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Research Paper

P53 codon 72 polymorphism and ovarian cancer risk: a meta-analysis ☆

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Abstract

Objective: *p53* is a tumor suppressor gene and is involved in the etiology of ovarian cancer. Studies investigating the associations between the *p53* codon 72 polymorphism and ovarian cancer risk showed conflicting results. We performed this meta-analysis from eligible studies to evaluate this purported relationship. **Methods:** This meta-analysis was performed from 9 case-control studies, including 825 ovarian cases and 1073 controls. The fixed and random effect models were used to estimate the odds ratios(ORs) for various contrasts of this polymorphism. **Results:** The combined results based on all studies showed that a significantly decreased risk was associated with the variant Pro/Pro genotype, compared with Arg/Pro+Arg/Arg genotypes(OR, 0.70; 95%CI, 0.51~0.95). When stratifying the studies by ethnicity, we found that individuals with the variant genotype Pro/Pro had a significantly decreased risk of ovarian cancer compared with Arg/Arg genotype(OR, 0.43; 95%CI, 0.20~0.89) and Arg/Pro+Arg/Arg genotypes(OR, 0.61; 95%CI, 0.37~0.99) among Africans. **Conclusion:** This meta-analysis suggests that the *p53* codon 72 polymorphism may contribute to genetic susceptibility to ovarian cancer. More studies based on larger sample size should be performed to confirm the findings.

Key words: p_{53}; ovarian cancer; genetic susceptibility; meta-analysis

INTRODUCTION

Ovarian cancer is the most frequent malignancies among females, and it is the leading cause of death from gynecological cancer worldwide. It is estimated that the risk of developing ovarian cancer in a woman's lifetime is 1 in 70[1]. The majority of the patients at the time of diagnosis present with advanced stage of disease[2]. Moreover, some patients do not response to chemotherapy very well. The association between HPV infection and gynecological cancers has been reported in many studies[3-6]. High risk HPV oncoprotein E6 binds to p53 to promote its degradation via ubiquitin dependent proteolysis[4]. Thus, inactivation of p53 by HPV-E6 is similar to a functional *p53* mutation[3]. Hormonal and reproductive factors were thought to be associated with the development of ovarian cancer[1]. Epidemiologic studies also found a correlation with eggs, milk and dairy products in general to the incidence of ovarian cancer[7], suggesting an influence of the estrogen and progesterone contents of animal-derived food we consume[8]. As ovarian cancer is a multistep disease, it is reasonable that genetic variations such as functional polymorphisms may be associated with the development of ovarian cancer.

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p53, located at chromosome 17p13, is a tumor suppressor gene. It was referred as altered in many cancer cases[9]. The p53 protein is known as the cellular gatekeeper for growth and division, as it plays an essential role in safeguarding the integrity of the genome[10]. This protein is involved in many important physiological processes, such as cell cycle arrest, gene transcription, DNA repair and apoptosis. If a mutation occurs, p53 may lose its normal functions, leading to cell cycle pathways or loss of apoptosis control and, as a consequence, to unchecked cell proliferation and tumorigenesis. The *p53* gene harbors a polymorphism at codon 72 with a single-base change that causes an amino acid replacement in the transactivation domain of the protein of Arg(CGC) by Pro(CCC)[11]. Single nucleotide polymorphism(SNP) at codon 72 of the *p53* gene has been associated with cancers of lung[12-14], esophagus[15], cervix[16], breast[17] and so on.

Over the past few years, a number of case-control studies were conducted to investigate the association between *p53* codon 72 polymorphism and ovarian cancer risk in humans. However, these studies reported conflicting results. Because of the limited sample size in the study design, a single study may have been unpowered to detect the effects of this polymorphism with risk of ovarian cancer. The purpose of this meta-analysis is to quantitatively summarize the evidence for such a purported relationship.

MATERIALS AND METHODS

Identification and eligibility of relevant studies

Eligible studies were identified by searching the PubMed database(last search update May 20, 2008, using the search terms "*p53* and ovarian cancer"). Studies were obtained if there were available data for *p53* Arg72Pro polymorphism with ovarian cancer in a case-control design. The search was limited to English-language papers. Additional studies were identified by a manual search of references from original studies. Of the studies with the same or overlapping data by the same investigators, we selected the most recent ones with the most subjects. Studies included in our meta-analysis had to meet all the following criteria:① use an unrelated case-control design and ②contain available genotype frequency. Major reasons for exclusion of studies were: ①no control; ②duplicate; and ③no usable data reported.

