Int J Clin Exp Med 2017;10(1):123-134
www.ijcem.com /ISSN:1940-5901/IJCEM0040533

Review Article

p53 codon 72 polymorphism is associated with human papillomavirus-related esophageal cancer risk: a meta-analysis

Lianghai Wang[1*], Zhiyu Zhang[1*], Jing Li[1], Xiaodan Yu[1], Qianqian Yu[4], Jun Hou[2], Feng Li[1,3]

Departments of [1]Pathology and Key Laboratories for Xinjiang Endemic and Ethnic Diseases, [2]Immunology, School of Medicine, Shihezi University, Shihezi, Xinjiang, China; [3]Department of Pathology, Beijing Chaoyang Hospital, Capital Medical University, Beijing, China; [4]Department of Oncology, Tongji Hospital, Huazhong University of Science and Technology, Wuhan, China. [*]Equal contributors.

Received September 23, 2016; Accepted October 28, 2016; Epub January 15, 2017; Published January 30, 2017

Abstract: *Background:* p53 codon 72 polymorphism is associated with esophageal cancer (EC). Human papillomavirus (HPV) infection is considered as a risk factor of EC. However, the association of p53 codon 72 polymorphism with the risk of HPV-related EC remains inconsistent. Hence, we aimed to investigate the association between p53 codon 72 polymorphism and HPV-related EC risk through meta-analysis. *Methods:* All eligible studies published before November 1, 2015 were selected by searching PubMed, Embase, China National Knowledge Infrastructure (CNKI), and WanFang with the following key words: "p53", "HPV" or "human papillomavirus", and "esophageal cancer". Crude odds ratio (OR) with 95% confidence interval (CI) was used to assess the association. Statistical analyses were performed using Review Manager 5.2 and Stata/SE 12.0. *Results:* Twelve studies including 1682 HPV-related EC cases were included in this meta-analysis. p53 codon 72 genotypes were associated with HPV-related EC in an allelic model (Arg *vs.* Pro: OR=1.66, 95% CI=1.19-2.32, *P*=0.003), a homozygous model (ArgArg *vs*. ProPro: OR=1.73, 95% CI=1.26-2.37, *P*=0.0007), and a recessive model (ArgArg *vs*. ArgPro+ProPro: OR=2.39, 95% CI=1.45-3.94, *P*=0.0006). By contrast, significant association was not seen in a heterozygous model (ArgPro *vs.* ProPro: OR=0.85, 95% CI=0.61-1.19, *P*=0.33) and a dominant model (ArgArg+ArgPro *vs.* ProPro: OR=1.24, 95% CI=0.93-1.65, *P*=0.14). A greater association was observed in the subgroup of studies performing PCR-RFLP or real-time PCR for p53 genotyping and studies performing PCR to detect HPV status in allelic and recessive models. *Conclusion:* p53 codon 72 Arg homozygous genotype is a high risk factor of HPV-related EC. Individuals carrying ArgArg genotype exhibit an increased risk of EC with HPV infection.

Keywords: Esophageal cancer, meta-analysis, p53 codon 72 polymorphism, human papillomavirus

Introduction

Esophageal cancer (EC) is the sixth leading cause of cancer-related deaths worldwide [1]. Approximately 455,800 new esophageal cancer cases and 400,200 deaths occurred in 2012 worldwide [2]. EC is considered as a serious malignancy because of its extremely aggressive histopathological features and poor survival rate [3]. Dietary and environmental factors, such as smoking, alcohol consumption, obesity, high soil nitrate levels, and HPV infection, are risk factors that predispose individuals to EC [4-6]. Nevertheless, some individuals without these known risk factors develop EC. This phenomenon suggests that genetic factors also play an important role in esophageal carcinogenesis [7].

P53, a tumor suppressor gene located on chromosome 17p13, contains 11 exons and encodes a 53 kDa nuclear phosphoprotein (TP53; GenBank NM_000546.2). Activated p53 suppresses carcinogenesis mainly by inducing the cell cycle arrest, senescence, and apoptosis of damaged cells [8]. p53 is commonly mutated in all kinds of human tumors. The most common polymorphism of p53 is at the 72nd amino acid residue with an arginine (Arg) to proline (Pro) change because of a G-to-C

transversion [9]. p53 Arg72Pro polymorphism is associated with some malignancies, such as cervical cancer [10], lung cancer [11], bladder cancer [12], thyroid carcinoma [13], nasopharyngeal carcinoma [14], skin cancer [15], prostate cancer [16], and gastric cancer [17]. The association between p53 codon 72 polymorphism and EC susceptibility has been extensively investigated, but inconclusive results have been obtained [18-29].

HPV infectious agents function as either direct carcinogens or promoters in esophageal carcinogenesis [30]. A meta-analysis has demonstrated that HPV increases the risk of EC by three-fold [31]. The E6 protein of HPV binds to and induces the degradation of p53 tumor suppressor protein via a ubiquitin-mediated process [32]. The role of p53 Arg72Pro polymorphism in the development of HPV-related cancer was first proposed in 1998 [33]. Since then, studies have investigated the combined influences of p53 codon 72 polymorphism and HPV infection on the risk of EC. However, results remain inconsistent. Furthermore, whether p53 Arg72Pro polymorphism can increase the risk of HPV-related EC remains unclear. Thus, this study aimed to assess the relationship of p53 Arg72Pro polymorphisms with the risk of HPV-related EC.

Materials and methods

Search strategy

We examined the databases of PubMed (1946-), Embase (1945-), China National Knowledge Infrastructure (CNKI) (1979-), and WanFang (1982-) until November 1, 2015 with the following search items: “p53”, “HPV” or “human papillomavirus”, and “esophageal cancer”.

Inclusion and exclusion criteria

The following inclusion criteria were used: (1) articles were published in English or Chinese; (2) EC cases were diagnosed pathologically or histologically; (3) the association of p53 Arg72Pro polymorphism with the risk of HPV-related esophageal cancer was evaluated; (4) the number of individual genotypes was provided in HPV-positive and HPV-negative groups or calculated from the original article.

The title and abstract of each study identified in the search was scanned to exclude clearly irrelevant publications. The exclusion criteria were as follows: (1) overlapping of data. When studies were duplicated (identified by author names and institution), the study based on the largest number of patients was selected; (2) reviews, meta-analysis, or case reports; and (3) non-extractable relevant raw data (the number of cases for a given p53 genotype or HPV status). If studies did not report sufficient or clear data, the corresponding authors were contacted by e-mail to request the information. The remaining articles were browsed to determine whether they contained relevant information.

Data extraction

Two investigators (ZZ and XY) independently reviewed and extracted information from all eligible publications in accordance with the selection criteria. Disagreement was resolved by a third independent reviewer (JL) whenever a conflict occurred. The following information was obtained from each study: first author, publication year, country where study was conducted, histological type, specimen source, detection methods of p53 codon 72 polymorphism and HPV status, genotype distribution in HPV-positive and negative EC cases.

