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BRIEF ARTICLE

TP53 Arg72Pro polymorphism is associated with esophageal cancer risk: A meta-analysis

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Abstract

AIM: To investigate the association between *TP53* Arg72Pro polymorphism and esophageal cancer (EC) risk using meta-analysis.

METHODS: All eligible studies published before March 1, 2010 were selected by searching PubMed using keywords "p53" or "*TP53*", "polymorphism" or "variation", "esophageal" and "cancer" or "carcinoma". Crude odds ratios (ORs) with 95% confidence intervals (CIs) were assessed for EC risk associated with *TP53* Arg72Pro polymorphism using fixed- and random-effects models.

RESULTS: Nine case-control studies involving 5545 subjects were included in this meta-analysis. Significantly reduced risk of EC was associated with *TP53* genotypes for Arg/Arg + Arg/Pro *vs* Pro/Pro (OR = 0.73, 95% CI: 0.57-0.94, $P = 0.014$). Subgroup analyses according to the source of controls and the specimens used for determining *TP53* Arg72Pro genotypes or sample size showed that significantly reduced risk was observed only in studies which have population-based controls (Arg/Arg *vs* Pro/Pro: OR = 0.56, 95% CI: 0.47-0.66, $P < 0.001$), and use white blood cells or normal tissue to assess *TP53* genotypes of cases (Arg/Arg *vs* Pro/Pro: OR = 0.56, 95% CI: 0.47-0.65, $P < 0.001$) or include at least 200 subjects (Arg/Arg *vs* Pro/Pro: OR = 0.56, 95% CI: 0.47-0.65, $P < 0.001$). Analysis restricted to well-designed studies also supported the significantly decreased risk of EC (Arg/Arg *vs* Pro/Pro: OR = 0.54, 95% CI: 0.46-0.64, $P < 0.001$).

CONCLUSION: *TP53* Arg72 carriers are significantly associated with decreased EC risk. Nevertheless, more well-designed studies are needed to confirm our findings.

Key words: *TP53*; Codon 72; Polymorphism; Esophageal cancer; Meta-analysis

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INTRODUCTION

Esophageal cancer (EC) is the eighth most common can-

cer and sixth most deadly cancer worldwide. China and southern and eastern Africa are the relatively high risk areas[1,2]. There are two main forms of EC histologically: esophageal squamous cell carcinoma (ESCC) and esophageal adenocarcinoma (EA). ESCC constitutes the majority (over 90%) of EC, but the incidence rates of EA have sharply increased in many Western countries recently[3-5]. The development of EC is a multifactorial process associated with a variety of risk factors. The two major risk factors of EC are tobacco smoking and alcohol drinking[6-8]. Inherited predisposition may also explain the high rates of EC[9].

TP53 is a major regulator of the cell response to stress and serves as a tumor suppressor by inducing cell cycle arrest or apoptosis[10]. Inactivation of the TP53 signaling pathway has been seen in most human cancers[11]. Previously, polymorphisms of *TP53* have been reported to be the possible risk factors for some kinds of tumors[12]. The most common polymorphism of *TP53* is at the 72nd amino acid residue, with an arginine (Arg) to proline (Pro) change because of a G→C transverse[13]. Differences in the biochemical or biological characteristics of these wild-type *TP53* variants have been reported[14]. The Arg72 variant can better induce apoptosis than the Pro72 variant, indicating that the two polymorphic variants of *TP53* are functionally distinct, which may influence the cancer risk or treatment[15].

A number of studies have reported the role of *TP53* Arg72Pro polymorphism in cancers such as cervical cancer[16], lung cancer[17], breast cancer[18], and gastric cancer[19], but little is known about the association of *TP53* polymorphism with EC. In recent years, several studies focused on the association between *TP53* Arg72Pro polymorphism and EC susceptibility, with inconsistent results[20-29]. Hence, we performed a meta-analysis of all eligible studies to estimate the association between *TP53* polymorphism and the risk of EC.

