RESEARCH ARTICLE

Association Between p53 codon 72 Polymorphism and Cervical Cancer Risk Among Asians: a Huge Review and Meta-analysis

Xin Zhou*, Yang Gu, Shu-Lan Zhang

Abstract

Objective: The aim of this Human Genome Epidemiology (HuGE) review and meta-analysis was to derive a more precise estimation of the association between p53 codon 72 polymorphism (Arg72Pro, rs1042522 G>C) and cervical cancer risk among Asians. Methods: A literature search of Pubmed, Embase, Web of Science and CBM databases from inception through June 2012 was conducted. The meta-analysis was performed using STATA 12.0 software. Crude odds ratios (ORs) with 95% confidence intervals (CIs) were used to assess the strength of any association. Twenty-eight case-control studies were included with a total of 3,580 cervical cancer cases and 3,827 healthy controls. When all the eligible studies were pooled into the meta-analysis, the results showed that the Pro/Pro genotype was associated with increased risk of cervical cancer under the heterozygous model (Pro/Pro vs. Arg/Pro: OR = 1.25, 95%CI: 1.02-1.53, P= 0.005). However, no statistically significant associations were found under four other genetic models (Pro vs. Arg: OR = 0.97, 95%CI: 0.85-1.10, P= 0.624; Pro/Pro + Arg/Pro vs. Arg/Arg: OR = 0.84, 95%CI: 0.70-1.01, P= 0.058; Pro/Pro vs. Arg/Arg + Arg/Pro: OR = 1.13, 95%CI: 0.92-1.39, P= 0.242; Pro/Pro vs. Arg/Arg: OR = 0.97, 95%CI: 0.76-1.22, P= 0.765; respectively). In the subgroup analysis based on country, the Pro/Pro genotype and Pro carrier showed significant associations with increased risk of cervical cancer among Indian populations, but not among Chinese, Japanese and Korean populations. Conclusion: Results from the current meta-analysis suggests that p53 codon 72 polymorphism might be associated with increased risk of cervical cancer, especially among Indians.

Keywords: Cervical cancer - p53 gene - polymorphism - Asian - susceptibility - meta-analysis

Asian Pacific J Cancer Prev, **13 (10)**, 4909-4914

Introduction

Cervical cancer 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 7,950 deaths in the United States (Jemal et al., 2010). Cervical cancer has predominantly been considered a genetic disease, characterized by sequential accumulation of genetic alterations (Lax, 2004; Soliman et al., 2005). Cervical 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 cervical 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 cervical cancer (Zucchetto et al., 2009; Yang et al., 2010). Therefore, the identification of genetic factors may be helpful in better understanding the mechanisms underlying cervical 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 single nucleotide polymorphisms (SNPs) in the p53 gene, and codon 72 polymorphism (Arg72Pro, rs1042522 G>C) 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 cervical cancer risk. However, the specific association is still controversial due to different ethnicities, tumor types or differentiation. For these

*Department of Obstetrics and Gynecology, Shengjing Hospital of China Medical University, Shenyang, China *For correspondence: cmu_zx@126.com*

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 cervical cancer risk among Asians.

Materials and Methods

Literature search strategy

Relevant papers published before June 1th, 2012 were identified through a search of Pubmed, Embase, Web of Science and CBM databases using the following terms: ("genetic polymorphism" or "polymorphism" or "SNP" or "gene mutation" or "genetic variants") and ("cervical neoplasms" or "cancer of cervical" or "cervical cancer" or "cervical tumors" or "cervical carcinogenesis") and ("p53 genes" or "TP53 genes" or "genes, p53"). The references of the eligible articles or textbooks were also reviewed to check through manual searches to find other potentially studies. Any disagreement was resolved by discussion between the authors.

Inclusion and exclusion criteria

To be eligible for inclusion in this meta-analysis, the following criteria were established: (i) case-control studies that addressed cervical cancer cases and healthy controls; (ii) studies that evaluated the association between p53 Arg72Pro polymorphism and cervical cancer risk among Asians; (iii) studies that included sufficient genotype data for extraction. Studies were excluded when: (i) not case-control studies that evaluated the association between p53 Arg72Pro polymorphism and cervical cancer risk among Asians; (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 Hardy-Weinberg equilibrium (HWE).

