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Association of the TP53 Arg72Pro Polymorphism with Oral Squamous Cell Carcinoma: A Meta-Analysis

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Abstract

Background: The loss of function in *TP53* gene is an early event of carcinogenesis and is now considered as a full etiological factor in oral squamous cell carcinoma (OSCC). The most common polymorphism in this gene that is associated to OSCC and has been extensively studied as a potential risk factor for the development of malignancies is the single nucleotide polymorphism (SNP) encoding either proline or arginine at residue 72. Today, despite the multiplicity of publications and approaches used, the contradiction of the results have not remove the ambiguity of the possible impact of this polymorphism in OSCC. So we aimed this meta-analysis to investigate the distribution of *TP53* codon 72 genotypes and alleles in patients with OSCC and healthy matched controls, by using an ethnicity subgroups analysis.

Method: A literature search was conducted to identify studies concerning *TP53* codon 72 polymorphism and OSCC risk. Retrieved publications from 2000 to 2014 were classified by ethnicity, according to the sampling collection continent. Allelic frequencies were estimated by using genotypic data and Hardy-Weinberg Equilibrium and distributions were checked with Chi-2 test. Statistical tests for contrast models of association were performed with Proline allele as reference stratum.

Results: Arg allele distribution was almost similar in both cases and controls for African and Caucasian populations whereas Arg frequency was significantly greater in cases than in controls for Asians (p=0.011). After stratified statistical analyses, we've found again a significant association between Arginine allele and OSCC risk in the Asian subgroup (OR=1.31; 95% CI=1.09-1.58; *P*=0.004).

Conclusion: This current study revealed that allelic distribution of *TP53* Arg72Pro polymorphism may depend on ethnicity and latitude, and highlighted that Arginine carrier in Asian populations may be considered to be predisposed to OSCC.

Keywords: *TP53* • *Arg72Pro* polymorphism • OSSC • Meta-analysis

Abbreviations: CI: Confidence Interval • HPV: Human Papilloma Virus • HWE: Hardy-Weinberg Equilibrium • OR: Odds-Ratio • OSCC: Oral Squamous Cell Carcinoma • SNP: Single Nucleotide Polymorphism

Introduction

Oral squamous cell carcinoma (OSCC) are multifactor tumors mainly correlated with tobacco smoke, alcohol abuse, betel nut chewing, high-risk human papillomavirus (HPV) infection and molecular alterations of genes involved in cell cycle regulation like *TP53* [1]. The inactivation or degradation of *TP53*, the main "guardian of the genome", is now considered as a full etiological factor in carcinogenesis and the main event that precedes most cancers [2]. This gene is a tumor suppressor gene and is the most frequently mutated in human cancers. More than 50% of cancers in humans express a mutation in this gene [3-5]. The encoded protein mediates in the prevention of neoplastic transformation by repairing DNA damages after replication, or by inducing apoptosis in case DNA damages couldn't be repaired [6].

In cancerous tissues, particularly in oral squamous cells, the loss of function at *TP53* is generally associated with three molecular causes: the genotoxic effect of risk factors such as alcohol, tobacco, betel nut, the inhibitory effect of the *TP53* antagonist gene *MDM2* or the oncotic action of E6-HPV [7-9]. Now-a-days, the study of the *TP53* gene signaling pathways, as well as the control of its protein stability or expression constitutes the new approaches to anticancer research [10,11].

TP53 is a sequence-specific DNA-binding transcription factor comprising four domains: a highly charged acidic region (transactivation domain), a hydrophobic proline-rich region (protein interaction domain), a central region (DNA binding domain), and a highly basic COOH-terminal region (oligomerization domain) [12].

The most common *TP53* polymorphism that is associated to OSCC and has been extensively studied as a potential risk factor for the development of malignancies is the single nucleotide polymorphism (SNP) encoding either proline or arginine at residue 72 within the proline-rich domain [4,5,8,13]. This non-conservative amino acid change is associated with altered electrophoretic mobility in the mutant protein that contain Arg72 allele, thus suggesting a structural or conformational modification of the *TP53* protein [12].

