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Polymorphism of the p53 Codon 72 and the Risk of HPV Associated with Oral Squamous Cell Carcinoma

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Abstract

Epidemiological studies have evaluated the associations between polymorphisms of p53 codon 72 and HPV associated with OSCC susceptibility, but the results remain inconclusive. We aimed to conduct a meta-analysis the association between polymorphisms of p53 codon 72 and HPV associated with OSCC risk. PubMed, Embase, Medline, and ISI Web of Science databases were used to collect data. Twelve studies including 2307 cases and 2405 controls were used to investigate the association of polymorphisms of p53 codon 72 and OSCC risk. Our results suggested that there was no association between p53 codon 72 gene polymorphism and OSCC risk (OR=1.71, 95%CI=0.95-1.14, $P_{heterogeneity}$=0.000. for Pro allele vs. Arg allele; OR=1.08, 95%CI=0.85-1.37, $P_{heterogeneity}$=0.227 for Pro/Pro vs. Arg/Arg; OR=1.11, 95%CI=0.85-1.45, $P_{heterogeneity}$=0.044 for Pro/Pro vs. Arg/Arg and Arg/Pro; OR=1.11, 95%CI=0.85-1.45, $P_{heterogeneity}$=0.000 for Pro/Pro and Arg/Pro vs. Arg/Arg), even when we separately investigated sub-group analysis among Asian and non-Asian. Furthermore, the results of this meta-analysis also showed that p53 codon 72 polymorphism wasn't associated with HPVs-related oral cancer (OR=1.28, 95%CI=0.87-1.88, $P_{heterogeneity}$=0.105 for Pro allele vs. Arg allele; OR=1.47, 95%CI=0.83-2.60, $P_{heterogeneity}$=0.249 for Pro/Pro vs. Arg/Arg; OR=1.08, 95%CI=0.68-1.72, $P_{heterogeneity}$=0.000 for Arg/Arg vs Arg/Pro; OR=1.52, 95%CI=0.70-3.31, $P_{heterogeneity}$=0.091 for Pro/Pro vs Arg/Pro and Arg/Arg, OR=1.12, 95%CI=0.74-1.70, $P_{heterogeneity}$=0.061 for Pro/Pro and Arg/Pro vs. Arg/Arg). Overall, this meta-analysis suggested that there was no significant association of p53 codon 72 polymorphism with OSCC risk, and p53 codon 72 also wasn't a risk factor for HPVs-related oral cancer. Further research is needed to assess possible gene–gene or gene-environment-lifestyle interactions on periodontal disease.

Key words:

Oral squamous cell carcinoma; p53; Polymorphism; Meta-analysis

Abbreviations

OSCC: Oral Squamous Cell Carcinoma; HPV: Human Papillomavirus; ORs: Odds Ratios; CIs: Confidence Intervals

Introduction

Cancers of the oral cavity is the sixth most common cancer, accounting for 3-4% of all cancers worldwide [23], whereas oral squamous cell carcinoma (OSCC) accounted for more than 95% of all oral malignant neoplasms [19]. The far greater worldwide problem is that the new cases annually exceed 481,000. It is considered to be a complex disease caused by genetic and environmental factors, such as viral infection, smoking, alcohol drinking, and genetic variations [7,24,32].

Genetic mutation may affect individual susceptibility to cancer. Recently, some studies have focused on searching numerous candidate genes for oral cancer, and investigated the genetic marker that may affect immune responses and resulted in individuals more susceptible to OSCC. The human p53 gene is a tumor suppressor gene, containing a nucleotide polymorphism for amino acid codon 72, exon 4 of the p53 protein [3]. The higher risk of p53 gene with p53 Arg homozygous genotype compared to Pro homozygous genotype was previously shown in developing cervical cancer upon HPV infection [26]. Additionally, some studies researched other cancers such as lung cancer [31]; ovarian cancer [30] and nasopharyngeal [28] have shown a higher risk for cancer associated with homozygotic status and a protective Arg allele. At the same times, some studies have reported an association of p53 codon 72 gene polymorphism with human papillomavirus (HPV)-related cancer [4, 15]. However, several studies failed to confirm this association [9,13]. So far, a few studies have reported the association of the p53 codon 72 polymorphism with OSCC risk, but the results were inconsistent [5,14,17]. Although some studies concerning the association between this polymorphism and OSCC susceptibility or between p53 codon 72 polymorphism and HPV infection have been published, results were inconsistent.

