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Original Article

p53 Arg72Pro polymorphism and risk of basal cell carcinoma: a meta analysis

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Abstract: Purpose: We attempted to comprehensively assess the possible association between *p53* Arg72Pro polymorphism and the risk of basal cell carcinoma (BCC). Methods: We performed a literature search of case-control association studies on *p53* Arg72Pro polymorphism and BCC susceptibility in PubMed and EMBASE. 7 eligible studies were finally identified and their data were extracted for this meta-analysis. BCC risk was determined with the fixed effects model using a pooled odds ratio (OR). Results: Using distinct genetic models, we found that *p53* Arg72Pro polymorphism was not associated with the overall risk of BCC. We observed a similar trend towards the association when performing subgroup analysis for Caucasians and Asians. Conclusion: Our results suggest that presence of the common *p53* Arg72Pro polymorphism may not play a role in the development of BCC. Larger studies are needed to better confirm the association.

Keywords: *p53*, BCC, polymorphism, risk

Introduction

Skin cancer is a common tumor in human and it is categorized into melanoma and nonmelanoma skin cancers according to cell types and tissues affected [1]. Nonmelanoma skin cancer, including squamous cell carcinoma (SCC) and basal cell carcinoma (BCC), has become a significant health burden in Americans [2, 3]. Compared to other cancers combined, BCC is thought to be a disease with the highest incidence rate among fair-skinned people. Although solar UV radiation is identified as an important risk factor for BCC [4, 5], cumulative data have also pointed to the key role of genetic factors played in susceptibility to this disease. *p53*, a highly mutated tumor suppressor gene in cancer, is a central component in BCC oncogenesis [6].

A common polymorphism of the *p53* gene is a substitution from arginine to proline at codon 72 in exon 4. This polymorphism is located in a proline-rich region and plays a crucial role in apoptosis induction [7, 8]. The Arg allele functionally differs from the Pro allele as a result of their distinct biological and biochemical activities [9], and it is this difference that has led to a substantial increase in investigations on the association of *p53* Arg72Pro polymorphism and BCC susceptibility. Some authors found this polymorphism was especially relevant to BCC risk [10-12]. Other authors, however, failed to detect a significant association or even observed an opposite result [13-15]. The predisposition role was also unclearly demonstrated in a recent study [16].

The inconsistent and uncertain results highlight the importance of further studies to identify whether there is a potential association between *p53* Arg72Pro polymorphism and BCC risk. With these in mind, we conducted a meta-analysis, a reliable analytical tool for comparing the different studies of the same polymorphism, to derive a more accurate estimate.

Materials and methods

Publication search

The eligible studies were identified by searching the PubMed and EMBASE using the search terms: "*p53*" or "*p53* Arg72Pro" or "*p53* codon 72", "polymorphism" and "skin cancer" or "basal cell carcinoma" (last search was up-

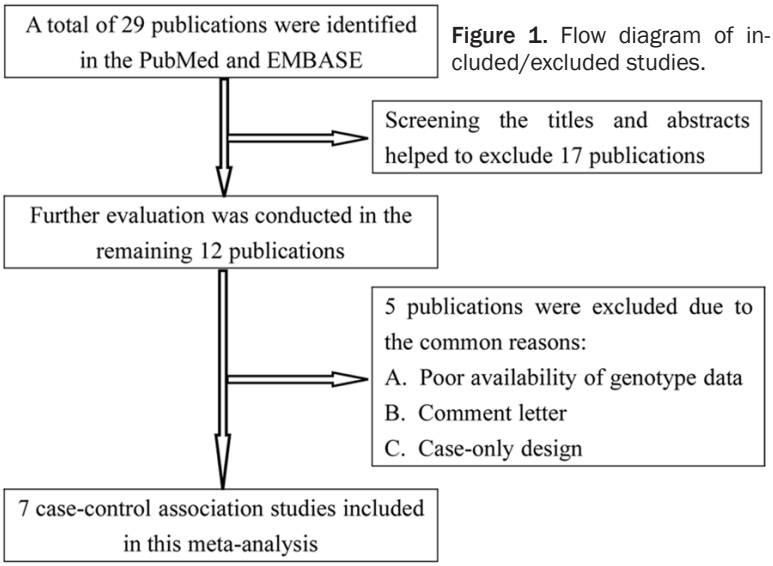

Figure 1. Flow diagram of included/excluded studies.

dated on Jan. 19, 2013). The reference lists from the extracted publications were scrutinized to ensure that relevant articles were not missed. When more than one study used the same study population, only the most recent or the largest one was selected in this meta-analysis.