Several reports have described differences in functional properties of wild-type *TP53*, including susceptibility to malignant transformation, ubiquitin-mediated degradation by high-risk HPV E6-protein, induction of apoptosis or cell cycle progression after damage [1,9,12,14,15].

The possible impact of *TP53* codon 72 genotypes on malignancies development yet remains an ongoing issue of debate because of contradictory results of statistical and *in silico* analysis. Hou and colleagues in 2015 tried to illustrate these contradictory results through the picture bellow, showing different trends and weights of association between Arg72 allele of *TP53*

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protein and OSCC risk through 12 studies [16] (Figure 1). These contradictory results could be explained by the different geographic distribution of genotypic frequency of *TP53* codon 72 polymorphism. The allelic frequency is said to be depend on ethnicity and geographic latitude [17-21].

For this purpose, the aim of this meta-analysis was to investigate the distribution of *TP53* codon 72 genotypes and alleles in patients with OSCC and healthy matched controls, and study the impact of this amino-acid variability on the risk of developing OSCC, by using ethnicity subgroups analysis.

Research Methodology

Publications selection process

Were included in this meta-analysis all case-control studies published before December 2018, concerning *TP53* Arg72Pro polymorphism and OSCC, with detailed genotypic frequencies in the cases and controls. We excluded all review articles, meta-analysis and case-only studies.

We carried out a comprehensive search in *PubMed* and *Science Direct* databases with the following keywords: "*TP53* codon 72" - "Arg72Pro polymorphism" - "oral cancer" - "oral squamous cell carcinoma". All eligible studies were retrieved, and their references were checked for additional relevant publications.

Quality assessment

The quality of the included studies was assessed according to the concordance of Hardy-Weinberg equilibrium (HWE) for the genotypic distribution in controls, to detect possible selection bias [16,22,23]. Studies with genotypic distribution of controls in concordance with HWE (P>0.05) were defined as high-quality studies, while studies inconsistent with HWE ($P \leq 0.05$) were classified as low-quality studies.

A symetry Begg's funnel plot that allows detecting potential publication bias in a meta-analytic study was also performed to assess the quality of publications. Publications in the inefficiency zone, which deviate from confidence funnel-shaped interval, are therefore suspected to be biased [24-30].

Statistical analysis

Allelic frequencies were estimated by using genotyping data extracted from selected publications and HWE formula. Stratified analysis was performed according to three ethnic groups and geographical latitude: Africans corresponding to black-skinned Sahelian and Sub-Saharan, Asians are populations living in East, Southeast and Central Asia and Caucasians are white European and white non-hispanic American.

We first check the distribution of Arginine and Proline alleles in ethnic subgroups by using Chi-2 test. STATA version 12.0 software (Stata Corporation, College Station, TX) was used for this statistical comparison.

Statistical tests for contrast models of association were performed with Proline allele as reference stratum. The strength of the association was estimated through an online dedicated website by the pooled odds ratio (OR) with its corresponding 95% confidence interval (95% CI) and *P*-value [24]. The pooled ORs were calculated for following contrasts models, using Proline allele as reference stratum : Arg/Arg *vs.* Pro/Pro, Arg/Arg *vs.* Arg/Pro, Arg/Pro *vs.* Pro/Pro, Arg/Arg + Arg/Pro *vs.* Pro/Pro, Arg/Arg *vs.* Arg/Pro + Pro/Pro and Allele Arg *vs.* Allele Pro.

