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ORIGINAL ARTICLE

LEP and LEPR polymorphisms in non-Hodgkin lymphoma risk: A systematic review and pooled analysis

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Summary

Purpose: *The purpose of this systematic meta-analysis was to evaluate the association between leptin (LEP) and leptin receptor (LEPR) gene polymorphisms and non-Hodgkin lymphoma (NHL) risk.*

Methods: *All studies published up to July 2014 on the association between LEP and LEPR polymorphisms and NHL risk were identified by searching PubMed, Web of Science, EMBASE, and Google Scholar. Odds ratios (ORs) with 95% confidence intervals (CIs) for LEP and LEPR polymorphisms and NHL were calculated with fixed-effects and random-effects models.*

Results: *LEP G2528A polymorphism was associated with increased, yet not statistically significant risk of NHL (homozygote comparison, OR=1.27, 95% CI=1.01-1.60, p=0.63; heterozygote comparison, OR=1.13, 95% CI=0.86-1.49, p=0.14; dominant model, OR=1.18, 95% CI=0.99-1.41, p=0.21; recessive model, OR=1.18, 95% CI=0.97-1.43, p=0.78; additive model, OR=1.14, 95% CI=1.01-1.28, p=0.52). Significant decrease of NHL risk was found in LEP A19G polymorphism, while no links were detected with the LEPR polymorphisms studied. In subgroup analysis, the pooled results showed that LEP A19G polymorphism was associated with decreased risk of follicular lymphoma (FL) (homozygote comparison, OR=0.56, 95% CI=0.37-0.85, p=0.69). However, no evidence of a significant association was observed in diffuse large B-cell lymphoma (DLBCL) for variant genotypes of all single nucleotide polymorphisms (SNPs).*

Conclusions: *LEP G2548A polymorphism contributes to NHL susceptibility. Also, our results provide evidence that LEP A19G polymorphism is associated with decreased risk of NHL, especially in FL. Further large-scale and well-designed studies are needed to confirm this association.*

Key words: *genetic polymorphism, LEP, LEPR, meta-analysis, NHL*

Introduction

NHL incidence rates have been increasing in both developed and developing countries with about 70,800 new cases annually in the United States [1]. In China, the most common subtype of NHL is DLBCL, whereas FL is less common than in Western countries. However, the exact reasons and risk factors for NHL remain unidentified.

Obesity has been increasing in developed and developing countries, due to societal and environmental changes with high-fat foods and low physical activity. Obesity is a positive chronic imbalance between energy intake and expenditure mediated through the LEP signalling pathway [2]. Associations between polymorphisms in the LEP and LEPR genes and NHL have also been reported. Skibila et al. reported that the LEP A19G allele was associated with NHL risk [3]. A similar study from the UK found that LEPR Q223R genotype was associated with increased FL risk among women [4]. Zhang et al. did not find any significant association between the LEP and LEPR polymorphisms and NHL risk in a Chinese population [5]. Fewer studies reported the association between LEP and LEPR and NHL risk in Chinese popula-

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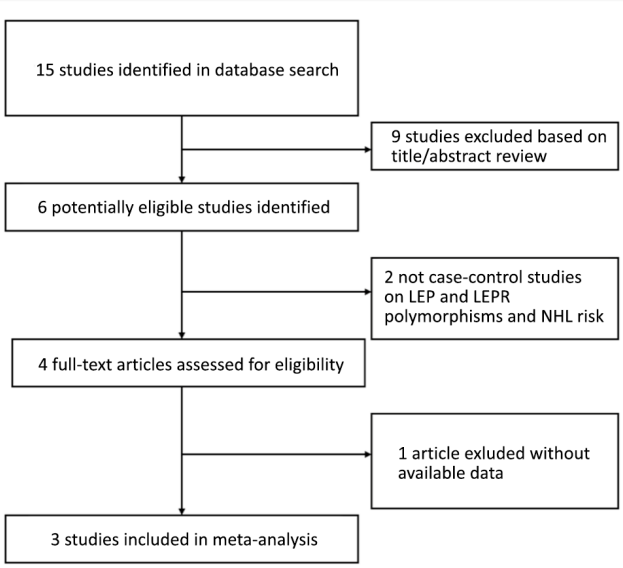

Figure 1. Flow diagram of study identification.

tion, though some previous studies in developed countries concluded that obesity was a risk factor of NHL [6].

