Gastric Cancer (2011) 14:242–247
DOI 10.1007/s10120-011-0034-4

ORIGINAL ARTICLE

p53 codon 72 polymorphism in patients with gastric and colorectal cancer in a Korean population

Hye-Rim Song · Sun-Seog Kweon · Hee Nam Kim · Jin-Mei Piao · Woo-Jun Yun · Jin-Su Choi · Jun-Eul Hwang · Ju-Young Yoon · Hyeong-Rok Kim · Young-Kyu Park · Soo-Hyun Kim · Yoo-Duk Choi · Min-Ho Shin

Received: 2 November 2010 / Accepted: 13 February 2011 / Published online: 2 April 2011

Abstract
Background The common p53 codon 72 polymorphism has been investigated as a risk factor for cancer in different populations; however, the results have been inconsistent. This study investigated the risk of developing gastric or colorectal cancer associated with the p53 codon 72 polymorphism in a Korean population.
Methods We conducted a large-scale case–control study that included 2,213 gastric cancer patients; 1,829 colorectal cancer patients; and 1,700 healthy controls. Genotyping was performed with real-time polymerase chain reaction (PCR), using a TaqMan single-nucleotide polymorphism (SNP) genotyping assay.
Results The frequencies of Arg/Arg, Arg/Pro, and Pro/Pro genotypes of the p53 codon 72 polymorphism were 43.3, 42.0, and 13.0% in the gastric cancer patients; 40.5, 45.0, and 14.0% in the colorectal cancer patients; and 43.2, 45.6, and 11.2% in the controls, respectively. The Pro/Pro genotype was associated with an increased risk of gastric [age- and sex-adjusted odds ratio (OR) = 1.25, 95% confidence interval (CI) = 1.01–1.56, $P = 0.04$] and colorectal cancer (OR = 1.36, 95% CI = 1.07–1.72, $P = 0.01$). There were no significant interactions between the p53 codon 72 polymorphism and smoking or drinking.
Conclusions Our results suggest that the Pro/Pro genotype is associated with modest increases in the risks of gastric cancer and colorectal cancer in a Korean population.

Keywords p53 codon 72 polymorphism · Gastric cancer · Colorectal cancer

Introduction

Gastric and colorectal cancers are the most common cancers in the world. Although the incidence and mortality of gastric cancer have fallen dramatically worldwide, the

H.-R. Song · S.-S. Kweon · J.-M. Piao · W.-J. Yun · J.-S. Choi · M.-H. Shin (✉)
Department of Preventive Medicine, Chonnam National University Medical School, 5, Hak 1-dong, Dong-gu, Gwangju 501-746, South Korea
e-mail: mhshinx@paran.com

S.-S. Kweon
Jeonnam Regional Cancer Center, Chonnam National University Hwasun Hospital, Hwasun, Korea

H. N. Kim
Genome Research Center for Hematopoietic Diseases, Chonnam National University Hwasun Hospital, Hwasun, Korea

J.-E. Hwang · J.-Y. Yoon
Department of Hemato-Oncology, Chonnam National University Medical School, Kwangju, Korea

H.-R. Kim · Y.-K. Park
Department of Surgery, Chonnam National University Hwasun Hospital, Hwasun, Korea

S.-H. Kim
Department of Laboratory Medicine, Chonnam National University Medical School, Gwangju, Korea

Y.-D. Choi
Department of Pathology, Chonnam National University Medical School, Gwangju, Korea

J.-M. Piao
Yanbian University College of Medicine, 121 Juzi Street, Yanji 133000, Jilin Province, China

current mortality is 43/100,000 in Korea and the age-adjusted incidence is as high as 70/100,000 in Korean males [1, 2]. Colorectal cancer is thought to be less common among Asians compared with Caucasians; however, recent studies in Korea and Japan have shown not only high incidence rates, but also an increasing trend in the population [3]. Gastric and colorectal cancer are described by a multistep genetic model, in which mutations within several genes, including that encoding p53, accumulate during the progression from a normal epithelium to adenoma to invasive cancer [4–6].