Data extraction

Data were independently extracted by two reviewers (Z.Z. and G.F.) using a standardized data extraction form and discrepancies were adjudicated by a third reviewer (M.W.) until consensus was achieved on every item. The following data were considered: author name, year, country and ethnicity, matching condition, number of cases and controls, minor allele frequency(MAF) in controls, source of DNA, genotyping methods, and Hardy-Weinberg equilibrium in controls. Different ethnicity descents were categorized as European, Asian and African.

Statistical analysis

The strength of the association between *p53* Arg72Pro polymorphism and cancer was measured by odds ratios (ORs) and 95% confidence intervals(CIs). We first estimated the risk of the variant genotype Pro/Pro, compared with the wild-type Arg/Arg homozygote, and then evaluated the risks of Pro/Pro+Arg/Pro versus Arg/Arg and Pro/Pro versus Arg/Pro+Arg/Arg, assuming dominant and recessive effects of the variant Pro allele, respectively. In addition to comparisons for total subjects, studies were categorized into different subgroup analyses according to the ethnicity. Between-study heterogeneity in the studies was measured using the Q statistic[18] (When $P < 0.10$, the heterogeneity was considered significant). Values of each study were combined with models of both fixed effects and random effects [19]. Fixed effects model was used when the heterogeneity between the studies was absent; otherwise the random effects model was applied. If there was no heterogeneity, the two methods produced identical results. Random effects were more appropriate when heterogeneity was present[19].

Funnel plot was used to estimate the potential publication bias, in which the standard error of log(OR) of each study was plotted against its OR. Visual inspection of asymmetry in funnel plots was conducted to estimate the potential publication bias. The Begg rank correlation method and the Egger weighted regression method were used to evaluate the bias. The publication bias was consider significant when the $P < 0.10$. All analyses were done with Stata software (version 8.2; StataCorp LP, College Station, TX) and Review Manager(version 4.2; Oxford, England). All the *P* values were two-sided.

RESULTS

Study characteristics

Totally, nine studies were identified[20-28], including 825 cases and 1073 controls. Characteristics of studies included in this meta-analysis are listed in ***Table 1***. There were six studies of European descent, two studies of Asian descent, one study of African descent. A classical PCR-RFLP or Allele Specific-PCR was performed in 8 of the 9 eligible studies. Only one study used sequencing method[26]. In the nine eligible studies, genomic DNA in two studies was extracted from tissue[20-21], 3 from blood[24,27-28], and the others from both tissue and

Table 1 **Characteristics of eligible studies considered in the meta-analysis**

First author	Year	Country/Racial descent	No. of cases	No. of controls	Arg/Arg of cases	Arg/Pro of cases	Pro/Pro of cases	Arg/Arg of controls	Arg/Pro of controls	Pro/Pro of controls	MAF in controls
Buller	1997	America/ European	190	52	98	79	13	30	18	4	0.25
Peller	1999	Israel/European	13	13	7	6	0	8	5	0	0.19
Hogdall	2002	Denmark/European	211	83	118	73	20	48	27	8	0.26
Li	2002	China/Asian	39	50	14	20	5	10	26	14	0.54
Pegoraro	2003	South Africa/African	85	340	14	41	30	32	147	161	0.69
Agorastos	2004	Greece/European	51	30	26	22	3	6	19	5	0.48
Morari	2006	Brazil/European	69	222	23	46	0	117	91	14	0.27
Santos	2006	Portugal/ European	99	188	49	40	10	117	58	13	0.22
Ueda	2006	Japan/Asian	68	95	21	41	6	34	54	7	0.36

MAF: minor allele frequency.

blood[22-23,25-26]. Distributions of genotypes among all controls were consistent with Hardy-Weinberg equilibrium except for the study conducted by Ueda *et al.* [28] (chi square = 5.32, $P = 0.021$).

Quantitative synthesis

There was a wide variation in the *p53* codon72Pro allele frequency across different ethnicities, ranging from 0.19 in an European population[26] to 0.69 in an African population[25]. The mean frequency of Pro allele was 0.28 for European, 0.45 for Asian, and 0.69 for African.

