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ORIGINAL ARTICLE

Lack of association between LEPR Q223R polymorphisms and cancer susceptibility: Evidence from a meta-analysis

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Summary

Purpose: *The results from the published studies on the association between LEPR genetic polymorphisms and cancer risk are conflicting. The common LEPR Q223R genetic polymorphism has been reported to be functional and may contribute to genetic susceptibility to cancer. However, the association between LEPR Q223R genetic polymorphism and cancer risk remains inconclusive.*

Methods: *To better understand the role of LEPR Q223R genetic polymorphism in global cancer, we conducted this comprehensive meta-analysis encompassing 9139 cases and 11282 controls.*

Results: *Overall, the LEPR Q223R genetic polymorphism did not significantly affect the risk of cancer. In the stratified analysis, there was no significant association of LEPR Q223R variant with breast cancer, colorectal cancer and non-Hodgkin's lymphoma (NHL) under any models. Moreover, significantly increased risks were found in Asian and African in all genetic models tested. When stratified by study design, no significantly increased susceptibility to cancer was found among any studies. No significantly differences in sample size in cases were found among genotypes.*

Conclusions: *These findings suggested lack of association between LEPR Q223R polymorphisms and cancer susceptibility, but the LEPR Q223R genetic polymorphism may increase the susceptibility to cancers in Asian and African individuals. Large, well designed epidemiological studies are needed to validate our findings.*

Key words: *cancer, genetic polymorphism, meta-analysis, LEPR, Q223R, rs1137101*

Introduction

Cancer is one of the leading causes of death around the world. This disease has become a worldwide public health problem [1]. The exact mechanism of carcinogenesis is not yet fully elucidated [2]. Recently, it has become clear that genetic variations contribute to the development and progression of cancer [2,3]. However, due to various reasons, including the considerable heterogeneity of the disease, the identification of susceptibility genes is difficult and most associations have not been reproduced.

Obesity has been found to be associated with increased risk of cancer. Leptin (LEP, also called OB for obese), an adipocyte-derived hormone, produced predominantly by the white adipose tissue, regulates appetite and weight, body metabolism and reproductive functions together with the leptin receptor (LEPR) [4]. The LEP gene, located at chromosome 7q31.3, encodes a 16 kDa protein that has been consistently shown to be associated with endocrinologic metabolism [5]. It has been also suggested that leptin could contribute to serum insulin levels and the development of type 2 diabetes [6] and that lep-

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tin is involved in the pathophysiology of obesity [7,8] and carcinogenesis [9-14]. In addition to the regulation of body weight, leptin also influences hematopoiesis, reproduction, angiogenesis and immune processes [15]. There is also evidence suggesting that it might play an important role in the initiation and progression of human cancers [16].

A number of investigators have studied the possible association between the LEPR Q223R genetic polymorphism and cancer risk, but the results have been conflicting [9,11,14,17-35]. Thus, the association between the LEPR Q223R genetic polymorphism and cancers requires further investigation.

In an attempt to clarify this inconsistency, we have combined all the hospital- and population-based published studies up to February 2014 in a meta-analysis to acquire a comprehensive picture of the role of LEPR Q223R gene using multiple research methods and models.

In this study, a comprehensive meta-analysis was performed on previous reports to investigate the association of LEPR Q223R genetic polymorphism with all cancers, different kinds of cancers, different kinds of ethnicities, different kinds of populations, different kinds of genotyping methods and different kinds of sample size in cases.

