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Meta-analysis of associations between the *TP53* Arg72Pro polymorphism with risk of head and neck carcinomas based on case-control studies

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ABSTRACT. Genetic factors have been shown to play a role in the development of head and neck cancers (HNCs). However, studies investigating the association between the *TP53* Arg72Pro polymorphism and HNCs susceptibility have yielded conflicting results. Hence, we performed a meta-analysis of all eligible studies (up to January 1, 2012) to derive a more precise estimation of this association in order to increase understanding of the possible risk factors of HNCs. Twenty-seven case-control studies involving 3966 cases and 4387 controls were included in our analysis. Overall, no evidence of association was observed between the *TP53* Arg72Pro single nucleotide polymorphism (SNP) and the risk of HNCs in any genetic model (Arg/Arg *vs* Pro/Pro: odds ratio (OR) = 0.83, 95% confidence interval (CI): 0.65-1.06; Arg/Pro *vs* Pro/Pro: OR = 0.88, 95%CI= 0.70-1.10; Arg/Arg+Arg/Pro *vs* Pro/Pro: OR = 0.87, 95%CI= 0.70-1.09; Arg/Arg *vs* Arg/Pro+Pro/Pro: OR = 0.95, 95%CI= 0.82-1.11). Nevertheless, the *TP53* Arg72Pro polymorphism shows diverse

effects across different subtypes of HNCs. For example, there was a lack of association of this polymorphism with oral cavity cancer, whereas a significant association with nasopharyngeal cancer was observed. Results of this meta-analysis suggest that the *TP53* Arg72Pro polymorphism might have different effects on the risk of various subtypes of HNCs.

Key words: Head and neck carcinomas; p53 codon 72; Gene polymorphism; Meta-analysis

INTRODUCTION

Head and neck carcinomas (HNCs), including cancers of the oral cavity, pharynx, and larynx, represent the sixth most frequent cancer and the seventh leading cause of cancer-related deaths in the world. There are approximately 540,000 new cases and 271,000 deaths worldwide that are associated with HNCs annually (Parkin et al., 1999). Development of HNCs is a multifactorial process that is associated with a variety of risk factors. Major risk factors include tobacco smoking, alcohol consumption, and betel-quid chewing. Genetic factors have also been shown to play roles in the development of HNCs (Hiyama et al., 2002; Yokoyama and Omori, 2005).

As a major regulator of the cellular response to stress, TP53 serves as a tumor suppressor by inducing cell cycle arrest or apoptosis. Indeed, the *TP53* gene is frequently mutated in various types of human cancers, including HNCs (Hiyama et al., 2004; Karsai et al., 2007). Besides mutations, polymorphisms of *TP53* have also been reported as possible risk factors for a number of tumors. A common single nucleotide polymorphism (SNP) at codon 72 of *TP53* (Pro72Arg, rs1042522) results in two protein forms with different biological and biochemical properties (Thomas et al., 1999). In particular, the Arg72 variant induces markedly better apoptosis compared to the Pro72 variant, and these two functionally distinct polymorphic variants of *TP53* may influence cancer risk or treatment (Dumont et al., 2003).

The association between the *TP53* Arg72Pro polymorphism and HNCs has received considerable attention. However, the results are conflicting and inconclusive (Yung et al., 1997; Nagpal et al., 2002; Hadhri-Guiga et al., 2007), which may be partially due to differences among the populations studied, as well as particular methodological and study design features. Hence, we performed a meta-analysis of all eligible studies to derive a more precise estimation of the association, which may help to clarify the possible influence of this SNP on the risk of HNCs.

MATERIAL AND METHODS

Identification and eligibility of relevant studies

We conducted a literature search of the PubMed database and the Chinese Biomedical Literature Database (CBM) using the following key words and subject terms: "*p53*", "*TP53*", "codon 72", "polymorphism", "oral cancer", "laryngeal cancer", "nasopharyngeal carcinoma", "cancers of the pharynx and larynx", "head and neck squamous cell carcinoma", and "head and neck carcinoma", along with their combinations. References of the retrieved publications (up to January 1, 2012) were also screened. The language of publication was restricted to English or Chinese, and only research articles were included. If an article reported results of separate studies, each study was treated as a separate comparison in our meta-analysis.

