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Original Article

Genetic association between leptin-2548G/A polymorphism and risk of cancer: a meta analysis

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Abstract: Objective: Abundance of evidence implicated that leptin may play a decisive role in cancer occurrence, but the reported results varied across the individually published studies. The objective of this study is to access to what extent the extensively studied -2548G/A polymorphism of *LEP* gene acts on the onset of multiple cancers. Methods: Eligible studies included in this meta-analysis were identified electronically in PubMed and Embase, and manually in relevant literature. Crude odds ratio (OR) with corresponding 95% confidence interval (CI) was calculated to estimate the risk of cancer associated with the -2548G/A polymorphism. Results: 12 association studies with a total of 5,618 cancer cases and 6,509 healthy controls were pooled into this meta-analysis. The results revealed that compared with the G allele, the A allele was associated with modestly increased risk of overall cancer (OR, 1.21; 95% CI, 1.02-1.44). Following further stratified analyses, a borderline association was indicated in prostate cancer (OR, 1.18; 95% CI, 1.00-1.39), breast cancer (OR, 1.11; 95% CI, 1.00-1.22) and Caucasians (OR, 1.19; 95% CI, 1.00-1.41). Conclusions: This meta-analysis reveals that the A allele of -2548G/A polymorphism may be a determinant of cancer development.

Keywords: Leptin, polymorphism, cancer, risk

Introduction

Leptin is an adipocyte-derived cytokine with a central role in food uptake, nutrient absorption and energy metabolism by acting in hypothalamus. Leptin maintains body weight in a normal condition though suppressing food intake and promoting body fat consumption mediated by negative feedback regulatory loop under the control of sympathetic nervous system [1, 2]. In addition to the obvious role in body weight regulation, leptin is considered a new endocrine mediator involved in immune response, fertility, and hematopoiesis [3]. Increased leptin levels have been frequently found in obese subjects, with higher expression in females relative to males [3-5]. However, the mechanisms of obesity, leptin, and tumorigenesis still remain poorly understood.

Leptin functions as a mitogen in a panel of cell types, such as vascular endothelial cells [6], myelocytic and primitive hematopoietic progenitor cells [7], normal and malignant breast epithelial cells [8]. Moreover, leptin participates in several neoplastic processes, including inhibiting apoptosis, mediating immune suppression and promoting cell proliferation [9, 10]. Several epidemiological studies have reported the correlation between leptin and multiple cancers. Significantly elevated serum levels of leptin were found in breast cancer cell lines in comparison to the same patients of benign cancer cell lines [11, 12]. Meanwhile, reports estimating the effects of leptin on cancers of prostate, esophagus, and colon showed leptin was a risk factor for these cancers [13, 14]. These data suggest that leptin is likely to play a key role in carcinogenesis.

In the leptin gene 5' promoter region, there is a G to A substitution at nucleotide -2548 upstream of the ATG start site. The A allele of -2548G/A polymorphism was found to be asso-

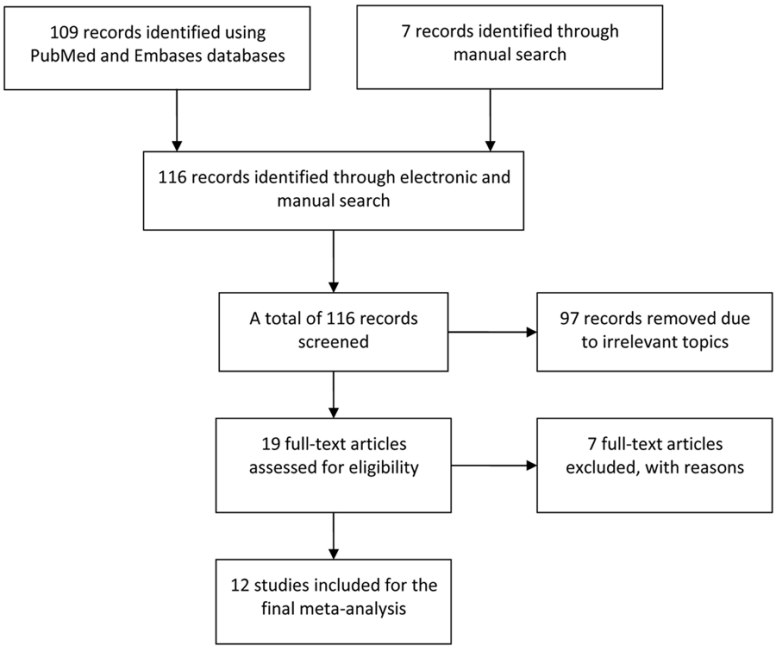

Figure 1. Flow chart of selection of studies and specific reasons for exclusion from the meta-analysis.