Results

Studies characteristics

A total of 16 studies met the inclusion criteria (Figure 2). Publications characteristics are summarized in Table 1. Overall number of participants was

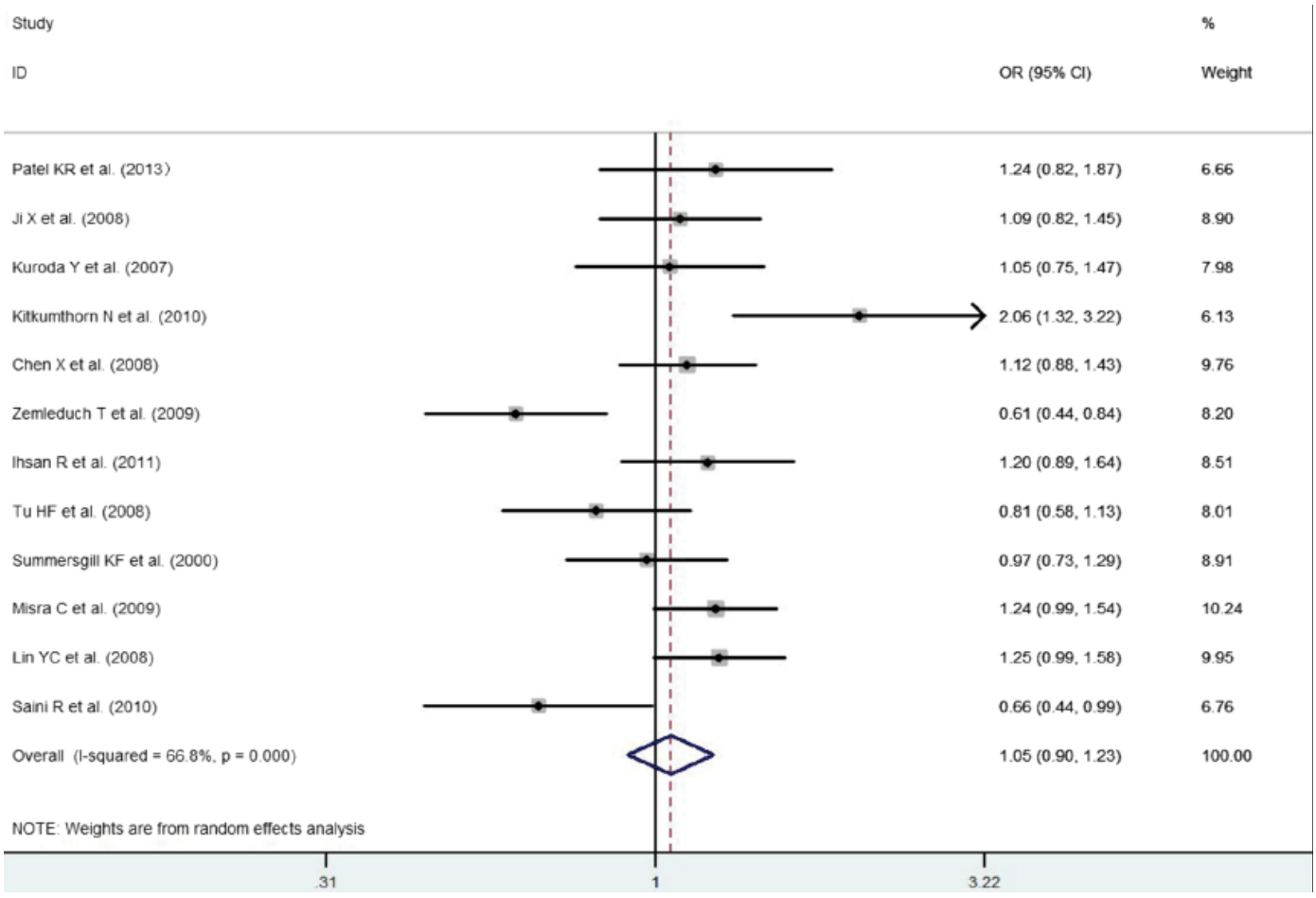

Figure 1. The contradictory results of association between Arg72 allele and OSCC risk in 12 studies throughout the world [16].