Inclusion and exclusion criteria

The following inclusion criteria were used in literature selection for the meta-analysis: a) published in peer-reviewed journals, b) focused on *TP53* Arg72Pro polymorphism and risk of HNCs, and c) contained genotype frequency data. The major exclusion criteria were: a) not case-control studies, b) control population included malignant tumor patients, and c) duplication of a previous publication.

Data extraction

Two investigators (W.H. Ren and D.K. Jiang) reviewed and extracted information from all eligible publications independently according to the inclusion and exclusion criteria listed above. Disagreements were worked out by discussion between the two reviewers. The following characteristics were collected from each study: first author's surname, year of publication, country of origin, ethnicity (categorized as Asian, Caucasian, and Other), source of case and control groups, specimens used for assessment of the *TP53* Arg72Pro genotypes, tumor subtype (oral cancer, nasopharyngeal cancer, pharyngeal cancer, laryngeal cancer, and oropharyngeal cancer), total number of cases and controls, and number of cases and controls with the Arg/Arg, Arg/Pro, and Pro/Pro genotypes, respectively.

Quality score assessment

The quality of the studies included was also independently assessed by the same two reviewers according to the predefined scale for quality assessment (Table 1), which was described previously (Jiang et al., 2011). Briefly, these scores were based on both traditional epidemiological considerations and cancer genetic issues. Any disagreement was resolved by discussion between the two reviewers. Scores ranged from 0 (worst) to 15 (best). Reports with scores below 10 were classified as "low quality", and those scoring 10 and above were classified as "high quality".

Statistical analysis

We first assessed Hardy-Weinberg equilibrium (HWE) in each study using goodness-of-fit tests (chi-squared or Fisher's exact test) only in control groups. Crude odds ratios (ORs) with 95% confidence intervals (CIs) were used to measure the strength of association between the *TP53* Arg72Pro polymorphism and risk of overall and subtypes of HNCs. The pooled ORs were estimated according to the random-effects model (the DerSimonian and Laird model) for the codominant model (homozygote comparison: Arg/Arg *vs* Pro/Pro; heterozygote comparison: Arg/Pro *vs* Pro/Pro), dominant model (Arg/Arg+Arg/Pro *vs* Pro/Pro), and recessive model (Arg/Arg *vs* Arg/Pro+Pro/Pro), respectively. Stratified analyses were also performed by ethnicity (Caucasian, Asian, and Other) and quality score of studies (<10 and ≥ 10). A chi-squared-based Q-test was performed to evaluate the between-study heterogeneity. One-way sensitivity analyses were performed to assess the stability of the meta-analysis results. The potential publication bias was estimated using the Egger linear regression test and by visual inspection of the funnel plot. $P < 0.05$ was considered to be statistically significant. All statistical tests were preformed with the STATA version 10.0 software (Stata Corporation, College Station, TX, USA).

Table 1. Scales for quality assessment.

Criteria	Score
Source of cases	
Selected from population or cancer registry	3
Selected from hospital	2
Selected from pathology archives, but without description	1
Not described	0
Source of controls	
Population-based	3
Blood donors or volunteers	2
Hospital-based (cancer-free patients)	1
Not described	0
Specimens used for determining genotypes	
White blood cells or normal tissues	3
Tumor tissues or exfoliated cells of tissue	0
Hardy-Weinberg equilibrium in controls	
Hardy-Weinberg equilibrium	3
Hardy-Weinberg disequilibrium	0
Total sample size	
Larger than 1000	3
Larger than 500, but less than 1000	2
Larger than 200, but less than 500	1
Less than 200	0

RESULTS

Literature search, screening, and data collection

To perform the meta-analysis, we first conducted a literature search (the selection process is shown in **Figure S1**).