ciated with higher leptin levels before diet and lower BMI loss in women [15]. It is also reported that frequency of the G allele is higher in the overweight subjects and men carrying this allele have lower leptin concentration [16]. As compared to the GA/GG carriers, leptin secretion rate and leptin mRNA levels of adipose tissue are obviously higher in carriers with the AA genotype [17]. The functional influence of the -2548G/A polymorphism on leptin expression stimulates great interest of many investigators to examine its association with various cancers [18-24]. However, the inconsistent results fail to help derive a conclusive estimate of the effect size. Therefore, we performed a meta-analysis of early-release publications to clarify whether the -2548G/A polymorphism acts on cancer susceptibility in the first place.

Methods

Literature search

To identify the potentially possible publications, we conducted a computer-based search in PubMed (http://www.ncbi.nlm.nih.gov/) and Embase databases (http://www.embase.com), supplemented with a manual search of references cited in relevant meta-analyses and review articles to derive additional usable data for this meta-analysis. We used search terminology (polymorphism or polymorphisms) AND ((leptin) OR (*LEP*) OR (-2548A/G) OR (rs7799039)) AND (cancer) and their synonyms (variants, genotypes) to identify studies for this study.

Inclusion criteria

We checked eligibility of the studies prior to including them in the meta-analysis according to the following criteria: (1) a case-control study with matching control subjects; (2) investigated cancer risk associated with the -2548G/A polymorphism; and (3) reported available genotype frequencies for both patient and control populations.

Data extraction

Two independent authors extracted data in duplicate using a standard protocol. Data gathered from each study included name of first author, year of publication, ethnicity/origin of subjects, country of study where it was conducted, cancer type (if the cancer was investigated in less than two studies, it was merged into "others" group in the meta-analysis), mean age (range) of cases, and genotyping information on the -2548G/A polymorphism. If a study reported racially different subpopulations, we treated each subpopulation as a separate comparison. In case of disputes over certain extracted items, all authors participated in discussion until a consensus was reached.

Data analysis

The strength of an association between the -2548G/A polymorphism and cancer risk was estimated by calculating crude odds ratio (OR) with corresponding 95% confidence interval (CI) for AA vs. GG, AA + GA vs. GG, AA vs. GA + GG, A vs. G, and GA vs. GG genetic models. Cochran Q test and I^2 statistic were used to measure the extent of inconsistency among the results. Absence of significant heterogeneity

Table 1. Summary of articles included in the meta-analysis

Study	Publication year	Country	Ethnicity	Cancer type	Total sample		Mean age (range)
					case	control	
Slattery et al.	2008	USA	Caucasian	CRC	1565	1965	- (30-90)
Pechlivanis et al.	2009	Czech	Caucasian	CRC	659	711	62 (27-85)
Vasku et al.	2009	Czech	Caucasian	CRC	100	100	68 ± 10.2
Ribeiro et al.	2004	Portugal	Caucasian	PCa	143	118	67 (47-88)
Moore et al.	2009	USA	Caucasian	PCa	947	863	58.7
Ribeiro et al.	2012	Portugal	Caucasian	PCa	449	555	68.1
Snoussi et al.	2006	Tunisia	African	BC	308	222	50 ± 24
Cleveland et al.	2010	USA	Caucasian	BC	1059	1101	-
Ribeiro et al.	2006	Portugal	Caucasian	LC	124	139	63 (38-89)
Chovanec et al.	2009	Czech	Caucasian	EC	66	535	64.3 ± 10.3
Yapijakis et al.	2009	Greece	Caucasian	OC	150	152	54.2 ± 10.2 (40-83)
Kim et al.	2012	Korea	Asian	GC	48	48	55.2 ± 9.9

Abbreviations: CRC, colorectal cancer; PCa, prostate cancer; BC, breast cancer; LC, lung cancer; EC, endometrial cancer; OC, oral cancer; GC, gastric cancer.

