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ORIGINAL ARTICLE

Genetic G2548A polymorphism of leptin gene and risk of cancer: a meta-analysis of 6860 cases and 7956 controls

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Summary

Purpose: *The results from the published studies on the association between LEP (leptin) genetic polymorphism and cancer risk are conflicting. The common G2548A genetic polymorphism has been reported to be functional and may contribute to genetic susceptibility to cancers. However, the association between LEP G2548A genetic polymorphism and cancer risk remains inconclusive.*

Methods: *To better understand the role of LEP G2548A genetic polymorphism in global cancer, we conducted this comprehensive meta-analysis encompassing 6860 cases and 7956 controls.*

Results: *Overall, the LEP G2548A genetic polymorphism was associated with higher cancer risk in three genetic models (AA vs GG, AA vs AG/GG, A vs G). In the stratified analysis, there was significant association of LEP G2548A variant with non-Hodgkin's lymphoma (NHL) under homozygous co-dominant model (OR=1.27, 95% CI 1.01-1.60) and additive genetic model (OR=1.14, 95% CI 1.01-1.28). Moreover, a significantly increased cancer risk was found in three genetic models (AA vs GG, AA vs AG/GG, A vs G) among Caucasian population. For Asians, no significant associations were observed in any genetic model tested.*

Conclusions: *These findings suggest that the LEP G2548A genetic polymorphism may increase the susceptibility of cancers in NHL, especially in the homozygote co-dominant model and the additive genetic model among Caucasian populations. The phenomenon also indicates that the SNP functions as a recessive mutation, which needs to be verified or linked with functional studies.*

Key words: *cancer, genetic polymorphism, meta-analysis, LEP, G2548A, rs7799039*

Introduction

Cancer is one of the leading causes of death worldwide and has become a global public health problem [1]. Until now the exact mechanism of carcinogenesis is not yet fully elucidated [2]. Recently, it has become clear that a genetic variation contributes 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 clarified.

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 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 influence

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serum insulin levels and the development of type II diabetes [6] and that leptin 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, angiogensis and immune processes [15]. There is evidence suggesting that LEP genetic polymorphism 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 LEP G2548A (rs7799039) genetic polymorphism and cancer risk, but the results have been conflicting [9,12,13,17-28]. Thus, the association between the LEP G2548A (rs7799039) 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 June 2014 in a meta-analysis to give a comprehensive picture of the role of LEP G2548A (rs7799039) gene using multiple research methods and models.

In this study, a comprehensive meta-analysis was performed on previous reports to investigate the association of LEP G2548A (rs7799039) genetic polymorphism with all cancers, different kinds of cancers, different kinds of ethnicities, different kinds of populations, different kinds of genotype method, and different kinds of sample size in 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 (update to June 2014) was conducted using the search terms including "leptin" or "leptin gene" or "LEP" or "G2548A" or "rs7799039", "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 LEP G2548A (rs7799039) genetic polymorphism and cancers. Data extraction of all variables and outcomes of interest and assessment of the methodological quality were performed independently by two readers (PC.L. and H.S.). Disagreements were resolved by discussion and consensus. 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 LEP G2548A (rs7799039) genetic polymorphism and cancer risk; (2) a 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 were diagnosed by histopathology; and (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.

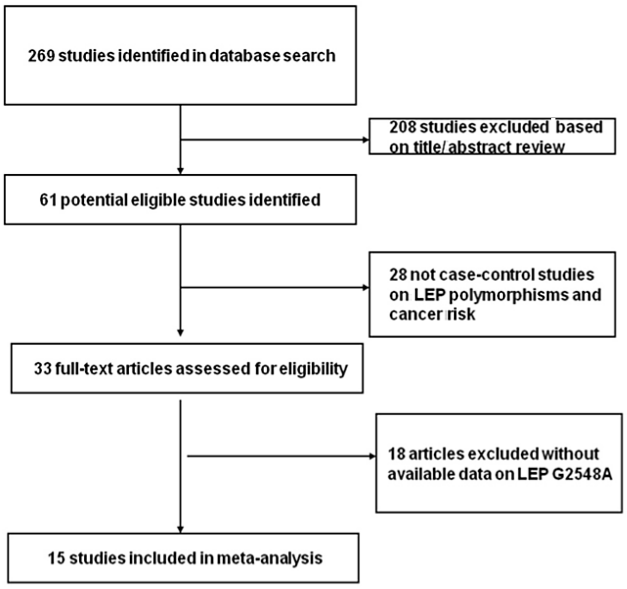

Figure 1. Flow diagram of studies' identification.