Data extraction

Using a standardized form, data from published studies were extracted independently by two authors to populate the necessary information. For each study, the following characteristics were collected: the first author, year of publication, country, language, study design, numbers of subjects, source of cases and controls, pathological type, detecting sample, genotype method, allele and genotype frequencies, and evidence of HWE in controls. In case of conflicting evaluations, an agreement was reached following a discussion between the authors.

Statistical analysis

The strength of the association between p53 codon 72 polymorphism and cervical cancer risk was measured by ORs with 95%CIs under five genetic models, including allele model (Pro vs. Arg), dominant model (Pro/Pro + Arg/Pro vs. Arg/Arg), recessive model (Pro/Pro vs. Arg/Arg + Arg/Pro), homozygous model (Pro/Pro vs. Arg/Arg), and heterozygous model (Pro/Pro vs. Arg/Pro). The statistical significance of the pooled ORs was examined by Z test. Between-study variations and heterogeneities were estimated using Cochran's Q-statistic, and $P < 0.05$ was considered to be manifestation of statistically significant heterogeneity (Higgins and Thompson, 2002). We also quantified the effect of heterogeneity by using I^2 test, which ranges from 0 to 100% and represents the proportion of inter-study variability that can be contributed to heterogeneity rather than by chance (Zintzaras and Ioannidis, 2005). When a significant Q-test ($P < 0.05$) or $I^2 > 50\%$ indicated that heterogeneity among studies existed, the random effects model (DerSimonian Laird method) was conducted for meta-analysis. Otherwise, the fixed effects model (Mantel-Haenszel method) was used. To establish the effect of heterogeneity on the conclusions of meta-analyses, we also performed subgroup analysis by country, language and HWE test. We tested whether genotype frequencies of controls were in HWE using the χ^2 test. Sensitivity was performed by omitting each study in turn to assess the stability of results. Begger's funnel plots were used to detect publication bias. In addition, Egger's linear regression test which measures funnel plot asymmetry using a natural logarithm scale of OR was used to evaluate the publication bias (Peters et al., 2006). All the P values were two-sided. All analyses were calculated using STATA Version 12.0 software (Stata Corp, College Station, TX).

Results

Studies included in the meta-analysis

According to the inclusion criteria, 28 studies (Minaguchi et al., 1998; Ngan et al., 1999; Baek et al., 2000; Kim et al., 2000; Kim et al., 2001; Yang et al., 2001; Bhattacharya et al., 2002; Kawamata et al., 2002; Nagpal et al., 2002; Saranath et al., 2002; Xi et al., 2002; Cho et al., 2003; Katiyar et al., 2003; Cho et al., 2004; Lee et al., 2004; Li et al., 2004; Wang et al., 2004; Wu et al., 2004; Yoshimitsu et al., 2004; Masatsugu et al., 2005; Mitra et

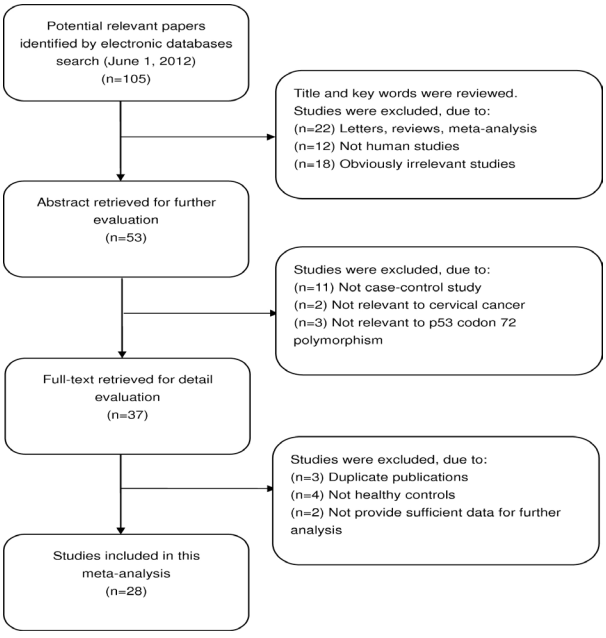

Figure 1. Flow Chart of Literature Search and Study Selection

Table 1. Meta-analysis of the Association Between p53 codon72 Polymorphism and Cervical Cancer Risk

