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Meta-analysis of an association of codon 72 polymorphisms of the p53 gene with increased endometrial cancer risk

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ABSTRACT. Polymorphisms of the p53 gene have been associated with susceptibility to endometrial cancer. However, whether there is a specific association is still controversial. We investigated a possible association between p53 codon 72 polymorphism and endometrial cancer risk by conducting a meta-analysis. Publications addressing this association were selected from the Pubmed, Embase and CBM databases (up to January 2011). Data were extracted from the studies by two independent reviewers. The meta-analysis was performed using RevMan 5.0.25 and STATA 9.2 softwares. The odds ratio (OR) with 95% confidence intervals (CI) was calculated. Then, 10 case-control studies were retrieved, with a total of 917 endometrial cancer patients and 1680 healthy controls. Meta-analysis results showed that the Pro allele and Pro carrier (Arg/Pro + Pro/Pro) of p53 codon 72 polymorphism were significantly related with endometrial cancer risk (OR = 1.25, 95%CI = 1.10-1.41, P = 0.0005; OR = 1.34, 95%CI = 1.12-1.59, P = 0.001, respectively). In the subgroup analysis, based on ethnicity, studies were divided into Asian and Caucasian populations; the Pro allele and Pro carrier (Arg/Pro + Pro/Pro) of p53 codon 72

polymorphism were significantly related with endometrial cancer risk in Asian populations (OR = 1.41, 95%CI = 1.19-1.66, P < 0.0001; OR = 1.66, 95%CI = 1.30-2.13, P < 0.0001, respectively), but not in Caucasian populations (both P > 0.05). We concluded that the Pro allele (Arg/Pro + Pro/Pro) of p53 codon 72 polymorphism is a potential risk factor for endometrial cancer.

Key words: Endometrial cancer; Polymorphism; Susceptibility; Meta-analysis; p53 gene

INTRODUCTION

Endometrial cancer (EC) is one of the most common gynecological malignancies, and its prevalence has increased during the last 10 years (Pecorelli et al., 2003). In 2010, there were 43,470 newly diagnosed cases and 7950 deaths in the United States (Jemal et al., 2010). EC has predominantly been considered a genetic disease, characterized by sequential accumulation of genetic alterations (Lax, 2004; Soliman et al., 2005). Endometrial carcinogenesis is a multi-factorial interaction between environmental triggers and genetic susceptibility. Mutagens in the living environment can create DNA adducts and strand breaks, causing genomic instability. Loss of genomic stability and the resulting gene alterations appear to be a crucial molecular and pathogenic step that occurs early in the endometrial carcinogenesis process. Recent studies have revealed that genetic variants in genes controlling carcinogen metabolism, DNA repair and cell proliferation or apoptosis may be important in determining individual susceptibility to the occurrence and progression of EC (Zucchetto et al., 2009; Yang et al., 2010). Therefore, the identification of genetic factors may be helpful in better understanding the mechanisms underlying endometrial carcinogenesis and improving cancer detection and molecular staging.

The p53 tumor suppressor gene, which is located on chromosome 17p13, is one of the most commonly mutated genes in all types of human cancer (Harris and Hollstein, 1993). The p53 gene, which induces cell cycle arrest, apoptosis or DNA damage repair, negatively regulates the cell cycle and requires loss of function mutations for tumor formation (Berchuck et al., 1994). There are several polymorphisms in the p53 gene, and codon 72 polymorphism (rs1042522) in exon 4 is the most common candidate (Whibley et al., 2009). This polymorphism changes amino acid residue 72 from arginine to proline (Arg→Pro), which can be easily detected by polymerase chain reaction (PCR) (Grochola et al., 2010). These two alleles of p53 codon 72 polymorphism exhibit different oncogenic properties, but contradictory outcomes have been reported in various types of cancers (Fan et al., 2000; Koushik et al., 2004).

Over the past decade, considerable epidemiological studies have focused on the association between p53 codon 72 polymorphism and EC susceptibility. However, the specific association is still controversial due to different ethnicities, tumor types or differentiation. For these reasons, we conducted this meta-analysis to derive a more precise estimation of these associations by conducting pooled analysis from all eligible case-control studies published to date. To the best of our knowledge, this is the first meta-analysis that has investigated the association between p53 codon 72 polymorphism and EC risk.