As shown in ***Fig. 1a***, individuals with variant homozygote Pro/Pro had a decreased risk of ovarian cancer compared with wild-type Arg/Arg carriers(OR, 0.66; 95%CI, 0.36~1.22, $P = 0.03$ for heterogeneity), although it is not significant. In the dominant model (***Fig. 1b***), individuals with the combined genotype(Pro/Pro+Arg/Pro) had no effect on the risk of ovarian cancer compared with the wild-type genotype Arg/Arg(OR, 1.00; 95%CI, 0.66~1.51, $P = 0.001$ for heterogeneity). In the recessive model(***Fig. 1c***), however, a significantly decreased risk was associated with the variant genotype Pro/Pro compared with the(Arg/Pro+Arg/Arg) genotype (OR,0.70;95%CI, 0.51~0.95,$P = 0.25$ for heterogeneity).

When stratified by ethnicity, a significantly decreased risk was also associated with the variant genotype Pro/Pro in both homozygote model and recessive model among Africans[OR, 0.43; 95%CI, 0.20~0.89(***Fig. 1a***), OR, 0.61; 95%CI, 0.37~0.99(***Fig. 1c***)]. The results for stratified comparisons of the meta-analysis were listed in ***Table 2***.

Test of heterogeneity and publication bias

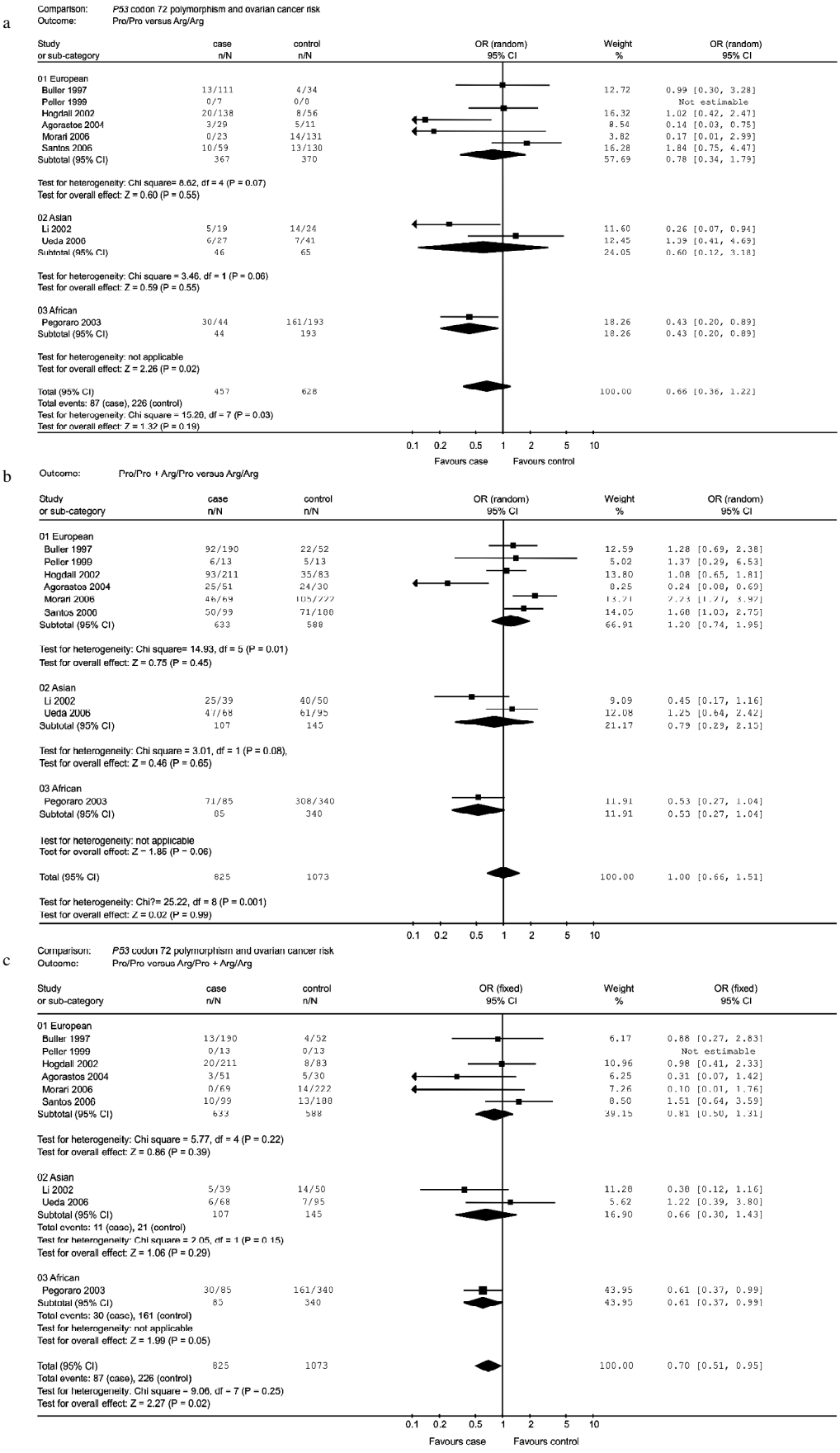
Statistical tests showed significant heterogeneity among studies in dominant(chi square = 25.22, $P = 0.001$) and homozygotes model(chi square = 15.26, $P = 0.03$), but not in recessive model(chi square = 9.06, $P = 0.25$). When we further evaluated the source of heterogeneity for the dominant and homozygote model by ethnicity, we found that ethnicity(Pro/Pro+Arg/Pro versus Arg/Arg:chi square = 5.73, $P = 0.057$; Pro/Pro versus Arg/Arg:chi square = 4.58, $P = 0.101$) may contribute to substantial altered heterogeneity.