Subgroups	Pro vs. Arg (Allele model)				Pro/Pro + Arg/Pro vs. Arg/Arg (Dominant model)				Pro/Pro vs. Arg/Arg + Arg/Pro (Recessive model)				Pro/Pro vs. Arg/Arg (Homozygous model)				Pro/Pro vs. Arg/Pro (Heterozygous model)			
	OR	95%CI	P	P_h	OR	95%CI	P	P_h	OR	95%CI	P	P_h	OR	95%CI	P	P_h	OR	95%CI	P	P_h
Country																				
China	0.93	0.75-1.15	0.518†	<0.001	0.77	0.57-1.04	0.089†	0.002	1.16	0.85-1.58	0.347†	0.028	0.95	0.67-1.36	0.790†	0.021	1.35	1.00-1.81	0.047	0.093
Korea	0.97	0.78-1.20	0.758	0.146	0.98	0.68-1.40	0.900†	0.026	0.88	0.66-1.18	0.392	0.963	0.91	0.67-1.24	0.541	0.874	0.89	0.64-1.23	0.473	0.527
Japan	1.18	0.82-1.71	0.379†	<0.001	1.11	0.78-1.58	0.566†	0.044	1.28	0.65-2.52	0.473†	<0.001	1.35	0.63-2.89	0.446†	<0.001	1.21	0.68-2.17	0.517†	0.003
India	0.86	0.63-1.15	0.303†	0.05	0.54	0.36-0.81	0.003	0.234	1.22	0.74-2.00	0.435†	0.068	0.69	0.35-1.38	0.298†	0.035	1.53	1.00-2.33	0.049	0.212
Language																				
English	1	0.88-1.13	0.978†	<0.001	0.9	0.75-1.07	0.221†	0.002	1.13	0.91-1.40	0.281†	0.001	0.99	0.78-1.25	0.923†	0.004	1.21	0.96-1.52	0.109†	0.002
Chinese	0.86	0.52-1.42	0.554†	<0.001	0.66	0.36-1.19	0.167†	0.002	1.17	0.62-2.22	0.621†	0.03	0.89	0.38-2.08	0.782†	0.002	1.53	1.01-2.32	0.043	0.719
HWE test																				
HWE	0.98	0.84-1.15	0.836†	<0.001	0.9	0.73-1.11	0.308†	<0.001	1.08	0.84-1.38	0.565†	<0.001	0.97	0.72-1.29	0.812†	<0.001	1.16	0.91-1.47	0.238†	0.003
Non-HWE	0.93	0.73-1.17	0.524	0.071	0.68	0.47-0.97	0.035	0.08	1.31	0.98-1.75	0.068	0.424	0.98	0.66-1.45	0.916	0.251	1.65	1.19-2.28	0.003	0.751
Overall	0.97	0.85-1.10	0.624†	<0.001	0.84	0.70-1.01	0.058†	<0.001	1.13	0.92-1.39	0.242†	<0.001	0.97	0.76-1.22	0.765	<0.001	1.25	1.02-1.53	0.029†	0.005

HWE, Hardy-Weinberg equilibrium; OR, odds ratios; 95%CI, 95% confidence interval; Ph, P value of heterogeneity test; †estimates for random effects model

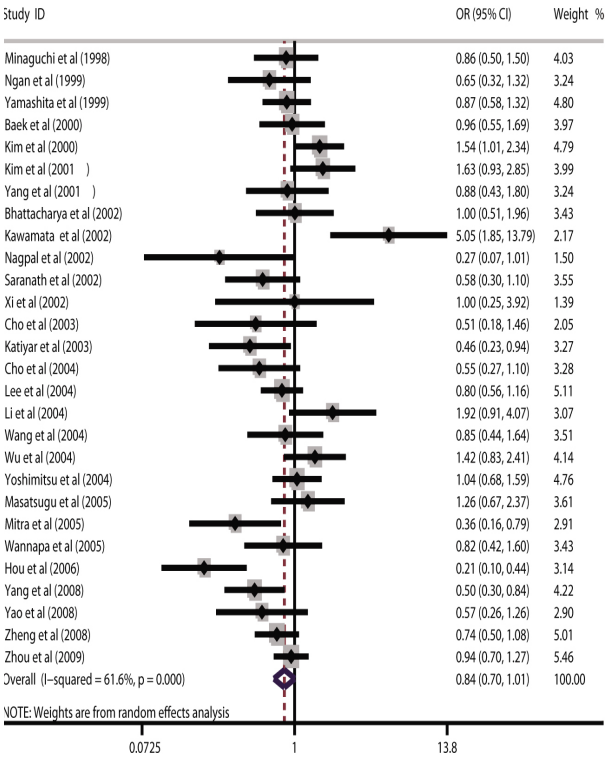

Figure 2. Forest Plot of ORs with a Random-effects Model for Associations Between p53 Codon 72 Polymorphism and Cervical Cancer Risk Among Asians Under the Dominant Model (Pro/Pro + Arg/Pro vs. Arg/Arg)