Inclusion criteria

The inclusion criteria were as follows: (a) studies investigating the association of the *p53* Arg72Pro polymorphism and BCC risk, (b) full-text articles with a case-control design, (c) studies with genotype frequencies in full detail for the estimate of odds ratios (ORs) with the corresponding 95% confidence intervals (CIs), and (d) published before Jan. 19, 2013. According to the criteria above, all relevant studies were checked for their eligibility for this analysis.

Data extraction

Eligible studies were identified by two reviewers and contested articles were adjudicated by a third reviewer. The following information was recorded for each of the eligible studies: first author's name, publication date, ethnicity of case and control subjects, control source, total numbers of cases and controls, and counts of Arg/Arg, Arg/Pro, Pro/Pro genotypes in cases and controls. When a single study provided detailed data for racially different populations, they were separately treated and grouped into Caucasians or Asians.

Statistical analysis

The goodness-of-fit chi-square test was applied to detect Hardy-Weinberg equilibrium (HWE) for the control group in each study. $P < 0.05$ was considered significant HWE departure. The pooled ORs with 95% CIs were estimated to examine the relationship between risk of BCC and *p53* Arg72Pro polymorphism. The meta-analysis was performed for several genetic contrast models, including Arg/Arg vs. Pro/Pro, Arg/Arg + Arg/Pro vs. Pro/Pro, Arg/Arg vs. Arg/Pro + Pro/Pro, allele Arg vs. allele Pro, and Arg/Pro vs. Pro/Pro. Subgroup analyses were performed by ethnicity and source of controls.

Heterogeneity is a potential problem when performing a meta-analysis and it was determined using the chi-square-based Q-test [17]. If $P > 0.05$, which indicated absence of heterogeneity, we applied the fixed-effects model (the Mantel-Haenszel method) to pool the data from single comparisons [18]. Otherwise, we employed the random-effects model (the DerSimonian and Laird method) [19].

Another limitation of meta-analysis is publication bias. In order to assess the possible bias, we carried out Egger's test, a type of linear regression approach to examine the funnel plot asymmetry on the natural logarithm scale of OR. We evaluated the significance of the intercept using the t-test and considered *p*-value < 0.05 as statistically significant [20]. All statistical data were analyzed with STATA version 12.0 (Stata Corporation, College Station, TX, USA). A *P*-value of < .05 was considered statistically significant.

Results

Study characteristics

A total of 29 relevant publications were identified by the PubMed and EMBASE search. 17 publications were excluded by screening the titles and abstracts and 12 were evaluated in full text. Of these, 5 articles were ultimately ruled out. Three articles were excluded for

Table 1. Main characteristics summarized for all studies included in the meta-analysis

Study	Publication Year	Country of origin	Ethnicity	Control source	Methods	Case						Control						*P* values for HWE
						Sample	Arg/Arg	Arg/Pro	Pro/Pro	Arg	Pro	Sample	Arg/Arg	Arg/Pro	Pro/Pro	Arg	Pro	
Dokianakis	2000	Greece	Caucasian	NA	NA	21	15	3	3	33	9	59	12	41	6	65	53	0.002
Bastiaes	2001	Netherland	Caucasian	HB	PCR	114	63	43	8	169	59	157	75	72	10	222	92	0.180
McGregor	2002	England	Caucasian	HB	PCR	89	66	23	0	155	23	156	85	66	5	236	76	0.064
Han	2006	USA	Caucasian	PB	TaqMan	285	154	108	23	416	154	816	474	297	45	1245	387	0.864
Pezeshki	2006	Iran	Asian	PB	AS-PCR	91	34	47	10	115	67	465	162	217	86	541	389	0.376
Bendesky	2007	Mexico	Caucasian	HB	PCR	204	108	74	22	290	118	238	126	94	18	346	130	0.935
Almquist	2011	USA	Caucasian	PB	PCR-RFLP	837	485	295	57	1265	409	767	446	274	47	1166	368	0.571

PCR-polymerase chain reaction, PCR-RFLP-PCR-restriction fragment length polymorphism, AS-PCR-allele-specific-PCR, TaqMan-TaqManSNP, NA-not available, HB-hospital-based studies, PB-population-based studies, HWE-Hardy-Weinberg equilibrium.

