Association of p53 codon 72 Arg>Pro polymorphism and risk of cancer in Iranian population: A systematic review and meta-analysis

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Abstract

Background: Different studies have investigated the association between p53 codon 72 Arg>Pro polymorphism and cancer risk. Because of the lack of consensus of the results in individual studies, we conducted this meta-analysis by pooling all currently available case-control studies to estimate the effect of p53 codon 72 Arg/Pro polymorphism on cancer susceptibility in Iranian population.

Methods: A comprehensive search was undertaken and primary data from all peer-reviewed journals indexed in PubMed, Google Scholar, Scopus, Magiran, Scientific Information Databank (SID), Iran Medex, and CAB abstract electronic were used to conduct this meta-analysis. We considered some exclusion and inclusion criteria to select the articles. Statistical heterogeneity was explored using the I-square. Publication bias was assessed graphically and statistically by Begg’s funnel plot and Egger test. All statistical analyses were performed using StatsDirect software and a two-tailed test. P-value less than 0.05 was considered statistically significant for any test.

Results: Our dataset, which included 35 case-control studies, consisted of 2426 cancer cases and 2928 controls. Pooled OR and 95%CI indicated that codon 72 Arg>Pro polymorphism was not associated with odds of developing cancer among Iranian population in the dominant model (Pro/Pro + Arg/Pro vs. Arg/Arg: OR= 0.96, 95%CI= 0.74 to 1.24 chi2= 0.06, p= 0.8). Moreover, no significant association was detected in variant allele (Pro vs Arg: OR= 1.075, 95%CI= 0.91 to 1.25), homozygous (Pro/Pro vs Arg/Arg: OR=0.91 95%CI= 0.66 to 1.25), and heterozygous (Arg/Pro vs Arg/Arg: OR= 0.84, 95%CI= 0.7 to 1).

Conclusion: Our study revealed that p53 codon 72 Arg>Pro polymorphism was not associated with overall cancer odds in Iranian population.

Keywords: Meta-analysis, Cancer, p53, Iran
4 is a common polymorphism and is associated with an increased risk of various types of cancer (16). The p53 P72 allele is weaker than the R72 allele in inducing apoptosis and suppressing cellular transformation, but appears to be better at initiating senescence and cell cycle arrest (17, 18). Jiang et al. performed a meta-analysis by pooling 17 publications to evaluate the possible effect of the p53 Codon 72 Arg/Pro polymorphism on oral cancer risk. They found no significant association between p53 Codon 72 Arg/Pro polymorphism and risk of oral cancer (19). Wang et al. performed a meta-analysis by pooling 14 publications and suggested that the p53 Codon 72 Arg/Pro polymorphism is a risk factor for lung cancer in the Asian population (20). Zhou et al. performed a meta-analysis by pooling 12 publications and suggested that the p53 Codon 72 polymorphism may be associated with gastric cancer among Asians, and they further indicated that difference in genotype distribution may be associated with the location, stage, and histological differentiation of gastric cancer (21). Also, Irshad et al. performed a meta-analysis by pooling 5 publications, and they found that the Codon 72 Arg>Pro polymorphism of the p53 gene might not contribute to cancer susceptibility in the Saudi population (22). As discussed earlier, previous case-control studies have investigated the association between mentioned polymorphism and cancer risk in the Iranian population. Due to the small sample size and low statistical power in each of the performed studies, the results were not reliable enough to determine the effect of this polymorphism on cancer susceptibility. Meta-analysis is a useful statistical tool for combining the results from individual studies to provide more trustworthy results (23). To date, no meta-analysis has been conducted on the Iranian population to evaluate this association. Therefore, we conducted this meta-analysis to pool all the published studies and determine the association between p53 Codon 72 G>C polymorphism and cancer risk.