TP53, which encodes p53, is a tumor suppressor gene and key player in the stress responses that preserve genomic stability, responding to a variety of insults, including DNA damage, hypoxia, metabolic stress, and oncogene activation [7, 8]. Mutations in p53 occur in at least 50% of all cancers, and more than 90% of these eliminate the ability of p53 to bind its DNA targets, underscoring the importance of this protein in tumorigenesis [9]. Recently, several common polymorphisms in *TP53* have been described, including a codon 72 polymorphism (rs1042522), which involves the substitution of arginine (CGC) by proline (CCC) in exon 4. The area around exon 4 in *TP53* encodes amino acids that lie close to the central hydrophobic area, which determines the conformation of the protein and, consequently, DNA-specific binding [10]. Changes in its amino acid sequence can alter the ability of p53 to bind to response elements in target genes, alter recognition motifs for post-translational modifications, or alter p53 stability and interactions with other proteins [11–14]. Such changes may contribute to tumor progression and a poor prognosis [15].

The p53 codon 72 polymorphism is associated with an increased risk of a number of cancers, including gastric and colorectal cancers [16–19]. In addition, several studies have linked environmental factors such as cigarette smoking, heavy alcohol consumption, micronutrient deficiency, and dietary carcinogen exposure to these cancers [19, 20]. However, the results have been inconsistent. Therefore, we designed a large-scale case–control study to evaluate the potential role of the p53 codon 72 polymorphism in gastric and colorectal cancer risk in Korea. We also assessed interactions between the p53 codon 72 polymorphism and such environmental factors as age, cigarette smoking, and alcohol consumption; additionally, we determined the risk based on TNM stage, anatomical tumor site, and histological type.

Methods

Subjects

The study population consisted of 2,213 patients with newly diagnosed gastric cancer, 1,829 patients with newly diagnosed colorectal cancer, and 1,700 population-based controls. In all enrolled patients (cases) the disease was pathologically confirmed by Chonnam National University Hwasun Hospital between April 2004 and June 2008. Patients with secondary or recurrent tumors were excluded. The tumor stages were classified according to the TNM classification, including clinical or pathological TNM stages. Gastric cancer was classified by anatomical site as cardia (C16.0) or non-cardia (C16.1–16.8) and by histological type, as intestinal, diffuse, or mixed type. Colorectal cancer was classified by anatomical site as right (C18.0–18.4), left (C18.5–18.7), or rectum (C20.9).

The control group ($n = 1{,}700$) consisted of participants in the Thyroid Disease Prevalence Study conducted from July 2004 to January 2006 in Yeonggwang and Muan Counties of Jeollanam-do Province and in Namwon City of Jeollabuk-do, Korea. A total of 4,018 subjects, aged 50.6 ± 14.6 years (range 20–74 years), were randomly selected by 5-year age strata and sex. Of the total number, 3,486 were eligible subjects. Of those eligible, 1,700 (48.8% of the eligible subjects; 821 men and 879 women), aged 52.2 ± 14.3 years, underwent clinical examinations. At the time of their peripheral blood collections, all case and control subjects provided their informed consent to participate in this study. This study was approved by the Institutional Review Board of the Chonnam National University Hwasun Hospital in Hwasun, Korea.

Genotyping

Genomic DNA was extracted from peripheral blood using a QIAamp DNA Blood Mini Kit (Qiagen, Valencia, CA, USA), according to the manufacturer's protocol. Genotyping was performed with real-time polymerase chain reaction (PCR), using a TaqMan (Sigma-Proligo, The Woodlands, TX, USA) single-nucleotide polymorphism (SNP) genotyping assay. PCR primers and probes were designed and synthesized by Sigma-Aldrich (Singapore). PCR primers producing a 122-bp amplicon were as follows: forward primer, 5′-TCCAGATGAAGCTCCCAG AATG-3′ and reverse primer, 5′-GGGAAGGGACAGA AGATGACAG-3′. Dual-labeled probes were 5′-FAM-CTGCTCCCCCCGTGGCCCC-3′ for the C allele and 5′-HEX-CTGCTCCCCGCGTGGCCCC-3′ for the G allele. Real-time PCR was performed using a Rotor-Gene 3000 multiplex system (Corbett Research, Sydney, Australia) in a 10-μL reaction volume containing 200 nM PCR primer, 10-10 nM each probe, 0.5 U f-taq polymerase (Solgent, Daejeon, Korea), and 40 ng of genomic DNA.

