

# Association between the Cyclin D<sub>1</sub> G870A polymorphism and the susceptibility to and prognosis of upper aerodigestive tract squamous cell carcinomas: an updated meta-analysis

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**Purpose:** Several publications have investigated the association between the Cyclin D<sub>1</sub> G to A substitution at nucleotide 870 (CCND1 G870A) polymorphism and squamous cell carcinoma (SCC) of the upper aerodigestive tract (UADT), but their conclusions still remain controversial. We conducted a meta-analysis to precisely evaluate this association.

**Patients and methods:** We electronically searched the Chinese National Knowledge Infrastructure, PubMed, and Embase (up to January 2015) databases for case-control studies on the association between the CCND1 G870A polymorphism and SCC of the UADT, and 23 studies were included in total.

**Results:** The meta-analysis results showed that there was a significant association between the CCND1 G870A polymorphism and the risk of SCC of the UADT (AA vs GG: odds ratio [OR] =1.33, 95% confidence interval [CI] =1.01–1.74,  $P<0.001$  for heterogeneity; GA/AA vs GG: OR =1.24, 95% CI =1.01–1.51,  $P<0.001$  for heterogeneity; AA vs GA/GG: OR =1.16, 95% CI =0.97–1.39,  $P<0.001$  for heterogeneity; allele A vs allele G: OR =1.14, 95% CI =1.00–1.30,  $P<0.001$  for heterogeneity; GA vs GG: OR =1.18, 95% CI =0.98–1.42,  $P<0.001$  for heterogeneity). However, when analyzing prognosis, allele G was a potential risk factor for poor tumor differentiation (AA vs GA/GG: OR =2.60, 95% CI =1.15–5.86,  $P=0.836$  for heterogeneity) and reduced disease-free intervals (OR =2.08, 95% CI =1.17–3.69,  $P=0.134$  for heterogeneity). In the subgroup analysis, the cancer susceptibility of Asian groups, population-based control groups, nasopharyngeal cancer groups, and esophageal SCC groups were more likely to be affected by the CCND1 G870A polymorphism. No significant publication bias was found in our analysis ( $P=0.961$  for Egger's test and  $P=0.245$  for Begg's test).

**Conclusion:** The results of the present meta-analysis suggest that the variant CCND1 870A allele might confer an elevated risk of SCC of the UADT, particularly among Asians and individuals who have esophageal or nasopharyngeal cancers. Moreover, the CCND1 870A allele might also confer better tumor differentiation grades and longer disease-free intervals.

**Keywords:** CCND1 G870A polymorphism, squamous cell carcinoma, predictive value, screen

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## Introduction

Cancers of the upper aerodigestive tract (UADT), including the oral cavity, pharynx, larynx, and esophagus, are the fourth most common type of cancer and account for approximately 5%–8% of all malignancies worldwide.<sup>1,2</sup> Among UADT cancers, squamous cell carcinomas (SCCs) constitute the most abundant histologic type.<sup>3</sup> Although the detailed mechanisms of the carcinogenesis of SCC of the UADT still

remain ambiguous, several studies suggest that genetic factors play an important role in this process. Thus, it is of great importance to identify potential genetic factors to help screen the susceptible population.

Cyclin D<sub>1</sub> (CCND1) is a key regulator in the transition from the G<sub>1</sub> phase to the S phase during cell cycle progression.<sup>4</sup> Several publications have reported that *CCND1* gene amplification is involved in the pathogenesis of a variety of cancers, including breast, prostate, esophagus, and lung cancer.<sup>5–8</sup> The *CCND1* gene has an important polymorphism (rs603965) at codon 242 in exon 4 that results in a silent G to A substitution at nucleotide 870 (G870A).<sup>9</sup> The shift from allele G (wild-type gene) to allele A (variant gene) leads to the expression of an altered protein that has a longer half-life and thus enables cells to more easily bypass the G<sub>1</sub>/S cell cycle checkpoint.<sup>10,11</sup> Additionally, evidence has shown that the carriers of the AA genotype are more likely to have numerous cancers, including brain, liver, and breast cancer.<sup>12–14</sup>

The association between the CCND1 G870A polymorphism and SCC of the UADT has been investigated by different authors, but their conclusions still remain controversial. A recent meta-analysis by Wen et al<sup>15</sup> showed a possible relationship between the CCND1 G870A polymorphism and esophageal cancer risk, which was contrary to the results found from an earlier meta-analysis conducted by Cai et al.<sup>16</sup> We consider that this difference results from sample sizes. Another meta-analysis by Tang et al<sup>17</sup> pooled head and neck cancers of different histological types together, preventing a detailed subgroup analysis; thus, they obtained unconvincing results with high heterogeneity. These studies did not assess the influence of the CCND1 G870A polymorphism on the prognosis of UADT cancers. In addition, four additional studies reporting the association of the CCND1 G870A polymorphism with UADT SSC have been published. Therefore, we performed this meta-analysis including all relevant published studies to provide complementary and updated information on the relationship between the CCND1 G870A polymorphism and the susceptibility and prognosis of UADT SCC.

