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ORIGINAL ARTICLE

Genetic association between p73 G4C14–A4T14 polymorphism and risk of squamous cell carcinoma

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Abstract This study is to evaluate the association between p73 G4C14–A4T14 polymorphism and squamous cell carcinoma (SCC) risk in diverse populations. We searched the PubMed, Embase, China National Knowledge Infrastructure, and Chinese Biomedicine databases for all articles on the association between p73 G4C14–A4T14 polymorphism and SCC risk through March 2014. We performed a comprehensive meta-analysis of six case–control studies that included 1,758 SCC cases and 2,970 case-free controls. All analyses were performed using STATA 11.0, using two-sided *P* values. Overall, this meta-analysis showed that the p73 G4C14–A4T14 polymorphism was associated with a significantly increased risk of SCC in three genetic models. However, after excluding one study deviating from Hardy–Weinberg equilibrium, the results then demonstrated that the p73 G4C14–A4T14 polymorphism was only associated with elevated risk of cervical squamous cell carcinoma (for AT/GC vs GC/GC: OR 1.51, 95 % CI 1.14–2.00, $P_{\text{heterogeneity}} = 0.996$; for AT/AT+AT/GC vs GC/GC: OR 1.42, 95 % CI 1.08–1.87, $P_{\text{heterogeneity}} = 0.994$) in subgroup analysis by tumor sites. No publication bias was found in the present study. This meta-analysis suggests that the p73 G4C14–A4T14 polymorphism is associated with an increased risk of cervical squamous cell carcinoma. Further large and well-designed studies are needed to confirm this association.

Keywords Squamous cell carcinoma · P73 · Polymorphism · Meta-analysis

Introduction

Squamous cell carcinoma (SCC) represents one of the most commonly diagnosed tumors and results in significant mortality worldwide [1]. Malignant transformation of stratifying epithelium commonly results in SCC. Stratifying epithelia are present in organs and tissues, providing a protective barrier between the external environment and the organisms such as lung, oesophagus, cervix, mouth, and skin [2]. SCC is a complicated multistep process involving multiple genetic and epigenetic alterations, particularly activation of tumor promoting signals and inhibition of growth suppressor signals. Greater understanding of the basic biochemical and genetic pathways involved in the molecular pathogenesis of SCC is crucial to the development of novel therapeutic strategies that can target molecular aberrations and their downstream targets of the activated pathways [3, 4]. SCC, like all human tumors, is caused by abnormalities in DNA sequence or gene expression. Genetic variants in genes controlling essential cellular activities, such as cell-cycle regulation, DNA damage/repair, and apoptosis, may modulate SCC risk. Recent genetic association studies on SCC risk have focused on identifying effects of single nucleotide polymorphisms (SNPs) in candidate genes [5–8].

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One of the candidates is the p73 gene, a homology of p53, and is localized at chromosome 1p36.2–3, a region that is frequently deleted in human cancer [9]. Functionally, p73 activates the promoters of several p53-responsive genes participating in DNA repair, cell-cycle control, and apoptosis and inhibits cell growth in a p53-like manner by delaying cell cycle and inducing apoptosis [10]. There is now increasing evidence to indicate that the p73 gene is potentially important in the pathogenesis of various cancers, including SCC [11–14]. It has been suggested that different levels of p73 in the cell might directly modulate p53 activity after a DNA damage response [10]. Although there is evidence that loss of heterozygosity of P73 gene is associated with human cancers, the biological significance of P73 for SCC has yet to be studied in detail [15]. The two common SNPs at positions 4 (G to A) and 14 (C to T) in the noncoding region of exon 2 of the p73 gene are in complete linkage disequilibrium with one another. This polymorphism lies just upstream of the translation initiation of exon 2, in a region which may potentially alter gene expression, perhaps through control of the efficiency of translation initiation [9, 10]. Up to now, a few molecular epidemiological studies have investigated the association between the p73 G4C14–A4T14 polymorphism and SCC risk [11, 14, 16–18]. However, the results remain controversial and ambiguous. Because a single study might have been insufficient to detect the overall effects, a quantitative synthesis of the accumulated data from different studies is to provide crucial evidence on the association of p73 G4C14–A4T14 polymorphism with SCC risk. Thus, in this study, we conducted a meta-analysis to combine all studies available and validate whether the p73 G4C14–A4T14 polymorphism contributes to SCC susceptibility.