MATERIAL AND METHODS

Literature search strategy

We performed an electronic search of the Pubmed, Embase and CBM databases to retrieve papers linking p53 codon 72 polymorphism and EC risk available by January 2011 without language restrictions, using the following query: ["p53 Genes" or "TP53 Genes" or "Genes, p53"] and ["Polymorphism, Single Nucleotide" or "SNPs" or "Polymorphism, Genetic"] and ["Endometrial Cancers" or "Endometrial Cancer" or "Endometrial Neoplasms"]. The reference lists of major textbooks, reviews, and included articles were identified through manual searches to find other potentially eligible studies. If more than one article was published by the same author using the same case series, we selected the research with the largest sample size. When pertinent data were not included, or when data that were presented were unclear, the authors were directly contacted.

Inclusion and exclusion criteria

To be eligible for inclusion in this meta-analysis, the following criteria were established: i) case-control studies that addressed EC cases and healthy controls; ii) studies that evaluated the association between p53 codon 72 polymorphism and EC risk; iii) studies that included sufficient genotype data for extraction. Studies were excluded when: i) not case-control studies that evaluated the association between p53 codon 72 polymorphism and EC risk; ii) case reports, letters, reviews, meta-analysis and editorial articles; iii) studies that were based on incomplete raw data and those with no usable data reported; iv) studies that included duplicate data; v) family-based design was used; vi) and healthy controls were not in HWE.

Data extraction

Using a standardized form, data from published studies were extracted independently by two reviewers (Gu Y and Zhou X) to populate the necessary information. The following information was extracted from each of the articles included: first author, year of publication, country, language, ethnicity, study design, diagnostic criteria, source of cases and controls, number of cases and controls, mean age, sample, detection methods, polymorphism genotype frequency and evidence of Hardy-Weinberg equilibrium (HWE) in controls. In case of conflicting evaluations, an agreement was reached following a discussion with a third reviewer (Zhang SL).

Quality assessment of studies included

The quality of papers was also independently assessed by two reviewers (Gu Y and Zhou X) based on the STROBE quality scoring system (Vandenbroucke et al., 2007). Thirty items relevant to quality appraisal were used for assessment in this meta-analysis. Quality scores ranged from 0 to 30. We defined 10, 20 and 30 scores as low, moderate and high grade, respectively. Any discrepancies between the two reviewers were resolved by discussion and consultation with a third reviewer (Zhang SL).

Statistical analysis

Meta-analysis was performed using RevMan 5.0.25 (provided by The Cochrane Collaboration) and STATA package version 9.2 (Stata Corporation, College Station, USA). The strength of the associations between p53 codon 72 polymorphism and EC risk were estimated by the odds ratio (OR) and 95% confidence interval (95%CI). Between-study heterogeneities were estimated using Cochran's *Q* test (Higgins and Thompson, 2002; Zintzaras and Ioannidis, 2005). We also quantified the effect of heterogeneity by the I^2 test. I^2 ranges between 0 and 100% and represents the proportion of inter-study variability that can be attributed to heterogeneity rather than chance. I^2 values of 25, 50 and 75% were defined as low, moderate and high estimates, respectively. When a significant Q test ($P < 0.10$ or $I^2 > 50\%$) indicated heterogeneity across studies, the random effects model was used for meta-analysis; otherwise, the fixed effects model was used (Viechtbauer, 2007). Before estimating the effect of associations between p53 codon 72 polymorphism and EC risk, we tested whether genotype frequencies of controls were in HWE using the χ^2 test. Subgroup analysis based on ethnicity was used to explore and to explain the diversity among the results of different studies. Sensitivity analysis was mainly performed by sequential omission of individual studies or non-HWE studies. Publication bias was investigated by the Begg funnel plot, and funnel plot asymmetry was assessed by the Egger linear regression test (Peters et al., 2006), statistical significance was considered when the P value of the Egger test was ≤0.10. All P values were two-sided. To ensure the reliability and the accuracy of the results, two reviewers (Gu Y and Zhou X) populated the data in the statistics programs independently and got the same results.

