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ORIGINAL ARTICLE

Correlation of Q223R and K109R polymorphisms in leptin receptor gene with susceptibility of breast cancer: A systematic review and meta-analysis

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Abstract

Background: Increasing evidence has suggested a strong association of Q223R (rs1137101) and K109R (rs1137100) polymorphisms in leptin receptor (LEPR) gene with susceptibility of breast cancer (BC), but inconsistent results were obtained. To provide a quantitative assessment of this association, a systematic review and meta-analysis was performed.

Methods: A literature search of PubMed, EMBASE, Google Scholar, and the Chinese National Knowledge Infrastructure was collected. Odds ratios (ORs) and 95% confidence intervals (95% CIs) were calculated.

Results: A total of 20 case-control studies for Q223R polymorphism and 8 case-control studies for K109R polymorphism were included. Significant association between Q223R polymorphism and BC risk was not found in total, Asian or Caucasian population, but in African population: allelic model, OR = 0.72, 95% CI = 0.60-0.86, $p < 0.001$; recessive model, OR = 0.67, 95%CI = 0.52-0.87, $P = 0.003$; dominant model, OR = 1.58, 95% CI = 1.15-2.17, $p = 0.004$; homozygous model, OR = 0.51, 95% CI = 0.36-0.78, $p < 0.001$. Significant association between K109R polymorphism and BC risk was not found in total or Caucasian population, but in Asian population: dominant model, OR = 0.24, 95% CI = 0.07-0.84, $p = 0.03$; heterozygous model, OR = 1.87, 95% CI = 1.07-3.26, $p = 0.03$.

Conclusion: The available evidence suggests that Q223R polymorphism may be significantly associated with BC risk in African population. K109R polymorphism may be significantly associated with BC risk in Asian population.

Keywords: Breast cancer; Leptin receptor; Meta-analysis; Polymorphism; System review

1. INTRODUCTION

Breast cancer (BC) is the leading cause of cancer death, followed by colorectal and lung cancer for incidence.[1] Even though lots of factors are being investigated to explain these trends and the different incidence rates of BC in various populations, there is yet no consensus. Among those factors, mutation in BRCA1 and BRCA2 have been investigated for a long time. Others factors which have been reported are alteration in menstruation (early menarche age and delayed menopause), alteration in reproduction (late age at first birth), hormone levels, intake of alcohol, as well as obesity.[2] It has been reported that obesity and weight gain were risk factors and associated with poor prognosis of BC and the mechanisms for this connection may be related to resistance to insulin, chronic hyperinsulinemia, local inflammation, adipokine secretion, such as leptin (LEP), and more exposure of estrogen.[3] Nevertheless, the exact pathogenesis is still unclear. Thus, the main focus for BC risk was gradually shifted to obesity-related genes.

LEP is a 16-kDa adipocyte-derived peptide hormone that plays a vital role in conrtolling food intake, energy expenditure and neuroendocrine function. In obese subjects, high levels of leptin have been frequently observed.[4] In addition to playing an important role in regulating energy expenditure and body weight, leptin is vital for tumor cell growth and exerts its biologic effects through selective binding to the leptin receptor (LEPR). LEPR, which is encoded by LEPR gene (located on chromosome 1p21) is a single membrane-spanning receptor of the class I cytokine receptor family and expressed in many tissues including the mammary gland.[5,6] Therefore, it was hypothesized that polymorphisms

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in the LEPR gene could modulate individual differences in levels of LEPR and thus may play a role in contributing to an alteration in the biologic effects of LEP, leading to an effect on the susceptibility to BC. Several polymorphisms in the LEPR gene including rs1137101, rs1137100, rs1137100, rs8179183, rs4655537, and rs3762274 have been identified. In addition, several common sequence variants have been described and their potential associations with obesity have been proposed.[7] Nevertheless, their potential associations with BC risk have not been fully investigated. Among them, Q223R (rs1137101)[8–27] and K109R (rs1137100)[8,13,16,21–23,27,28] polymorphisms for BC have been most commonly studied. However, the results were inconsistent. Taking K109R, for example, several studies reported positive relationships,[16,22,23,28] whereas others held different views.[8,13,21,27] The results of those published meta-analyses[29–34] were also inconclusive and contradictory because of limited sample sizes or diverse ethnicity. Thus, more comprehensive and well-designed meta-analyses with larger samples should be performed.

As some new studies published, a system review and meta-analysis of all relevant literatures for the association between Q223R and K109R polymorphisms and BC risk was conducted in order to raise more reliable evidence and insights.

2. METHODS

2.1. Searching strategy

An electronic literature search which was restricted to humans was conducted on PubMed, EMBASE, Google Scholar, and the Chinese National Knowledge Infrastructure databases without language restrictions using the following searching strategy: (*leptin receptor* or *LEPR* or *Q223R* or *K109R* or *rs1137101* or *rs1137100*) and (*polymorphisms* or *SNP* or *variant* or *variants* or *variation* or *genotype* or *genetic* or *mutation*) and (*BC* or *mammary cancer* or *mammary adenocarcinoma*). The last search was updated in February 21, 2023.

2.2. Inclusion and exclusion criteria

Studies were included if they met the following criteria: (a) studies had a case-control design to assess the association between LEPR Q223R (rs1137101) and/or K109R (rs1137100) polymorphisms and BC risk in humans; (b) genotype frequencies were provided. (c) the full text was available and it reported genotype frequencies in cases and controls, or sufficient data to estimate odds ratios (ORs) and 95% confidence intervals (CIs).

Studies were excluded if they: (a) were not a case-control study; (b) did not report precise genotypes; (c) were duplicate publications of data from the same study; (d) were meta-analyses, letters, reviews, or editorial articles; and (e) investigated other polymorphisms of LEPR.

2.3. Data extraction

Two authors (S.L.Z. and J.R.Y.) independently selected eligible studies and extracted the following data: the surname of first author, year of publication, ethnicity, country, sample size, type of controls, genotyping method, genotype distribution, *p* value for the Hardy-Weinberg equilibrium among controls, and matched parameters.