Ultimately, 29 studies involving the association of the *TP53* Arg72Pro polymorphism with susceptibility to HNCs were collected. However, one of the studies (Brant et al., 2007) lacked genotype data of control groups, and was therefore excluded from the analysis. Moreover, five of the remaining 28 studies (Shen et al., 2002; Lu et al., 2007; Ji et al., 2008; Chen et al., 2007, 2008) were carried out in the same research group. Of these five studies, Chen et al. (2007) included cases of all different HNCs subtypes, and contained the most cases. Therefore, this study, but not the other four, was included in the evaluation of overall HNCs in our meta-analysis. However, the genotype data of the *TP53* Arg72Pro SNP in different subtypes of HNCs were not provided in this report (Chen et al., 2007) or in that of Lu et al. (2007). Hence, we chose the other three studies (Shen et al., 2002; Ji et al., 2008; Chen et al., 2008) in the meta-analysis of specific HNCs subtypes, excluding the data from Chen et al. (2007) and Lu et al. (2007). Shen et al. (2002) analyzed oral, pharyngeal, and laryngeal cancer specifically, whereas Ji et al. (2008) and Chen et al. (2008) studied oropharyngeal cancer as well as oral cancer. Overall, a total of 27 studies consisting of 3966 HNCs cases and 4387 controls were included in our meta-analysis (Yung et al., 1997; Golovleva et al., 1997; McWilliams et al., 2000; Hamel et al., 2000; Summersgill et al., 2000; Tandle et al., 2001; Sourvinos et al., 2001; Nagpal et al., 2002; Shen et al., 2002; Tsai et al., 2002; Tiwawech et al., 2003; Kietthubthew et al., 2003; Katiyar et al., 2003; Scheckenbach et al., 2004; Cortezzi et al., 2004; Hsieh et al., 2005; Sousa et al., 2006; Twu et al., 2006; Hadhri-Guiga et al., 2007; Perrone et al., 2007; Kuroda et al., 2007; Ji et al., 2008; Chen et al., 2007, 2008; Lin et al., 2008; Tu et al., 2008; Misra et al., 2009) (Table 2). The genotype distribution of the *TP53* Arg72Pro polymorphism is summarized in Table 3.

Table 2. Main characteristics of studies included in the meta-analysis.

First author	Year	Country	Ethnicity	Case source	Control source	Sample type of cases	Tumor site (number of cases)	Sample size (case/control)	Quality score
Golovleva et al.	1997	Sweden	Caucasian	Hospital	Blood donor	Blood	Nasopharynx (64)	64/99	10
Yung et al.	1997	China (Hong Kong)	Asian	Hospital	Hospital	Tumor tissue	Nasopharynx (20)	20/31	6
McWilliams et al.	2000	USA	Caucasian	Hospital	Population	Blood	Oral cavity (65), Nasal/sinus (4), Oropharynx (12), Hypopharynx (2), Supraglottic (20), Glottic (11), Subglottic (25), Other sites (21)	160/149	12
Hamel et al.	2000	Canada	Caucasian	Population	Population	Blood	Oral cavity (N = 69), Pharynx (N = 24), Nasal cavity (N = 4), Larynx (N = 66)	163/163	13
Summersgill et al.	2000	USA	Caucasian	Hospital	Unknown	Cytology specimens	Oral cavity (202)	202/333	4
Tandle et al.	2001	India	Asian	Hospital	Population	Blood	Oral cavity (72)	72/153	9
Sourvinos et al.	2001	Greece	Caucasian	Hospital	Blood donor	Cytology specimens	Larynx (37)	37/40	7
Shen et al.	2002	USA	Caucasian	Hospital	Blood donor	Blood	Oral cavity (105), Pharynx (121), Larynx (78)	304/333	12
Nagpal et al.	2002	India	Asian	Hospital	Population	Tumor tissue	Oral cavity (110)	110/26	8
Tsai et al.	2002	China (Taiwan)	Asian	Hospital	Blood donor	Blood	Nasopharynx (50)	50/59	10
Tiwawech et al.	2003	Thailand	Asian	Cancer Center	Cancer Center	Blood	Nasopharynx (102)	102/148	10
Kietthubthew et al.	2003	Thailand	Asian	Hospital	Volunteers	Blood	Oral cavity (97)	97/97	7
Katiyar et al.	2003	India	Asian	Hospital	Hospital	Tumor tissue	Oral cavity (44)	44/20	6
Scheckenbach et al.	2004	Germany	Caucasian	Hospital	Population	Tumor tissue	Oral cavity (13), Oropharynx (33), Hypopharynx (33), Larynx (44), Ear (1), Nose (1)	122/193	9
Cortezzi et al.	2004	Brazil	Others	Hospital	Hospital	Tumor tissue	Oropharynx (21), Larynx (15), Oral cavity (11), Other sites (3)	50/142	6
Hsieh et al.	2005	China (Taiwan)	Asian	Hospital	Blood donor	Blood	Oral cavity (523), Oropharynx (49), Hypopharynx (57)	629/317	13
Sousa et al.	2006	Portuga	Caucasian	Cancer Center	Cancer Center	Blood	Nasopharynx (107)	107/285	10
Twu et al.	2006	China (Taiwan)	Asian	Unknown	Unknown	Blood	Hypopharynx (53)	53/53	6
Chen et al.	2007	USA	Caucasian	Cancer Center	Blood donor	Blood	Pharynx (383), Oral cavity (246), Larynx (189)	818/821	13
Hadhri-Guiga et al.	2007	Tunisia	Others	Hospital	Population	Blood	Nasopharynx (115)	115/83	11
Perrone et al.	2007	Italy	Caucasian	Unknown	Blood donor	Tumor tissue	Oropharynx (77)	77/141	6
Kuroda et al.	2007	Japan	Asian	Hospital	Hospital	Blood	Oral cavity (100)	100/271	10
Ji et al.	2008	USA	Caucasian	Hospital	Volunteers	Blood	Oropharynx (188)	188/342	12
Lin et al.	2008	China (Taiwan)	Asian	Hospital	Hospital	Blood	Oral cavity (297)	297/280	11
Chen et al.	2008	USA	Caucasian	Hospital	Hospital	Blood	Oral cavity (326)	326/349	11
Tu et al.	2008	China (Taiwan)	Asian	Hospital	Hospital	Blood	Oral cavity (189)	189/116	10
Misra et al.	2009	India	Asian	Hospital	Hospital	Blood	Oral cavity (308)	308/342	11

