Association of mRNA expression of TP53 and the TP53 codon 72 Arg/Pro gene polymorphism with colorectal cancer risk in Asian population: a bioinformatics analysis and meta-analysis

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Background: The relationship between TP53 codon 72 Pro/Arg gene polymorphism and colorectal cancer risk in Asians is still controversial, and this bioinformatics analysis and meta-analysis was performed to assess the associations.

Methods: The association studies were identified from PubMed, and eligible reports were included. RevMan 5.3.1 software, OncoLnc, cBioPortal, and Oncomine online tools were used for statistical analysis. A random/fixed effects model was used in meta-analysis. The data were reported as risk ratios or mean differences with corresponding 95% CI.

Results: We confirmed that TP53 was associated with colorectal cancer, the alteration frequency of TP53 was 53% mutation and 7% deep deletion, and TP53 mRNA expression was different in different types of colorectal cancer based on The Cancer Genome Atlas database. Then, 18 studies were included that examine the association of TP53 codon 72 gene polymorphism with colorectal cancer risk in Asians. The meta-analysis indicated that TP53 Pro allele and Pro/Pro genotype were associated with colorectal cancer risk in Asian population, but Arg/Arg genotype was not (Pro allele: odds ratios [OR]=1.20, 95% CI: 1.06 to 1.35, P=0.003; Pro/Pro genotype: OR=1.39, 95% CI: 1.15 to 1.69, P=0.0007; Arg/Arg genotype: OR=0.86, 95% CI: 0.74 to 1.00, P=0.05). Interestingly, in the meta-analysis of the controls from the population-based studies, we found that TP53 codon 72 Pro/Arg gene polymorphism was associated with colorectal cancer risk (Pro allele: OR=1.33, 95% CI: 1.15 to 1.55, P=0.0002; Pro/Pro genotype: OR=1.61, 95% CI: 1.28 to 2.02, P<0.0001; Arg/Arg genotype: OR=0.77, 95% CI: 0.63 to 0.93, P=0.009).

Conclusion: TP53 was associated with colorectal cancer, but the different value levels of mRNA expression were not associated with survival rate of colon and rectal cancer. TP53 Pro allele and Pro/Pro genotype were associated with colorectal cancer risk in Asians.

Keywords: colorectal carcinoma, TP53 codon 72, gene polymorphism, mutation, bioinformatics analysis, meta-analysis

Introduction
ColoRectal cancer, associated with multiple genetic alterations, is the third most common cancer diagnosis and the second and third leading cause of cancer mortality in men and women, respectively. However, the majority of colorectal cancer cases is the result of sporadic tumorigenesis via the adenoma–carcinoma sequence. Although the survival rate of patients with colorectal cancer has improved, it is still lower than that of patients with other types of cancer. Finding a gene marker that can allow for better screening and earlier diagnosis of colorectal cancer could improve outcomes.
The tumor protein p53 gene (TP53), located on chromosome 17p13, contains homozygous mutations in 50%–60% of human cancers. About 90% of these mutations encode missense mutant proteins that span ~190 different codons localized in the DNA-binding domain of the gene and protein. TP53 Arg72Pro mutation (rs1042522), a transversion of CGC to CCC (Arg to Pro), creates three different genotypes: CGC/CGC (Arg/Arg), CGC/CCC (Arg/Pro), and CCC/CCC (Pro/Pro). These forms of p53 differ in their ability to induce growth arrest and apoptosis. These mutations produce a protein with a reduced capacity to bind to a specific DNA sequence that regulates the p53 transcriptional pathway. Several studies reported that the mutation or alterations of TP53 gene have an effect on the prognosis and treatment of cancer. TP53 codon 72 Pro/Arg gene polymorphism has also been reported to be associated with colorectal cancer outcome.