Methods

Search Strategy for Identification of Studies

We followed “PRISMA” 2012 checklist criteria for meta-analysis. To cover overall publications, we used the following keywords: “p53 gene polymorphism”, “p53 gene mutation”, “p53 gene variation”, “p53 codon 72 Arg>Pro”, “Carcinoma” and “cancer risk”, and “in Iranian population”. The full texts of all relevant studies were analyzed carefully to determine whether data on the topic and abstract of interest were intact. Furthermore, the reference lists of the relevant articles and systematic reviews were investigated to ensure that no data were missed. In the selected case-control studies, blood and tissue samples of patients were collected from clinical hospitals and laboratories, and control samples were randomly selected from those who referred to clinical centers, who had no previous history of cancer and no signs and symptoms of malignancy.

Inclusion criteria

The following criteria were used to select the studies: (1) a case-control design; (2) assessment of the p53 Codon 72 Arg>Pro and cancer risk in Iranian population; (3) recruiting histologically and pathologically confirmed cancer patients and healthy controls; (4) adequate genotyping data so that odds ratios (24) with 95% confidence intervals (CIs) could be calculated; (5) the selected studies had to be conducted on human samples; and (6) inclusion of genotype frequency of cases and controls.

Exclusion criteria

Exclusion criteria were as follow: (1) not enough information on the distribution of p53 Codon 72 polymorphism; (2) case-only studies; (3) duplicated publications; (4) the studies that used cell line and animal subjects; (5) genotype frequency missing; (6) studies that investigated the levels of p53 mRNA expression; and (7) review articles.

Information sources

The retrieved studies were searched through the PubMed, Google Scholar, Scopus, Magiran, Scientific Information Databank (SID), Iran Medex, and CAB abstract electronic databases. Publications in English and Persian languages from 2006 to December 2016 were included in this manuscript.

Extracted Information

Two researchers independently extracted the crude data according to the inclusion and exclusion criteria listed above to prove the validity of the retrieved information. The prepared data included the first author’s name, date of publication, type of cancer, ethnicity, number of cases and controls, and genotype frequencies. Disputes were settled by referring to a third researcher.

Statistical analysis

The association between p53 Codon 72 Arg>Pro polymorphism and cancer risk was obtained by pooling odds ratio (OR) and 95% confidence intervals (CI). In the present study, estimation of the pooled effect was based on the weighted average from the results of the individual studies. Weighted average for each study was calculated based on sample size and variance of samples.

The random-effects (DerSimonian and Laird method) and fixed effect models (Mantel and Haenszel method) were applied. I² statistics and Cochran’s Q statistic (p<0.10) were used to check out heterogeneity assumption (I² static is the percentage of the observed total variation across studies that are due to heterogeneity rather than chance). A value of 0% indicates no observed heterogeneity, and larger values show increasing heterogeneity. Q is the weighted of squares on a standardized scale, which is reported with a p-value, with low p-values indicating the presence of heterogeneity. If p < 0.05, the results were pooled by the random-effects model, otherwise, fixed effect model was used.

To evaluate the publication bias among the included studies, Begg’s funnel plot and Egger’s linear regression test were performed. The Hardy-Weinberg equilibrium was calculated in the control groups using a goodness of fit test for each study. All the statistical analyses were performed using the STATA 12.0 software (StataCorp, College Station, TX, USA) and SPSS 20 software (SPSS, Inc., Chicago, IL, USA).
performed using Stats Direct software and a two-tailed test. P-value less than 0.05 was considered statistically significant for any test.

**Results**

**Characteristics of publications and meta-analysis databases**

In this study, 157 relevant articles were recovered by literature search. However, considering the inclusion and exclusion criteria, 67 articles were excluded because they were not relevant; moreover, 58 articles were excluded for being duplicates, not being performed on human subjects, and being review articles. After careful screening, 32 eligible case-control studies on the association between p53 Codon 72 Arg>Pro polymorphism and cancer risk in the Iranian population (Fig. 1) were selected. Information including authors, date of publication, cancer type, distribution of genotypes (cases and controls), and the Hardy-Weinberg equilibrium are presented in Table 1.

**Evaluation of heterogeneity**

To analyze heterogeneity among the studies, Q test, I^2 statistics, and heterogeneity were noticed in all the 5 genetic models. The random effects model was used to calculate the odds ratio and 95% confidence interval (Table 2).