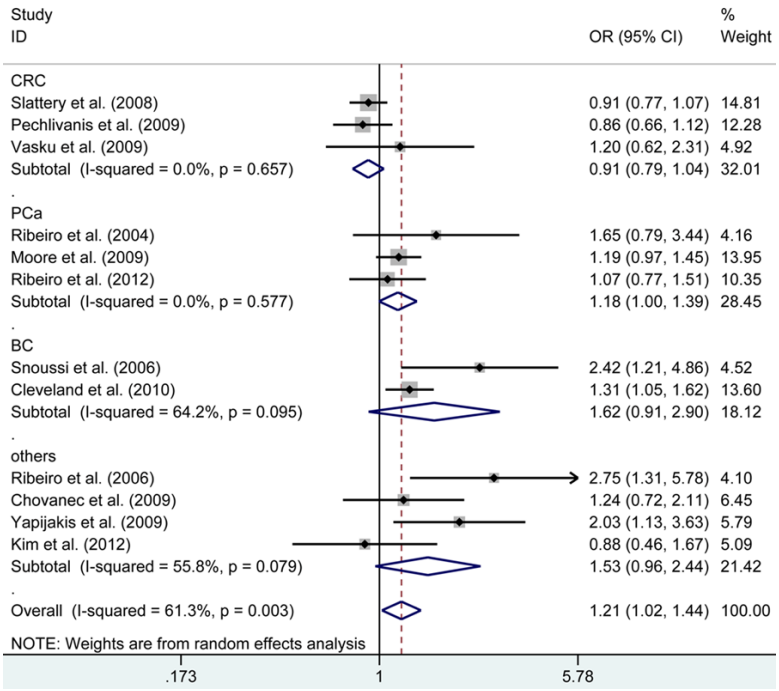

Figure 2. Meta-analysis with a random-effects model for the association between cancer risk and the -2548G/A polymorphism (AA vs. GA + GG) is illustrated in subgroup analysis by cancer type. OR: odds ratio; CI: confidence interval; P and I^2, measure to quantify the degree of heterogeneity in meta-analyses.

was fixed at P values less than 0.1 and I^2 exceeding 50% [25]. The summary OR estimate across studies was pooled by the fixed effects model using the Mantel-Haenszel method (P > 0.1 and I^2 < 50%) or by the random-effects model using the DerSimonian and Laird method (P < 0.1 and I^2 > 50%) [26, 27]. We performed sensitivity and subgroup analyses to identify the main source of heterogeneity. Publication bias was evaluated by funnel plots and Egger's test [28]. All statistical analyses were done with STATA software, V.12.0 (Stata Corporation, College Station, TX). A P-value < 0.1 was considered as an indication for significant results.

Results

Eligible studies

Search of electronic databases resulted in 12 articles [18-24, 29-33] that met the predescribed inclusion criteria and were selected for the meta-analysis. Flow chart showing exclusion/inclusion of studies is detailed in **Figure 1**. As shown in **Table 1**, subjects from 10 studies were Caucasians and the remaining were Asians or Africans. Of the 12 studies, 7 types of cancer were involved including colorectal cancer (CRC, 3 studies), prostate cancer (PCa, 3 studies), breast cancer (BC, 2 studies) and other four cancers, with each type investigated in one

Table 2. Meta-analysis of the association between the *LEP* -2548G/A polymorphism and cancer risk

