RESEARCH ARTICLE


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 (Berruch 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
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. We tested whether genotype frequencies of controls were in HWE using the χ² 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...

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

<table>
<thead>
<tr>
<th>Subgroups</th>
<th>OR (95%CI)</th>
<th>P</th>
<th>OR (95%CI)</th>
<th>P</th>
<th>OR (95%CI)</th>
<th>P</th>
<th>OR (95%CI)</th>
<th>P</th>
<th>OR (95%CI)</th>
<th>P</th>
<th>OR (95%CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>China</td>
<td>0.93 (0.751-1.15)</td>
<td>0.518</td>
<td>1.001</td>
<td>0.77</td>
<td>0.571-1.04</td>
<td>0.899</td>
<td>0.002</td>
<td>1.16</td>
<td>0.85-1.58</td>
<td>0.347</td>
<td>0.282</td>
<td>0.05</td>
</tr>
<tr>
<td>Korea</td>
<td>0.97 (0.781-1.20)</td>
<td>0.758</td>
<td>0.146</td>
<td>0.98</td>
<td>0.68-1.40</td>
<td>0.900</td>
<td>0.026</td>
<td>0.88</td>
<td>0.66-1.18</td>
<td>0.392</td>
<td>0.963</td>
<td>0.91</td>
</tr>
<tr>
<td>Japan</td>
<td>1.18 (0.82-1.71)</td>
<td>0.379</td>
<td>0.001</td>
<td>1.11</td>
<td>0.78-1.58</td>
<td>0.566</td>
<td>0.044</td>
<td>1.28</td>
<td>0.65-2.52</td>
<td>0.473</td>
<td>&lt;0.001</td>
<td>1.35</td>
</tr>
<tr>
<td>India</td>
<td>0.86 (0.63-1.15)</td>
<td>0.303</td>
<td>0.005</td>
<td>0.54</td>
<td>0.36-0.83</td>
<td>0.003</td>
<td>0.234</td>
<td>1.22</td>
<td>0.74-2.05</td>
<td>0.458</td>
<td>0.069</td>
<td>0.60</td>
</tr>
</tbody>
</table>

Language

| English   | 0.86 (0.81-0.97) | 0.001 | 0.9 | 0.75-1.07 | 0.221 | 0.002 | 1.13 | 0.91-1.40 | 0.281 | 0.001 | 0.99 | 0.78-1.35 | 0.923 | 0.004 | 1.21 | 0.96-1.52 | 0.097 | 0.002 |
| Chinese   | 0.86 (0.52-1.42) | 0.554 | 0.001 | 0.66 | 0.36-1.09 | 0.167 | 0.002 | 1.17 | 0.62-2.23 | 0.221 | 0.03 | 0.006 | 1.03 | 0.61-1.64 | 0.782 | 0.002 | 1.01 | 1.03-2.03 | 0.043 | 0.719 |

HWE test

| HWE       | 0.98 (0.84-1.15) | 0.861 | 0.001 | 0.9 | 0.73-1.11 | 0.381 | 0.001 | 1.08 | 0.84-1.38 | 0.567 | <0.001 | 0.97 | 0.72-1.29 | 0.812 | 0.005 | 1.16 | 0.91-1.47 | 0.238 | 0.003 |
| Non-HWE   | 0.93 (0.73-1.52) | 0.071 | 0.68 | 0.47-0.97 | 0.035 | 0.008 | 1.31 | 0.98-1.75 | 0.064 | 0.424 | 0.003 | 0.96 | 0.64-1.45 | 0.161 | 0.251 | 1.69 | 1.19-2.28 | 0.003 | 0.751 |

Overall    | 0.97 (0.85-1.06) | 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 | 1.02-1.52 | 0.029 | 0.005 |

**Figure 2. Forest Plot of ORs with a Random-effects Model for Associations Between p53 codon72 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 codon72 Polymorphism and Cervical Cancer Risk Among Asians Under the Dominant Model (Pro/Pro + Arg/Pro vs. Arg/Arg)**

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 = 1.53, 95%CI: 1.00-2.33, 0.003; Pro/Pro vs. Arg/Arg: OR = 0.54, 95%CI: 0.36-0.81, P = 0.003; Pro/Pro vs. Arg/Arg: OR = 1.53, 95%CI: 1.00-2.33, 0.003).
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


genetic variation in the sex hormone metabolic pathway
and endometrial cancer risk: pathway-based evaluation


polymorphism and cervical cancer. *Acta Academiae Zunyi*, 1, 3-5.

promoters: implication in regulation of gene expression and

association of p53Arg72Pro alleles with cervical cancer in

p53 Arg72Pro polymorphism and cervical carcinoma in
Uigur and Han women in Xinjiang. *Zhonghua Bing Li Xue Za Zhi*, 36, 511-5.

E6/E7 protein interacted genes and risk of cervical cancer

Zintzaras E and Ioannidis JP (2005). Heterogeneity testing in

exon 4 BstUI polymorphism and endometrial cancer in

related factors and gynecological conditions in relation to