Indian Journal of Experimental Biology
Vol. 57, August 2019, pp. 580-585

Association of *TP53* gene codon 72 polymorphism with incidence of cervical cancer in Chhattisgarh

Yashwant K Ratre, Vijaylakshmi Jain, Dnyanesh Amle, Pradeep K Patra & Pankaj K Mishra*

Medical Biotechnology, Department of Biochemistry, Pt. Jawahar Lal Nehru Memorial Medical College, Raipur, India

Received 22 March 2017; *revised 11 July 2018*

TP53 gene encoding polymorphisms is a risk allele in terms of carcinogenesis. Here, we studied the risk assessment and association of *TP53* to understand the cancer biology and behaviour in cervical cancer patients and possible anticancer drug development interfering with p53 protein production. *TP53* gene encodes a central protein of apoptosis pathway p53 and its allelic variant has been postulated to play a vital role in carcinogenesis in addition to a variety of neurodegenerative disorders. We undertook a case control study, to examine the possible association of *TP53* gene codon 72 polymorphism in leukocyte DNA from a total of 200 subjects (100 controls and 100 cases). *TP53* codon *Arg72Pro* (rs1042522) genotype was identified using allele specific PCR and RFLP with statistical analysis using Vassar Stats (online). In Chhattisgarh population, individuals with GC and GG genotypes of *TP53* gene codon 72 polymorphism has a significantly higher risk of cervical cancer (OR=6.36, 95%CI=2.8-14.03 and OR=7.42, 95%CI=3.5-15.9) as compared to CC genotype (OR=1) which was taken as reference. The 'G' allele was found to confer a significant risk of cervical cancer (OR= 3.69, 95%CI= 2.40-5.5) compared to 'C' allele. The present case control study demonstrated the prevalence of the *Arg/Arg* (GG) genotype in women with cervical cancer among Chhattisgarh population.

Keywords: Homozygosity, Human papillomavirus, PCR-RFLP

Cervical carcinoma is the second most commonly diagnosed and the fourth leading cause of cancer death in women worldwide. Average life years lost due to cervical cancer is estimated at 25.3 years[1]. In developing countries, about 88% deaths occur due to cancer, exclusively from cervical cancer[2]. Approximately 365.71 million women in Indian population are above 15 years of age and are at risk of developing cervical cancer. According to the World Health Organiztion (WHO), approximately 570,000 new cases were diagnosed in 2018[3]. In India, 132,000 new cases of cervical cancer with 74,000 deaths were recorded in 2017, which is nearly 1/3 of the global cervical cancer deaths[4]. By 2020, this number is likely to increase to 149,000 new cases due to the demographic effect of population growth and increased life expectancy[5]. Persistent infection by high-risk human papillomavirus (HPV), sexual behaviour, unbalanced diet, and genetic factors considered as risk factors for developing cervical cancer[6,7]. About 50,000 new cases and 250,000 cervical cancer deaths worldwide each year showed association with HPV[8]. Cervical cancer patients have revealed prominent deviation of 2-fold higher risk during 2012-2016[9]. Common monogenic types of molecularly diagnosed invasive cancer were reported HPV-16 and 18 meanwhile HPV-16 have been found more commonly[10,11]. Sexual behaviour behaviour is the major risk factor for HPV infection, along with the early age of onset of sexual activity, multiple sexual partners, and co-infection with HIV[12].

The human tumor suppressor gene *TP53* encodes a phosphoprotein p53, plays important role in cell-cycle regulation, DNA repair, apoptosis pathways and in the maintenance of genome stability by preventing mutations[13]. Abrogation of p53 function by viral oncoprotein E6 of HPV is the major event in cervical carcinogenesis[14]. E6 inhibits p53 activity followed by proteolytic degradation through the ubiquitin pathway[15,16]. P53-Arg72 protein influencs more than the p53-Pro72 protein in protecting cells from tumorigenesis[17,18]. The Arg/Arg genotype *vs*. Arg/Pro or Pro/Pro genotypes at codon 72 of the *TP53* gene is used as a risk marker in cervical neoplasia[19]. Codon72 polymorphism (*Arg72Pro*, rs1042522 G>C) in exon 4, the most common candidate for single nucleotide polymorphisms (SNPs) in *TP53* gene, is the result of

*Correspondence:
E-mail: pkjbiotech@gmail.com

substitution of arginine (CGC) to proline (CCC) at residue 72[20]. In this study, we have made an attempt to determine the allelic and genotype frequencies of *TP53* codon 72 polymorphisms in the Chhattisgarh population and assessed its association with cervical carcinoma.

