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ORIGINAL RESEARCH

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.[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 C**G**C to C**C**C (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 Oncolnc, 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.[30,31] 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.[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 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

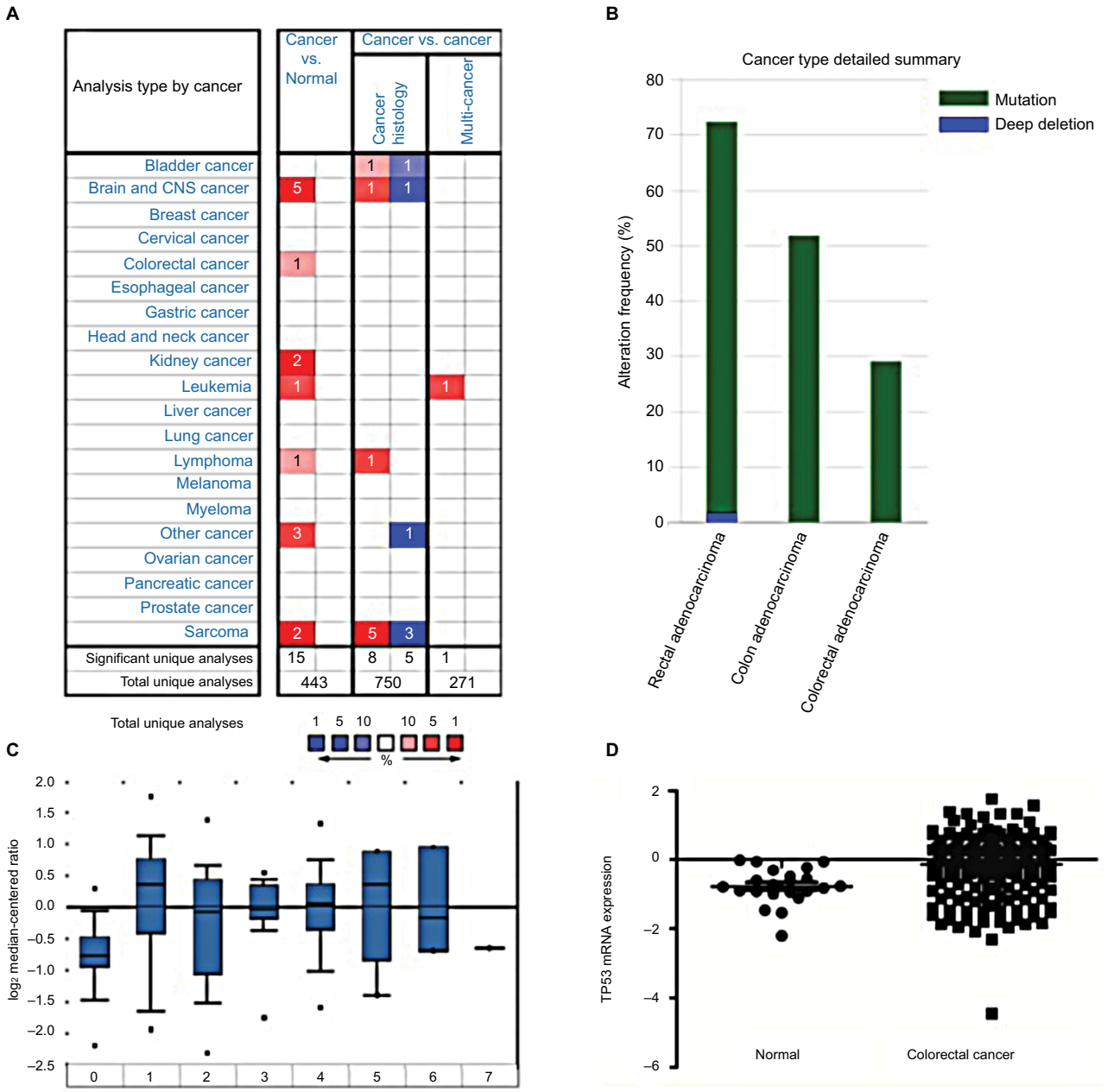


Figure 1 (**A**) The association of TP53 with colorectal cancer; the redder the square, the more related with cancer. (**B**) The mutation and deletion frequency in rectal cancer. (**C**) The log2 median-centered ratio of the different types of colorectal cancer compared with normal samples. (**D**)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