2.4. Assessment of methodological quality

The quality of included studies was assessed independently by two investigators (S.L.Z. and J.R.Y.) using the Newcastle–Ottawa Scale.[35] Scores of 0 to 4 were considered to indicate poor methodological quality; scores of 5 to 9, high quality.[36] Any disagreements about scoring were resolved through comprehensive reassessment by the other authors. Only high-quality studies were included in the meta-analysis.

2.5. Statistical analysis

The strength of association of Q223R and K109R polymorphisms with BC risk was calculated in terms of unadjusted OR with 95% CIs based on genotype frequencies in cases and controls. The significance of pooled OR was determined using the Z test, with $p < 0.05$ defined as significant. Meta-analysis was conducted using a fixed-effect model when $p > 0.10$ for the Q test, indicating lack of heterogeneity among studies; otherwise, meta-analysis was conducted using a random-effect model. All statistical tests for meta-analyses were performed using Review Manager 5.3 (Cochrane Collaboration). Publication bias was assessed using Begg's funnel plot and Egger's weighted regression in Stata 12.0 (Stata Corp, College Station, TX, USA), with $p < 0.05$ considered statistically significant.

3. RESULTS

3.1. Description of studies

The search strategy retrieved 522 potentially relevant studies. Four hundred ninety-seven of which were excluded on the basis of titles and abstracts (Fig. 1). Another study[34] was excluded because it was review article, one studies[37] were excluded because it was a case-only study, two studies[38,39] were excluded they were not case-control studies. Ultimately, 21 studies[8–28] were included in this meta-analysis. Their characteristics and genotype distributions are summarized in Table 1.

Twenty studies[8–27] focused on Q223R and eight[8,13,16,21–23,27,28] on K109R. The distribution of genotypes in controls was consistent with the Hardy-Weinberg equilibrium in all but five studies.[12,18,21,22,25] The mean Newcastle–Ottawa score for the 12 studies was 6.60 (range, 5-8). Thus the overall quality of the included studies was adequate.

3.2. Quantitative data synthesis

3.2.1. Q223R and BC risk

Meta-analysis of data from 6238 cases and 7105 controls in 20 studies[8–27] did not indicate a significant association between Q223R polymorphism and BC risk (Table 2): allelic model, OR = 0.89, 95% CI = 0.77-1.04, $p = 0.13$; recessive model, OR = 0.99, 95% CI = 0.75-1.08, $p = 0.26$; dominant model, OR = 1.15, 95% CI = 0.89-1.48, $p = 0.29$; homozygous model, OR = 0.84, 95% CI = 0.62-1.13, $p = 0.25$; heterozygous model, OR = 0.90, 95% CI = 0.70-1.15, $p = 0.38$.

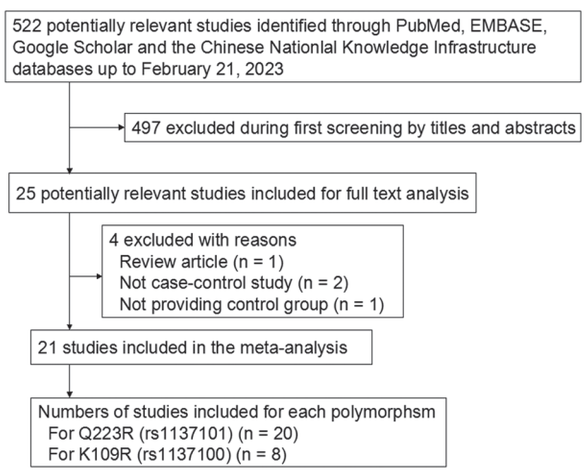

Fig. 1 Flowchart showing search strategies, selection criteria, and included studies.