Therefore, determining the relationship of TP53 gene polymorphism and mutation with colorectal cancer will provide important clinical insight. Overall survival, mutation, and correlation analysis of TP53 were made using the Oncomine, Oncomine, and cBioPortal online tools based on The Cancer Genome Atlas (TCGA) database. A meta-analysis was also conducted to assess these associations.

**Methods**

**Bioinformatics analysis**

TCGA (http://cancergenome.nih.gov/) provides researchers with extraordinary amounts of molecular data with cancer information. The cBioPortal (online tool, www.cbioportal.org, based on TCGA database) and the Oncomine (online tool, www.oncomine.org/, based on TCGA database) were used to identify and confirm the correlation of TP53 with cancers or colorectal cancer. cBioPortal was also used to identify the mutation status of TP53 gene. The Oncolnc (online tool, http://www.oncolnc.org, based on TCGA database) was conducted to perform the survival analysis of TP53 in colorectal cancer. Column analyses (Scatter) and T-test were performed using GraphPad Prism version 6.0 (GraphPad Software, La Jolla, CA, USA, www.graphpad.com).

**Meta-analysis**

**Search strategy**

The search was conducted in the databases of PubMed on October 1, 2017, and the relevant investigations were included. The retrieval strategy of “(colorectal cancer OR colorectal carcinoma) AND polymorphism AND TP53” was entered into the PubMed database.

Inclusion criteria were as follows: 1) the outcome must be colorectal cancer; 2) the study included two comparison groups (case group vs. control group); and 3) the report should give the data of TP53 genotype distribution.

Exclusion criteria were as follows: 1) Case reports, editorials, and review articles; 2) preliminary result not on TP53 gene polymorphism or colorectal cancer; and 3) investigating the role of TP53 gene expression in colorectal cancer risk.

**Data extraction**

For the full-text articles that were retrieved, two investigators independently reviewed and checked the included reports to assess the available data and randomization. First author’s surname, year of publication, ethnicity, source of the control group, and the number of cases and controls for TP53 were extracted from each recruited investigation. Frequencies of allele of TP53 were calculated for case group and control group.

**Statistical analysis**

RevMan 5.3 was used for this meta-analysis. For dichotomous data, we calculated odds ratios (ORs) corresponding to 95% CI. The heterogeneity was evaluated by the $Q$-test and $I^2$ statistic. The $I^2$ statistic ranges from 0% to 100%, a value of 0% indicated no observed heterogeneity and larger values show increasing heterogeneity. If $I^2$<50% and $P$-value ≥0.1, we considered heterogeneity was not significant, and the fixed-effects model was used for analysis. Otherwise, the potential inconsistency among all included studies was analyzed carefully. If the heterogeneity was not excluded, we used the random-effects model.

**Results**

The relationship of TP53 with colorectal cancer and TP53 mRNA expression in colorectal cancer

The information on TP53 genes was freely available in Oncomine online tool. It was confirmed that TP53 was associated with colorectal cancers based on TCGA datasets (Figure 1A). The TP53 mRNA expression was shown in different types of colorectal cancer based on TCGA colorectal cancer datasets (237 samples, 20,423 measured genes; Figure 1B). It indicated that there was much more alteration frequency of mutation and deep deletion in rectal adenocarcinoma. The top three significant mRNA expressions were colon mucinous adenocarcinoma ($P=1.11E-5$, fold change=1.668, 22 samples), rectal adenocarcinoma ($P=6.31E-6$, fold change=2.169, 10 samples), and colon adenocarcinoma ($P=1.11E-5$, fold change=2.008, 17 samples).

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The top three significant mRNA expressions were colon mucinous adenocarcinoma, rectal adenocarcinoma, and colon adenocarcinoma.
change=1.633, 60 samples), and cecum adenocarcinoma ($P=4.55E^{-4}$, fold change=1.827, 22 samples) compared with normal samples (22 samples; Figure 1C). It suggested that TP53 mRNA expression was different in different types of colorectal cancer. Figure 1D shows that TP53 mRNA expression rate was highly expressed in colorectal cancer tissues relative to normal colorectal tissues, and it has statistical significance between the two groups (95% CI $[-0.9922$ to $-0.0705]$, $P=0.007$).