Statistics

The strength of relationship between LEP G2548A (rs7799039) genetic polymorphism and cancer was assessed by using crude OR with 95% CI. We examined the association between the LEP G2548A (rs7799039) genetic polymorphism and cancer risk using the following genetic models: homozygote codominant model (AA vs GG), heterozygote codominant 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 heterogeneity [29]. The 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 [30]. I2 was also used to assess the heterogeneity in this meta-analysis. If I2> 50%, heterogeneity existed [31]. 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) [32]. All statistical analyses were performed using STATA 12.0 software (Stata Corp., College Station, Texas, USA) and Review Manager 5.2 (The Cochrane Collaboration, http://ims.cochrane.org/revman).

Results

Eligible studies

Overall, 15 relevant studies involving 6,860 cases and 7,956 controls were selected in this meta-analysis [9,12,13,17-25,27,28]. The main characteristics of these studies are shown in Table 1. Genotype and allele distributions of LEP G2548A (rs7799039) 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 3 breast cancer studies [9,21,26], 3 colorectal cancer studies [19,23,24], 2 prostate cancer studies [12,20], 2 NHL studies [17,18] and the others (including one acute leukemia study [28], one oral cancer study [22], one lung cancer study [13], one gastric cancer study [27], one endometrial cancer study [25]). Cancers were diagnosed histopathogically in most studies. There were 12 studies [12,13,17,18,20-26,28] with patients of Caucasian descent, one study [27] of Asian descent, one study [19] of Mixed descent and one study [9] of African descent. Population-based controls were carried out in 5 studies, while hospital-based controls were carried out in 9 studies. 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 and SNPMan. The sample size in cases of half of the studies was over 300 patients. The genotype distributions of controls were all in agreement with HWE except for 3 studies not estimable [13,21,22].

Meta-analysis

Overall, as shown in Table 2, we observed that the LEP G2548A (rs7799039) genetic polymor-

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

First author [Ref]	*Year*	*Country*	*Ethnicity*	*Cancer type*	*Cases/ Controls*	*Source of controls*	*Genotype method*	*Polymorphisms*	P_{HWE} *in controls*
Ribeiro [12]	2004	Portugal	Caucasian	Prostate cancer	143/118	HB	PCR-RFLP	G2548A	0.145
Skibola [17]	2004	USA	Caucasian	NHL	376/805	PB	TaqMan	G2548A	0.158
Willett [18]	2005	UK	Caucasian	NHL	699/914	PB	TaqMan	G2548A	0.141
Ribeiro [13]	2006	Portugal	Caucasian	Lung cancer	140/341	HB	PCR-RFLP	G2548A	0.006
Snoussi [9]	2006	Tunisia	African	Breast cancer	308/222	HB	PCR-RFLP	G2548A	0.063
Slattery [19]	2008	USA	Mixed	Colorectal cancer	1565/1965	Mixed	TaqMan	G2548A	0.173
Moore [20]	2009	Finland	Caucasian	Prostate cancer	1053/1053	PB	TaqMan	G2548A	0.707
Teras [21]	2009	USA	Caucasian	Breast cancer	641/650	PB	SNP-stream	G2548A	/
Yapijakis [22]	2009	Greece & Germany	Caucasian	Oral cancer	150/152	HB	PCR-RFLP	G2548A	<0.05
Pechlivanis [23]	2009	Czech	Caucasian	Colorectal cancer	702/752	HB	TaqMan	G2548A	0.188
Vasku [24]	2009	Czech	Caucasian	Colorectal cancer	102/101	HB	PCR-sequencing	G2548A	0.333
Chovanec [25]	2009	Czech	Caucasian	Endometrial cancer	67/67	HB	PCR-RFLP	G2548A	0.624
Cleveland [26]	2010	USA	Caucasian	Breast cancer	1065/1108	PB	PCR-RFLP	G2548A	0.118
Kim [27]	2012	Korea	Asian	Gastric cancer	48/48	HB	PCR-RFLP	G2548A	0.729
Tavil [28]	2012	Turkey	Caucasian	ALL	72/70	HB	PCR-RFLP	G2548A	0.235