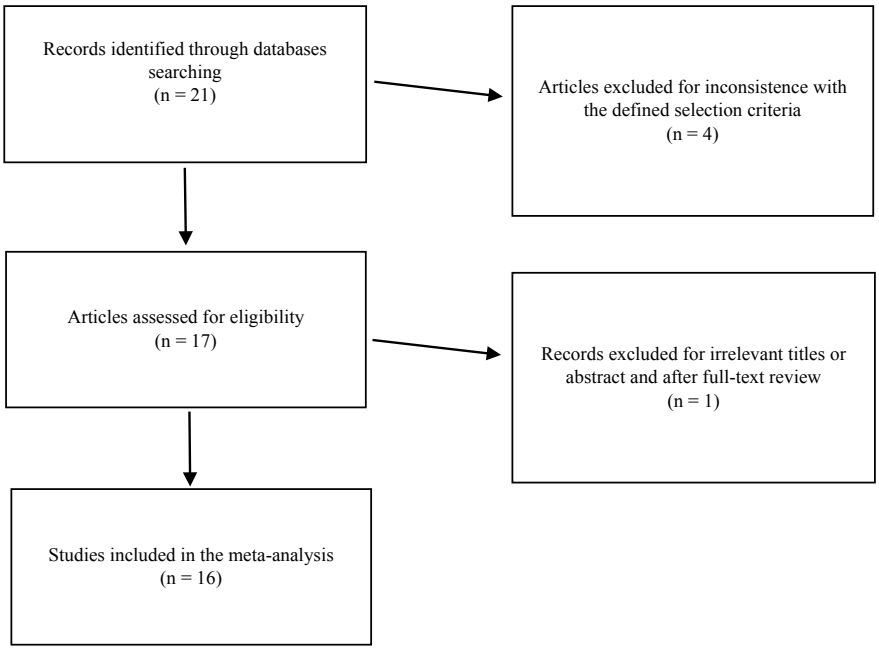

Figure 2. Flow chart of the publication selection process.

Table 1. Characteristics of 16 studies included in this meta-analysis.

First author [Reference]	Country	Year of publication	Ethnicity	Genotyping Methods	Samples Size (case/control)
Ba S A [25]	Senegal	2014	African	PCR-RFLP	51/87
Chen X [15]	Texas, USA	2008	Caucasian	PCR-RFLP	326/349
Hamel N [26]	Montreal, Canada	2000	Caucasian	PCR-RFLP	163/163
Ji X [9]	Texas, USA	2008	Caucasian	PCR-RFLP	188/342
Kietthubthew S [7]	Southern Thailand	2003	Asian	PCR-RFLP	97/97
Lin Y C [27]	Taiwan	2008	Asian	PCR-RFLP	297/280
Lu J [28]	Texas, USA	2007	Caucasian	PCR-RFLP	716/719
Mojtahedi Z [3]	Iran	2010	Asian	PCR-SSP	132/123
Perrone F [1]	Italia	2007	Caucasian	Two-step PCR	77/141
Scheckenbach K [12]	Germany	2004	Caucasian	RT-PCR ; Direct sequencing	122/193
Shen H [4]	Texas, USA	2002	Caucasian	PCR-RFLP	304/333
Sina M [29]	Iran	2014	Asian	ARMS-PCR (Alleles spec.)	55/100
Tu H F [30]	Taiwan	2008	Asian	Direct sequencing	189/116
Twu C W [13]	Taiwan	2006	Asian	PCR-RFLP	53/53
Yang W [5]	China	2008	Asian	Direct sequencing	435/550
Yu H [8]	Texas, USA	2011	Caucasian	PCR-RFLP	1083/1090
Overall :			9024 participants		4288/4736

Note: PCR: Polymerase Chain Reaction, ARMS-PCR: Amplification Refractory Mutation System PCR, PCR-RFLP: PCR-Restriction Fragment Length Polymorphism, PCR-SSP: PCR-Sequence Specific Primers, RT-PCR: Reverse Transcriptase PCR.

