JBUON 2014; 19(3): 847-854
ISSN: 1107-0625, online ISSN: 2241-6293 • www.jbuon.com
E-mail: editorial_office@jbuon.com

ORIGINAL ARTICLE

Association of LEPR K109R polymorphisms with cancer risk: A systematic review and pooled analysis

Hui Shi[1,2], Hexi Shu[1,3], Changjia Huang[1,3], Jinpeng Gong[1,3], Yunji Yang[1], Run Liu[1], Yong Yang[1], Pengcheng Liu[1,2]

[1]Shanghai Tenth People's Hospital , Tongji University, School of Medicine , Shanghai , China; [2]Department of First Clinical Medical College, Nanjing Medical University, Nanjing, Jiangsu, China; [3]The Medical Department of Soochow University, Suzhou , Jiangsu, China

Summary

Purpose: *This meta-analysis was conducted to evaluate the association between LEPR K109R (rs1137100) genetic polymorphism and cancer risk.*

Methods: *To better understand the role of LEPR K109R(rs1137100) genetic polymorphism in global cancer, we conducted this comprehensive meta-analysis encompassing 5819 cases and 8068 controls.*

Results: *Overall, the LEPR K109R(rs1137100) genetic polymorphism did not significantly affect the risk of cancer. In the stratified analysis, significant associations were found between the LEPR K109R(rs1137100) genetic polymorphism and breast cancer under additive genetic model (odds ratio/OR=0.67, 95% CI 0.61-0.73). For prostate cancer, there was no significant association of LEPR K109R(rs1137100) variant with this disease under any model. For lung cancer, there was significant association of LEPR K109R(rs1137100) variant with the disease under heterozygous co-dominant model (OR=0.72, 95% CI 0.55-0.96), recessive genetic model (OR=0.76, 95% CI 0.61-0.94) and additive genetic model (OR=0.89, 95% CI 0.80-0.99). For gastric cancer, significant association was found in the 3 genetic models (AG vs GG, AA/AG vs GG and A vs G), the ORS (95%CI) being 2.93 (1.25-6.86), 2.93 (1.25-6.86) and 2.25 (1.07-4.72), respectively. Moreover, no significant cancer risk was found in any genetic model among Caucasian and Asian populations. When stratified by study design, no significantly elevated susceptibility to cancer was found among any studies. No significant differences in the genotype method and sample size in cases were found among genotypes.*

Conclusion: *These findings suggested that the LEPR K109R(rs1137100) genetic polymorphism may decrease the susceptibility in breast cancer, especially in the additive genetic model. The findings also indicate that single nucleotide polymorphism (SNP) functions as a recessive mutation, which needs to be verified or linked with functional studies.*

Key words: *LEPR, K109R, rs1137100, cancer, genetic polymorphism, meta-analysis*

Introduction

Cancer is a worldwide public health problem [1] and the process of carcinogenesis is not yet elucidated [2]. However, genetic variation may contribute to susceptibility of cancer [2,3]. Obesity has been reported that may increase the risk of cancer. Leptin (LEP, also called OB for obese), an adipocyte-derived hormone predominantly produced by 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 II diabetes [6] and that it is involved in the pathophysiology of obesity [7,8] and carcinogenesis [9-14]. Apart from regulating body weight, leptin also can influence reproduction, hematopoiesis, angiogenesis and immune processes [15]. There is evidence suggesting that it might play a very important role in the initiation and development of human

Correspondence to: Pengcheng Liu, MD. 301 Yanchang Middle Road, Shanghai 20072, China.Tel: +86 132 62 227 613, Fax: +86 132 66 301 051, E-mail: liupengcheng1990@163.com
Received: 04/04/2014; Accepted: 19/04/2014

