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Original Article

Cyclin D1 rs9344 G>A polymorphism and gastric cancer risk: a meta-analysis

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Abstract: The association between *Cyclin D1* (*CCND1*) rs9344 G>A (G870A) polymorphism and gastric cancer (GC) has been extensively investigated; however, the results remain conflicting. In the present study, we performed a meta-analysis to further address this issue. We carried out a meta-analysis, recruiting seven publications with 1,350 GC cases and 1,823 controls, to obtain a more comprehensive evaluation between the *CCND1* rs9344 G>A polymorphism and the susceptibility of gastric cancer. After combining all eligible studies, we found null association between CCND1 rs9344 G>A polymorphism and GC in all genetic models. In a stratified analysis by ethnicity, significant decreases in GC risk were observed for Caucasians in one genetic model: AA vs. GA+GG (OR, 0.65; 95% CI, 0.44-0.96; $P = 0.032$). Begg's Funnel plots and Egger's tests were created to measure the publication bias, and the shape of funnel was symmetry in four genetic models, suggesting the stability of our findings. The results highlight that CCND1 rs9344 G>A variants may be associated with the risk of gastric cancer among Caucasians.

Keywords: *Cyclin D1*, polymorphism, gastric cancer, meta-analysis

Introduction

It is estimated that a total of 951,600 new gastric cancer (GC) cases and 723,100 deaths occurred in 2012 worldwide, accounting for more than 6% of the total cancer cases and 8% of total cancer related deaths [1]. The incidence rates of GC vary widely across countries. The aetiology of GC is mixed. Evidence is mounting that GC is a complex disease resulting from interactions between genetic and environmental factors [2, 3]. Contributing various environmental risk factors for GC are not completely understood. Of late, several beneficial developments, including the lowering reliance on salt preserved foods, the increasing use of fridges, the elevating availability and intake of fresh produce and the effective control and treatment of chronic infection with *H. pylori* due to improved sanitation and antibiotics, decreased the incidence of GC. Many epidemiological studies highlighted that susceptibility to GC was affected by both genetic and environmental factors [4-6].

The *cyclin D1* (*CCND1*) gene located on human chromosome 1q31-32, which regulate the transition of cell cycle through the restriction point in G1 phase to S phase. The molecule mechanisms of *CCND1*, such as gene amplification, posttranscriptional modifications, rearrangements and polymorphisms can alter protein levels and impair CCND1 function, which may contribute to carcinogenesis [7]. In addition, Wnt/β-catenin signaling is associated with both tumorigenesis and the development of cancer [8]. Some target genes of this signal pathway have been identified *in vitro*, and CCND1 is one of the most important proteins [9]. The accumulating evidence showed that over-expression of CCND1 existed in many malignances, which might be correlated with metastases and poor prognoses of malignancy [10-12].

Some prior studies indicated that CCND1 is overexpressed in gastric cancer [13, 14]. *CCND1* gene is polymorphic, and multiple single nucleotide polymorphisms (SNPs) have been established, such as rs9344 G>A (G870A),

rs207471996 A>C, rs7177 A>C, rs602652 G>A and rs647451 C>T polymorphisms etc. Among them, the *CCND1* rs9344 G>A was the most widely studied for its implication in the susceptibility of GC. A meta-analysis indicated that the *CCND1* A870G variants might not be a risk factor for the development of GC [15]. However, in that study, only two case-control studies were included, the power was limited. Considering the vital role of *CCND1* rs9344 G>A gene in the development of GC, we conducted an updated meta-analysis to assess the GC susceptibility associated with *CCND1* rs9344 G>A variants. To the best of our knowledge, the current study is the most comprehensive meta-analysis performed to date with respect to the relationship between *CCND1* rs9344 G>A variants and GC risk.

Materials and methods

Search strategy

We extensively searched the PubMed, Embase, and CBM (Chinese Bio-Medicine), as well as CNKI (China National Knowledge Infrastructure) databases for all potential publications investigating the relationship of *CCND1* rs9344 G>A variants with GC risk. The last search update was September 10, 2015. The combination search terms were '*Cyclin D1*' or '*CCND1*' or 'cancer' or 'neoplasm' or 'carcinoma' or 'tumor' and 'gastric' or 'stomach', annexed with 'variant' or 'SNP' or 'mutation' or 'polymorphism'. There was no language restriction. All relevant studies conducted in human being were included. Additional publications were supplemented by searching of all references listed in the retrieved reviews or the included articles.