MATERIALS AND METHODS

Publication search

We searched the articles using the terms "p53" or "*TP53*", "polymorphism" or "variation", "esophageal" and "cancer" or "carcinoma" in Medline database utilizing the PubMed engine, and all eligible studies were published before March 1, 2010. We evaluated all associated publications to retrieve the most eligible literatures. Their reference lists were hand-searched to find other relevant publications. Articles were limited to English language papers.

Inclusion and exclusion criteria

The following inclusion criteria were used to select literatures for the meta-analysis: (1) published in peer-reviewed journals; (2) articles about *TP53* Arg72Pro polymorphism and risk of EC; and (3) containing useful genotype frequencies. The exclusion criteria were: (1) none-case-control studies; (2) control population including malignant tumor patients; (3) the genotype frequencies of control group departing from Hardy-Weinberg equilibrium (HWE); and (4) duplicated publications.

Data extraction

Two investigators (Jiang and Yao) reviewed and extracted information from all eligible publications independently, according to the inclusion and exclusion criteria listed above. An agreement was reached by discussion between the two reviewers whenever there was a conflict. The following items were collected from each study: first author's surname, year of publication, country of origin, ethnicity, source of controls, specimens used for assessment of *TP53* Arg72Pro genotypes, total number of cases and controls as well as numbers of cases and controls with Arg/Arg, Arg/Pro and Pro/Pro genotypes, respectively.

Statistic analysis

Crude odds ratios (ORs) with 95% confidence intervals (CIs) were used to assess the association between *TP53* Arg72Pro polymorphism and EC risk. The pooled ORs were performed for homozygote comparison (Arg/Arg *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 performed based on the source of controls, the specimens used for determining *TP53* Arg72Pro genotypes and sample size (cases and controls in total). A Chi-square-based Q-test was performed to check the heterogeneity[30]. If $P \geqslant 0.1$ was obtained in the heterogeneity test, ORs were pooled according to the fixed-effects model (the Mantel-Haenszel model)[31], otherwise the random-effects model (the DerSimonian and Laird model) was used[32]. One-way sensitivity analyses were performed to evaluate the stability of the meta-analysis results[33]. The potential publication bias was estimated using Egger's linear regression test by visual inspection of the Funnel plot. $P < 0.05$ was considered statistically significant in publication bias[34]. If publication bias existed, the Duval and Tweedie non-parametric "trim and fill" method was used to adjust for it[35]. All statistical tests were performed with the software STATA version 10.0 (Stata Corporation, College station, TX).

RESULTS

Study characteristics

Eighteen studies were identified through literature search and selection based on the inclusion criteria. By the extraction of data, seven articles which are not case-control studies and one review article were excluded. Among the remaining 10 studies, one study[29] was excluded due to the genotype frequencies of controls deviated from HWE. In one study[24], two groups of controls (a high risk population and a low risk population) were used. However, the genotype frequencies of the low-risk population controls deviated from HWE. Therefore, only the high-risk population controls of this study were included in the final analysis.

The characteristics of nine eligible case-control studies are summarized in Table 1. The sample size of the 9

Table 1 Main characteristics of included studies in the meta-analysis

First author (yr)	Country	Ethnicity	Source of controls	Specimens	Sample size (case/control)
Lee[20] (2000)	China (Taiwan)	Asian	Hospital	White blood cells	90/254
Peixoto[21] (2001)	China	Asian	Population	Exfoliated esophageal cells	32/57
Hamajima[22] (2002)	Japan	Asian	Hospital	White blood cells	102/241
Li[23] (2002)	China	Asian	Population/blood donors	Tumor tissue	62/131
Hu[24] (2003)	China	Asian	Population	White blood cells	120/130
Vos[25] (2003)	South Africa	African	Unknown	Tumor tissue, White blood cells	73/115
Hong[26] (2005)	China	Asian	Population	Normal Esophageal tissue	758/1420
Cai[27] (2006)	China	Asian	Population	White blood cells	204/389
Shao[28] (2008)	China	Asian	Population	White blood cells	673/694

Table 2 Distribution of *TP53* Arg72Pro genotypes among esophageal cancer cases and controls included in the meta-analysis *n* (%)