## Patients and methods

### Literature search strategy

We performed an electronic search of the Chinese National Knowledge Infrastructure, PubMed, and Embase (up to January 2015) databases for case-control studies on the association between the CCND1 G870A polymorphism and SCC of the UADT. The following terms were used in combination: Cyclin D<sub>1</sub>, CCND1, polymorphism, squamous cell

carcinoma, oral cancer, laryngeal cancer, pharyngeal cancer, esophageal cancer, and case-control study. Manual searches were also conducted to identify relevant publications from the citation lists of the included articles.

### Inclusion and exclusion criteria

Studies were included if they met the following criteria: 1) a case-control study design concerning the relationship between the CCND1 G870A polymorphism and SCC of the UADT; 2) SCC confirmed via histopathological evidence; 3) tumor sites located in the UADT (including oral cavity, larynx, pharynx, and esophagus); 4) reported odds ratios (ORs) with a 95% confidence interval (CI) (or crude data that allowed the 95% CI to be calculated); and 5) published in English or Chinese.

Studies were excluded if they met the following criteria: 1) case series, case reports, reviews, and descriptive studies; 2) reports with a small number of participants (fewer than 20 patients); 3) crude data were not given or ORs could not be calculated; and 4) not published in English or Chinese.

### Data extraction

Two authors independently read the full texts and extracted relevant data from each publication. The following data were extracted: the first author, year of publication, country, ethnicity of subjects, type of controls, genotyping methods, Hardy-Weinberg equilibrium (HWE) in controls, and genotype distributions of cases and controls. After the first extraction, the data were rechecked by two authors, and disagreements during the extraction were resolved by consensus.

### Statistical analysis

Statistical analyses were performed using Stata software version 12.0 (Stata Corporation, College Station, TX, USA). We pooled the ORs with 95% CIs to analyze the association between the CCND1 G870A polymorphism and susceptibility to SCC of the UADT. Four genetic models were evaluated, including the allele-contrast model (A vs G), the codominant model (AA vs GG and GA vs GG), the dominant model (GA/AA vs GG), and the recessive model (AA versus GA/GG) (GG wild-type homozygotes, GA heterozygotes, and AA variant homozygotes). The *I*-squared (*I*<sup>2</sup>) statistic was used to evaluate statistical heterogeneity among studies, and *I*<sup>2</sup> values of <25% and >50% reflected low and high heterogeneity, respectively.<sup>18,19</sup> In our analysis, both the fixed-effects model and random-effects model were used. The random-effects model was used only when the *P*-values

of the heterogeneity test were less than 0.1. In addition, funnel plots and Egger's linear regression test were used to detect publication bias.<sup>20</sup>

## Results

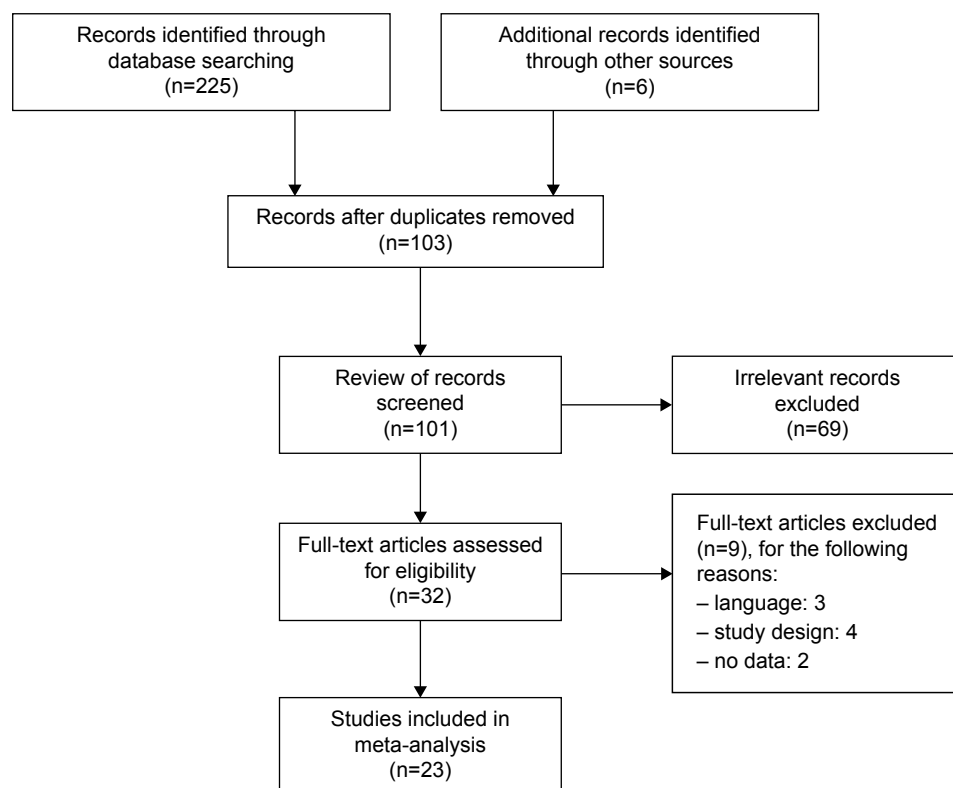
A total of 231 articles were identified after searching the Chinese National Knowledge Infrastructure, PubMed, and Embase databases. After the exclusion of 128 articles that were irrelevant to our research, 103 remained. In total, 32 articles were retrieved for full-text review, and finally, nine of them were excluded because the crude data could not be extracted. Therefore, 23 studies matched the inclusion criteria and were chosen for the following meta-analysis (Figure 1).<sup>21–43</sup>