Table 1

Characteristics of studies included in the meta-analysis

First author	Year	Ethnicity	Country	Genotyp-ingmethod	*p* for HWE	Control source	Sample size (Cases/ Controls)	No. of cases (n)			No. of controls			NOS score	Matched parameters
LEPR Q223R (rs1137101)								AA	AG	GG	AA	AG	GG		
Woo et al[8]	2006	Asian	Korea	PCR	0.513	PB	45/45	0	12	33	0	8	37	8	Age, BMI
Snoussi et al[9]	2006	African	Tunisia	PCR	0.162	PB	308/222	65	145	98	30	90	102	6	Age, Family history,
Gallicchio et al[10]	2007	Caucasian	America	TaqMan	0.261	HB	53/872	14	24	15	278	443	151	7	Age, BMI
Okobia et al[11]	2008	African	Nigerian	PCR-RFLP	0.704	HB	209/209	56	107	46	46	107	56	6	Age
Han et al[12]	2008	Asian	China	PCR-RFLP	< 0.001	PB	240/500	33	41	166	12	78	410	7	Age, regional occupation, race
Ulybina et al[13]	2008	Caucasian	Russia	PCR	0.993	HB	110/105	24	69	17	36	51	18	6	Age
Teras et al[14]	2009	Caucasian	America	PCR	0.672	PB	641/650	128	332	181	125	314	211	7	Age, race (White, Black, other), and blood draw date
Cleveland et al[15]	2009	Caucasian	America	PCR	0.333	PB	1049/1098	173	521	355	187	551	360	7	Age, BMI, menopausal status
Nyante et al[16]	2011	Caucasian	America	PCR	0.563	PB	1972/1775	494	952	526	416	874	485	8	Age,r ace
Kim et al[17]	2012	Asian	Korea	PCR	0.975	PB	390/447	8	88	294	6	91	350	7	Age, BMI, age at menarche, age at menopause
Anuradha et al[18]	2012	Asian	India	PCR-RFLP	< 0.001	PB	194/186	17	92	85	8	110	68	7	Age
Mohammadzadeh et al[19]	2014	Asian	Iran	PCR-RFLP	0.693	PB	100/100	19	56	25	6	40	54	8	Age, family history
Mahmoudi et al[20]	2015	Asian	Iran	PCR-RFLP	0.730	HB	45/41	1	25	19	6	18	17	5	Undetermined
Khandouzi et al[21]	2016	Asian	India	PCR-RFLP	0.001	HB	205/205	5	54	146	9	37	159	5	Undetermined
Rodrigoet al[22]	2017	Asian	Sri Lanka	PCR	< 0.001	PB	80/80	65	9	6	60	6	14	8	Age, BMI, menopausal status
Huerta et al[23]	2017	Caucasian	Mexico	PCR	0.074	PB	142/132	58	52	32	32	76	24	6	Age, weight, height, BMI, familial history of cancer
El-Hussiny et al[24]	2017	African	Egypt	PCR-RFLP	0.146	PB	48/48	9	15	24	2	24	22	8	Age, BMI, familial history of cancer
Fard et al[25]	2020	Asian	Iran	PCR-RFLP	< 0.001	PB	158/158	21	10	127	42	8	108	7	Age, BMI
Tayel et al[26]	2020	Caucasian	Egypt	PCR	0.447	PB	40/30	6	13	21	13	12	5	8	Age, menstrual state
Hołysz et al[27]	2021	Caucasian	Poland	PCR-RFLP	0.536	PB	209/202	33	110	66	45	96	61	6	Age, weight, height, BMI
LEPR K109R (rs1137100)								AA	AG	GG	AA	AG	GG		
Woo et al[8]	2006	Asian	Korea	PCR	0.217	PB	44/45	0	13	31	0	14	31	8	Age, BMI
Liu et al[28]	2007	Asian	Taiwan	PCR-RFLP	0.006	PB	47/41	2	13	32	4	7	30	6	Age
Ulybina et al[13]	2008	Caucasian	Russia	PCR	0.383	PB	110/105	58	45	7	42	52	11	6	Age
Nyante et al[16]	2011	Caucasian	America	PCR	0.476	PB	1970/1776	122	673	1175	79	615	1082	8	Age, race
Khandouzi et al[21]	2016	Asian	India	PCR-RFLP	0.203	HB	205/205	9	59	137	13	64	128	5	Undetermined
Rodrigo et al[22]	2017	Asian	Sri Lanka	PCR	0.293	PB	80/80	34	22	24	59	18	3	8	Age, BMI, menopausal status
Huerta et al[23]	2017	Caucasian	Mexico	PCR	0.128	PB	142/132	94	42	6	60	52	20	6	Age, weight, height, BMI, familial history of cancer
Hołysz et al[27]	2021	Caucasian	Poland	PCR-RFLP	0.062	PB	209/202	19	92	98	25	75	102	6	Age, weight, height, BMI

BMI = body mass index; HB = hospital-based source of control; HWE = Hardy-Weinberg equilibrium; HRM = high-resolution melting; LEPR = leptin receptor; NOS = Newcastle–Ottawa Scale; PB = population-based source of control; PCR = polymerase chain reaction; RFLP = restriction fragment length polymorphism.

Next, meta-analysis of data from 1457 Asian cases and 1762 Asian controls in nine studies[8,12,17–22,25] also showed no evidence of a significant association between the Q223R polymorphism and BC risk (Table 2): allelic model, OR = 0.79, 95% CI = 0.54-1.16, p = 0.24; recessive model, OR = 0.75, 95% CI = 0.51-1.09, p = 0.13; dominant model, OR = 1.33, 95% CI = 0.58-3.03, p = 0.50; homozygous model, OR = 0.66, 95% CI = 0.26-1.63, p = 0.36; heterozygous model, OR = 0.92, 95% CI = 0.42-2.01, p = 0.83.

Similarly, no evidence of an association between the Q223R polymorphism and BC risk was observed in the meta-analysis of data from 4216 Caucasian cases and 4864 Caucasian controls in eight studies[10,13–16,23,26,27] (Table 2): allelic model, OR = 1.07, 95% CI = 0.93-1.23, p = 0.36; recessive model, OR = 1.07, 95% CI = 0.89-1.30, p = 0.46; dominant model, OR = 0.92, 95% CI = 0.72-1.17, p = 0.50; homozygous model, OR = 1.13, 95% CI = 0.87-1.46, p = 0.35; heterozygous model, OR = 1.04, 95% CI = 0.81-1.33, p = 0.76.

Last, meta-analysis of data from 565 African cases and 479 African controls in three studies[9,11,24] indicated a significant association between Q223R polymorphism and BC risk in African population (Table 2 and Fig. 2): allelic model, OR = 0.72, 95% CI = 0.60-0.86, p < 0.001; recessive model, OR = 0.67, 95% CI = 0.52-0.87, p = 0.003; dominant model, OR = 1.58, 95% CI = 1.15-2.17, p = 0.004; homozygous model, OR = 0.51, 95% CI = 0.36-0.78, p < 0.001.

3.2.2. K109R and BC risk

Meta-analysis of data from 2807 cases and 2586 controls in eight studies[8,13,16,21–23,27,28] did not indicate a significant association between the Q223R polymorphism and BC risk (Table 3): allelic model, OR = 1.03, 95% CI = 0.73-1.44, p = 0.87; recessive model, OR = 0.96, 95% CI = 0.66-1.38, p = 0.82; dominant model, OR = 0.93, 95% CI = 0.54-1.61, p = 0.80; homozygous model, OR = 1.09, 95% CI = 0.52-2.27, p = 0.83; heterozygous model, OR = 0.99, 95% CI = 0.65-1.51, p = 0.96.

Next, meta-analysis of data from 376 Asian cases and 371 Asian controls in four studies[8,21,22,28] indicated a significant association between K109R polymorphism and BC risk (Table 3 and Fig. 2): dominant model, OR = 0.24, 95% CI = 0.07-0.84, p = 0.03; heterozygous model, OR = 1.87, 95% CI = 1.07-3.26, p = 0.03.