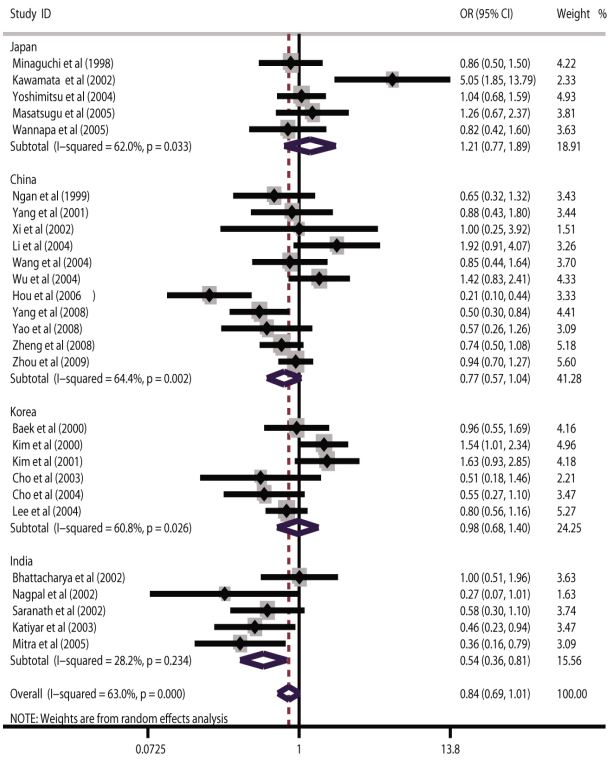

Figure 3. Subgroup Analysis by Country of ORs with a Random-effects Model for Associations Between p53 codon 72 Polymorphism and Cervical Cancer Risk Among Asians under the Dominant Model (Pro/Pro + Arg/Pro vs. Arg/Arg)

al., 2005; Wannapa et al., 2005; Hou et al 2006; Yang et al., 2008; Yao et al., 2008; Zheng et al., 2008; Zhou et al., 2009) were included and 103 were excluded in this meta-analysis. The flow chart of study selection is shown in Figure 1. The total of cervical cancer cases and healthy controls were 3,580 and 3,827 respectively in these nine case-control studies, which evaluated the relationship between p53 codon 72 polymorphism and cervical cancer risk. The publication year of involved studies ranged from 1998 to 2009. Source of controls was mainly based on healthy population. Diverse genotyping methods were mainly used polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP). HWE test was conducted on genotype distribution of the controls in all included studies. However, there were eight studies showed evidence of deviation from HWE ($P < 0.05$).

Quantitative data synthesis

A summary of the meta-analysis findings of the association between p53 codon 72 polymorphism and gastrointestinal cancer risk is provided in Table 1. The heterogeneity was significant ($P < 0.05$), so random effect models were used. The meta-analysis result showed that the Pro/Pro genotype was related to cervical cancer risk under the heterozygous model (Pro/Pro vs. Arg/Pro: OR = 1.25, 95%CI: 1.02-1.53, P = 0.005). However, no statistically significant associations were found under other four genetic models (Pro vs. Arg: OR = 0.97, 95%CI: 0.85-1.10, P= 0.624; Pro/Pro + Arg/Pro vs. Arg/Arg: OR = 0.84, 95%CI: 0.70-1.01, P= 0.058; Pro/Pro vs. Arg/Arg + Arg/Pro: OR = 1.13, 95%CI: 0.92-1.39, P = 0.242; Pro/Pro vs. Arg/Arg: OR = 0.97, 95%CI: 0.76-1.22, P = 0.765; respectively) (Figure 2).

