

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, OncoPrint, cBioPortal, and OncoPrint 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.^{1,2} 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.³ Finding a gene marker that can allow for better screening and earlier diagnosis of colorectal cancer could improve outcomes.

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The tumor protein p53 gene (TP53), located on chromosome 17p13, contains homozygous mutations in 50%–60% of human cancers.^{4,5} 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.⁵ 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.⁶ These mutations produce a protein with a reduced capacity to bind to a specific DNA sequence that regulates the p53 transcriptional pathway.⁶ Several studies reported that the mutation or alterations of TP53 gene have an effect on the prognosis and treatment of cancer.^{7–11} TP53 codon 72 Pro/Arg gene polymorphism has also been reported to be associated with colorectal cancer outcome.^{12–29}

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 OncoPrint, OncoPrint, 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 OncoPrint (online tool, www.oncoprint.org/, based on TCGA database) were used to identify and confirm the correlation of TP53 with cancers or colorectal cancer.^{30,31} cBioPortal was also used to identify the mutation status of TP53 gene. The OncoPrint (online tool, <http://www.oncoprint.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.³²

Results

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

The information on TP53 genes was freely available in OncoPrint 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

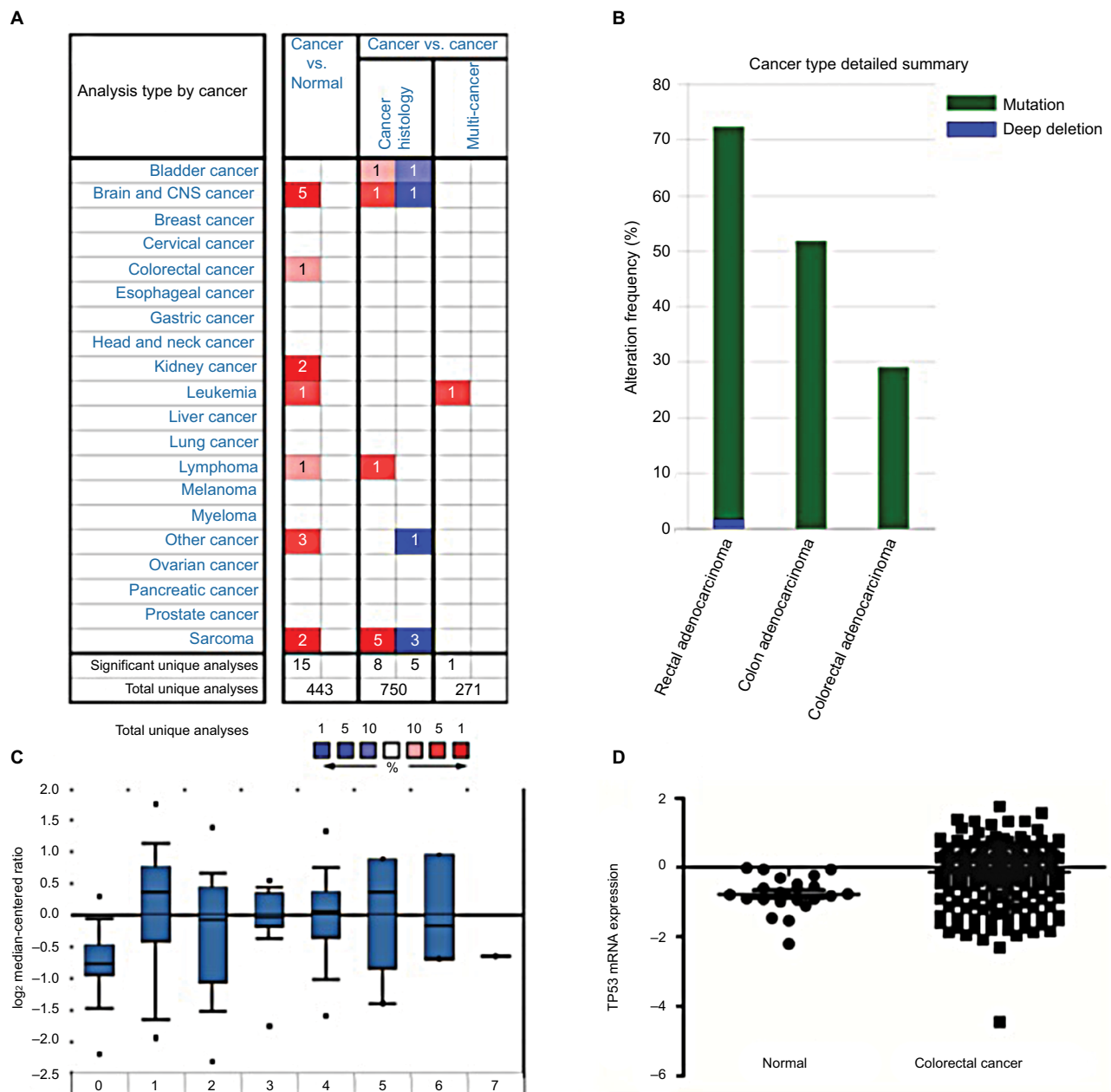


Figure 1 (A) The association of TP53 with colorectal cancer; the redder the square, the more related with cancer. (B) The mutation and deletion frequency in rectal cancer. (C) The log₂ median-centered ratio of the different types of colorectal cancer compared with normal samples. (D) The mRNA expression rate of TP53 in colorectal cancer and normal samples.

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

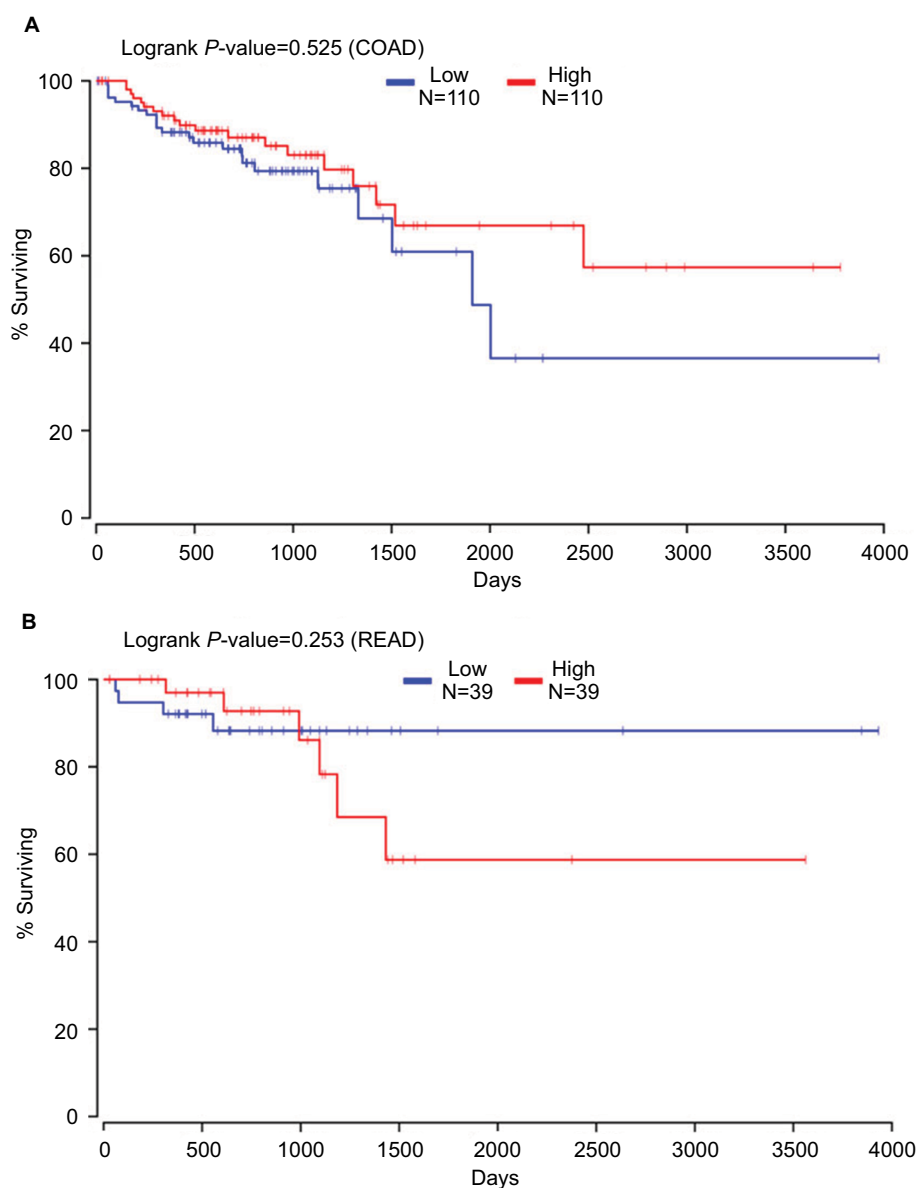


Figure 3 (A) The overall survival of RNA expression of TP53 in COAD. **(B)** The overall survival of RNA expression of TP53 in READ.