Materials and methods

Publication search

We searched the PubMed, Embase, China National Knowledge Infrastructure (CNKI), and Chinese Biomedicine databases for all articles on the association between p73 G4C14–A4T14 polymorphism and SCC risk through March 2014. The following key words were used in this search: squamous cell carcinoma, polymorphism/variant, and p73. In addition, references of retrieved articles were scanned. Reviews, comments, and letters were also checked for additional studies. The language of the reviewed articles was limited to English and Chinese. All the studies must meet the following criteria: (1) use a case–control design; (2) the outcome had to be SCC; and (3) sufficient published genotype data were presented to calculate the odds ratios (OR) with 95 % confidence intervals (CI). Additionally, if more than one article was published using the same case series, we selected the study with the largest sample size.

Data extraction

Data were extracted from each study by two investigators independently according to the inclusion criteria listed above. Characteristics abstracted from the studies included the first author's name, year of publication, country of origin, ethnicity, tumor sites, definition of study patients (cases), genotyping method, total number of cases and controls, and genotype distributions in cases and controls.

Statistical analysis

The strength of the association between the p73 G4C14–A4T14 polymorphism and SCC risk was assessed by ORs with 95 % CIs. The significance of the pooled OR was determined by the Z test, and $P < 0.05$ was considered as statistically significant. For p73 G4C14–A4T14, the meta-analysis examined the association between AT allele and SCC risk compared with that for GC allele (AT vs GC); codominant model (AT/GC vs GC/GC, AT/AT vs GC/GC), dominant model (AT/AT+AT/GC vs GC/GC), and recessive model (AT/AT vs AT/GC+GC/GC) were also used. Subgroup analyses were performed based on ethnicity.

Heterogeneity in this meta-analysis was checked by using the Chi-square-based Q test [19]. When $P > 0.10$, the pooled OR of each study was calculated by using the fixed-effects model [20]; otherwise, the random-effects model [21] was used. The departure of frequencies of p73 G4C14–A4T14 polymorphism from expectation under Hardy–Weinberg equilibrium (HWE) was assessed by the Chi-square test in controls, and a $P < 0.05$ was considered significant. Publication bias was evaluated by visual inspection of symmetry of Begg's funnel plot and assessment of Egger's test [22, 23] ($P < 0.05$ was regarded as representative of statistical significance). All analyses were performed using STATA 11.0 (STATA Corp., College Station, TX, USA), using two-sided P values.

Results

Characteristics of the studies

A total of 131 papers were relevant to the search words. After rigorous abstracts and contents assessment, only 14 publications met the crude inclusion criteria and were subject to further examination. Among them, one was excluded for without healthy control, five were not

focusing on p73 G4C14–A4T14 polymorphism, and three were not present the usable data and the hand searching yielded one study (Fig. 1). Therefore, six case–control studies involving 1,758 cases and 2,970 controls were available for this analysis. As shown in Table 1, among those six studies, there were four studies about Asians and two studies about Caucasians, respectively. The distribution of genotypes in the controls of all studies was consistent with HWE except for one study [16] (Table 1).