Statistical analysis

A t- test was used to evaluate differences in continuous variables and the χ^2 test was used for categorical variables

in the demographic characteristics of the subjects. Adjusted odds ratios (ORs) and their 95% confidence intervals (CIs) were calculated using logistic regression models, adjusted for age and sex, to estimate the association between genotype and gastric cancer and colorectal cancer. Subjects with the wild-type genotype (p53 codon 72 Arg/Arg) were considered to have a baseline risk. The expected frequency of control genotypes was checked by the Hardy–Weinberg equilibrium test. Interactions of genotype with age, smoking, and alcohol consumption were estimated using a logistic regression model, which included an interaction term, as well as variables for exposure (smoking and alcohol drinking), genotypes, and potential confounders (sex and age). The subjects for whom there were missing data for smoking, drinking, TNM stage, anatomical site, and histological type were excluded in the interaction analysis related to these variables. All tests were conducted at the $P = 0.05$ level of significance, and were done using SPSS for Windows version 16.0 (SPSS, Chicago, IL, USA).

Results

The demographic and tumor characteristics of the subjects are summarized in Table 1. Because one of the colorectal cancers could not be genotyped, our ultimate sample pool included 2,213 gastric cancers; 1,828 colorectal cancers; and 1,700 controls. Compared with the controls, both cancer groups were older, included fewer females, and had fewer drinkers. The proportion of smokers in the gastric cancer group was higher than that in the controls, while the proportion among the colorectal cancer cases was lower than that in the controls.

Table 2 shows the genotype distributions for the p53 codon 72 polymorphism in gastric and colorectal cancer. The observed genotype frequencies among the controls were in Hardy–Weinberg equilibrium ($P = 0.516$). Compared with Arg/Arg, the Pro/Pro genotype was significantly associated with increased risks of gastric [odds ratio (OR) = 1.276; 95% confidence interval (CI) = 1.026–1.587] and colorectal cancer (OR = 1.343; 95% CI = 1.056–1.693).

As shown in Table 3, the OR of the Pro/Pro genotype was higher in gastric cardia cancer (OR = 2.476; 95% CI = 1.339–4.580) than in gastric non-cardia cancer (OR = 1.249; 95% CI = 1.001–1.558). Interestingly, in contrast to previous studies, stratification analyses by the histological type of gastric cancer indicated that the Pro/Pro genotype was associated with an increased risk of only the intestinal type (OR = 1.401; 95% CI = 1.076–1.823), but not of the diffuse (OR = 1.17; 95% CI = 0.86–1.60) and mixed types (OR = 1.08; 95% CI = 0.68–1.71). We did not find any significant associations between the p53 codon 72 polymorphism and other subgroups. Age, smoking, and drinking did not modify the association between the p53 codon 72 genotypes and the risk of gastric or colorectal cancer (Table 4).

Table 1 General characteristics of subjects

Characteristics	Controls	Gastric cancer	Colorectal cancer
No.	1,700	2,213	1,828
Age, years (range)	52.2 (20–74)	60.2 (21–87)*	61.9 (22–88)**
≤65 Years	1,321 (77.7)	1,314 (59.4)	984 (53.9)
>65 Years	379 (22.3)	899 (40.6)*	844 (46.1)**
Sex			
Male	821 (48.3)	1,510 (68.2)	1,148 (62.8)
Female	879 (51.7)	703 (31.8)*	680 (37.2)**
Smoking habit			
Never	1,000 (58.8)	1,127 (50.9)	1,137 (62.2)
Ever	655 (38.5)	997 (45.1)*	581 (31.8)**
Missing data	45 (2.6)	89 (4.0)	110 (6.0)
Drinking habit			
Never	825 (48.5)	1,198 (54.1)	1,084 (59.3)
Current	833 (49.0)	921 (41.6)*	622 (34.1)**
Missing data	42 (2.5)	94 (4.3)	122 (6.7)
TNM stage			
I		1,138 (51.4)	291 (15.9)
II		305 (13.8)	546 (29.9)
III		290 (13.1)	614 (33.6)
IV		386 (17.4)	230 (12.6)
Unspecified stage		94 (4.2)	147 (8.0)
Tumor site			
Gastric cancer			
Cardia		106 (4.8)	
Non-cardia		2,093 (94.6)	
Unspecified site		14 (0.6)	
Colorectal cancer			
Right colon			**377 (20.6)**
Left colon			**450 (24.6)**
Rectum			996 (54.5)
Multiple sites			**5 (0.2)**
Histological type			
Intestinal		1,286 (58.1)	
Diffuse		561 (25.4)	
Mixed		240 (10.8)	
Unspecified type		126 (5.7)	