To further evaluate the role of p53 gene polymorphism in the development OSCC, we performed this meta-analysis which combining a large case-control study to explore the relation with a stronger statistical power.

Materials and Methods

Search strategy for identification of studies

In the present study, we collected information using the PubMed, Embase, Medline, and ISI Web of Science databases (last search updated on March 2th, 2013). Key words are used as following: "oral cancer", "oral squamous cell carcinomas", "OSCC", "p53",

"polymorphism" and the combined phrases. Additionally, a hand search of references from original studies or review articles which involving the association between p53 gene polymorphisms and OSCC was implemented without language restrictions.

Data extraction criteria

In our study, three investigators independently extracted the data and reached consensus on all items. All publications should were comply with the following criterias: (1) first author's name, the year and location of publication; (2) ethnicity of the study population; (3) genotyping methods; (4) frequency of genotype and allele counts of studied polymorphisms between patients and controls in order to estimate Odds Ratio (OR) and its corresponding 95% Confidence Interval (CI).

Statistical analysis

We assessed the association of p53 codon 72 with oral squamous cell carcinomas risk under allele, homozygous, heterozygote and dominant and recessive models, respectively. ORs and their 95%CIs were calculated to the differences of alleles or genotypes between cases and controls.

The deviation of Hardy-Weinberg equilibrium was assessed by the Pearson χ^2 test, and the Heterogeneity of data was quantified using the I^2 statistic which was documented for the low, moderate, and high with I^2 values of 25%, 50%, and 75%, respectively [10]. If the I^2 value was<25%, implying no evidence of heterogeneity, a Mantel–Haenszel fixed-effects model was used to calculate ORs and 95%CIs; otherwise, we used the DerSimonian and Laird random-effects model.

Finally, the Begg test and visual funnel plot inspection were used to assess the publication bias [2]. *P* values<0.05 are considered statistically significant. All analyses were done with Stata software, version 12.0 and the P values were two-sided.

Results

Characteristics of study population

The distributions of demographic characteristics and potential risk factors are summarized in Table 1. The association of tobacco smoking, alcohol intake, betel quid chewing with disease outcome was assessed by χ2 test. More smokers, alcohol users and betel chewers were seen in oral squamous cell carcinomas cases group than in control group (P<0.05), and HPV was found to be significantly associated with OSCC (P<0.05) when compared to controls. As shown in Table 2, the main features of the eligible papers were described. There were 12 articles relevant to the search terms and manual search [4,6,8,15,16,18,20-22,25,27,29]. 12 studies involving 2307 cases and 2405 controls evaluated the p53 codon 72 gene polymorphism with oral squamous cell carcinomas risk, and there were 8 studies [8,15,16,18,20-22,29] taking the Asian population as the research object, while four studies [4,6,25,27] were contraposing the non-Asian population including Caucasian and mixed ethnicity. The distribution of genotypes in the controls was all in agreement with HWE for all except three studies [6,15,16].