Table 3. Distribution of *TP53* Arg72Pro genotypes among HNC cases and controls included in the meta-analysis.

First author	Year	Tumor site	Cases (No.)			Controls (No.)			P value of HWE in controls
			Arg/Arg	Arg/Pro	Pro/Pro	Arg/Arg	Arg/Pro	Pro/Pro	
Golovleva et al.	1997	Nasopharynx	15	26	23	30	46	23	0.511
Yung et al.	1997	Nasopharynx	6	11	3	10	13	8	0.379
McWilliams et al.	2000	Mixed	79	53	8	63	44	13	0.223
Hamel et al.	2000	Mixed	88	68	7	95	61	7	0.464
Summersgill et al.	2000	Oral cavity	107	76	19	185	118	30	0.087
Tandle et al.	2001	Oral cavity	6	52	14	22	100	31	<0.01
Sourvinos et al.	2001	Larynx	27	9	1	12	23	5	0.235
Shen et al.	2002	Mixed	158	125	21	175	134	24	0.810
Shen et al.	2002	Oral cavity	55	41	9	175	134	24	0.810
Shen et al.	2002	Pharynx	66	47	8	175	134	24	0.810
Shen et al.	2002	Larynx	37	37	4	175	134	24	0.810
Nagpal et al.	2002	Oral cavity	31	58	21	13	11	2	0.875
Tsai et al.	2002	Nasopharynx	20	14	16	25	26	8	0.766
Tiwawech et al.	2003	Nasopharynx	24	52	26	50	70	28	0.691
Kietthubthew et al.	2003	Oral cavity	32	44	21	35	34	28	0.003
Katiyar et al.	2003	Oral cavity	10	24	10	5	12	3	0.340
Scheckenbach et al.	2004	Mixed	66	55	1	114	66	13	0.426
Scheckenbach et al.	2004	Pharynx	31	31	1	114	66	13	0.426
Cortezzi et al.	2004	Mixed	26	16	8	71	61	10	0.519
Hsieh et al.	2005	Mixed	187	328	114	128	177	66	0.723
Hsieh et al.	2005	Oral cavity	149	274	100	128	177	66	0.723
Sousa et al.	2006	Nasopharynx	62	32	13	178	93	14	0.684
Twu et al.	2006	Mixed	12	27	14	22	24	7	0.910
Chen et al.	2007	Mixed	442	313	63	442	327	52	0.408
Hadhri-Guiga et al.	2007	Nasopharynx	44	48	23	32	45	6	0.059
Perrone et al.	2007	Oropharynx	63	8	6	84	47	10	0.351
Kuroda et al.	2007	Oral cavity	41	44	15	109	117	45	0.160
Ji et al.	2008	Oropharynx	103	74	11	179	140	23	0.529
Lin et al.	2008	Oral cavity	96	155	46	72	152	56	0.135
Chen et al.	2008	Oral cavity	183	121	22	181	144	24	0.516
Tu et al.	2008	Oral cavity	53	106	30	41	60	15	0.335
Misra et al.	2009	Oral cavity	87	155	66	85	159	98	0.203