Funnel plot and Egger's test were used to evaluate the possible publication bias of the studies. ***Fig. 2*** indicated the Begg's funnel plot of Egger's test. No publication bias was observed for *p53* codon 72 polymorphism Pro/Pro+Arg/Pro genotypes versus Arg/Arg genotype($t = -1.79$, $P = 0.116$), Pro/Pro versus Arg/Pro+Arg/Arg genotype($t = -0.65$, $P = 0.542$), Pro/Pro versus Arg/Arg genotype($t = -1.02$, $P = 0.347$)(***Fig. 2***).

DISCUSSION

The variation in the function of genes responsible for DNA repair and cell cycle control in the presence of carcinogen-mediated damage is a reasonable and convincing mechanism for explaining the variation in individual susceptibility to ovarian cancer. As the *p53* is involved in many important physiological processes, therefore it represents a suitable candidate for a ovarian cancer susceptibility gene. In the present study, we performed a meta-analysis to evaluate the association between the *p53* codon 72 polymorphism and ovarian cancer risk. We found that a significantly decreased risk was associated with the variant genotype Pro/Pro, compared with Arg/Pro+Arg/Arg genotypes(OR, 0.70; 95%CI, 0.51~0.95). When stratifying by ethnicity, a significantly decreased risk was also associated with the variant genotype Pro/Pro in both homozygote model (OR, 0.43; 95%CI, 0.20~0.89) and recessive model among Africans(OR, 0.61; 95%CI, 0.37~0.99). Considering the relatively small sample size, our result should be regarded as preliminary. Nevertheless, to the best of our knowledge, this is the first meta-analysis concerning the relationship between *p53* codon 72 polymorphism and ovarian cancer risk.

Ovarian cancer is thought to be the result of an accumulation of genetic changes involving loss of tumor suppressor genes and activation of proto-oncogenes[29,30]. Various genetic aberrations are present in about half of ovarian cancer, with mutation of *p53* gene being one of the most frequently described[29,30]. As for polymorphism of codon 72 in exon 4 of *p53*, the frequency of breast, lung, prostate, and cervical carcinomas has been