These studies are dated from 1998 to 2014 with case-control designs and included a total of 11,542 subjects, of whom 5,338 (46.2%) were histopathologically diagnosed with SCC of the UADT. Detailed information extracted from the included publications is provided in Table 1. Of the 23 included studies, there were ten groups of Caucasians,<sup>21–23,25,28,31,32,34,38,43</sup> ten groups of Asians,<sup>21,26,27,29,35–37,39–42</sup> and three groups of mixed ethnicities.<sup>24,30,33</sup> Among the 23 included studies, the classic polymerase chain reaction-restriction fragment length polymorphism assay was the most frequently used

method to genotype the CCND1 G870A polymorphism. Genotyping distributions of the control populations were consistent with HWE in all studies except for those in two studies. Lin et al<sup>29</sup> did not report the precise distribution of genotypes GG and GA in their study and combined them as GG + GA. Seven studies were hospital-based<sup>24,25,31,33,35,37,40</sup> and 16 were population-based.<sup>21–23,26–30,32,34,36,38,39,41–43</sup>

Overall, the meta-analysis results suggested that there was a significant association between the CCND1 G870A polymorphism and risk of SCC of the UADT under the codominant model (AA vs GG: OR = 1.33, 95% CI = 1.01–1.74,  $P < 0.001$  for heterogeneity), the dominant model (GA/AA vs GG: OR = 1.24, 95% CI = 1.01–1.51,  $P < 0.001$  for heterogeneity), and the recessive model (AA vs GA/GG: OR = 1.16, 95% CI = 0.97–1.39,  $P < 0.001$  for heterogeneity). Borderline elevated risks were also found in the allele-contrast model (allele A vs allele G: OR = 1.14, 95% CI = 1.00–1.30,  $P < 0.001$  for heterogeneity) and the codominant model (GA vs GG: OR = 1.18, 95% CI = 0.98–1.42,  $P < 0.001$  for heterogeneity).

We also examined associations between the CCND1 G870A polymorphism and the patient prognosis of SCC, including tumor differentiation, tumor size, lymph node involvement, recurrence, and disease-free interval.



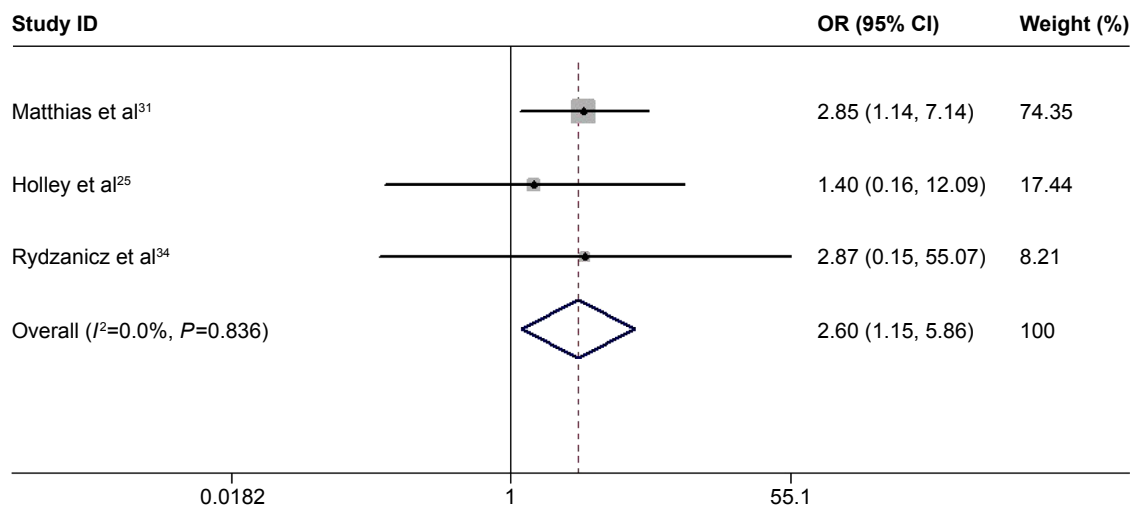
**Figure 1** Flowchart of screening studies.