Abbreviations: COAD, colon adenocarcinoma; READ, rectal adenocarcinoma.

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).

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:

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

Author, year	Country/ District	Control source	Case			Control		
			Pro/Pro	Pro/Arg	Arg/Arg	Pro/Pro	Pro/Arg	Arg/Arg
Kawajiri et al 1993 ¹²	Japan	Population based	16	32	36	38	165	144
Murata et al 1996 ¹³	Japan	Hospital based	14	55	46	23	76	53
Wang et al 1999 ¹⁴	China	Hospital based	10	33	18	27	70	43
Hamajima et al 2002 ¹⁵	Japan	Hospital based	17	72	58	43	107	91
Zhu et al 2007 ¹⁶	China	Population based	85	117	83	105	321	244
Cao et al 2009 ¹⁷	Korea	Population based	35	67	54	39	140	114
Mojtahedi et al 2010 ¹⁸	Iran	Population based	23	63	46	28	77	58
Aizat et al 2011 ¹⁹	Malaysia	Hospital based	44	88	70	25	101	75
Dastjerdi 2011 ²⁰	Iran	Population based	52	101	97	61	113	76
Joshi et al 2011 ²¹	Japan	Population based	104	342	239	107	361	310
Song et al 2011 ²²	Korea	Population based	244	844	740	190	776	734
Zhang et al 2012 ²³	China	Hospital based	98	199	147	102	271	196
Oh et al 2014 ²⁴	Korea	Hospital based	76	247	222	65	218	145
Singamsetty et al 2014 ²⁵	India	Population based	39	48	16	25	45	37
Djansugurova et al 2015 ²⁶	Kazakhstan	Population based	29	28	13	15	47	25
Zahary et al 2015 ²⁷	Malaysia	Population based	34	43	27	14	57	33
Kamiza et al 2016 ²⁸	Taiwan	Population based	44	52	24	38	66	36
Rivu et al 2017 ²⁹	Bangladesh	Population based	61	138	89	38	98	159

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

Genetic contrasts	Number of studies	Q-test P-value	Model selected	OR (95%CI)	P-value
Pro allele vs. Arg allele	18	<0.00001	Random	1.20 (1.06 to 1.35)	0.003
Pro/Pro vs. (Pro/Arg+Arg/Arg)	18	<0.00001	Random	1.39 (1.15 to 1.69)	0.0007
Arg/Arg vs. (Pro/Arg+Pro/Pro)	18	<0.00001	Random	0.86 (0.74 to 1.00)	0.05
Population					
Pro allele vs. Arg allele	12	<0.00001	Random	1.33 (1.15 to 1.55)	0.0002
Pro/Pro vs. (Pro/Arg+Arg/Arg)	12	0.0002	Random	1.61 (1.28 to 2.02)	<0.0001
Arg/Arg vs. (Pro/Arg+Pro/Pro)	12	<0.0001	Random	0.77 (0.63 to 0.93)	0.009
Hospital					
Pro allele vs. Arg allele	6	0.08	Random	0.98 (0.84 to 1.14)	0.77
Pro/Pro vs. (Pro/Arg+Arg/Arg)	6	0.04	Random	1.03 (0.75 to 1.41)	0.88
Arg/Arg vs. (Pro/Arg+Pro/Pro)	6	0.42	Fixed	1.09 (0.94 to 1.26)	0.27

Abbreviation: OR, odds ratio.

OR=1.03, 95% CI: 0.75 to 1.41, $P=0.88$; Arg/Arg genotype: OR=1.09, 95% CI: 0.94 to 1.26, $P=0.27$; Table 2).

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.

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). Abderahmane 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