Quantitative synthesis

p53 codon 72 gene polymorphism and OSCC:

The association between p53 codon 72 gene polymorphism with OSCC risk was listed in Table 3. There was no significant association of all genotypes polymorphism including allele, homozygote, heterozygote, dominant models and recessive model with OSCC risk (OR=1.71, 95%CI=0.95-1.14, $P_{heterogeneity}$=0.000. for Pro allele vs. Arg allele; OR=1.08, 95%CI=0.85-1.37, $P_{heterogeneity}$=0.227 for Pro/Pro vs. Arg/Arg; OR=1.11, 95%CI=0.85-1.45, $P_{heterogeneity}$=0.044 for Pro/Pro vs. Arg/Arg and Arg/Pro; OR=1.11, 95%CI=0.85-1.45, $P_{heterogeneity}$=0.000 for Pro/Pro and Arg/Pro vs. Arg/Arg) (Figure 1). In our ethnicity-stratified analyses, the results also did not show any association between p53 codon 72 gene polymorphism with OSCC risk, and heterogeneity was still exist among studies in subgroup (Table 2 and Figure 1).

Categories	Cases n (%)	Controls n (%)	*p*-value
Smoking status			
Ever	1079 (70.5)	951 (50.1)	<0.001
Never	451 (29.5)	946 (49.9)	
Alcohol use			
Ever	884 (65.6)	718 (48.4)	<0.001
Never	464 (34.4)	767 (51.6)	
Betel quid chewing			
Ever	509 (75.7)	277 (30.5)	<0.001
Never	163 (24.3)	632 (69.5)	
HPV			
Positive	302 (29.6)	211 (21.4)	<0.001
Negative	718 (70.4)	776 (78.6)	

Table 1: Distribution of demographic variables and genotypes between cancer cases and controls.

p53 polymorphism and human papillomavirus infection in OSCC

We obtained information for 180 HPV-positive cases and 352 HPV-negative cases with oral cancer. The controls were firstly used for comparison of HPVs infection with the oral cancer cases; however, they also served as a separate population for the evaluation of the association of p53 codon 72 polymorphism and HPVs. There is no association between p53 codon 72 polymorphism and HPV infection (OR=1.28, 95%CI=0.87-1.88, $P_{heterogeneity}$=0.105 for Pro allele vs. Arg allele; OR=1.47, 95%CI=0.83-2.60, $P_{heterogeneity}$=0.249 for Pro/Pro vs. Arg/Arg; OR=1.08, 95%CI=0.68-1.72, $P_{heterogeneity}$=0.000 for Arg/Arg vs Arg/Pro; OR=1.52, 95%CI=0.70-3.31, $P_{heterogeneity}$=0.091 for Pro/Pro vs Arg/Pro and Arg/Arg, OR=1.12, 95%CI=0.74-1.70, $P_{heterogeneity}$=0.061 for Pro/Pro and Arg/Pro vs. Arg/Arg) (Table 4).