* $P < 0.05$ Gastric cancer compared with control; ** $P < 0.05$ colorectal cancer compared with control

Right colon: cecum, ascending colon, hepatic flexure, transverse colon

Left colon: descending and sigmoid colon, splenic flexure

Multiple sites: overlapping lesion of colon

Table 2 p53 codon 72 polymorphisms and adjusted odds ratios for gastric and colorectal cancers

p53 Arg72Pro	Controls	Gastric cancer	Colorectal cancer	Gastric cancer		Colorectal cancer	
				OR (95% CI)	*P* value	OR (95% CI)	*P* value
Arg/Arg	734 (43.2)	939 (42.4)	740 (40.5)	1		1	
Arg/Pro	776 (45.6)	977 (44.1)	844 (46.1)	0.99 (0.86–1.14)	0.88	1.08 (0.93–1.26)	0.33
Pro/Pro	190 (11.2)	297 (13.4)	244 (13.3)	1.28 (1.03–1.59)	0.03	1.34 (1.06–1.69)	0.01
Arg	2,244 (66.0)	2,855 (64.5)	2,324 (63.6)	1		1	
Pro	1,156 (34.0)	1,571 (35.5)	1,332 (36.4)	1.09 (0.98–1.20)	0.10	1.13 (0.98–1.31)	0.10

OR odds ratio adjusted for age and sex, *CI* confidence interval

Table 3 Association between p53 codon 72 polymorphisms and clinicopathological characteristics

	Arg/Pro versus Arg/Arg OR (95% CI)	Pro/Pro versus Arg/Arg OR (95% CI)
Gastric cancer		
TNM stage		
I + II	1.00 (0.85–1.17)	1.34 (1.05–1.71)
III + IV	0.97 (0.80–1.19)	1.23 (0.91–1.67)
Tumor site		
Cardia	1.53 (0.97–2.42)	2.48 (1.34–4.58)
Non-cardia	0.97 (0.84–1.12)	1.25 (1.00–1.56)
Histological type		
Intestinal	1.04 (0.87–1.23)	1.40 (1.08–1.82)
Diffuse	0.96 (0.78–1.18)	1.17 (0.86–1.60)
Mixed	0.95 (0.71–1.29)	1.08 (0.68–1.71)
Colorectal cancer		
TNM stage		
I + II	1.15 (0.95–1.39)	1.38 (1.03–1.85)
III + IV	1.03 (0.86–1.25)	1.43 (1.08–1.88)
Tumor site		
Right colon	**0.95 (0.74–1.22)**	**1.40 (0.97–2.01)**
Left colon	**0.99 (0.79–1.26)**	**1.27 (0.89–1.80)**
Rectum	1.20 (1.00–1.44)	1.39 (1.06–1.82)

Multiple site cancers are not included in this analysis by tumor site

OR odds ratio adjusted for age and sex, *CI* confidence interval

Right colon: cecum, ascending colon, hepatic flexure, transverse colon

Left colon: descending and sigmoid colon, splenic flexure

Multiple sites: overlapping lesion of colon

Discussion

In this case-control study, we investigated the association between the p53 codon 72 polymorphism and susceptibility to gastric and colorectal cancers in a Korean population. We found that the genotype distribution differed significantly between the patients with gastric and colorectal cancer and the controls. Subgroup analyses in gastric cancer showed that the OR of the Pro/Pro genotype was higher in cardia cancer than in non-cardia cancer and was higher in the intestinal type than in the diffuse and mixed types.