Methods

Search strategy and data extraction

In this meta-analysis, a comprehensive literature search of the US National Library of Medicine's PubMed database, ISI Web of Knowledge, Medline, Embase and Google Scholar Search (updated to February 2014) was conducted using the search terms including "leptin receptor" or "leptin gene receptor" or "leptin receptor gene" or "LEPR" or "Q223R" or "rs1137101" , "polymorphisms" or "variation" or "mutation" or "SNP" , "tumour" or "tumor" or "cancer" or "neoplasm" or "phyma" or "oncoma" or "knub" or "carcinoma" or "malignancy", and the combined phrases in order to obtain all genetic studies on the relationship of LEPR Q223R genetic polymorphism and cancers. We also used a hand search of references of original studies or review articles on this topic to identify additional studies. Eligible studies were selected according to the following explicit inclusion criteria: (1) a case-control study on the association between LEPR Q223R genetic polymorphism and cancer risk; (2) detailed number of different genotypes for estimating an odds ratio (OR) with 95% confidence interval (CI); (3) when several publications reported on the same population data, the largest or most complete study was chosen; (4) cases with carcinomas were diagnosed by histopathology; (5) animal studies, case reports, review articles, abstracts, editorials, reports with incomplete data, and studies based on pedigree data were excluded (Figure 1). For each eligible study, the following information was recorded: the first author's name, the year of publication, country, ethnicity, cancer type, genotyping methods, sources of controls, racial descent of the study population, genotype and allele distributions and main results of each study.

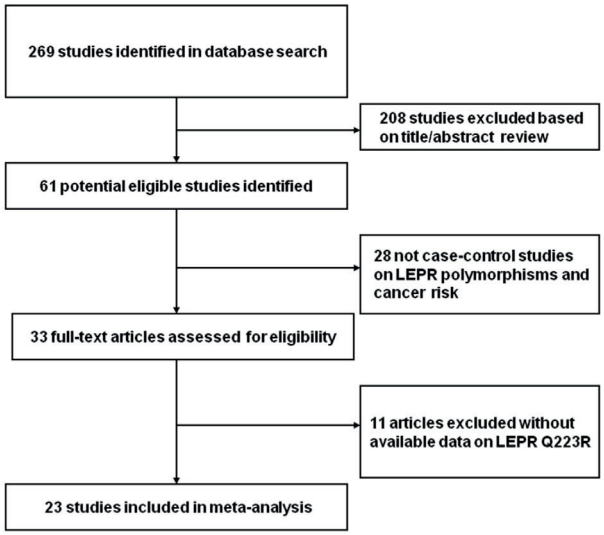

Figure 1. Flow diagram of study identification

Statistics

The strength of the relationship between LEPR Q223R genetic polymorphism and cancer was assessed by using crude OR with 95% CI. We examined the association between the LEPR Q223R genetic polymorphism and cancer risk using the following genetic models: homozygote co-dominant model (AA vs GG), heterozygote co-dominant model (AG vs GG), dominant genetic model (AA/AG vs GG), recessive genetic model (AA vs AG/GG) and additive genetic model (A vs G). Firstly, we checked the Hardy-Weinberg equilibrium (HWE) in controls for each study. Then we performed Q-test for evaluating the heterogeneity [36]. Fixed effects model was used to pool the data when the p-value of Q-test was ≥0.05; otherwise, the random effects model was selected [37]. I^2 was also used to assess the heterogeneity in this meta-analysis. If I^2> 50%, the heterogeneity exists [38]. We also performed sensitivity analysis and subgroup analysis to explore the reason of heterogeneity. Both funnel plot and Egger's test were used to assess the publication bias ($p<0.05$ was representative of statistical significance) [39]. All statistical analyses were performed using STATA 12.0 software (Stata Corp., College Station, TX) and Review Manager 5.2 (The Cochrane Collaboration, http://ims.cochrane.org/revman).

