The association between *LEPR* Q223R polymorphisms and breast cancer risk

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Abstract Recently, we have read with great interest the article entitled “The association between polymorphisms in the leptin receptor (*LEPR*) gene and risk of breast cancer: a systematic review and pooled analysis” published online by Wang et al. (Breast Cancer Res Treat 136:231–239, 2012). This article suggests that the A allele of *LEPR* gene rs1137101 variant was low-penetrant risk factor for developing breast cancer. The result is encouraging. Nevertheless, several key issues are worth noticing.

Keywords *LEPR* · Polymorphism · Breast cancer · Risk · Meta-analysis

The human leptin receptor (*LEPR*) gene was mapped to 1p31 and has one long isoform and three short isoforms [1].

Several single nucleotide polymorphisms (SNPs) have been identified in the human *LEPR* gene, and the potential associations of these SNPs with breast cancer risk have been proposed [2–4]. Among them, rs1137101 (668 A > G, Gln223Arg, Q223R) in the human *LEPR* gene was one of the most studied SNPs. However, the results from published studies [5–15] remained conflicting rather than conclusive.

Recently, we have read with great interest the article entitled “The association between polymorphisms in the *LEPR* gene and risk of breast cancer: a systematic review and pooled analysis” published online in Breast Cancer Res Treat 136:231–239, 2012 [2]. Wang et al. performed a meta-analysis to investigate the association between the *LEPR* Q223R polymorphisms and breast cancer risk on the basis of 9 case–control studies with 4644 cases and 5485 controls. The authors found that elevated breast cancer risk was associated with *LEPR* rs1137101 polymorphism when all studies were pooled in the meta-analysis [allele contrast model: odds ratio (OR) = 0.71, 95 % confidence interval (95 % CI) = 0.551–0.997]. In the stratified analysis by ethnicity, significantly increased risks were also found among Asians for allele contrast model (OR = 0.414, 95 % CI 0.312–0.550) and dominant model (OR = 0.537, 95 % CI 0.370–0.781); for Africans, significantly increased risks were also found for allele contrast model (OR = 0.716, 95 % CI 0.595–0.861), homozygote co-dominant (OR = 0.537, 95 % CI 0.370–0.781) and dominant model (OR = 1.595, 95 % CI 1.207–2.108). It is an interesting study.

Nevertheless, careful examinations of the data provided by Wang et al. [2] (shown in Table 2 in their original article) reveal four key issues that are worth paying attention. First, the data reported by Wang et al.

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[2] for the study of Snoussi et al. [5] did not seem in accord with the data provided by Snoussi et al. [5] in their original publication. The numbers reported by Snoussi et al. for AA and GG are 98 and 65 in cases and 102 and 30 in controls, respectively [5]. Interestingly enough, after carefully examining the data reported by Wang et al., the numbers are 65 and 98 in cases, and 30 and 90 in controls, respectively [2]. Second, the data reported by Wang et al. [2] for the study of Gallicchio et al. [7] did not seem in line with the data provided by Gallicchio et al. [7] in their original publication. The numbers reported by Gallicchio et al. for AA and GG are 14 and 15 in cases, and 278 and 151 in controls, respectively [7]. Interestingly enough, after carefully examining the data reported by Wang et al., the numbers are 15 and 14 in cases, and 151 and 278 in controls, respectively [2]. Third, the data reported by Wang et al. [2] for the study of Teras et al. [11] did not seem in accord with the data provided by Teras et al. [11] in their original publication. The numbers reported by Teras et al. for GG are 181 in cases and 211 in controls, respectively [11]. Interestingly enough, after carefully examining the data reported by Wang et al., the numbers are 128 in cases and 125 in controls, respectively [2]. Fourth, the data reported by Wang et al. [2] for the study of Okobia et al. [8] did not seem in line with the data provided by Okobia et al. [8] in their original publication. The numbers reported by Okobia et al. for AA and GG are 46 and 56 in cases, and 56 and 46 in controls, respectively [11]. Interestingly enough, after carefully examining the data reported by Wang et al., the numbers are 56 and 46 in cases, and 46 and 56 in controls,

respectively [2]. Therefore, the conclusions by Wang et al. [2] are not entirely credible. In order to clarify the association between *LEPR* Q223R polymorphisms and breast cancer risk comprehensively and objectively, an updated meta-analysis was re-conducted on the basis of a total of 11 studies with 5117 cases and 6023 controls. Further subgroup analysis was also carried out in this study stratified by source of control, ethnicity and Hardy–Weinberg equilibrium (HWE) in controls. In addition, cumulative meta-analysis was performed to investigate the tendency of results by accumulating single study year by year, which could be used to identify whether new relevant studies are needed or not. We hope that our results will provide objective and comprehensive evidence for the association between *LEPR* Q223R polymorphisms and breast cancer risk.