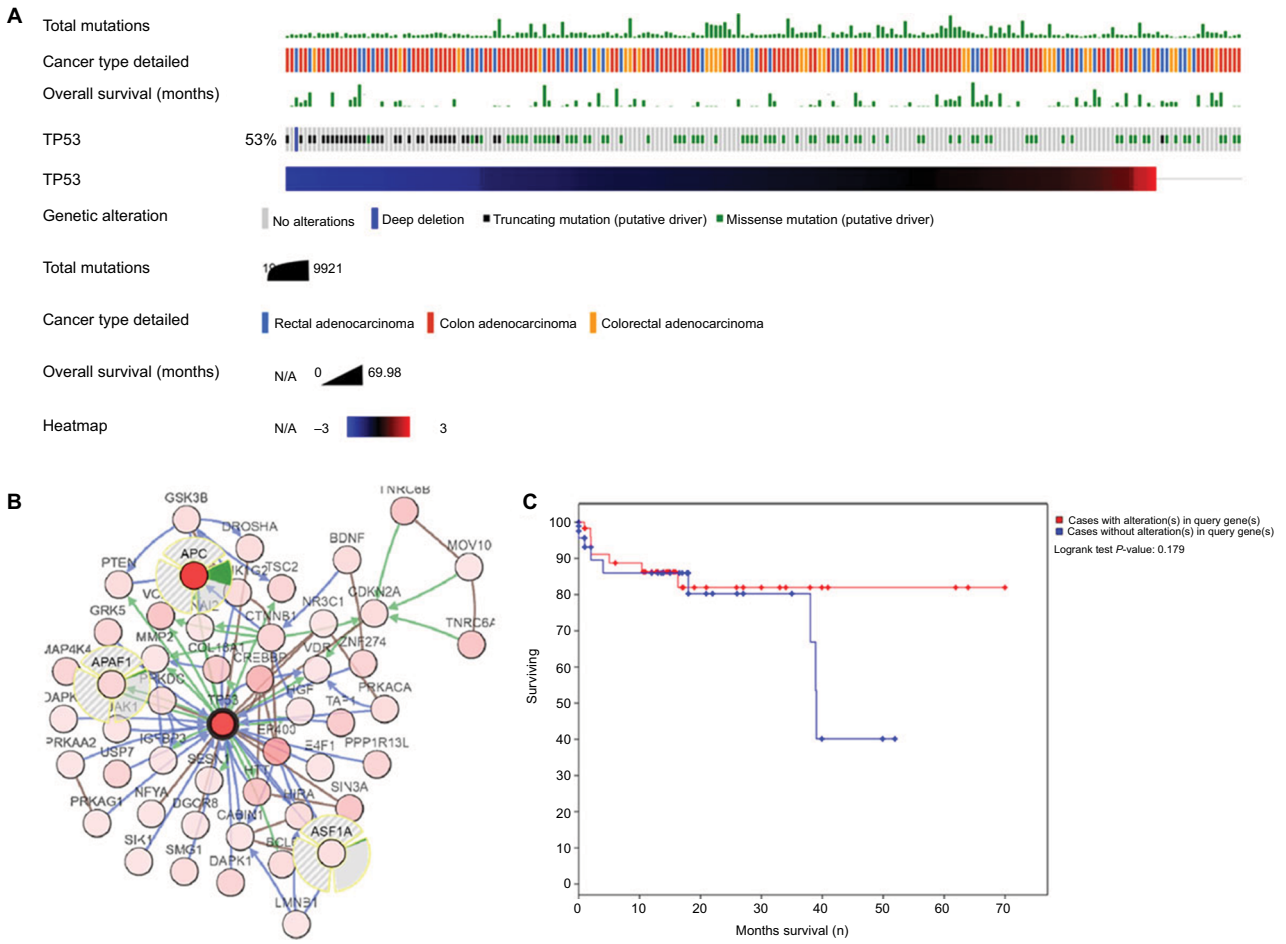


Figure 2 (**A**) The mutation, cancer type, overall survival, and heatmap in TP53. (**B**) The frequently altered neighbor genes of TP53. (**C**) The overall survival of TP53 alteration compared with nonalteration.
Abbreviation: N/A, not applicable.