Variables	No. Of studies	AA vs. GG		AA + GA vs. GG		AA vs. GA + GG		A vs. G		GA vs. GG	
		OR (95% CI)	P_{het}	OR (95% CI)	P_{het}	OR (95% CI)	P_{het}	OR (95% CI)	P_{het}	OR (95% CI)	P_{het}
All	12	1.14 (0.99, 1.32)	0.085	1.02 (0.96, 1.08)	0.974	1.21 (1.02, 1.44)	0.003	1.04 (0.99, 1.09)	0.356	1.01 (0.94, 1.08)	0.976
Cancer type											
CRC	3	0.93 (0.80, 1.08)	0.722	0.99 (0.91, 1.08)	0.878	0.91 (0.79, 1.04)	0.657	0.97 (0.91, 1.04)	0.735	1.01 (0.91, 1.11)	0.870
PCa	3	1.15 (0.92, 1.44)	0.296	1.03 (0.93, 1.15)	0.562	1.18 (1.00, 1.39)	0.577	1.07 (0.98, 1.17)	0.370	1.03 (0.90, 1.17)	0.546
BC	2	1.65 (0.77, 3.56)	0.037	1.04 (0.93, 1.18)	0.207	1.62 (0.91, 2.90)	0.095	1.11 (1.00, 1.22)	0.095	1.01 (0.88, 1.16)	0.236
others	4	1.37 (0.98, 1.91)	0.621	1.02 (0.84, 1.25)	0.968	1.53 (0.96, 2.44)	0.079	1.12 (0.96, 1.32)	0.874	0.97 (0.76, 1.23)	0.873
Ethnicity											
Caucasian	10	1.09 (0.96, 1.24)	0.232	1.01 (0.95, 1.07)	0.991	1.19 (1.00, 1.41)	0.006	1.03 (0.98, 1.08)	0.561	1.00 (0.94, 1.07)	0.979
African	1	2.65 (1.30, 5.41)	-	1.24 (0.93, 1.66)	-	2.42 (1.21, 4.86)	-	1.35 (1.05, 1.73)	-	1.20 (0.88, 1.63)	-
Asian	1	1.00 (0.49, 2.01)	-	1.00 (0.57, 1.77)	-	0.88 (0.46, 1.67)	-	0.95 (0.62, 1.45)	-	1.02 (0.38, 2.68)	-

P_{het}: *p* value for heterogeneity based on Q test, OR: odds ratio, CI: confidence interval.

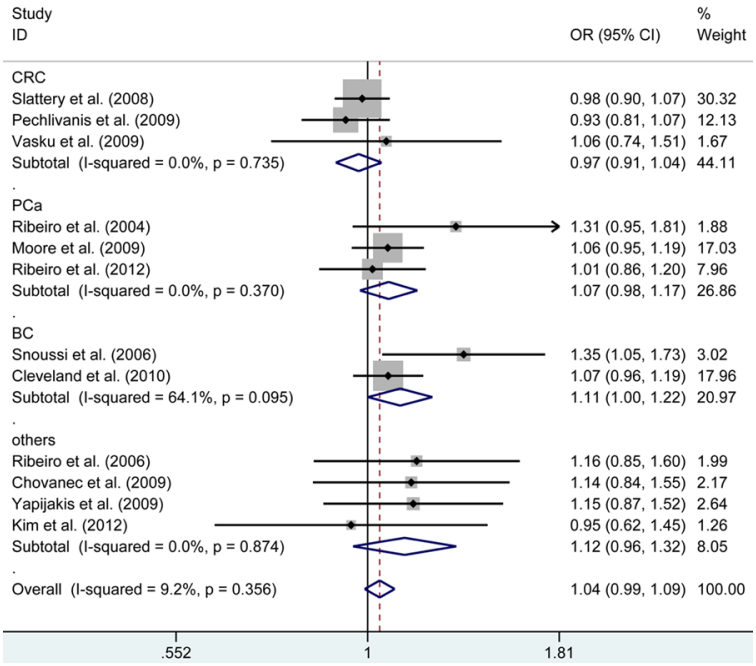

Figure 3. Meta-analysis with a fixed-effects model for the association between cancer risk and the -2548G/A polymorphism (A vs. G) is illustrated in subgroup analysis by cancer type. OR: odds ratio; CI: confidence interval; P and I^2, measure to quantify the degree of heterogeneity in meta-analyses.