In the subgroup analysis based on country, the results showed that the Pro/Pro and Pro carrier were significantly related to cervical cancer risk among Indians (Pro/Pro + Arg/Pro vs. Arg/Arg: OR = 0.54, 95%CI: 0.36-0.81, P = 0.003; Pro/Pro vs. Arg/Pro: OR = 1.53, 95%CI: 1.00-2.33,

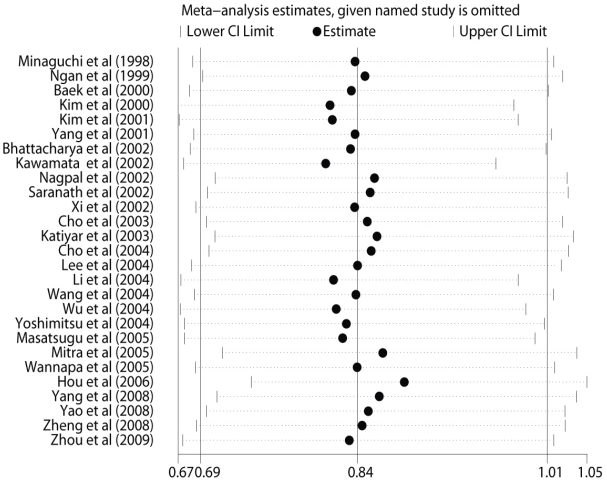

Figure 4. Sensitivity Analysis of the Summary Odds Ratio Coefficients on the Association Between p53 Codon 72 Polymorphism and Cervical Cancer Risk among Asians under the Dominant Model (Pro/Pro + Arg/Pro vs. Arg/Arg). Results were computed by omitting each study in turn. Meta-analysis random-effects estimates (exponential form) were used. The two ends of the dotted lines represent the 95% CI

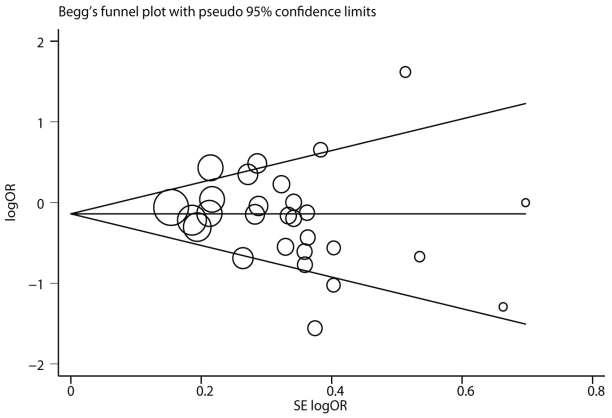

Figure 5. Begger's Funnel Plot of Publication Bias in Selection of Studies on the Association Between p53 Codon 72 Polymorphism and Cervical Cancer Risk among Asians under the Dominant Model (Pro/Pro + Arg/Pro vs. Arg/Arg). Each point represents a separate study for the indicated association. Log[OR], natural logarithm of OR. Horizontal line, mean magnitude of the effect

P = 0.049; respectively), but not among China, Japan and Korea populations (Figure 3). Further subgroup analysis by language, the pooled results showed that there was no significant association between p53 codon 72 polymorphism and cervical cancer risk. Furthermore, in subgroup analysis by HWE test, we found significant associations between p53 codon 72 polymorphism and cervical cancer risk (Table 1).

Sensitivity analysis

Sensitivity analysis was performed to assess the influence of each individual study on the pooled ORs by omission of individual studies. The analysis results suggested that no individual study significantly affected the pooled ORs under dominant model of p53 codon 72 polymorphism (Figure 4), indicating that our results are statistically robust.

Publication bias

Publication bias exists to the extent that available research results are unrepresentative of all research results. Begger's funnel plot and Egger's linear regression test were performed to assess the publication bias of included studies. The shapes of the funnel plots did not reveal any evidence of obvious asymmetry under dominant genetic model (Figure 5). Egger's test also showed that there was no significantly statistical evidence of publication bias for any of the genetic models (all $P > 0.05$).

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 SNPs in the p53 gene are associated with the production of the p53 protein in cervical carcinogenesis (Risinger et al., 1992; Sherman, 2000). Expression of the p53 protein was associated with both poor prognosis and metastasis in cervical cancer (Ozalp et al., 2003). Recently, a number of molecular epidemiological studies have been conducted to examine the association between p53 codon 72 polymorphism (Arg72Pro, rs1042522 G>C) and cervical cancer risk. Roh et al have demonstrated that there is a significant association between p53 gene polymorphisms and cervical cancer risk in Korean women (Roh et al., 2004). Other genetic studies also confirmed that the Pro/Pro genotype of p53 codon 72 polymorphism may increase the risk of cervical cancer in Japanese populations and p53 gene polymorphisms appear to be related to a higher grade of cervical cancer (Ashton et al., 2009; Nunobiki et al., 2009). However, Zubor et al did not demonstrate any significant association between p53 codon 72 polymorphism and the risk of cervical cancer in Caucasians (Zubor et al., 2009). Therefore, the possible influence of p53 codon 72 polymorphism on p53 production as well as tumor development and progression in cervical cancer is still controversial. It was necessary to investigate the influence of p53 codon 72 polymorphism on susceptibility to cervical cancer by means of meta-analysis.