Table 1. Characteristics of studies included in the meta-analysis

First author [Ref no.]	*Year*	*Country*	*Ethnicity*	*Cancer type*	*Cases/ controls*	*Source of controls*	*Genotyping method*	*Poly-morphisms*	P_{HWE} *in controls*
Kote-Jaral [17]	2003	UK	Caucasian	Prostate	273/262	PB	PCR-RFLP	Q223R	0.006
Skibola [18]	2004	USA	Caucasian	NHL	376/805	PB	TaqMan	Q223R	0.120
Willett [19]	2005	UK	Caucasian	NHL	699/914	PB	TaqMan	Q223R	0.214
Woo [20]	2006	Korea	Asian	Breast	45/45	HB	PCR-sequencing	Q223R	0.513
Snoussi [9]	2006	Tunisia	African	Breast	308/222	HB	PCR-RFLP	Q223R	0.162
Gallicchio [21]	2007	USA	Caucasian	Breast	53/872	PB	TaqMan	Q223R	0.261
Chia [14]	2007	USA	Caucasian	Colorectal cancer	157/191	HB	PCR-sequencing	Q223R	/
Han [11]	2008	China	Asian	Breast	240/500	HB	PCR-RFLP	Q223R	0.001
Okobia [22]	2008	Nigeria	African	Breast	209/209	HB	PCR-RFLP	Q223R	0.704
Ulybina [23]	2008	Russia	Caucasian	Breast	110/105	HB	Real-time PCR	Q223R	0.993
Doecke [24]	2008	Australia	Caucasian	Esophageal	774/1352	PB	Sequenom iPLEX	Q223R	0.792
Ulybina [23]	2008	Russia	Caucasian	Endometrial	191/105	HB	Real-time PCR	Q223R	0.993
Teras [25]	2009	USA	Caucasian	Breast	641/650	PB	SNPstream	Q223R	0.672
Yapijakis [26]	2009	Greece & Germany	Caucasian	Oral	150/152	HB	PCR-RFLP	Q223R	0.002
Pechlivanis [27]	2009	Czech	Caucasian	Colorectal	659/711	HB	TaqMan	Q223R	0.428
Vasku [28]	2009	Czech	Caucasian	Colorectal	100/100	HB	PCR-sequencing	Q223R	0.398
Cleveland [29]	2010	USA	Caucasian	Breast	1059/1101	PB	PCR-RFLP	Q223R	0.333
Dai [30]	2010	China	Asian	Hepatocel-lular	82/102	HB	PCR-RFLP	Q223R	0.486
Nyante [31]	2011	USA	Mixed	Breast	1972/1776	PB	IIIumina	Q223R	0.563
GozDziewska [32]	2011	Poland	Caucasian	ALL	52/43	HB	PCR-RFLP	Q223R	0.678
Kim [33]	2012	Korea	Asian	Breast	390/447	HB	MassARAY	Q223R	0.975
Li [34]	2012	China	Asian	Lung	744/832	PB	PCR-RFLP	Q223R	<0.05
Kim [33]	2012	Korea	Asian	Gastric	48/48	HB	PCR-RFLP	Q223R	<0.05

HWE: Hardy-Weinberg equilibrium, NHL: non-Hodgkin's lymphoma, ALL: acute lymphoblastic leukemia, HB: hospital based, PB: population based, RFLP: Restriction fragment length polymorphisms polymerase chain reaction

Results

Eligible studies

Overall, 23 relevant studies involving 9139 cases and 11282 controls were selected in this meta-analysis [9,11,14,17-35]. The main characteristics of these studies are shown in Table 1. Genotype and allele distributions of LEPR Q223R genetic polymorphism among cancer cases and controls and p-value of HWE in controls are shown in Table 1 . All studies were case-control studies, including 10 breast cancer studies [9,11,20-23,25,29,31,33], 3 colorectal cancer studies [14,27,28], 2 NHL studies [18,19], and others (including one acute lymphocytic leukemia (ALL) study [32], one oral cancer study [26], one lung cancer study [34], one gastric cancer study [35], one hepatocellular cancer study [30], one prostate cancer study [17], one esophageal cancer study [24], and one endometrial cancer study [23]). Cancers were diagnosed histopathologically in most studies. There were 14 studies [14,17-19,21,23-29,32] with patients of Caucasian descent, 6 studies [11,20,30,33-35] of Asian descent and 2 studies [9,22] of African descent. Population-based controls studies were 9, while hospital-based controls studies were 14. All studies were reported in English. The genotyping methods contained the classic polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) assay, TaqMAN, PCR-Sequencing, Sequenom iPLEX , SNPstream, IIIumlna and MassARAY. The sample size in

cases of most studies was over 300 patients. The genotype distributions of controls were all in agreement with HWE except for 6 studies where the distributions could not be estimated [11,14,17,26,34,35].