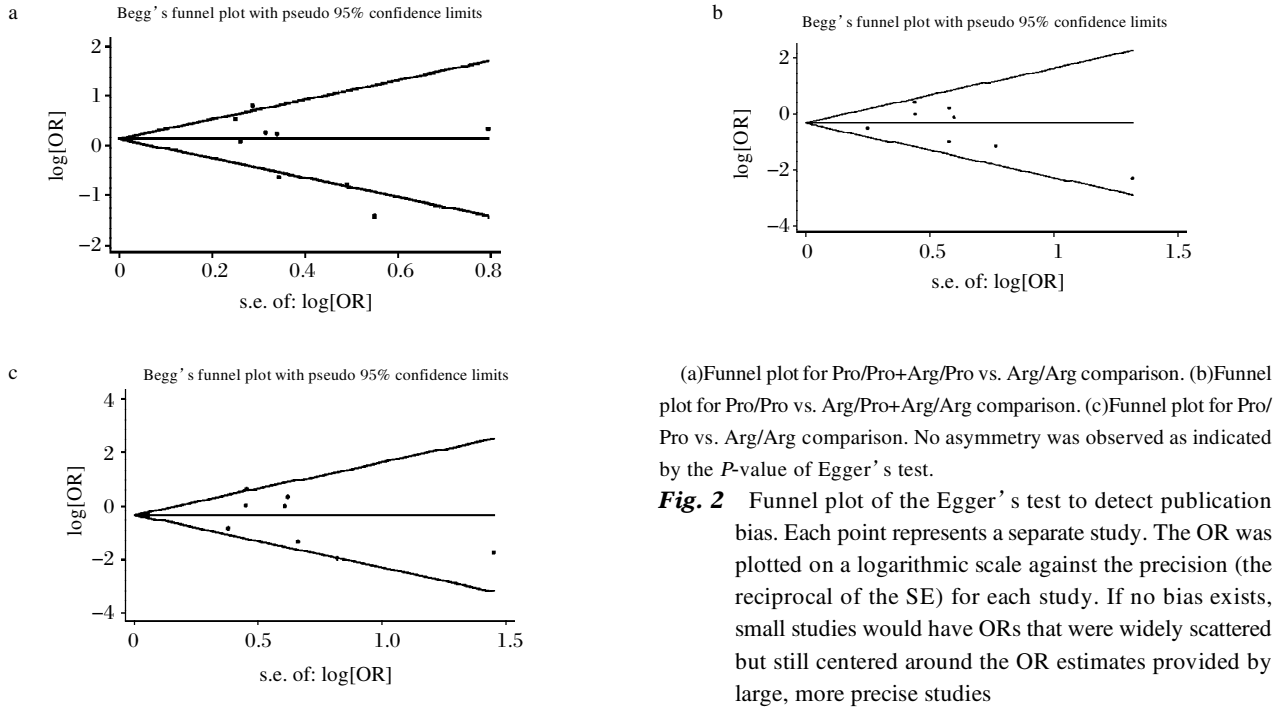
◆, pooled OR and its 95% CI. (a)Homozygote model. (b)Dominant model. (c)Recessive model.

Fig. 1 ORs(log scale) of ovarian cancer associated with the *p53* Arg72Pro polymorphism. For each comparison, the estimate of OR and its 95% CI was plotted with a box and a horizontal line.

Table 2 **Meta-analysis of *p53* codon 72 polymorphism and the risk of ovarian cancer**

Stratification of ovarian cancer	No. of studies	OR,95% CI(Pro/Pro+ Arg/Pro vs. Arg/Arg)	*P* for heterogeneity	OR, 95% CI (Pro/Pro vs. Arg/Pro+Arg/Arg)	*P* for heterogeneity	OR, 95% CI(Pro/ Pro vs. Arg/Arg)	*P* for heterogeneity
Total	9	1.00 (0.66, 1.51)	0.001	0.70 (0.51, 0.95)	0.25	0.66 (0.36, 1.22)	0.03
European	6	1.20 (0.74, 1.95)	0.01	0.81 (0.50, 1.31)	0.22	0.78 (0.34, 1.79)	0.07
Asian	2	0.79 (0.29, 2.15)	0.08	0.66 (0.30, 1.43)	0.15	0.60 (0.12, 3.18)	0.06
African	1	0.53 (0.27, 1.04)	NA	0.61 (0.37, 0.99)	NA	0.43 (0.20, 0.89)	NA

NA: Not applicable.



(a)Funnel plot for Pro/Pro+Arg/Pro vs. Arg/Arg comparison. (b)Funnel plot for Pro/Pro vs. Arg/Pro+Arg/Arg comparison. (c)Funnel plot for Pro/Pro vs. Arg/Arg comparison. No asymmetry was observed as indicated by the *P*-value of Egger's test.

Fig. 2 Funnel plot of the Egger's test to detect publication bias. Each point represents a separate study. The OR was plotted on a logarithmic scale against the precision (the reciprocal of the SE) for each study. If no bias exists, small studies would have ORs that were widely scattered but still centered around the OR estimates provided by large, more precise studies

suggested to be related to the presence of Arg/Arg, Arg/Pro, or Pro/Pro genotype[5,31-33]. A number of studies have reported the role of *p53* codon 72 polymorphism in ovarian cancer risk. However, these results remain conflicting, probably because of the limitations in these studies. In our meta-analysis, we observed that most of the selected studies contained a small sample size and therefore did not have adequate power to detect the possible risk for *p53* codon 72 polymorphism. In addition, few studies adopted a second method to verify their genotyping results, thus the misclassification may influence the results. Moreover, selection bias may also affect the relation between this polymorphism and ovarian cancer because one study in our database was inconsistent with the Hardy-Weinberg equilibrium[28].