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 Oncolnc 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

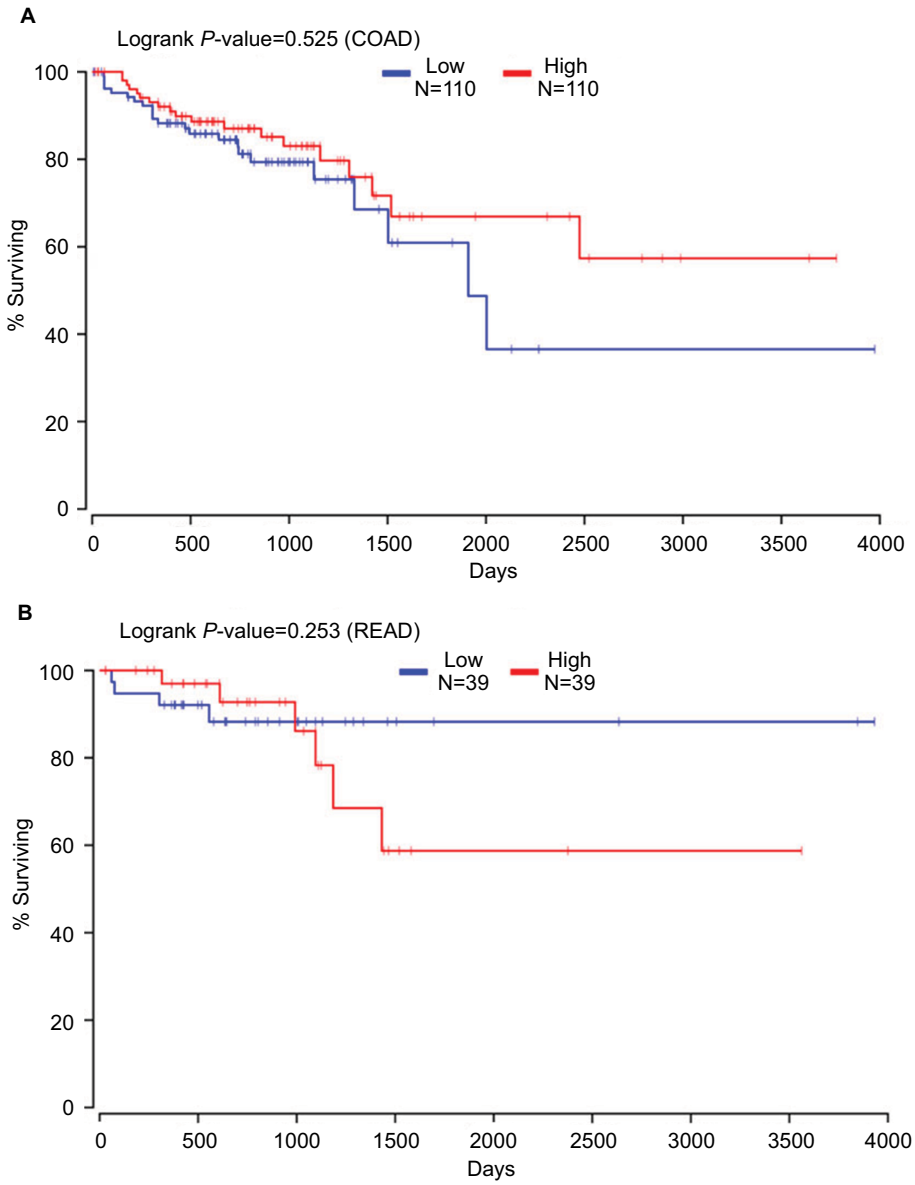


Figure 3 (**A**) The overall survival of RNA expression of TP53 in COAD.(**B**) The overall survival of RNA expression of TP53 in READ.
Abbreviations: COAD, colon adenocarcinoma; READ, rectal adenocarcinoma.

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.

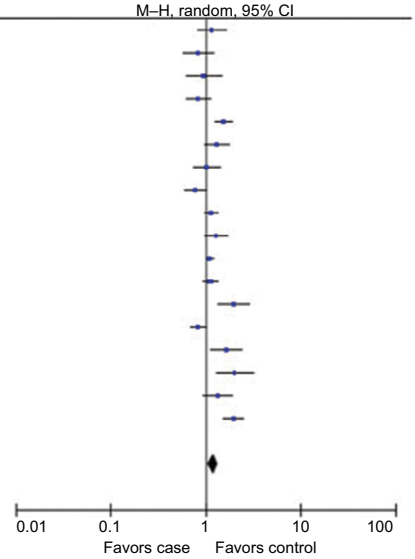
TP53 Arg72Pro mutation (rs1042522), one of the mutations in TP53, creates three different genotypes: Arg/Arg, Arg/Pro, and Pro/Pro. It is reported that the mutation or alterations of TP53 gene have a certain effect on the prognosis and treatment of cancer.[7–11] Dahabreh et al[33] indicated that TP53 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 al[34] 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