HWE = Hardy-Weinberg equilibrium.

Quality assessment of the literature and data analysis

We also conducted a quality assessment for all studies as described above. Sixteen of the 27 (59%) publications included in this analysis were considered to be of high quality. Furthermore, deviations from HWE were tested from the genotype distribution of *TP53* Arg72Pro in all control groups, and the results are shown in Table 3. The distribution of *TP53* Arg72Pro genotypes deviated from HWE in two studies (Tandle et al., 2001; Kietthubthew et al., 2003).

Meta-analysis results

We first conducted a meta-analysis on all HNCs. The results showed no significant correlation between the risk of HNCs and the *TP53* Arg72Pro SNP in any genetic model (homozygous comparison: OR = 0.83, 95%CI= 0.65-1.06; heterozygotes compared: OR = 0.88, 95%CI= 0.70-1.10; dominant model: OR = 0.87, 95%CI= 0.70-1.09; recessive model: OR = 0.95, 95%CI= 0.82-1.11; Table 4). However, the Q-test indicated heterogeneity in all models (Table 4).

In order to determine the cause of the heterogeneity and to obtain accurate results, we conducted a stratified analysis according to ethnic groups as well as the quality score of studies. A similar conclusion was reached in all genetic models, except that a strong correlation between the risk of HNCs and the *TP53* Arg72Pro SNP was revealed in the Others group under the homozygous comparison, the heterozygous comparison, and the dominant models ($P < 0.05$, Table 4).

Table 4. Meta-analysis results on *TP53* Arg72Pro polymorphism and the risk of overall head and neck carcinoma.

Study groups	N[a]	Smaple size (case/control)	Arg/Arg *vs* Pro/Pro			Arg/Pro *vs* Pro/Pro			Arg/Arg+Arg/Pro *vs* Pro/Pro			Arg/Arg *vs* Arg/Pro+Pro/Pro		
			OR (95%CI)	P[b]	P[c]	OR (95%CI)	P[b]	P[c]	OR (95%CI)	P[b]	P[c]	OR (95%CI)	P[b]	P[c]
Total	24	3966/4387	0.83 (0.65-1.06)[d]	0.001	0.142	0.88 (0.70-1.10)[d]	0.002	0.262	0.87 (0.70-1.09)[d]	0.002	0.222	0.95 (0.82-1.11)[d]	0.001	0.518
Quality of studies														
<10	11	884/1229	0.87 (0.52-1.44)[d]	0.031	0.585	0.92 (0.58-1.48)[d]	0.037	0.74	0.95 (0.62-1.43)[d]	0.071	0.793	0.99 (0.66-1.48)[d]	<0.001	0.962
≥10	13	3082/3158	0.83 (0.62-1.10)[d]	0.003	0.19	0.86 (0.66-1.12)[d]	0.006	0.267	0.84 (0.65-1.10)[d]	0.002	0.202	0.96 (0.86-1.07)	0.343	0.445
Ethnicity														
Caucasian	9	1730/2195	0.99 (0.63-1.57)[d]	0.015	0.982	0.86 (0.55-1.35)[d]	0.024	0.503	0.93 (0.61-1.41)[d]	0.027	0.74	1.11 (0.84-1.47)[d]	0.001	0.455
Asian	13	2071/1967	0.84 (0.61-1.15)[d]	0.013	0.267	1.09 (0.92-1.30)	0.204	0.311	0.97 (0.76-1.24)[d]	0.054	0.813	0.85 (0.70-1.04)[d]	0.079	0.112
Others	2	165/225	0.40 (0.19-0.82)	0.739	0.012	0.30 (0.14-0.62)	0.825	0.001	0.34 (0.17-0.68)	0.725	0.002	1.03 (0.67-1.58)	0.835	0.895

[a]Number of comparisons. [b]P value of Q-test for heterogeneity test. [c]Statistically significant results. [d]Random effect model was used when P value for heterogeneity test < 0.1; otherwise, fixed effect model was used.