Statistical analysis

Odds ratio (OR) and 95% confidence intervals (CI) were used to quantify the strength of the association between p53 Arg72Pro polymorphism and HPV-related EC by using five genetic models: allelic model (Arg *vs.* Pro), homozygous model (ArgArg *vs.* ProPro), heterozygous model (ArgPro *vs.* ProPro), dominant model (ArgArg+ArgPro *vs.* ProPro), and recessive model (ArgArg *vs.* ArgPro+ProPro). I^2 statistic was employed to quantify the proportion of the total variation because of the calculated heterogeneity. An I^2 of > 50% was interpreted as significant heterogeneity among the studies. The fixed-effects model (FEM) was initially used to pool the results of the included studies. If I^2 > 50%, a random-effects model (REM) was used. To evaluate the stability of the results, sensitivity analysis was performed to evaluate the influence of individual study on the estimated summary relative risks. Publication bias was calculated using the Begger’s test and visualized using funnel plot (P < 0.05 was considered representative of statistically significant publication bias). All statistical analyses were conducted

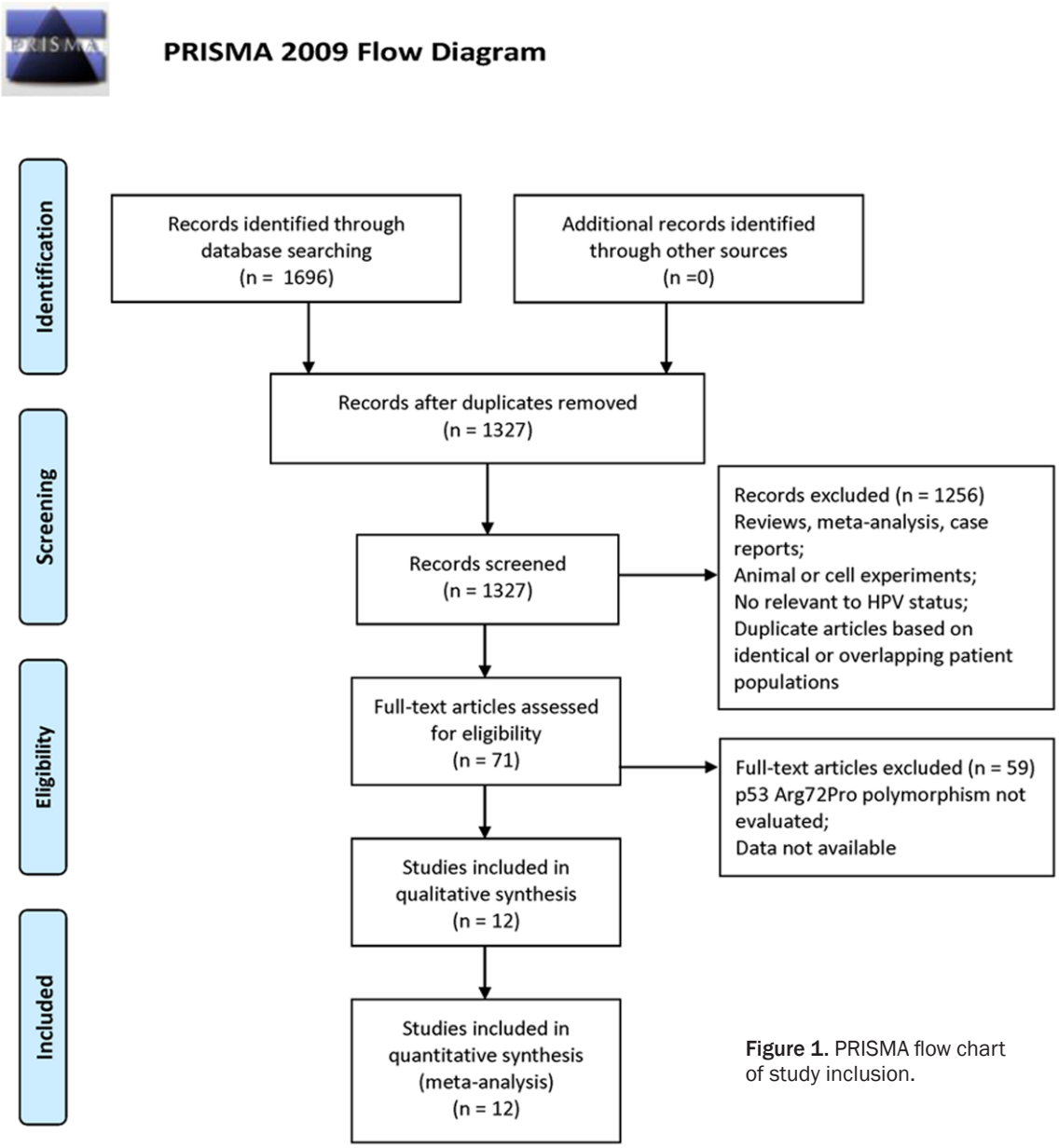


Figure 1. PRISMA flow chart of study inclusion.

using Review Manager version 5.2 and Stata/SE 12.0.

Results

Study characteristics

We initially identified a total of 1696 studies from PubMed, Embase, CNKI, and WanFang databases. After irrelevant studies were deduplicated and excluded, 12 studies containing 1682 EC cases were included in this meta-analysis [34-45]. A flow chart illustrating the screening process was shown in **Figure 1**. The main characteristics of the studies and all of the related distribution patterns of p53 Arg72Pro polymorphism genotype and HPV frequencies in EC cases are summarized in **Table 1**. Nine studies included pure ESCC cohorts [34, 37-42, 44, 45], two studies included mixed histologic cohorts [35, 36], and one study did not mention histologic clearly [43]. Four studies assessed p53 codon 72 polymorphism by direct sequencing [34, 39, 41, 42], one study detected p53 polymorphism through real-time PCR [40], and the remaining seven studies performed PCR-RFLP [35-38, 43-45]. Six studies assessed HPV status by PCR [35-37, 42, 44,

Table 1. Characteristics of the included studies

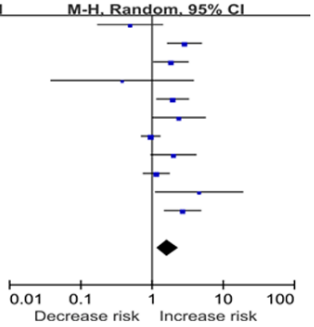
Study	Country	Ethnicity	Type	Source	ArgArg		ArgPro		ProPro		p53 testing method	HPV testing method
					HPV+	HPV-	HPV+	HPV-	HPV+	HPV-		
Pantelis A, 2007 [34]	Germany	Caucasians	ESCC	Tissue	3	28	5	11	1	5	Sequencing	Sequencing
He B, 2005 [35]	China	Asians	Mixed	Tissue	39	8	16	27	10	10	PCR-RFLP	PCR
Liu C, 2006 [36]	China	Asians	Mixed	Tissue	30	17	12	26	9	10	PCR-RFLP	PCR
Peixoto Guimaraes D, 2001 [37]	China	Asians	ESCC	Cytobrush	0	8	1	12	1	10	PCR-RFLP	PCR
Yao E, 2008 [38]	China	Asians	ESCC	Tissue	40	40	14	37	6	13	PCR-RFLP	ISH
Kawaguchi H, 2000 [39]	Japan	Asians	ESCC	Tissue	12	25	2	17	3	16	Sequencing	Sequencing
Yu Q, 2014 [40]	China	Asians	ESCC	Serology	38	29	80	75	50	36	Real-time PCR	ELISA
Li T, 2002 [41]	China	Asians	ESCC	Tissue	21	6	10	11	8	6	Sequencing	PCR and ISH
Yang W, 2008 [42]	China	Asians	ESCC	Tissue	265	108	15	4	28	15	Sequencing	PCR
Li X, 2012 [43]	China	Asians	NA	Tissue	18	1	17	1	5	3	PCR-RFLP	ISH
Lu XM, 2004 [44]	China	Asians	ESCC	Tissue	39	20	8	16	8	13	PCR-RFLP	PCR
Zhou X-h, 2012 [45]	China	Asians	ESCC	Tissue	81	24	NA	NA	NA	NA	PCR-RFLP	PCR