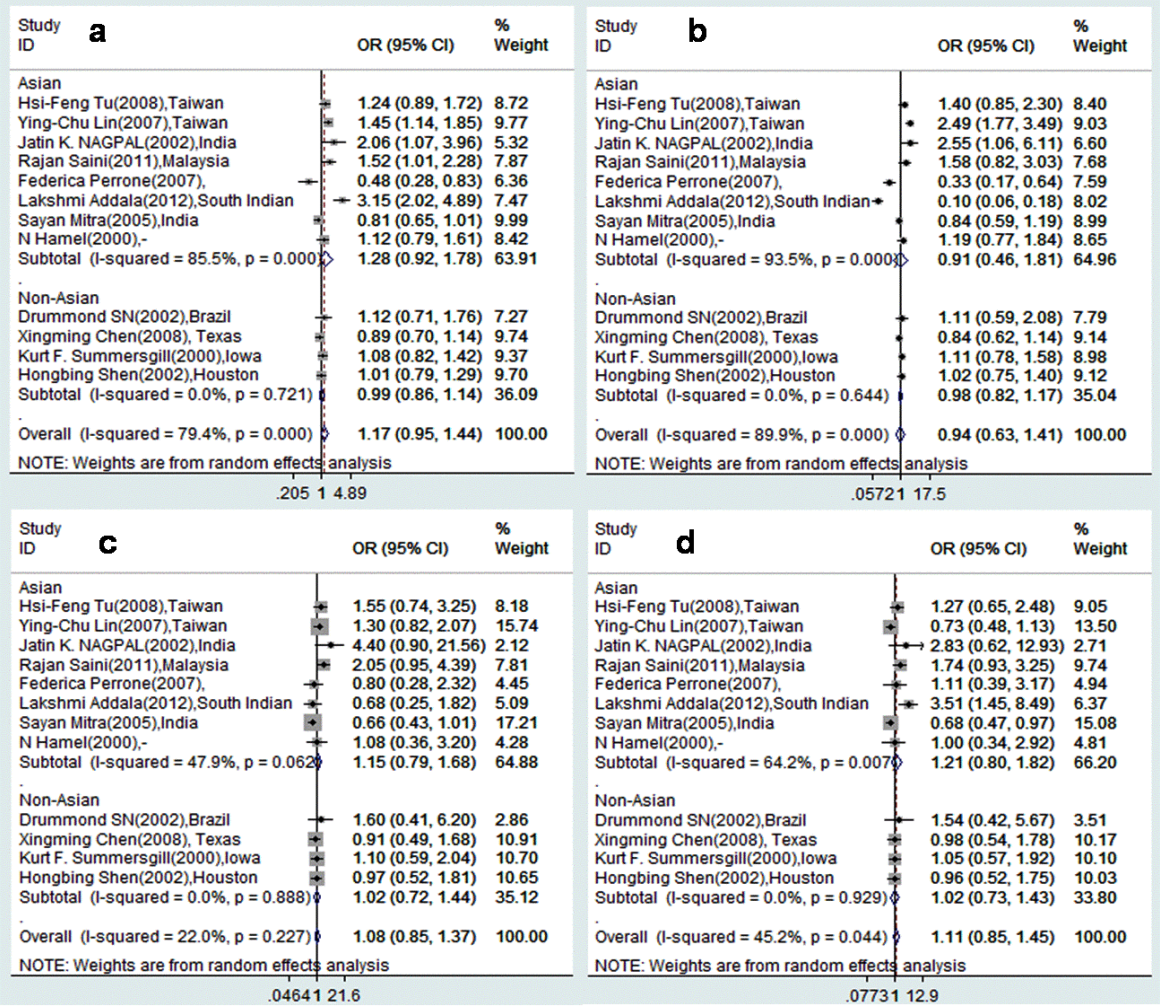

Figure 1: These Forest plots illustrate the association of the p53 codon 72 polymorphism with OSCC for (a) Pro allele vs. Arg allele, (b) Pro/Pro and Arg/Pro vs. Arg/Arg, (c) Pro/Pro vs. Arg/Arg, (d) Pro/Pro vs. Arg/Arg and Arg/Pro. For each study, the odds ratio(OR) and 95% confidence interval (CI) values are indicted.

Publication Bias

As reflected by the funnel plots (Figure 2) and the corresponding Begg test, there was a low probability of publication bias for p53 codon 72 gene polymorphism with OSCC risk under study.

First author	Year	Country	Racial descent	Cases/controls	Genotyping method	P_{HWE}
Tu, H.F	2008	Taiwan	Asian	189/116	PCR-RFLP	0.336
Lin, Y.Chu	2007	Taiwan	Asian	297/280	PCR	<0.05
Nagpal, J. K.	2002	India	Asian	110/26	PCR-RFLP	0.875
Saini R	2011	Malaysia	Asian	99/90	PCR-RFLP	0.215
Perrone, F	2007	-	Asian	77/141	PCR	0.343
Lakshmi A	2012	Malaysia	Asian	150/150	PCR	<0.05

Drummond, S.N	2002	Brazil	Mixed	82/82	PCR-RFLP	<0.05
Chen, X.M	2008	Texas	Caucasian	326/349	PCR-RFLP	0.518
Mitra, S.Y	2005	India	Asian	308/342	PCR-RFLP	0.203
Hamel, N	2000	-	Asian	163/163	PCR	0.472
Summersgill, K.F	2000	Iowa	Caucasian	202/333	PCR-RFLP	0.082
Shen, H.B	2002	Houston	Caucasian	304/333	PCR	0.811

Table 2: Characteristics of studies included in the meta-analysis. HWE: Hardy–Weinberg equilibrium, P < 0.05 was considered significant.