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

Table 2. Meta-analysis of the association between LEP G2548A polymorphism and cancer risk

Variables	*No.of*	*Homozygous co-dominant*		*Heterozygous co-dominant*		*Recessive*		*Dominant*		*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	15	**1.28(1.07-1.54)**	0.003	1.04(0.96-1.13)	0.157	**1.19(1.02-1.40)**	0.000	1.08(1.00-1.16)	0.764	**1.12(1.03-1.21)**	0.008
HWE[a]	12	**1.23(1.02-1.49)**	0.004	1.06(0.98-1.15)	0.171	1.14(0.98-1.34)	0.006	1.08(1.00-1.17)	0.052	**1.11(1.01-1.21)**	0.005
Cancer type											
Breast	3	1.91(0.82-4.45)	0.025	1.02(0.86-1.21)	0.033	1.35(0.88-2.07)	0.004	1.13(0.96-1.32)	0.022	1.29(0.94-1.76)	0.029
Colorectal	3	0.89(0.76-1.05)	0.490	1.01(0.89-1.15)	0.581	0.89(0.77-1.02)	0.528	0.98(0.87-1.10)	0.524	0.95(0.88-1.03)	0.461
Prostate	2	1.76(0.80-3.86)	0.063	1.14(0.92-1.41)	0.021	**1.30(1.06-1.58)**	0.382	1.22(1.00-1.49)	0.020	1.30(0.94-1.80)	0.074
NHL	2	**1.27(1.01-1.60)**	0.625	1.14(0.95-1.38)	0.143	1.18(0.97-1.43)	0.780	1.18(0.99-1.41)	0.210	**1.14(1.01-1.28)**	0.523
ALL	1	0.90(0.36-2.22)	/	1.00(0.41-2.42)	/	0.90(0.46-1.78)	/	0.95(0.42-2.15)	/	0.93(0.58-1.50)	/
Oral	1	2.06(1.00-4.26)	/	0.81(0.46-1.44)	/	**2.40(1.33-4.34)**	/	1.02(0.59-1.77)	/	1.32(0.96-1.82)	/
Lung	1	1.63(0.91-2.92)	/	0.76(0.49-1.19)	/	**1.91(1.13-3.23)**	/	0.92(0.61-1.39)	/	1.15(0.87-1.53)	/
Gastric	1	0.88(0.05-14.69)	/	1.29(0.07-22.42)	/	0.69(0.30-1.61)	/	1.00(0.06-16.46)	/	0.76(0.37-1.57)	/
Endometrial	1	1.45(0.55-3.81)	/	1.39(0.58-3.33)	/	1.16(0.55-2.47)	/	1.41(0.62-3.21)	/	1.20(0.74-1.95)	/
Ethnicity											
Caucasian	12	**1.27(1.07-1.51)**	0.083	1.01(0.92-1.11)	0.154	**1.21(1.04-1.41)**	0.014	1.07(0.98-1.17)	0.160	**1.11(1.03-1.21)**	0.127
Asian	1	0.88(0.05-14.69)	/	1.29(0.07-22.42)	/	0.69(0.30-1.61)	/	1.00(0.06-16.46)	/	0.76(0.37-1.57)	/
African	1	**3.17(1.54-6.51)**	/	**1.45(1.01-2.07)**	/	**2.62(1.30-5.26)**	/	**1.62(1.14-2.29)**	/	**1.55(1.19-2.02)**	/
Mixed	1	0.92(0.76-1.11)	/	1.06(0.91-1.23)	/	0.89(0.75-1.05)	/	1.02(0.88-1.17)	/	0.97(0.88-1.07)	/
Source of controls											
Hospital	9	**1.52(1.01-2.28)**	0.004	1.05(0.90-1.22)	0.100	1.36(0.97-1.91)	0.003	1.09(0.95-1.27)	0.037	1.17(0.97-1.40)	0.006
Population	5	**1.29(1.12-1.49)**	0.960	1.03(0.92-1.16)	0.208	**1.18(1.03-1.36)**	0.155	1.10(0.99-1.23)	0.413	**1.13(1.05-1.21)**	0.927
Mixed	1	0.92(0.76-1.11)	/	1.06(0.91-1.23)	/	0.89(0.75-1.05)	/	1.02(0.88-1.17)	/	0.97(0.88-1.07)	/
Genotype method											
PCR-RFLP	8	**1.67(1.26-2.22)**	0.203	1.03(0.90-1.19)	0.059	**1.51(1.16-1.98)**	0.094	1.15(1.00-1.31)	0.080	**1.23(1.08-1.40)**	0.165
TaqMan	5	1.07(0.88-1.31)	0.032	1.05(0.95-1.15)	0.364	1.05(0.88-1.25)	0.027	1.05(0.96-1.15)	0.176	1.04(0.94-1.15)	0.029
PCR-sequencing	1	1.23(0.58-2.62)	/	0.96(0.51-1.80)	/	1.26(0.65-2.47)	/	1.04(0.59-1.86)	/	1.11(0.75-1.64)	/
SNPstream	1	/	/	/	/	0.93(0.73-1.17)	/	/	/	/	/
Sample size in cases											
<300	7	**1.61(1.18-2.19)**	0.579	1.04(0.82-1.33)	0.170	**1.41(1.02-1.94)**	0.148	1.17(0.93-1.47)	0.276	**1.21(1.04-1.40)**	0.449
≥300	8	1.19(0.96-1.47)	0.001	1.04(0.96-1.13)	0.176	1.12(0.95-1.32)	0.001	1.07(0.99-1.15)	0.059	1.09(0.99-1.21)	0.003