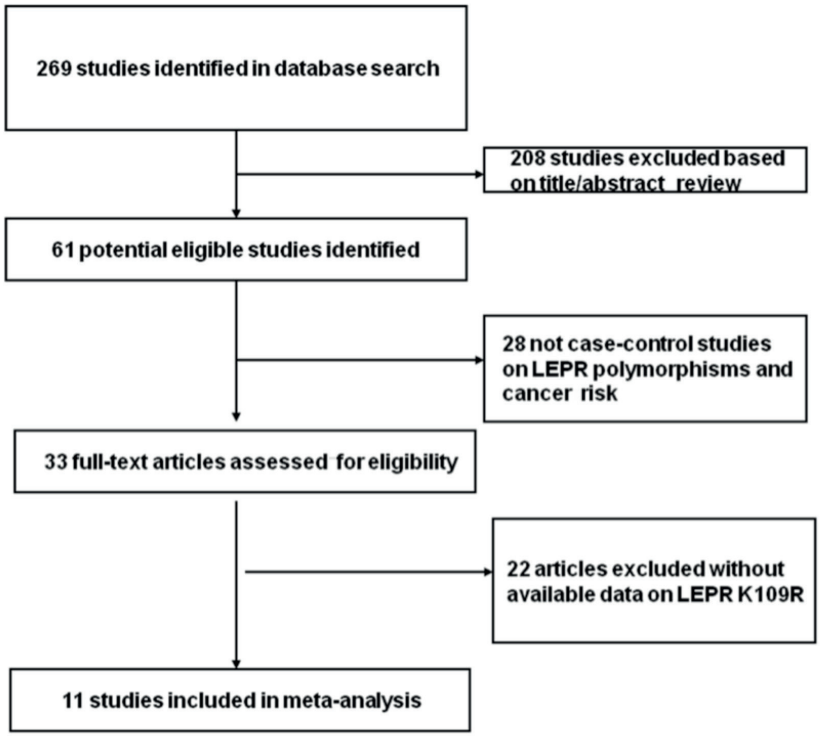

Figure 1. Flow diagram of study identification.

cancers [16].

A considerable number of researchers have studied the association between the LEPR K109R(rs1137100) genetic polymorphism and cancer risk, with conflicting results [10,14,17-25]. Thus, the association between the LEPR K109R(rs1137100) 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 K109R(rs1137100) gene polymorphism in relation to carcinogenesis using multiple research methods and models.

This meta-analysis included different kinds of cancers, different kinds of ethnicities, different kinds of populations, different kinds of genotyping methods and different kinds of sample size of cases.

Methods

Search strategy and data extraction

In this meta-analysis, a comprehensive literature research 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 following search terms: "leptin receptor" or "leptin gene receptor" or "leptin receptor gene" or "LEPR" or "K109R" or "rs1137100", "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 over the relationship of LEPR K109R(rs1137100) genetic polymorphism and cancers.

We also used a hand search of references of original studies or reviewed 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 K109R(rs1137100) genetic polymorphism and cancer risk; (2) detailed number of different genotypes for estimating OR with 95% CI; (3) when several publications reported on the same population data, the largest or most complete study was chosen; (4) cases with carcinomas diagnosed by histopathology; (5) animal studies, case reports, review articles, abstracts, editori-

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

Name	*Year*	*Country*	*Ethnicity*	*Cancer type*	*Cases/controls*	*Source of controls*	*Genotype method*	*Polymorphisms*	P_{HWE} *in controls*
Kote-Jaral	2003	UK	Caucasian	Prostate cancer	273/262	PB	PCR-RFLP	K109R	0.547
Woo	2006	Korea	Asian	Breast cancer	45/45	HB	PCR-sequencing	K109R	0.217
Liu	2007	Taiwan	Asian	Breast cancer	47/41	HB	PCR-RFLP	K109R	0.006
Chia	2007	USA	Caucasian	Colorectal cancer	157/191	HB	PCR-sequencing	K109R	/
Ulybina	2008	Russia	Caucasian	Breast cancer	110/105	HB	Real-time PCR	K109R	0.383
Doecke	2008	Australia	Caucasian	Esophageal cancer	774/1352	PB	Sequenom iPLEX	K109R	0.034
Ulybina	2008	Russia	Caucasian	Endometrial cancer	191/105	HB	Real-time PCR	K109R	0.383
Moore	2009	Finland	Caucasian	Prostate cancer	947/863	PB	TaqMan	K109R	0.814
Teras	2009	USA	Caucasian	Breast cancer	641/650	PB	SNPstream	K109R	/
Nyante	2011	USA	Mixed	Breast cancer	1972/1776	PB	IIIumina	K109R	<0.05
Li	2012	China	Asian	Lung cancer	744/832	PB	PCR-RFLP	K109R	<0.05
Kim	2012	Korea	Asian	Gastric cancer	48/48	HB	PCR-RFLP	K109R	0.278

HWE: Hardy-Weinberg equilibrium, HB: Hospital based, PB: Population based, RFLP: Restriction fragment length polymorphisms polymerase chain reaction

als, 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.