RESULTS

Studies included in the meta-analysis

The search strategy retrieved 31 potentially relevant studies. According to the inclusion criteria, only 10 case-control studies (Esteller et al., 1997; Peller et al., 1999; Agorastos et al., 2004; Roh et al., 2004; Niwa et al., 2005; Ueda et al., 2006; Ashton et al., 2009; Nunobiki et al., 2009; Zubor et al., 2009; Ghasemi et al., 2010) with full-text were included in this meta-analysis and 21 studies were excluded. The flow chart for the study selection is summarized in Figure 1. These 10 case-control studies included a total of 917 EC cases and 1680 healthy controls. All studies included were case-control studies that evaluated the association between p53 codon 72 polymorphism and EC risk. The publishing year of the included studies ranged from 1997 to 2010. All included articles were written in English. The source of controls was mainly based on healthy population. Diverse genotyping methods were mainly used polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) and -direct sequencing (PCR-DS). The HWE test was performed on all included studies, all of them were shown to be in HWE ($P > 0.05$) except one by Ueda et al. (2006). The baseline characteristics and methodological quality of all included studies are summarized in Table 1. The genotype distribution and frequency are summarized in Table 2.

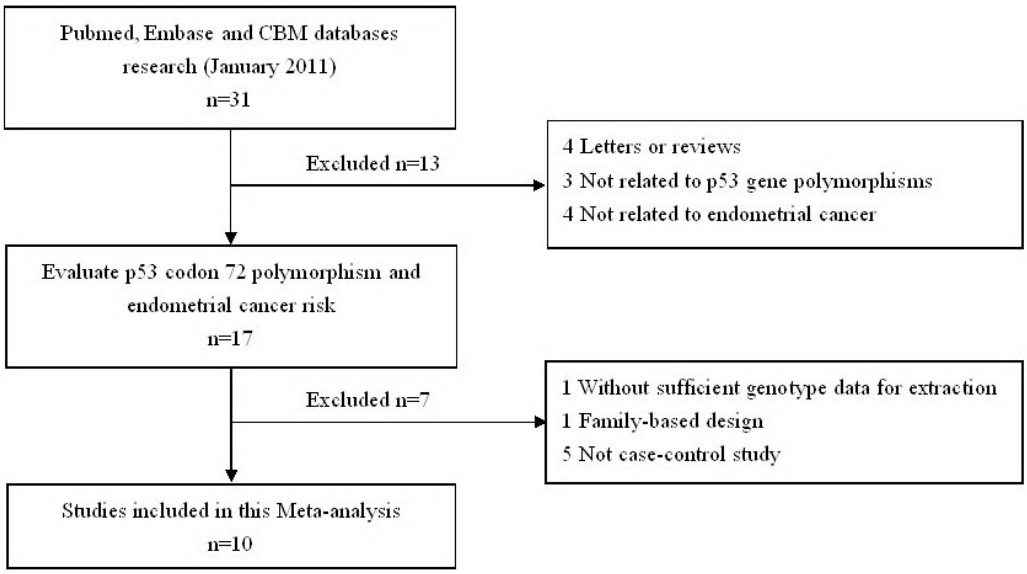

Figure 1. Flow chart showing study selection procedure.

Table 1. Baseline characteristics of studies included in meta-analysis.

Reference	Country	Ethnicity	Sample	Number of subjects		Age (range)		Diagnosis	Detection	Quality
				Cases	Controls	Cases	Controls	method	method	scores
Esteller et al., 1997	Spain	Caucasian	Endometrial tissue	80	60	45-82	44-76	Histopathology	PCR-RFLP	22
Peller et al., 1999	Israel	Caucasian	Blood / Tissue	27	13	-	-	Histopathology	PCR-DS	27
Agorastos et al., 2004	Greece	Caucasian	Endometrial tissue	56	30	-	-	Histopathology	PCR-RFLP	31
Rho et al., 2004	Korea	Asian	Blood	95	285	50 ± 12	48 ± 10	Histopathology	PCR-RFLP	34
Niwa et al., 2005	Japan	Asian	Endometrial tissue	114	442	32-88	35-84	Histopathology	PCR-RFLP	32
Ueda et al., 2006	Japan	Asian	Blood	108	95	-	-	Histopathology	PCR-RFLP	33
Ashton et al., 2009	Australia	Caucasian	Blood	191	291	-	-	Histopathology	PCR-RFLP	38
Nunobiki et al., 2009	Japan	Asian	Blood	95	102	-	-	Histopathology	PCR-RFLP	40
Zubor et al., 2009	Slovakia	Caucasian	Blood	121	330	35-86	18-80	Histopathology	PCR-DS	36
Ghasemi et al., 2010	Iran	Asian	Blood	30	32	-	-	Histopathology	PCR-RFLP	33

PCR = polymerase chain reaction; RFLP = restriction fragment length polymorphism; DS = direct sequencing.