A number of case-control studies have focused on the association between LEP and LEPR polymorphisms and NHL risk [3-5]. However, the association between LEP and LEPR polymorphisms and cancers requires further investigation. Therefore, because it is highly necessary to clarify this inconsistency, we have combined all eligible studies up to July 2014 in a meta-analysis to evaluate the association between LEP and LEPR polymorphisms and NHL risk.

Methods

Search strategy and selection criteria

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 July 2014) was conducted using search terms including "leptin" or "leptin receptor" or "LEP" or "LEPR", "polymorphisms" or "variation" or "mutation" or "SNP", "non-Hodgkin lymphoma" or "NHL" or "lymphoma" or "Hodgkin" or "non-Hodgkin", and the combined phrases in order to obtain all genetic studies on the relationship of LEP and LEPR polymorphisms and NHL. 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 and LEPR polymorphisms and NHL risk; (2) detailed number of different genotypes for estimating ORs with 95% CI; (3) when several publications reported on the same population data, the largest or most complete study was chosen; (4) cases with NHL were diagnosed histopathologically; (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: first author's name, year of publication, ethnicity, genotyping methods, sources of control, racial descent of the study population, genotype and allele distributions and main results of each study.

Data extraction

Statistics

The strength of the relationship between LEP and LEPR polymorphisms and NHL was assessed by using crude OR with 95% CI. We examined the association between the LEP and LEPR polymorphisms and NHL risk using the following genetic models: homozygote comparison, heterozygote comparison, dominant genetic model, recessive genetic model and additive model. Firstly, we checked the Hardy-Weinberg equilibrium (HWE) in controls for each study. Then, we performed Q-test for evaluating the heterogeneity [7]. 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 [8]. I^2 was also used to assess the heterogeneity in this meta-analysis. If I^2>50%, heterogeneity existed [9]. 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 represented statistical significance) [10]. All statistical analyses was performed using STATA 12.0 software and Review Manager 5.2.

Results

Identification and characteristics of relevant studies

Overall, 3 relevant studies involving 3926 cases and 5785 controls were selected in this meta-anaysis [3-5]. The main characteristics of these studies are shown in Table 1. All studies were case-control studies. NHL were histopathologically diagnosed in most studies. There was only 1 study [5] of Asian population, and 2 studies [3,4] of Caucasian population. Population-based controls assessment was carried out in 2 studies, while hospital-based controls in 1 study. All studies were reported in English and the genotyping method was Taqman. The genotype distributions of controls were all in agreement with HWE.

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

First author(year)	*Country*	*Ethnicity*	*Sample size (case/control)*	*Source of controls*	*Genotype studied*	*Genotyping*
Skibola (2004)	USA	Caucasian	376/805	PB	LEP G2548A, LEP A19G, LEPR Q223R	Taqman
Willett (2005)	UK	Caucasian	699/914	PB	LEP G2548A, LEP A19G, LEPR Q223R	Taqman
Zhang (2012)	China	Asian	514/557	HB	LEP G2548A, LEP A19G, LEPR rs1327118	Taqman

LEP: leptin, LEPR: leptin receptor, PB: Population-based, HB: Hospital-based, TaqMan: Taqman-based assays

Table 2. Subgroup analyses of LEP or LEPR polymorphisms and non-Hodgkin lymphoma risk

