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Original Article

Impact of *p73* gene polymorphism on cancer susceptibility: a meta analysis

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Abstract: Previous studies examining the association between *p73* G4A and gastric cancer risk have produced inconsistent results. The objective of this study was to clarify whether *p73* G4A plays a major role in the development of gastric cancer. Studies that had examined the association between *p73* G4A and gastric cancer risk were identified through PubMed, Science Direct, and CNKI. We selected eligible studies based on inclusion criteria. Odds ratios were estimated using distinct genetic models, and the heterogeneity between studies was explored using Cochran's Q statistic along with the I^2 statistic. Overall, we found no evidence of a significant association between *p73* G4A and risk of gastric cancer. A same trend was also indicated in subgroup analysis by ethnicity. The heterogeneity tests revealed that there was no significant heterogeneity across studies. Our meta-analysis indicates that *p73* G4A might not have a major effect on risk of gastric cancer. A much larger study is required to validate our findings.

Keywords: *p73*, polymorphism, gastric cancer

Introduction

The *p53* gene functions positively in tumor suppression and is known as a guardian of genome integrity [1]. *p53* activates transcriptional programming that promotes cell cycle arrest, facilitates DNA repair and stimulates apoptosis through binding to the promoter components of downstream target genes, such as *p21* [2-4]. *p73* resides at chromosome 1p36 and belongs to the *p53* family [5]. As it shares substantial sequence homology with *p53*, *p73* may serve as a tumor suppressor and act efficiently in the prohibition of uncontrolled proliferation, the induction of apoptosis, and the transactivation of *p53*-responsive genes like *p21* [6, 7]. Elevated expression of *p73* has been reported in human cancers, and such elevation may be connected with p53 defects [8].

p73 is a highly polymorphic gene and approximately nineteen single nucleotide polymorphisms (SNPs) have been described [9]. A functional dinucleotide polymorphism at positions 4 (G→A) and 14 of exon 2 (C→T) (G4C14-to-A4T14, simply designed as G4A hereafter) contains two SNPs in complete linkage disequilibrium [10]. The dinucleotide polymorphism may form a stem-loop structure to modulate gene expression by modifying the translational efficiency [5], indicating a possible role in the development of cancer. *p73* G4A has been linked with many types of human cancer [11-13], but gastric cancer is one of the most invasive cancers that has been widely connected with *p73* G4A [14-18]. Disparity arises when *p73* G4A is studied in gastric cancer samples with different populations. A study with Italian samples showed *p73* G4A may be a risk factor for gastric cancer [15]. A recent observation emerged contradictorily to the previous finding and suggested that there was no significant association between *p73* G4A and samples with Japanese ancestry [14]. In order to clarify whether *p73* G4A plays a major role in the development of gastric cancer, we collected all