Table 2. The genotype distribution and frequency of all included studies.

Reference	Case							Control							HWE test	
	Total	Arg/Arg	Arg/Pro	Pro/Pro	Arg	Pro	RF	Total	Arg/Arg	Arg/Pro	Pro/Pro	Arg	Pro	RF	χ^2	P
Esteller et al., 1997	80	36	36	8	108	288	0.727	60	29	23	8	81	39	0.325	0.957	0.328
Peller et al., 1999	27	17	7	3	41	21	0.339	13	8	5	0	21	5	0.192	0.737	0.391
Agorastos et al., 2004	56	24	28	4	76	112	0.596	30	6	19	5	31	29	0.483	2.156	0.142
Roh et al., 2004	95	29	66	0	124	66	0.347	0.347	166	119	0	451	119	0.209	19.842	0.209
Niwa et al., 2005	114	53	37	66	143	2442	0.945	442	178	210	54	566	318	0.360	0.436	0.509
Ueda et al., 2006	108	55	45	8	155	360	0.699	95	34	54	7	122	68	0.358	5.324	0.021
Ashton et al., 2009	191	101	75	15	277	1125	0.802	290	166	107	17	439	141	0.243	0.002	0.965
Nunobiki et al., 2009	102	44	48	10	136	480	0.779	95	34	54	7	122	68	0.358	5.324	0.021
Zubor et al., 2009	121	69	44	8	182	352	0.659	330	200	113	17	513	147	0.223	0.040	0.841
Ghasemi et al., 2010	30	13	15	2	41	30	0.423	32	7	21	4	35	29	0.453	3.362	0.067

HWE = Hardy-Weinberg equilibrium; RF = risk frequency.

Main results, subgroup and sensitivity analysis

Meta-analysis results showed that the Pro allele and Pro carrier (Arg/Pro + Pro/Pro) of p53 codon 72 polymorphism were significantly related to EC risk (OR = 1.25, 95%CI = 1.10-1.41, P = 0.0005; OR = 1.34, 95%CI = 1.12-1.59, P = 0.001; respectively). However, no association was found between Arg carrier (Arg/Arg + Arg/Pro) and EC risk (OR = 0.78, 95%CI = 0.58-1.07, P = 0.12) (Figure 2).