Our meta-analysis quantitatively assessed the association between p53 codon 72 polymorphism and cervical cancer risk among Asians. Finally, 28 case-control studies were included and comprised a total of 3,580 cervical cancer patients and 3,827 healthy controls. Meta-analysis results showed that the Pro/Pro genotype of p53 codon 72 polymorphism was significantly related to cervical cancer risk among Asians, suggested that the Pro/Pro genotype may be a risk factor. In addition, we performed subgroup analysis based on country. The results showed that the Pro/Pro and Pro carrier may be risk factors for cervical cancer among Indians, while no associations were found among China, Japan and Korea populations, suggesting a possible role of geographical differences in genetic backgrounds and the environment they lived in. Such evidence on the functionality of p53 codon

72 polymorphism may lead to a better understanding of cervical cancer biology and behavior. It was also a strong rationale for the development of novel anti-cancer drugs interfering with p53 protein production in cervical carcinogenesis.

In interpreting our results of the current meta-analysis, some limitations need to be addressed. Firstly, the sample size is still relatively small and might not provide sufficient power to estimate the association between p53 codon 72 polymorphism and cervical cancer risk among Asians. In addition, the selection bias may exist because of the differences in the source of controls or detection samples. Besides, our meta-analysis was based on unadjusted ORs estimates because not all published presented adjusted ORs or when they did, the ORs were not adjusted by the same potential confounders, such as age, gender, geographic distribution, etc. Nevertheless, it is well acknowledged that many other factors, such as gene-gene or gene-environment interaction may affect the risk of cervical cancer. Finally, although all cases and controls of each study were well defined with similar inclusion criteria, there may be potential factors that were not taken into account that may have influenced our results. In spite of these limitations, our meta-analysis still had some advantages. To the best of our knowledge, this is the first meta-analysis of the relationship of p53 codon 72 polymorphism and cervical cancer risk among Asians. It is worthwhile to mention that we established perfectly searching strategy based on computer-assisted and manual search, which allowed the eligible studies included as possible as it can. By this means, the quality of studies included in current meta-analysis was satisfactory according to our selection criteria. Besides, explicit methods for study selection, data extraction, and data analysis were well designed before initiating. Last but not the least, there was no evidence of publication bias in this meta-analysis and the sensitivity analysis indicated that the results are statistically robust.

In conclusion, our meta-analysis indicates that p53 codon 72 polymorphism might be associated with increased risk of cervical cancer, especially among Indians. 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.

Acknowledgements

This work was supported by National Science Foundation of China, No. 81101990. All authors read and approved the final manuscript. The author(s) declare that they have no competing interests.

References

Ashton KA, Proietto A, Otton G, et al (2009). Polymorphisms in TP53 and MDM2 combined are associated with high grade endometrial cancer. *Gynecol Oncol*, **113**, 109-14.

Baek WK, Cho JW, Suh SI, et al (2000). p53 codon 72 polymorphism and risk of cervical carcinoma in Korean women. *J Korean Med Sci*, **15**, 65-7.

Berchuck A, Kohler MF, Marks JR, et al (1994). The p53 tumor suppressor gene frequently is altered in gynecologic cancers. *Am J Obstet Gynecol*, **170**, 246-52.

Bhattacharya P, Duttagupta C, Sengupta S (2002). Proline homozygosity in codon 72 of p53: a risk genotype for human papillomavirus related cervical cancer in Indian women. *Cancer Lett*, **188**, 207-11.

Cho NH, Lim SY, Kim YT, et al (2003). G2 checkpoint in uterine cervical cancer with HPV 16 E6 according to p53 polymorphism and its screening value. *Gynecol Oncol,* **90**, 15-22.

Fan R, Wu MT, Miller D, et al (2000). The p53 codon 72 polymorphism and lung cancer risk. *Cancer Epidemiol Biomarkers Prev*, **9**, 1037-42.