**Table 1. Distribution of p53 codon 72 Arg>Pro polymorphism included in the meta-analysis**

<table>
<thead>
<tr>
<th>Authors</th>
<th>Years</th>
<th>Cancer Type</th>
<th>Control Genotype</th>
<th>Case Genotype</th>
<th>HWE P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Arg/Arg</td>
<td>Arg/Pro</td>
<td>Arg/Arg</td>
</tr>
<tr>
<td>Zahra Eyedian</td>
<td>2016</td>
<td>Lung</td>
<td>88</td>
<td>88</td>
<td>24</td>
</tr>
<tr>
<td>Fatemeh Keshavarz</td>
<td>2016</td>
<td>Breast</td>
<td>20</td>
<td>38</td>
<td>25</td>
</tr>
<tr>
<td>FarinazBehfajarj</td>
<td>2015</td>
<td>Prostate</td>
<td>35</td>
<td>44</td>
<td>17</td>
</tr>
<tr>
<td>SahrArgohari-</td>
<td>2015</td>
<td>Breast</td>
<td>22</td>
<td>54</td>
<td>28</td>
</tr>
<tr>
<td>Mehdi Nikbakht</td>
<td>2015</td>
<td>CML</td>
<td>16</td>
<td>22</td>
<td>7</td>
</tr>
<tr>
<td>Hosseini-Asl</td>
<td>2015</td>
<td>Gastric</td>
<td>18</td>
<td>21</td>
<td>2</td>
</tr>
<tr>
<td>MinooYaghmae</td>
<td>2015</td>
<td>Uterine / Leiomyoma</td>
<td>53</td>
<td>72</td>
<td>24</td>
</tr>
<tr>
<td>Mehdi Nikbakht</td>
<td>2015</td>
<td>AML</td>
<td>7</td>
<td>48</td>
<td>4</td>
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<tr>
<td>Robab Sheikh</td>
<td>2014</td>
<td>Breast</td>
<td>51</td>
<td>88</td>
<td>41</td>
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<tr>
<td>Mohammad Taheri</td>
<td>2014</td>
<td>Gastric</td>
<td>30</td>
<td>50</td>
<td>18</td>
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<tr>
<td>RoghayehDelghan</td>
<td>2014</td>
<td>Thyroid</td>
<td>8</td>
<td>24</td>
<td>8</td>
</tr>
<tr>
<td>Rahim Golmohammadi</td>
<td>2013</td>
<td>Breast</td>
<td>75</td>
<td>90</td>
<td>40</td>
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<tr>
<td>Boyajian</td>
<td>2013</td>
<td>Esophageal</td>
<td>38</td>
<td>37</td>
<td>17</td>
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<tr>
<td>MasomehFaghihi</td>
<td>2012</td>
<td>Colorectal</td>
<td>162</td>
<td>217</td>
<td>86</td>
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<td>Mohammad Ali</td>
<td>2012</td>
<td>Breast</td>
<td>5</td>
<td>13</td>
<td>2</td>
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<tr>
<td>Mohammad Ali</td>
<td>2012</td>
<td>Thyroid</td>
<td>19</td>
<td>40</td>
<td>41</td>
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<td>Abbas Doosti</td>
<td>2011</td>
<td>Breast</td>
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<td>Prostate</td>
<td>44</td>
<td>63</td>
<td>16</td>
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<tr>
<td>Mehdi Nikbakht</td>
<td>2011</td>
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<td>58</td>
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<tr>
<td>Mehdi Nikbakht</td>
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<td>Skin</td>
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<td>82</td>
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<tr>
<td>Abbas Doosti</td>
<td>2011</td>
<td>Colorectal</td>
<td>6</td>
<td>11</td>
<td>3</td>
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<tr>
<td>Mohammad Mazani</td>
<td>2011</td>
<td>Gastric</td>
<td>27</td>
<td>58</td>
<td>15</td>
</tr>
<tr>
<td>Barzegar</td>
<td>2011</td>
<td>Gastric</td>
<td>31</td>
<td>57</td>
<td>12</td>
</tr>
</tbody>
</table>
The association between p53 codon 72 Arg>Pro polymorphism and cancer risk