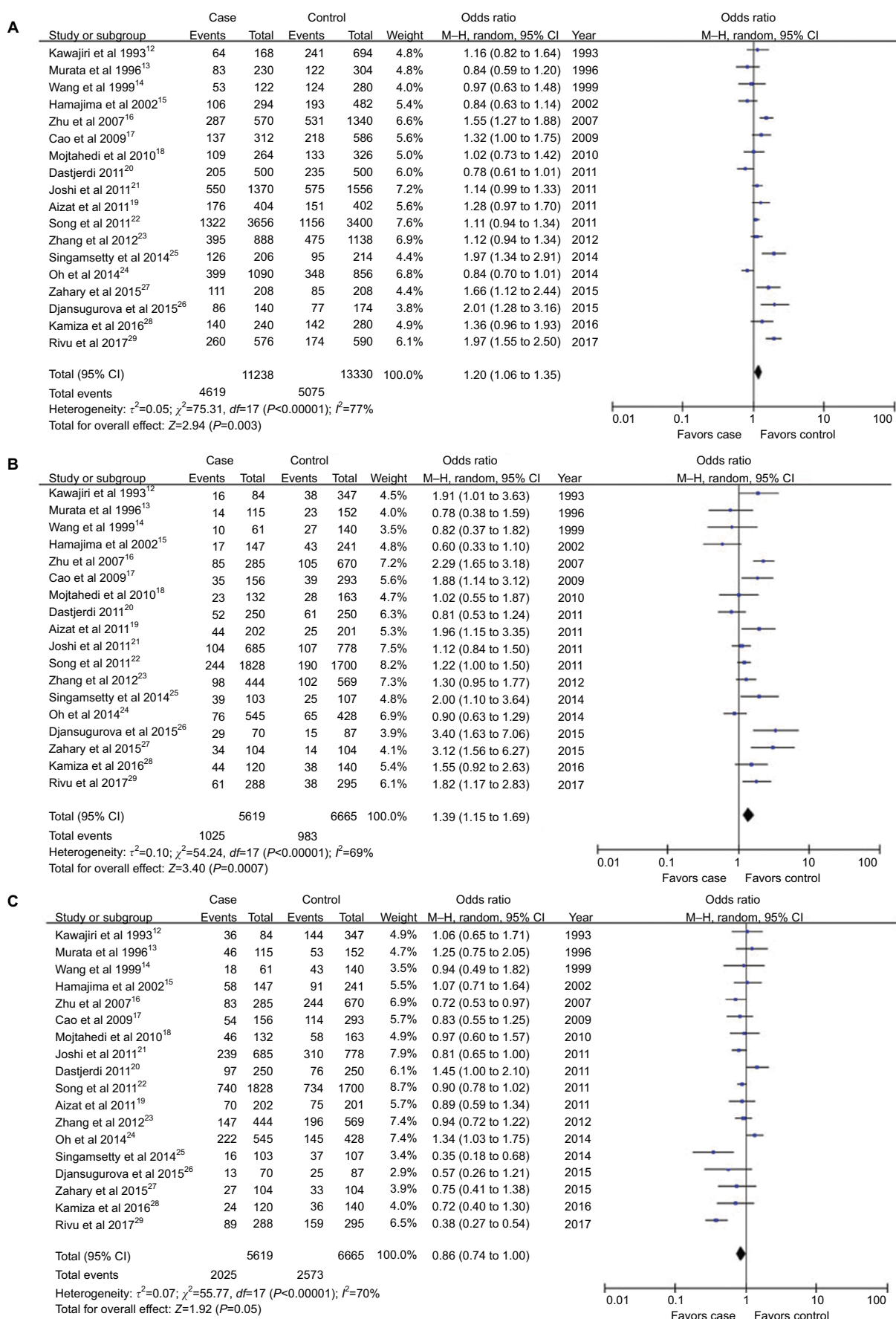


Figure 4 (A) The forest plot of the association between Pro allele and colorectal cancer risk. **(B)** The forest plot of the association between Pro/Pro genotype and colorectal cancer risk. **(C)** The forest plot of the association between Arg/Arg genotype and colorectal cancer risk.

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.^{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.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.³⁹ Loes et al⁴⁰ 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 al⁴¹ suggested that TP53 and BAX inhibitions were 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 al⁴² 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.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 al⁴³ 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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Disclosure

The authors report no conflicts of interest in this work.