ESCC: esophageal squamous cell carcinoma; Mixed: esophageal squamous cell carcinoma and esophageal adenocarcinoma; NA: not available; PCR: polymerase chain reaction; PCR-RFLP: polymerase chain reaction with restriction fragment length polymorphism; ISH: in situ hybridization; ELISA: enzyme-linked immunosorbent assay.

A

Study or Subgroup	HPV+ Events	Total	HPV- Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
Annette Pantelis 2007	11	18	67	88	6.1%	0.49 [0.17, 1.43]
Baochang He 2005	94	130	43	90	11.1%	2.85 [1.62, 5.02]
Changjun Liu 2006	72	102	60	106	11.0%	1.84 [1.04, 3.27]
Denise Peixoto 2001	1	4	28	60	1.8%	0.38 [0.04, 3.87]
Ensheng Yao 2008	94	120	117	180	11.5%	1.95 [1.14, 3.31]
Hidetoshi Kawaguchi 2000	26	34	67	116	7.7%	2.38 [0.99, 5.70]
Qianqian Yu 2014	156	336	133	280	14.2%	0.96 [0.70, 1.32]
Tao Li 2002	52	78	23	46	9.0%	2.00 [0.95, 4.21]
Wenjun Yang 2008	527	598	220	254	12.7%	1.15 [0.74, 1.78]
Xiangli Li 2012	53	80	3	10	4.1%	4.58 [1.10, 19.13]
Xiaomei Lu 2004	86	110	56	98	10.6%	2.69 [1.47, 4.92]
Total (95% CI)		**1610**		**1328**	**100.0%**	**1.66 [1.19, 2.32]**
Total events	1172		817			

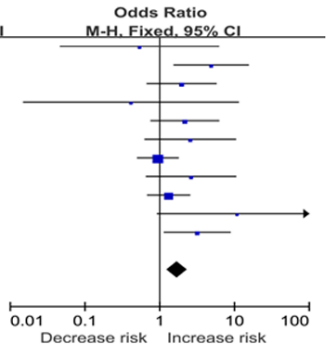
Heterogeneity: Tau² = 0.18; Chi² = 28.58, df = 10 (P = 0.001); I² = 65%
Test for overall effect: Z = 2.97 (P = 0.003)



B

Study or Subgroup	HPV+ Events	Total	HPV- Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Annette Pantelis 2007	3	4	28	33	2.6%	0.54 [0.05, 6.24]
Baochang He 2005	39	49	8	18	4.2%	4.88 [1.53, 15.56]
Changjun Liu 2006	30	39	17	27	8.1%	1.96 [0.67, 5.77]
Denise Peixoto 2001	0	1	8	18	2.1%	0.41 [0.01, 11.46]
Ensheng Yao 2008	40	46	40	53	8.4%	2.17 [0.75, 6.27]
Hidetoshi Kawaguchi 2000	12	15	25	41	4.7%	2.56 [0.62, 10.51]
Qianqian Yu 2014	38	88	29	65	33.0%	0.94 [0.49, 1.80]
Tao Li 2002	21	29	6	12	4.1%	2.63 [0.65, 10.58]
Wenjun Yang 2008	265	293	108	123	25.3%	1.31 [0.68, 2.56]
Xiangli Li 2012	18	23	1	4	0.6%	10.80 [0.91, 127.75]
Xiaomei Lu 2004	39	47	20	33	7.0%	3.17 [1.13, 8.90]
Total (95% CI)		**634**		**427**	**100.0%**	**1.73 [1.26, 2.37]**
Total events	505		290			

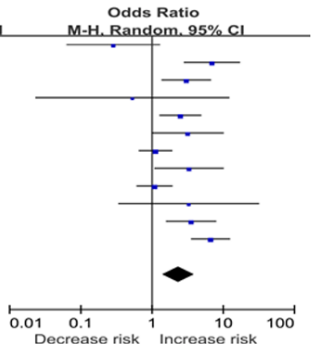
Heterogeneity: Chi² = 12.99, df = 10 (P = 0.22); I² = 23%
Test for overall effect: Z = 3.38 (P = 0.0007)



C

Study or Subgroup	HPV+ Events	Total	HPV- Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
Annette Pantelis 2007	3	9	28	44	6.0%	0.29 [0.06, 1.30]
Baochang He 2005	39	65	8	45	9.2%	6.94 [2.79, 17.26]
Changjun Liu 2006	30	51	17	53	9.8%	3.03 [1.36, 6.75]
Denise Peixoto 2001	0	2	8	30	2.1%	0.53 [0.02, 12.20]
Ensheng Yao 2008	40	60	40	90	10.6%	2.50 [1.27, 4.93]
Hidetoshi Kawaguchi 2000	12	17	25	58	7.7%	3.17 [0.99, 10.16]
Qianqian Yu 2014	38	168	29	140	11.4%	1.12 [0.65, 1.93]
Tao Li 2002	21	39	6	23	7.9%	3.31 [1.07, 10.17]
Wenjun Yang 2008	265	308	108	127	11.2%	1.08 [0.60, 1.95]
Xiangli Li 2012	18	40	1	5	3.5%	3.27 [0.34, 31.94]
Xiaomei Lu 2004	39	55	20	49	9.8%	3.53 [1.57, 7.98]
Xinghui Zhou 2012	81	111	24	83	10.9%	6.64 [3.52, 12.50]
Total (95% CI)		**925**		**747**	**100.0%**	**2.39 [1.45, 3.94]**
Total events	586		314			

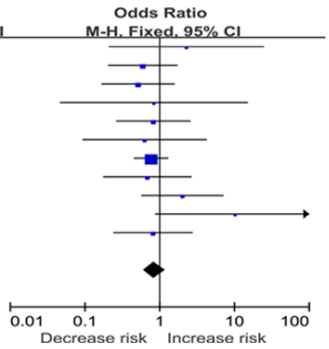
Heterogeneity: Tau² = 0.49; Chi² = 39.94, df = 11 (P < 0.0001); I² = 72%
Test for overall effect: Z = 3.42 (P = 0.0006)