9024 including 4288 cases and 4736 controls.

Quality assessment

Data extracted from included studies and their quality assessment according to HWE test in controls is presented in Table 2. Two publications with genotype distribution in controls departing from HWE were classified as low quality studies while the other fourteen publications in agreement with HWE were defined as high-quality studies [1,3-5,7-9,12,13,15,25-30].

The symmetrical Begg's funnel plot showed two publications in the zone of inefficiency that we then suspected to be biased (Figure 3) [5,13].

Meta-analysis

Allelic distribution: We have first classified studies in three ethnic subgroups according to the samplings continents: 1 publication with 51 cases and 87 controls was African, 7 articles with 1258 cases and 1319 controls were Asians and 8 articles with 2979 cases and 3330 controls were Caucasians [1,3-5,7-9,12,13,15,25-30].

The allelic distributions presented in Table 2 showed that in Africa and in Caucasians, the Arginine allele distribution is almost similar in both cases and controls (Africa: 29.4% in cases, 32.8% in controls; Caucasians: 73.5% in cases, 73.3% in controls) while a clear difference was noticed in Asia (67.9% in cases, 61.9% in controls). Comparison by khi-2 test of Arg allelic frequencies between cases and controls in Table 3 was statistically significant in Asian subgroups (P=0.011). We then concluded that Arginine allele of codon 72 of *TP53* may be a risk factor for OSCC in Asian population.

Contrast models analysis in subgroups: In order to validate the hypothesis aforementioned in allelic distribution and check out the effect of Arginine allele in the different ethnic groups, we tested three statistical parameters (Odds ratio, p-value and 95% CI) in contrast models of association, by using the proline allele as a reference stratum (Table 4).

We found in Asian subgroup significant associations between the

Table 2. Distribution of *TP53* codon 72 genotypes and alleles among cases and controls in the studies included in this meta-analysis and quality assessment of their controls according to HWE test.