		Homozygote comparison		*Heterozygote comparison*		*Dominant model*		*Recessive model*		*Additive model*	
Variable	*N*	*OR (95% CI)*	p	*OR (95% CI)*	p	*OR (95% CI)*	p	*OR (95% CI)*	p	*OR (95% CI)*	p
NHL											
LEP G2548A	2	**1.27 (1.01-1.60)**	0.63	1.13 (0.86-1.49)	0.14	1.18 (0.99-1.41)	0.21	1.18 (0.97-1.43)	0.78	**1.14 (1.01-1.28)**	0.52
LEP A19G	3	**0.74 (0.59-0.94)**	0.52	0.95 (0.82-1.10)	0.65	0.91 (0.79-1.04)	0.87	**0.76 (0.61-0.94)**	0.37	**0.89 (0.80-0.99)**	0.82
LEPR Q223R	2	0.90 (0.71-1.13)	0.77	0.95 (0.79-1.14)	0.63	0.93 (0.78-1.11)	0.62	0.93 (0.76-1.14)	0.95	0.95 (0.84-1.06)	0.69
LEPR rs1327118	1	0.94 (0.36-2.46)	NR	0.90 (0.68-1.20)	NR	0.90 (0.68-1.19)	NR	0.96 (0.37-2.51)	NR	0.92 (0.72-1.18)	NR
DLBCL											
LEP G2548A	2	1.29 (0.95-1.76)	0.92	1.11 (0.86-1.44)	0.54	1.17 (0.92-1.49)	0.64	1.21 (0.93-1.59)	0.81	1.14 (0.98-1.34)	0.88
LEP A19G	2	0.81 (0.57-1.16)	0.26	0.97 (0.76-1.24)	0.49	0.93 (0.74-1.17)	0.86	0.80 (0.47-1.35)	0.15	0.92 (0.78 -1.08)	0.55
LEPR Q223R	2	0.82 (0.58-1.14)	0.62	0.95 (0.74-1.23)	0.67	0.92 (0.72-1.17)	0.85	0.85 (0.64-1.14)	0.42	0.91 (0.78-1.07)	0.79
FL											
LEP G2548A	2	1.17 (0.83- 1.64)	0.30	1.22 (0.75-1.97)	0.08	1.20 (0.77-1.87)	0.09	1.02 (0.76-1.37)	0.84	1.10 (0.93-1.30)	0.22
LEP A19G	2	**0.56 (0.37-0.85)**	0.69	1.09 (0.75-1.60)	0.13	0.96 (0.68-1.35)	0.16	**0.54 (0.37-0.81)**	0.94	0.84 (0.71-1.00)	0.31
LEPR Q223R	2	1.26 (0.90-1.76)	0.63	1.10 (0.83-1.45)	0.70	1.14 (0.88-1.48)	0.90	1.18 (0.89-1.56)	0.41	1.12 (0.94-1.32)	0.70

LEP: leptin, LEPR: leptin receptor, N: number of studies in each analysis, OR: odds ratio, CI: confidence interval, p: value for heterogeneity, NR: not reported, NHL: Non-Hodgkin's lymphoma, DLBCL: diffuse large B cell lymphoma, FL: follicular lymphoma. Statistically significant results ($p< 0.05$) are highlighted in bold.

Quantitative synthesis

Overall, as shown in Table 2, we observed that the LEP A19G polymorphism decreased NHL risk in the homozygote (AA vs GG; OR=0.74; 95% CI=0.59-0.94, p=0.52; Figure 2), the recessive model (AA/AG vs GG; OR=0.76; 95% CI=0.61-0.94; p=0.37; Figure 3), and the additive model (A vs G; OR=0.89; 95% CI=0.80-0.99; p=0.82; Figure 4). We also observed that the LEP G2548A polymorphism increased NHL risk in the homozygote model (AA vs GG; OR=1.27; 95% CI=1.01-1.60; p=0.63; Figure 2), and the additive (A vs G; OR=1.14; 95% CI=1.01-1.28; p=0.52; Figure 4) when all the eligible studies were pooled into the meta-analyses. In the homozygote comparison, heterozygote comparison, dominant genetic, recessive genetic and additive models, all the p values of Q-test were > 0.05 and I^2 values were < 50%.