To measure the association between p53 Codon 72 Arg>Pro polymorphism and cancer odds, all the 35 studies were pooled together (2426 cancer cases and 2928 controls). Pooled OR and 95% CI indicated no association between p53 Codon 72 Arg>Pro polymorphism and cancer odds in variant allele (Pro vs. Arg: OR= 1.075, 95%CI= 0.91 to 1.25, chi² (test odds ratio differs from 1) = 0.83, p = 0.36) and homozygous (Pro/Pro vs. Arg/Arg: OR= 0.911, 95%CI= 0.66 to 1.25, chi² = 0.32, p = 0.57). Similarly, recessive genetic model and dominant model were not associated with an increased odds of developing cancer (Pro/Pro vs. Arg/Arg+ Arg/Pro: OR = 0.91, 95%CI= 0.72 to 1.16, chi² = 0.49, p = 0.48), (Pro/Pro+Arg/Pro vs. Arg/Arg: 164.2 0.000 79.3 0.88 (-1.48,3.26 ) 0.45 Random).

Sensitivity analysis
We performed sensitivity analysis to evaluate the effect

Publication bias
Begg’s funnel plot and Egger’s linear regression test were used to evaluate publication bias the included studies. The appearance of the shape of funnel plot and Egger’s linear regression test did not show any evidence of publication bias among all comparison models (Table 2 and Figs. 7-11).

Table 2
Result of heterogeneity and publication bias in the meta-analysis

Comparison     Heterogeneity analysis     Egger’s linear regression test     Models

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Heterogeneity analysis</th>
<th>Egger’s linear regression test</th>
<th>Models</th>
</tr>
</thead>
<tbody>
<tr>
<td>Q</td>
<td>P</td>
<td>I² (%)</td>
<td>Intercept</td>
</tr>
<tr>
<td>Pro vs. Arg</td>
<td>58.38</td>
<td>0.005</td>
<td>41.8</td>
</tr>
<tr>
<td>Pro/Pro vs. Arg/Arg</td>
<td>153.6</td>
<td>0.000</td>
<td>77.9</td>
</tr>
<tr>
<td>Arg/Pro vs. Arg/Arg</td>
<td>91.87</td>
<td>0.000</td>
<td>63</td>
</tr>
<tr>
<td>Pro/Pro + Arg/Pro vs. Arg/Arg</td>
<td>164.2</td>
<td>0.000</td>
<td>79.3</td>
</tr>
<tr>
<td>Pro/Pro vs. Arg/Arg+ Arg/Pro</td>
<td>126.6</td>
<td>0.000</td>
<td>73.2</td>
</tr>
</tbody>
</table>

Pro vs. Arg/Arg: OR = 0.96, 95%CI= 0.74 to 1.24, chi²= 0.06, p= 0.8 (Figs. 2-6).

Forest plot of odds ratio with 95% CI of overall cancer risk associated with p53 codon 72 Arg>Pro polymorphism for allele model

Odds ratio meta-analysis plot (random effects)

Forest plot of odds ratio with 95% CI of overall cancer risk associated with p53 codon 72 Arg>Pro polymorphism for homozygous model

Odds ratio meta-analysis plot (random effects)
results of meta-analysis revealed that pooled ORs were of each study included in the present meta-analysis. The associated with p53 codon 72 Arg>Pro polymorphism for heterozygous model

**Discussion**

Several epidemiological studies have indicated that cancer is a multi-factorial disease and that nutrition, use of

Fig. 4. Forest plot of odds ratio with 95% CI of overall cancer risk associated with p53 codon 72 Arg>Pro polymorphism for heterozygous model

Fig. 5. Forest plot of odds ratio with 95% CI of overall cancer risk associated with p53 codon 72 Arg>Pro polymorphism for recessive model of each study included in the present meta-analysis. The results of meta-analysis revealed that pooled ORs were generally similar in all the 5 models.