Table 2

Overall meta-analysis of the association between LEPR Q223R (rs1137101) polymorphism and breast cancer risk

Genetic model	OR [95 % CI]	Z (*p* value)	Heterogeneity of study design			Analysis model
			$\chi 2$	df (*p* value)	I^2 (%)	
Q223R polymorphism in total population from 20 case-control studies[8–27] (6238 cases and 7105 controls)						
Allelic model (G-allele vs. A-allele)	0.89 [0.77, 1.04]	1.50 (0.13)	108.55	19 (<0.001)	82	Random
Recessive model (GG vs AG + AA)	0.99 [0.75, 1.08]	1.14 (0.26)	71.42	19 (<0.001)	73	Random
Dominant model (AA vs AG + GG)	1.15 [0.89, 1.48]	1.06 (0.29)	84.70	18 (<0.001)	79	Random
Homozygous model (GG vs AA)	0.84 [0.62, 1.13]	1.14 (0.25)	89.36	18 (<0.001)	80	Random
Heterozygous model (AG vs AA)	0.90 [0.70, 1.15]	0.87 (0.38)	62.31	18 (<0.001)	71	Random
Q223R polymorphism in Asian population from 9 case-control studies[8,12,17–22,25] (1457 cases and 1762 controls)						
Allelic model (G-allele vs. A-allele)	0.79 [0.54, 1.16]	1.19 (0.24)	63.69	8 (<0.001)	87	Random
Recessive model (GG vs AG + AA)	0.75 [0.51, 1.09]	1.50 (0.13)	38.56	8 (<0.001)	79	Random
Dominant model (AA vs AG + GG)	1.33 [0.58, 3.03]	0.67 (0.50)	47.99	7 (<0.001)	85	Random
Homozygous model (GG vs AA)	0.66 [0.26, 1.63]	0.91 (0.36)	52.65	7 (<0.001)	87	Random
Heterozygous model (AG vs AA)	0.92 [0.42, 2.01]	0.22 (0.83)	30.33	7 (<0.001)	77	Random
Q223R polymorphism in Caucasian population from 8 case-control studies[10,13–16,23,26,27] (4264 cases and 4912 controls)						
Allelic model (G-allele vs A-allele)	1.07 [0.93, 1.23]	0.91 (0.36)	23.91	7 (0.001)	71	Random
Recessive model (GG vs AG + AA)	1.07 [0.89, 1.30]	0.74 (0.46)	16.75	7 (0.02)	58	Random
Dominant model (AA vs AG + GG)	0.92 [0.72, 1.17]	0.67 (0.50)	23.92	7 (0.001)	71	Random
Homozygous model (GG vs AA)	1.13 [0.87, 1.46]	0.93 (0.35)	18.70	7 (0.009)	63	Random
Heterozygous model (AG vs AA)	1.04 [0.81, 1.33]	0.31 (0.76)	22.26	7 (0.002)	69	Random
Q223R polymorphism in African population from 3 case-control studies[9,11,24] (517 cases and 431 controls)						
Allelic model (G-allele vs A-allele)	0.72 [0.60, 0.86]	3.62 (<0.001)	2.06	2 (0.36)	3	Fixed
Recessive model (GG vs AG + AA)	0.67 [0.52, 0.87]	2.97 (0.003)	3.50	2 (0.17)	43	Fixed
Dominant model (AA vs AG + GG)	1.58 [1.15, 2.17]	2.85 (0.004)	3.09	2 (0.21)	35	Fixed
Homozygous model (GG vs AA)	0.51 [0.36, 0.74]	3.60 (<0.001)	2.06	2 (0.36)	3	Fixed
Heterozygous model (AG vs AA)	0.72 [0.51, 1.00]	1.96 (0.05)	4.08	2 (0.13)	51	Fixed

95% CI = 95% confidence interval; LEPR = leptin receptor; OR = odds ratio.

Last, meta-analysis of data from 2431 Caucasian cases and 2215 Caucasian controls in four studies[13,16,23,27] did not indicate a significant association between the Q223R polymorphism and BC risk was observed (Table 3): allelic model, OR = 0.75, 95% CI = 0.55-1.02, p = 0.07; recessive, OR = 0.73, 95% CI = 0.49-1.09, p = 0.12; dominant model, OR = 1.45, 95% CI = 0.97-2.18, p = 0.07; homozygous model, OR = 0.59, 95% CI = 0.31-1.11, p = 0.10; heterozygous model, OR = 0.75, 95% CI = 0.51-1.10, p = 0.14.

3.2.3. Sensitivity analysis

To assess the reliability of the outcomes in the meta-analysis, we repeated the meta-analysis after excluding five studies in which the p value associated with the Hardy-Weinberg equilibrium was less than 0.05[12,18,21,22,25,28] one by one.

Any of the individual study[12,18,21,22,25,28] deleted did not materially influence the pooled ORs and CIs under all genetic models for either Q223R or K109R polymorphisms (data not shown), indicating that our findings were stable and reliable.

3.2.4. Publication bias

No obvious asymmetry was observed in allelic model of Q223R polymorphism in Begg's funnel plots (p = 0.347, Fig. 3A) and Egger's tests (t = 0.60, p = 0.556, Fig. 3B). Similarly, no obvious asymmetry was observed in allelic model of K109R polymorphism in Begg's funnel plots (p = 0.174, Fig. 3C) and Egger's tests (t = 0.87, p = 0.419, Fig. 3D). These findings indicated no potential publication bias.