Inclusion criteria

Studies were recruited in this meta-analysis if they met the major included criteria: (1) designed as a case-control study evaluating the correlation of *CCND1* rs9344 G>A variants to GC susceptibility, (2) solid evidence for GC diagnosis, (3) provide genotype counts of *CCND1* rs9344 G>A variants between GC cases and controls for assessing odds ratios (ORs) and 95% confidence intervals (CIs) and (4) control genotype distributions was in agreement with Hardy-Weinberg equilibrium (HWE). Additionally, the latest investigation including the largest number of subjects was selected when the data were overlapping.

Exclusion criteria

The major exclusion criteria were: (1) not case-control study design, (2) reviews and (3) overlapping data.

Data extraction

The information listed below was carefully and independently extracted from each included study by three reviewers (S. Zhang, Y. Wang and H. Jiang): the first author, year of publication, country, ethnicity, region of gastric cancer, source of controls, number of cases and controls and HWE in controls. Discrepancy was addressed by discussion between the all reviewers.

Statistical analysis

Deviation from HWE in controls was tested by an internet-based the goodness-of-fit test (http://ihg.gsf.de/cgi-bin/hw/hwa1.pl). In this analysis, the strength of relationship between the *CCND1* rs9344 G>A variants and GC risk was measured by crude ORs with the corresponding 95% CIs. The significance was measured by the Z-test and *P*-value, and $P<0.05$ (two-tailed) was accepted as statistical significance criterion. Heterogeneity across studies was estimated by a Cocharan's Chi-square-based Q statistic and I^2 statistical tests [16]. If $P<0.10$ or $I^2>50\%$, the ORs were pooled by the random-effects model (the DerSimonian-Laird method) [17]; otherwise, the fixed-effects model was utilized (the Mantel-Haenszel method) [18]. Sub-group analyses were conducted to measure the specific effect according to different factors, such as ethnicity and the region of gastric cancer. The Begg's funnel plot and Egger's linear regression test were utilized to assess publication bias, which was estimated by visual inspection of an asymmetric plot [19, 20]. The consistence of the conclusions was checked by one-way sensitivity analysis. Further stratified analyses and Galbraith radial plot were harnessed to detect the source of heterogeneity. In this meta-analysis, all statistical analyses were conducted by STATA software (version 12.0).

Results

Eligible articles for meta-analysis

As shown in **Figure 1**, an extensively electronic search yielded a total of 750 potentially rele-

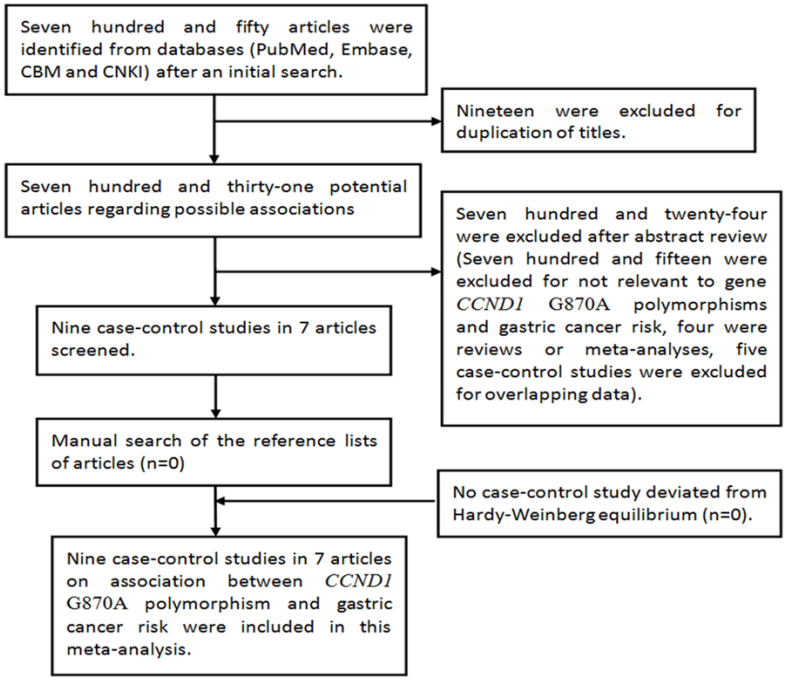

Figure 1. Flow diagram of articles selection process.

vant publications. There were some subgroups in two publications, we considered them separately [21, 22]. After applying additional filters, nine case-control studies in seven publications were eligible for inclusion [21-26].