The characters of the gene set of TP53 altered in 212 samples
We used cBioPortal to display the following information about TP53 based on TCGA (Nature 2012) database. The total mutations, cancer type detail, overall survival, mutation fusion amp homdel, and heat map are shown in Figure 2A. There are three types of colorectal cancer (rectal adenocarcinoma [ERAD], colon adenocarcinoma [COAD], and colorectal adenocarcinoma) shown. The alteration frequency of
TP53 is shown in Figure 2A, 53% (112/212 sequenced cases/patients) was mutation and 7% was deep deletion (Figure 2A). The overall survival range was from 1.94 to 69.98 months (Figure 2A). The heatmap shows the mRNA expression level of TP53 in 212 sequenced cases. The network contains 51 nodes, including TP53 gene and the 50 most frequently altered neighbor genes (50/222), and the top three (APAF1, APC, ASF1A) are marked with round symbols (Figure 2B). This indicated that TP53 alteration was closely related to these neighbor genes. Figure 2C shows the overall survival Kaplan–Meier estimate of cases with or without alterations (Logrank test P-value = 0.179). It suggested that there is no significant difference in overall survival in the two groups.

The Kaplan plot and RNA expression level for TP53

The survival information of TP53 gene was freely available in Oncomine online tool (Based on TCGA database, 440 patients in COAD, and 159 patients in ERAD). It was found that the low RNA expression of TP53 group was worse than high expression in overall survival for COAD (Logrank P = 0.253), and the mortality of the low expression group was 22/110, compared to 19/110 in the high group (P > 0.05; Figure 3A). However, low RNA expression of TP53 is better than high expression in overall survival of READ (Logrank P = 0.525). The mortality of the low expression group was 4/39, compared to 5/39 in the high expression group (P > 0.05; Figure 3B). But, there was no statistically significant difference in the survival rate of high and low expression groups in both COAD and READ. This suggested that the different expression levels of mRNA might have little correlation with the survival rate.

Association of TP53 codon 72 Pro/Arg gene polymorphism with colorectal cancer risk

Eighteen studies about the relationship between TP53 codon 72 Pro/Arg gene polymorphism and colorectal cancer risk were included in this meta-analysis (Table 1). We found
that TP53 Pro allele and Pro/Pro genotype were associated with colorectal cancer risk, but Arg/Arg genotype was not (Pro allele: OR=1.20, 95% CI: 1.06 to 1.35, P=0.003; Pro/Pro genotype: OR=1.39, 95% CI: 1.15 to 1.69, P=0.0007; Arg/Arg genotype: OR=0.86, 95% CI: 0.74 to 1.00, P=0.05; Table 2; Figure 4A–C).

**Figure 3** (A) The overall survival of RNA expression of TP53 in COAD. (B) The overall survival of RNA expression of TP53 in READ. **Abbreviations:** COAD, colon adenocarcinoma; READ, rectal adenocarcinoma.

**Association of TP53 codon 72 Pro/Arg gene polymorphism with colorectal cancer risk according to the control source**

The controls in 12 population-based studies of the relationship between TP53 codon 72 Pro/Arg gene polymorphism and colorectal cancer risk were included in this meta-analysis. We found that TP53 codon 72 Pro/Arg gene polymorphism was associated with colorectal cancer risk (Pro allele: OR=1.33, 95% CI: 1.15 to 1.55, P=0.0002; Pro/Pro genotype: OR=1.61, 95% CI: 1.28 to 2.02, P<0.0001; Arg/Arg genotype: OR=0.77, 95% CI: 0.63 to 0.93, P=0.009; Table 2).