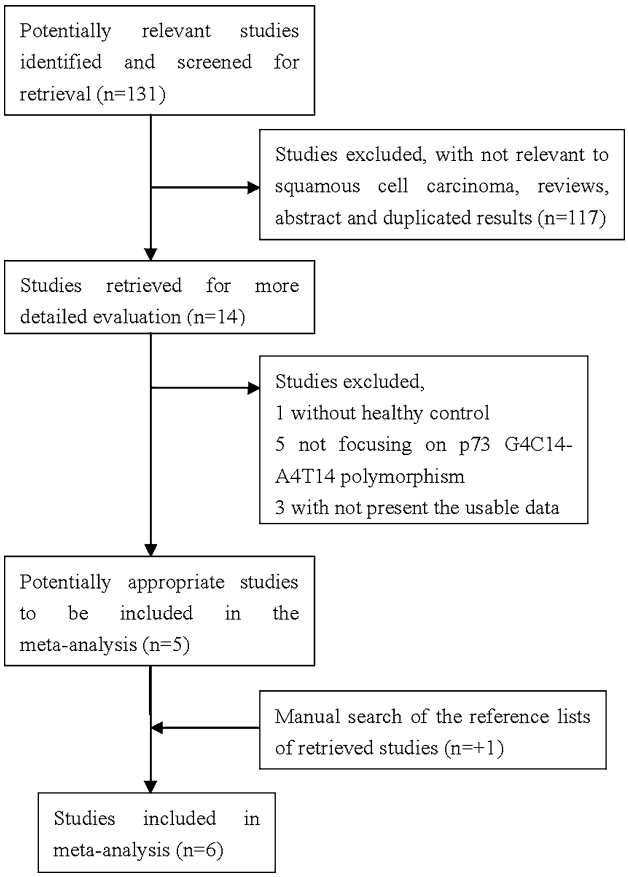

Fig. 1 Flow chart of selection of studies and specific reasons for exclusion from the meta-analysis

Quantitative synthesis

The evaluations of the association of p73 G4C14–A4T14 polymorphism with the risk of squamous cell carcinoma are shown in Table 2. Overall, this meta-analysis showed that the p73 G4C14–A4T14 polymorphism was associated with a significantly increased SCC risk in three genetic models (for AT/GC vs GC/GC: OR 1.25, 95 % CI 1.10–1.42, $P_{\text{heterogeneity}} = 0.287$; for AT vs GC: OR 1.15, 95 % CI 1.04–1.27, $P_{\text{heterogeneity}} = 0.908$; for AT/AT+AT/GC vs GC/GC: OR 1.23, 95 % CI 1.08–1.39, $P_{\text{heterogeneity}} = 0.523$) (Fig. 2). In subgroup analysis by ethnicity, statistically significantly elevated SCC risks were found among Caucasians, but not among Asian (Table 2; Fig. 2). However, limiting the analysis to the studies within HWE did not reveal an association between the p73 G4C14–A4T14 polymorphism and SCC risk in overall comparison and subgroup analysis by ethnicity (Table 2). Furthermore, when stratifying by tumor sites, significantly elevated risks were observed for cervical squamous cell carcinoma (CSCC) in two genetic models (for AT/GC vs GC/GC: OR 1.51, 95 % CI 1.14–2.00, $P_{\text{heterogeneity}} = 0.996$; for AT/AT+AT/GC vs GC/GC: OR 1.42, 95 % CI 1.08–1.87, $P_{\text{heterogeneity}} = 0.994$) (Fig. 3), but not in the other sites (Table 2). There was no heterogeneity among studies in overall comparisons and also subgroup analyses.

Publication bias

Begg's funnel plot and Egger's test were performed to assess publication bias among the literatures. No evidence of publication bias was observed in any comparison model (for AT/GC vs GC/GC, Egger's test $P = 0.705$; for AT/AT

Table 1 Characteristics of studies included in this meta-analysis

Author	Year	Country	Ethnicity	Tumor site	Genotyping methods	Sample size (case/control)	Case			Control			P_{HWE}
							GC/GC	GC/AT	AT/AT	GC/GC	GC/AT	AT/AT	
Li	2004	USA	Caucasian	SCCHN	PCR–CTPP	708/1229	399	271	38	773	387	69	0.028
Niwa	2004	Japan	Asian	CSCC	PCR–CTPP	76/442	40	34	2	270	150	22	0.843
Zheng	2006	China	Asian	CSCC	PCR–RFLP	82/100	58	22	2	77	19	4	0.062
Ge	2006	China	Asian	ESCC	PCR–RFLP	348/630	214	113	21	391	210	29	0.906
Chen	2008	USA	Caucasian	SCCHN	PCR–RFLP	326/349	195	111	20	214	115	20	0.387
Sun	2012	China	Asian	CSCC	PCR–CTPP	218/220	107	100	11	128	80	12	0.913

PCR-CTPP polymerase chain reaction with confronting two-pair primers, *PCR–RFLP* polymerase chain reaction–restriction fragment length polymorphism, *HWE* Hardy–Weinberg equilibrium

Table 2 Quantitative analyses of the p73 G4C14–A4T14 polymorphism on squamous cell carcinoma risk