4. DISCUSSION

Polymorphisms in LEPR gene and their potential associations with cancer risk have been explored.[40,41] In recent years, increasing evidence from meta-analyses have indicated a significant association between LEPR polymorphisms and BC risk. Meta-analysis by Wang et al[32] with nine case-control studies suggested that Q223R and K109R polymorphisms were significantly correlated with BC risk and the A allele of Q223R variant and the G allele of K109R variant were low-penetrant risk factors for developing BC. Meta-analysis by Wang et al[29] with 11 case-control studies also showed A allele of Q233R variant was low-penetrant risk factor for developing BC. Meta-analysis by Shi et al[33] with five case-control studies indicated that the K109R genetic polymorphism did not significantly affect the risk of cancer, but in the stratified analysis, A allele of K109R were found protective against under additive genetic model. Meta-analysis by Liu and Liu[31] with nine case-control studies showed that the association between Q223R and BC risk was only statistically significant in East Asians, but not in Caucasians or Africans. Similarly, meta-analysis by Luan et al[34] with 13 case-control studies

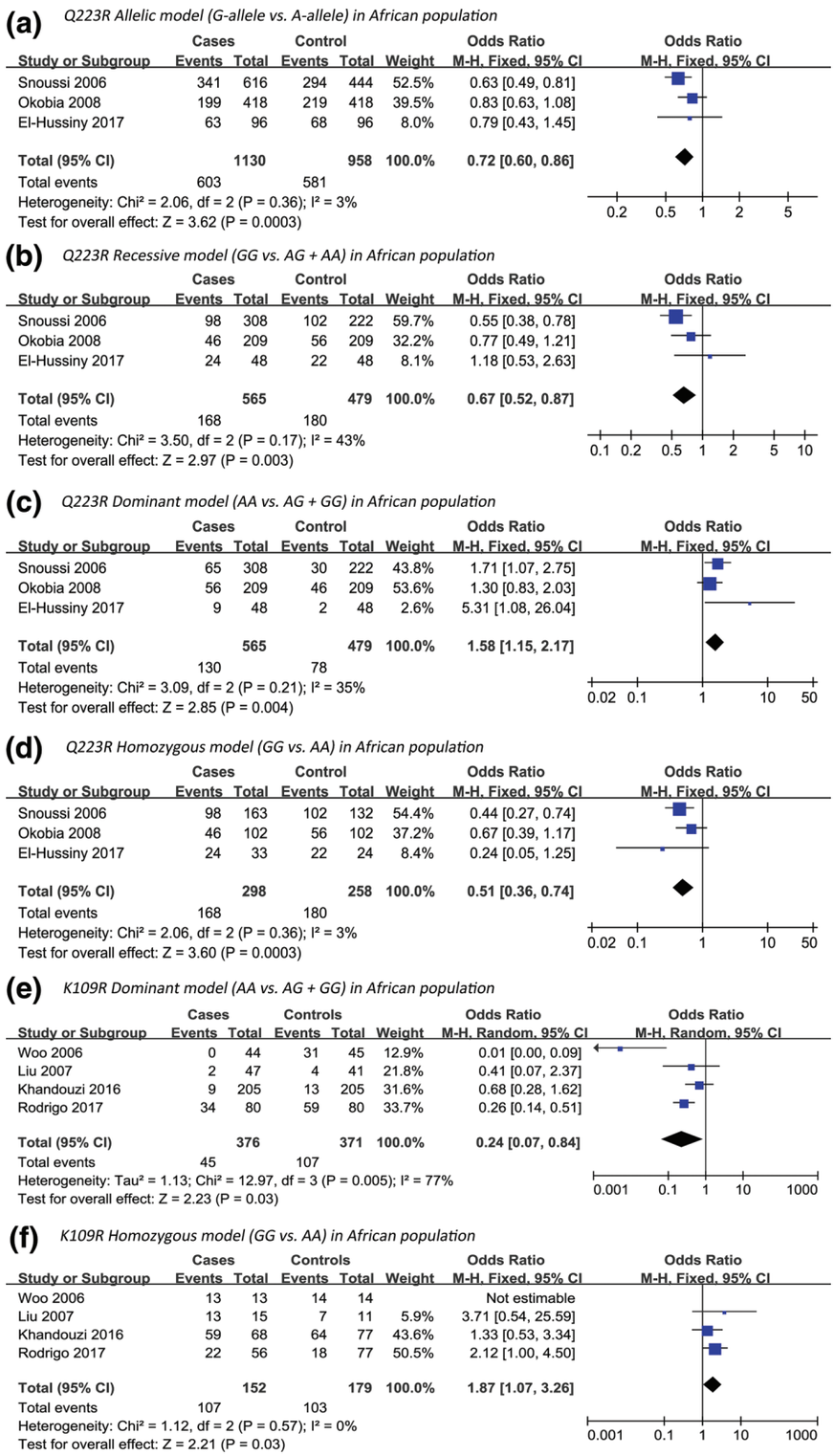

Fig. 2 Forest plot showing the relationship between LEPR Q223R (rs1137101) and breast cancer risk according to different genetic models in African population: (A) allelic model (G-allele vs A-allele), (B) recessive model (GG vs AG + AA), (C) dominant model (AA vs AG + GG), (D) homozygous model (GG vs AA) Forest plot showing the relationship between K109R (rs1137100) and breast cancer risk according to different genetic models in African population: (E) dominant model (AA vs AG + GG), (E) heterozygous model (AG vs AA). CI = confidence interval; df = degree of freedom; M-H = Mantel-Haenszel.

showed that Q223R polymorphism could decrease BC risk in Asians but not in overall individuals and Caucasians. Different from their results,[29–34] the data from the current meta-analysis with 20 case-control studies indicated that G-allele and GG genotype but not A allele of Q223R may protect against BC only in Africans. On the contrary, A-allele and AA genotype of Q223R

Table 3

Overall meta-analysis of the association between LEPR K109R (rs1137100) polymorphism and breast cancer risk