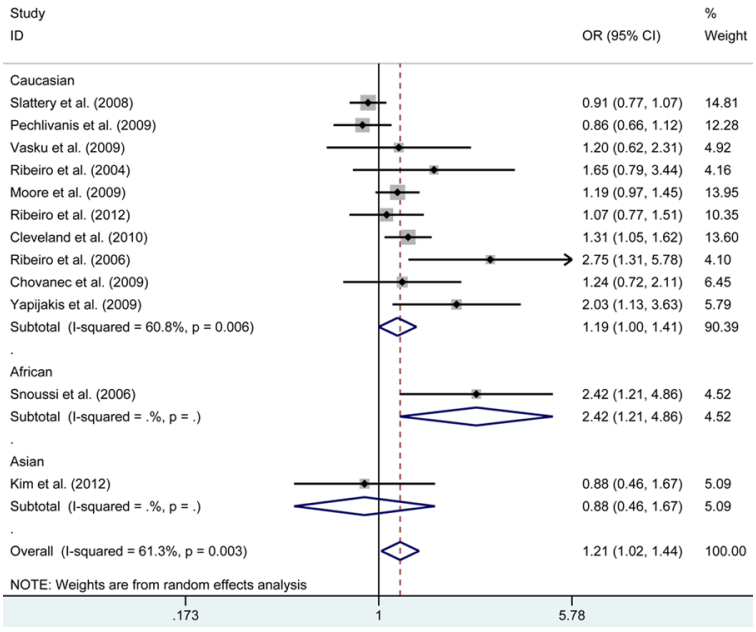

Figure 4. Meta-analysis with a random-effects model for the association between cancer risk and the -2548G/A polymorphism (AA vs. GA + GG) is illustrated in subgroup analysis by cancer type. OR: odds ratio; CI: confidence interval; P and I^2, measure to quantify the degree of heterogeneity in meta-analyses.

study. Details of the study characteristics are described in **Table 1**.

Meta-analysis results

In a combined meta-analysis (5,618 cases, 6,509 controls) of the association between the -2548G/A polymorphism and cancer susceptibility, we observed an OR of 1.21 under the AA vs. GA + GG genetic model (95% CI, 1.02-1.44) (**Figure 2**), whereas other genetic models did not provide any statistically significant results (**Table 2**).

In the subgroup analysis by cancer type, while we failed to found significant associations, we did observe a borderline increased risk of PCa under the AA vs. GA + GG model (OR, 1.18; 95% CI, 1.00-1.39) (**Figure 2**) and BC under the allele model (OR, 1.11; 95% CI, 1.00-1.22) (**Figure 3**).

We also evaluated the effect of the -2548G/A polymorphism according to ethnicity and obtained an OR of 1.19 in carriage of the AA genotype relative to the GA + GG genotypes (95% CI, 1.00-1.41) (**Figure 4**) in Caucasian populations. Additionally, subgroup of African population demonstrated that the -2548G/A polymorphism was significantly associated with cancer risk. However, these findings may lack statistical power due to the constraint of limited data pooled.

Significant between-study heterogeneity was indicated in this meta-analysis. The results presented P values of 0.085 and 0.003 for the AA vs. GG and AA vs. GA + GG comparisons respectively. With the help of subgroup analyses and sensitivity analyses, we identified three studies [20, 21, 23], with significant deviations from HWE, largely contributed to the obvious heterogeneity. Removal of them from the total meta-analysis successfully increased the homogeneity across studies (P,

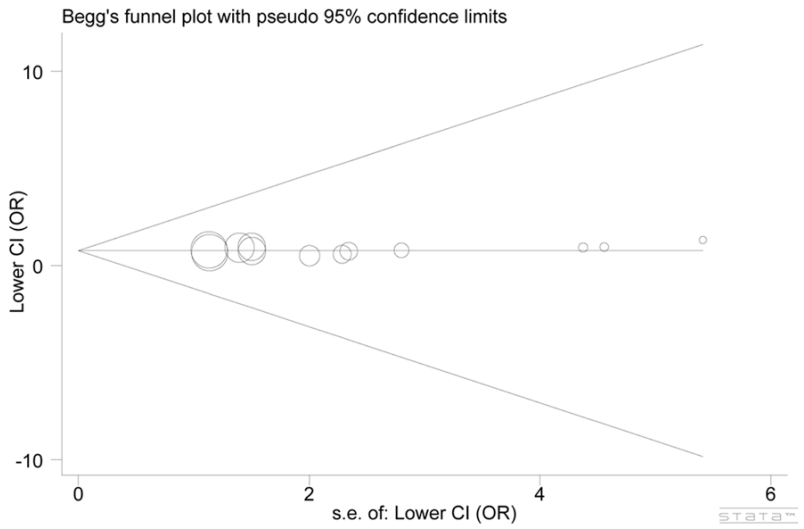

Figure 5. Funnel plot for the 12 included studies under the AA vs. GG genetic model. P, 0.373 for Begg's test; P, 0.596 for Egger's test; the circles represent the weight of individual study.