Materials and Methods

Sample collection

The study subjects comprised of 100 histopathologically proven cervical carcinoma patients and 100 healthy controls between 30 and 70 years of age with the identical ethnic population. Five mL blood samples in EDTA vials from all subjects were collected by venipuncture. Written informed consent was obtained from all subjects with the approval of the relevant institutional ethical committee (No/MCR/Biochem/2014/1203) for study benefits of humans in general. Cervical cancer patients and age-matched controls were registered under the Department of Oncology and Radiotherapy, Dr. Bhim Rao Ambedkar Memorial Hospital, Raipur, Chhattisgarh, India as per inclusion - exclusion criteria. Cases and controls were interviewed regarding age, parity and menstrual history. Clinical laboratory tests including total bilirubin, direct bilirubin, serum creatinine, serum urea, serum sodium, serum potassium, ALT, AST, hemoglobin, platelets and WBC count were also performed for comparative analysis of cases versus control (Table 1).

Table 1 — General characteristics of study subjects

Characteristics		Group 1 Cervical cancer (N=100) (Mean ± SD)/n (%)	Group 2 Control group (N=100) (Mean±SD) /n (%)	p Value
Age (Years)		50.98±8.23	44.58±10.91	0.06
Marital status (married)		91(91)	96(96)	0.1
Unmarried		9(9)	4(4)	
Occupation	Housewife	74(74)	72 (72)	0.99
	Labor	11(11)	10 (10)	
	Farmer	11(11)	10 (10)	
	Service	4(4)	8(8)	
Hypertension		26(26)	20(20)	0.3
Diabetes		45(45)	28(28)	0.01*
Tuberculosis		5(5)	1(1)	0.1
Menopause (yes)		81(81)	61(61)	0.001*
Age at menopause (years)		45.2±4.33	45.8±7.15	0.09
Parity		3.5±1.5	3.4±1.4	0.1
Pallor		38(38)	31(31)	0.18
Icterus		3(3)	0	0.12
Cyanosis		2(2)	0	0.24
WBC count (cells/mm^3)		6570±2353	8830±1603	0.002*
Hb (g/dL)		10.8±1.72	12.20±10.33	0.09
Platelets (lac cells/mm^3)		2.24±0.59	3.05±0.59	<0.0001*
Total bilirubin (mg%)		0.38±0.18	0.48±0.29	0.005*
Direct bilirubin (mg%)		0.15±0.12	0.15±0.12	0.8
ALT (IU/L)		22.73±12.53	26.4±10.5	0.2
AST (IU/L)		23.61±16.07	21.03±9.54	0.1
Na (mMol/L)		139±4.4	138.3±2.32	0.5
K (mMol/L)		3.92±0.54	3.8±0.4	0.31
Serum urea (mg/dL)		19.65±11.45	21.76±9.78	0.2
Serum creatinine (mg/dL)		3.16±6.89	0.91±0.27	0.15

[P <0.05 showed significant results]

Table 2 — FIGO staging of cervical cancer in study subjects (N=100)

Stages	Subtypes	Occurrence frequency
I	A	4
	B	3
II	A	16
	B	27
III	A	5
	B	40
1V	A	2
	B	3

Inclusion and exclusion criteria

All cervical cancer cases meeting the following criteria were eligible for this study: 30 to 70 years age of women residents of Chhattisgarh with no previous history of any cancer. Cytological and histopathologically proven cases of carcinoma cervix with FIGO classified staged were only included (Table 2). The studied cases had not been exposed to chemo and/ or radiotherapy before. Healthy age-matched subjects with similar ethnicity and free from any type of cancer were selected as controls.

DNA isolation and genotyping of *TP53* codon *Arg72Pro* (rs1042522)

Genomic DNA was extracted from peripheral blood leukocytes by modifying standard salting-out method. The DNA quality and quantity was measured using agarose gel electrophoresis and spectrophotometer at 260 nm. *TP53* gene codon *Arg72Pro* (rs1042522) genotype was determined using the PCR-RFLP methods of Bailey[21] and Tanimoto[22]. The PCR primer TP53: 5′-CCTGAAAACAACGTTCTGGTAA-3′ and 5′-GCA TTGAAGTCTCATGGAAG-3′ (Sigma-Aldrich, India) used for the analysis was flanking exon 4, *Bst*UI polymorphic site[23,24].

Briefly, PCR was carried out in a 10.0 µL reaction mixture containing 4.0 µL genomic DNA, 5.0 µL master mix (Thermo Fisher Scientific, India) and 0.5 µL each reverse and forward primers using a thermal cycler (Applied Biosystems). Amplification was performed with denaturation at 95ºC for 5.0 min followed by 35 cycles of 30 s denaturation at 95ºC, 30 s annealing at 56.8ºC, 30 s extension at 72ºC, and finally 7.0 min incubation at 72ºC. Resulting PCR

products were 432 bp depending on the absence of the intron3 16 bp duplication in the template. Length polymorphism was directly evident by running 2% agarose gel electrophoresis, which was stained with ethidium bromide and bands were visualized by gel documentation system (Omega, India) (Fig. 1).