References

1. Donovan MG, Selmin OI, Doetschman TC, Romagnolo DF. Mediterranean diet: prevention of colorectal cancer. *Front Nutr*. 2017;4:59.
2. Torre LA, Bray F, Siegel RL, et al. Global cancer statistics, 2012. *CA Cancer J Clin*. 2015;65(2):87–108.
3. Kim BR, Jeong YA, Na YJ, Ferlay J, Lortet-Tieulent J, Jemal A. Genipin suppresses colorectal cancer cells by inhibiting the Sonic Hedgehog pathway. *Oncotarget*. 2017;8(60):101952–101964.
4. Baugh EH, Ke H, Levine AJ, Bonneau RA, Chan CS. Why are there hotspot mutations in the TP53 gene in human cancers? *Cell Death Differ*. 2018;25(1):154–160.
5. Rivlin N, Brosh R, Oren M, Rotter V. Mutations in the p53 tumor suppressor gene: important milestones at the various steps of tumorigenesis. *Genes Cancer*. 2011;2(4):466–474.
6. Naccarati A, Polakova V, Pardini B, et al. Mutations and polymorphisms in TP53 gene—an overview on the role in colorectal cancer. *Mutagenesis*. 2012;27(2):211–218.
7. Zhang J, Yan S, Liu X, et al. Gender-related prognostic value and genomic pattern of intra-tumor heterogeneity in colorectal cancer. *Carcinogenesis*. 2017;38(8):837–846.
8. Muller PA, Vousden KH. Mutant p53 in cancer: new functions and therapeutic opportunities. *Cancer Cell*. 2014;25(3):304–317.
9. Bellini MF, Cadamuro AC, Succi M, Proença MA, Silva AE. Alterations of the TP53 gene in gastric and esophageal carcinogenesis. *J Biomed Biotechnol*. 2012;2012:891961.
10. Olivier M, Hollstein M, Hainaut P. TP53 mutations in human cancers: origins, consequences, and clinical use. *Cold Spring Harb Perspect Biol*. 2010;2(1):a001008.
11. Petitjean A, Achatz MI, Borresen-Dale AL, Hainaut P, Olivier M. TP53 mutations in human cancers: functional selection and impact on cancer prognosis and outcomes. *Oncogene*. 2007;26(15):2157–2165.
12. Kawajiri K, Nakachi K, Imai K, Watanabe J, Hayashi S. Germ line polymorphisms of p53 and CYP1A1 genes involved in human lung cancer. *Carcinogenesis*. 1993;14(6):1085–1089.
13. Murata M, Tagawa M, Kimura M, Kimura H, Watanabe S, Saisho H. Analysis of a germ line polymorphism of the p53 gene in lung cancer patients; discrete results with smoking history. *Carcinogenesis*. 1996;17(2):261–264.