Table 2. Meta-analysis results for *Arg72Pro* polymorphism and cancer risk

Subgroups	Arg/Arg vs. Pro/Pro		Arg/Arg + Arg/Pro vs. Pro/Pro		Arg/Arg vs. Arg/Pro + Pro/Pro		Allele Arg vs. Allele Pro		Arg/Pro vs. Pro/Pro	
	OR (95% CI)	P_h	OR (95% CI)	P_h	OR (95% CI)	P_h	OR (95% CI)	P_h	OR (95% CI)	P_h
Ethnicity										
Caucasian	0.98 (0.87, 1.11)	0.994	0.99 (0.90, 1.09)	1.000	1.03 (0.92, 1.15)	0.074	1.00 (0.93, 1.08)	0.675	0.96 (0.83, 1.12)	0.984
Asian	1.18 (0.73, 1.93)		1.09 (0.79, 1.52)		1.07 (0.70, 1.65)		1.09 (0.84, 1.40)		1.15 (0.75, 1.76)	
Source of control										
Hospital	0.99 (0.78, 1.26)	0.931	0.99 (0.82, 1.19)	0.958	1.13 (0.91, 1.40)	0.507	1.04 (0.90, 1.20)	0.644	0.96 (0.72, 1.28)	0.925
Population	0.99 (0.86, 1.14)	0.741	1.00 (0.89, 1.11)	0.836	0.98 (0.87, 1.11)	0.814	0.99 (0.91, 1.07)	0.698	1.00 (0.84, 1.17)	0.754
Others	1.25 (0.46, 3.40)		0.95 (0.46, 1.98)		3.51 (1.42, 8.71)		1.43 (0.83, 2.47)		0.57 (0.13, 2.44)	
All	1.00 (0.88, 1.12)	0.988	0.99 (0.91, 1.09)	0.998	1.04 (0.93, 1.15)	0.122	1.01 (0.94, 1.08)	0.744	0.98 (0.85, 1.13)	0.971

P_h: *p*-value of heterogeneity test; CI: confidence interval; OR: odds ratio. All models are evaluated with the fixed effects model, because the *p* values for heterogeneity test are > 0.05.