Genetic model	OR [95 % CI]	Z (*p* value)	Heterogeneity of study design			Analysis model
			$\chi 2$	df (*p* value)	I^2 (%)	
K109R polymorphism in total population from 8 case-control studies[8,13,16,21–23,27,28] (2807 cases and 2586 controls)						
Allelic model (G-allele vs A-allele)	1.03 [0.73, 1.44]	0.16 (0.87)	51.93	7 (<0.001)	87	Random
Recessive model (GG vs AG + AA)	0.96 [0.66, 1.38]	0.22 (0.82)	25.41	7 (<0.001)	72	Random
Dominant model (AA vs AG + GG)	0.93 [0.54, 1.61]	0.25 (0.80)	35.69	6 (<0.001)	83	Random
Homozygous model (GG vs AA)	1.09 [0.52, 2.27]	0.22 (0.83)	34.90	6 (<0.001)	83	Random
Heterozygous model (AG vs AA)	0.99 [0.65, 1.51]	0.05 (0.96)	18.30	6 (0.006)	67	Random
K109R polymorphism in Asian population from 4 case-control studies[8,21,22,28] (376 cases and 371 controls)						
Allelic model (G-allele vs A-allele)	1.59 [0.77, 3.26]	1.26 (0.21)	18.61	3 (<0.001)	84	Random
Recessive model (GG vs AG + AA)	1.63 [0.70, 3.82]	1.13 (0.26)	12.98	3 (0.005)	77	Random
Dominant model (AA vs AG + GG)	0.24 [0.07, 0.84]	2.23 (0.03)	12.97	3 (0.005)	77	Fixed
Homozygous model (GG vs AA)	4.31 [0.89, 20.78]	1.82 (0.07)	7.94	2 (0.02)	75	Random
Heterozygous model (AG vs AA)	1.87 [1.07, 3.26]	2.21 (0.03)	1.12	2 (0.57)	0	Fixed
K109R polymorphism in Caucasian population from 4 case-control studies[13,16,23,27] (2431 cases and 2215 controls)						
Allelic model (G-allele vs A-allele)	0.75 [0.55, 1.02]	1.83 (0.07)	14.99	3 (0.002)	80	Random
Recessive model (GG vs AG + AA)	0.73 [0.49, 1.09]	1.54 (0.12)	8.54	3 (0.04)	65	Random
Dominant model (AA vs AG + GG)	1.45 [0.97, 2.18]	1.80 (0.07)	8.98	3 (0.03)	67	Random
Homozygous model (GG vs AA)	0.59 [0.31, 1.11]	1.65 (0.10)	10.61	3 (0.01)	72	Random
Heterozygous model (AG vs AA)	0.75 [0.51, 1.10]	1.48 (0.14)	7.41	3 (0.06)	60	Random

95% CI = 95% confidence interval; LEPR = leptin receptor; OR = odds ratio.

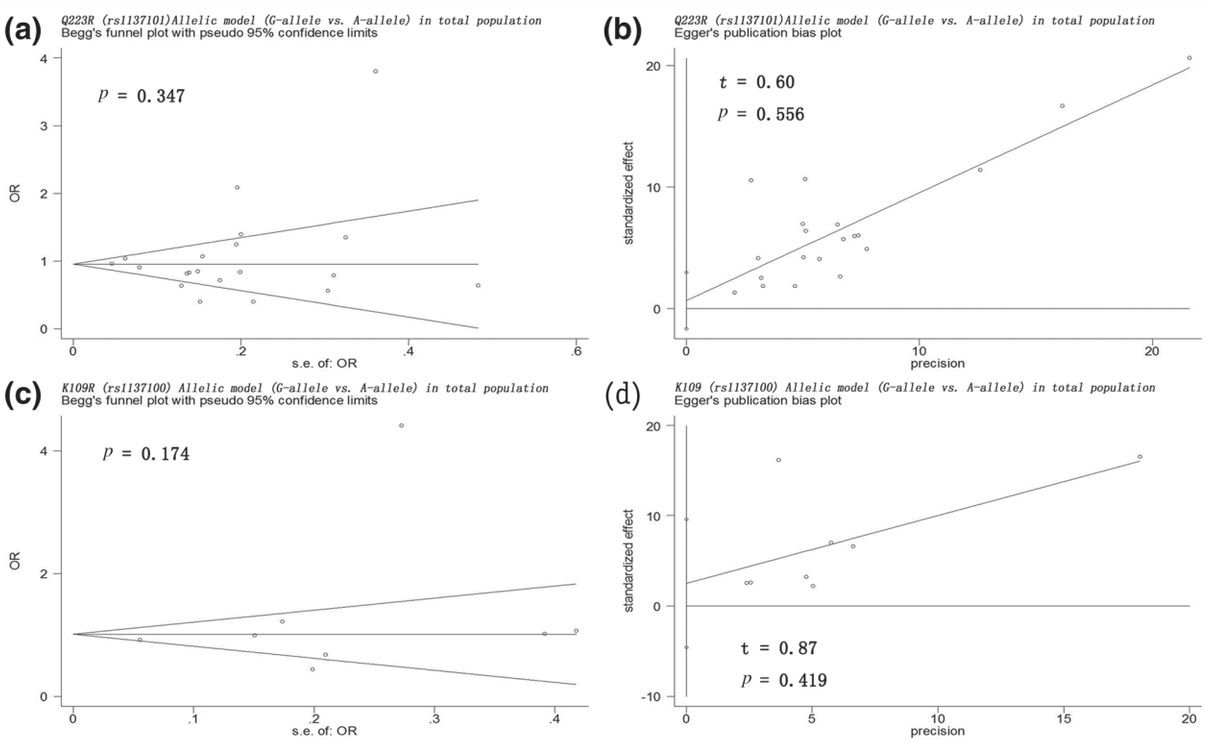

Fig. 3 Begg's funnel plot (A) and Egger's test (B) to assess publication bias risk in analysis of the association between LEPR Q223R polymorphism and breast cancer risk according to allelic model. Begg's funnel plot (C) and Egger's test (D) to assess publication bias risk in analysis of the association between LEPR K109R polymorphism and breast cancer risk according to allelic model.

may confer increasing BC risk in Africans. It is possible that larger sample size may lead to the identification of statistically significant correlation. The current study contains more case-control studies with larger sample, making our results should be more reliable. It is worth mentioning that the results of a meta-analysis by Sayad et al[42] with only 14 case-control studies for Q223R published in 2021 were similar to ours. Our data also suggested that GG genotype of K109R in Asian population may also protect against BC, while AG genotype of K109R in Asian population may confer elevated susceptibility of BC.