Meta-analysis

Overall, as shown in Table 2, we observed that the LEPR Q223R genetic polymorphism did not significantly affect the risk of cancer when all the eligible studies were pooled into the meta-analysis. When the 6 studies in which the genotype distributions of controls did not agree with HWE were excluded, no significant association was observed in any genetic model. In the all genetic models, all the p-values of Q test were lower than 0.05 and I2 values were higher than 50%. So we performed the sensitivity analysis by deleting one single study from the overall pooled analysis each time to check the influence of the removed data. However, the results revealed that no extreme sensitive study changed the between-study heterogeneities.

We then evaluated the effects of the LEPR Q223R genetic polymorphism according to specific cancer types, different ethnicities, different sources of controls, different detection method and different sample size in cases. As shown in Table 2, we found that LEPR Q223R genetic polymorphism reduced oral cancer risk and increased lung cancer risk in all the 5 models (AA vs GG, AG vs GG, AA/AG vs GG, AA vs AG/GG, and A vs G). For oral cancer, the ORs (95%CI) were 0.22 (0.08-0.60), 0.37 (10.14-0.97), 0.30 (0.12-0.78), 0.54 (0.34-0.87) and 0.62 (0.44-0.86), respectively; for lung cancer, the ORs (95%CI) were 2.35 (1.82-3.02), 2.01 (1.55-2.59), 2.17 (1.73-2.72), 1.59 (1.29-1.96) and 1.70 (1.47-1.96), respectively. For hepatocellular cancer, significant association was found in the following models: AA vs GG:OR=6.98 (1.47-33.07); AA vs AG/GG:OR=6.94 (1.48-32.66); A vs G:OR=2.06 (1.16-3.66). For endometrial cancer, significant association was found in the following models: AA vs GG: OR=0.49 (0.24-0.99); AA vs AG/GG: OR=0.52 (0.31-0.89); A vs G: OR=0.70 (0.50-0.98). We also found that the LEPR Q223R genetic polymorphism did not significantly affect the risk of breast cancer, colorectal cancer and NHL in any genetic model tested. In the stratified analysis by ethnicity, significantly increased risks were found in Asians and Africans in all the genetic models tested. For Caucasians, significant associations were observed in the recessive model (AA vs AG/GG, OR=0.86 (0.76-0.98)) and the additive model (A vs G, OR=0.92 (0.86-0.99)). According to the source of controls, no significant association was observed in any genetic model in the population-based or the hospital-based studies. According to the detection method, signification effects in the recessive genetic model were observed in the PCR-RFLP subgroup. For the real time PCR subgroup, significant decreasing effects in homozygous co-dominant, recessive and additive genetic models were observed. According to the sample size in cases, no significant association was observed in any genetic model in small sample (<300) or big sample (≥300) studies.

Publication bias

Both Begg's funnel plot and Egger's test were performed to assess the publication bias. The shape of the funnel plots did not reveal any evidence of obvious asymmetry in the overall meta-analysis. Then, the Egger's test was used to provide statistical evidence of funnel plot symmetry. The results still did not show any obvious evidence of publication bias (AA vs GG, p=0.474; AG vs GG, p=0.493; AA/AG vs GG, p=0.542; AA vs AG/GG, p=0.375 (Figure 2); A vs G, p=0.382).