Fig. 6. Forest plot of odds ratio with 95% CI of overall cancer risk associated with p53 codon 72 Arg>Pro polymorphism for dominant model

Fig. 7. Funnel plot detecting biases in the identification and selection of studies for allele dominant model

Fig. 8. Funnel plot detecting biases in the identification and selection of studies for homozygous dominant model
Association of p53 codon with risk of cancer

Fig. 9. Funnel plot detecting biases in the identification and selection of studies for heterozygous dominant model

Fig. 10. Funnel plot detecting biases in the identification and selection of studies for recessive dominant model

Fig. 11. Funnel plot detecting biases in the identification and selection of studies for dominant model

tobacco and/or alcohol, viral infections, genetic factors, and UV exposure are cancer risk factors. Furthermore, some genetic predisposing factors are involved in carcinogenesis. Genetic alteration could occur in oncogenes, tumor suppressors, and growth of regulator genes (25). TP53 is the most important tumor suppressor gene that plays an important role in response to DNA damage, so this is considered as “guardian of the genome”. P53 is one of the most frequently mutated genes in human malignancies and more than 50% of human cancers (26). In addition to mutations, genetic polymorphisms could also have an effect on the P53 function. In particular, P53 Codon 72 (P53c72) single nucleotide polymorphism (SNP), which could result in either arginine (25) or proline (Pro) alleles, creates 3 different genotypes: Arg/Arg, Arg/Pro, and Pro/Pro (27). The proteins p53Arg72 and p53Pro72 have dissimilar biochemical and biological possessions, for example, dissimilarity in the binding to parts of the transcriptional apparatus and dissimilarity in the initiation of transcription (10). The p53Arg72 protein persuades apoptosis faster and represses alteration more competently than the p53Pro72 protein (27). There have been reports showing possible involvement of P53c72 polymorphism in individuals’ susceptibility to cancers including mouth cancer, breast cancer, thyroid cancer, colorectal, and prostate cancer, which seem to have a mutation in this gene (9, 11, 13, 14, 24). The mentioned case-control studies showed the contribution of P53c72 polymorphism to the carcinogenesis although these studies were done with a small sample size and the results from these individual studies lacked consensus. Thus, we performed the current meta-analysis with more number of cases and controls. Furthermore, to our knowledge, this was the first meta-analysis to assess the association of the P53c72 polymorphism with cancer susceptibility among Iranian population.

The overall pooled results of this meta-analysis revealed no association between variant allele of p53 c 72 G>C polymorphism with an increased or decreased cancer odds. Our results demonstrated that the p53 Codon 72 G>C polymorphism is not a significant cause of cancer odds among the Iranian population. Also, in the dominant model (Pro/Pro +Arg/Pro vs. Arg/Arg) codon 72 Arg>Pro polymorphism was not associated with a diminished odds of cancer among this population. A number of studies indicated that TP53 Arg72Pro have no influence on breast cancer odds (9, 28), colorectal cancer odds (29), and skin cancer odds (30), whereas some other studies revealed an association between this polymorphism with cancer odds; for instance, Doosti et al. reported that homozygous individuals with the Arg allele have a higher odds of developing breast cancer than heterozygote ones (31). Babaei et al. found that cases with Pro/Pro had an increased odds of developing prostate cancer compared to those with Arg/Arg (32). Similar to our result, no association was found in meta-analysis of p53 Codon 72 Arg>Pro polymorphism with cancer odds in Saudi and Indian populations in all genetic models (33-35). This meta-analysis had some limitations. First, in the present study the p53 Codon 72 Arg/Pro polymorphism, which might have influenced the odds of cancer in combination with other genetic polymorphisms (gene-gene and gene-environment interaction), was not considered. Second, we found heterogeneity in the overall analysis. Third, our meta-analysis was based on unadjusted estimates, while a more precise analysis could be performed if individual data were available that would allow for an adjustment estimate (by age and sex). Despite these limitations, our meta-analysis had several strengths. First, the number of studies included in the analysis was relatively large. Second, we included studies published in English and Persian languages that covered all Iranian based publications.

Conclusion
A meta-analysis is an approach of statistical analysis,
which combines both statistically notable and none- statistically notable results from individual studies to improve statistical efficiency by enlarging the sample size. Our results revealed that p53 Codon 72 Arg>Pro polymorphism may considerably modulate the overall cancer odds among Iranian population.

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Conflict of Interests
The authors declare that they have no competing interests.

References