Genotype	Race	Number of cases/ controls	Random effects odds ratio (p-value)	95%CI	I2 (%)	Heterogeneity chi-squard (p-valuea)
Pro/Pro vs. Arg/Arg	All	2307/2405	1.08 (0.54)	0.85-1.37	22	14.11 (0.227)
	Asian	1393/1308	1.15 (0.47)	0.79-1.68	47.9	13.43 (0.062)
	Non-Asian	914/1097	1.02 (0.92)	0.72-1.44	0	0.64 (0.89)
Arg/Pro vs. Arg/Arg	All	2307/2405	1.11 (0.34)	0.69-1.77	91.8	133.57 (0.000)
	Asian	1393/1308	1.18 (0.33)	0.52-2.68	94.7	131.81 (0.000)
	Non-Asian	914/1097	1.02 (0.86)	0.85-1.23	0	1.65 (0.931)
Pro/Pro vs. Arg/Arg and Arg/Pro	All	2307/2405	1.11 (0.46)	0.85-1.45	45.2	20.06 (0.044)
	Asian	1393/1308	1.21 (0.37)	0.80-1.82	64.2	19.56 (0.007)
	Non-Asian	914/1097	1.02 (0.89)	0.73-1.43	0	3.58 (0.929)
Pro/Pro and Arg/Pro vs. Arg/Arg	All	2307/2405	0.95 (0.78)	0.63-1.41	89.9	109.38 (0.000)
	Asian	1393/1308	0.91 (0.79)	0.46-1.81	93.5	107.68 (0.000)
	Non-Asian	914/1097	0.98 (0.86)	0.82-1.17	0	1.67 (0.644)
Pro allele vs. Arg allele	All	2307/2405	1.17 (0.14)	0.95-1.14	79.4	53.4 (0.000)
	Asian	1393/1308	1.28 (0.14)	0.92-1.78	85.5	48.38 (0.000)
	Non-Asian	914/1097	0.99 (0.93)	0.86-1.14	0	1.34 (0.72)

Table 3: The results of the meta-analysis concerning the association of the composite genotype with OSCC. OR, odds ratio; CI, confidence interval. aP value for heterogeneity.

Discussion

The p53 tumor suppressor gene is one of the most commonly mutated genes in human cancer [11]. The single nucleotide polymorphism of p53 was described in the promoter region in codon 47 and 72 in exon 4. Among them, codon 72 polymorphism has been reported to be associated with the risk of several cancers, such as lung cancer [31], ovarian cancer [30] and nasopharyngeal [28]. There are many studies to investigate the association between the p53 codon 72 polymorphism and the risk of oral cancer, but results have been inconsistent. Bau et al. observed that those who had Arg/Arg at p53 codon 72 showed a 2.68-fold increased risk of oral cancer compared to those with Pro/Pro [1]. Jing et al reported that the Arg allele frequency was significantly lower in comparison with controls in patients with oral cancer [12]. This meta-analysis summarizing the result of 12 previous studies shown an association between the p53 codon 72 gene polymorphism and OSCC. In order to obtain more reliable estimates, we focused a large number of primary studies and provided sufficient information to further research this polymorphism.

A meta-analysis, including 2307 cases and 2405 controls from 12 eligible case-control studies, explored the association between the p53 codon 72 gene polymorphism and OSCC. Our results demonstrated that there was no significant association of p53 codon 72 polymorphism with OSCC risk. To better understanding the precise contribution of genetic polymorphism of p53 to OSCC, we studied the

ethnic subgroup for some genetic polymorphism meta-analysis, and proved no association between this polymorphism and OSCC in a specific ethnicity, there was no significance for Asian and non- Asian populations.