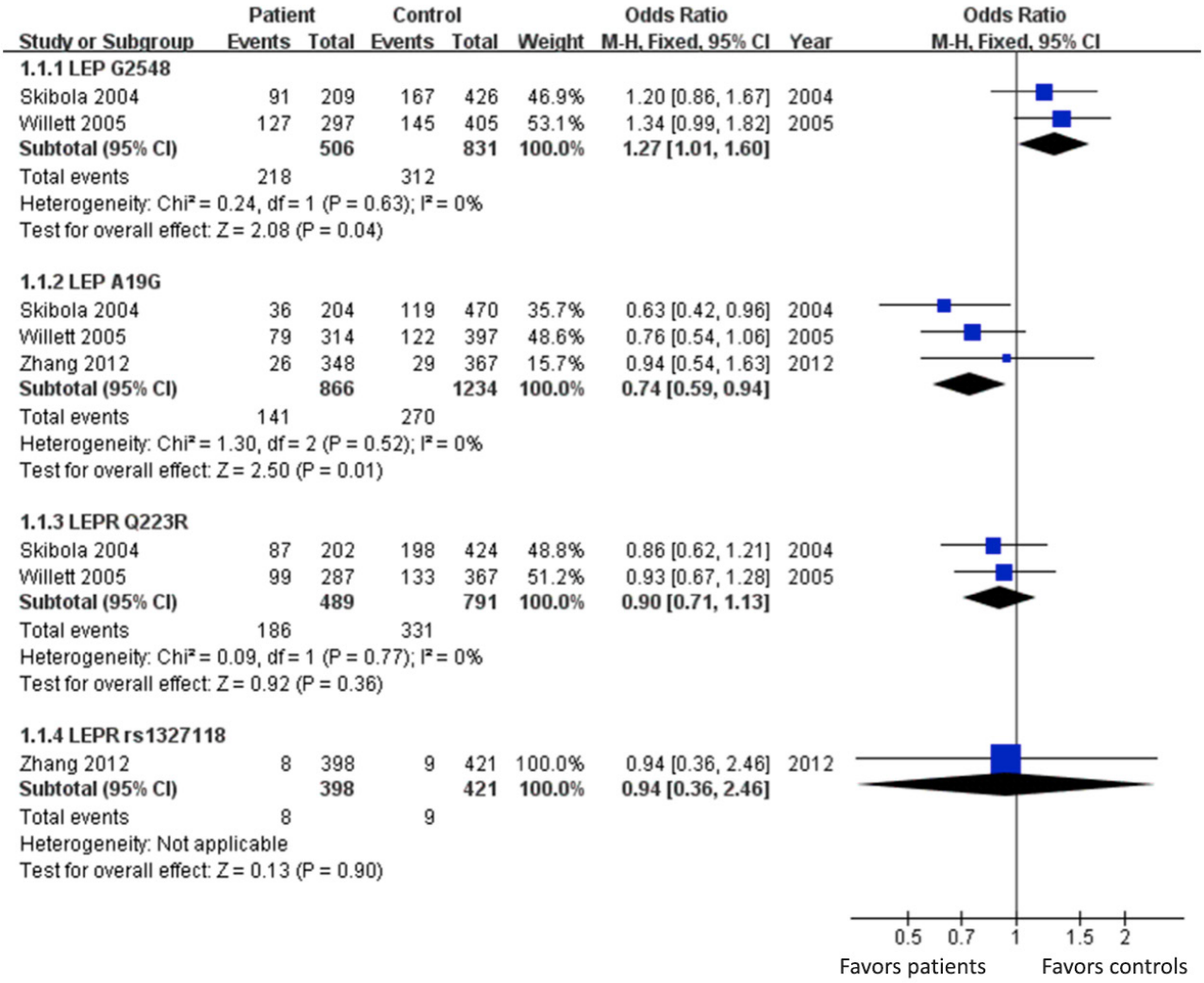

Figure 2. Forest plot of homozygote comparison of LEP or LEPR polymorphisms and non-Hodgkin lymphoma risk (fixed model). The overall OR is shown. The OR of each study is marked with a blue diamond. The overall OR is indicated by black diamond.

We then evaluated the effects of the LEP and LEPR polymorphisms according to different NHL types. The results of stratified analyses are listed in Table 2. Subgroup analyses for NHL types indicated that the pooled ORs for the homozygote (AA vs GG; OR=0.56; 95% CI 0.37-0.85) (Figure 5) and the recessive model (OR=0.54; 95% CI 0.37-0.81) (Figure 6) suggested that the LEP A19G polymorphism was significantly associated with a decreased FL risk, while no significant association was observed in any genetic model for DLBCL.

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. Egger's test was used to provide statistical evidence of funnel plot symmetry. The results did not present any obvious evidence of publication bias.