Discussion

This meta-analysis of 23 studies involving 9139 cases and 11282 controls was conducted in order to yield a valid conclusion concerning the potential association between LEPR Q223R genetic polymorphism and cancer risk. Clues from epidemiological studies have shown that overweight and obesity might be associated with increased risk of cancer of the endometrium, kidney, colon and gallbladder in women and breast cancer in postmenopausal women [40], and increased death rates for cancers at multiple specific sites [41]. Polymorphism-associated low enzyme activity may cause reduction of conjugation, and thus the reduced elimination of oxidative intermediates radicals and electrophiles, resulting in the production of increased carcinogenic substrates rather than detoxification. Polymorphisms in LEPR may therefore influence carcinogens' levels and potentially play a role in carcinogenesis. However, studies focusing on the association of the LEPR Q223R genetic polymorphism with cancer susceptibility produced controversial conclusions [9,11,14,17-35]. The lack of concordance across many of these

Table 2. Meta-analysis of the association between LEPR Q223R polymorphism and cancer risk

Variables	*No.of studies*	*Homozygous co-dominant*		*Heterozygous co-dominant*		*Recessive*		*Dominant*		*Additive*	
		AA vs GG	P_{het} [b]	*AG vs GG*	P_{het} [b]	*(AA vs AG+GG)*	P_{het} [b]	*(AA+AG vs GG)*	P_{het} [b]	*A vs G*	P_{het} [b]
All	23	1.15 (0.91-1.45)	0.000	1.10 (0.97-1.24)	0.001	1.05 (0.89-1.24)	0.000	1.13 (0.97-1.31)	0.000	1.08 (0.96-1.22)	0.000
HWE[a]	17	1.01 (0.86-1.19)	0.006	1.01 (0.94-1.09)	0.579	0.97 (0.84-1.10)	0.003	1.03 (0.94-1.13)	0.137	1.01 (0.93-1.10)	0.001
Cancer type											
Breast	10	1.41 (0.99-2.00)	0.000	1.09 (0.96-1.24)	0.185	1.26 (0.94-1.69)	0.000	1.22 (1.00-1.47)	0.001	1.19 (1.00-1.43)	0.000
Colorectal	3	0.87 (0.65-1.16)	0.507	0.94 (0.73-1.22)	0.420	0.90 (0.70-1.15)	0.315	0.92 (0.72-1.17)	0.789	0.93 (0.81-1.08)	0.413
NHL[c]	2	0.90 (0.71-1.13)	0.768	0.95 (0.79-1.14)	0.630	0.93 (0.76-1.14)	0.947	0.93 (0.78-1.11)	0.617	0.95 (0.84-1.06)	0.692
ALL[d]	1	2.49 (0.70-8.83)	/	1.40 (0.57-3.46)	/	2.04 (0.65-6.41)	/	1.61 (0.68-3.80)	/	1.52 (0.85-2.73)	/
Oral	1	**0.22 (0.08-0.60)**	/	**0.37 (0.14-0.97)**	/	**0.54 (0.34-0.87)**	/	**0.30 (0.12-0.78)**	/	**0.62 (0.44-0.86)**	/
Lung	1	**2.34 (1.82-3.02)**	/	**2.01 (1.55-2.59)**	/	**1.59 (1.29-1.96)**	/	**2.17 (1.73-2.72)**	/	**1.70 (1.47-1.96)**	/
Gastric	1	/	/	/	/	/	/	/	/	1.00 (0.57-1.76)	/
Hepato-cellular	1	**6.98 (1.47-33.07)**	/	1.03 (0.48-2.22)	/	**6.94 (1.48-32.66)**	/	1.60 (0.81-3.14)	/	**2.06 (1.16-3.66)**	/