[a]Conforming to Hardy-Weinberg equilibrium in controls, [b]p value of the *Q* test for heterogeneity test, NHL: non-Hodgkin's lymphoma, ALL: acute lymphoblastic leukemia. The numbers in parentheses represent 95% confidence interval. The bold numbers mean that the OR values for the contrast models are significant.

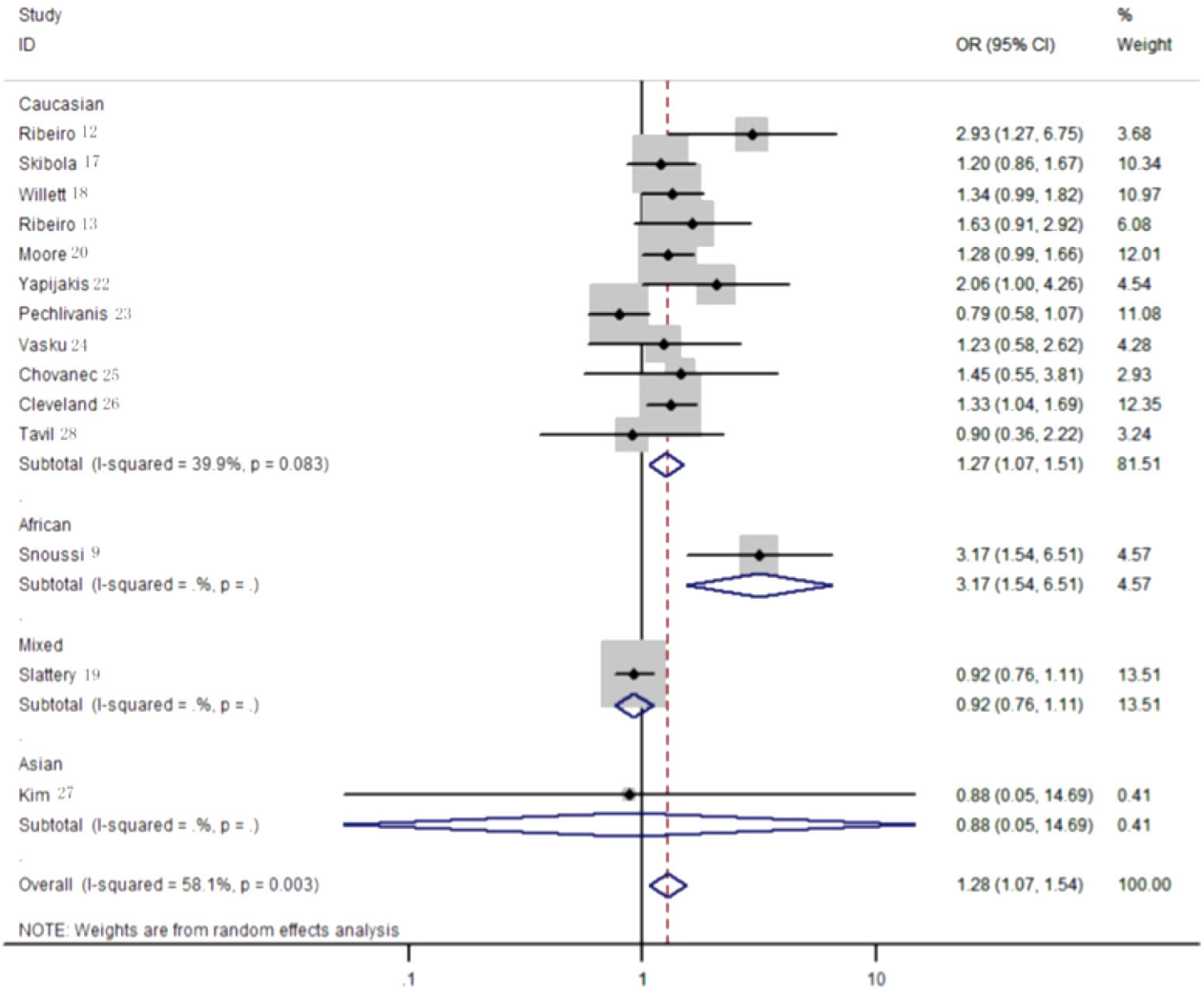

Figure 2. Subgroup analysis of the association between LEP G2548A (rs7799039) polymorphism and cancer risk by ethnicity (AA vs GG) (random model). The overall OR is shown. The OR of each study is marked with a black dot. The % weight of OR is indicated by a grey square. The overall OR is indicated by blue diamond.

phism increased the cancer risk in the homozygote codominant model (AA vs GG, OR=1.28, 95% CI 1.07-1.54) (Figure 2), recessive genetic model (AA vs AG/GG, OR=1.19, 95% CI 1.02-1.40) (Figure 3), and additive genetic model (A vs G, OR=1.12, 95% CI 1.03-1.21) (Figure 4) when all the eligible studies were pooled into the meta-analysis. But when the 3 studies whose genotype distributions of controls were not in agreement with HWE and were excluded, no significant association was observed in the recessive genetic model. In most genetic models, p values of Q test were < 0.05, and I2 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. However, the results revealed that no extremely sensitive study changed the between-study heterogeneities.

We then evaluated the effects of the LEP G2548A (rs7799039) 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 LEP G2548A (rs7799039) genetic polymorphism increased NHL risk in 2 genetic models (AA vs GG, and A vs G). For NHL, the ORs (95% CI) were 1.27 (1.01-1.60), and 1.14 (1.01-1.28), respectively. For prostate cancer, significant association was found in the recessive genetic model: AA vs AG/GG: OR=1.30, 95% CI 1.06-1.58. For the recessive genetic model, significant association was found in