Statistics

The strength of the relationship between LEPR K109R(rs1137100) genetic polymorphism and cancer was assessed by using crude OR with 95% CI. We examined the association between the LEPR K109R(rs1137100) 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 [26]. 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 [27]. I2 was also used to assess the heterogeneity in this meta-analysis. If I2>50%, heterogeneity existed [28]. 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 showed statistical significance) [29]. All statistical analyses were performed using STATA 12.0 software and Review Manager 5.2.

Results

Eligible studies

Overall, 12 relevant studies involving 5819 cases and 8068 controls were selected in this meta-analysis [10,14,17-25]. The main characteristics of these studies are shown in Table 1. Genotype and allele distributions of LEPR K109R(rs1137100) 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 5 breast cancer studies [10,18,19,22,23], 2 prostate cancer studies [17,21], and the others including one esophageal cancer study [20], one endometrial cancer study [19], one colorectal cancer study [14], one lung cancer study [24], and one gat-

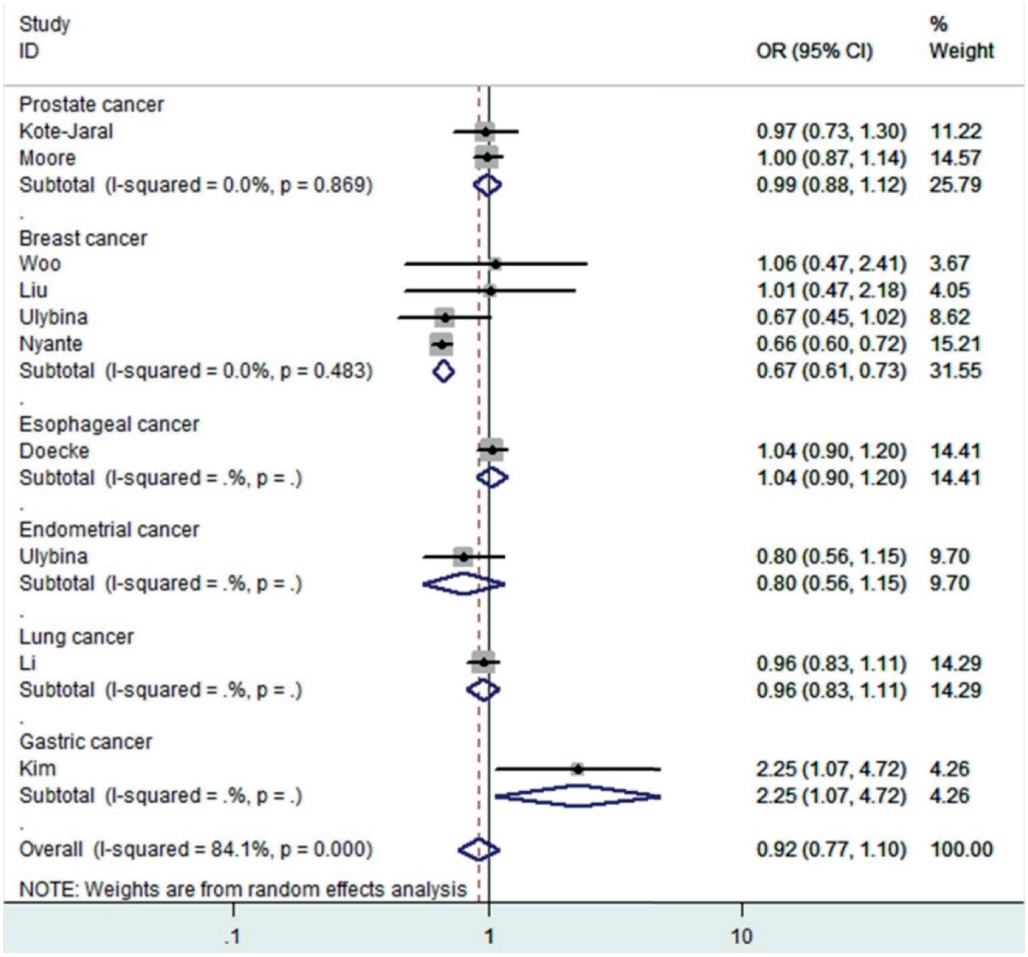

Figure 2. Subgroup analysis of the association between LEPR K109R(rs1137100) polymorphism and cancer risk by cancer type (A vs G) (Random model). The overall odds ratio (OR) is shown. The OR of each study is marked with a black dot. The % weight of OR is indicated by a gray square. The overall OR is indicated by a blue diamond.