Grochola LF, Zeron-Medina J, Meriaux S, et al (2010). Single-nucleotide polymorphisms in the p53 signaling pathway. *Cold Spring Harb Perspect Biol*, **2**, a001032.

Harris CC, Hollstein M (1993). Clinical implications of the p53 tumor-suppressor gene. *N Engl J Med*, **329**, 1318-27.

Higgins JP, Thompson SG (2002). Quantifying heterogeneity in a meta-analysis. *Stat Med*, **21**, 1539-58.

Hou MM, Xi MR, Cao ZY, et al (2006). P53 codon 72 polymorphism in cervical cancers and its correlation with HPV16,18E6. *Sichuan Da Xue Xue Bao Yi Xue Ban*, **37**, 404-7.

Jemal A, Siegel R, Xu J, et al (2010). Cancer statistics, 2010. *CA Cancer J Clin*, **60**, 277-300.

Katiyar S, Thelma BK, Murthy NS, et al (2003). 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*, **252**, 117-24.

Kawamata Y, Mitsuhashi A, Unno Y, et al (2002). HPV 16-E6-mediated degradation of intrinsic p53 is compensated by upregulation of p53 gene expression in normal cervical keratinocytes. *Int J Oncol*, **21**, 561-7.

Kim JW, Lee CG, Park YG, et al (2000). Combined analysis of germline polymorphisms of p53, GSTM1, GSTT1, CYP1A1, and CYP2E1: relation to the incidence rate of cervical carcinoma. *Cancer*, **88**, 2082-91.

Kim JW, Roh JW, Park NH, et al (2001). Polymorphism of TP53 codon 72 and the risk of cervical cancer among Korean women. *Am J Obstet Gynecol*, **184**, 55-8.

Koushik A, Platt RW, Franco EL (2004). p53 codon 72 polymorphism and cervical neoplasia: a meta-analysis review. *Cancer Epidemiol Biomarkers Prev*, **13**, 11-22.

Lax SF (2004). Molecular genetic pathways in various types of endometrial carcinoma: from a phenotypical to a molecular-based classification. *Virchows Arch*, **444**, 213-23.

Lee JE, Lee SJ, Namkoong SE, et al (2004). Gene-gene and gene-environmental interactions of p53, p21, and IRF-1 polymorphisms in Korean women with cervix cancer. *Int J Gynecol Cancer*, **14**, 118-25.

Li CY, Liu JH, Huang BJ (2004). Correlation between P53 codon 72 polymorphism and tumorigenesis of cervical cancer. *Ai Zheng*, **23**, 1396-9.

Minaguchi T, Kanamori Y, Matsushima M, et al (1998). 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*, **58**, 4585-6.

Mitra S, Misra C, Singh RK, et al (2005). Association of specific genotype and haplotype of p53 gene with cervical cancer in India. *J Clin Pathol*, **58**, 26-31.

Nagpal JK, Sahni S, Das BR (2002). P53 codon 72 polymorphism and susceptibility to development of human papilloma virus-associated cervical cancer in Indian women. *Eur J Clin*