Discussion

This meta-analysis of 3 studies involving 3926 cases and 5785 controls was conducted in order to yield a valid conclusion concerning the potential association between LEP and LEPR polymorphisms and NHL risk. Skibola et al. observed that genetic polymorphisms in the LEP and LEPR genes that are associated with an obese phenotype were associated with increased NHL risk [3], and suggested that the regulation of the immune function of leptin and its receptor may resolve the mechanisms underlying the relationship be-

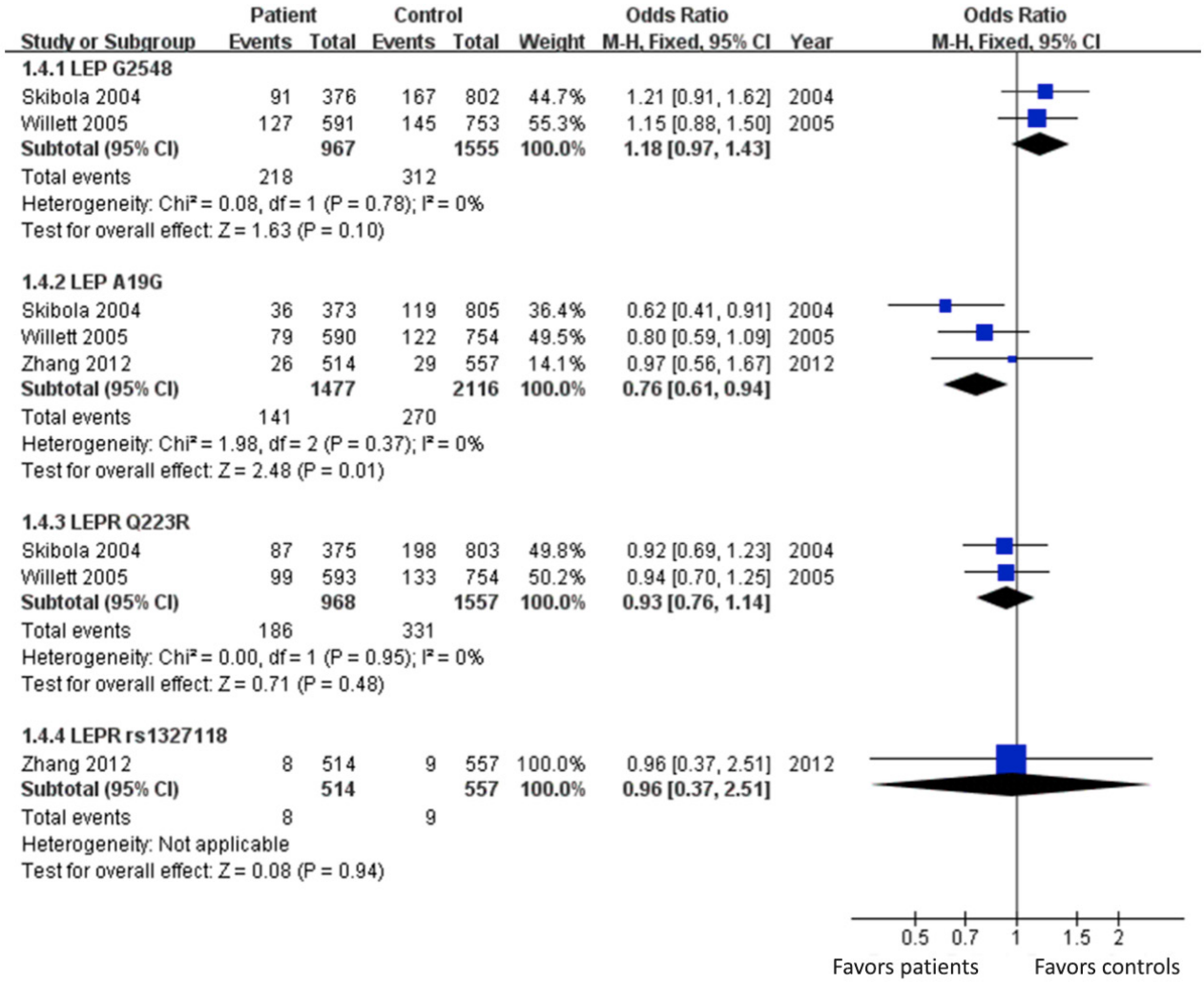

Figure 3. Forest plot of recessive model of LEP or LEPR polymorphisms and non-Hodgkin lymphoma risk (fixed model). The overall OR is shown. The OR of each study is marked with a blue diamond. The overall OR is indicated by black diamond.