ric cancer study [25]. Cancers were diagnosed histopathologically in most studies. There were 7 studies [14,17,19-22] of Caucasian descent, 4 studies [10,18,24,25] of Asian descent, and one study [23] of mixed descent. Population-based controls were coming from 6 studies, while hospital-based controls were coming from 6 studies. All studies were reported in English. The genotyping methods contained the classic polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) assay, Real-time PCR , PCR-Sequencing, Sequenom iPLEX, Taqman, SNPstream and IIIumina. The cases' sample size in half of the studies was over 250 patients. The genotype distributions of controls were all in agreement with HWE except 4 studies not estimable [10,20,23,24].

Meta-analysis

Overall, as shown in Table 2, we observed that the LEPR K109R(rs1137100) 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 where the genotype distributions of controls were not in agreement with HWE were excluded, no significant association was observed in any genetic model. In all genetic models, all the p-values of Q-test were < 0.05 and I^2 values were > 50%. So we performed sensitivity analysis by deleting one single study from the overall pooled analysis each time to check the influence of the removed data. The results revealed that no extreme sensitive study changed the between-study heterogeneities.

We then evaluated the effects of the LEPR K109R(rs1137100) 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 K109R(rs1137100) genetic polymorphism decreased breast cancer risk in additive genetic models (A vs G; OR=0.67/95% CI 0.61-0.73) (Figure 2). For gastric cancer, significant asso-

Table 2. Meta-analysis of the association between LEPR K109R polymorphism and cancer risk