Variables	N[a]	AT/GC versus GC/GC		AT/AT versus GC/GC		AT versus GC		AT/AT+AT/GC versus GC/GC (dominant)		AT/AT versus AT/GC+GC/GC (recessive)	
		OR (95 % CI)	P^b	OR (95 % CI)	P^b	OR (95 % CI)	P^b	OR (95 % CI)	P^b	OR (95 % CI)	P^b
Total	6	**1.25 (1.10–1.42)**	0.287	1.08 (0.83–1.43)	0.933	**1.15 (1.04–1.27)**	0.908	**1.23 (1.08–1.39)**	0.523	1.00 (0.77–1.31)	0.822
Ethnicities											
Caucasian	2	**1.27 (1.07–1.50)**	0.202	1.08 (0.76–1.53)	0.943	**1.16 (1.01–1.32)**	0.415	**1.24 (1.06–1.46)**	0.257	0.99 (0.70–1.39)	0.756
Asian	4	1.22 (1.00–1.49)	0.213	1.11 (0.71–1.72)	0.729	1.14 (0.97–1.34)	0.835	1.21 (1.00–1.46)	0.415	1.03 (0.67–1.58)	0.561
HWE in controls											
Yes	5	1.17 (0.99–1.39)	0.285	1.10 (0.77–1.59)	0.861	1.12 (0.98–1.28)	0.892	1.16 (0.99–1.37)	0.509	1.04 (0.73–1.49)	0.725
Ethnicities											
Caucasian	1	1.06 (0.77–1.47)	–	1.10 (0.57–2.10)	–	1.06 (0.82–1.36)	–	1.07 (0.78–1.45)	–	1.08 (0.57–2.04)	–
Asian	4	1.22 (1.00–1.49)	0.213	1.11 (0.71–1.72)	0.729	1.14 (0.97–1.34)	0.835	1.21 (1.00–1.46)	0.415	1.03 (0.67–1.58)	0.561
Tumor site											
CSCC	3	**1.51 (1.14–2.00)**	0.996	0.88 (0.45–1.72)	0.748	1.23 (0.98–1.53)	0.974	**1.42 (1.08–1.87)**	0.994	0.75 (0.39–1.45)	0.762
Others	2	1.02 (0.82–1.26)	0.735	1.22 (0.79–1.88)	0.675	1.06 (0.90–1.25)	0.98	1.04 (0.85–1.28)	0.853	1.21 (0.79–1.86)	0.627
No	1	**1.36 (1.11–1.65)**	–	1.07 (0.71–1.61)	–	**1.20 (1.02–1.40)**	–	**1.31 (1.09–1.59)**	–	0.95 (0.64–1.43)	–

The table given in bold indicates statistically significant values

[a] Number of comparisons

[b] *P* value of *Q* test for heterogeneity test. Random-effects model was used when *P* value for heterogeneity test, 0.10; otherwise, fixed-effects model was used

vs GC/GC, Egger's test $P = 0.157$; for AT vs GC, Egger's test $P = 0.977$; for AT/AT+AT/GC vs GC/GC, Egger's test $P = 0.768$; for AT/AT vs AT/GC+GC/GC, Egger's test $P = 0.243$) (Fig. 4).

Discussion

It is now widely accepted that genetic and environmental factors contribute to squamous cell carcinoma susceptibility and outcome. Many factors may contribute to the development of SCC, including tobacco smoking, alcohol consumption, viral infection, and genetic factors. Although smoking and alcohol intake play a major role in the etiology of SCC, only a small fraction of smokers and drinkers are likely to develop SCC, suggesting the existence of genetic and other risk factors [24, 25]. SCC is a complex multistep process involving the acquisition of DNA mutations that confer the malignant phenotype as well as epigenetic alterations. The tumor protein p73 (TP73) gene is a well-studied gene. It belongs to the TP53 gene family and involves in the cell-cycle arrest or induction of apoptosis [10, 26]. Two common single nucleotide polymorphisms G4A (rs2273953) and C14T (rs1801173) have been showed to be located in exon 2 of TP73, which are in complete linkage disequilibrium, and therefore, it is called G4C14–A4T14. The TP73 polymorphism (G4C14–A4T14) has been investigated and several studies have focused on the role of this polymorphism in SCC [11, 13, 14, 16–18]. However, the data reported for individual study were limited and not able to support a convincible conclusion.