The controls in six hospital-based studies of the relationship between TP53 codon 72 Pro/Arg gene polymorphism and colorectal cancer risk were included in this meta-analysis. We found that TP53 codon 72 Pro/Arg gene polymorphism was not associated with colorectal cancer risk (Pro allele: OR=0.98, 95% CI: 0.84 to 1.14, P=0.77; Pro/Pro genotype:
In this informatics analysis, we confirmed that TP53 was associated with colorectal cancer, the alteration frequency of TP53 was 53% mutation and 7% deep deletion, and TP53 mRNA was highly expressed in colorectal cancer tissues compared with normal colorectal tissues. Additionally, the different expression levels of mRNA might have no correlation with the survival rate either in the COAD group or READ group (P > 0.05). It seems that in the READ group, the group with a lower level of mRNA expression had a higher overall survival. TP53 alteration frequency was different in different types of colorectal cancer, so we hypothesized that mutation or alteration of TP53 may play a key role in colorectal cancer.

TP53 Arg72Pro mutation (rs1042522), one of the mutations in TP53, creates three different genotypes: Arg/Arg, Arg/Pro, and Pro/Pro. It is reported that the mutation or alterations of TP53 gene have a certain effect on the prognosis and treatment of cancer.7–11 Dahabreh et al33 indicated that TP53 Arg72Pro gene polymorphism has no relationship with colorectal cancer in White (4961 cases, 5647 controls) and East Asian populations (968 cases, 2031 controls). Abderrahmane et al34 also reported that there was no significant association between TP53 Arg72Pro and colorectal cancer in the Algerian population. However, a HuGE review and meta-analysis (18,718 case and 21,261 controls) showed that the TP53 Arg72Pro gene polymorphism increases risk of cancer in Asians and Americans only.35 There is still controversy.

In this study, meta-analysis was conducted to see which genotype was more associated with colorectal cancer risk in different populations.

Table 1 Characteristics of the studies evaluating the effects of p53 codon 72 Arg/Pro gene polymorphism on colorectal cancer risk

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Country/District</th>
<th>Control source</th>
<th>Case Pro/Pro</th>
<th>Pro/Arg</th>
<th>Arg/Arg</th>
<th>Control Pro/Pro</th>
<th>Pro/Arg</th>
<th>Arg/Arg</th>
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<td>55</td>
<td>46</td>
<td>23</td>
<td>76</td>
<td>53</td>
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<tr>
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<td>Hospital based</td>
<td>10</td>
<td>33</td>
<td>18</td>
<td>27</td>
<td>70</td>
<td>43</td>
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<td>72</td>
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<td>Population based</td>
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<th>Number of studies</th>
<th>Q-test P-value</th>
<th>Model selected</th>
<th>OR (95%CI)</th>
<th>P-value</th>
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<td>Random</td>
<td>1.20 (1.06 to 1.35)</td>
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<td>1.39 (1.15 to 1.69)</td>
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<td>&lt;0.00001</td>
<td>Random</td>
<td>0.86 (0.74 to 1.00)</td>
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<td>Pro/Pro vs. (Pro/Arg+Arg/Arg)</td>
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<td>0.0002</td>
<td>Random</td>
<td>1.61 (1.28 to 2.02)</td>
<td>&lt;0.0001</td>
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<tr>
<td>Arg/Arg vs. (Pro/Arg+Pro/Pro)</td>
<td>12</td>
<td>&lt;0.0001</td>
<td>Random</td>
<td>0.77 (0.63 to 0.93)</td>
<td>0.009</td>
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<td>Hospital Pro allele vs. Arg allele</td>
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<td>0.42</td>
<td>Fixed</td>
<td>1.09 (0.94 to 1.26)</td>
<td>0.27</td>
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Abbreviation: OR, odds ratio.