Table 1 Characteristics of the studies included in the analysis

References	Country	Ethnicity	Type of controls	Genotyping method	Genotype distribution				P-value for HWE				
					Cases		Controls						
					Sample size	GG	GA	AA		Sample size	GG	GA	AA
Matthias et al <sup>31</sup> Zheng et al <sup>43</sup>	Germany	Caucasian	Cancer-free controls (HB)	PCR-RFLP	384	100	193	91	191	55	101	35	0.34
	USA	Caucasian	Healthy controls (age-, sex-, ethnicity-, smoking-matched; PB)	PCR-RFLP	233	62	116	55	248	78	129	41	0.31
Wong et al <sup>40</sup> Zhang et al <sup>42</sup>	People's Republic of China	Asian	Cancer-free controls (HB)	PCR-SSCP	70	15	36	19	93	17	49	27	0.52
	People's Republic of China	Asian	Healthy controls (PB)	PCR-SSCP	120	11	74	35	183	38	102	43	0.12
Yu et al <sup>41</sup> Wang et al <sup>39</sup>	People's Republic of China	Asian	Healthy controls (PB)	PCR-RFLP	321	68	157	96	345	58	177	110	0.35
	People's Republic of China	Asian	Healthy controls (PB)	PCR-SSCP	120	11	74	35	122	25	68	29	0.20
Monteiro et al <sup>32</sup>	Portugal	Caucasian	Healthy controls (PB)	PCR-RFLP	66	23	30	13	110	14	49	47	0.83
Nishimoto et al <sup>33</sup>	Brazil	Mixed	Cancer-free controls (HB)	PCR-DHPLC	147	53	68	26	135	40	69	26	0.70
Holley et al <sup>25</sup>	Germany	Caucasian	Cancer-free controls (HB)	PCR-RFLP	174	66	94	14	155	40	87	28	0.11
Rydzanicz et al <sup>34</sup>	Poland	Caucasian	Cancer-free controls (PB)	PCR-RFLP	63	12	41	10	102	38	43	21	0.18
Sathyan et al <sup>35</sup>	India	Asian	Cancer-free controls (age-, sex-matched; HB)	PCR-SSCP	146	36	71	39	137	40	61	36	0.20
Gomes et al <sup>24</sup>	Brazil	Mixed	Cancer-free controls (age-, sex-, smoking-matched; HB)	PCR-RFLP	80	25	30	25	80	28	29	23	0.01
Marsit et al <sup>30</sup>	USA	Mixed	Cancer-free controls (age-, sex-, inhabitation-matched; PB)	ABI 3500 Sequence Detection System	698	210	314	174	777	238	396	143	0.33
Sui et al <sup>36</sup>	People's Republic of China	Asian	Healthy controls (age-, sex-matched; PB)	PCR-RFLP	241	60	110	71	272	115	124	33	0.96
Akbari et al <sup>21</sup>	Iran	Caucasian	Cancer-free controls (PB)	ABI 7000 Sequence Detection System	744	169	364	211	1,368	268	666	434	0.66
Kurmano et al <sup>28</sup>	Kazakhstan	Caucasian	Healthy controls (PB)	ABI 7700 Sequence Detection System	98	19	42	37	86	24	46	16	0.46
Tsai et al <sup>37</sup>	People's Republic of China	Asian	Healthy controls (age-, sex-, habits-matched; HB)	PCR-RFLP	620	84	323	213	620	100	365	155	0.000003
Hussain et al <sup>26</sup>	India	Asian	Healthy controls (PB)	PCR-RFLP	151	20	99	32	151	56	72	23	0.99
Lin et al <sup>29</sup>	People's Republic of China	Asian	Healthy controls (PB)	PCR-RFLP	295	194 <sup>a</sup>	–	101	331	219 <sup>a</sup>	–	112	–
Verim et al <sup>38</sup>	Turkey	Caucasian	Healthy controls (age-matched; PB)	PCR-RFLP	65	12	32	21	83	23	37	23	0.32
Djansugurova et al <sup>23</sup>	Kazakhstan	Caucasian	Healthy controls (PB)	ABI 7000 Sequence Detection System	115	22	49	44	100	28	54	18	0.36
Jiang et al <sup>27</sup>	People's Republic of China	Asian	Healthy controls (age-, sex-, inhabitation-matched; PB)	PCR-RFLP	304	64	156	84	413	108	191	114	0.13
Atac et al <sup>22</sup>	Germany	Caucasian	Cancer-free controls (PB)	BigDye Terminator Sequencing Kit	83	13	55	15	102	20	56	26	0.30

Note: <sup>a</sup>GG + GA.

Abbreviations: HB, hospital-based study; PB, population-based study; PCR-RFLP, polymerase chain reaction-restriction fragment length polymorphism; PCR-SSCP, polymerase chain reaction-single strand conformation polymorphism; PCR-DHPLC, polymerase chain reaction-denaturing high performance liquid chromatography; HWE, Hardy-Weinberg equilibrium.



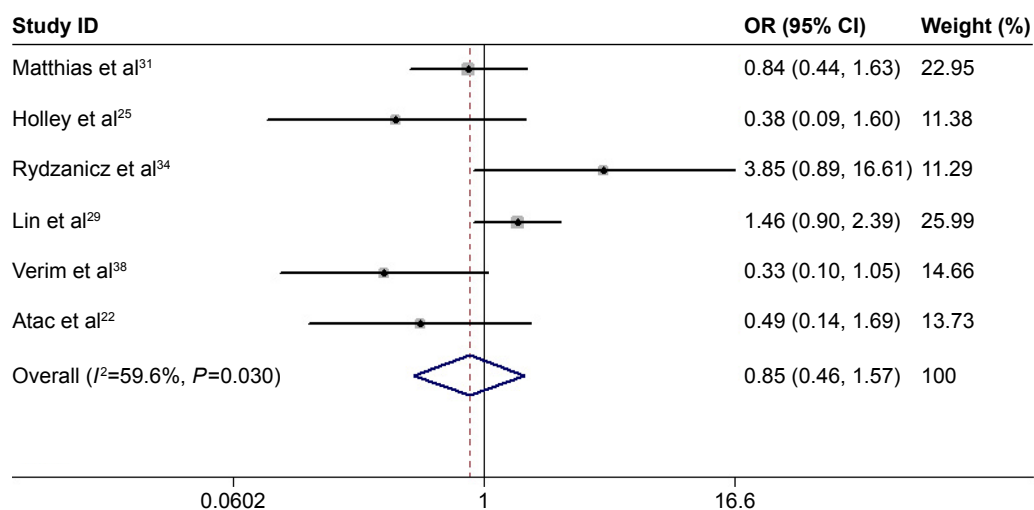
**Figure 2** Meta-analysis of the association between the CCND1 G870A polymorphism and tumor differentiation.