Several case–control studies have examined the association between the p53 codon 72 polymorphism and the risk of gastric cancer. In a Chinese study of 206 gastric cancer patients and 415 healthy controls, Mu et al. [21] showed that patients carrying the Pro/Pro genotype had a borderline increased risk of developing gastric cancer. Yi et al. [17] analyzed 291 cases and 216 controls in a Korean population and found that the p53 codon 72 Pro/Pro genotype was associated with a 3.9-fold increased risk of gastric cancer. These results are consistent with our, larger, study. By contrast, two studies reported that the Arg/Arg genotype was associated with an increased risk of gastric cancer [16, 22], while other studies found no association [20, 23–27]. Although the reason for these inconsistencies is unclear, they may be explained by differences in ethnicity, small numbers of patients, and substantial interindividual variation in the susceptibility to genetic events and tumor development.

We also found a possible increased risk of colorectal cancer associated with the Pro/Pro genotype. An earlier colorectal cancer study of a Chinese population reported that the p53 codon 72 Pro/Pro genotype had a significant dose-dependent effect on colorectal cancer risk (OR = 1.6; 95% CI = 1.17–2.18 vs. OR = 2.37; 95% CI = 1.61–3.47 for Arg/Pro vs. Pro/Pro) [19]. Although we did not find a dose-dependent effect, our results are in line with those of Zhu et al. [19]. Conversely, three Caucasian studies with small sample sizes (from $n = 53$ to $n = 93$) found a significant association between the Arg/Arg genotype and an increased risk of colorectal cancer [28–30], while two larger studies, one with 442 cases and 904 controls in the United States [18] and one with 352 cases and 316 controls in Spain [31], found no association between the p53 codon 72 polymorphism and the risk of colorectal cancer.

In the present study, subgroup analysis in gastric cancer demonstrated that the effect size of the Pro/Pro genotype was larger in cardia cancer than in non-cardia cancer and

Table 4 Interaction between p53 polymorphisms and smoking and drinking habit and age for gastric and colorectal cancer risk

	Arg/Pro versus Arg/Arg OR (95% CI)	Pro/Pro versus Arg/Arg OR (95% CI)	*P* for interaction[a]
Gastric cancer			
Smoking habit			
Never	0.93 (0.76–1.13)	1.38 (1.03–1.85)	
Ever	1.16 (0.93–1.44)	1.21 (0.86–1.69)	0.18
Drinking habit			
Never	0.99 (0.80–1.23)	1.31 (0.96–1.80)	
Current	1.05 (0.85–1.29)	1.23 (0.89–1.69)	0.86
Age			
≤65 Years	0.97 (0.82–1.16)	1.26 (0.97–1.63)	
>65 Years	1.02 (0.79–1.33)	1.36 (0.90–2.05)	0.90
Colorectal cancer			
Smoking habit			
Never	1.07 (0.87–1.32)	1.49 (1.09–2.02)	
Ever	1.13 (0.88–1.93)	1.32 (0.91–1.93)	0.99
Drinking habit			
Never	1.09 (0.87–1.36)	1.30 (0.93–1.81)	
Current	1.08 (0.86–1.36)	1.46 (0.03–2.07)	0.99
Age			
≤65 Years	0.99 (0.82–1.19)	1.34 (1.02–1.77)	
>65 Years	1.30 (0.96–1.69)	1.31 (0.86–2.00)	0.61

OR adjusted for age and sex

[a] *P* value for heterogeneity

larger in the intestinal type than in the diffuse and mixed types. It has been postulated that gastric cardia cancer and gastric non-cardia cancer differ in their epidemiological characteristics, etiology, pathogenesis, and clinical behavior [2]. Like the differences in epidemiology and pathogenesis according to tumor location, histological research has suggested that the intestinal and diffuse types of gastric cancer also have distinct characteristics. The intestinal type predominates in high-risk geographic areas such as East Asia, and is related to the prevalence of *Helicobacter pylori* infection among the elderly, whereas the diffuse type is found more uniformly worldwide and is apparently unrelated to *H. pylori* prevalence [2]. The exact biological mechanism underlying these differences is unclear; thus, a well-designed study is needed to elucidate the role of p53 codon 72 polymorphism in gastric tumorigenesis.