Next, we analyzed the correlation of the *TP53* Arg72Pro SNP with the risk of different HNC subtypes. Overall, *TP53* genotypes showed no significant correlation to oral, oropharyngeal, laryngeal, or mixed cancers under all genetic models (Table 5). However, a strong correlation was found between *TP53* genotypes and nasopharyngeal cancer with the homozygous comparison (OR = 0.47, 95%CI = 0.32-0.68), the heterozygous (OR = 0.53, 95%CI = 0.037-0.75), and the dominant model (OR = 0.51, 95%CI = 0.37-071) (Table 5).

Furthermore, we carried out stratified analysis according to ethnic groups as well as quality score of the studies in various HNC subtypes. It should be noted that in order to accurately interpret the results of statistical analyses, a particular HNC subtype was chosen for analysis only when three or more independent studies addressed it. Therefore, we were only able to analyze the associations with oral and nasopharyngeal cancers in the stratified analysis. No correlation was identified between the susceptibility of oral cancer and the *TP53* Arg72Pro SNP in all subgroups under all genetic models. However, analysis of high-quality publications only indicated that the susceptibility of nasopharyngeal cancer was significantly correlated with the *TP53* Arg72Pro SNP in the homozygous comparison (OR = 0.44, 95%CI = 0.30-0.64), the heterozygous comparison (OR = 0.48, 95%CI = 0.34-0.69), and the dominant model (OR = 0.47, 95%CI = 0.34-0.66). In the analysis stratified by ethnic groups, we found that a high correlation between the risk of nasopharyngeal cancer and the *TP53* Arg72Pro SNP in the Caucasian group with the homozygous comparison (OR = 0.43, 95%CI = 0.24-0.78), the heterozygous comparison (OR = 0.47, 95%CI = 0.27-0.83), and the dominant model (OR = 0.46, 95%CI = 0.28-0.78), whereas in the Asian group, only the homozygous comparison model (OR = 0.55, 95%CI = 0.32-0.95) indicated a significant correlation between the SNP and the risk of nasopharyngeal cancer (Table 5).

Assessment of publication bias

We also assessed the publication bias using funnel plots, which showed a pattern close to symmetric, indicating no publication bias (Figure 1 shows the funnel plot of overall Arg/Arg *vs* Pro/Pro). In addition, the Egger test was used to quantitatively evaluate the funnel plot symmetry, further revealing no publication bias (homozygous comparison, P = 0.487; heterozygous comparison, P = 0.235; dominant model, P = 0.364; recessive model, P = 0.816).

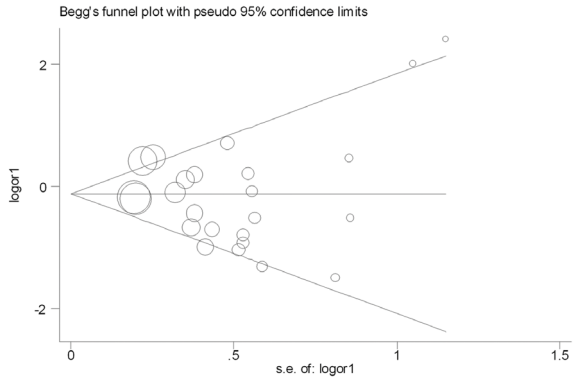

Figure 1. Begg's funnel plot of the *TP53* Arg72Pro polymorphism and HNC risk for the homozygote comparison model (Arg/Arg *vs* Pro/Pro). Each open circle represents a separate study for the indicated association, and its size is proportional to the sample size of that study.

Table 5. Meta-analysis results on *TP53* Arg72Pro polymorphism and the risk of different subtypes of HNCs.