**Note:** Diamonds represent pooled estimates, and the width of the diamonds represents 95% CIs of the summary point estimate of effect.

**Abbreviations:** CCND1, Cyclin D<sub>1</sub>; G870A, G to A substitution at nucleotide 870; CI, confidence interval; OR, odds ratio.

Differentiation was graded as moderate ( $G_{0-2}$ ) or poor ( $G_3$ ). Tumor size was graded as large (T3 + T4) or small (T1 + T2). Lymph node involvement and recurrence were graded as positive or negative. Tumor differentiation was reported in three studies,<sup>25,31,34</sup> and the meta-analysis results showed that patients with AA genotypes were less likely to have poorly differentiated tumors (AA vs GA/GG: OR =2.60, 95% CI =1.15–5.86,  $P=0.836$  for heterogeneity, Figure 2). However, we did not find any significant association with AA genotypes for lymph node involvement, tumor size, and recurrence (AA vs GA/GG: OR =0.85, 95% CI =0.46–1.57,  $P=0.03$  for heterogeneity,

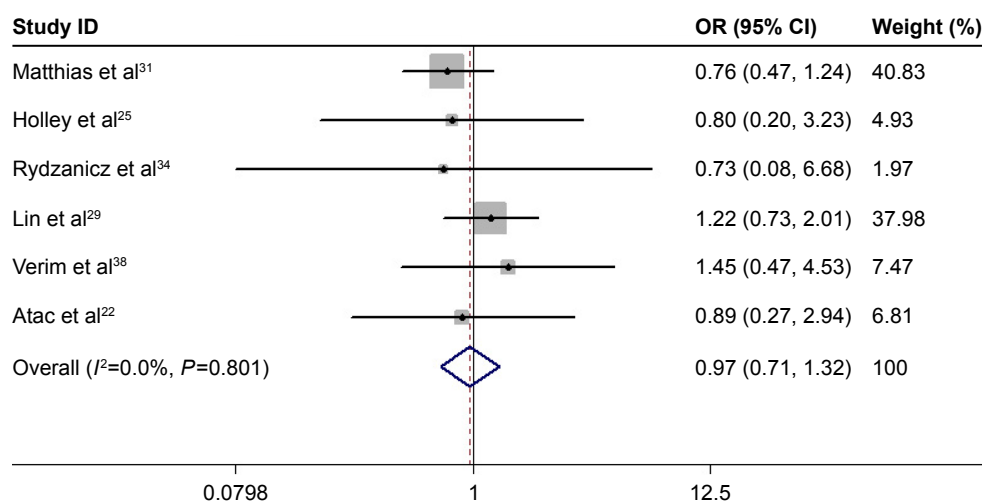
Figure 3; OR =0.97, 95% CI =0.71–1.32,  $P=0.801$  for heterogeneity, Figure 4; OR =0.60, 95% CI =0.36–1.01,  $P=0.328$  for heterogeneity, Figure 5, respectively). The survival or disease-free interval was extracted as the hazard ratio with a 95% CI. Two studies reported the disease-free interval,<sup>29,31</sup> and two studies reported the survival.<sup>30,40</sup> Pooled data demonstrated that allele G was a potential risk factor for reductions in the disease-free interval (OR =2.08, 95% CI =1.17–3.69,  $P=0.134$  for heterogeneity, Figure 6), but this effect was not found for the survival interval (OR =0.91, 95% CI =0.37–2.23,  $P=0.074$  for heterogeneity, Figure 6).



**Figure 3** Meta-analysis of the association between the CCND1 G870A polymorphism and lymph node involvement.

**Notes:** Diamonds represent pooled estimates, and the width of the diamonds represents the 95% CIs of the summary point estimate of the effect. Weights are from random effects analysis.

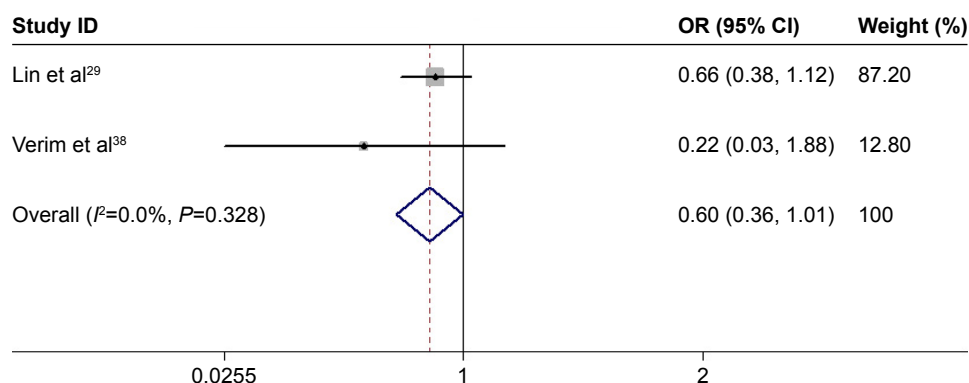
**Abbreviations:** CCND1, Cyclin D<sub>1</sub>; G870A, G to A substitution at nucleotide 870; CI, confidence interval; OR, odds ratio.