First author (yr)	Cases			Controls		
	Arg/Arg	Arg/Pro	Pro/Pro	Arg/Arg	Arg/Pro	Pro/Pro
Lee[20] (2000)	20 (22.2)	46 (51.1)	24 (26.7)	94 (37)	116 (45.7)	44 (17.3)
Peixoto[21] (2001)	8 (25)	13 (40.6)	11 (34.4)	9 (15.8)	24 (42.1)	24 (42.1)
Hamajima[22] (2002)	37 (36.3)	51 (50)	14 (13.7)	91 (37.8)	107 (44.4)	43 (17.8)
Li[23] (2002)	27 (43.5)	21 (33.9)	14 (22.6)	29 (22.1)	67 (51.1)	35 (26.7)
Hu[24] (2003)	29 (24.2)	60 (50)	32 (26.7)	38 (29.2)	68 (52.3)	24 (18.5)
Vos[25] (2003)	26 (35.6)	42 (57.5)	5 (6.8)	37 (32.2)	62 (53.9)	16 (13.9)
Hong[26] (2005)	199 (26.3)	340 (44.9)	219 (28.9)	425 (29.9)	731 (51.5)	264 (18.6)
Cai[27] (2006)	41 (20.1)	89 (43.6)	74 (36.3)	117 (30.1)	178 (45.8)	94 (24.2)
Shao[28] (2008)	163 (24.2)	306 (45.5)	204 (30.3)	195 (28.1)	366 (52.7)	133 (19.2)

Arg: Arginine; Pro: Proline.

studies ranged from 89 to 2178. In total, 2114 EC cases and 3431 controls were included in the meta-analysis. Distribution of *TP53* genotype frequencies among EC cases and controls of the nine studies are shown in Table 2. The frequencies of heterozygote genotype among the cases of the studies using the specimens of exfoliated esophageal cells[21] or tumor tissues[23] were obviously lower than those of other studies. In studies with at least 200 samples, there was not a wide variation of Arg72 and Pro72 allele frequencies among controls, with the Arg72 allele frequencies ranging from 53% to 60%[20,22,24,26-28]. But in studies with less than 200 samples, the control groups represented diverse frequencies of the Arg72 allele, which were 37%[21], 48%[23] and 59%[25], respectively.

Meta-analysis results

When all the eligible studies were pooled into the meta-analysis, evidence was found in an association between significantly decreased EC risk and the variant genotypes of *TP53* in the dominant model (OR = 0.73, 95% CI: 0.57-0.94, $P = 0.014$, Table 3). However, significant inter-study heterogeneity existed in all genetic models (Table 3). In order to figure out the main reasons of the heterogeneity among studies and obtain exact consequence on the relationship between *TP53* Arg72Pro polymorphism and EC susceptibility, stratified analyses were then performed.

In stratified analysis according to the source of controls, significant association between reduced EC risk and *TP53* genotypes was found solely in subgroup of studies with population-based controls in all genetic models (homozygote comparison: OR = 0.56, 95% CI: 0.47-0.66, $P < 0.001$; dominant model: OR = 0.57, 95% CI: 0.50-0.66, $P < 0.001$; recessive model: OR = 0.80, 95% CI: 0.70-0.92, $P = 0.001$; Table 3). Significantly increased EC risk, however, was observed in the subgroup of a study with different source of controls selected from population and blood donors in homozygote comparison (OR = 2.33, 95% CI: 1.03-5.24, $P = 0.041$) and recessive model (OR = 2.71, 95% CI: 1.42-5.02, $P = 0.003$, Table 3). No evidence of association was observed in studies without clear presentation of hospital-based controls or the source of controls (Table 3).