Study groups	n[a]	Sample size (case/control)	Arg/Arg *vs* Pro/Pro			Arg/Pro *vs* Pro/Pro			Arg/Arg+Arg/Pro *vs* Pro/Pro			Arg/Arg *vs* Arg/Pro+Pro/Pro		
			OR (95%CI)	P[b]	P[c]	OR (95%CI)	P[b]	P[c]	OR (95%CI)	P[b]	P[c]	OR (95%CI)	P[b]	P[c]
Oral cavity quality of studies	12	2373/2691	1.02 (0.85-1.22)	0.160	0.819	1.12 (0.95-1.33)	0.823	0.175	1.09 (0.93-1.28)	0.535	0.275	0.97 (0.86-1.09)	0.107	0.608
<10	5	525/629	0.81 (0.54-1.21)	0.384	0.305	1.11 (0.77-1.61)	0.533	0.564	1.00 (0.71-1.41)	0.451	0.992	0.79 (0.61-1.04)	0.441	0.089
≥10	7	1848/2062	1.08 (0.88-1.33)	0.119	0.437	1.13 (0.93-1.36)	0.737	0.219	1.12 (0.94-1.34)	0.415	0.217	1.02 (0.89-1.17)	0.101	0.760
Ethnicity														
Caucasian	3	633/1015	0.97 (0.66-1.42)	0.850	0.864	0.93 (0.63-1.38)	0.919	0.721	0.95 (0.65-1.38)	0.920	0.791	1.04 (0.85-1.08)	0.491	0.693
Asian	9	1740/1676	0.99 (0.72-1.36)[d]	0.058	0.964	1.17 (0.97-1.41)	0.711	0.095	1.13 (0.94-1.34)	0.336	0.184	0.90 (0.71-1.13)[d]	0.062	0.362
Nasopharynx	6	458/705	0.47 (0.32-0.68)	0.727	<0.001	0.53 (0.037-0.75)	0.117	<0.001	0.51 (0.37-0.71)	0.255	<0.001	0.80 (0.62-1.03)	0.885	0.081
quality of studies														
<10	1	20/31	1.60 (0.30-8.49)	-	0.581	2.26 (0.48-10.64)	-	0.304	1.97 (0.45-8.55)	-	0.365	0.90 (0.27-3.04)	-	0.865
≥10	5	438/674	0.44 (0.30-0.64)	0.961	<0.001	0.48 (0.34-0.69)	0.263	<0.001	0.47 (0.34-0.66)	0.534	<0.001	0.79 (0.61-1.03)	0.792	0.081
Ethnicity														
Caucasian	2	171/384	0.43 (0.24-0.78)	0.630	0.005	0.47 (0.27-0.83)	0.467	0.01	0.46 (0.28-0.78)	0.492	0.004	0.79 (0.54-1.16)	0.708	0.227
Asian	3	172/238	0.55 (0.32-0.95)	0.374	0.032	0.71 (0.26-1.91)[d]	0.066	0.497	0.64 (0.40-1.03)	0.129	0.065	0.72 (0.47-1.10)	0.654	0.128
Others	1	115/83	0.36 (0.13-0.98)	-	0.046	0.28 (0.10-0.75)	-	0.011	0.31 (0.12-0.80)	-	0.016	0.99 (0.55-1.76)	-	0.967
Oropharynx	2	265/483	1.22 (0.66-2.28)	0.954	0.530	0.62 (0.16-2.31)[d]	0.071	0.472	1.07 (0.58-1.96)	0.703	0.828	1.76 (0.65-4.77)[d]	0.008	0.265
Pharynx	2	184/526	1.43 (0.66-3.08)	0.312	0.367	1.59 (0.73-3.43)	0.115	0.241	1.48 (0.70-3.14)	0.203	0.303	0.92 (0.66-1.28)	0.188	0.617
Larynx	2	115/373	3.01 (0.37-24.60)[d]	0.088	0.303	1.71 (0.63-4.68)	0.898	0.295	1.92 (0.73-5.08)	0.307	0.187	2.16 (0.29-16.04)[d]	<0.001	0.451
Mixed site	8	2279/2196	0.88 (0.62-1.27)[d]	0.067	0.505	0.97 (0.67-1.41)[d]	0.056	0.890	0.93 (0.66-1.31)[d]	0.065	0.665	0.93 (0.82-1.05)	0.428	0.212

[a]Number of comparisons. [b]P value of Q-test for heterogeneity test. [c]Statistically significant results. [d]Random effects model was used when P value for heterogeneity test < 0.1; otherwise, fixed effects model was used.