Variables	*No.of*	*Homozygous co-dominant*		*Heterozygous co-dominant*		*Recessive*		*Dominiant*		*Additive*	
	studies	*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	12	0.76 (0.48-1.21)	0.000	0.97 (0.80-1.19)	0.016	0.84 (0.62-1.14)	0.000	0.91 (0.76-1.10)	0.015	0.92 (0.77-1.10)	0.000
HWE[a]	6	0.89 (0.70-1.13)	0.442	0.96 (0.67-1.38)	0.056	0.99 (0.85-1.15)	0.716	0.94 (0.65-1.36)	0.038	0.97 (0.87-1.08)	0.099
Cancer type											
Breast	5	0.48 (0.22-1.04)	0.105	0.94 (0.57-1.56)	0.094	0.67 (0.34-1.30)	0.000	0.76 (0.59-1.00)	0.277	0.67 (0.61-0.73)	0.483
Prostate	2	0.96 (0.74-1.25)	0.938	0.93 (0.72-1.20)	0.933	1.01 (0.86-1.19)	0.798	0.94 (0.74-1.20)	0.999	0.99 (0.88-1.12)	0.869
Esopha-geal	1	1.20 (0.86-1.68)	/	1.25 (0.89-1.76)	/	1.00 (0.84-1.19)	/	1.22 (0.88-1.70)	/	1.04 (0.90-1.20)	/
Endome-rial	1	0.60 (0.25-1.43)	/	0.80 (0.48-1.32)	/	0.68 (0.30-1.55)	/	0.76 (0.47-1.24)	/	0.80 (0.56-1.15)	/
Colorectal	1	/	/	/	/	1.20 (0.69-2.10)	/	/	/	/	/
Lung	1	0.87 (0.66-1.14)	/	0.72 (0.55-0.96)	/	1.07 (0.87-1.31)	/	0.80 (0.62-1.03)	/	0.96 (0.83-1.11)	/
Gastric	1	/	/	2.93 (1.25-6.86)	/	/	/	2.93 (1.25-6.86)	/	2.25 (1.07-4.72)	/
Ethnicity											
Caucasian	7	0.97 (0.77-1.22)	0.312	0.94 (0.76-1.16)	0.279	0.99 (0.89-1.10)	0.853	0.92 (0.73-1.15)	0.205	0.97 (0.87-1.08)	0.271
Asian	4	0.88 (0.68-1.16)	0.323	1.68 (0.51-5.57)	0.459	1.05 (0.87-1.28)	0.812	1.58 (0.55-4.50)	0.009	1.13 (0.79-1.60)	0.177
Mixed	1	0.33 (0.27-0.41)	/	1.04 (0.92-1.18)	/	0.33 (0.27-0.40)	/	0.79 (0.70-0.88)	/	0.66 (0.60-0.72)	/
Source of controls											
Popula-tion	6	0.78 (0.45-1.36)	0.000	0.97 (0.81-1.15)	0.108	0.83 (0.56-1.22)	0.000	0.88 (0.75-1.04)	0.109	0.91 (0.73-1.13)	0.000
Hospital	6	0.65 (0.33-1.25)	0.334	1.21 (0.58-2.56)	0.011	0.91 (0.64-1.30)	0.648	1.13 (0.55-2.32)	0.011	0.96 (0.67-1.39)	0.079
Genotyping method											
PCR-RFLP	4	0.89 (0.69-1.14)	0.607	1.32 (0.63-2.78)	0.008	1.03 (0.87-1.23)	0.757	1.27 (0.67-2.39)	0.023	1.04 (0.83-1.30)	0.178
Real-time PCR	2	0.54 (0.28-1.04)	0.700	0.72 (0.49-1.04)	0.529	0.63 (0.34-1.20)	0.818	0.69 (0.48-0.98)	0.507	0.74 (0.57-0.97)	0.531
PCR-Se-quencing	2	/	/	/	/	1.17 (0.73-1.87)	0.839	/	/	1.06 (0.47-2.41)	/
Sequenom iPLEX	1	1.20 (0.86-1.68)	/	1.25 (0.89-1.76)	/	1.00 (0.84-1.19)	/	1.22 (0.88-1.70)	/	1.04 (0.90-1.20)	/
TaqMan	1	0.96 (0.73-1.28)	/	0.93 (0.70-1.22)	/	1.02 (0.85-1.23)	/	0.94 (0.73-1.23)	/	1.00 (0.87-1.14)	/
SNPstream	1	/	/	/	/	0.96 (0.76-1.21)	/	/	/	/	/
IIIumina	1	0.33 (0.27-0.41)	/	1.04 (0.92-1.18)	/	0.33 (0.27-0.40)	/	0.79 (0.70-0.88)	/	0.66 (0.60-0.72)	/
Sample size in cases											
<250	6	0.65 (0.33-1.25)	0.334	1.21 (0.58-2.56)	0.011	0.91 (0.64-1.30)	0.648	1.13 (0.55-2.32)	0.011	0.96 (0.67-1.39)	0.079
≥250	6	0.78 (0.45-1.36)	0.000	0.97 (0.81-1.15)	0.108	0.83 (0.56-1.22)	0.000	0.88 (0.75-1.04)	0.109	0.91 (0.73-1.13)	0.000

[a] Conforming to Hardy-Weinberg equilibrium in controls, [b] *P* value of the Q-test for heterogeneity testpolymerase chain reaction

ciation was found in the 3 genetic models (AG vs GG, AA/AG vs GG, A vs G), the ORs (95%CI) were 2.93 (1.25-6.86), 2.93 (1.25-6.86) and 2.25 (1.07-4.72), respectively. For lung cancer, significant association was found in the heterozygous co-dominant genetic models (AG vs GG; OR=0.72/95%CI 0.55-0.96). In the stratified analysis by ethnicity, significantly decreased risks were found in mixed in all genetic models except heterozygous co-dominant genetic model (Table 2). For Caucasian and Asian, no significant associations were observed in any genetic model tested. According to the source of controls, no significant association was observed in any genetic model in population-based or hospital-based studies. According to the detection method, significant effects in most genetic models were observed in the real-time PCR and IIIumina subgroup. According to the sample size in cases, no significant association was observed in any genetic model in small sample (<250) or big sample (≥250) studies.