We divided the included studies into four subgroups according to the specimens used. As a result, significantly reduced EC risk was found only in subgroups where white blood cells or normal tissue were used to determine *TP53* genotypes in different genetic models (homozygote comparison: OR = 0.56, 95% CI: 0.47-0.65, $P < 0.001$; dominant model: OR = 0.58, 95% CI: 0.51-0.67, $P < 0.001$; recessive model: OR = 0.78, 95% CI: 0.68-0.88, $P < 0.001$; Table 3). Nevertheless, significantly excessive risk of EC was observed in the subgroup of a study using tumor tissue to extract genomic DNA for genotyping *TP53* by homozygote comparison and recessive model (Table 3). This study also has different sources of controls. No significant association was observed in the studies using mixed specimens of white blood cells and tumor tissues or exfoliated esophageal cells to assess *TP53* genotypes (Table 3).

We also stratified the included studies into two sub-

Table 3 Results of meta-analysis for *TP53* Arg72Pro polymorphism and esophageal cancer risk

Study groups	n^1	Sample size (case/control)	Arg/Arg *vs* Pro/Pro			Arg/Arg+Arg/Pro *vs* Pro/Pro			Arg/Arg *vs* Arg/Pro+Pro/Pro		
			OR (95% CI)	P^2	P^3	OR (95% CI)	P^2	P^3	OR (95% CI)	P^2	P^3
Total	9	2114/3431	0.76 (0.54-1.07)[4]	0.114	0.001	0.73 (0.57-0.94)[4]	0.014	0.009	0.89 (0.69-1.13)[4]	0.334	0.004
Source of controls											
Population	5	1787/2690	0.56 (0.47-0.66)	< 0.001	0.273	0.57 (0.50-0.66)	< 0.001	0.404	0.80 (0.70-0.92)	0.001	0.324
Population/blood donors	1	62/131	2.33 (1.03-5.24)	0.041	-	1.25 (0.61-2.54)	0.538	-	2.71 (1.42-5.20)	0.003	-
Hospital	2	119/495	0.70 (0.22-2.18)[4]	0.533	0.022	0.80 (0.37-2.04)[4]	0.754	0.051	0.69 (0.36-1.31)[4]	0.252	0.08
Unknown	1	73/115	2.25 (0.73-6.91)	0.157	-	2.20 (0.77-6.28)	0.142	-	1.17 (0.63-2.16)	0.626	-
Specimen of cases											
White blood cells or normal tissue	6	1947/3128	0.56 (0.47-0.65)	< 0.001	0.233	0.58 (0.51-0.67)	< 0.001	0.219	0.78 (0.68-0.88)	< 0.001	0.321
White blood cells/tumor tissue	1	73/115	2.25 (0.73-6.91)	0.157	-	2.20 (0.77-6.28)	0.142	-	1.17 (0.63-2.16)	0.626	-
Tumor tissue	1	62/131	2.33 (1.03-5.24)	0.041	-	1.25 (0.61-2.54)	0.538	-	2.71 (1.42-5.20)	0.003	-
Exfoliated esophageal cells	1	32/57	1.94 (0.59-6.38)	0.275	-	1.39 (0.56-3.41)	0.474	-	1.78 (0.61-5.19)	0.292	-
Sample size											
⩾ 200 subjects	6	1947/3128	0.56 (0.47-0.65)	< 0.001	0.233	0.58 (0.51-0.67)	< 0.001	0.219	0.78 (0.68-0.88)	< 0.001	0.321
< 200 subjects	3	167/303	2.21 (1.24-3.93)	0.007	0.969	1.47 (0.90-2.40)	0.121	0.677	1.73 (1.15-2.61)	0.009	0.182

[1]Number of comparisons; [2]*P* value for the association; [3]*P* value for the heterogeneity; [4]Random effects model was used when *P* value for heterogeneity test < 0.1, otherwise, fixed-effects model was used. Arg: Arginine; Pro: Proline; OR: Odds ratio.

groups by sample size. One included studies with at least 200 participants, and the other included studies with less than 200 participants. Interestingly, studies in the former subgroup also used white blood cells or normal tissue as the specimens to assess *TP53* genotypes, and significant association between reduced EC risk and *TP53* genotypes was observed in all genetic models (Table 3). However, in the latter subgroup, significantly increased EC risk was found in homozygote comparison (OR = 2.21, 95% CI: 1.24-3.93, $P = 0.007$) and recessive model (OR = 1.73, 95% CI: 1.15-2.61, $P = 0.009$).