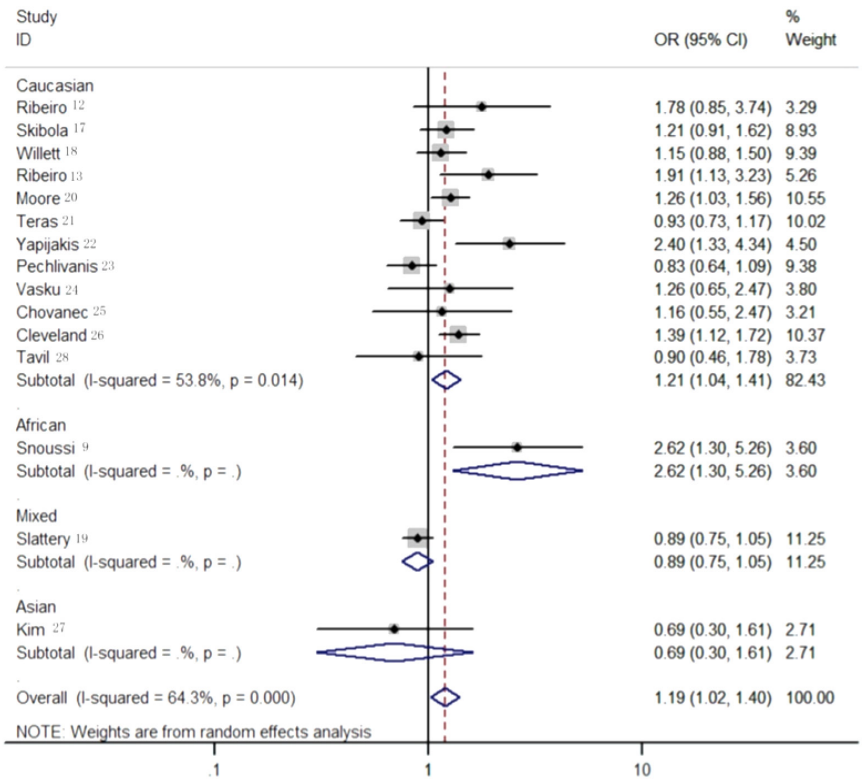

Figure 3. Subgroup analysis of the association between LEP G2548A (rs7799039) polymorphism and cancer risk by ethnicity (AA vs AG/GG) (random model). The overall OR is shown. The OR of each study is marked with a black dot. The % weight of OR is indicated by a grey square. The overall OR is indicated by blue diamond.

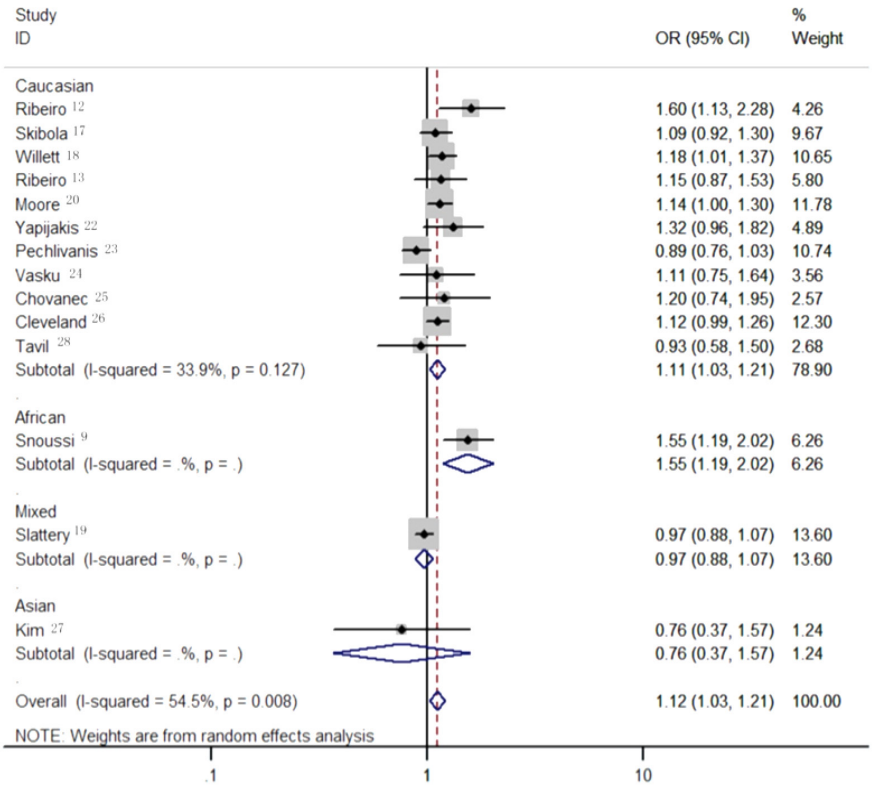

Figure 4. Subgroup analysis of the association between LEP G2548A (rs7799039) polymorphism and cancer risk by ethnicity (A vs G) (random model). The overall OR is shown. The OR of each study is marked with a black dot. The % weight of OR is indicated by a grey square. The overall OR is indicated by blue diamond. The overall OR is shown. The OR of each study is marked with a black dot. The % weight of OR is indicated by a grey square. The overall OR is indicated by blue diamond.