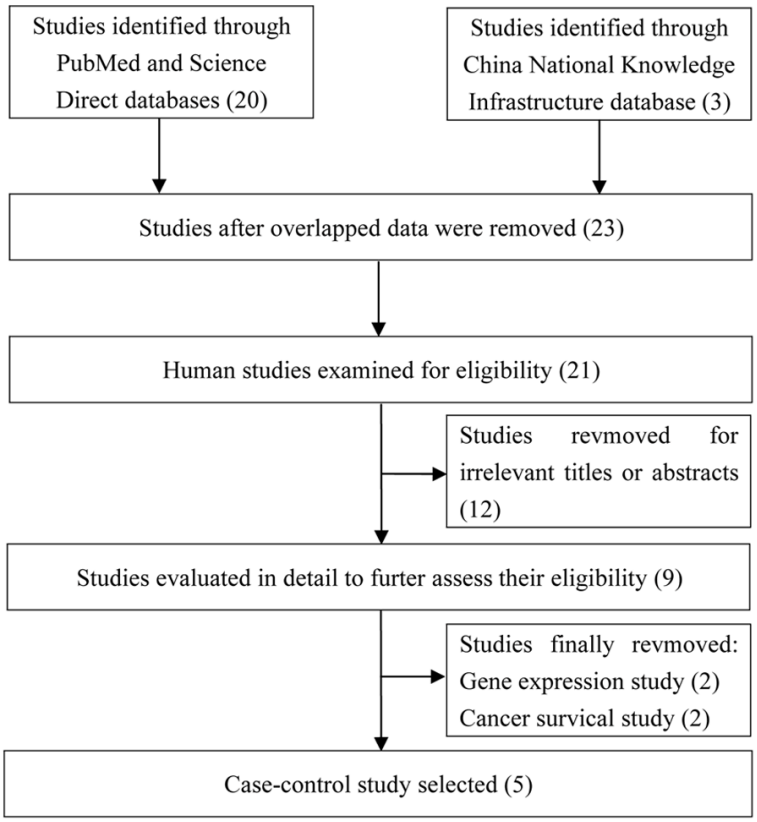

Figure 1. Flow diagram of the literature search.

eligible publications to date and performed a meta-analysis.

Material and methods

Identification of relevant studies

To identify all case-control studies that had examined the association between *p73* G4A and gastric cancer risk, we conducted a systematic search in the PubMed, Science Direct and China National Knowledge Infrastructure (CNKI) databases. The last search was conducted on January 31, 2014. (polymorphism) OR (polymorphisms) AND (*p73*) OR (*TP73*) AND (gastric cancer) OR (stomach cancer) was the strategy we used in literature search. Additional studies were identified by hand searching citations of meta-analyses and review articles. We included the studies that had a case-control design; that examined the association between *p73* G4A and gastric cancer risk; that provided all information required for the calculation of odds ratios (ORs); that published in English or Chinese. We excluded the studies with incomplete genotype information, using *p73* G4A to predict survival of cancer patients or concerning *p73* G4A expression and gastric cancer.

Data extraction

Two investigators reviewed all articles. Then the first investigator extracted the following information from each of the eligible studies: first author, publication journal, year of publication, country where the study was performed, ethnicity, study design, genotype distribution, genotyping method, and number of cases and controls. All extracted data were examined by the second investigator to ensure the accuracy of information. A senior investigator was consulted if there were disagreements.

Statistical analysis

The association between *p73* G4A and gastric cancer risk was assessed by calculating ORs for AT vs. GC, AT/AT vs. GC/GC, AT/GC vs. GC/GC, AT/AT + AT/GC vs. GC/GC, and AT/AT vs. AT/GC + GC/GC. Cochran's Q statistic [19] along with the I^2 statistic [20] was adopted to measure statistical heterogeneity and to quantify the proportion of the total variation due to heterogeneity rather than by chance, respectively ($P < 0.10$ or $I^2 > 50\%$ was con-sidered statistically significant). To summ-arize the ORs for each study, we selected the fixed-effect model (the Mantel-Haenszel method) [21] if no significant heterogeneity was present. Alternatively, the random-effect model (the DerSimonian and Laird method) [22] was applied. Test for Hardy-Weinberg equilibrium (HWE) in control group was conducted using a goodness-of-ft test (chi-square or Fisher's exact test). Begg's funnel plots and Egger's linear regression test were utilized to examine potential publication bias in this study [23]. Statistical significance was established at a $P < 0.10$ and all analyses were performed using STATA software, version 12.0 (Stata Corporation, College Station, TX).