**Figure 4** Meta-analysis of the association between the CCND1 G870A polymorphism and tumor size.

**Notes:** Diamonds represent pooled estimates, and the width of the diamonds represents 95% CIs of the summary point estimate of the effect. Weights are from random effects analysis.

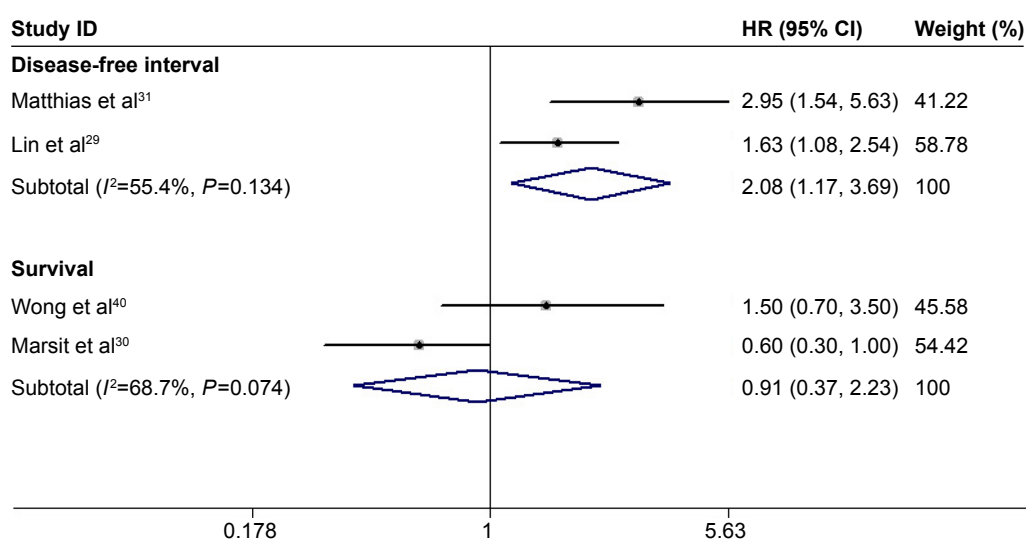
**Abbreviations:** CCND1, Cyclin D<sub>1</sub>; G870A, G to A substitution at nucleotide 870; CI, confidence interval; OR, odds ratio.



**Figure 5** Meta-analysis of the association between the CCND1 G870A polymorphism and tumor recurrence.

**Note:** Diamonds represent pooled estimates, and the width of the diamonds represents 95% CIs of the summary point estimate of the effect.

**Abbreviations:** CCND1, Cyclin D<sub>1</sub>; G870A, G to A substitution at nucleotide 870; CI, confidence interval; OR, odds ratio.



**Figure 6** Meta-analysis of the association between the CCND1 G870A polymorphism and disease-free and survival intervals.

**Notes:** Diamonds represent pooled estimates, and the width of the diamonds represents the 95% CIs of the summary point estimate of the effect. Weights are from random effects analysis.

**Abbreviations:** CCND1, Cyclin D<sub>1</sub>; G870A, G to A substitution at nucleotide 870; CI, confidence interval; HR, hazard ratio.

## Subgroup and sensitivity analysis

Considering the strong evidence of heterogeneity, subgroup analyses stratified by ethnicity (Caucasian, Asian, or Mixed), type of control (hospital-based or population-based), smoking status (ever smoking or never smoking), and tumor site (oral cavity, larynx, pharynx, nasopharynx, or esophagus) were conducted. The main results of the subgroup analysis are shown in Table 2. In the subgroup stratified by ethnicity, a significantly increased cancer risk was found among Asians under all genetic models. In the subgroup by source of controls, population-based studies suggested an elevated risk of SCC of the UADT. The subgroup analysis of the tumor site revealed that the risks of nasopharyngeal cancer and esophageal SCC were more likely to be affected by the CCND1 G870A polymorphism. No significant risk effect was found in the subgroup analysis by smoking status.

Sensitivity analysis was performed by excluding the two studies that deviated from HWE.<sup>24,37</sup> Additionally, the meta-analysis results in any genetic model were not statistically altered (data not shown). In addition, after excluding each single study one by one, the pooled results were not significantly attenuated, which confirmed the robustness of the data (data not shown).

## Publication bias

A funnel plot of log OR vs standard error was constructed for the recessive model, under which all 23 studies were covered (Figure 7). Visual inspection of the funnel plots did not show any remarkable asymmetry. In addition, Egger's and Begg's tests showed no significant publication bias ( $P=0.961$  for Egger's test and  $P=0.245$  for Begg's test, respectively).