In the current study, we conducted a meta-analysis to examine the association between p73 G4C14–A4T14 polymorphism and SCC risk. To our knowledge, this is the first comprehensive meta-analysis that investigated the relationship between p73 G4C14–A4T14 polymorphism and SCC risk. This meta-analysis conducted here included 1758 cases and 2970 controls from six case–control studies. Overall, this meta-analysis showed that the p73 G4C14–A4T14 polymorphism was associated with a significantly increased SCC risk in three genetic models. In subgroup analysis by ethnicity, statistically significantly elevated SCC risks were found among Caucasians, but not among Asian. However, limiting the analysis to the studies within HWE did not reveal an association between the p73 G4C14–A4T14 polymorphism and SCC risk in overall comparison and subgroup analysis by ethnicity. Furthermore, when stratifying by tumor sites, significantly elevated risks were observed for cervical squamous cell carcinoma in two genetic models (for AT/GC vs GC/GC: OR 1.51, 95 % CI 1.14–2.00, $P_{\text{heterogeneity}} = 0.996$; for AT/AT+AT/GC vs GC/GC: OR 1.42, 95 % CI 1.08–1.87,

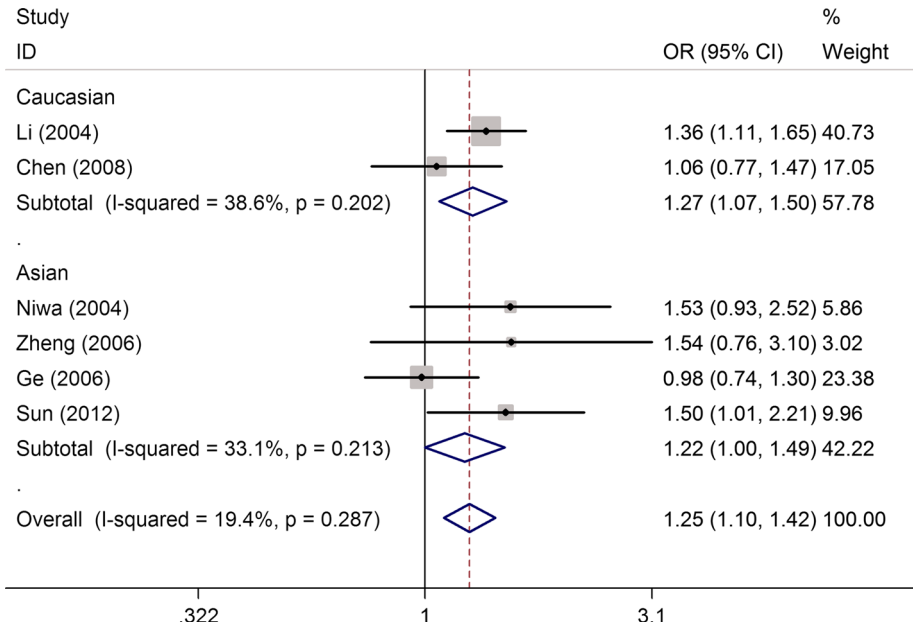

Fig. 2 Odds ratios (OR) and 95 % confidence interval (CI) of individual studies and pooled data for the association of p73 G4C14–A4T14 polymorphism and SCC risk in subgroup analysis by ethnicity (AT/GC vs GC/GC). I^2, measure to quantify the degree of heterogeneity in meta-analyses