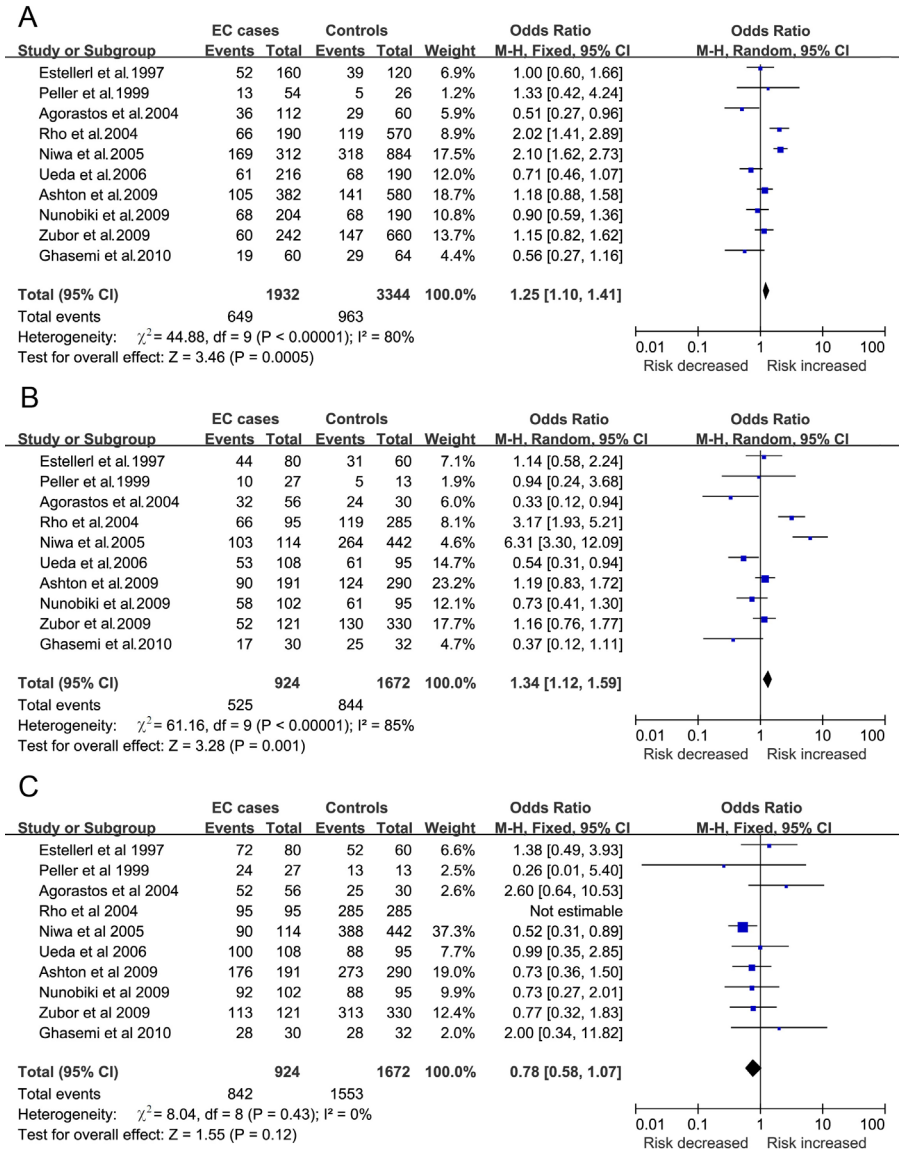

Figure 2. Forest plot showed the association between p53 codon 72 polymorphism and endometrial cancer risk: **A.** Pro allele versus Arg allele, **B.** Pro carrier versus Arg/Arg, **C.** Arg carrier versus Pro/Pro.

In the subgroup analysis based on ethnicity, included studies were divided into Caucasian and Asian populations. Subgroup analysis results showed that the Pro allele and Pro carrier (Arg/Pro + Pro/Pro) of p53 codon 72 polymorphism were significantly related to EC risk in Asian populations (OR = 1.41, 95%CI = 1.19-1.66, P < 0.0001; OR = 1.66, 95%CI = 1.30-2.13, P < 0.0001; respectively). However, no association was also found between Arg carrier (Arg/Arg + Arg/Pro) and EC risk in Asian populations (OR = 0.67, 95%CI = 0.44-1.03, P = 0.07). Unfortunately, the Pro allele, Pro carrier (Arg/Pro + Pro/Pro) and Arg carrier (Arg/Arg + Arg/Pro) showed no association with EC risk in Caucasian populations (OR = 1.06, 95%CI = 0.88-1.29, P = 0.54; OR = 1.08, 95%CI = 0.84-1.37, P = 0.56; OR = 0.93, 95%CI = 0.59-1.46, P = 0.74; respectively). In subgroup analysis by tumor differentiation, the pooled results showed that there was no significant difference in genotype distribution between grade 1 and grade 2/3 patients (Pro allele: OR = 0.90, 95%CI = 0.58-1.40, P = 0.64; Pro carrier: OR = 0.51, 95%CI = 0.17-1.49, P = 0.22; Arg carrier: OR = 1.70, 95%CI = 0.65-1.76, P = 0.80). Furthermore, in subgroup analysis by tumor type, no association was also found between type I and type II patients (Pro allele: OR = 059, 95%CI = 0.35-0.99, P = 0.05; Pro carrier: OR = 0.80, 95%CI = 0.33-1.93, P = 0.61; Arg carrier: OR = 1.11, 95%CI = 0.57-1.48, P = 0.51).

Sensitivity analysis was performed by sequential omission of individual studies. The significance of pooled OR in all-individuals analysis and subgroup analysis was not substantially influenced by omitting any single study. Furthermore, we also performed a sensitivity analysis by omission of one non-HWE study (Ueda et al., 2006). There was also no obvious influence on all-individuals analysis and subgroup analysis.