The general information of selected studies in this current meta-analysis is listed in Table 1. The summary odds ratios of the associations between *LEPR* Q223R polymorphisms and breast cancer risk are listed in Table 2. Overall, we did not observe significant associations between *LEPR* Q223R polymorphisms and breast cancer risk under the genetic models of GG versus AA, GA versus AA, GA + GG versus AA and G-allele versus A-allele (OR = 1.04 with 95 % CI 0.87–1.24, OR = 1.08 with 95 % CI 0.91–1.29, OR = 1.08 with 95 % CI 0.86–1.35 and OR = 1.01 with 95 % CI 0.92–1.12, respectively) (Fig. 1a–d). The cumulative meta-analysis accumulated the studies in accordance with the year of publications and the results showed that there were still no significant associations between *LEPR* Q223R polymorphisms and breast cancer risk under the

Table 1 Main characteristics of selected articles included in this meta-analysis

First author	Year	Country	Ethnicity	Source of control	Cases	Controls	<i>P</i> value of HWE
Snoussi [5]	2006	Tunisian	African	Unknown	308	222	0.161890
Woo [6]	2006	Korean	Asian	Hospital-based control	45	45	0.512816
Gallicchio [7]	2007	USA	Caucasian	Population-based control	53	872	0.260877
Okobia [8]	2008	Nigeria	African	Hospital-based control	209	209	0.704077
Han [9]	2008	China	Asian	Hospital-based control	240	500	0.000903
Ulybina [10]	2008	Russian	Caucasian	Hospital-based control	110	105	0.993124
Teras [11]	2009	USA	Caucasian	Population-based control	641	650	0.671541
Cleveland [12]	2010	USA	Caucasian	Population-based control	1049	1098	0.333380
Nyante [13]	2011	USA	Mixed	Population-based control	1972	1775	0.563216
Kim [14]	2012	Korean	Asian	Hospital-based control	390	447	0.975365
Mohammadzadeh [15]	2014	Iran	Asian	Hospital-based control	100	100	0.692835

HWE Hardy–Weinberg equilibrium

Table 2 The summary odds ratio for the association of *LEPR* Q223R polymorphisms with breast cancer risk

Genetic model	Cases/controls	Heterogeneity test		Analysis model	Summary OR (95 % CI)	Hypothesis test		df	Begg's test		Egger's test		
		Q	P			Z	P		Z	P	t	P	
Total													
GG versus AA	2737/3339	53.54	0.000	Random-effects model	1.04 (0.87–1.24)	0.46	0.648	9	0.36	0.721	0.31	0.767	
GA versus AA	3410/3980	37.30	0.000	Random-effects model	1.08 (0.91–1.29)	0.91	0.363	9	0.00	1.000	0.30	0.771	
GA + GG versus AA	5072/5978	57.12	0.000	Random-effects model	1.08 (0.86–1.35)	0.66	0.508	9	0.00	1.000	0.21	0.841	
G versus A	10,234/12,046	75.97	0.000	Random-effects model	1.01 (0.92–1.12)	0.25	0.803	10	0.47	0.640	0.22	0.827	
Stratification by HWE													
Yes													
GG versus AA	2534/2917	20.02	0.010	Random-effects model	1.12 (1.01–1.28)	2.21	0.027	8	0.73	0.466	1.72	0.128	
GA versus AA	3336/3890	18.87	0.016	Random-effects model	1.16 (1.01–1.31)	2.13	0.033	8	0.94	0.348	1.81	0.114	
GA + GG versus AA	4832/5478	25.34	0.001	Random-effects model	1.21 (1.03–1.42)	2.32	0.020	8	0.73	0.466	1.69	0.134	
G versus A	9754/11,046	33.31	0.000	Random-effects model	1.08 (1.00–1.16)	2.02	0.043	9	0.72	0.474	1.24	0.251	
Stratification by ethnicity													
Caucasian													
GG versus AA	907/1366	4.19	0.241	Fixed-effects model	1.02 (0.91–1.14)	0.32	0.748	3	0.34	0.734	1.35	0.310	
GA versus AA	1285/1985	3.95	0.267	Fixed-effects model	1.06 (0.94–1.20)	0.92	0.385	3	1.02	0.308	1.39	0.299	
GA + GG versus AA	1853/2725	4.15	0.245	Fixed-effects model	1.06 (0.93–1.20)	0.82	0.414	3	0.34	0.734	2.11	0.169	
G versus A	3706/5450	5.38	0.146	Fixed-effects model	1.01 (0.96–1.06)	0.30	0.764	3	1.02	0.308	1.38	0.300	
Asian													
GG versus AA	545/838	52.31	0.000	Random-effects model	0.56 (0.10–3.30)	0.64	0.524	2	0.00	1.000	1.43	0.389	
GA versus AA	251/281	28.09	0.000	Random-effects model	0.75 (0.20–2.80)	0.42	0.674	2	0.00	1.000	0.51	0.698	
GA + GG versus AA	730/1047	45.90	0.000	Random-effects model	0.63 (0.11–3.76)	0.50	0.616	2	0.00	1.000	0.33	0.800	
G versus A	1550/2184	63.86	0.000	Random-effects model	0.79 (0.43–1.47)	0.74	0.462	3	0.34	1.000	0.39	0.734	
Stratification by source of control													
Population-based control													
GG versus AA	1886/2213	3.91	0.271	Fixed-effects model	1.03 (0.96–1.10)	0.82	0.412	3	0.34	1.000	0.54	0.642	
GA versus AA	2670/3257	0.07	0.995	Fixed-effects model	1.01 (0.93–1.09)	0.25	0.801	3	1.70	0.089	5.85	0.028	
GA + GG versus AA	3715/4395	0.79	0.851	Fixed-effects model	1.02 (0.94–1.11)	0.52	0.603	3	0.34	0.734	0.71	0.553	
G versus A	7430/8790	4.61	0.203	Fixed-effects model	1.01 (0.98–1.05)	0.72	0.469	3	0.34	1.000	0.47	0.687	
Hospital-based control													
GG versus AA	688/994	46.89	0.000	Random-effects model	0.81 (0.44–1.47)	0.70	0.483	4	0.24	1.000	0.39	0.725	
GA versus AA	497/531	30.27	0.000	Random-effects model	0.99 (0.56–1.77)	0.02	0.981	4	0.73	0.462	0.70	0.535	
GA + GG versus AA	1049/1361	47.39	0.000	Random-effects model	0.90 (0.42–1.91)	0.27	0.786	4	0.73	0.462	0.59	0.594	
G versus A	2188/2812	64.10	0.000	Random-effects model	0.91 (0.67–1.23)	0.61	0.541	5	0.00	1.000	0.34	0.348	