Prostate	1	0.82 (0.52-1.29)	/	0.85 (0.58-1.26)	/	0.89 (0.59-1.34)	/	0.84 (0.59-1.19)	/	0.88 (0.69-1.13)	/
Esopha-geal	1	0.94 (0.72-1.21)	/	1.10 (0.87-1.39)	/	0.87 (0.72-1.06)	/	1.04 (0.83-1.30)	/	0.96 (0.84-1.08)	/
Endome-trial	1	**0.49 (0.24-0.99)**	/	0.91 (0.48-1.73)	/	**0.52 (0.31-0.89)**	/	0.73 (0.40-1.35)	/	**0.70 (0.50-0.98)**	/
Ethnicity											
Caucasian	14	0.87 (0.75-1.01)	0.105	0.98 (0.89-1.07)	0.757	**0.86 (0.76-0.98)**	0.059	0.95 (0.87-1.03)	0.578	**0.92 (0.86-0.99)**	0.127
Asian	6	**3.40 (1.68-6.88)**	0.015	**1.43 (1.06-1.93)**	0.066	**2.99 (1.22-7.32)**	0.000	**1.73 (1.29-2.30)**	0.043	**1.63 (1.25-2.13)**	0.005
African	2	**1.85 (1.23-2.79)**	0.275	**1.47 (1.08-2.01)**	0.302	**1.48 (1.07-2.05)**	0.403	**1.58 (1.14-2.20)**	0.245	**1.39 (1.07-1.80)**	0.159
Mixed	1	0.91 (0.76-1.09)	/	0.92 (0.78-1.08)	/	0.97 (0.84-1.12)	/	0.92 (0.79-1.06)	/	0.96 (0.87-1.05)	/
Source of controls											
Hospital	14	1.29 (0.77-2.19)	0.000	1.15 (0.97-1.37)	0.234	1.16 (0.79-1.71)	0.000	1.21 (0.95-1.55)	0.001	1.14 (0.91-1.43)	0.000
Popula-tion	9	1.06 (0.82-1.36)	0.000	1.06 (0.89-1.26)	0.000	1.01 (0.86-1.19)	0.000	1.06 (0.87-1.29)	0.000	1.03 (0.90-1.19)	0.000
Genotype method											
PCR-RFLP	10	1.65 (1.00-2.74)	0.000	1.18 (0.89-1.56)	0.000	**1.47 (1.01-2.15)**	0.000	1.31 (0.94-1.82)	0.000	1.28 (1.00-1.66)	0.000
TaqMan	4	0.95 (0.77-1.18)	0.260	0.94 (0.81-1.09)	0.927	1.00 (0.83-1.21)	0.212	0.94 (0.82-1.08)	0.710	0.97 (0.88-1.08)	0.307
PCR-se-quencing	3	0.68 (0.30-1.51)	/	1.38 (0.77-2.48)	0.634	0.75 (0.46-1.20)	0.269	1.18 (0.67-2.07)	0.403	0.97 (0.53-1.78)	0.196
Real-time PCR	2	**0.57 (0.33-0.98)**	0.511	1.10 (0.67-1.80)	0.368	**0.53 (0.35-0.79)**	0.960	0.88 (0.55-1.40)	0.371	**0.74 (0.58-0.96)**	0.597
Sequen-om IPLEX	1	0.94 (0.72-1.21)	/	1.10 (0.87-1.39)	/	0.87 (0.72-1.06)	/	1.04 (0.83-1.30)	/	0.96 (0.84-1.08)	/
SNP-stream	1	0.84 (0.61-1.15)	/	1.03 (0.77-1.38)	/	0.82 (0.65-1.04)	/	0.95 (0.72-1.26)	/	0.90 (0.77-1.06)	/
IIIumlna	1	0.91 (0.76-1.09)	/	0.92 (0.78-1.08)	/	0.97 (0.84-1.12)	/	0.92 (0.79-1.06)	/	0.96 (0.87-1.050	/
MassARAY	1	1.59 (0.54-4.63)	/	1.15 (0.83-1.60)	/	1.54 (0.53-4.48)	/	1.18 (0.85-1.63)	/	1.18 (0.88-1.58)	/
Sample size in cases											
<300	13	1.24 (0.68-2.27)	0.000	1.08 (0.90-1.29)	0.513	1.15 (0.73-1.81)	0.000	1.15 (0.86-1.52)	0.005	1.12 (0.85-1.46)	0.000
≥300	10	1.11 (0.87-1.41)	0.000	1.10 (0.94-1.30)	0.000	1.03 (0.89-1.19)	0.000	1.11 (0.92-1.340	0.000	1.07 (0.94-1.22)	0.000

[a] Conforming to Hardy-Weinberg equilibrium in controls, [b] p value of the Q-test for heterogeneity test. [c] non-Hodgkin's lymphoma, [d] acute lymphoblastic leukemia. Bold numbers denote that the OR values for contrast models are significant.