A

Study or subgroup	Case Events	Case Total	Control Events	Control Total	Weight	Odds ratio M–H, random, 95% CI	Year
Kawajiri et al 1993[12]	64	168	241	694	4.8%	1.16 (0.82 to 1.64)	1993
Murata et al 1996[13]	83	230	122	304	4.8%	0.84 (0.59 to 1.20)	1996
Wang et al 1999[14]	53	122	124	280	4.0%	0.97 (0.63 to 1.48)	1999
Hamajima et al 2002[15]	106	294	193	482	5.4%	0.84 (0.63 to 1.14)	2002
Zhu et al 2007[16]	287	570	531	1340	6.6%	1.55 (1.27 to 1.88)	2007
Cao et al 2009[17]	137	312	218	586	5.6%	1.32 (1.00 to 1.75)	2009
Mojtahedi et al 2010[18]	109	264	133	326	5.0%	1.02 (0.73 to 1.42)	2010
Dastjerdi 2011[20]	205	500	235	500	6.0%	0.78 (0.61 to 1.01)	2011
Joshi et al 2011[21]	550	1370	575	1556	7.2%	1.14 (0.99 to 1.33)	2011
Aizat et al 2011[19]	176	404	151	402	5.6%	1.28 (0.97 to 1.70)	2011
Song et al 2011[22]	1322	3656	1156	3400	7.6%	1.11 (0.94 to 1.34)	2011
Zhang et al 2012[23]	395	888	475	1138	6.9%	1.12 (0.94 to 1.34)	2012
Singamsetty et al 2014[25]	126	206	95	214	4.4%	1.97 (1.34 to 2.91)	2014
Oh et al 2014[24]	399	1090	348	856	6.8%	0.84 (0.70 to 1.01)	2014
Zahary et al 2015[27]	111	208	85	208	4.4%	1.66 (1.12 to 2.44)	2015
Djansugurova et al 2015[26]	86	140	77	174	3.8%	2.01 (1.28 to 3.16)	2015
Kamiza et al 2016[28]	140	240	142	280	4.9%	1.36 (0.96 to 1.93)	2016
Rivu et al 2017[29]	260	576	174	590	6.1%	1.97 (1.55 to 2.50)	2017
Total (95% CI)		11238		13330	100.0%	1.20 (1.06 to 1.35)	
Total events	4619		5075				

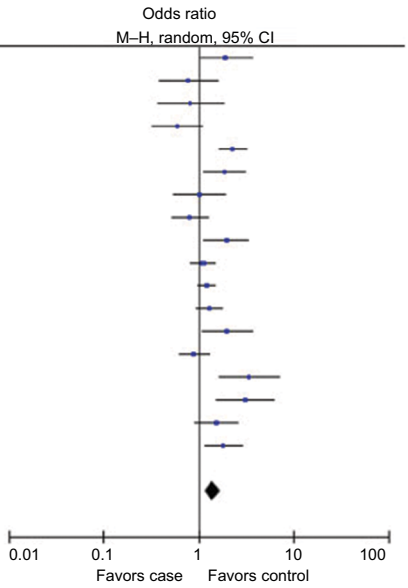
Heterogeneity: τ^2=0.05; χ^2=75.31, *df*=17 (*P*<0.00001); I^2=77%
Total for overall effect: *Z*=2.94 (*P*=0.003)



B

Study or subgroup	Case Events	Case Total	Control Events	Control Total	Weight	Odds ratio M–H, random, 95% CI	Year
Kawajiri et al 1993[12]	16	84	38	347	4.5%	1.91 (1.01 to 3.63)	1993
Murata et al 1996[13]	14	115	23	152	4.0%	0.78 (0.38 to 1.59)	1996
Wang et al 1999[14]	10	61	27	140	3.5%	0.82 (0.37 to 1.82)	1999
Hamajima et al 2002[15]	17	147	43	241	4.8%	0.60 (0.33 to 1.10)	2002
Zhu et al 2007[16]	85	285	105	670	7.2%	2.29 (1.65 to 3.18)	2007
Cao et al 2009[17]	35	156	39	293	5.6%	1.88 (1.14 to 3.12)	2009
Mojtahedi et al 2010[18]	23	132	28	163	4.7%	1.02 (0.55 to 1.87)	2010
Dastjerdi 2011[20]	52	250	61	250	6.3%	0.81 (0.53 to 1.24)	2011
Aizat et al 2011[19]	44	202	25	201	5.3%	1.96 (1.15 to 3.35)	2011
Joshi et al 2011[21]	104	685	107	778	7.5%	1.12 (0.84 to 1.50)	2011
Song et al 2011[22]	244	1828	190	1700	8.2%	1.22 (1.00 to 1.50)	2011
Zhang et al 2012[23]	98	444	102	569	7.3%	1.30 (0.95 to 1.77)	2012
Singamsetty et al 2014[25]	39	103	25	107	4.8%	2.00 (1.10 to 3.64)	2014
Oh et al 2014[24]	76	545	65	428	6.9%	0.90 (0.63 to 1.29)	2014
Djansugurova et al 2015[26]	29	70	15	87	3.9%	3.40 (1.63 to 7.06)	2015
Zahary et al 2015[27]	34	104	14	104	4.1%	3.12 (1.56 to 6.27)	2015
Kamiza et al 2016[28]	44	120	38	140	5.4%	1.55 (0.92 to 2.63)	2016
Rivu et al 2017[29]	61	288	38	295	6.1%	1.82 (1.17 to 2.83)	2017
Total (95% CI)		5619		6665	100.0%	1.39 (1.15 to 1.69)	
Total events	1025		983				