Publication bias

Both Begg's funnel plot and Egger's test were performed to assess publication bias. The shape of the funnel plots did not reveal any evidence of obvious asymmetry in the overall meta-analysis. Then, Egger's test was used to provide statistical evidence of the funnel plot symmetry. The results still did not present any obvious evidence of publication bias (AA vs GG, p=0.436; AG vs. GG, p=0.814; AA/AG vs GG, p=0.129; AA vs AG/GG, p=0.976; A vs G, p=0.246).

Discussion

This meta-analysis of 12 studies involving 5819 cases and 8068 controls was conducted in order to draw a valid conclusion concerning the potential association between LEPR K109R(rs1137100) 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 [30], and increased death rates for cancers at multiple specific sites [31]. Polymorphism-associated low enzyme activity may cause reduction of conjugation, and thus reduced elimination of oxidative intermediate 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 K109R(rs1137100) genetic polymorphism with cancer susceptibility produced controversial conclusions [10,14,17-25]. The lack of concordance across many of these studies reflects limitations, such as small sample sizes, ethnic differences, 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, there was significant association between this polymorphism and low breast cancer risk under additive genetic model (A vs G). Patients carrying the A allele had less cancer risk than did patients homozygous for the G allele. Besides, there was significant association between this polymorphism and higher gastric cancer risk under three genetic models (AG vs GG, AA/AG vs GG, A vs G). These results suggested that A allele had stronger effects on an individual's phenotype than G allele. So individuals with AA/AG genotype could have higher risk of gastric cancer than those with GG genotype. The pooled effects for all genetic models comparisons suggested no significant association between the LEPR K109R(rs1137100) genetic polymorphism and prostate cancer risk. Furthermore, we found that for Caucasians and Asians, no significant associations were observed in any genetic model tested , while mixed individuals with AA genotype had lower risk of cancer compared to Asians and Caucasians under all genetic models except the heterozygous co-dominant genetic model. This inconsistency between the three ethnicities could be explained taking into account that different ethnic groups live with multiple lifestyles and environmental factors, and that different populations carry different genotype and/or allele frequencies of this locus polymorphism that may lead to various degrees of cancer susceptibility. In our meta-analysis, we also observed consistent results between hospital-based 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.

It is certain that some limitations existed in our meta-analysis. First, the sample size was not large enough, which might have led to false positive or false negative results. If the number of patients in a subgroup was low, it was hard to get a firm conclusion. Second, because the original data was unavailable, it was hard to adjust the roles of several related factors such as lifestyle, alcohol and smoking in cancer development. Third, the influence of publication bias could not be completely excluded.

Conclusions

Our meta-analysis suggested that the LEPR K109R(rs1137100) genetic polymorphism did not significantly affect the risk of cancer, but this genetic polymorphism decreased the susceptibility in breast cancer, especially in the additive genetic model. The fact also indicates that the SNP functions as a recessive mutation, which needs to be verified or linked with functional studies. Large well designed epidemiological studies are needed to validate our findings.