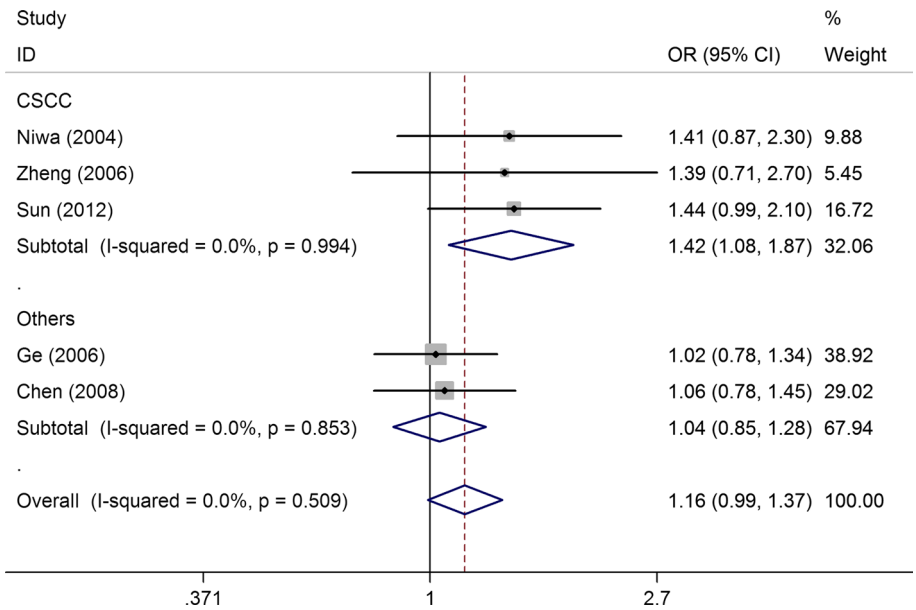

Fig. 3 Forest plot showed the association of p73 G4C14–A4T14 polymorphism and SCC risk in subgroup analysis by tumor sites (AT/AT+AT/GC vs GC/GC)

$P_{\text{heterogeneity}} = 0.994$), but not in the other sites. Therefore, our meta-analysis suggests that the p73 G4C14–A4T14 polymorphism is associated with an increased CSCC risk. This conclusion is supported by the reported potential biological function of TP73 G4C14–A4T14 polymorphism. Since the TP73 protein plays key roles in the induction of apoptosis and cell-cycle control [10, 25], it may be reasonable to speculate that the TP73 G4C14–A4T14 polymorphism may affect SCC risk through influencing the expression of TP73 protein. However, due to the relatively small sample sizes and insufficient numbers of studies, the results need to be further validated and confirmed.

The TP73 G4C14–A4T14 polymorphism and cancer risk has been investigated by several meta-analyses [27–29]. Liu and colleagues conducted a comprehensive meta-analysis about TP73 G4C14–A4T14 polymorphism and cancer risk based on 27 case–control studies [27]. Compared with their work, we only focus on the association of TP73 G4C14–A4T14 polymorphism with squamous cell carcinoma, while they analyzed a variety of cancers, including lung cancer, gastric cancer, colorectal cancer, and esophageal carcinoma. [27]. Additionally, our meta-analysis suggests that the p73 G4C14–A4T14 polymorphism is associated with an increased CSCC risk, which is

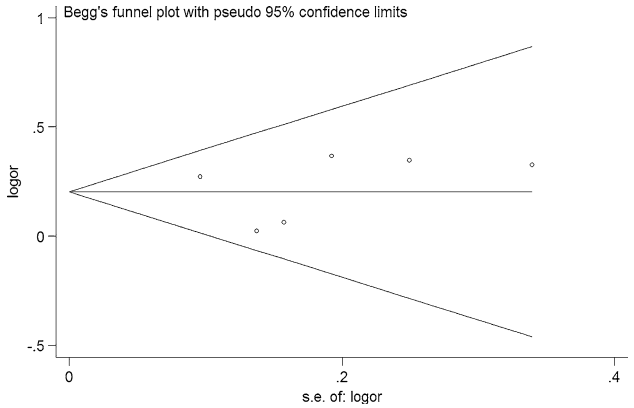

Fig. 4 Begg's funnel plot for publication bias test (AT/AT+AT/GC vs GC/GC). Each *point* represents a separate study for the indicated association

consistent with the previous meta-analysis conducted by Wang et al. [29]. Compared with Wang's work, we identified more eligible studies for CSCC [11, 13, 17], whereas Wang and colleagues only analyzed two studies.

In interpreting the current results, some limitations should be considered. First, only published studies were considered in this meta-analysis, some so called grey literatures might be still missed, which may have biased our results. Second, our results were based on an unadjusted estimated, owing to limit detailed information in individual study. Third, only Chinese and English studies were included in this meta-analysis which might have led to bias. Forth, the majority studies used were investigation in Asians. In the subgroup analyses, the number of Caucasians was relatively small, not having enough statistical power to explore the real association. In spite of these, our meta-analysis has some advantages. First, the search and selection studies were conducted strictly. Second, no publication bias was detected, indicating that the whole pooled results may be unbiased.

In conclusion, this meta-analysis suggests that the p73 G4C14–A4T14 polymorphism is associated with an increased risk of cervical squamous cell carcinoma. Caution must be made about the interpretation of the results because of the limited sample size. More well-designed studies with adequately sized populations are necessary to validate our findings.

Conflict of interest The authors have declared that no competing interests exist.

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