We performed the analysis only in well-designed studies with population-based controls with at least 200 participants using white blood cells or normal tissue to determine *TP53* genotypes. Significantly decreased risk of EC was found in all genetic models (homozygote comparison: OR = 0.54, 95% CI: 0.46-0.64, $P < 0.001$; dominant model: OR = 0.56, 95% CI: 0.49-0.65, $P < 0.001$; recessive model: OR = 0.79, 95% CI: 0.69-0.91, $P = 0.001$; Figure 1).

Sensitivity analysis

A single study involved in the meta-analysis was deleted each time to reflect the effects of individual data-set on the pooled ORs, and most of the corresponding pooled ORs were not materially altered (data not shown).

Publication bias

Both Begg's funnel plot and Egger's test were performed to assess the publication bias of literatures. Begg's funnel plots did not reveal any evidence of obvious asymmetry except for heterozygote comparison and dominant model in the overall meta-analysis (figures not shown). The Egger's test results suggested that publication bias was evident in heterozygote comparison ($P = 0.003$) and dominant model ($P = 0.004$), but not evident in homozygote comparison ($P = 0.058$) and recessive model ($P = 0.389$). The Duval and Tweedie non-parametric "trim and fill' method was used to adjust for publication bias. Meta-analysis with and without using "trim and fill" method did not draw different conclusions (data not shown), indicating that our results were statistically robust.

DISCUSSION

Since the identification of *TP53* Arg72Pro polymorphism[13], a number of studies[20-29] have investigated the genetic effect of this polymorphism on EC susceptibility, but the results are inconclusive. This led us to undertake the present meta-analysis, which could quantitify all the available data and might help us to distinguish the true from the false, to explore a more robust estimate of the effect of this polymorphism on EC risk. The main finding of our meta-analysis with 9 published studies including 2114 cases and 3431 controls is that *TP53* Arg72 carriers are significantly associated with decreased EC risk, and the results of increased risk or no effect of this polymorphism on EC may be due to methodological errors such as selection bias, inappropriate specimens used for genotype assessment, or limited statistical power.

We found that the distribution of *TP53* Arg72Pro genotypes in controls deviated from HWE in the study by Yang *et al*[29], although it has a relatively large sample size including 435 cases and 550 controls. Yang *et al*[29] reported that *TP53* Arg/Arg genotype was associated with significantly increased EC risk (OR = 6.48, 95% CI: 4.65-9.03), which is contrary to our results of meta-analysis. It is well known that deviation from HWE may be due to genetic reasons including non-random mating, or the alleles reflecting recent mutations that have not reached equilibrium, as well as methodological reasons including biased selection of subjects from the population, or genotyping errors[36,37]. In despite of the reasons of disequilibrium, the results of genetic association studies might be spurious if the controls were not in HWE[38,39]. In order to guarantee the criteria for the eligible studies, only studies with controls in HWE were included in this meta-analysis.