Study characteristics

In total, nine separate case-control studies involving 1,350 GC cases and 1,823 controls were recruited in this meta-analysis [21-26]. Among them, six were Asians [22-26], three were Caucasians [21, 27]. As for the region of GC, three investigated cardiac gastric cancer [21-23], six investigated non-cardiac gastric cancer [21, 22, 24-27]. The information of each study is listed in **Table 1**. The frequency of the *CCND1* rs9344 G>A polymorphism and allele among cases and controls is listed in **Table 2**.

Meta-analysis results

After combining all eligible studies, we found null association of *CCND1* rs9344 G>A polymorphism with GC under all genetic model: A vs. G (OR, 0.99; 95% CI, 0.81-1.22; *P* = 0.950), AA vs. GG (OR, 0.95; 95% CI, 0.63-1.43; *P* = 0.803), AA+GA vs. GG (OR, 0.97; 95% CI, 0.69-1.36; *P* = 0.849) and AA vs. GA+GG (OR, 0.98; 95% CI, 0.73-1.32; *P* = 0.901) (**Table 3**; **Figure 2**). In a stratified analysis by ethnicity, significant decreases in GC risk were observed for Caucasians in one genetic model: AA vs. GA+GG (OR, 0.66; 95% CI, 0.47-0.95; *P* = 0.024), (**Table 3**). In a stratified analysis by region of GC, there was null association of *CCND1* rs9344 G>A polymorphism with GC (**Table 3**).

Tests for publication bias, sensitivity analyses, and heterogeneity

Begg's Funnel plot and Egger's linear regression test were created to measure the publication bias (**Figure 3**), and the shape of Begg's funnel was symmetry in four genetic model, suggesting no significant publication bias in this analysis (A vs. G: Begg's test *P* = 0.754, Egger's test *P* = 0.980; AA vs. GG: Begg's test *P* = 1.000, Egger's test *P* = 0.897; AA+GA vs. GG: Begg's test *P* = 0.602, Egger's test *P* = 0.667; AA vs. GA+GG: Begg's test P = 0.754, Egger's test P = 0.799).

We performed one-way sensitivity analyses to measure the influence of an individual study dataset on the pooled ORs with each dataset omitted in turn. The results indicated the findings of meta-analysis were stable (**Figure 4**) (data not shown).

As shown in **Table 3**, significant heterogeneity was found among the included studies. Since ethnicity, the region of GC, the source of control, sample sizes and publication year can influence the heterogeneity, we conduct subgroup analyses and the results were presented in **Table 3**. The results showed that non-cardiac gastric cancer, Asian populations, hospital-based study, sample sizes (<400 subjects) and publication year (≥2007) may contribute to the major source of heterogeneity. We used Galbraith radial plot to detect the outliers in the allele model, as shown in **Figure 5**, and found two studies [25, 26] might contribute to the major sources of heterogeneity.

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

Study	Year	Country	Ethnicity	Type of control	No. of cases/ controls	Region of gastric cancer	Genotype Method
Bukum et al.	2013	Turkey	Caucasians	HB	58/59	non-cardiac gastric cancer	PCR-RFLP
liu et al.	2009	China	Asians	HB	115/112	non-cardiac gastric cancer	PCR-RFLP
Tahara et al.	2009	Japan	Asians	HB	11/359	cardiac gastric cancer	PCR-RFLP
Tahara et al.	2009	Japan	Asians	HB	371/359	non-cardiac gastric cancer	PCR-RFLP
Jia et al.	2008	China	Asians	HB	159/162	non-cardiac gastric cancer	PCR-RFLP
Song et al.	2007	Korea	Asians	PB	253/442	non-cardiac gastric cancer	SSCP
Geddert et al.	2005	German	Caucasians	PB	95/253	cardiac gastric cancer	PCR-RFLP
Geddert et al.	2005	German	Caucasians	PB	191/253	non-cardiac gastric cancer	PCR-RFLP
Zhang et al.	2003	China	Asians	PB	87/183	cardiac gastric cancer	SSCP

PB: population-based; HB: hospital-based; PCR-RFLP: polymerase chain reaction-restriction fragment length polymorphism; SSCP: single-strand conformation polymorphism.