Table 1. Characteristics of studies included in p73 G4C14-to-A4T14 polymorphisms and gastric cancer

Study	Ethnicity	Country	Design	HWE	Total cases	Total controls	GC/GC		AT/GC		AT/AT	
							Case	Controls	Case	Controls	Case	Controls
Shirai et al.	Asian	Japan	HCC	0.826	388	419	220	239	142	156	26	24
De Feo et al.	Caucasian	Italy	HCC	0.183	114	295	84	214	22	71	8	10
Zhang et al.	Asian	China	PCC	0.246	373	412	123	102	168	194	82	116
Ge et al.	Asian	China	HCC	0.906	259	630	146	391	99	210	14	29
Hamajima et al.	Asian	Japan	HCC	0.201	144	241	84	133	51	97	9	11

HCC, hospital-based case-control study; PCC, population-based case-control study; HWE, Hardy-Weinberg equilibrium.

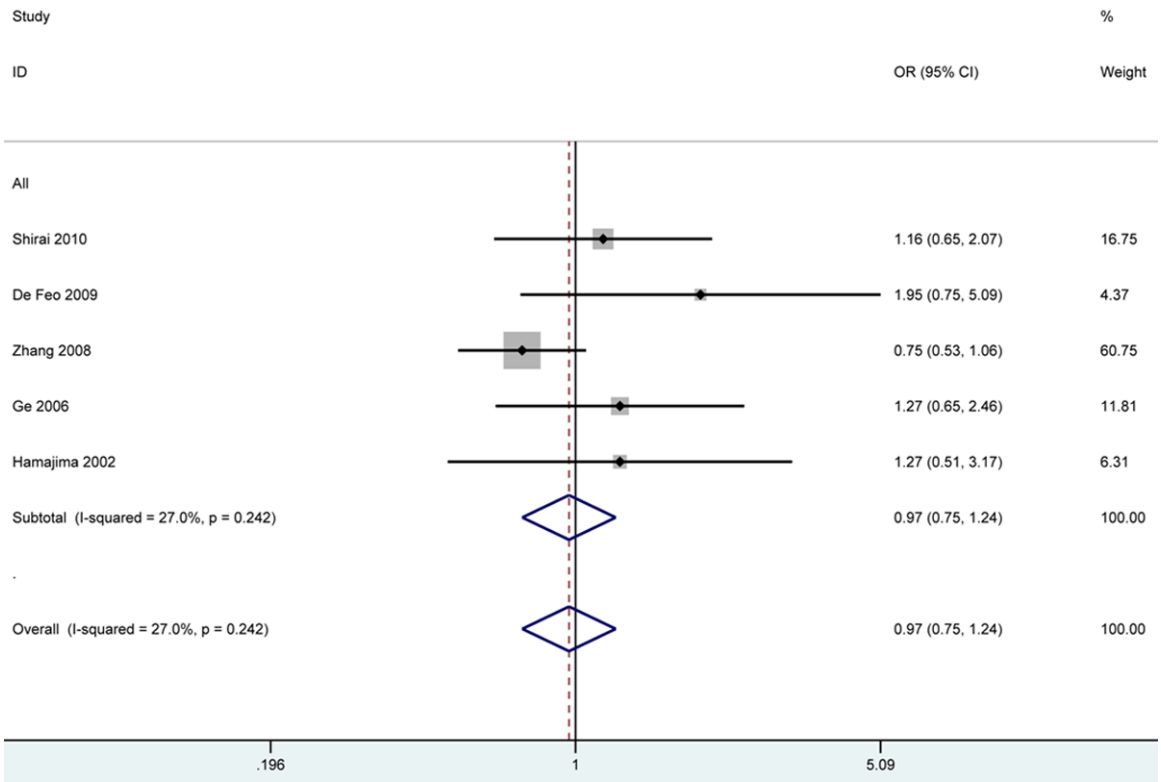

Figure 2. Forest plot of gastric cancer risk with *p73* G4A in overal comparison under the AT/AT vs. GC/GC contrast model.

Results

Literature selection and study characteristics

The search of PubMed, Science Direct and CNKI resulted in nine articles, eleven articles and three articles, respectively. We identified twenty-three studies in total. Among these, we selected five eligible studies (1,279 cases and 1,991 controls) [14-18] after screening titles, abstracts or full-texts. **Figure 1** graphically describes the study selection process. As shown in **Table 1**, 80% of the studies used samples with Asian ancestry and 20% with Caucasian samples. All studies were case-control designed and there was no deviation from HWE ($P > 0.10$).