Publication bias

Publication bias of the literature was assessed by the Begg funnel plot and the Egger linear regression test. The Egger linear regression test was used to measure the asymmetry of the funnel plot. All funnel plots of the included studies appeared to be symmetrical (Figure 3). The Egger test also showed that there was no statistical significance for all evaluations of publication bias. Findings of the Egger publication bias test are shown in Table 3.

DISCUSSION

There is growing evidence that genetic variation plays an important role in the determination of individual susceptibility to complex disease traits. Functional polymorphisms, which affect the regulation of gene expression, can contribute to differences between individuals in susceptibility to various cancers (Ye, 2000). Several studies have shown that p53 gene polymorphisms are associated with the production of the p53 protein in endometrial carcinogenesis (Risinger et al., 1992; Sherman, 2000). Expression of p53 protein was associated with both poor prognosis and metastasis in EC (Ozalp et al., 2003). Recently, a number of molecular epidemiological studies have been conducted to examine the association between p53 codon 72 polymorphism and EC risk. Roh et al. (2004) demonstrated that there is a significant association between p53 gene polymorphisms and EC risk in Korean women. Nunobiki et al. (2009) also confirmed that the Pro/Pro genotype of p53 codon 72 polymorphism may increase the risk of EC in the Japanese population. Ashton et al. (2009) showed that p53 gene

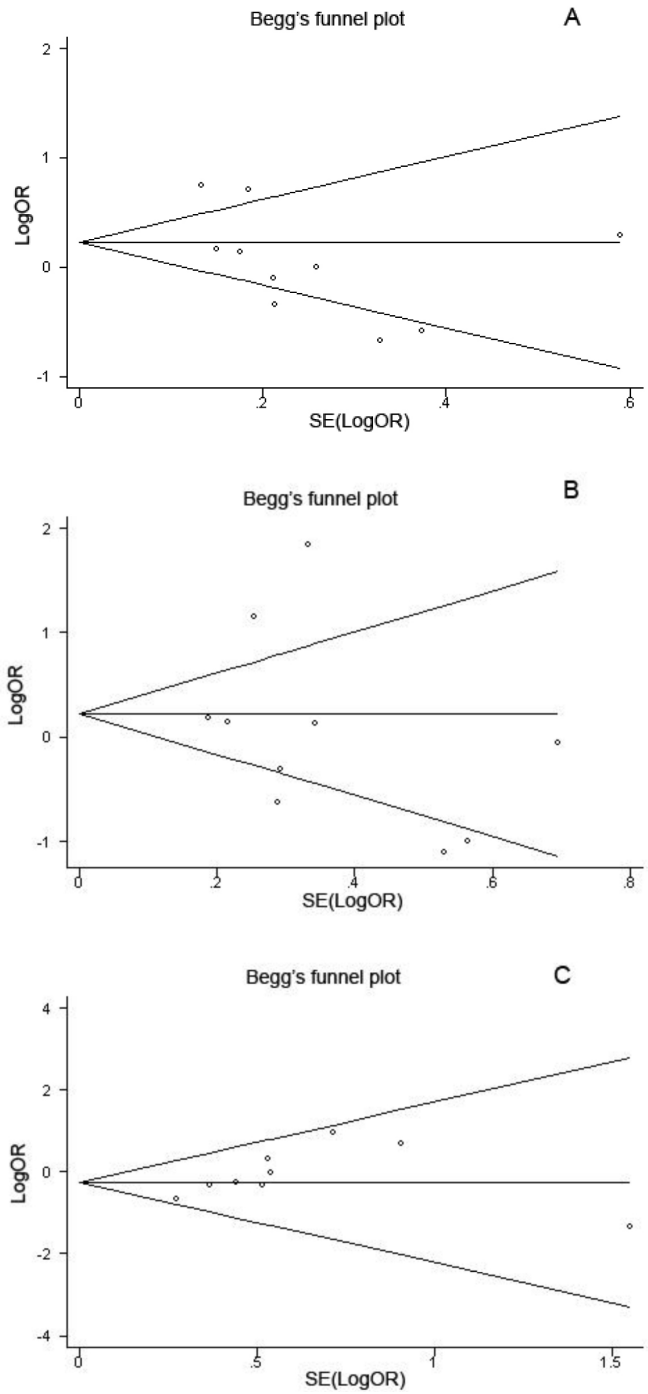

Figure 3. Begg's funnel plot of publication bias for the association between p53 codon 72 polymorphism and endometrial cancer risk: **A.** Pro allele versus Arg allele, **B.** Pro carrier versus Arg/Arg, **C.** Arg carrier versus Pro/Pro.