Table 2. Distribution of *CCND1* G870A polymorphism genotypes and alleles among gastric cancer patients and controls

		Case			Control			Case		Control		HWE, *P* value
Study	Year	AA	AG	GG	AA	AG	GG	A	G	A	G	
Bukum et al.	2013	13	28	16	17	31	11	54	60	65	53	0.635
liu et al.	2009	52	46	17	27	49	36	150	80	103	121	0.207
Tahara et al.												
Overall	2009	97	197	98	81	180	98	391	393	342	376	0.924
Cardia	2009	3	3	5	81	180	98	9	13	342	376	0.924
Non-cardia	2009	88	188	95	81	180	98	364	378	342	376	0.924
Jia et al.	2008	47	81	31	61	85	16	175	143	207	117	0.081
Song et al.	2007	57	125	71	114	226	102	239	267	454	430	0.623
Geddert et al.												
Overall	2005	43	188	55	54	136	63	274	298	244	262	0.224
Cardia	2005	14	55	26	54	136	63	83	107	244	262	0.224
Non-cardia	2005	29	133	29	54	136	63	191	191	244	262	0.224
Zhang et al.	2003	28	40	19	43	102	38	96	78	188	178	0.118

HWE: Hardy-Weinberg equilibrium.

Discussion

Up to now, several studies [21-26] and one meta-analyses [15] have investigated the relationship of *CCND1* rs9344 G>A polymorphism with GC; however, the results were inconclusive and ambiguous. Therefore, we conducted an updated meta-analysis and attempted to get a comprehensive assessment. To the best of our knowledge, this is the most extensive analysis focusing on the correlation between *CCND1* rs9344 G>A polymorphism and GC susceptibility. We found null association of *CCND1* rs9344 G>A polymorphism with overall GC under all genetic model. In a stratified analysis by ethnicity, *CCND1* rs9344 G>A variants was associated with the decreased risk of GC among Caucasians (AA vs. GA+GG: OR, 0.65; 95% CI, 0.44-0.96; P = 0.032), but not Asians.

CCND1 binds to and activates CDK4 and CDK6, which phosphorylates the retinoblastoma protein and further affects the gene amplification, transcription and posttranscriptional modifications that promote progression to the S-phase of the cell cycle [28]. Thus, CCND1 regulates cell proliferation and differentiation [29, 30]. The upregulation of CCND1 can accelerate cell proliferation, impair the cell cycle, alter the capacity of cells to undergo DNA repair, which promotes tumorigenesis and enhance the metastatic efficiency of malignancy [31-33]. Some