We found no interaction between the p53 codon 72 polymorphism and age, smoking, or drinking in gastric and colorectal cancer. Previously, Sul et al. [20] reported no interaction between the p53 codon 72 polymorphism and smoking or alcohol for gastric cancer. Zhu et al. [19] indicated that there was no interaction between alcohol consumption and the p53 codon 72 genotype in relation to colorectal cancer [19]. These findings are consistent with our results.

There are certain limitations to our study. First, we cannot rule out the possibility that differential misclassification bias occurred in our study, because we gathered information about smoking and drinking retrospectively from electronic medical records in both case groups, while we gathered information about these factors from cross-sectional surveys in the controls. Second, we did not consider other genetic polymorphisms.

The major strength of our study is its large sample size. Studies with small sample sizes may have insufficient statistical power to detect a slight effect or may generate a fluctuating risk estimate. As our study was based on a relatively large number of cases and controls, we were able to examine the potential effect modification of risk factors for gastric and colorectal cancers and to conduct analyses separately by tumor characteristics in gastric and colorectal cancers.

In conclusion, our results suggest that the p53 codon 72 Pro/Pro genotype is associated with a modest increased risk of gastric and colorectal cancer among Koreans, and that age, smoking, and drinking do not modify the association between the p53 codon 72 polymorphism and gastric and colorectal cancers.

Acknowledgments This work was supported by research grants from the National R&D Program for Cancer Control, Ministry for Health and Welfare, Republic of Korea.