D

Study or Subgroup	HPV+ Events	Total	HPV- Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Annette Pantelis 2007	5	6	11	16	1.4%	2.27 [0.21, 24.88]
Baochang He 2005	16	26	27	37	11.6%	0.59 [0.20, 1.73]
Changjun Liu 2006	12	21	26	36	11.1%	0.51 [0.17, 1.59]
Denise Peixoto 2001	1	2	12	22	1.4%	0.83 [0.05, 15.09]
Ensheng Yao 2008	14	20	37	50	8.6%	0.82 [0.26, 2.58]
Hidetoshi Kawaguchi 2000	2	5	17	33	3.6%	0.63 [0.09, 4.26]
Qianqian Yu 2014	80	130	75	111	42.3%	0.77 [0.45, 1.31]
Tao Li 2002	10	18	11	17	6.8%	0.68 [0.17, 2.66]
Wenjun Yang 2008	15	43	4	19	4.9%	2.01 [0.56, 7.14]
Xiangli Li 2012	17	22	1	4	0.5%	10.20 [0.86, 120.96]
Xiaomei Lu 2004	8	16	16	29	7.7%	0.81 [0.24, 2.76]
Total (95% CI)		**309**		**374**	**100.0%**	**0.85 [0.61, 1.19]**
Total events	180		237			

Heterogeneity: Chi² = 7.84, df = 10 (P = 0.64); I² = 0%
Test for overall effect: Z = 0.96 (P = 0.33)



E

Study or Subgroup	HPV+ Events	Total	HPV- Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Annette Pantelis 2007	8	9	39	44	1.7%	1.03 [0.11, 10.01]
Baochang He 2005	55	65	35	45	7.5%	1.57 [0.59, 4.16]
Changjun Liu 2006	42	51	43	53	8.8%	1.09 [0.40, 2.94]
Denise Peixoto 2001	1	2	20	30	1.5%	0.50 [0.03, 8.85]
Ensheng Yao 2008	54	60	77	90	7.3%	1.52 [0.54, 4.25]
Hidetoshi Kawaguchi 2000	14	17	42	58	4.0%	1.78 [0.45, 7.02]
Qianqian Yu 2014	118	168	104	140	39.9%	0.82 [0.49, 1.35]
Tao Li 2002	31	39	17	23	5.2%	1.37 [0.41, 4.60]
Wenjun Yang 2008	280	308	112	127	17.0%	1.34 [0.69, 2.60]
Xiangli Li 2012	35	40	2	5	0.5%	10.50 [1.39, 79.13]
Xiaomei Lu 2004	47	55	36	49	6.5%	2.12 [0.79, 5.66]
Total (95% CI)		**814**		**664**	**100.0%**	**1.24 [0.93, 1.65]**
Total events	685		527			

Heterogeneity: Chi² = 9.29, df = 10 (P = 0.50); I² = 0%
Test for overall effect: Z = 1.48 (P = 0.14)

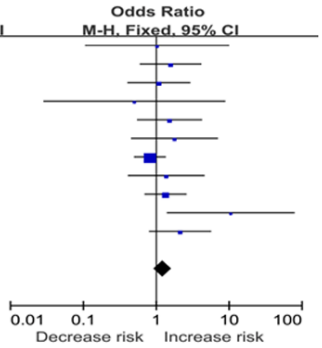


Figure 2. Forest plot of ORs for the association of p53 codon 72 polymorphism in allelic (A), homozygous (B), recessive (C), heterozygous (D), and dominant (E) models with HPV-related esophageal cancer.

Table 2. Stratified analysis of pooled odds ratios for the association of p53 codon 72 polymorphism in allelic and recessive models with HPV-related esophageal cancer

Stratified analysis	No. of studies	Sample size (HPV+/HPV-)	OR	95% CI	*P* value	Model	I^2
Allelic model							
P53 genotyping method							
Sequencing	4	616/377	1.34	0.77-2.32	0.3	REM	55%
No sequencing	7	556/440	1.88	1.19-2.97	0.006	REM	72%
HPV detection method							
PCR only	6	832/430	1.87	1.28-2.74	0.001	REM	51%
No PCR	5	340/387	1.46	0.81-2.60	0.21	REM	70%
Recessive model							
P53 genotyping method							
Sequencing	4	301/167	1.43	0.58-3.54	0.44	REM	67%
No sequencing	8	285/147	3.07	1.74-5.43	0.0001	REM	70%
HPV detection method							
PCR only	7	475/191	3.19	1.68-6.06	0.0004	REM	73%
No PCR	5	111/123	1.54	0.75-3.13	0.24	REM	60%

45], two studies by ISH [38, 43], one study through both PCR and ISH [41], two studies performed squencing [34, 39], and one study used ELISA [40].

Overall analyses

All 12 studies were included in the meta-analysis to assess the association of the recessive model (ArgArg *vs*. ArgPro+ProPro) with HPV-related EC. A total of 11 studies, including 1478 HPV-related EC cases, were evaluated to determine the relationship of allelic (Arg *vs.* Pro), homozygous (ArgArg *vs*. ProPro), heterozygous (ArgPro *vs.* ProPro) and dominant (ArgArg+ ArgPro *vs.* ProPro) models with HPV-related EC. Results showed that p53 codon 72 Arg homozygous genotype was significantly associated with HPV-related EC in three genetic comparison models ($OR_{allelic\ model}$=1.66, 95% CI=1.19-2.32, *P*=0.003, I^2=65%; $OR_{homozygous\ model}$=1.73, 95% CI=1.26-2.37, *P*=0.0007, I^2=23%; $OR_{recessive\ model}$=2.39, 95% CI=1.45-3.94, *P*=0.0006, I^2=72%; **Figure 2**). By contrast, p53 genotypes were not significantly correlated with HPV-related EC in the heterozygous model (OR=0.33, 95% CI=0.61-1.19, *P*=0.33, I^2=0%) and the dominant model (OR=1.24, 95% CI=0.93-1.65, *P*=0.14, I^2=0%).

Subgroup analyses

Due to the significant heterogeneity of included studies in the allelic model and the recessive model (I^2=65% and 72%, respectively; **Figure 2**), we conducted subgroup analyses according to detection methods of p53 codon 72 polymorphism and HPV status (**Table 2**). The association between p53 Arg72Pro polymorphisms and the risk of HPV-related EC appeared to be greater among studies performing PCR-RFLP or real-time PCR for p53 genotyping (pooled OR allelic model=1.88, 95% CI=1.19-2.97, P= 0.006, I^2=72%; OR recessive model=3.07, 95% CI=1.74-5.43, P=0.0001, I^2=70%) compared with studies using direct p53 sequencing, and studies performing PCR to detect HPV status (OR allelic model=1.87, 95% CI=1.28-2.74, P=0.001, I^2=51%; OR recessive model=3.19, 95% CI=1.68-6.06, P=0.0004, I^2=73%) compared with studies using ISH, ELISA or sequencing.