First author [Reference]	Sample size (case/control)	Genotype & allelic frequencies in cases				Genotype & allelic frequencies in controls				*P*-value of HWE in controls	HWE test in controls
		Arg/Arg % - (n)	Arg/Pro % - (n)	Pro/Pro % - (n)	Alleles Arg/ Pro (%)	Arg/Arg % - (n)	Arg/Pro % - (n)	Pro/Pro % - (n)	Alleles Arg/ Pro (%)		
Ba S A [25]	51/87	6 % (3)	47 % (24)	47 % (24)	29,4/70,6	14 % (12)	38 % (33)	48 % (42)	32,8/67,2	0,159	High quality
Chen X [15]	326/349	56,1 % (183)	37,1 % (121)	6,8 % (22)	74,6/25,4	51,9 % (181)	41,2 % (144)	6,9 % (24)	72,5/27,5	0,740	High quality
Hamel N [26]	163/163	54,0 % (88)	41,7 % (68)	4,3 % (7)	74,8/25,2	58,3 % (95)	37,4 % (61)	4,3 % (7)	77,0/33,0	0,576	High quality
Ji X [9]	188/342	54,8 % (103)	39,4 % (74)	5,8 % (11)	74,5/25,5	52,4 % (179)	40,9 % (140)	6,7 % (23)	72,8/27,2	0,734	High quality
Kietthubthew S [7]	97/97	33 % (32)	45 % (44)	22 % (21)	55,5/44,5	36 % (35)	35 % (34)	29 % (28)	53,5/46,5	0,003	*Low quality***
Lin Y C [27]	297/280	33,2 % (96)	52,2 % (155)	15,5 % (46)	59,3/40,7	25,7 % (72)	54,3 % (152)	20,0 % (56)	52,8/47,2	0,370	High quality
Lu J [28]	716/719	55,9 % (400)	37,7 % (270)	6,4 % (46)	74,7/25,3	54,0 % (388)	40,2 % (289)	5,8 % (42)	74,1/25,9	0,636	High quality
Mojtahedi Z [3]	132/123	37,1 % (49)	47,7 % (63)	15,2 % (20)	55,5/44,5	35,8 % (44)	51,2 % (63)	13,0 % (16)	61,4/38,6	0,422	High quality
Perrone F [1]	77/141	81,8 % (63)	10,4 % (8)	7,8 % (6)	87,0/13,0	59,6 % (84)	33,3 % (47)	7,1 % (10)	76,2/23,8	0,420	High quality
Scheckenbach K [12]	122/193	54 % (66)	1 % (1)	45 % (55)	54,5/45,5	59 % (114)	7 % (13)	34 % (66)	62,5/37,5	0,000	*Low quality****
Shen H [4]	304/333	52,0 % (158)	41,1 % (125)	6,9 % (21)	72,5/27,5	52,6 % (175)	40,2 % (134)	7,2 % (24)	72,7/27,3	0,898	High quality
Sina M [29]	55/100	36,4 % (20)	45,5 % (25)	18,2 % (10)	59,1/40,9	40,0 % (40)	48,0 % (48)	12,0 % (12)	64,0/36,0	0,676	High quality
Tu H F[30]	189/116	28,0 % (53)	56,1 % (106)	15,9 % (30)	56,1/43,9	35,3 % (41)	51,7 % (60)	13,0 % (15)	61,1/38,9	0,378	High quality
Twu C W [13]	53/53	22,6 % (12)	51,0 % (27)	26,4 % (14)	48,1/51,9	41,5 % (22)	45,3 % (24)	13,2 % (7)	64,1/35,9	0,879	High quality
Yang W [5]	435/550	85,7 % (373)	4,4 % (19)	9,9 % (43)	87,9/12,1	49,6 % (273)	35,8 % (197)	14,6 % (80)	67,5/32,5	0,065	High quality
Yu H [8]	1083/1090	54,8 % (593)	37,4 % (405)	7,8 % (85)	73,5/26,5	54,8 % (597)	39,3 % (428)	5,9 % (65)	74,4/25,6	0,741	High quality
Overall	4288/4736	53,4 % (2292)	35,8 % (1535)	10,8 % (461)	71,3/28,7	49,7 % (2352)	39,4 % (1867)	10,9 % (517)	69,4/30,6	0,469	High quality
Stratified by ethnicity											
African	51/87	6 % (3)	47 % (24)	47 % (24)	29,4/70,6	14 % (12)	38 % (33)	48 % (42)	32,8/67,2	0,159	High quality
Asian	1258/1319	50,5 % (635)	34,9 % (439)	14,6 % (184)	67,9/32,1	40 % (527)	43,8 % (578)	16,2 % (214)	61,9/38,1	0,475	High quality
Caucasian	2979/3330	55,5 % (1654)	36 % (1072)	8,5 % (253)	73,5/26,5	54,5 % (1813)	37,7 % (1256)	7,8 % (261)	73,3/26,7	0,721	High quality

