP, Dosik M, Kaplan M, Chu CC, Chavan S, et al. Analysis of single nucleotide polymorphisms in the promoter region of interleukin-10 by denaturing high-performance liquid chromatography. *J Biomol Tech*. 2005;16:154–66.
27. Langsenlehner U, Krippel P, Renner W, Yazdani-Biuki B, Eder T, Koppel H, Wascher TC, Paulweber B, Samonigg H. Interleukin-10 promoter polymorphism is associated with decreased breast cancer risk. *Breast Cancer Res Treat*. 2005;90:113–5.
28. Sabet S, El-Sayed SK, Mohamed HT, El-Shinawi M, Mohamed MM. Inflammatory breast cancer: High incidence of GCC haplotypes (-1082A/G, -819T/C, and - 592A/C) in the interleukin-10 gene promoter correlates with over-expression of interleukin-10 in patients' carcinoma tissues. *Tumour Biol*. 2017;39:1010428317713393.
29. Tian K, Zhang R, Wang X. Association of interleukin-10 polymorphisms and haplotypes with the risk of breast cancer in northern China. *Int J Clin Exp Pathol*. 2017;10:6989–96.
30. Abdollahi-Zadeh H, Hakkakian N, Asadollahi R, Gharesifard B, Sarvari J, Kamali E, Talei A. **Interleukin10 Promoter Polymorphisms and Breast Cancer Risk in Iranian Women**. *Iranian J Immunol* 2005, 3.
31. He JR, Chen LJ, Su Y, Cen YL, Tang LY, Yu DD, Chen WQ, Wang SM, Song EW, Ren ZF. Joint effects of Epstein-Barr virus and polymorphisms in interleukin-10 and interferon-gamma on breast cancer risk. *J Infect Dis*. 2012;205:64–71.
32. Scola L, Vaglica M, Crivello A, Palmeri L, Forte GI, Macaluso MC, Giacalone A, Di Noto L, Bongiovanni A, Raimondi C, et al. Cytokine gene polymorphisms and breast cancer susceptibility. *Ann N Y Acad Sci*. 2006;1089:104–9.
33. Onay VU, Briollais L, Knight JA, Shi E, Wang Y, Wells S, Li H, Rajendram I, Andrulis IL, Ozcelik H. SNP-SNP interactions in breast cancer susceptibility. *BMC Cancer*. 2006;6:114.
34. Balasubramanian SP, Azmy IA, Higham SE, Wilson AG, Cross SS, Cox A, Brown NJ, Reed MW. Interleukin gene polymorphisms and breast cancer: a case control study and systematic literature review. *BMC Cancer*. 2006;6:188.

35. Pharoah PD, Tyrer J, Dunning AM, Easton DF, Ponder BA, Investigators S. Association between common variation in 120 candidate genes and breast cancer risk. *PLoS Genet.* 2007;3:e42.
36. Smith KC, Bateman AC, Fussell HM, Howell WM. Cytokine gene polymorphisms and breast cancer susceptibility and prognosis. *Eur J Immunogenet.* 2004;31:167–73.
37. Meijiang L. The relationship between interleukin gene polymorphism and females genetic susceptibility to breast cancer in Western Guangxi. *Journal of Youjiang Medical University for Nationalities.* 2014;36:339–43.
38. Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. *Eur J Epidemiol.* 2010;25:603–5.
39. Moghimi M, Ahrar H, Karimi-Zarchi M, Aghili K, Salari M, Zare-Shehneh M, Neamatzadeh H. Association of IL-10 rs1800871 and rs1800872 Polymorphisms with Breast Cancer Risk: A Systematic Review and Meta-Analysis. *Asian Pac J Cancer Prev.* 2018;19:3353–9.
40. Alotaibi MR, Hassan ZK, Al-Rejaie SS, Alshammari MA, Almutairi MM, Alhoshani AR, Alanazi WA, Hafez MM, Al-Shabanah OA. Characterization of Apoptosis in a Breast Cancer Cell Line after IL-10 Silencing. *Asian Pac J Cancer Prev.* 2018;19:777–83.
41. Sheikhpour E, Noorbakhsh P, Foroughi E, Farahnak S, Nasiri R, Neamatzadeh H. A Survey on the Role of Interleukin-10 in Breast Cancer: A Narrative. *Rep Biochem Mol Biol.* 2018;7:30–7.
42. Hydes TJ, Burton R, Inskip H, Bellis MA, Sheron N. A comparison of gender-linked population cancer risks between alcohol and tobacco: how many cigarettes are there in a bottle of wine? *BMC Public Health.* 2019;19:316.
43. Hofmann SR, Laass MW, Fehrs A, Schuppan D, Zavallos VF, Salminger D, Mabert K, Hedrich CM. IL10 promoter haplotypes may contribute to altered cytokine expression and systemic inflammation in celiac disease. *Clin Immunol.* 2018;190:15–21.
44. Zupin L, Polesello V, Catamo E, Crovella S, Segat L. Interleukin-10 gene promoter polymorphisms in celiac patients from north-eastern Italy. *Hum Immunol.* 2014;75:656–61.
45. Westendorp RG, Langermans JA, Huizinga TW, Elouali AH, Verweij CL, Boomsma DI, Vandenbroucke JP. Genetic influence on cytokine production and fatal meningococcal disease. *Lancet.* 1997;349:170–3.
46. Dai ZJ, Wang XJ, Zhao Y, Ma XB, Kang HF, Min WL, Lin S, Yang PT, Liu XX: **Effects of interleukin-10 polymorphisms (rs1800896, rs1800871, and rs1800872) on breast cancer risk: evidence from an updated meta-analysis.** *Genet Test Mol Biomarkers* 2014, **18**:439–445.
47. Abedinzadeh M, Neamatzadeh H, Jafari M, Forat-Yazdi M, Nasiri R, Farahnak S, Foroughi E, Zare-Shehneh M: **Association of Interleukin-10 -1082A > G (rs1800896) Polymorphism with Predisposition to Breast Cancer: a Meta-Analysis based on 17 Case-Control Studies.** *Rev Assoc Med Bras (1992)* 2018, **64**:756–764.

Figures

Figure 1

Flowchart of study selection for the present study.

Figure 2

Forest plots of IL-10 rs1800896 polymorphism and BC risk in Asians. (A) (G vs. A); (B) (GG vs. AA); (C) (GA vs. AA); (D) (GG+GA vs. AA).

Figure 3

Forest plots of IL-10 rs1800871 polymorphism and BC risk in the Caucasians (CT vs. TT).

Figure 4

Forest plots of IL-10 rs1800872 polymorphism and breast cancer risk in Asians and Caucasians. (A) IL-10 rs1800872 polymorphism in Asians (AA vs. CC); (B) IL-10 rs1800872 polymorphism in Asians (A vs. C); (C) IL-10 rs1800872 polymorphism in Caucasians (A vs. C).

Figure 5

Funnel plot of the association between IL-10 gene and breast cancer. (A) rs1800896; (B) rs1800871; (C) rs1800872.