Sensitivity analysis and publication bias

Sensitivity analysis was performed to address the potential bias due to the quality of the included studies. As shown in **Figure 3**, the results for all studies were stabilized, and thus, no individual study was found to influence the

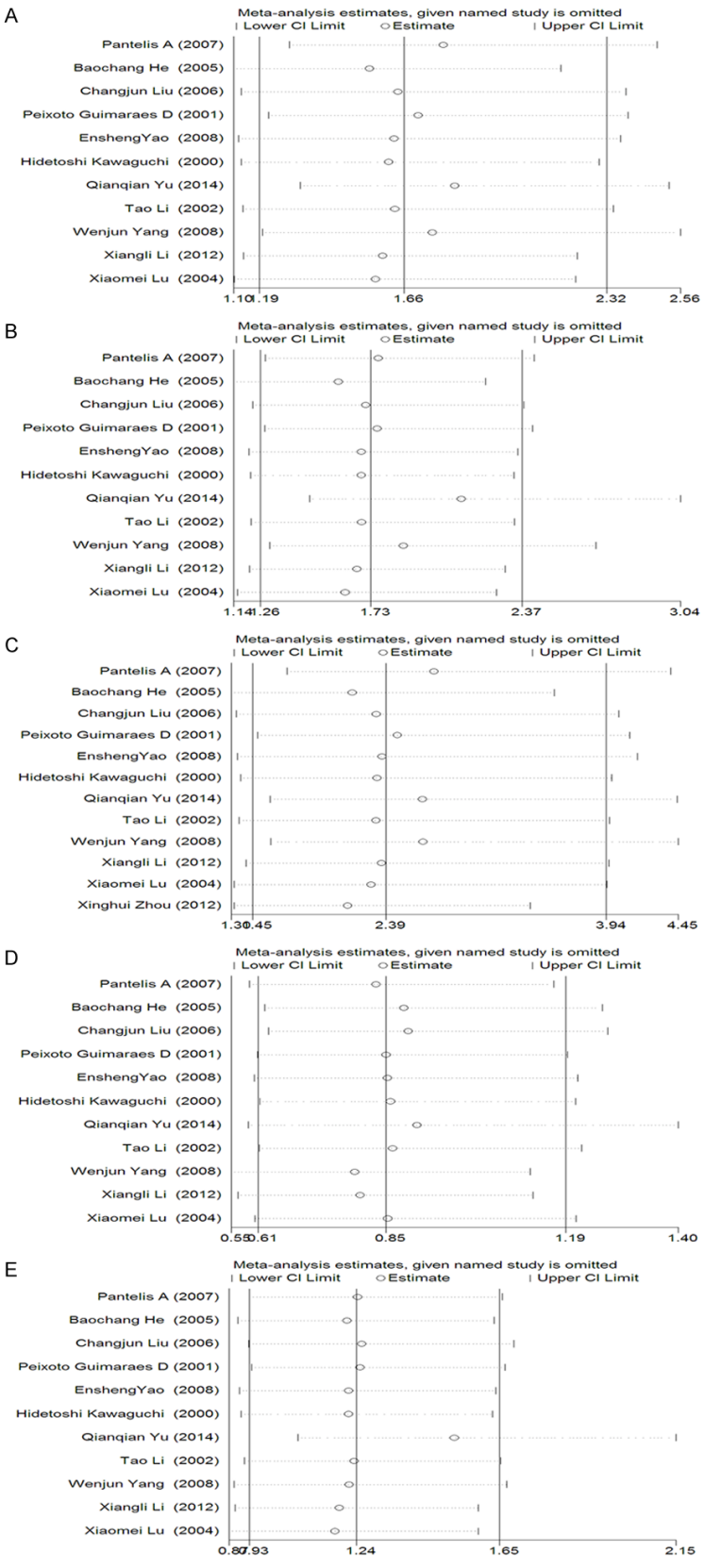


Figure 3. Sensitivity analysis in allelic (A), homozygous (B), recessive (C), heterozygous (D), and dominant (E) models.

combined results. The shape of the funnel plot of the allelic, recessive, and homozygous models in overall analyses showed a relatively symmetrical distribution (**Figure 4**). The result of Bgger's test revealed no significant publication bias for allelic (P=1.000), homozygous (P=0.640), and recessive (P=0.304) models, which further suggesting the absence of substantial publication bias.

Discussion

P53 is a major regulator of cell responses to stress; p53 also functions as a tumor suppressor by inducing cell cycle arrest and apoptosis [46]. A common polymorphism occurs at codon 72 of exon 4 in the transactivation domain of p53 [47]. HPV exhibits a formidable binding affinity to p53 by encoding oncogenic protein E6; as a result, p53 is ubiquitinated and degraded; an uncontrollable cell cycle also occurred [48]. In 1998, Storey and co-workers reported that p53 codon 72 Arg homozygous genotype represents a significant risk factor of the development of HPV-related cancers [33]. Since then, related studies have been published, but results remain inconclusive [49-60]. A meta-analysis has revealed that p53 Arg72Pro polymorphism is not associated with the risk of HPV-related head and neck squamous cell carcinoma [61]. Another meta-analysis has demonstrated that Arg72-Pro is associated with the progression of squamous intraepithelial lesions to cervical cancer in the presence of HPV-positive Arg variant of p53 [62]. However, definitive conclusion between p53 Arg72Pro