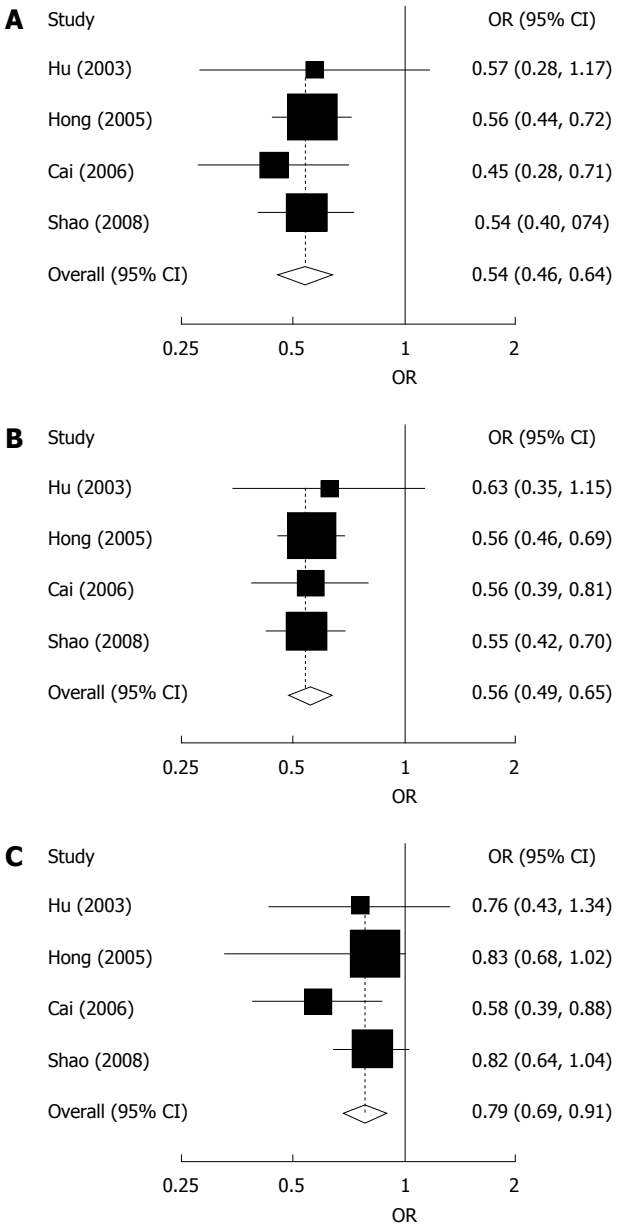

Figure 1 Forest plots for the relationship between *TP53* Arg72Pro polymorphism and esophageal cancer risk in studies with population-based controls with at least 200 participants, using white blood cells or normal tissues to determine TP53 genotypes. A: Homozygote comparison; B: Dominant model; C: Recessive model. The first authors' surname and year of publication are given in the left part of the figure. The size of the black square corresponding to each study is proportional to the sample size. The centre of each square represents the odds ratio (OR) and the horizontal line shows the corresponding 95% CI. The pooled OR was obtained using fixed-effects model and is represented by hollow diamond, where its centre indicates the OR and its ends correspond to the 95% CI. Arg: Arginine; Pro: Proline.

In the present study, statistically significant inter-study heterogeneity of genotype effect was detected in different genetic models when all the eligible studies were pooled into the meta-analysis. Pooling despite the presence of heterogeneity may yield the mean of varying effect sizes, but the biological interpretation of such a mean and its clinical application would be very difficult[40,41]. Therefore, it is important to explore the source of heterogeneity rather than obtaining a potentially meaningless pooled summary measure[42]. In order to identify the source of heterogeneity and ascertain the exact genetic effect of *TP53* Arg72Pro polymorphism on EC risk, we stratified the studies according to the source of controls, the specimens used for assessment of *TP53* genotypes and sample size. We found that the heterogeneity was remarkably decreased when the studies were divided according to the specimens used and sample size, indicating that the two factors may contribute to the observed heterogeneity.

In two of the nine included studies where the specimens used for assessment of *TP53* genotype were exfoliated esophageal cells[21] or tumor tissues[23], the frequencies of heterozygote genotype were obviously lower than those of other studies. This indicates that loss of heterozygosity (LOH) may exist and the distribution of *TP53* genotypes in these cases may not be the same as that in normal tissue or cells. Generally, spurious results may be obtained from genetic association studies with inappropriate material for determining genotypes[16]. In our meta-analysis, significant association between *TP53* Arg72Pro polymorphism and reduced EC risk was not observed in subgroups using inappropriate material to determine *TP53* genotypes but only in the subgroups using white blood cells or normal tissues. Consequently, in genetic association studies, DNA from white blood cells or normal tissues should be used for determining genetic polymorphism, but not tumor tissue or exfoliated cells, in which LOH is a frequent event[43,44].