**Table 2 Meta-analysis of the association of the effects of p53 codon 72 Arg/Pro gene polymorphism on colorectal cancer risk**

Discussion

In this informatics analysis, we confirmed that TP53 was associated with colorectal cancer, the alteration frequency of TP53 was 53% mutation and 7% deep deletion, and TP53 mRNA was highly expressed in colorectal cancer tissues compared with normal colorectal tissues. Additionally, the different expression levels of mRNA might have no correlation with the survival rate either in the COAD group or READ group (P > 0.05). It seems that in the READ group, the group with a lower level of mRNA expression had a higher overall survival. TP53 alteration frequency was different in different types of colorectal cancer, so we hypothesized that mutation or alteration of TP53 may play a key role in colorectal cancer.
Figure 4  (A) The forest plot of the association between Pro allele and colorectal cancer risk.  (B) The forest plot of the association between Pro/Pro genotype and colorectal cancer risk.  (C) The forest plot of the association between Arg/Arg genotype and colorectal cancer risk.
the Asian population. Finally, we found that TP53 Pro allele and Pro/Pro genotype were associated with colorectal cancer risk, but Arg/Arg genotype was not, in the Asian population. In the subgroup analysis, we found that TP53 codon 72 Pro/Arg gene polymorphism was associated with colorectal cancer risk in the meta-analysis of controls from the population-based trials. However, TP53 codon 72 Pro/Arg gene polymorphism was not associated with colorectal cancer risk in the meta-analysis of controls from the hospital-based trial.

TP53 is the most frequently mutated tumor promoting gene in cancer.\textsuperscript{36,37} It was reported that p53-deficiency leads to a high rate of spontaneous tumors in mice. Moreover, deletion of p53 and mutation of TP53 lead to tumor cell death and promote tumor progression.\textsuperscript{38} Our study also showed that there is a high overall survival rate in the READ group (Figure 3B). It might be because there is much more alteration frequency (mutation, deep deletion) of TP53 in the READ group (Figure 1B). If we could change the TP53 mutation or deletion, it may trigger tumor cell abolition.\textsuperscript{39} Loes et al\textsuperscript{40} reported the mutations of KRAS and BRAF to be a strong prognostic parameter in patients with metastatic colorectal cancer after treatment with partial liver resections, but not TP53. Chen et al\textsuperscript{41} suggested that TP53 and BAX inhibitions are closely related with STEDB1. Histone methyltransferase SETDB1 inhibits the expression of TP53 to promote the progression of colorectal cancer, so TP53 may play a role by regulating the other genes in colorectal cancer. Our results showed that APAF1, APC, and ASF1A may be three of the most frequently altered neighbor genes. Further research about this association is necessary.

In a previous study, Tian et al\textsuperscript{42} performed a meta-analysis aimed to shed new light on the precise association between TP53 variants and colorectal cancer, including 14 studies in Asian population. They reported that TP53 Arg72Pro polymorphism CC genotype may contribute to an increased risk of colorectal cancer among Asians.\textsuperscript{43} In our meta-analysis, we included more studies and found that Pro allele and TP53 Pro/Pro genotype were also associated with colorectal cancer risk, but Arg/Arg genotype was not, in Asian population. The results from our meta-analysis might be more robust. Then, we used the fixed effects model of meta-analysis to pool the OR for the association between TP53 Arg/Arg genotype and colorectal cancer in Asians, and we found that TP53 Arg/Arg genotype was associated with colorectal cancer in Asians. However, Asadi et al\textsuperscript{44} reported that TP53 Arg/Arg gene polymorphism is not a risk factor for colorectal cancer in the Iranian Azari population. This suggests that risks associated with mutation of TP53 are related to ethnicity. In brief, whether TP53 gene polymorphism or gene mutation has a relationship with age, sex, and pathological type of colorectal cancer is still unknown, and further research is needed.

Conclusions
TP53 is associated with colorectal cancer, but the different value levels of mRNA expression might have no association with survival rate of colorectal cancer. TP53 Pro allele and Pro/Pro genotype were associated with colorectal cancer risk in Asian population. More alteration or mutation research should be designed to confirm these findings in the future.

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