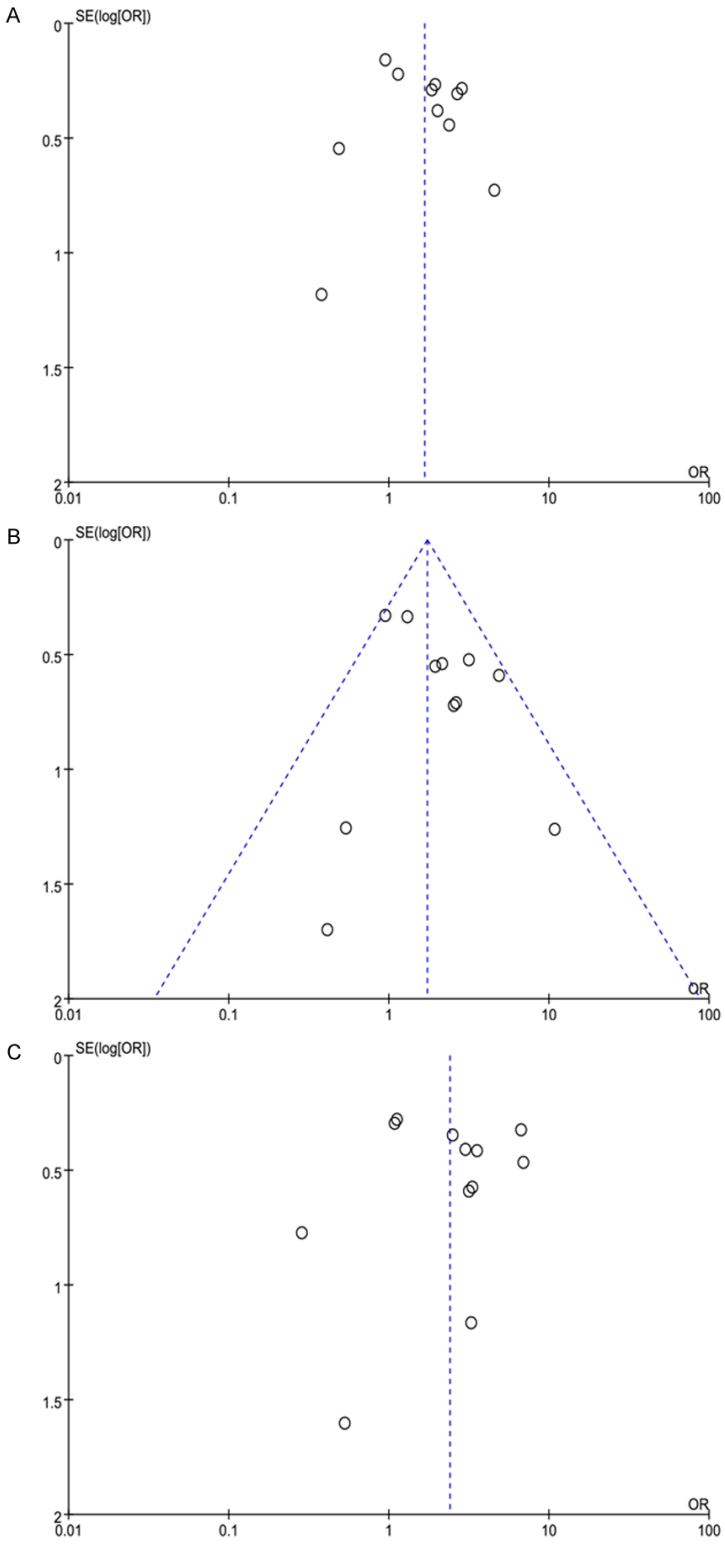


Figure 4. Funnel plot for the association of p53 codon 72 polymorphism in allelic (A), homozygous (B), and recessive (C) models with HPV-related esophageal cancer.

polymorphism and HPV-related esophageal cancer has yet to be obtained [34-45].

We performed this meta-analysis to obtain a more robust estimate of the relationship between p53 polymorphism with the risk of HPV-related EC. A total of 1682 HPV-related EC cases were evaluated in all of the 12 included studies. The results indicated that the p53 codon 72 Arg homozygous genotype is a high-risk factor of HPV-related EC ($OR_{Arg\ vs.\ Pro}$=1.66, 95% CI=1.19-2.32; $OR_{ArgArg\ vs.\ ProPro}$=1.73, 95% CI=1.26-2.37; $OR_{ArgPro\ vs.\ ProPro}$=0.85, 95% CI=0.61-1.19; $OR_{ArgArg+ArgPro\ vs.\ ProPro}$=1.24, 95% CI=0.93-1.65; $OR_{ArgArg\ vs\ ArgPro+ProPro}$=2.39, 95% CI=1.45-3.94). Our results are consistent with those of Habbous' study [62], who demonstrated that p53 Arg allele plays an important role in cervical cancer development among HPV-positive patients. Our results also agree with those of Storey's study [33], who stated that the arginine-encoding allele represents a significant risk factor of the development of HPV-associated cancers.

Of the 12 included studies, 2 did not find any association between p53 codon 72 polymorphism and HPV-related esophageal cancer. Pantelis and co-workers analyzed the association of these factors in Germany, a geographic region with a low incidence of esophageal cancer [34]. Peixoto and co-workers extracted DNA from exfoliated cells to analyze p53 codon 72 polymorphism and to detect HPV from 32 cases [37]. These varying results are likely attributed to the regional or DNA extraction source. However, subgroup analysis according to ethnicity or source of samples was not conducted in this meta-analysis because of the limited number of included studies.

Heterogeneity between studies is very common in genetic association analysis involved in meta-analysis. Heterogeneity of the allelic model and the recessive model in overall analyses was high. To identify the source of heterogeneity, we removed non-Asian populations [34]. However, we found that heterogeneity was not remarkably decreased (data not shown); thus, ethnicity may not contribute to the observed heterogeneity.

Some possible limitations of our meta-analysis include the following. First, the sample sizes of the studies included in this meta-analysis except those in three studies were small [40, 42, 45]. Second, we included studies published in English and Chinese. Therefore, some relevant reports published in other languages may be missed. Finally, the result of this meta-analysis did not measure potential confounders or adjust for their effects because not all eligible studies have comprehensive information, such as smoking and alcohol consumption.

In conclusion, this meta-analysis suggested that p53 codon 72 Arg homozygous genotype is a high risk factor of HPV-related EC. Individuals carrying ArgArg genotype are at an increased risk of EC with HPV infection. Further well-designed and extensive studies should be conducted to validate this association in different populations.

Acknowledgements

This work was supported by the National Natural Science Foundation of China (Grant Nos. 81460416, 81560399), Ministry of Science and Technology of China (Grant No. 2012AA02A503), and Scientific Research Start-up Capital for High-level Talents of Shihezi University (Grant Nos. RCZX201444 and RCZX201229).

Disclosure of conflict of interest

None.

Address correspondence to: Jun Hou, Department of Immunology, School of Medicine, Shihezi University, Shihezi, Xinjiang, China. E-mail: houjun229@163.com; Feng Li, Department of Pathology, Beijing Chaoyang Hospital, Capital Medical University, Beijing, China. E-mail: lifeng7855@126.com

References

[1] Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, Parkin DM, Forman D and Bray F. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer 2015; 136: E359-386.

[2] Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J and Jemal A. Global cancer statistics, 2012. CA Cancer J Clin 2015; 65: 87-108.

[3] Napier KJ, Scheerer M and Misra S. Esophageal cancer: a review of epidemiology, pathogenesis, staging workup and treatment modalities. World J Gastrointest Oncol 2014; 6: 112-120.

[4] Zhang Y. Epidemiology of esophageal cancer. World J Gastroenterol 2013; 19: 5598-5606.

[5] Trevellin E, Scarpa M, Carraro A, Lunardi F, Kotsafti A, Porzionato A, Saadeh L, Cagol M, Alfieri R, Tedeschi U, Calabrese F, Castoro C and Vettor R. Esophageal adenocarcinoma and obesity: peritumoral adipose tissue plays a role in lymph node invasion. Oncotarget 2015; 6: 11203-11215.

[6] Li X, Gao C, Yang Y, Zhou F, Li M, Jin Q and Gao L. Systematic review with meta-analysis: the association between human papillomavirus infection and oesophageal cancer. Aliment Pharmacol Ther 2014; 39: 270-281.

[7] Hiyama T, Yoshihara M, Tanaka S and Chayama K. Genetic polymorphisms and esophageal cancer risk. Int J Cancer 2007; 121: 1643-1658.

[8] Brady CA and Attardi LD. p53 at a glance. J Cell Sci 2010; 123: 2527-2532.

[9] Matlashewski GJ, Tuck S, Pim D, Lamb P, Schneider J and Crawford LV. Primary structure polymorphism at amino acid residue 72 of human p53. Mol Cell Biol 1987; 7: 961-963.

[10] Zhou X, Gu Y and Zhang SL. Association between p53 codon 72 polymorphism and cervical cancer risk among Asians: a HuGE review and meta-analysis. Asian Pac J Cancer Prev 2012; 13: 4909-4914.

[11] Ye XH, Bu ZB, Feng J, Peng L, Liao XB, Zhu XL, Sun XL, Yu HG, Yan DF and Yan SX. Association between the TP53 polymorphisms and lung cancer risk: a meta-analysis. Mol Biol Rep 2014; 41: 373-385.

[12] Xu T, Xu ZC, Zou Q, Yu B and Huang XE. P53 Arg72Pro polymorphism and bladder cancer risk--meta-analysis evidence for a link in Asians but not Caucasians. Asian Pac J Cancer Prev 2012; 13: 2349-2354.