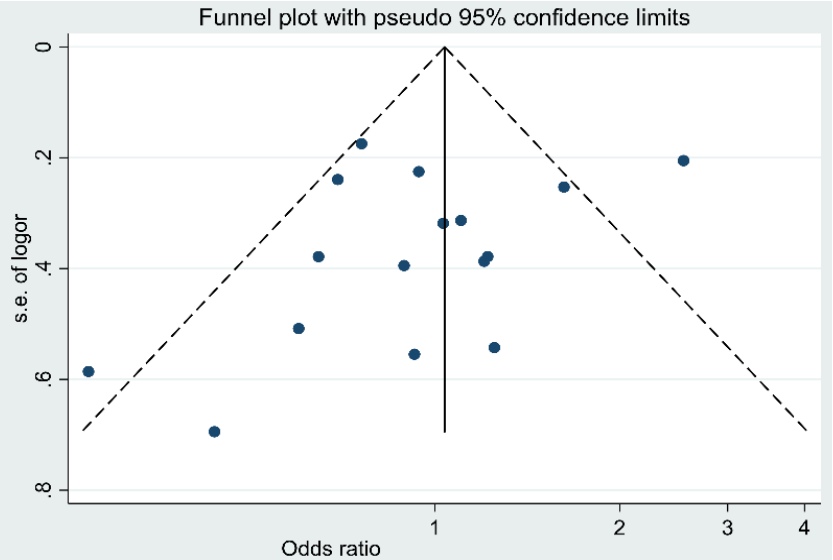

Figure 3. Begg's funnel plot analysis to detect publication bias with pseudo 95% confidence limits. Each point represents an individual study for the indicated association; the *x-axis* shows the results of studies expressed as odds-ratio; the *y-axis* shows the studies precisions; the *middle solid line* indicates the overall effect from the meta-analysis.

Table 3. Arginine allele distribution & Khi-2 test comparison between cases and controls in ethnic subgroups.

Ethnicity	Arg allele cases vs controls		
	Arg allele frequencies	z-value	p-value
African	29.4%/32.8%	0.817	0.366
Asian	67.9%/61.9	6.441	**0.011**
Caucasian	73.5%/73.3	0.379	0.538

Table 4. Meta-analysis of the associations between *TP53* codon 72 polymorphism and OSCC risk - Ethnicity subgroups analysis.

Variables			Contrast models											
			Arg/Arg vs. Pro/Pro		Arg/Arg vs. Arg/Pro		Arg/Pro vs. Pro/Pro		Arg/Arg + Arg/Pro vs. Pro/Pro		Arg/Arg vs. Arg/Pro + Pro/Pro		Allele Arg vs. Allele Pro	
			Test of association											
Ethnicity	Number of studies	Sample size (case/control)	OR [CI 95 %]	P	OR [CI 95 %]	P	OR [CI 95 %]	P	OR [CI 95 %]	P	OR [CI 95 %]	P	OR [CI 95 %]	P_{OR}
African	1	51/87	0,44 [0,11-1,72]	0,225	0,34 [0,09-1,34]	0,115	1,27 [0,61-2,63]	0,516	1,05 [0,53-2,1]	0,887	0,39 [0,1-1,45]	0,149	0,86 [0,71-1,04]	0,110
Asian	7	1258/1319	1,4 [1,11-1,76]	0,003	1,59 [1,34-1,88]	0,000	0,88 [0,7-1,11]	0,296	1,13 [0,91-1,4]	0,261	1,53 [1,31-1,79]	0,000	1,31 [1,09-1,58]	0,004
Caucasian	8	2979/3330	0,94 [0,78-1,13]	0,522	1,07 [0,96-1,19]	0,214	0,88 [0,73-1,07]	0,192	0,92 [0,77-1,1]	0,342	1,04 [0,94-1,15]	0,390	1,03 [0,6-1,77]	0,920
All Studies	16	4288/4736	1,09 [0,95-1,25]	0,207	1,19 [1,09-1,3]	0,000	0,92 [0,8-1,06]	0,263	1,02 [0,89-1,17]	0,806	1,1 [0,91-1,33]	0,000	1,01 [0,83-1,23]	0,350

Figure 4. Forest plots of OSCC risk associated with the *TP53* Arg72Pro polymorphism in all included studies, stratified by ethnicity. *Boxes* represent the ORs of individual studies; *diamonds* represent the summary ORs; *horizontal lines* represent the 95% CIs. **a.** Arg/Arg vs. Pro/Pro. **b.** Arg/Arg vs. Arg/Pro. **c.** Arg/Pro vs. Pro/Pro. **d.** Arg/Arg + Arg/Pro vs. Pro/Pro. **e.** Arg/Arg vs. Arg/Pro + Pro/Pro. **f.** Allele Arg vs. Allele Pro.