Significant results were obtained and we really hope they would provide a reference for future studies, nonetheless, several limitations that may affect interpretation of the results still existed in this work. First, the significant results on Q223R were only got from two case-control studies in African population. Given the limited sample size, more multicenter studies with larger sample sizes are necessary to clarify the relationships. Indeed, neither in total nor in Asian and Caucasian population significant association between Q223R polymorphism and BC risk was observed. Second, the *p* value for HWE was less than 0.05 in five studies of Q223R polymorphism[12,18,21,22,25] and one study of K109R polymorphism,[28] suggesting that these populations may not be representative of the broader target population. Nevertheless, we decided to retain these studies in the meta-analysis because the corresponding pooled ORs were not substantially altered in any of the five models after excluding one at a time. Third, confounding factors, such as menopausal, menstruation status, tumor status, BMI, or age may affect the results. However, not all studies reported these baseline data or aggregated them in different ways, resulting in a failure to include them in the meta-analysis. Last, methods which were used to test polymorphisms were not uniform and they varied in sensitivity and specificity, leading to a reduction of the robustness in this meta-analysis.

In conclusion, this study performed an extensive assessment based on a larger sample size than the previous pooled analysis and suggested that LEPR Q223R polymorphism may be significantly associated with BC risk in African population. And LEPR K109R polymorphism may be significantly associated with BC risk in Asian population.

REFERENCES

1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 2021;**71**:209–49.
2. Fahad Ullah M. Breast cancer: current perspectives on the disease status. *Adv Exp Med Biol* 2019;**1152**:51–64.
3. Carpenter CL, Ross RK, Paganini-Hill A, Bernstein L. Effect of family history, obesity and exercise on breast cancer risk among postmenopausal women. *Int J Cancer* 2003;**106**:96–102.
4. Lorincz AM, Sukumar S. Molecular links between obesity and breast cancer. *Endocr Relat Cancer* 2006;**13**:279–92.
5. Kentish SJ, Vincent AD, Kennaway DJ, Wittert GA, Page AJ. High-fat diet-induced obesity ablates gastric vagal afferent circadian rhythms. *J Neurosci* 2016;**36**:3199–207.
6. Wang D, Xu C, Wang T, Li H, Li Y, Ren J, et al. Discovery and functional characterization of leptin and its receptors in Japanese quail (*Coturnix japonica*). *Gen Comp Endocr* 2016;**225**:1–12.
7. Thompson DB, Ravussin E, Bennett PH, Bogardus C. Structure and sequence variation at the human leptin receptor gene in lean and obese Pima Indians. *Hum Mol Genet* 1997;**6**:675–9.
8. Woo HY, Park H, Ki CS, Park YL, Bae WG, et al. Relationships among serum leptin, leptin receptor gene polymorphisms, and breast cancer in Korea. *Cancer Lett* 2006;**237**:137–42.
9. Snoussi K, Strosberg AD, Bouaouina N, Ahmed SB, Helal AN, Chouchane L. Leptin and leptin receptor polymorphisms are associated with increased risk and poor prognosis of breast carcinoma. *BMC Cancer* 2006;**6**:1–10.
10. Gallicchio L, McSorley MA, Newschaffer CJ, Huang HY, Thuita LW, Hoffman SC, et al. Body mass, polymorphisms in obesity-related genes, and the risk of developing breast cancer among women with benign breast disease. *Cancer Detect Prev* 2007;**31**:95–101.
11. Okobia MN, Bunker CH, Garte SJ, Zmuda JM, Ezeome ER, Anyanwu SN, et al. Leptin receptor Gln223Arg polymorphism and breast cancer risk in Nigerian women: a case control study. *BMC Cancer* 2008;**8**:338–8.
12. Han CZ, Du LL, Jing JX, Zhao XW, Tian FG, Shi J, et al. Associations among lipids, leptin, and leptin receptor gene Gin223Arg polymorphisms and breast cancer in China. *Biol Trace Elem Res* 2008;**126**:38–48.
13. Ulybina YM, Imyanitov EN, Vasilyev DA, Berstein LM. Polymorphic markers associated with genes responsible for lipid and carbohydrate metabolism disorders and insulin resistance in cancer patients. *Mol Biol* 2008;**42**:843–51.
14. Teras LR, Goodman M, Patel AV, Bouzyk M, Tang W, Diver WR, et al. No association between polymorphisms in LEP, LEPR, ADIPOQ, ADIPOR1, or ADIPOR2 and postmenopausal breast cancer risk. *CEBP* 2009;**18**:2553.
15. Cleveland RJ, Gammon MD, Long CM, Gaudet MM, Eng SM, Teitelbaum SL, et al. Common genetic variations in the LEP and LEPR genes, obesity and breast cancer incidence and survival. *Breast Cancer Res Tr* 2009;**120**:745–52.
16. Nyante SJ, Gammon MD, Kaufman JS, Bensen JT, Lin DY, Barnholtz-Sloan JS, et al. Common genetic variation in adiponectin, leptin, and leptin receptor and association with breast cancer subtypes. *Breast Cancer Res Tr* 2011;**129**:593–606.
17. Kim KZ, Shin A, Lee YS, Kim SY, Kim Y, Lee ES, et al. Polymorphisms in adiposity-related genes are associated with age at menarche and menopause in breast cancer patients and healthy women. *Hum Reprod* 2012;**27**:2193–200.
18. Anuradha C, Ranjit PM, Surekha D, Raghunadharao D, Rani NS, Vishnupriya S. Association of leptin receptor (LEPR) Q223R polymorphism with breast cancer. *GJMR* 2012;**12**:21–9.
19. Mohammadzadeh G, Ghaffari MA, Bafandeh A, Hosseini SM. Effect of leptin receptor Q223R polymorphism on breast cancer risk. *Iran J Basic Med Sci* 2014;**17**:588–94.
20. Mahmoudi R, Noori Alavicheh B, Nazer Mozaffari MA, Fararouei M, Nikseresht M, et al. Polymorphisms of leptin (-2548 G/A) and leptin receptor (Q223R) genes in Iranian women with breast cancer. *Int J Genomics* 2015;**2015**:1–6.
21. Khandouzi M, Deka M, Baruah MN, Rozati R, Kordafshari M, Kashyap P, et al. Genetic variation in adiponectin, leptin and leptin receptor with reference to risk of breast cancer in northeast obese women in India. *Biosci Biotech Res C* 2016;**9**:163–70.
22. Rodrigo C, Tennekoon KH, Karunanayake EH, De Silva K, Amarasinghe I, Wijayasiri A, et al. Circulating leptin, soluble leptin receptor, free leptin index, visfatin and selected leptin and leptin receptor gene polymorphisms in sporadic breast cancer. *Endocr J* 2017;**64**:393–401.
23. Huerta L, Cabrera C, Montes R, Cuellar H, López J, Covarrubias S, et al. Association between leptin and leptin receptor gene polymorphisms and breast cancer risk in premenopausal and postmenopausal Mexican women. *Cancer Res Front* 2017;**3**:56–63.
24. El-Hussiny MAB, Atwa MA, Rashad WE, Shaheen DA, Elkady NM. Leptin receptor Q223R polymorphism in Egyptian female patients with breast cancer. *Wspolczesna Onkol* 2017;**21**:42–7.
25. Fard ZT. Evaluation of leptin receptor Q223R (rs1137101) polymorphism based on histopathological and body mass index characteristics in Iranian females with breast cancer. *Int J Cancer Manag* 2020;**13**:e92731.
26. Tayel SI, Alhanafy AM, Ahmed SM, Eltorgoman AA, Elsayed IE, et al. Biochemical study on modifying role of variants of leptin gene and its receptor on serum leptin levels in breast cancer. *Mol Biol Rep* 2020;**47**:3807–20.
27. Hołysz H, Paszel-Jaworska A, Romaniuk-Drapała A, Grodecka-Gazdecka S, Rubiś B. LEP (– 2548G> A LEP) and LEPR (223Gln> Arg, 109Lys> Arg) polymorphisms as breast cancer risk factors in the Polish female population. *Mol Biol Rep* 2021;**48**:3237–44.
28. Liu CL, Chang YC, Cheng SP, Chern SR, Yang TL, Lee JJ, et al. The roles of serum leptin concentration and polymorphism in leptin receptor gene at codon 109 in breast cancer. *Oncology (Huntingt)* 2007;**72**:75–81.
29. Wang Y, Yang H, Gao H, Wang H. The association between LEPR Q223R polymorphisms and breast cancer risk. *Breast Cancer Res Tr* 2015;**151**:1–6.