[13] Wang F, Wang P, Wang B, Fu ZJ, Yuan Y, Yan SL, Zhao WJ and Wang YG. Association between TP53 Arg72Pro polymorphism and thyroid carcinoma risk. Tumour Biol 2014; 35: 2723-2728.

[14] Zhuo XL, Cai L, Xiang ZL, Zhuo WL, Wang Y and Zhang XY. TP53 codon 72 polymorphism contributes to nasopharyngeal cancer susceptibility: a meta-analysis. Arch Med Res 2009; 40: 299-305.
[15] Ye J, Li XF, Wang YD and Yuan Y. Arg72Pro polymorphism of TP53 gene and the risk of skin cancer: a meta-analysis. PLoS One 2013; 8: e79983.
[16] Lu Y, Liu Y, Zeng J, He Y, Peng Q, Deng Y, Wang J, Xie L, Li T, Qin X and Li S. Association of p53 codon 72 polymorphism with prostate cancer: an update meta-analysis. Tumour Biol 2014; 35: 3997-4005.
[17] Zhou Y, Li N, Zhuang W, Liu GJ, Wu TX, Yao X, Du L, Wei ML and Wu XT. P53 codon 72 polymorphism and gastric cancer: a meta-analysis of the literature. Int J Cancer 2007; 121: 1481-1486.
[18] Cai L, Mu LN, Lu H, Lu QY, You NC, Yu SZ, Le AD, Zhao J, Zhou XF, Marshall J, Heber D and Zhang ZF. Dietary selenium intake and genetic polymorphisms of the GSTP1 and p53 genes on the risk of esophageal squamous cell carcinoma. Cancer Epidemiol Biomarkers Prev 2006; 15: 294-300.
[19] Canova C, Hashibe M, Simonato L, Nelis M, Metspalu A, Lagiou P, Trichopoulos D, Ahrens W, Pigeot I, Merletti F, Richiardi L, Talamini R, Barzan L, Macfarlane GJ, Macfarlane TV, Holcatova I, Bencko V, Benhamou S, Bouchardy C, Kjaerheim K, Lowry R, Agudo A, Castellsague X, Conway DI, McKinney PA, Znaor A, McCartan BE, Healy CM, Marron M and Brennan P. Genetic associations of 115 polymorphisms with cancers of the upper aerodigestive tract across 10 European countries: the ARCAGE project. Cancer Res 2009; 69: 2956-2965.
[20] Cao YY, Ge H, Chen LQ, Chen ZF, Wen DG, Li Y and Zhang JH. [Correlation of 53BP1 and p53 polymorphisms to susceptibility to esophageal squamous cell carcinoma and gastric cardiac adenocarcinoma]. Ai Zheng 2007; 26: 1052-1057.
[21] Hamajima N, Matsuo K, Suzuki T, Nakamura T, Matsuura A, Hatooka S, Shinoda M, Kodera Y, Yamamura Y, Hirai T, Kato T and Tajima K. No associations of p73 G4C14-to-A4T14 at exon 2 and p53 Arg72Pro polymorphisms with the risk of digestive tract cancers in Japanese. Cancer Lett 2002; 181: 81-85.
[22] Hong Y, Miao X, Zhang X, Ding F, Luo A, Guo Y, Tan W, Liu Z and Lin D. The role of P53 and MDM2 polymorphisms in the risk of esophageal squamous cell carcinoma. Cancer Res 2005; 65: 9582-9587.
[23] Hu N, Li WJ, Su H, Wang C, Goldstein AM, Albert PS, Emmert-Buck MR, Kong LH, Roth MJ, Dawsey SM, He LJ, Cao SF, Ding T, Giffen C and Taylor PR. Common genetic variants of TP53 and BRCA2 in esophageal cancer patients and healthy individuals from low and high risk areas of northern China. Cancer Detect Prev 2003; 27: 132-138.
[24] Lee JM, Lee YC, Yang SY, Shi WL, Lee CJ, Luh SP, Chen CJ, Hsieh CY and Wu MT. Genetic polymorphisms of p53 and GSTP1, but not NAT2,are associated with susceptibility to squamous-cell carcinoma of the esophagus. Int J Cancer 2000; 89: 458-464.
[25] Liu G, Cescon DW, Zhai R, Zhou W, Kulke MH, Ma C, Xu W, Su L, Asomaning K, Heist RS, Wain JC, Lynch TJ and Christiani DC. p53 Arg72Pro, MDM2 T309G and CCND1 G870A polymorphisms are not associated with susceptibility to esophageal adenocarcinoma. Dis Esophagus 2010; 23: 36-39.
[26] Piao JM, Kim HN, Song HR, Kweon SS, Choi JS, Yoon JY, Chung IJ, Kim SH and Shin MH. p53 codon 72 polymorphism and the risk of esophageal cancer: a Korean case-control study. Dis Esophagus 2011; 24: 596-600.
[27] Vos M, Adams CH, Victor TC and van Helden PD. Polymorphisms and mutations found in the regions flanking exons 5 to 8 of the TP53 gene in a population at high risk for esophageal cancer in South Africa. Cancer Genet Cytogenet 2003; 140: 23-30.
[28] Zhang JH, Li Y, Wang R, Wen DG, Wu ML and He M. [p53 gene polymorphism with susceptibility to esophageal cancer and lung cancer in Chinese population]. Zhonghua Zhong Liu Za Zhi 2003; 25: 365-367.
[29] Zhang L, Xing D, He Z and Lin D. [p53 gene codon 72 polymorphism and susceptibility to esophageal squamous cell carcinoma in a Chinese population]. Zhonghua Yi Xue Yi Chuan Xue Za Zhi 2002; 19: 10-13.
[30] Syrjanen KJ. HPV infections and oesophageal cancer. J Clin Pathol 2002; 55: 721-728.
[31] Liyanage SS, Rahman B, Ridda I, Newall AT, Tabrizi SN, Garland SM, Segelov E, Seale H, Crowe PJ, Moa A and Macintyre CR. The aetiological role of human papillomavirus in oesophageal squamous cell carcinoma: a meta-analysis. PLoS One 2013; 8: e69238.
[32] Rampias T, Sasaki C and Psyrri A. Molecular mechanisms of HPV induced carcinogenesis in head and neck. Oral Oncol 2014; 50: 356-363.
[33] Storey A, Thomas M, Kalita A, Harwood C, Gardiol D, Mantovani F, Breuer J, Leigh IM, Matlashewski G and Banks L. Role of a p53 polymorphism in the development of human papillomavirus-associated cancer. Nature 1998; 393: 229-234.
[34] Pantelis A, Pantelis D, Ruemmele P, Hartmann A, Hofstaedter F, Buettner R, Bootz F and