Five µL PCR products were subjected to restriction digestion with *Bst*UI (Thermo Fisher Scientific, India) in a 10.0 µL digestion mixture at 37ºC for 16 h. *Bst*UI digestion may produce polymorphic DNA fragments of 2 different sizes: 432 bp, *Bst*UI digestion resistant (Pro at codon 72) and 230 bp *Bst*UI digested (Arg at codon72) without intron3 insertion. Digested products were separated in 2% agarose gel, stained with ethidium bromide and visualized by gel documentation system (Omega, India) (Fig. 2).

Statistical analysis

The sample size of each SNP was calculated by Vassar Stats (online). The continuous variable of each parameter studied was summarized as mean ± SD and Student's t-test. The association between *TP53* gene codon 72 polymorphism and cervical cancer risk was analyzed by calculating the crude odds ratios (OR) at 95 per cent confidence intervals (95%CI) using the chi-square (χ^2) test. The p-values reported in the study were calculated with a significance level of P <0.05. Hardy–Weinberg analysis was evaluated for each group by using 2×3 and 2×2 contingency table analysis of genotype and allele frequency.

Results

The assessment of general characteristics of study subjects was carried out by applying suitable statistical methods. The subjects were matched for demographic profiling including age, marital status and occupation, past and personal history of hypertension, tuberculosis, menstrual history (age at menopause) and parity. The general examination was also performed to know pallor, icterus, cyanosis and level of Hb, direct bilirubin, ALT, AST, serum sodium, serum potassium, serum creatinine and serum urea showed non-significant results. The frequency of diabetes and menopause was found significantly higher in cervical cancer subjects and the WBC count, platelets and total bilirubin were noted significantly lower in the cervical cancer group over the controls (Table 1).

The assessment of genotype distribution of *TP53* codon 72 polymorphism at exon 4 (*Arg72Pro*) proved

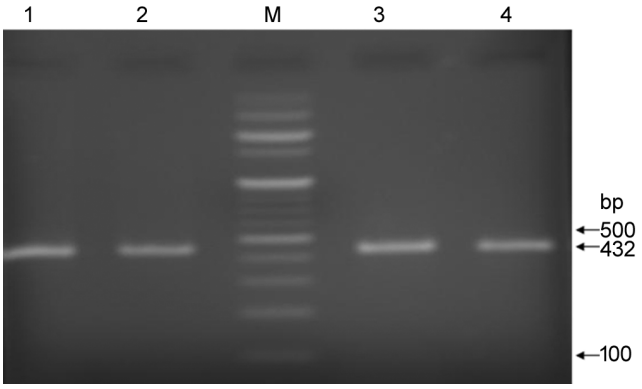

Fig. 1 — Standardized PCR product. Lane 1, 2, 3 and 4 showing band at 432 bp indicating standardization of primer, Lane M showing ladder (100 bp).

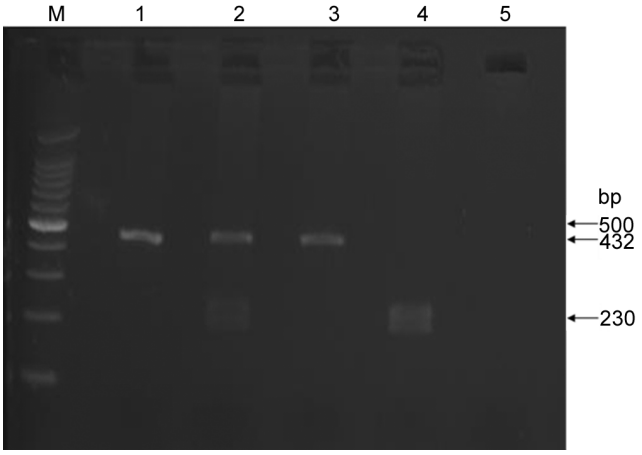

Fig. 2 — Representative gel showed the *TP53* codon 72 polymorphisms. Lane M has the DNA marker Lane1 and Lane 3 showed CC homozygous genotype (432 bp); Lane 4 shows the GG homozygous genotype (230 bp); Lane 5 has showed no amplification.

the linkage between GC genotype frequency and risk of developing cervical cancer (OR=6.36, 95%CI=2.8-14.03), as compared to the frequency of CC genotype. A similar pattern was followed in case of GG genotype frequency (OR=7. 42, 95%CI=3.5-15.9). Allele distribution of *TP53* codon 72 polymorphism at exon4 (*Arg72Pro*) demonstrated the significantly higher frequency of 'G' allele (67.5%) in cervical cancer subjects compared to 'C' allele (32.5%). Further 'G' allele was found to confer a significant risk of cervical cancer with Odds ratio of 3.69 (95%CI= 2.40-5.5) (Table 3).