Genotype	Random effects odds ratio (p-value)	95%CI	I^2 (%)	Heterogeneity chi-squard (*p*-value[a])
Pro/Pro vs. Arg/Arg	1.47 (0.02)	0.83-2.60	25.9	5.40 (0.25)
Arg/Pro vs. Arg/Arg	1.08 (0.74)	0.68-1.72	0	1.94 (0.75)
Pro/Pro vs. Arg/Arg and Arg/Pro	1.52 (0.29)	0.70-3.31	50	8.0 (0.09)
Pro/Pro and Arg/Pro vs. Arg/Arg	1.12 (0.59)	0.74-1.70	0	2.70 (0.61)
Pro allele vs. Arg allele	1.28 (0.28)	0.88-1.88	47.8	7.67 (0.11)

Table 4: The results of the meta-analysis concerning the association of p53 codon 72 polymorphism and HPVs with OSCC cases. OR, odds ratio; CI, confidence interval. aP value for heterogeneity.

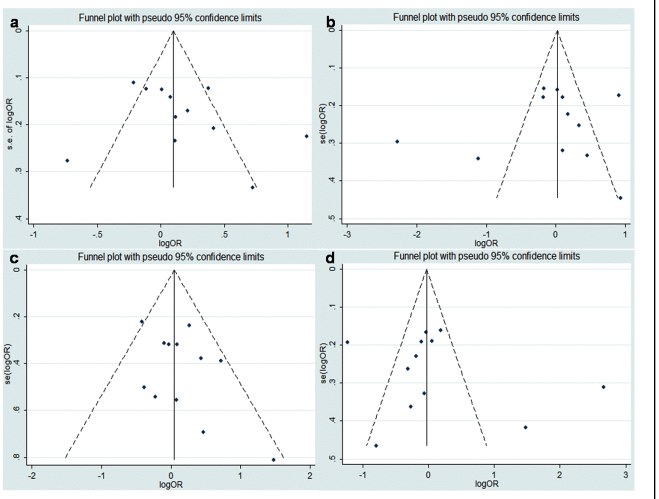

Figure 2: Begg's funnel plot for publication bias test. Each point represents a separate study for the indicated association. s.e: standardized effect. a, b, c, d represent allele comparison, recessive model comparison, homozygote model comparison and dominant genetic model comparison for p53 codon 72, respectively.

For genetic study, the most serious confounding factor was ethnicity, besides, infection with oncogenic mucosal human papillomaviruses (HPVs) and life habits (smoking, alcohol use and betel quid chewing) seemingly have a great influence on susceptibility to OSCC. So we investigated the association of tobacco smoking, alcohol intake, betel quid chewing and HPVs with OSCC outcome by $\chi 2$ test, and studied the presence of the polymorphism codon 72 in the promoter of p53 gene in individuals with HPVs of OSCC. We found that smoking, alcohol using, betel quid chewing and HPVs were risk factors for OSCC ($P<0.05$). p53 codon 72 genotype didn't increased risk for HPV-positive OSCC compared with HPV-negative OSCC (Table 4).

Some shortcomings of the analysis should be discussed. OSCC is a complex disease, and modifying factors such as smoking, alcohol, betel quid chewing and HPVs might possibly have an effect on genetic associations with OSCC phenotypes. Firstly, although we have considered modifying factors, samples were still not very large. Second, the data of studies about OSCC has some biases because of the heterogeneity in OSCC definition and the inappropriate selection of controls.

In Conclusion, from the results of this quantitative meta-analysis, combining data from 12 case-control studies, it showed that there was no significant association of p53 codon 72 polymorphism with OSCC risk, and p53 codon 72 also wasn't a risk factor for HPVs-related oral cancer. Further epidemiological studies including a larger and homogenous ethnic group, reporting on the gene-environment interaction, are necessary to verify these findings.

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