0.416 for AA vs. GG; P, 0.120 for AA vs. GA + GG). Interestingly, the significant association of the -2548G/A polymorphism and cancer risk observed under the AA vs. GA + GG genetic model in total sample was lost when we excluded the three studies (OR, 1.06; 95% CI, 0.97-1.16).

Publication bias

Begg's funnel plots and Egger's test were performed to diagnose the publication bias. No publication bias was detected for the studies of the -2548G/A polymorphism using the two analytic tools (AA vs. GG: P, 0.373 for Begg's test; P, 0.596 for Egger's test) (**Figure 5**).

Discussion

Association studies provide a potentially powerful approach for the identification of genetic variants involved in susceptibility to common disease. A large number of variants with modest but real effects on the risk of these diseases may exist in the human genome, and studies with thousands of subjects could convincingly identify such variants [34]. The current meta-analysis of 5,618 cases and 6,509 controls from 12 association studies was performed in an effort to estimate the effects of the well-characterized -2548G/A polymorphism on cancer risk. Overall, a moderately increased risk of cancer was found among the carriers of the AA genotype relative to the GA + GG genotypes. We also observed a marginal increase in the riskof PCa (AA vs. GA + GG) and BC (A vs. G). Subgroup analysis by ethnicity demonstrated similar effects ascribed to the -2548G/A polymorphism. Nevertheless, since the meta-analysis was on the basis of a relatively small sample size, from which we derived statistical evidence of a minor association between the -2548G/A polymorphism and cancer risk, so our results correlated with this polymorphism should always be treated as preliminary.

Leptin is a protein secreted from adipose tissue and has been shown in several reports to promote tumor growth [35]. A broad range of investigations have demonstrated strong evidence for an involvement of leptin in cell proliferation stimulation, apoptosis inhibition, cell migration and angiogenesis [8, 13, 36]. Many types of cancers, especially the commonly diagnosed CRC, PCa, and BC, have been hypothesized to result from aberrant expression of leptin under genetic control [30, 31, 33]. These evidence may explain the moderate but significant associations observed in the present analysis.

A recently published meta-analysis concerning CRC and PCa demonstrated that the -2548G/A polymorphism was associated with PCa rather than CRC [37]. In our meta-analysis, we combined all publications addressing the association of the -2548G/A polymorphism and cancer risk before June 19, 2013 and the results revealed a significantly elevated cancer risk, but only to implicate a marginal association in PCa. A major explanation for this disparity is the smaller number of subjects included in the former meta-analysis, which is a key factor required to reliably decide the polymorphism that confers susceptibility to common diseases. In addition, we found a borderline association between the A allele and cancer risk in the subjects of Caucasian descent, but not among those of Asian descent. One possibility is that

the small number of studies on Asians is insufficient enough to evaluate the exact effects of this polymorphism on cancer. More importantly, the A allele frequency is substantially different in Caucasians and Asians, with 45.4% in the former and 79.2% in the latter. The obvious difference implies that the role of the -2548G/A polymorphism in Asian cancer patients needs clarifying in future studies with a very large sample.

In our meta-analysis, we detected significant heterogeneity across studies and the overall results derived from the AA vs. GA + GG genetic model was quantitively modified when removing the studies deviated from HWE. Therefore, the association we attempted to validate should be further examined in a future larger study that restricts the analysis to the publications consistent with the law of HWE. Moreover, although the articles with usable data for this meta-analysis were comprehensively searched, the sample size for each cancer type is insufficiently large enough to identify the true association under investigation. To date, however, this is the first time that the association between the -2548G/A polymorphism and cancer risk has been systematically assessed, thus the findings may provide new insights for the understanding of the genetic predisposition to cancer.

To draw a conclusion, this meta-analysis provided supportive evidence for an association between the A allele of -2548G/A polymorphism and cancer risk. To expand the current understanding of the etiology of cancer in relation to the -2548G/A polymorphism, future larger and well-designed studies are required to confirm the findings of this investigation.

Disclosure of conflict of interest

None.

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