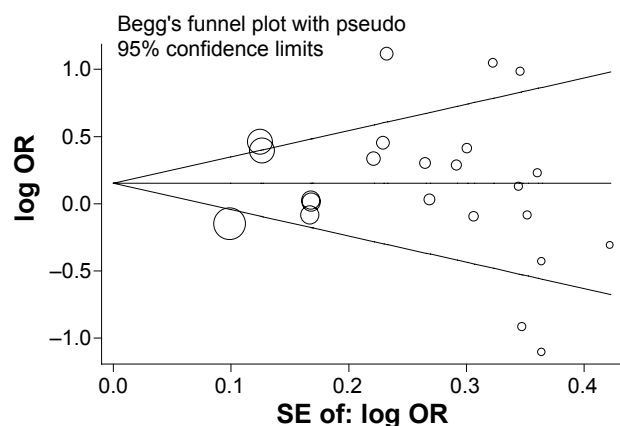
## Discussion

We were the first to conduct a meta-analysis involving 5,338 cases and 6,204 controls to evaluate the relationship between the CCND1 G870A polymorphism and susceptibility to SCC of the UADT. Furthermore, the influence of the polymorphism on the prognosis of SCC was also investigated. Finally, based on a total of 23 studies, our meta-analysis suggested that allele A of the CCND1 G870A polymorphism is associated with SCC development of the UADT, especially among Asian groups, groups with population-based controls, and groups of nasopharyngeal carcinoma and esophageal carcinoma. However, homozygous AA appeared to be a protective factor, as patients with AA genotypes had increased disease-free intervals and a higher degree of tumor differentiation.

**Table 2** Subgroup analysis of the included studies

Subgroup	Number of studies	AA versus GG		GA versus GG		GA/AA versus GG		AA versus GA/GG		Allele A versus allele G	
		OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value
Ethnicity											
Caucasian	10	1.08 (0.67, 1.74)	<0.01	1.05 (0.81, 1.36)	0.01	1.08 (0.79, 1.48)	<0.01	1.03 (0.71, 1.49)	<0.01	1.05 (0.83, 1.33)	<0.01
Asian	9	1.75 (1.16, 2.64)	<0.01	1.49 (1.07, 2.05)	<0.01	1.57 (1.12, 2.19)	<0.01	1.27 (1.01, 1.59)	<0.01	1.28 (1.06, 1.55)	<0.01
Mixed	3	1.20 (0.86, 1.67)	0.28	0.89 (0.72, 1.10)	0.63	0.99 (0.82, 1.20)	0.45	1.29 (0.97, 1.71)	0.29	1.07 (0.90, 1.28)	0.26
Type of controls											
Hospital-based	7	0.99 (0.65, 1.50)	<0.01	0.96 (0.80, 1.15)	0.52	0.98 (0.77, 1.24)	0.12	1.04 (0.75, 1.43)	0.01	1.00 (0.82, 1.22)	<0.01
Population-based	15	1.54 (1.08, 2.21)	<0.01	1.34 (1.04, 1.72)	<0.01	1.41 (1.07, 1.85)	<0.01	1.22 (0.97, 1.54)	<0.01	1.22 (1.02, 1.45)	<0.01
Smoking status											
Ever smoking	2	1.26 (0.51, 3.11)	0.02	0.97 (0.66, 1.43)	0.25	1.05 (0.60, 1.84)	0.09	1.34 (0.73, 2.44)	0.03	1.13 (0.75, 1.70)	0.02
Never smoking	2	0.57 (0.14, 2.27)	0.02	0.75 (0.48, 1.22)	0.34	0.68 (0.32, 1.46)	0.12	0.74 (0.26, 2.11)	0.03	0.79 (0.41, 1.51)	0.02
Tumor site											
Oral cavity SCC	7	1.04 (0.64, 1.68)	<0.01	1.03 (0.84, 1.27)	0.43	1.06 (0.80, 1.41)	0.12	0.99 (0.67, 1.46)	<0.01	1.03 (0.82, 1.29)	<0.01
Laryngeal SCC	4	0.86 (0.32, 2.29)	<0.01	1.13 (0.52, 2.46)	<0.01	1.03 (0.45, 2.36)	<0.01	0.80 (0.43, 1.51)	0.01	0.93 (0.56, 1.54)	<0.01
Pharyngeal SCC	1	2.01 (0.95, 4.24)	NA	1.39 (0.74, 2.63)	NA	1.55 (0.85, 2.84)	NA	1.60 (0.88, 2.92)	NA	1.38 (0.97, 1.98)	NA
NPC	1	4.12 (2.46, 6.92)	NA	1.70 (1.14, 2.25)	NA	2.21 (1.51, 3.23)	NA	3.02 (1.91, 4.78)	NA	2.04 (1.59, 2.62)	NA
Esophageal SCC	8	1.78 (1.10, 2.90)	<0.01	1.45 (0.98, 2.13)	<0.01	1.56 (1.04, 2.35)	<0.01	1.29 (0.97, 1.70)	<0.01	1.29 (1.03, 1.61)	<0.01

**Abbreviations:** NA, not applicable; SCC, squamous cell carcinoma; NPC, nasopharyngeal carcinoma; CI, confidence interval; OR, odds ratio.



**Figure 7** Funnel plot for the recessive model (AA vs GA/GG).

**Notes:** Each point represents a separate study for the indicated association. The horizontal line indicates the effect size.