Table 3. Summary of results of the meta-analysis

	No. of study	A vs. G			AA vs. GG			AA+GA vs. GG			AA vs. GA+GG		
		OR (95% CI)	*P*	*P* (Q-test)	OR (95% CI)	*P*	*P* (Q-test)	OR (95% CI)	*P*	*P* (Q-test)	OR (95% CI)	*P*	*P* (Q-test)
Total	9	0.99 (0.81-1.22)	0.950	<0.001	0.95 (0.63-1.43)	0.803	0.001	0.97 (0.69-1.36)	0.849	0.001	0.98 (0.73-1.32)	0.901	0.006
Ethnicity													
Asians	6	1.05 (0.78-1.41)	0.753	<0.001	1.05 (0.59-1.86)	0.869	<0.001	0.92 (0.60-1.42)	0.711	0.002	1.16 (0.80-1.69)	0.427	0.006
Caucasians	3	0.94 (0.77-1.13)	0.499	0.310	0.82 (0.53-1.26)	0.367	0.304	1.05 (0.55-2.02)	0.882	0.032	0.66 (0.47-0.95)	0.024	0.968
Region of GC													
Cardiac gastric cancer	3	0.95 (0.75-1.21)	0.699	0.356	0.89 (0.55-1.44)	0.625	0.374	0.85 (0.58-1.24)	0.395	0.557	1.04 (0.70-1.55)	0.829	0.121
Non-cardiac gastric cancer	6	1.01 (0.77-1.33)	0.921	<0.001	0.98 (0.57-1.70)	0.942	<0.001	1.04 (0.66-1.65)	0.857	<0.001	0.96 (0.67-1.37)	0.816	0.004
Source of control													
PB	4	0.95 (0.82-1.09)	0.428	0.300	0.86 (0.64-1.16)	0.328	0.324	1.03 (0.68-1.56)	0.877	0.036	0.86 (0.60-1.23)	0.399	0.107
HB	5	1.01 (0.67-1.53)	0.967	<0.001	0.97 (0.43-2.18)	0.937	<0.001	0.87 (0.46-1.64)	0.669	0.001	1.12 (0.68-1.83)	0.656	0.009
Sample sizes													
<400	5	1.02 (0.67-1.55)	0.927	<0.001	0.94 (0.40-2.21)	0.895	<0.001	0.92 (0.51-1.65)	0.769	0.003	1.07 (0.61-1.87)	0.816	0.001
≥400	4	0.98 (0.86-1.11)	0.711	0.390	0.94 (0.72-1.23)	0.668	0.439	1.03 (0.66-1.60)	0.892	0.017	0.89 (0.71-1.11)	0.298	0.413
Publication year													
≥2007	6	0.98 (0.72-1.34)	0.893	<0.001	0.92 (0.50-1.69)	0.787	<0.001	0.86 (0.54-1.37)	0.534	0.001	1.05 (0.72-1.53)	0.812	0.011
<2007	3	1.02 (0.85-1.22)	0.847	0.357	1.00 (0.67-1.49)	0.984	0.327	1.18 (0.72-1.93)	0.523	0.084	0.87 (0.49-1.53)	0.624	0.048