Invest, **32**, 943-8.
Ngan HY, Liu VW, Liu SS (1999). Risk of cervical cancer is not increased in Chinese carrying homozygous arginine at codon 72 of p53. *Br J Cancer*, **80**, 1828-9.
Niwa Y, Hamajima N, Atsuta Y, et al (2004). Genetic polymorphisms of p73 G4C14-to-A4T14 at exon 2 and p53 Arg72Pro and the risk of cervical cancer in Japanese. *Cancer Lett*, **205**, 55-60.
Nunobiki O, Ueda M, Yamamoto M, et al (2009). Polymorphisms of p53 codon 72 and MDM2 promoter 309 and the risk of endometrial cancer. *Hum Cell*, **22**, 101-6.
Ozalp S, Yalcin OT, Tanir HM, et al (2003). p53 overexpression as a prognostic indicator in endometrial carcinoma. *Eur J Gynaecol Oncol*, **24**, 275-8.
Pecorelli S, Favalli G, Zigliani L, et al (2003). Cancer in women. *Int J Gynaecol Obstet*, **82**, 369-79.
Peters JL, Sutton AJ, Jones DR, et al (2006). Comparison of two methods to detect publication bias in meta-analysis. *JAMA*, **295**, 676-80.
Qie M, Zhang Y and Wu J (2002). Study on the relationship between cervical cancer and p53 codon 72 polymorphism. *Hua Xi Yi Ke Da Xue Xue Bao*, **33**, 274-5.
Risinger JI, Dent GA, Ignar-Trowbridge D, et al (1992). p53 gene mutations in human endometrial carcinoma. *Mol Carcinog*, **5**, 250-3.
Roh JW, Kim JW, Park NH, et al (2004). p53 and p21 genetic polymorphisms and susceptibility to endometrial cancer. *Gynecol Oncol*, **93**, 499-505.
Saranath D, Khan Z, Tandle AT, et al (2002). HPV16/18 prevalence in cervical lesions/cancers and p53 genotypes in cervical cancer patients from India. *Gynecol Oncol*, **86**, 157-62.
Settheetham-Ishida W, Singto Y, Yuenyao P, et al (2004). Contribution of epigenetic risk factors but not p53 condon72 polymorphism to the development of cervical cancer in Northeastern Thailand. *Cancer Lett*, **2**, 205-11.
Sherman ME (2000). Theories of endometrial carcinogenesis: a multidisciplinary approach. *Mod Pathol*, **13**, 295-308.
Soliman PT, Oh JC, Schmeler KM, et al (2005). Risk factors for young premenopausal women with endometrial cancer. *Obstet Gynecol*, **105**, 575-80.
Ueda M, Terai Y, Kanda K, et al (2006). Germline polymorphism of p53 codon 72 in gynecological cancer. *Gynecol Oncol*, **100**, 173-8.
Wang XL, Pan XL, Zheng XZ, et al (2004). Correlation between P53 Condon72 polymorphism and cervical carcinoma among Uigur and Han People. *J Shihezi University*, **4**, 340-4.
Whibley C, Pharoah PD and Hollstein M (2009). p53 polymorphisms: cancer implications. *Nat Rev Cancer*, **9**, 95-107.
Wu MT, Liu CL, Ho CK, et al (2004). Genetic polymorphism of p53 and XRCC1 in cervical intraepithelial neoplasm in Taiwanese women. *J Formos Med Assoc*, **103**, 337-43.
Yamashita T, Yaginuma Y, Saitoh Y, et al (1999). 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*, **20**, 1733-6.
Yang A, Zheng X, Tao L, et al (2008). Studies on correlation between p21Ser31Arg, p53arg72Pro polymorphisms and cervical carcinoma in Uigur women in Xinjiang. *J Shihezi University*, **1**, 6-11.
Yang HP, Gonzalez Bosquet J, Li Q, et al (2010). Common genetic variation in the sex hormone metabolic pathway and endometrial cancer risk: pathway-based evaluation of candidate genes. *Carcinogenesis*, **31**, 827-33.
Yang YC, Chang CL, Chen ML (2001). Effect of p53 polymorphism on the susceptibility of cervical cancer. *Gynecol Obstet Invest*, **51**, 197-201.
Yao N, Zeng H, Lu J (2008). Correlation between p53 condon72 polymorphism and cervical cancer. *Acta Academiae Zunyi*, **1**, 3-5.
Ye S (2000). Polymorphism in matrix metalloproteinase gene promoters: implication in regulation of gene expression and susceptibility of various diseases. *Matrix Biol*, **19**, 623-9.
Zheng XZ, Yang AQ, Pan XL, et al (2008). Ethnicity determines association of p53Arg72Pro alleles with cervical cancer in China. *Eur J Cancer Prev*, **17**, 460-6.
Zheng XZ, Yang AQ, Pan XL, et al (2007). Relationship between p53 Arg72Pro polymorphism and cervical carcinoma in Uigur and Han women in Xinjiang. *Zhonghua Bing Li Xue Za Zhi*, **36**, 511-5.
Zhou X, Han S, Wang S, et al (2009). Polymorphisms in HPV E6/E7 protein interacted genes and risk of cervical cancer in Chinese women: a case-control analysis. *Gynecol Oncol*, **114**, 327-31.
Zintzaras E and Ioannidis JP (2005). Heterogeneity testing in meta-analysis of genome searches. *Genet Epidemiol*, **28**, 123-37.
Zubor P, Stanclova A, Kajo K, et al (2009). The p53 codon 72 exon 4 BstUI polymorphism and endometrial cancer in Caucasian women. *Oncology*, **76**, 173-83.
Zucchetto A, Serraino D, Polesel J, et al (2009). Hormone-related factors and gynecological conditions in relation to endometrial cancer risk. *Eur J Cancer Prev*, **18**, 316-21.