Heterogeneity: τ^2=0.10; χ^2=54.24, *df*=17 (*P*<0.00001); I^2=69%
Total for overall effect: *Z*=3.40 (*P*=0.0007)



C

Study or subgroup	Case Events	Case Total	Control Events	Control Total	Weight	Odds ratio M–H, random, 95% CI	Year
Kawajiri et al 1993[12]	36	84	144	347	4.9%	1.06 (0.65 to 1.71)	1993
Murata et al 1996[13]	46	115	53	152	4.7%	1.25 (0.75 to 2.05)	1996
Wang et al 1999[14]	18	61	43	140	3.5%	0.94 (0.49 to 1.82)	1999
Hamajima et al 2002[15]	58	147	91	241	5.5%	1.07 (0.71 to 1.64)	2002
Zhu et al 2007[16]	83	285	244	670	6.9%	0.72 (0.53 to 0.97)	2007
Cao et al 2009[17]	54	156	114	293	5.7%	0.83 (0.55 to 1.25)	2009
Mojtahedi et al 2010[18]	46	132	58	163	4.9%	0.97 (0.60 to 1.57)	2010
Joshi et al 2011[21]	239	685	310	778	7.9%	0.81 (0.65 to 1.00)	2011
Dastjerdi 2011[20]	97	250	76	250	6.1%	1.45 (1.00 to 2.10)	2011
Song et al 2011[22]	740	1828	734	1700	8.7%	0.90 (0.78 to 1.02)	2011
Aizat et al 2011[19]	70	202	75	201	5.7%	0.89 (0.59 to 1.34)	2011
Zhang et al 2012[23]	147	444	196	569	7.4%	0.94 (0.72 to 1.22)	2012
Oh et al 2014[24]	222	545	145	428	7.4%	1.34 (1.03 to 1.75)	2014
Singamsetty et al 2014[25]	16	103	37	107	3.4%	0.35 (0.18 to 0.68)	2014
Djansugurova et al 2015[26]	13	70	25	87	2.9%	0.57 (0.26 to 1.21)	2015
Zahary et al 2015[27]	27	104	33	104	3.9%	0.75 (0.41 to 1.38)	2015
Kamiza et al 2016[28]	24	120	36	140	4.0%	0.72 (0.40 to 1.30)	2016
Rivu et al 2017[29]	89	288	159	295	6.5%	0.38 (0.27 to 0.54)	2017
Total (95% CI)		5619		6665	100.0%	0.86 (0.74 to 1.00)	
Total events	2025		2573				

Heterogeneity: τ^2=0.07; χ^2=55.77, *df*=17 (*P*<0.00001); I^2=70%
Total for overall effect: *Z*=1.92 (*P*=0.05)

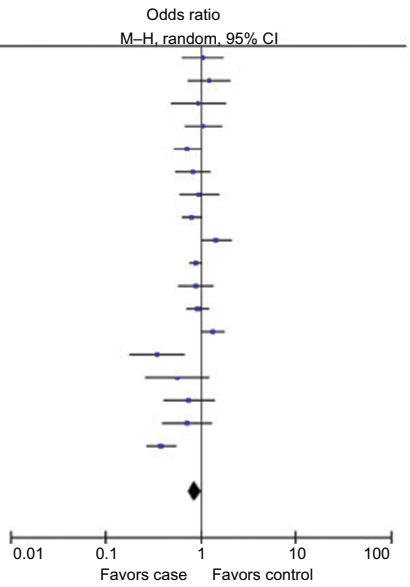


Figure 4 (**A**) The forest plot of the association between Pro allele and colorectal cancer risk. (**B**) The forest plot of the association between Pro/Pro genotype and colorectal cancer risk. (**C**) The forest plot of the association between Arg/Arg genotype and colorectal cancer risk.

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 al[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[41] 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 al[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.[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[43] 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.

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