tween NHL and obesity. Willett et al. [4] reported that variants in the LEP gene and obesity may be important in the pathogenesis of NHL. However, studies focusing on the association of the LEP and LEPR polymorphism with NHL susceptibility had controversial conclusions [3-5]. The lack of concordance across many of these studies reflects limitation in the studies, such as obesity, diet, hormone, 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 the LEP G25548A polymorphism and increased NHL cancer risk. Patients carrying the A allele of LEP G2548A had increased NHL risk compared to patients homozygous for the G allele. A marginally significant association between the LEP A19G polymorphism and decreased NHL risk was detected after comparison of homozygote, recessive and additive genetic models. Subgroup analyses for NHL types suggested that the LEP A19G polymorphism was significantly associated with decreased FL risk but not for DLBCL. Several factors such as environmental factors and genetic backgrounds might contribute to this discrepancy.

There were some limitations in our meta-analysis. First, the sample size in any given study was not sufficiently large, which could increase the probability of false positive or false negative results. It might be difficult to come to a sound conclusion if the number of included studies in subgroups is low. Second, because the original data was unavailable, it was difficult to evaluate

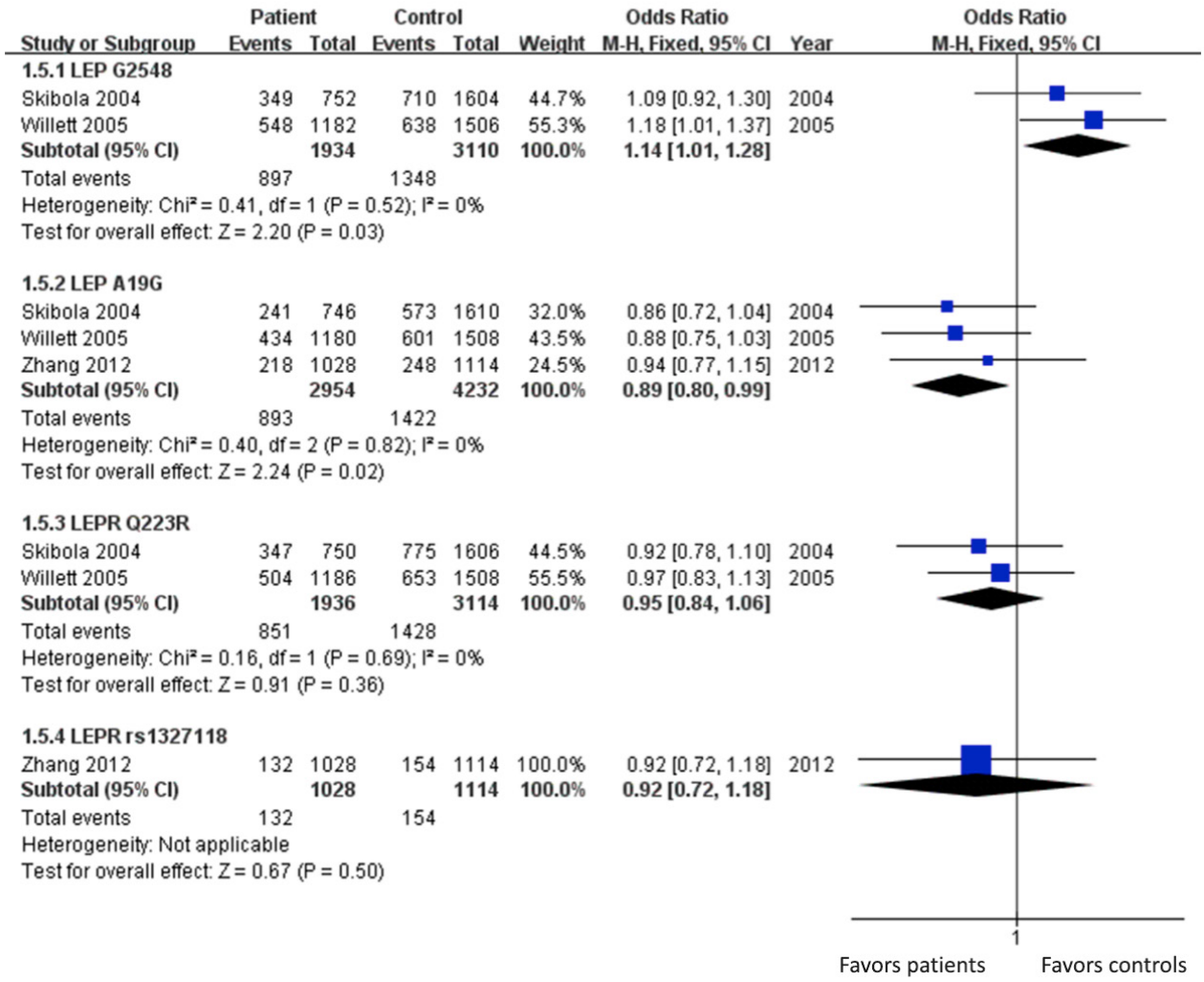

Figure 4. Forest plot of additive model of LEP or LEPR polymorphisms and non-Hodgkin lymphoma risk (fixed model). The overall OR is shown. The OR of each study is marked with a blue diamond. The overall OR is indicated by black diamond.

the roles of some special environmental factors and lifestyles such as diet, alcohol consumption and smoking status in developing NHL. 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 genetic polymorphism is significantly associated with higher NHL risk, and the LEP A19G genetic polymorphism is significantly associated with decreased NHL risk, especially FL. Large well designed epidemiological studies are needed to validate our findings.

Acknowledgement

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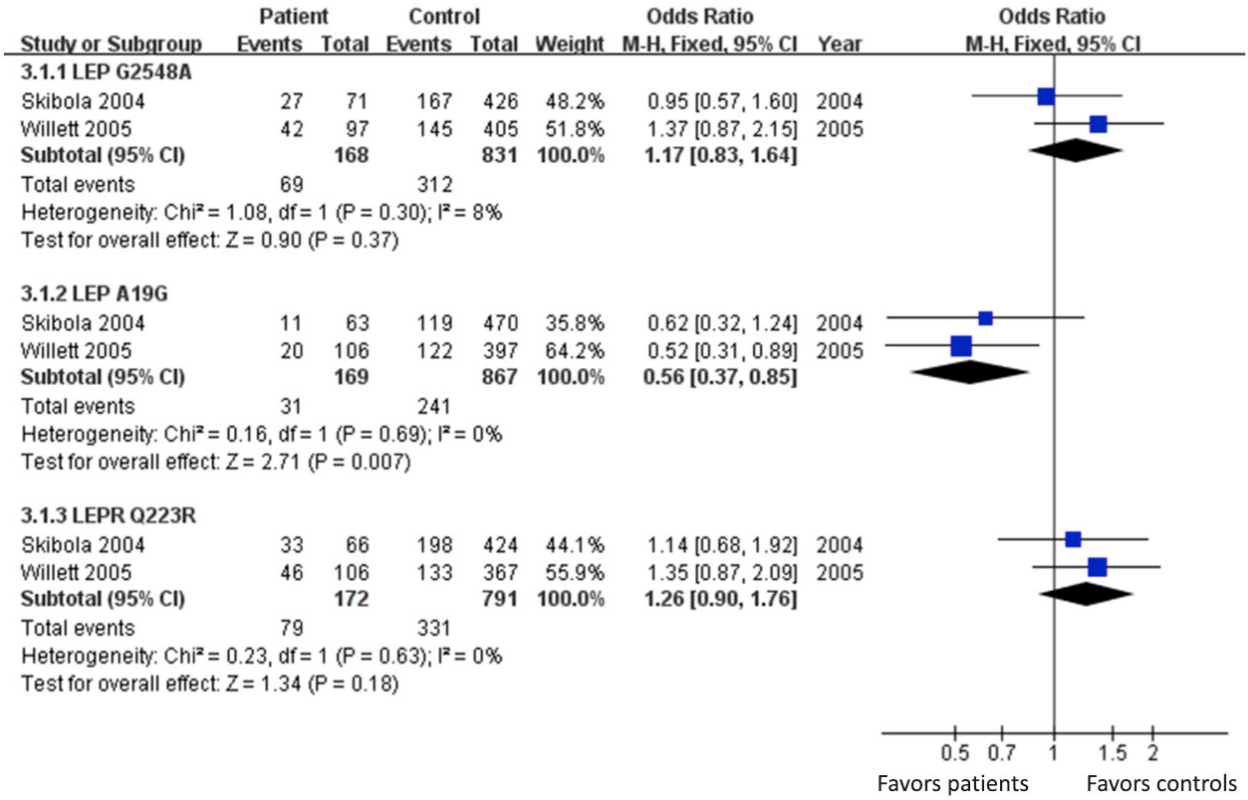