Lacking sufficient statistical power is an unnegligible problem in genetic association studies detecting the possible risk for the polymorphism[45]. It is likely that most genetic polymorphisms represent modest effects on disease susceptibility. An adequately powered study to detect single genetic associations would typically require a relatively large sample size, depending on the prevalence of the implicated polymorphism and the exact OR. Some of the eligible studies for our meta-analysis had a very small sample size and may have limited statistical power to detect a slight effect or may have generated a fluctuated risk estimate[46,47]. Carefully conducted meta-analysis of these data is essential to clarify whether these associations are true or not. Through stratified analysis, we found significantly increased EC risk associated with *TP53* genotypes in subgroups of the studies with less than 200 participants, which was contrary to the results in subgroup of the studies with at least 200 participants. Given that all of the studies with a sample size of less than 200 used inappropriate specimens for determining *TP53* genotypes, the results may be unreliable.

Some limitations of this meta-analysis should be addressed. Firstly, publication bias was detected for heterozygote comparison and dominant model in overall meta-analysis. The potential reason may be that results from small studies were more likely to be published if there was positive data reported. Therefore, well-designed studies with large sample size are required. Secondly, in the subgroup analyses by ethnicity, the included studies involved only Asians and Africans. Data concerning other ethnicities such as Caucasians were not found. For Africans, only

one study was conducted, with a small sample size of 73 cases and 115 controls, which has not enough statistical power to find the real association. Thus, additional studies are warranted to evaluate the effect of this functional polymorphism on EC risk in different ethnicities, especially in Africans and Caucasians. Thirdly, lack of original data, including data of genotypes and environmental risk factors, of the included studies limited our further evaluation of potential gene-environment interaction, especially the interaction between human papillomavirus (HPV) infection and *TP53* Arg72Pro polymorphism, which was investigated in several studies[23,48-50]. However, unlike HPV infection in cervical carcinoma, the role of HPV in the etiology of EC remains controversial[8]. A more precise analysis should be conducted if individual data are available.

Despite some limitations, the results of this meta-analysis still suggest that TP53 Arg72 allele is a protective factor for EC. The significantly reduced EC risk was found only in subgroup analyses of well-designed studies. Therefore, it is necessary to conduct large-sample studies using appropriate materials for assessment of genotypes, as well as homogeneous EC patients and unbiased selected controls. Such studies taking these factors into account may eventually lead to a better and comprehensive understanding of the association between *TP53* Arg72pro polymorphism and EC risk.

COMMENTS

Background

Esophageal cancer (EC) is the eighth most common cancer and sixth most deadly cancer worldwide. A common polymorphism of *TP53* at the 72nd amino acid residue, with an arginine (Arg) to proline (Pro) change because of a G→C transverse has been implicated as a risk factor for EC, but individual studies have been inconclusive or controversial.

Research frontiers

A number of studies have reported the role of *TP53* Arg72Pro polymorphism in cancers such as cervical cancer, lung cancer, breast cancer, and gastric cancer, but the association of *TP53* polymorphism with EC is not fully understood.

Innovations and breakthroughs

The present study demonstrated that *TP53* Arg72 carriers are significantly associated with decreased EC risk, and suggested that increased risk or no effect of Arg72 variant on EC reported may be due to methodological errors such as selection bias, inappropriate specimens used for genotype assessment, or limited statistical power.

Applications

In this report, the association between *TP53* Arg72Pro polymorphism and EC risk was observed, and the Arg72 allele decreased the EC risk, which is meaningful to early diagnosis, prevention and individual-based treatment of EC. Therefore, Arg72Pro polymorphism of the *TP53* gene might be a potential therapeutic target for EC.

Terminology

TP53 is a major regulator of the cellular response to stress and serves as a tumor suppressor by inducing cell cycle arrest or apoptosis. Inactivation of the TP53 signaling pathway has been seen in most human cancers and polymorphisms of *TP53* have also been reported to be the possible risk factors for some kinds of tumors.

Peer review

This study is an interesting meta-analysis on the association of *TP53* ArgPro polymorphism with EC risk. Out of the 9 studies that survived the selection criteria, they found that *TP53* Arg72 carriers were significantly associated with decreased EC risk. The authors concluded that previous reports of increased risk or no effect of this polymorphism on EC may be due to methodological errors such as selection bias, inappropriate specimen or limited statistical power and they give guidelines on how to avoid these pitfalls.

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