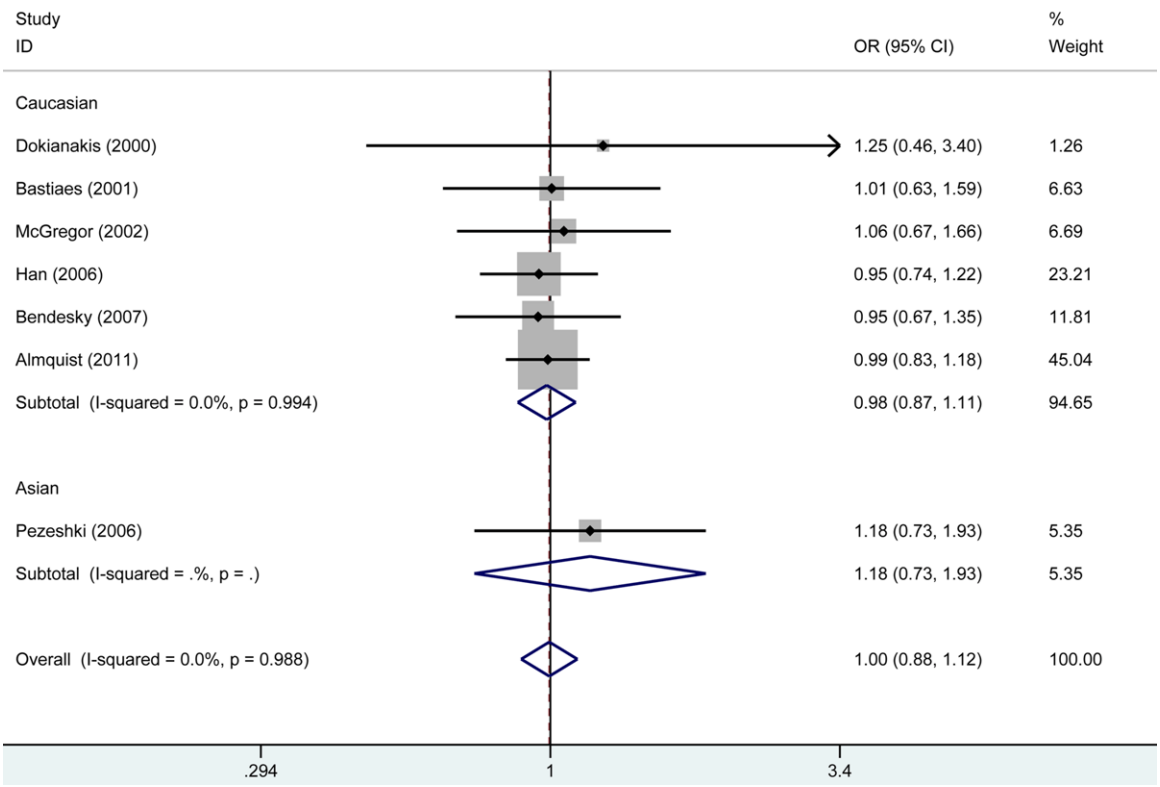

Figure 2. Forest plot of BCC risk associated with Arg72Pro polymorphism stratified by ethnicity under Arg/Arg vs. Pro/Pro model. The boxes and horizontal lines represent the OR and the corresponding 95% CI. The area of the boxes indicates the weight (inverse of the variance). The diamond correspond to the summary OR and 95% CI. No significant association between the Arg72Pro polymorphism and BCC risk was observed.

not stating the genotyping distribution of BCC [21-23], one was for a comment letter [24] and one was based on case-only design [25] (**Figure 1**). Therefore, 7 case-control studies [10-16] including a total of 1,641 cases and 2,658 controls were analyzed in the meta-analysis. **Table 1** lists the studies included and their main characteristics. Of the 7 studies, there were six studies of Caucasians and one study of Asians. In addition, three studies were population-based, three were hospital-based and only one was defined as "NA (not available)", which was categorized into "others" group in Stata analysis, because we could not obtain available data on control source. Genotype distribution in the controls was in agreement with HWE in all studies except for Dokianakis et al. [10].

Meta-analysis results

Table 2 presents the main results of this meta-analysis. Lack of significant heterogeneity was indicated among the studies. Overall, we found no significantly elevated BCC risk associated with *p53* Arg72Pro polymorphism when pooling all studies into the meta-analysis (ORArg/Arg vs. Pro/Pro = 1.00, 95% CI = 0.88-1.12, P = 0.988 for heterogeneity test, **Figure 2**; ORArg/Arg + Arg/Pro vs. Pro/Pro = 0.99, 95% CI = 0.91-1.09, P = 0.998 for heterogeneity test; ORArg/Arg vs. Arg/Pro + Pro/Pro = 1.04, 95% CI = 0.93-1.15, P = 0.122 for heterogeneity test; ORallele Arg vs. allele Pro = 1.01, 95% CI = 0.94-1.08, P = 0.744 for heterogeneity test; ORArg/Pro vs. Pro/Pro = 0.98, 95% CI = 0.85-1.13, P = 0.971 for heterogeneity test).

We then performed subgroup analysis by ethnicity. The genetic models tested did not show any significant association in Caucasians as well as in Asians (**Figure 2**). Similar results were revealed in the following analysis by control source. When the study with obvious deviation form HWE was deleted, the pooled ORs of the remaining studies were not quantitatively altered (data not shown), providing statistical evidence for our reliable results.