Codon 72 of the *p53* tumor suppressor gene is a well-known "polymorphic" site whereby the majority of Caucasian individuals express an arginine-containing p53 protein, while African-Americans express primarily a proline-containing p53[34]. Many studies have shown significant difference in the biochemical properties of the p53 protein depending on the particular polymorphic form[34-36]. Matlasewski *et al*[36]. found different effects of the 2 cDNAs inoculated into nude mice via transfected NIH-3T3 cell. When *p53*-Arg was used, seven of eight mice developed tumors, compared with five of eight when *p53*-Pro was used. In the latter case, the tumors were noted to be fewer, smaller and slower growing than those in *p53*-Arg transformed cells. Ovarian cancer is about 1.7 times more prevalent in Caucasians than in African-American. Interestingly, the *p53*-Arg allele is 1.7 times more prevalent in Caucasians than in African-American[34]. This indicates that the Arg allele is a risk factor for ovarian cancer. In our results, the Arg allele was also a risk allele when compared with the Pro allele.

Moreover, a lot of studies also reported the ovarian cancer was highly associated with HPV-infection. Wu *et al*.[6] found that 36% of the epithelial ovarian tumors were HPV-16 E6 positive, while only 6.7% of the normal ovarian tissue were HPV-16 E6 positive in their study, and HPV-16 infection was significantly high in cancer tissue than that in controls with an OR of 16.7(95%CI, 3.2-71.4, $P<0.01$). Storey *et al*.[5] reported that patients with HPV-associated tumors revealed a striking overexpression of homozygous arginine -72 *p53* com-

pared with the normal population and individuals homozygous for arginine -72 were about 7 times more susceptible to HPV-associated tumorigenesis than to heterozygote carriers. The mechanism is that E6 protein derived from HPV binds and induces the degradation of the cellular tumor-suppressor protein p53, and they found Arg form of *p53* was significantly more susceptible to E6-mediated degradation than Pro form. Therefore, the Arg-encoding allele represents a significant risk factor in the development of HPV-associated cancers. In addition, recent studies with HPV-induced cervical cancer showed that more cases have the homozygous Arg allele[37,38]. The summary OR from our meta-analysis revealed that a significantly decreased risk was associated with the variant genotype Pro/Pro, compared with Arg/Pro+Arg/Arg genotypes. Similar results were also found among Africans.

Conversely, others found that individuals with *p53* Pro/Pro genotypes have been shown to be more likely to develop lung cancer, and to have a slightly worse outcome[39-41]. The Pro allele has also been found in increased frequency in breast cancer and gastric cancer patients[42-45]. Dumont *et al*[46]. observed that Arg allele induced apoptosis markedly better than did the Pro allele. In the recent meta-analysis concerning the association between *p53* codon 72 polymorphism and gastric cancer in China conducted by Zhou *et al.*[45], they observed a significantly lower frequency of Arg/Arg in gastric cancer patients compared with non-cancer patients among Asians, indicating that the Pro allele was a risk factor. These studies suggested that *p53* codon 72 polymorphism may serve as a risk factor for different types of cancers and the discrepancy may be due to the differences of tumor characteristics, sample size, and ethnic variation of genotype frequency of *p53* codon 72 in different geographic regions.

Significant between-study heterogeneity of our meta-analysis was observed in dominant model and homozygous model, but not in the recessive model. A very important factor contributing to the heterogeneity is whether the genotype frequency was in Hardy-Weinberg equilibrium. Observed departures from the equilibrium suggested possible issues with the control group, indicating that the control group can not represent the general population very well. Ethnic admixture can also lead to departures from Hardy-Weinberg equilibrium, if the polymorphic site varies in genotype by race[47,48]. Moreover, there are some limitations in our meta-analysis. Firstly, the unpublished studies were not included in this analysis; therefore publication bias was inevitable, although we did not find it in Begg's funnel plot of the Egger's test. Secondly, we also could not get information from most studies on the presence or absence of HPV infection, which is an important factor for ovarian cancer. Finally, our results were based on unadjusted estimates, while a more precise analysis should be conducted if individual data were available, which would allow for adjusted estimation by age, diet, and so on[8].

In conclusion, our meta-analysis suggested that *p53* codon 72 polymorphism may contribute to the etiology of ovarian cancer. The difference in genotype distribution may be influenced by ethnicity. More and larger studies should be performed to clarify the possible role of *p53* codon 72 polymorphism in ovarian cancer.

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