References

1. Siegel R, Naishadham D, Jemal A. Cancer statistics, 2012. CA Cancer J Clin 2012;62:10-29.
2. Wright ME, Peters U, Gunter MJ et al. Association of variants in two vitamin transport genes with circulating vitamin e concentrations and prostate cancer risk. Cancer Res 2009;69:1429-1438.
3. Cheung WY, Liu G. Genetic variations in esophageal cancer risk and prognosis. Gastroenterol Clin North Am 2009;38:75-91.
4. Friedman JM, Halaas JL. Leptin and the regulation of body weight in mammals. Nature 1998;395:763-770.
5. Unger RH, Zhou YT, Orci L. Regulation of fatty acid homeostasis in cells: novel role of leptin. Proc Natl Acad Sci U S A 1999;96:2327-2332.
6. Lakka HM, Oksanen L, Tuomainen TP, Kontula K, Salonen JT. The common pentanucleotide polymorphism of the 3'-untranslated region of the leptin receptor gene is associated with serum insulin levels and the risk of type 2 diabetes in non-diabetic men: a prospective case-control study. J Intern Med 2000;248:77-83.
7. Lonnqvist F, Arner P, Nordfors L, Schalling M. Overexpression of the obese (ob) gene in adipose tissue of human obese subjects. Nat Med 1995;1:950-953.
8. Yiannakouris N, Yannakoulia M, Melistas L et al. The Q223R polymorphism of the leptin receptor gene is significantly associated with obesity and predicts a small percentage of body weight and body composition variability. J Clin Endocrinol Metab 2001;86:4434-4439.
9. Snoussi K, Strosberg AD, Bouaouina N et al. Leptin and leptin receptor polymorphisms are associated with increased risk and poor prognosis of breast carcinoma. BMC Cancer 2006;6:38.
10. Liu CL, Chang YC, Cheng SP et al. The roles of serum leptin concentration and polymorphism in leptin receptor gene at codon 109 in breast cancer. Oncology (Basel) 2007;72:75-81.
11. Han CZ, Du LL, Jing JX 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.
12. Ribeiro R, Vasconcelos A, Costa S et al. Overexpressing leptin genetic polymorphism (-2548 G/A) is associated with susceptibility to prostate cancer and risk of advanced disease. Prostate 2004;59:268-274.
13. Ribeiro R, Araujo AP, Coelho A et al. A functional polymorphism in the promoter region of leptin gene increases susceptibility for non-small cell lung cancer. Eur J Cancer 2006;42:1188-1193.
14. Chia VM, Newcomb PA, Lampe JW et al. Leptin concentrations, leptin receptor polymorphisms, and colorectal adenoma risk. Cancer Epidemiol Biomarkers Prev 2007;16:2697-2703.
15. Loffreda S, Yang SQ, Lin HZ et al. Leptin regulates proinflammatory immune responses. Faseb J 1998;12:57-65.
16. Russo VC, Metaxas S, Kobayashi K, Harris M, Werther GA. Antiapoptotic effects of leptin in human neuroblastoma cells. Endocrinology 2004;145:4103-4112.
17. Kote-Jarai Z, Singh R, Durocher F et al. Association between leptin receptor gene polymorphisms and early-onset prostate cancer. BJU Int 2003;92:109-112.
18. Woo HY, Park H, Ki CS, Park YL, Bae WG. Relationships among serum leptin, leptin receptor gene polymorphisms, and breast cancer in Korea. Cancer Lett 2006;237:137-142.
19. Ulybina I, Imianitov EN, Vasilev DA, Bershtein LM. Polymorphism of glucose intolerance and insulin resistance susceptibility genes in oncological patients. Mol Biol (Mosk) 2008;42:947-956.
20. Doecke JD, Zhao ZZ, Stark MS et al. Single nucleotide polymorphisms in obesity-related genes and the risk of esophageal cancers. Cancer Epidemiol Biomarkers Prev 2008;17:1007-1012.
21. Moore SC, Leitzmann MF, Albanes D et al. Adipokine genes and prostate cancer risk. Int J Cancer 2009;124:869-876.
22. Teras LR, Goodman M, Patel AV et al. No association between polymorphisms in LEP, LEPR, ADI-

POQ, ADIPOR1, or ADIPOR2 and postmenopausal breast cancer risk. Cancer Epidemiol Biomarkers Prev 2009;18:2553-2557.

23. Nyante SJ, Gammon MD, Kaufman JS et al. Common genetic variation in adiponectin, leptin, and leptin receptor and association with breast cancer subtypes. Breast Cancer Res Treat 2011;129:593-606.
24. Li Y, Geng J, Wang Y et al. The role of leptin receptor gene polymorphisms in determining the susceptibility and prognosis of NSCLC in Chinese patients. J Cancer Res Clin Oncol 2012;138:311-316.
25. Kim EY, Chin HM, Park SM et al. Susceptibility of gastric cancer according to leptin and leptin receptor gene polymorphisms in Korea. J Korean Surg Soc 2012;83:7-13.
26. DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials 1986;7:177-188.
27. Mantel N, Haenszel W. Statistical aspects of the analysis of data from retrospective studies of disease. J Natl Cancer Inst 1959;22:719-748.
28. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ 2003;327:557-560.
29. Egger M, Davey SG, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997;315:629-634.
30. Bianchini F, Kaaks R, Vainio H. Overweight, obesity, and cancer risk. Lancet Oncol 2002;3:565-574.
31. Calle EE, Rodriguez C, Walker-Thurmond K, Thun MJ. Overweight, obesity, and mortality from cancer in a prospectively studied cohort of U.S. adults. N Engl J Med 2003;348:1625-1638.