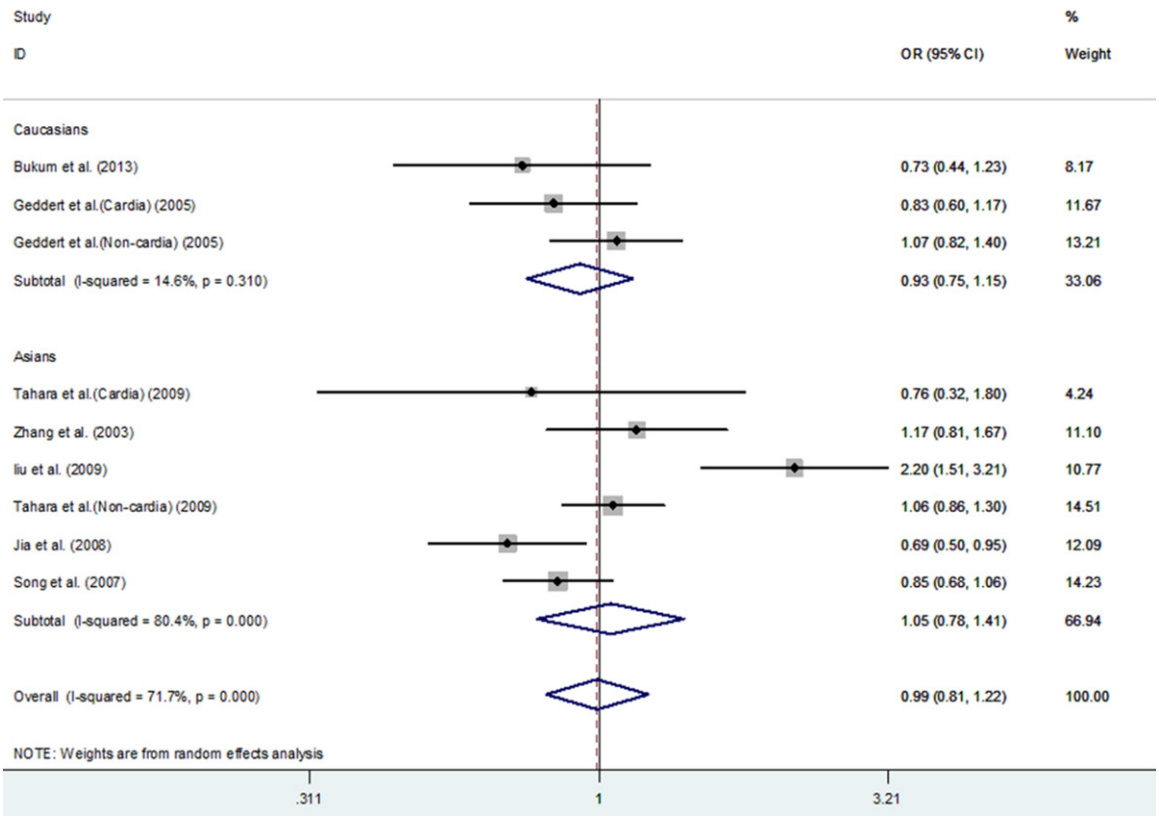

Figure 2. Meta-analysis with a random-effects model for the association between the risk of gastric cancer and the *CCND1* G870A polymorphism (A vs. G).

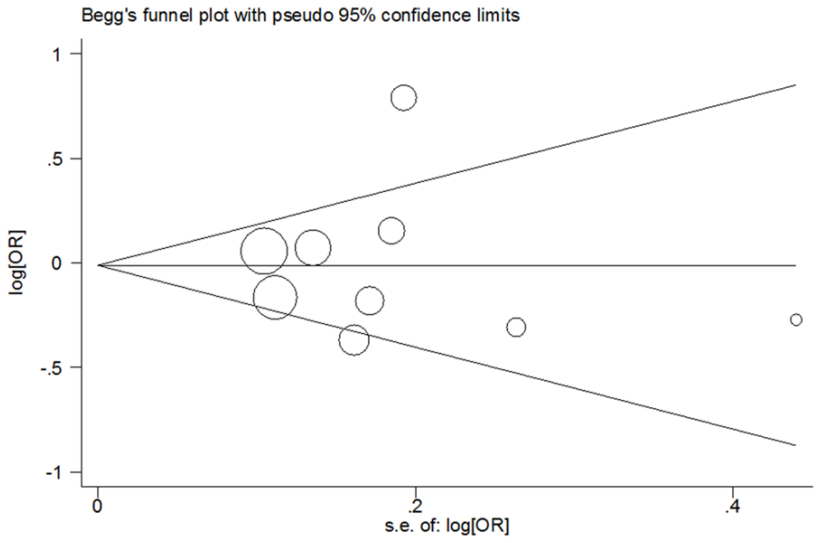

Figure 3. Begg's funnel plot of meta-analysis of between the *CCND1* G870A polymorphism and the risk of gastric cancer (A vs. G).

prior experimental studies showed that CCND1 is over-expressed in gastric cancer [13, 14]. With a growing interest in the correlation between *CCND1* rs9344 G>A and GC risk, several studies have explored the hypothesis that *CCND1* rs9344 G>A variants modify the risk of GC [21-26], but the findings are inconsistent. Based on our pooled analysis of 1,350 GC cases and 1,823 controls, the *CCND1* rs9344 G>A variants may not be associated with the risk of GC. While in a stratified analysis by ethnicity, the results highlighted that *CCND1* rs9344 G>A variants was associated with the decreased risk of GC among Caucasians. However, only three separate case-control studies [21, 27] involving 344 GC cases and 565 controls among Caucasians were included in this analysis, the power of this