oral cancer (OR=2.40, 95% CI 1.33-4.34), and lung cancer (OR=1.91, 95% CI 1.13-3.23). In the stratified analysis by ethnicity, significantly increased risks were found in Africans in all genetic models tested (Table 2). For Caucasians, significantly increased risks were found in the homozygote codominant model (AA vs GG, OR=1.27, 95% CI 1.07-1.51), the recessive genetic model (AA vs AG/GG, OR=1.21, 95% CI 1.04-1.41) and the additive genetic model (A vs G, OR=1.11, 95% CI 1.03-1.21). For Asians, no significant associations were observed in any genetic model tested. According to the source of controls, signification effects in 3 genetic models (AA vs GG, AA vs AG/GG, and A vs G) were observed in population-based studies, while in in-hospital-based studies, significant association was only observed in the homozygote codominant genetic model. According to the detection method, significant effects in most genetic models were observed in the PCR-RFLP subgroup. According to the sample size in cases, significatnt effects in 3 genetic models (AA vs GG, AA vs AG/GG, and A vs G) were observed in small-sample (<300) studies, while in big-sample (≥300) studies, no significant association was observed in any genetic model tested.

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, Egger's test was used to provide a statistical evidence of funnel plot symmetry. The results still did not present any obvious evidence of publication bias (AA vs GG, p=0.074; AG vs GG, p=0.551; AA/AG vs GG, p=0.284; AA vs AG/GG, p=0.125; A vs. G, p=0.204).

Discussion

This meta-analysis of 15 studies involving 6,860 cases and 7,956 controls was conducted in order to yield a valid conclusion concerning the potential association between LEP G2548A (rs7799039) 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 [33], and increased death rates for cancers at multiple specific sites [34]. Polymorphism-associated low enzyme activity may cause reduction of conjugation and, thus, reduced elimination of oxidative intermediates radicals and electrophiles, resulting in production of increased carcinogenic substrates rather than detoxification. Polymorphisms in LEP may therefore influence carcinogens levels and potentially play a role in carcinogenesis. However, studies focusing on the association of the LEP G2548A (rs7799039) genetic polymorphism with cancer susceptibility had controversial conclusions [9,13,18-28]. The lack of concordance across many of these studies reflects limitation in the studies, 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 a significant association between this polymorphism and high NHL risk under 2 genetic models (AA vs GG, and A vs G). Patients carrying the A allele had higher cancer risk than patients homozygous for the G allele. Besides, for prostate cancer, the associations were more significant in the recessive genetic model than in the dominant genetic model. These results suggested that homozygous AA had stronger effects on an individual's phenotype than heterozygous AG. So individuals with AA genotype could have a higher risk of colorectal cancer than those with AG genotype. The pooled effects for all genetic model comparison suggested no significant association between the LEP G2548A (rs7799039) genetic polymorphism and breast or colorectal cancer risk. Furthermore, we found that Caucasians and Africans with AA genotype had a higher risk of cancer compared to Asians under the 3 genetic models (AA vs GG, AA vs AG/GG, and A vs G). Inconsistency between the three ethnicities could be explained by the possibility that different ethnic groups live with multiple lifestyles and environmental factors, and different populations carry different genotypes, and/or allele frequencies of this locus polymorphism which may lead to various degrees of cancer susceptibility. In our meta-analysis, we also observed consistent results between hospital- and population-based studies, but we still believe that controls in population-based studies are more representative of general population than controls in hospital-based studies. Several factors such as environmental factors and genetic backgrounds might contribute to the discrepancy.

There are some limitations in our meta-anal-

ysis. First, the sample size in any given cancer was not sufficiently large, which could increase the probability of false-positive or false-negative results. It might be difficult to get a concrete conclusion if the number of the included studies in a subgroup was few. Besides, studies involved in different ethnicities should estimate the effects of this functional polymorphism on cancer risk. Second, because the original data of the eligible studies was unavailable, it was difficult for us to evaluate the roles of some special environmental factors and lifestyles such as diet, alcohol consumption, and smoking status in cancer development. 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 LEP G2548A (rs7799039) genetic polymorphism may increase the susceptibility of cancers in NHL, especially in the homozygote codominant model and the additive genetic model among Caucasian populations. Besides, the SNP also increases the susceptibility of prostate, oral and lung cancers in the recessive genetic model. The phenomenon 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.

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