**Abbreviations:** SE, standard error; log OR, natural logarithm of odds ratio.

The *CCND1* gene, which is located on chromosome 11q13, is polymorphic with a common G870A in the conserved splice donor region of exon 4 of the gene. The *CCND1* G870A polymorphism has been reported to have a promising role in predicting carcinogenesis of SCC, but this conclusion is still debated. Matthias et al<sup>31</sup> first investigated the influence of the *CCND1* G870A polymorphism on the susceptibility to SCC of the head and neck (SCCHN), and no significant correlation was found. However, they demonstrated that the GG genotype was associated with poor differentiation and a shortened time for tumor recurrence. Similarly, Monteiro et al<sup>32</sup> did not find any evident relationship between the *CCND1* G870A polymorphism and laryngeal SCC susceptibility. Their conclusion differed from that of Matthias et al<sup>31</sup> in that their data did not support an association between the *CCND1* genotype and tumor differentiation grade or recurrent disease. Marsit et al<sup>30</sup> found that the homozygous AA genotype was associated with a 1.5-fold elevated risk of SCCHN, which was in accordance with findings reported by Zheng et al,<sup>43</sup> but was opposite to that reported by Holley et al,<sup>25</sup> who found a significantly elevated risk (OR = 3.37, 95% CI = 1.61–9.80) for oral SCCs in subjects possessing the GG genotype. We considered that these discrepancies were due to several reasons: first, these studies all had relatively small sample sizes, which provided limited statistical power; second, these studies were conducted in different countries and included samples that may have had different genetic backgrounds; and third, gene polymorphisms may have different biological significances in various cancers, but some studies grouped tumors from various anatomic sites together. Thus, meta-analysis was required. A recent meta-analysis indicated that there was an overall lack of association

between the *CCND1* G870A polymorphism and head and neck cancer risk under all five genetic models, and no significant association was found in the subgroup analysis.<sup>44</sup> Cases in that study were diagnosed with different pathological types of cancers, which were located in the head and neck. In the current study, publications targeting SCC specifically originating from the UADT were collected, and subgroups were stratified by ethnicity, source of controls, smoking status, and tumor site. In the subgroup analysis of ethnicity, a remarkable association between *CCND1* allele A and elevated cancer risk was observed among Asians but not other ethnicities. This race-prevalent phenomenon, which might be due to the specific ethnic chromosomal aberrations and different genetic backgrounds, was also observed in lung cancer.<sup>45</sup> In the subgroup analysis of the source of controls, allele A was found to be associated with increased cancer risk in the population-based subgroup. Population-based controls were more likely to represent the general population compared with hospital-based controls. As for hospital-based controls, those with other diseases may be of higher risk in terms of exposure status, such as alcohol consumption, which may potentially influence the disease studied. Thus, selection bias from hospital-based studies might attenuate the overall results of the meta-analysis. As a result, investigators should use proper controls to reduce possible selection bias in future studies. Monteiro et al<sup>32</sup> reported that tobacco exposure contributed to *CCND1* dysregulation. In our meta-analysis, a total of seven studies reported the interaction between smoking and the *CCND1* G870A polymorphism in SCC susceptibility,<sup>25,26,36,37,39,42,43</sup> but only two of them provided detailed genotype distributions of subgroups concerning smoking status.<sup>37,43</sup> Pooled data of these two studies failed to find any significant correlation between the *CCND1* polymorphism and smoking. Another three studies on esophageal SCC revealed that smoking patients had a significantly higher allele A frequency compared to healthy smokers, but this disparity was not found among nonsmokers.<sup>26,39,42</sup> Consequently, our subgroup analysis results should be interpreted with caution because of the limited number and small sample sizes of the included studies. Wen et al's<sup>15</sup> meta-analysis suggested that the *CCND1* G870A polymorphism presents the potential for elevated risk in the development of esophageal malignancies, including both adenocarcinomas and SCCs. In the current study, the subgroup analysis of the tumor site showed that allele A was related to an elevated risk of nasopharyngeal and esophageal SCCs. However, only one study regarding nasopharyngeal carcinoma was included and the statistical power was limited.

Further analysis of the association between the CCND1 G870A polymorphism and the prognosis of SCC of the UADT was carried out. Patients with the AA genotype were more likely to have well-differentiated tumors, and allele G was a potential risk factor for reduced disease-free interval. Holley et al<sup>46</sup> reported that the GG genotype was associated with poorly differentiated tumors, which was inconsistent with our findings. However, when both CCND1 genotypes were included in a model with age and sex, CCND1 GG was no longer significantly associated ( $P=0.76$ , OR =1.17, 95% CI =0.43–3.23). Thus, more data were required to validate the association between the CCND1 G870A polymorphism and the prognosis of SCC of the UADT.

Our study still had some limitations. First, although Egger's test did not indicate any statistically significant differences in our study, publication bias still cannot be ignored because only publications in English and Chinese were included in our analysis. There is a possibility that we missed certain eligible studies. Second, the data pooled in our analysis were unadjusted; however, carcinogenesis is an intricate process influenced by many factors other than genes. Effects of the gene–gene and gene–environment interactions in the development of SCC of the UADT could not be evaluated. Third, the sample sizes of included studies were relatively small, which limited the power of our results.

## Conclusion

Despite these limitations, the results of the present meta-analysis suggest that the variant CCND1 870A allele might confer an elevated risk of SCC of the UADT, particularly among Asians and individuals who have esophageal or nasopharyngeal cancers. Moreover, the CCND1 870A allele might also promote higher tumor differentiation grades and longer disease-free intervals. These findings may help to understand the role of the CCND1 G870A polymorphism in the etiology of SCC of the UADT. In the future, large case–control studies that consider gene–gene and gene–environment interactions are warranted to verify these findings.

## Disclosure

The authors report no conflicts of interest in this work.

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