Table 3. Evaluation of publication bias by Egger's linear regression test.

Comparison	Coefficient	SE	*t*	P > |t|	95%CI
Pro allele versus Arg allele	-3.60	1.71	-2.10	0.07	[-7.56, 0.35]
Pro carrier versus Arg/Arg	-1.72	2.40	-0.72	0.49	[-7.25, 3.82]
Arg carrier versus Pro/Pro	1.31	0.75	1.75	0.12	[-0.46, 3.08]

SE = standard error; 95%CI = 95% confidence interval.

polymorphisms appear to be related to a higher grade of EC. However, Zubor et al. did not demonstrate any significant association between p53 codon 72 polymorphism and the risk of EC in Caucasian women (Zubor et al., 2009). Therefore, the possible influence of p53 codon 72 polymorphism on p53 production as well as tumor development and progression in EC is still controversial. It was necessary to investigate the influence of p53 codon 72 polymorphism on susceptibility to EC by means of meta-analysis. Meta-analysis is a method for gathering and making sense out of multiple research findings (Ng et al., 2006). It can help to obtain a more precise estimate of relationships between research themes (Ioannidis et al., 2001; Munafo, 2004). The aim of this study was to investigate the association between p53 codon 72 polymorphism and EC risk by conducting a meta-analysis of all eligible case-control studies published to date.

Our meta-analysis quantitatively assessed the association between p53 codon 72 polymorphism and EC risk. Finally, ten case-control studies were included and comprised a total of 917 EC cases and 1680 healthy controls. Meta-analysis results showed that the Pro allele and Pro carrier (Arg/Pro + Pro/Pro) of p53 codon 72 polymorphism were significantly related to EC risk, suggested that the Pro allele and Pro carrier (Arg/Pro + Pro/Pro) may be risk factors for EC. In addition, we performed subgroup analysis based on ethnicity. Subgroup analysis results showed that the Pro allele and Pro carrier (Arg/Pro + Pro/Pro) may be risk factors for EC in Asian populations, while no association was found between p53 codon 72 polymorphism and EC risk in Caucasian populations, suggesting a possible role of ethnic differences in genetic backgrounds and the environment they lived in. However, no association was found between p53 codon 72 polymorphism and EC risk in the subgroup analysis by tumor differentiation and tumor type. Such evidence on the functionality of p53 codon 72 polymorphism may lead to a better understanding of EC biology and behavior. It was also a strong rationale for the development of novel anti-cancer drugs interfering with p53 protein production in endometrial carcinogenesis.

Similar to other meta-analysis, several limitations of this study should be addressed. First of all, meta-analysis is a type of retrospective study and is limited by the qualities of primary studies. Second, although perfect searching strategy was designed before initiating this study, and even though computerized and manual searches were performed simultaneously, there was a possibility that suitable studies were not included. Third, we were unable to address all the sources of heterogeneity existing among studies for most polymorphisms, although we could make subgroup stratifications analysis by ethnicity, tumor differentiation or tumor type for the limited number of published studies. In addition, although all cases and controls of each study were well defined with similar inclusion criteria, there might have been potential factors that were not taken into account, which might have influenced our results. Most important of all, our meta-analysis only demonstrated that the Pro allele and Pro carrier (Arg/Pro + Pro/Pro) were associated with EC susceptibility among Asian populations, but not

among Caucasian populations, which might have been due to genetic background or environmental differences.

In conclusion, our meta-analysis of ten case-control studies demonstrated that the the Pro allele and Pro carrier (Arg/Pro + Pro/Pro) may be risk factors for EC, especially in Asian populations. As few studies are available in this field and current evidence remains limited, this conclusion should be further confirmed by large case-control studies with an adequate methodological quality and properly controlling for possible confounds.

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