DISCUSSION

Reasonable and rigorous experimental designs are essential for correlation studies between genetic polymorphisms and cancer risk. However, the analytical methods used in the studies included in this meta-analysis also have limitations. For example, in some studies, the source, as well as selection criteria of the control and case samples, was not evident (Hamel et al., 2000; Shen et al., 2002; Scheckenbach et al., 2004), which will cause deviations in the results. In other studies, DNA extracted from tumor tissue samples was used for *TP53* genotyping (Yung et al., 1997; Perrone et al., 2007), which is known to result in frequent loss of heterozygosity, and may result in false-positive conclusions. We also found deviations in HWE of the control samples in two studies (Tandle et al., 2001; Kietthubthew et al., 2003). In addition, some of the studies were carried out with very small sample sizes, which will result in insufficient statistical power, and may cause observed differences by chance. Because of all the problems mentioned above, we also conducted a quality assessment on the literature used in our meta-analysis.

No evidence of an association between the risk of HNCs and the *TP53* Arg72Pro SNP was observed in Asian and Caucasian populations, whereas a significant association was observed in the Others group. In addition, significant correlations between risk of nasopharyngeal cancer and the *TP53* Arg72Pro SNP were observed in the homozygous comparison, heterozygous comparison, and the dominant model in Caucasians, whereas in Asians, this correlation was only found to be significant in the homozygous comparison model. This result suggests that *TP53* polymorphisms might play different roles in different HNC sites, which would contribute to the discrepancy observed among different studies. Moreover, although the exact mechanism for this ethnic difference is yet to be established, several factors may account for it. First, different genetic backgrounds of the populations may cause functional differences in a particular polymorphism. Second, environmental differences may result in different susceptibilities of a particular SNP in different populations. Finally, random factors, such as selection bias, different matching criteria, adjustments in statistical analyses, misclassifications of disease status or genotyping, and publication bias may all be involved. Therefore, additional studies are warranted to further validate ethnic difference in the effect of this polymorphism on all types of HNC risks.

Recently, Francisco et al. (2011) conducted a meta-analysis to investigate the association between the *TP53* Arg72Pro polymorphism and risk of all cancers, including HNCs. In addition, one recent meta-analysis also detected no evidence of a significant association between the *TP53* Arg72Pro polymorphism and risk of oral cancer (Zhuo et al., 2009b), and another meta-analysis observed a significant association of the *TP53* Arg72Pro polymorphism with nasopharyngeal cancer susceptibility (Zhuo et al., 2009a), which are all consistent with our results. Nevertheless, three more eligible articles related to oral cancer (Tandle et al., 2001; Kietthubthew et al., 2003; Misra et al., 2009) and one more eligible article related to nasopharyngeal cancer (Golovleva et al., 1997) were included in our meta-analysis that were not included in the two previous meta-analyses.

This meta-analysis also has some limitations. First, reports written in languages other than English or Chinese, or those written in English or Chinese but have not been published, were not incorporated in this meta-analysis. Second, most studies investigating the association of the *TP53* Arg72Pro SNP with HNCs susceptibility mainly involve Asian and Caucasian populations. Thus, expansion of the population scope in future correlation

studies would help to assess the role of this functional polymorphism on the risk of HNCs among different races (especially the African population). Finally, some of the raw data, including genotype data and environmental risk factor data, were missing in some studies, thus preventing their further evaluation.

Although our meta-analysis of HNCs should be interpreted with caution and contains some limitations, the results suggest that the *TP53* Arg72Pro SNP is not relevant for the risk of HNCs. More studies investigating this relationship should be carried out in the future, and further analyses will clarify more accurately any potential correlation between this SNP with HNC risk.

Conflicts of interest

The authors have no conflict of interest.

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Supplementary material

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