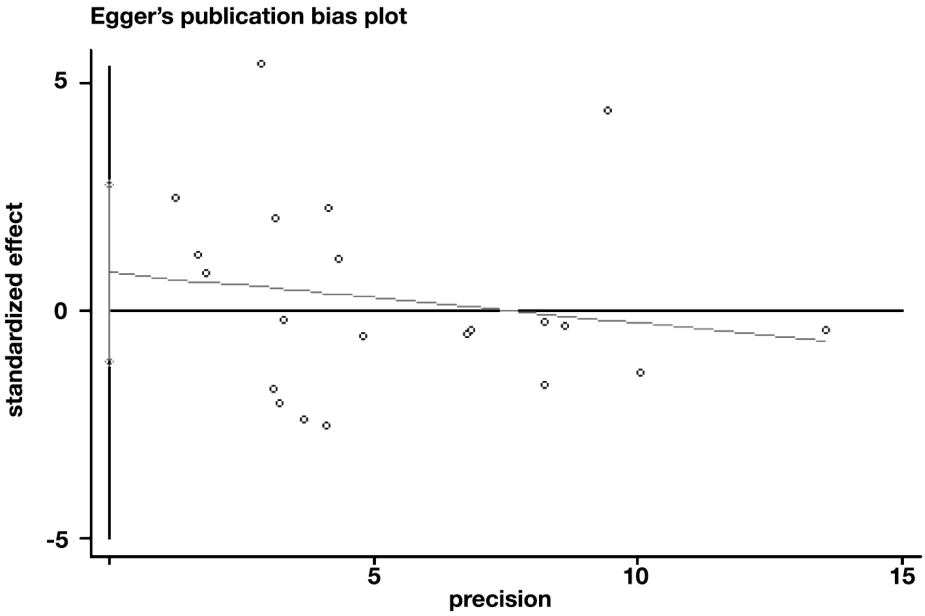

Figure 2. Egger's funnel plot of LEPR Q223R polymorphism and cancer risk for AA vs AG & GG contrast model.

studies reflects limitations in these studies, such as small sample sizes, ethnic differences and research methodology and so on. Meta-analysis is a powerful tool for summarizing the results from different studies by producing a single estimate of the major effect with enhanced precision.

In our analysis, the pooled effects for the comparison of all genetic models suggested no significant association between the LEPR Q223R genetic polymorphism and cancer risk. Furthermore, significantly increased associations were observed for Asians and Africans in all genetic models tested, while Caucasians with AA genotype had lower risk of cancer compared to GG genotype. Inconsistency between the different ethnicities can be explained by hypothesizing that different ethnic groups live with multiple lifestyles and environmental factors, and different populations carry different genotype and/or allele frequencies of this locus polymorphism that may lead to various degrees of cancer susceptibility.

In this meta-analysis we also observed no consistent results between hospital-based studies and population-based studies, but we still believe that controls in population-based studies are more representative of the general population than controls from hospital-based studies. Several factors, such as environmental factors and genetic backgrounds, might contribute to the discrepancy.

Our meta-analysis has some limitations. First, the sample size in any given cancer was not sufficiently large, which could increase the probability of a false positive or false negative result. It might be difficult to get a concrete conclusion if the number of included studies in subgroups was low. Besides, studies involved in different ethnicities were warranted to estimate the effects of this functional polymorphism on cancer risk. Second, due to the unavailability of some data of the eligible studies, it was difficult to evaluate the roles of some special environmental factors and lifestyles, such as diet, alcohol consumption, and smoking status in developing cancer. Third, the influence of bias in the present analysis could not be completely excluded because positive results are supposed to be published much more quickly than articles with negatives results.

Conclusions

Our meta-analysis suggested that the LEPR Q223R genetic polymorphism did not significantly affect the risk of cancer, but the LEPR Q223R genetic polymorphism may increased the susceptibility of cancers in Asian and African populations. Large, well designed epidemiological studies are needed to validate our findings.

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