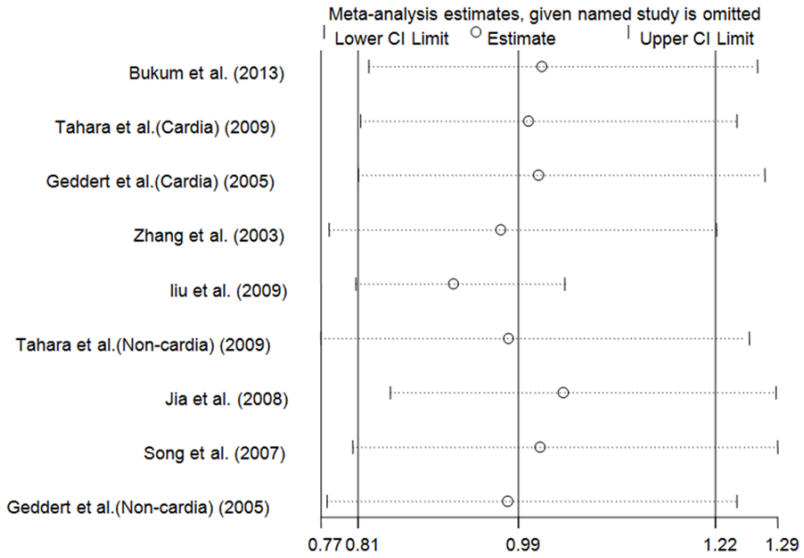

Figure 4. Sensitivity analysis of the influence of A vs. G in overall gastric cancer meta-analysis (random-effects estimates).

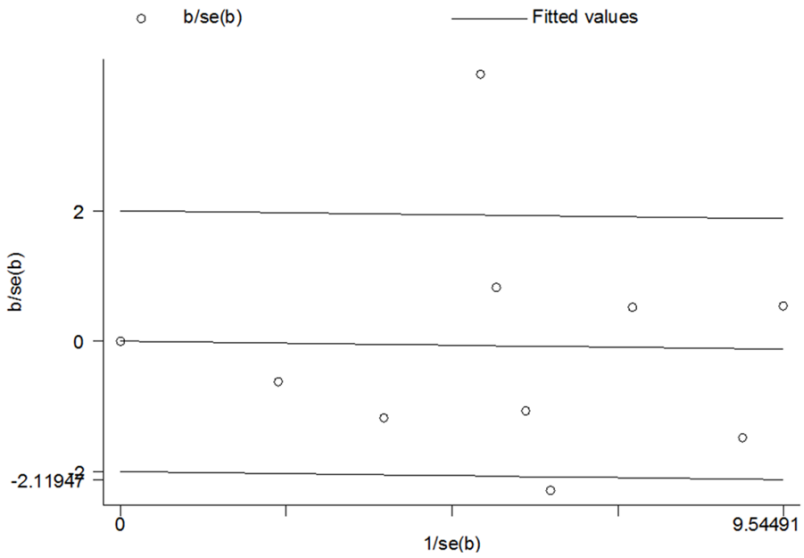

Figure 5. Galbraith radial plot of meta-analysis (A vs. G compare genetic model).

study was limited. Nevertheless, for practical reasons, further investigations with more intensive studies across different ethnicities incorporating with gene functional assessments are needed to validate our findings.

Significant heterogeneity was found across the publications regarding the *CCND1* rs9344 G>A polymorphism (**Table 3**). Potential sources of heterogeneity include region of GC, ethnicity, publication year, sample size, source of control and so on. When stratified analyses were conducted based on these potential bias factors, heterogeneity was significantly reduced in some subgroups, confirming the effects of region of GC, ethnicity, publication year, sample size, source of control, even for the same polymorphism (**Table 3**). We used Galbraith radial plot to identify the outliers in the allele model (**Figure 5**). Combined with **Figure 2**, we found two studies were outliers [25, 26], which might contribute to the major sources of heterogeneity.

However, some limitations should be addressed in interpreting these results. First, only nine case-control studies were included in this meta-analysis, and the sample sizes may have limited power to explore the relationship between *CCND1* rs9344 G>A gene polymorphism and GC susceptibility. Second, in the meta-analysis, all studies included were of Asians or Caucasians; no data for other ethnicities were available (e.g., Africans). Third, only published studies were included in this meta-analysis, some unpublished studies or certain studies that were not included in these databases were not identified, and these may have increased the chance of bias. Finally, significant heterogeneity was found among the publications, our findings should be interpreted with very caution.

In summary, in spite of the several limitations, the findings from our pooled analysis suggest that *CCND1* rs9344 G>A polymorphism may be a protective factors for GC among Caucasians. In the future, more large-scale studies considering various ethnicities are needed to further

the interpreting of gene-gene and gene-environment interactions between *CCND1* rs9344 G>A polymorphisms and GC risk.

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Disclosure of conflict of interest

None.

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