Main findings

Table 2 summarizes the main meta-analysis results for *p73* G4A. There was no statistically significant association between *p73* G4A and overall gastric cancer risk when all eligible studies were pooled together (AT vs. GC: OR = 0.98, 95% CI = 0.88-1.09, **Figure 2**; AT/AT vs. GC/GC: OR = 0.97, 95% CI = 0.75-1.24; AT/GC vs. GC/GC: OR = 0.97, 95% CI = 0.84-1.12; AT/AT + AT/GC vs. GC/GC: OR = 0.98, 95% CI = 0.87-1.12 AT/AT vs. AT/GC + GC/GC: OR = 0.97, 95% CI =

Table 2. Summary ORs and 95% CIs of p73 G4C14-to-A4T14 polymorphisms and gastric cancer risk

Genetic comparisons	Studies	OR (95% CI)	*P*-value	I^2 %	*P* for heterogeneity
Total	5				
AT vs. GC	5	0.98 (0.88, 1.09)	0.726	8.3	0.359
AT/AT vs. GC/GC	5	0.97 (0.75, 1.24)	0.783	27.0	0.242
AT/GC vs. GC/GC	5	0.97 (0.84, 1.12)	0.682	0	0.641
AT/AT + AT/GC vs. GC/GC	5	0.98 (0.87, 1.12)	0.789	0	0.689
AT/AT vs. AT/GC + GC/GC	5	0.97 (0.77, 1.23)	0.800	27.8	0.236
Asian					
AT vs. GC	4	0.97 (0.87, 1.09)	0.643	27.4	0.248
AT/AT vs. GC/GC	4	0.92 (0.71, 1.19)	0.530	9.4	0.346
AT/GC vs. GC/GC	4	0.98 (0.85, 1.14)	0.816	0	0.539
AT/AT + AT/GC vs. GC/GC	4	0.98 (0.86, 1.12)	0.820	0	0.524
AT/AT vs. AT/GC + GC/GC	4	0.93 (0.72, 1.18)	0.538	0	0.393

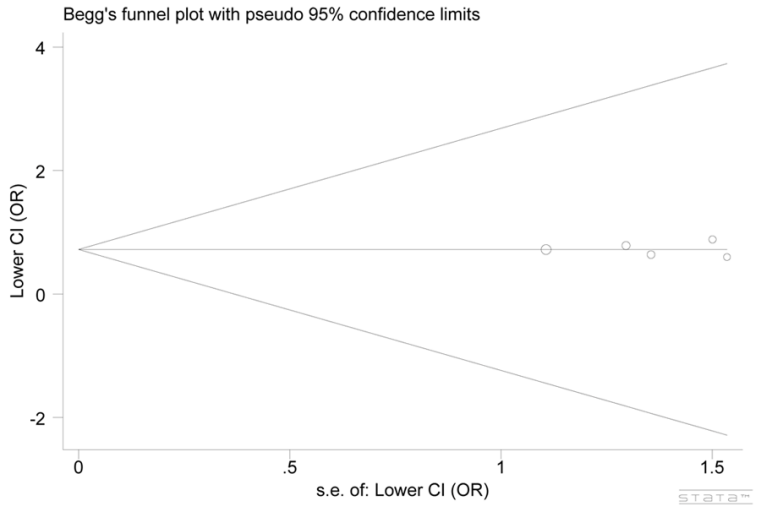

Figure 3. Begg's funnel plot of publication bias for *p73* G4A (AT/AT + AT/GC vs. GC/GC). Each point represents a separate study for the indicated association. Log [or], natural logarithm of OR. Horizontal line, mean effect size.