Stoehr R. p53 Codon 72 polymorphism, loss of heterozygosity and high-risk human papillomavirus infection in a low-incidence German esophageal squamous cell carcinoma patient cohort. Oncol Rep 2007; 17: 1243-1248.
[35] Baochang H. Study on p53 codon 72 polymorphism and human papillomavirus-associated esophageal cancer in Anyang area, Henan province. Chin J Gastro Hepa 2005; 374-376.
[36] Liu C. Study on correlations between HPV infections, the polymorphism and mutations of p53 codon 72 and esophageal cancer in anyang area [Master]. Zheng Zhou University 2006.
[37] Peixoto Guimaraes D, Hsin Lu S, Snijders P, Wilmotte R, Herrero R, Lenoir G, Montesano R, Meijer CJ, Walboomers J and Hainaut P. Absence of association between HPV DNA, TP53 codon 72 polymorphism, and risk of oesophageal cancer in a high-risk area of China. Cancer Lett 2001; 162: 231-235.
[38] Yao E. Association between p53 Arg72Pro polymorphism and HPV infection in Xinjiang Kazakh's esophageal cancer [Master]. Shihezi University 2008.
[39] Kawaguchi H, Ohno S, Araki K, Miyazaki M, Saeki H, Watanabe M, Tanaka S and Sugimachi K. p53 polymorphism in human papillomavirus-associated esophageal cancer. Cancer Res 2000; 60: 2753-2755.
[40] Yu Q, Yang J, Liu B, Li W, Hu G, Qiu H, Huang L, Xiong H and Yuan X. Combined effects of leukocyte telomere length, p53 polymorphism and human papillomavirus infection on esophageal squamous cell carcinoma in a Han Chinese population. Cancer Epidemiol 2014; 38: 569-575.
[41] Li T, Lu ZM, Guo M, Wu QJ, Chen KN, Xing HP, Mei Q and Ke Y. p53 Codon 72 polymorphism (C/G) and the risk of human papillomavirus-associated carcinomas in China. Cancer 2002; 95: 2571-2576.
[42] Yang W, Zhang Y, Tian X, Ning T and Ke Y. p53 codon 72 polymorphism and the risk of esophageal squamous cell carcinoma. Mol Carcinog 2008; 47: 100-104.
[43] Xiangli L. Relation between HPV16/18 infection and p53 polymorphisms with esophageal cancer in Tangshan area. China Medical Herald 2012; 154-156.
[44] Lu XM, Zhang YM, Lin RY, Liang XH, Zhang YL, Wang X, Zhang Y, Wang Y and Wen H. p53 polymorphism in human papillomavirus-associated Kazakh's esophageal cancer in Xinjiang, China. World J Gastroenterol 2004; 10: 2775-2778.
[45] Zhou X. Relationship between high risk HPV infection and p53 polymorphism and esophageal cancer. Chin J Nosocomiol 2012; 910-912.
[46] Levine AJ, Finlay CA and Hinds PW. P53 is a tumor suppressor gene. Cell 2004; 116: S67-69, 61 p following S69.
[47] Thomas M, Kalita A, Labrecque S, Pim D, Banks L and Matlashewski G. Two polymorphic variants of wild-type p53 differ biochemically and biologically. Mol Cell Biol 1999; 19: 1092-1100.
[48] Scheffner M, Werness BA, Huibregtse JM, Levine AJ and Howley PM. The E6 oncoprotein encoded by human papillomavirus types 16 and 18 promotes the degradation of p53. Cell 1990; 63: 1129-1136.
[49] Yamashita T, Yaginuma Y, Saitoh Y, Kawai K, Kurakane T, Hayashi H and Ishikawa M. Codon 72 polymorphism of p53 as a risk factor for patients with human papillomavirus-associated squamous intraepithelial lesions and invasive cancer of the uterine cervix. Carcinogenesis 1999; 20: 1733-1736.
[50] Wang Z, Sturgis EM, Zhang Y, Huang Z, Zhou Q, Wei Q and Li G. Combined p53-related genetic variants together with HPV infection increase oral cancer risk. Int J Cancer 2012; 131: E251-258.
[51] Tachezy R, Mikyskova I, Salakova M and Van Ranst M. Correlation between human papillomavirus-associated cervical cancer and p53 codon 72 arginine/proline polymorphism. Hum Genet 1999; 105: 564-566.
[52] Szarka K, Veress G, Konya J and Gergely L. Frequency of p53 codon 72 genotypes in human papillomavirus associated squamous intraepithelial lesions and cervical cancer. Anticancer Res 1999; 19: 2377-2379.
[53] Summersgill KF, Smith EM, Kirchner HL, Haugen TH and Turek LP. p53 polymorphism, human papillomavirus infection in the oral cavity, and oral cancer. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2000; 90: 334-339.
[54] Nagpal JK, Sahni S and Das BR. P53 codon 72 polymorphism and susceptibility to development of human papilloma virus-associated cervical cancer in Indian women. Eur J Clin Invest 2002; 32: 943-948.
[55] Nagpal JK, Patnaik S and Das BR. Prevalence of high-risk human papilloma virus types and its association with P53 codon 72 polymorphism in tobacco addicted oral squamous cell carcinoma (OSCC) patients of Eastern India. Int J Cancer 2002; 97: 649-653.
[56] Minaguchi T, Kanamori Y, Matsushima M, Yoshikawa H, Taketani Y and Nakamura Y. No evidence of correlation between polymorphism at codon 72 of p53 and risk of cervical cancer in Japanese patients with human papillomavirus 16/18 infection. Cancer Res 1998; 58: 4585-4586.

[57] Katiyar S, Thelma BK, Murthy NS, Hedau S, Jain N, Gopalkrishna V, Husain SA and Das BC. Polymorphism of the p53 codon 72 Arg/Pro and the risk of HPV type 16/18-associated cervical and oral cancer in India. Mol Cell Biochem 2003; 252: 117-124.

[58] Ji X, Neumann AS, Sturgis EM, Adler-Storthz K, Dahlstrom KR, Schiller JT, Wei Q and Li G. p53 codon 72 polymorphism associated with risk of human papillomavirus-associated squamous cell carcinoma of the oropharynx in never-smokers. Carcinogenesis 2008; 29: 875-879.

[59] Hoffmann M, Scheunemann D, Fazel A, Gorogh T, Kahn T and Gottschlich S. Human papillomavirus and p53 polymorphism in codon 72 in head and neck squamous cell carcinoma. Oncol Rep 2009; 21: 809-814.

[60] Cortezzi SS, Provazzi PJ, Sobrinho JS, Mann-Prado JC, Reis PM, de Freitas SE, Filho JF, Fukuyama EE, Cordeiro JA, Cury PM, Maniglia JV, Villa LL, Tajara EH and Rahal P. Analysis of human papillomavirus prevalence and TP53 polymorphism in head and neck squamous cell carcinomas. Cancer Genet Cytogenet 2004; 150: 44-49.

[61] Xia LY, Zeng XT, Li C, Leng WD and Fan MW. Association between p53 Arg72Pro polymorphism and the risk of human papillomavirus-related head and neck squamous cell carcinoma: a meta-analysis. Asian Pac J Cancer Prev 2013; 14: 6127-6130.

[62] Habbous S, Pang V, Eng L, Xu W, Kurtz G, Liu FF, Mackay H, Amir E and Liu G. p53 Arg72Pro polymorphism, HPV status and initiation, progression, and development of cervical cancer: a systematic review and meta-analysis. Clin Cancer Res 2012; 18: 6407-6415.