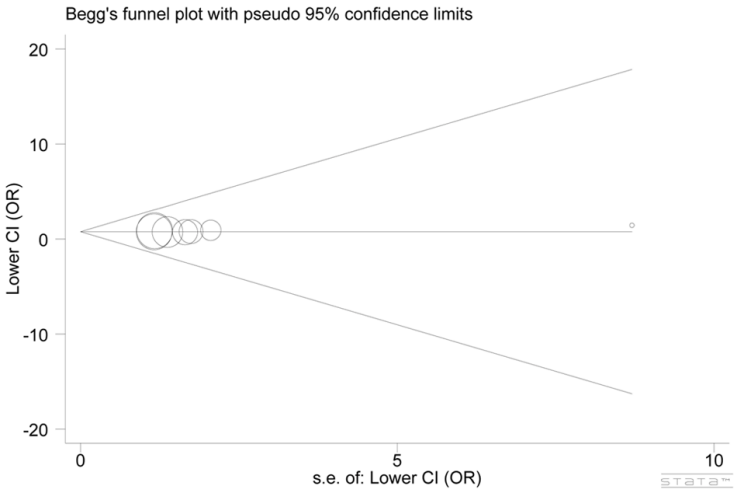

Figure 3. Begg's funnel plot for Arg72Pro polymorphism. Log OR is plotted versus standard error of Log OR for each included study. Each circle dot represents a separate study for the indicated association between Arg72Pro polymorphism and BCC risk under Arg/Arg vs. Arg/Pro + Pro/Pro model.

Publication bias

Evaluation of publication bias was performed by Begg's funnel plots and Egger's test. The shapes of the funnel plots did not reveal any evidence of obvious asymmetry. Then, the Egger's test also provided supportive evidence for the symmetrical funnel plots (Arg/Arg vs. Arg/Pro + Pro/Pro: $P = 0.368$ for Begg's test; $P = 0.229$ Egger's test, **Figure 3**).

Discussion

The widely-studied tumor suppressor gene *p53* is particularly important in cell cycle arrest, DNA repair, and apoptosis in response to DNA damage. *p53* is a frequently mutated in a long list of human cancer, indicating a central role it may have in the pathogenesis of cancer [26, 27]. A crucial domain of *p53* for signaling apoptosis following DNA damage lies in codon 72, with a proline (72P) to an arginine (72R) change in the sequence of encoded amino acids [8, 28-30]. The arginine and proline polymorphic alleles have been known to have distinct functional properties, including their ability to repair DNA damage, with attendant potential of cancer risk [9]. Several groups have now showed controversial evidence of the genetic susceptibility role of *p53* Arg72Pro polymorphism in BCC [11, 13]. The conflicting result could be substantiated by the fact that the individually published studies are conducted in different ethnic groups, geographical areas, and differing numbers of study subjects.

In this study, we performed a meta-analysis. It is a powerful way that could avoid the problems such as the insufficient detection power caused by the individual genetic studies in which a relatively small number of subjects were studied. In our meta-analysis, we found that *p53* Arg72Pro polymorphism was not overall associated with BCC susceptibility, although we had summarized all available published data to date. Then we continued to detect the possible relationship via subgroup analysis in Caucasians and in Asians, with no links observed in neither of the populations.

In contrast to the findings in overall populations and stratified analysis by ethnicity, an increased risk of BCC was suggested in subgroup of the study classified into "others" group (**Table 2**). Even though we cannot exclude that this observation is obtained by chance due to the limited statistical data, it might provide clues that *p53* Arg72Pro polymorphism possibly plays a role in the carcinogenesis of BCC. This supposition, however, merits further investigation.

p53 Arg72Pro polymorphism has been explored in other skin cancers, such as cutaneous melanoma and SCC. According to Shen et al. [31], the individuals who harbored the genotypes of Arg72Pro polymorphism were at higher risk for developing cutaneous melanomas. In contrast, Bastiaens et al. [13] indicated an opposite result. Such a controversy can be seen among the studies on SCC risk as well. Almquist et al. [15] demonstrated no predisposition role for *p53* Arg72Pro polymorphism, while other groups [32] found a clear association. These observations may have affected by possible problems of study designs, such as the use of inappropriate controls, small sample size, or the selection of tumor source where loss of heterozygosity probably modifies the genotype outcome [33].

The limitations of this analysis are as follows: first, the insufficient sample of each subgroup, especially the subgroup of Asians, population-based and hospital-based studies, may result in the lack of statistical power, leading to biased estimates. Second, ethnicity, and selection of control populations are potential sources of between-study heterogeneity, though it is undetected in this analysis, the combined results may be more or less influenced. Third, the pathogenesis of BCC is complex. Genetic effects in conjunction with environmental impact are known risk factors. We did not estimate the combined effects because of data insufficiency.

In conclusion, the present meat-analysis with the largest dataset to date did not show a statistically significant association of *p53* Arg72Pro polymorphism and the overall BCC risk. Larger standardized investigations are necessary to better define the true potential of the commonly-studied polymorphism in the disease.

Disclosure of conflict of interest

None.

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