0.77-1.23). Similar results were obtained in the stratified analysis by ethnicity (**Table 2**).

Tests of heterogeneity

In this study, none of the genetic models showed substantial heterogeneity between studies ($P > 0.10$, $I^2 > 50\%$, **Table 2**) and thereby the calculation of all pooled ORs was conducted using the fixed-effect model.

Publication bias

We examined if there was evidence of publication bias for studies included in this meta-analysis. The funnel plots showed no obvious asymmetries and Egger's test did not suggest statistical evidence for significant publication bias (AT/AT + AT/GC vs. GC/GC: $P = 0.997$, **Figure 3**).

Discussion

Genetic association study is considered as an effective way to determine cancer susceptibility associated with SNPs of candidate genes and has been widely applied in cancer research [24]. However, the studies including inadequate samples may have weak statistical power and thereby interfere with the precision of results, leading to false positive or false negative findings consequently [25]. For example, a population-based case-control study of Chinese samples (385 gastric cancer patients and 412 healthy controls) reported an increased risk of gastric cancer in relation to the *p73* G4A GC/GC genotype [16]. In contrast to this observation, another study with a comparable sample consisting of 388 Japanese cases and 419 race-matched controls suggested no significant association [14]. There may be a variety of explanations for this discrepancy, such as distinct ethnicities, analytic methods, diagnostic criteria, and gastric cancer subtypes applied, but the most likely explanation might be the insufficient detection power as a result of limited sample size.

Here, we performed a meta-analysis of published studies to evaluate the association between *p73* G4A and risk of gastric cancer, because no such analysis has been reported to date. Among the genetic models examined in this analysis, none of the models provided statistical evidence for a significant association between gastric cancer risk and *p73* G4A. A same trend was also indicated in the subgroup analysis by ethnicity. As reported in several studies [5, 26], the *p73* gene encodes for a protein that suppresses cell proliferation and stimulates apoptotic activity in a p53-like manner. In this sense, the negative association observed in our analysis can be reasonably explained, as *p73* may act as a tumor suppressor gene and functions effectively in the inhibition of cancer formation. However, the allele frequency of *p73* G4A varies between Caucasians and Asians, 15% among the former population and 23.7% among the latter [13]. Thus we hypothesized that ethnicity might be a crucial covariate and penetrance of *p73* G4A may differ depending on ethnicity.

Several meta-analysis of *p73* G4A and cancer susceptibility have been published over the past few years [27-29]. All of the analyses reported an increased global risk of cancer associated with *p73* G4A. Interestingly, the findings in subgroup analysis contradict each other. Two groups [27, 29] detected significant cancer risk variations in both Caucasians and Asians. Inconsistent with the previous significant association, De Feo et al. [28] suggested no evidence of an effect modification of *p73* for cancer risk in both of the ethnicities. This controversy might also be attributed to the small number of subjects included in each of the meta-analyses. These analyses included one or two studies of gastric cancer, its association with *p73* G4A was not independently evaluated owing to lack of data. This is another reason why we performed the present meta-analysis.

The heterogeneity test reveal-ed that there was no significant heterogeneity across studies. In addition, no evidence of publication bias was indicated in the two analytic methods, implicating that our current analyses were unbiased. But we should acknowledge that the overall sample is relatively small and needs to be expanded to derive a more precise estimate of the association between *p73* G4A and gastric cancer risk. Besides, gene-gene interaction such as the combination with *p53* exon 4 Arg72Pro and gene-environment interaction were not assessed, because there is no individual level data in the published studies. Such limitations highlight the need for further larger studies with consideration of gene-gene and gene-environment interactions.

To sum up, our meta-analysis suggests that *p73* G4A may not be associated with risk of gastric cancer. However, a future larger study that takes gene-gene and gene-environment interactions on *p73* G4A and gastric cancer risk into consideration is required to validate our findings.

Disclosure of conflict of interest

None.

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