14. Wang NM, Tsai CH, Yeh KT, Chen SJ, Chang JG. P53 codon 72Arg polymorphism is not a risk factor for carcinogenesis in the Chinese. *Int J Mol Med*. 1999;4(3):249–252.
15. Hamajima N, Matsuo K, Suzuki T, et al. No associations of p73 G4C14-to-A4T14 at exon 2 and p53 Arg72Pro polymorphisms with the risk of digestive tract cancers in Japanese. *Cancer Lett*. 2002;181(1):81–85.
16. Zhu ZZ, Wang AZ, Jia HR, et al. Association of the TP53 codon 72 polymorphism with colorectal cancer in a Chinese population. *Jpn J Clin Oncol*. 2007;37(5):385–390.
17. Cao Z, Song JH, Park YK, et al. The p53 codon 72 polymorphism and susceptibility to colorectal cancer in Korean patients. *Neoplasia*. 2009;56(2):114–118.
18. Mojtahedi Z, Haghshenas MR, Hosseini SV, Fattahi MJ, Ghaderi A. p 53 codon 72 polymorphism in stomach and colorectal adenocarcinomas in Iranian patients. *Indian J Cancer*. 2010;47(1):31–34.
19. Aizat AA, Shahpudin SN, Mustapha MA, et al. Association of Arg72Pro of P53 polymorphism with colorectal cancer susceptibility risk in Malaysian population. *Asian Pac J Cancer Prev*. 2011;12(11):2909–2913.
20. Dastjerdi MN. TP53 codon 72 polymorphism and P53 protein expression in colorectal cancer specimens in Isfahan. *Acta Med Iran*. 2011;49(2):71–77.
21. Joshi AM, Budhathoki S, Ohnaka K, et al. TP53 R72P and MDM2 SNP309 polymorphisms and colorectal cancer risk: the Fukuoka Colorectal Cancer Study. *Jpn J Clin Oncol*. 2011;41(2):232–238.
22. Song HR, Kweon SS, Kim HN, et al. p53 codon 72 polymorphism in patients with gastric and colorectal cancer in a Korean population. *Gastric Cancer*. 2011;14(3):242–248.
23. Zhang Y, Liu L, Tang Y, et al. Polymorphisms in TP53 and MDM2 contribute to higher risk of colorectal cancer in Chinese population: a hospital-based, case-control study. *Mol Biol Rep*. 2012;39(10):9661–9668.
24. Oh J, Kim JW, Lee BE, et al. Polymorphisms of the pri-miR-34b/c promoter and TP53 codon 72 are associated with risk of colorectal cancer. *Oncol Rep*. 2014;31(2):995–1002.
25. Singamsetty GK, Malempati S, Bhogadhi S, et al. TP53 alterations and colorectal cancer predisposition in south Indian population: a case-control study. *Tumour Biol*. 2014;35(3):2303–2311.
26. Djansugurova L, Zhunussova G, Khussainova E, et al. Association of DCC, MLH1, GSTT1, GSTM1, and TP53 gene polymorphisms with colorectal cancer in Kazakhstan. *Tumour Biol*. 2015;36(1):279–289.
27. Zahary MN, Ahmad Aizat AA, Kaur G, Yeh LY, Mazuwin M, Ankathil R. Polymorphisms of cell cycle regulator genes CCND1 G870A and TP53 C215G: association with colorectal cancer susceptibility risk in a Malaysian population. *Oncol Lett*. 2015;10(5):3216–3222.
28. Kamiza AB, Hsieh LL, Tang R, et al. TP53 polymorphisms and colorectal cancer risk in patients with lynch syndrome in Taiwan: a retrospective cohort study. *PLoS One*. 2016;11(12):e0167354.
29. Rivu SF, Apu MNH, Shabnaz S, et al. Association of TP53 codon 72 and CDH1 genetic polymorphisms with colorectal cancer risk in Bangladeshi population. *Cancer Epidemiol*. 2017;49:46–52.
30. Gao J, Aksoy BA, Dogrusoz U, et al. Integrative analysis of complex cancer genomics and clinical profiles using the cBioPortal. *Sci Signal*. 2013;6(269):p11.
31. Rhodes DR, Yu J, Shanker K, et al. ONCOMINE: a cancer microarray database and integrated data-mining platform. *Neoplasia*. 2004;6(1):1–6.
32. edited by Julian PTH, Sally G. *Cochrane Handbook for Systematic Reviews of Interventions*. Chichester; Hoboken NJ: John Wiley & Sons; 2008.
33. Dahabreh IJ, Linardou H, Bouzika P, Varvarigou V, Murray S. TP53 Arg72Pro polymorphism and colorectal cancer risk: a systematic review and meta-analysis. *Cancer Epidemiol Biomarkers Prev*. 2010;19(7):1840–1847.
34. Abderrahmane R, Louhibi L, Moghtit FZ, et al. TP53 Arg 72Pro and MDM2 SNP309 polymorphisms and colorectal cancer risk: a west Algerian population study. *Pathol Oncol Res*. 2015;21(3):629–635.
35. Khan MH, Khalil A, Rashid H. Evaluation of the p53 Arg72Pro polymorphism and its association with cancer risk: a HuGE review and meta-analysis. *Genet Res (Camb)*. 2015;97:e7.
36. Kandath C, McLellan MD, Vandin F, et al. Mutational landscape and significance across 12 major cancer types. *Nature*. 2013;502(7471):333–339.
37. Soussi T, Wiman KG. TP53: an oncogene in disguise. *Cell Death Differ*. 2015;22(8):1239–1249.
38. Donehower LA, Harvey M, Slagle BL, et al. Mice deficient for p53 are developmentally normal but susceptible to spontaneous tumours. *Nature*. 1992;356(6366):215–221.
39. Bykov VJN, Eriksson SE, Bianchi J, Wiman KG. Targeting mutant p53 for efficient cancer therapy. *Nat Rev Cancer*. 2018;18(2):89–102.
40. Loes IM, Immervoll H, Sorbye H, et al. Impact of KRAS, BRAF, PIK3CA, TP53 status and intraindividual mutation heterogeneity on outcome after liver resection for colorectal cancer metastases. *Int J Cancer*. 2016;139(3):647–656.
41. Chen K, Zhang F, Ding J, et al. Histone methyltransferase SETDB1 promotes the progression of colorectal cancer by inhibiting the expression of TP53. *J Cancer*. 2017;8(16):3318–3330.
42. Tian X, Dai S, Sun J, Jiang S, Jiang Y. The association between the TP53 Arg72Pro polymorphism and colorectal cancer: an updated meta-analysis based on 32 studies. *Oncotarget*. 2017;8(1):1156–1165.
43. Asadi M, Shanehbandi D, Zarintan A, et al. TP53 Gene Pro72Arg (rs1042522) single nucleotide polymorphism as not a risk factor for colorectal cancer in the Iranian Azari population. *Asian Pac J Cancer Prev*. 2017;18(12):3423–3427.

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