HWE Hardy–Weinberg equilibrium, *OR* odds ratio, 95 % *CI* 95 % confidence interval

genetic models of GG versus AA, GA versus AA, GA + GG versus AA and G-allele versus A-allele, the cumulative ORs were 1.15 with 95 % CI 0.79–1.66, 1.13 with 95 % CI 0.86–1.48, 1.12 with 95 % CI 0.83–1.52, and 1.06 with 95 % CI 0.88–1.29, respectively (Fig. 2a–d). Limiting the analysis to the studies with controls in agreement with HWE, we observed significant associations between *LEPR* Q223R polymorphisms and breast cancer risk (OR = 1.14 with 95 % CI 1.01–1.28 for GG versus AA, OR = 1.16 with 95 % CI 1.01–1.31 for GA versus AA, OR = 1.21 with 95 % CI 1.03–1.42 for GA + GG versus AA, and OR = 1.08 with 95 % CI 1.00–1.16 for G-allele versus A-allele, respectively) (Table 2). In subgroup analysis by source of control, we

did not observe any significant associations between *LEPR* Q223R polymorphisms and breast cancer under the genetic models of GG versus AA, GA versus AA, GA + GG versus AA, and G-allele versus A-allele on the basis of population-based controls and hospital-based controls (Table 2). We did not observe any associations between *LEPR* Q223R polymorphisms and breast cancer risk among the subgroups of Caucasian and Asian when stratified by ethnicity (Table 2).

Begg's test and Egger's test were carried out to check the publication bias of literatures. The shape of the funnel plot did not reveal any evidence of obvious asymmetry among total population (Fig. 3a–d). Moreover, Begg's test and Egger's test also provided

Fig. 1 Forest plots of the odds ratio for *LEPR* Q223R polymorphisms associated with breast cancer risk (**a** GG vs. AA, **b** GA vs. AA, **c** GA + GG vs. AA, **d** G-allele vs. A-allele)

Fig. 2 Forest plots for cumulative meta-analysis of odds ratio for *LEPR* Q223R polymorphisms associated with breast cancer risk (**a** GG vs. AA, **b** GA vs. AA, **c** GA + GG vs. AA, **d** G-allele vs. A-allele)

Fig. 3 Funnel plot analysis to detect publication bias for *LEPR* Q223R polymorphisms associated with breast cancer risk (**a** GG vs. AA, **b** GA vs. AA, **c** GA + GG vs. AA, **d** G-allele vs. A-allele)

Fig. 4 Sensitivity analysis on the association between *LEPR* Q223R polymorphisms and breast cancer risk (G-allele vs. A-allele)

statistical evidence of funnel plot symmetry at the same time. The results did not suggest any evidence of publication bias in this current meta-analysis, except for the analysis of GA versus AA on the basis of population-based controls, since the *P* value is equal to 0.028 in Egger's test (Table 2).

To evaluate the stability of the results of this meta-analysis, a sensitivity analysis was performed by deleting one study at a time. The deletion of any single study did not make a significant difference in the pooled effects, except for deleting Han et al.'s study (Fig. 4). The summary OR was 1.08 with 95 % CI 1.00–1.16 for the genetic model of G-allele versus A-allele when Han et al.'s study was removed.

In conclusion, the results of the study by Wang et al. [2] should be expounded with caution. To reach a definitive conclusion, large sample size and well-designed studies are needed to confirm the association between *LEPR* Q223R polymorphisms and breast cancer risk. We hope that our remark will contribute to a more accurate elaboration and substantiation of the results reported by Wang et al. [2].

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Conflict of interest None.

Ethical statements This article does not contain any studies with human participants or animals performed by any of the authors.

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