TP53 Arg72Pro polymorphism and OSCC risk for 4 contrasts models : Arg/Arg *vs.* Pro/Pro [OR=1.4; 95% CI=1.11-1.76; *P*=0.003]; Arg/Arg *vs.* Arg/Pro [OR=1.59; 95% CI=1.34-1.88; *P*=0.000]; Arg/Arg *vs.* Arg/Pro + Pro/Pro [OR=1.53; 95% CI=1.31-1.79; *P*=0.000] and Allele Arg *vs.* Allele Pro [OR=1.31; 95% CI=1.09-1.58; *P*=0.004].

Forest plots based on contrast models that we have tested were drawn to have an overall watch on meta-analysis results (Figure 4).

Discussion

Oral cancer is a public health problem in many countries and ranks among the ten most frequently diagnosed cancers all over the world, according to the 2018 GLOBOCAN report [31]. Since the identification of the *TP53* codon 72 polymorphism as potential risk factor for cancers, numerous studies have been devoted to explore the genetic effect of this polymorphism and its association with oral cancer risk. Some studies claimed that this SNP is a risk factor for oral cancer while other studies detected no effect in oral carcinogenesis, showing clear discrepancy between results across the world. The different patterns noticed in allelic distribution and genotypic frequencies of this polymorphism may be due to variations in methodological approaches, sample size, laboratory performance, DNA quality and source, variation in ethnic background or environmental exposures of study populations [16,32,33].

We have performed an ethnicity-stratified meta-analysis to check the association between *TP53* codon 72 polymorphism and OSCC risk. Overall, 16 publications with 9024 subjects (4288 cases and 4736 controls) were included in this study. Comparison of Arg allele frequencies between cases and controls was statistically significant only in Asian subgroup. Also, we've found significant associations between the *TP53* Arg72Pro polymorphism and OSCC risk for four contrasts models in Asians. Hence, this polymorphism was not significantly associated with any increased or a decreased risk of OSCC in Africans and Caucasians.

Several stratified meta-analysis based on *TP53* Arg72Pro polymorphism and different types of cancer have been performed to date, but evidence of the implication of this polymorphism remains unclear.

A meta-analysis by Koushik et al. in 2004 on cervical cancer risk and *TP53* Arg72Pro polymorphism revealed that the homozygote Arg/Arg genotype was significantly associated with an increased susceptibility to cervical cancer [34]. Also, a meta-analysis in Iran about breast cancer found that the risk of developing breast cancer is 1.58 higher in Iranian women with genotype Arg/Arg (95% CI: 1.01 to 2.45) [35].

On the contrary, Zhuo et al. in 2009 demonstrated that the Arg allele was associated with a decreased risk of nasopharyngeal cancer [36]. Another meta-analysis on nasopharyngeal cancer published in 2016 has meanwhile evidenced that the *TP53* codon 72 polymorphism could be as a risk factor [37].

Concerning oral cancer risk, a meta-analysis pooling nine studies published until May 2009 (1990 cases and 2074 controls) showed no association; likewise, another one published in 2013 with seventeen studies stratified according to ethnicity confirmed no significant association in Asians, Caucasians and mixed populations [22,38]. To our knowledge, our meta-analysis is the first to investigate the association of *TP53* codon 72 polymorphism with OSCC risk in the three ethnic populations, Caucasians, Asians and Africans and highlighted that Arg allele of *TP53* codon 72 could be considered as a risk factor for OSCC in Asian population.

Conclusion

The present meta-analysis shows that Arginine allele of *TP53* codon 72 polymorphism was significantly associated with OSCC risk in Asian population whereas any significant link was observed in Africans and Caucasians. Our study also confirmed that genotypes distribution of the *TP53* codon 72 polymorphism may be dependent on ethnicity and geographic latitude. Further extensive studies using functional approaches are then required to confirm the real influence of Arg72Pro polymorphism on OSCC risk.

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Conflict of Interest

No potential conflicts of interest were disclosed.

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