References

1. Ushijima T, Sasako M. Focus on gastric cancer. Cancer Cell. 2004;5(2):121–5.

2. Crew KD, Neugut AI. Epidemiology of gastric cancer. World J Gastroenterol. 2006;12(3):354–62.
3. Goh KL, Quek KF, Yeo GT, Hilmi IN, Lee CK, Hasnida N, et al. Colorectal cancer in Asians: a demographic and anatomic survey in Malaysian patients undergoing colonoscopy. Aliment Pharmacol Ther. 2005;22(9):859–64.
4. Tahara E. Molecular mechanism of stomach carcinogenesis. J Cancer Res Clin Oncol. 1993;119(5):265–72.
5. Vogelstein B, Fearon ER, Hamilton SR, Kern SE, Preisinger AC, Leppert M, et al. Genetic alterations during colorectal-tumor development. N Engl J Med. 1988;319(9):525–32.
6. Fearon ER, Vogelstein B. A genetic model for colorectal tumorigenesis. Cell. 1990;61(5):759–67.
7. Vogelstein B, Lane D, Levine AJ. Surfing the p53 network. Nature. 2000;408(6810):307–10.
8. Vousden KH, Lane DP. p53 in health and disease. Nat Rev Mol Cell Biol. 2007;8(4):275–83.
9. Vousden KH, Lu X. Live or let die: the cell's response to p53. Nat Rev Cancer. 2002;2(8):594–604.
10. Shepherd T, Tolbert D, Benedetti J, Macdonald J, Stemmermann G, Wiest J, et al. Alterations in exon 4 of the p53 gene in gastric carcinoma. Gastroenterology. 2000;118(6):1039–44.
11. Bergamaschi D, Gasco M, Hiller L, Sullivan A, Syed N, Trigiante G, et al. p53 polymorphism influences response in cancer chemotherapy via modulation of p73-dependent apoptosis. Cancer Cell. 2003;3(4):387–402.
12. Li Y, Prives C. Are interactions with p63 and p73 involved in mutant p53 gain of oncogenic function? Oncogene. 2007;26(15):2220–5.
13. Walker KK, Levine AJ. Identification of a novel p53 functional domain that is necessary for efficient growth suppression. Proc Natl Acad Sci USA. 1996;93(26):15335–40.
14. Thomas M, Kalita A, Labrecque S, Pim D, Banks L, Matlashewski G. Two polymorphic variants of wild-type p53 differ biochemically and biologically. Mol Cell Biol. 1999;19(2):1092–100.
15. Katkoori VR, Jia X, Shanmugam C, Wan W, Meleth S, Bumpers H, et al. Prognostic significance of p53 codon 72 polymorphism differs with race in colorectal adenocarcinoma. Clin Cancer Res. 2009;15(7):2406–16.
16. Shen H, Solari A, Wang X, Zhang Z, Xu Y, Wang L, et al. P53 codon 72 polymorphism and risk of gastric cancer in a Chinese population. Oncol Rep. 2004;11(5):1115–20.
17. Yi SY, Lee WJ. A p53 genetic polymorphism of gastric cancer: difference between early gastric cancer and advanced gastric cancer. World J Gastroenterol. 2006;12(40):6536–9.
18. Koushik A, Tranah GJ, Ma J, Stampfer MJ, Sesso HD, Fuchs CS, et al. p53 Arg72Pro polymorphism and risk of colorectal adenoma and cancer. Int J Cancer. 2006;119(8):1863–8.
19. Zhu ZZ, Wang AZ, Jia HR, Jin XX, He XL, Hou LF, et al. Association of the TP53 codon 72 polymorphism with colorectal cancer in a Chinese population. Jpn J Clin Oncol. 2007;37(5):385–90.
20. Sul J, GP Yu, QY Lu, ML Lu, Setiawan VW, Wang MR, et al. P53 Codon 72 polymorphisms: a case-control study of gastric cancer and potential interactions. Cancer Lett. 2006;238(2):210–23.
21. Mu LN, Lu QY, Yu SZ, Jiang QW, Cao W, You NC, et al. Green tea drinking and multigenetic index on the risk of stomach cancer in a Chinese population. Int J Cancer. 2005;116(6):972–83.
22. Perez-Perez GI, Bosques-Padilla FJ, Crosatti ML, Tijerina-Menchaca R, Garza-Gonzalez E. Role of p53 codon 72 polymorphism in the risk of development of distal gastric cancer. Scand J Gastroenterol. 2005;40(1):56–60.
23. Hamajima N, Matsuo K, Suzuki T, Nakamura T, Matsuura A, Hatooka S, 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):81–5.
24. Hiyama T, Tanaka S, Kitadai Y, Ito M, Sumii M, Yoshihara M, et al. p53 Codon 72 polymorphism in gastric cancer susceptibility in patients with *Helicobacter pylori*-associated chronic gastritis. Int J Cancer. 2002;100(3):304–8.
25. Wu MT, Chen MC, Wu DC. Influences of lifestyle habits and p53 codon 72 and p21 codon 31 polymorphisms on gastric cancer risk in Taiwan. Cancer Lett. 2004;205(1):61–8.
26. Lai KC, Chen WC, Tsai FJ, Li SY, Jeng LB. Arginine and proline alleles of the p53 gene are associated with different locations of gastric cancer. Hepatogastroenterology. 2005;52(63):944–8.
27. Chung WC, Lee KM, Lee BI, Chun JS, Lee SY, Chang UI, et al. P53 genetic polymorphism of gastric cancer in Korea. Korean J Intern Med. 2006;21(1):28–32.
28. Perez LO, Abba MC, Dulout FN, Golijow CD. Evaluation of p53 codon 72 polymorphism in adenocarcinomas of the colon and rectum in La Plata, Argentina. World J Gastroenterol. 2006;12(9):1426–9.
29. Dakouras A, Nikiteas N, Papadakis E, Perakis M, Valis D, Rallis G, et al. P53Arg72 homozygosity and its increased incidence in left-sided sporadic colorectal adenocarcinomas, in a Greek-Caucasian population. Anticancer Res. 2008;28(2A):1039–43.
30. Mammano E, Belluco C, Bonafe M, Olivieri F, Mugianesi E, Barbi C, et al. Association of p53 polymorphisms and colorectal cancer: modulation of risk and progression. Eur J Surg Oncol. 2009;35(4):415–9.
31. Gemignani F, Moreno V, Landi S, Moullan N, Chabrier A, Gutierrez-Enriquez S, et al. A TP53 polymorphism is associated with increased risk of colorectal cancer and with reduced levels of TP53 mRNA. Oncogene. 2004;23(10):1954–6.