Figure 5. Forest plot of homozygote comparison of LEP or LEPR polymorphisms and follicular lymphoma (FL) risk (fixed model). The overall OR is shown. The OR of each study is marked with a blue diamond. The overall OR is indicated by black diamond.

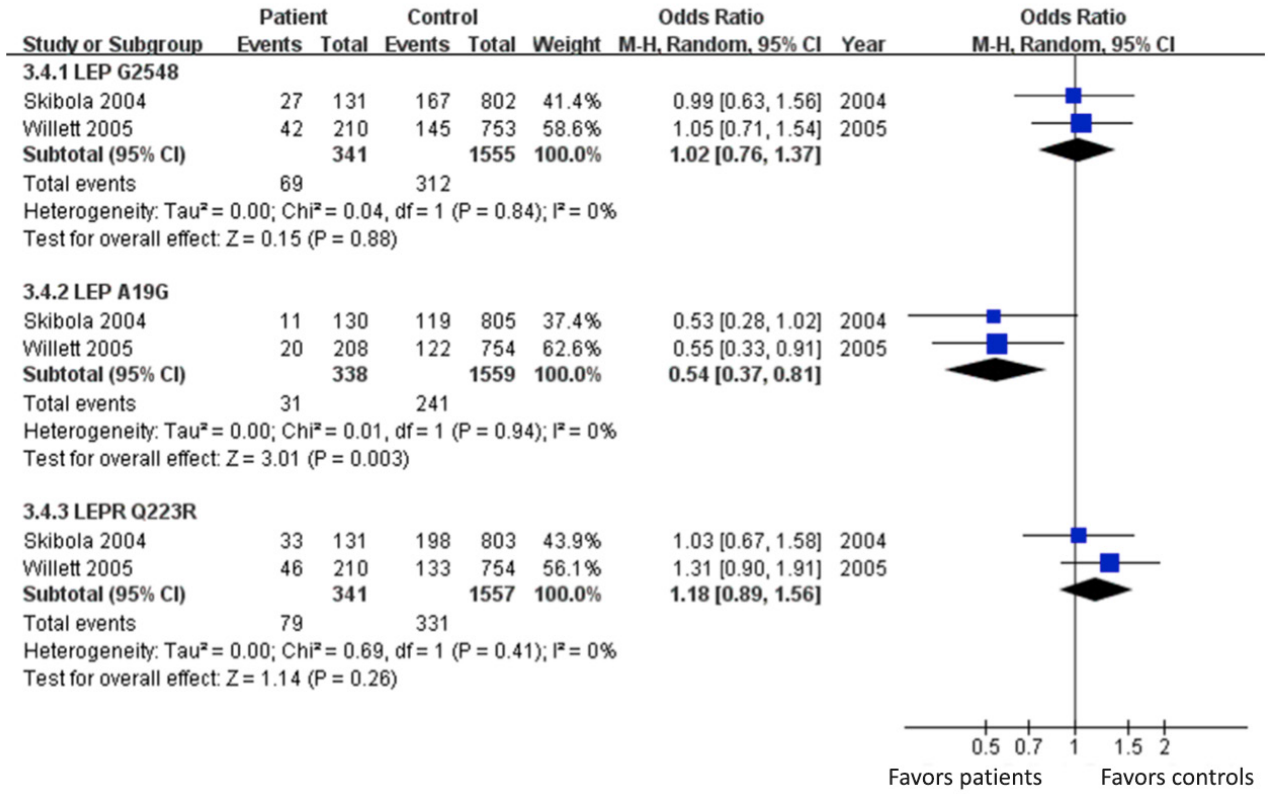

Figure 6. Forest plot of recessive model of LEP or LEPR polymorphisms and follicular lymphoma (FL) risk (fixed model). The overall OR is shown. The OR of each study is marked with a blue diamond. The overall OR is indicated by black diamond.

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