30. He B, Pan Y, Zhang Y, Xu YQ, Wang SK. Effect of LEPR Gln223Arg polymorphism on breast cancer risk in different ethnic populations: a meta-analysis. *Mol Biol Rep* 2012;**39**:3117–22.
31. Liu C, Liu L. Polymorphisms in three obesity-related genes (LEP, LEPR, and PON1) and breast cancer risk: a meta-analysis. *Tumor Biol* 2011;**32**:1233–40.
32. Wang LQ, Shen W, Xu L, Chen MB, Gong T, Lu PH, et al. The association between polymorphisms in the leptin receptor gene and risk of breast cancer: a systematic review and pooled analysis. *Breast Cancer Res Tr* 2012;**136**:231–9.
33. Shi H, Shu H, Huang C, Gong J, Yang Y, Liu R, et al. Association of LEPR K109R polymorphisms with cancer risk: a systematic review and pooled analysis. *J BUON* 2014;**19**:847–54.
34. Luan H, Zhang H, Li Y, Wang P, Cao L, Ma H, et al. Association of two obesity-related gene polymorphisms LEPG2548A rs7799039 and LEPRQ223R rs1137101 with the risk of breast cancer. *Oncotarget* 2017;**8**:59333–44.
35. Wells GA, Shea B, O'Connell D, Peterson J, Welch V, Losos M, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. 2019 Available at http://www.ohri.ca/programs/clinical_epidemiology/oxford.htm
36. Ownby RL, Crocco E, Acevedo A, John V, Loewenstein D. Depression and risk for Alzheimer disease: systematic review, meta-analysis. *Arch Gen Psychiat* 2006;**63**:530–8.
37. Méndez-Hernández A, Gallegos-Arreola MP, Moreno-Macías H, Fematt JE, Pérez-Morales R. LEP rs7799039, LEPR rs1137101, and ADIPOQ rs2241766 and 1501299 polymorphisms are associated with obesity and chemotherapy response in Mexican women with breast cancer. *Clin Breast Cancer* 2017;**17**:453–62.
38. Boothby-Shoemaker W, Benham V, Paithankar S, Shankar R, Chen B, Bernard JJ. The relationship between leptin, the leptin receptor and FGFR1 in primary human breast tumors. *Cells* 2020;**9**:2224.
39. Gu F, Kraft P, Rice M, Michels KB. Leptin and leptin receptor genes in relation to premenopausal breast cancer incidence and grade in Caucasian women. *Breast Cancer Res Tr* 2012;**131**:17–25.
40. Liu P, Shi H, Liu R, Yang Y, Yang Y, Huang C, et al. Lack of association between LEPR Q223R polymorphisms and cancer susceptibility: evidence from a meta-analysis. *J BUON* 2014;**19**:855–62.
41. Rong G, Tang W, Wang Y, Qiu H, Chen S. Investigation of leptin receptor rs1137101 G> A polymorphism with cancer risk: evidence from 35936 subjects. *Bioscience Rep* 2019;**39**:BSR20182240.
42. Sayad S, Dastgheib SA, Farbod M, Farbod M, Asadian F, Karimi-Zarchi M, et al. Association of PON1, LEP and LEPR polymorphisms with susceptibility to breast cancer: a meta-analysis. *Asian Pac J Cancer P* 2021;**22**:2323–34.