Discussion

The genotype frequency of *TP53* gene codon 72 polymorphism varied according to different ethnic

Table 3 — Genotypic and allele distribution of TP53 codon 72 polymorphism at exon 4 (*Arg72Pro)* in study subjects

Characteristics	Group 1 Cervical cancer (N=100)	Group 2 Control group (N=100)	p value	OR	95% CI
Genotypic distribution					
CC	14	53		1 (reference)	
GC	37	22	<0.0001	6.36	(2.8-14.0)
GG	49	25		7.42	(3.5-15.9)
Allele distribution					
C	65(32.5%)	128(64%)		1 (reference)	
G	135(67.5%)	72(36%)	<0.001	3.69	2.40-5.5

[In table values were shown in percentage (%); CI=confidence interval; OR= odds ratio]

groups[25,26]. Mutations in *TP53* codon 72 were showed association with a variety of human cancers, including cervical cancer encodes a tumor suppressor protein, which plays multiple roles in apoptosis, cell-cycle control, and DNA repair[27]. In the original study, an association between the majority allele 'G' of Arg form in codon 72 of the *TP53* gene and cervical cancer development was manifested. The frequency of SNPs of the *TP53* gene codon 72 (G/C) in patients with histologically confirmed cervical cancer patients established the association between *TP53* codon 72 polymorphism and risk of developing cervical cancer. There was a significant difference in frequencies between the Arg/Arg (GG) genotype (49%) among the cervical cancer cases compared to 25 per cent in the control group (P =>0.0001). The association between the p53 Arg/Arg genotype (GG) and the development of cervical cancer was statistically significant (OR=7.42; 95%CI=3.5-15.9) (Table 3). These results demonstrated that women with GG genotype have an increased risk for developing cervical cancer in Chhattisgarh population. Our finding favored the initial result of Storey[28], as well as the data of those that detected a higher prevalence of homozygosity for GG genotype in patients with cervical cancer. Storey and coworkers showed that the codon 72 Arg variant of *TP53* gene codes for a protein that is more sensitive to HPV16 and HPV18 degradation than the Pro variant. These observations were further supported by genotype analysis in a group of cervical cancer patients who showed a 7-fold enrichment of the 'G' allele over the 'C' allele as compared to healthy controls[29,30]. Some reports from other Indian population found a positive association between the p53 Arg/Arg (GG) genotype at codon 72 and HPV associated cervical cancer[31-33]. Our findings were showing the correlations with what has been found in other studies. In addition, Bhattacharya[34] provided evidence that the CC genotype was a risk factor in cervical cancer among Indian women and Zhou[35], demonstrated that the Pro/Pro (CC) genotype and 'C' allele carrier showed significant associations with increased risk of cervical cancer among the Indian population, but not among Chinese, Japanese, Moroccan and Korean populations by current meta-analysis[36,37]. Some studies also conclude over transmission of TP53 72C polymorphic variant lowers cervical cancer incidence[38,24].

Conclusion

The findings observed in this study must be interpreted in the light of the fact that, we have included already diagnosed cases only from single tertiary care center. The statistical significance in the study proves the association between p53 prevelance and cervical cancer. Furthermore, expansion of this study is needed to evaluate the HPV status of the subjects for early diagnosis of cervical cancer.

Acknowledgement

The authors are thankful to Department of Oncology and Radiotherapy, Dr. Bhim Rao Ambedkar Memorial Hospital, Raipur, Chhattisgarh for providing samples for study.

Conflict of Interest

The authors declare no conflict of interest.

References

1 McKenzie KP, Rogers RK, Njoroge JW, John-Stewart G, Richardson BA, Mugo NR, De Vuyst H, Pamnani RN, Rana FS, Warui D & Chung MH, Cervical squamous intraepithelial lesions among HIV-positive women on antiretroviral therapy in Kenya. *Curr HIV Res*, 9 (2011) 180.

2 Aswathy S, Quereshi MA, Kurian B & Leelamoni K, Cervical cancer screening: current knowledge & practice among women in a rural population of Kerala, India. *Indian J Med Res*, 136 (2012) 205.

3 WHO. Cervical cancer: early diagnosis and screening. 2018; https://www.who.int/cancer/prevention/diagnosis-screening/cervical-cancer/en/

4 Jain V, Ratre YK, Amle D, Mishra PK & Patra PK, Polymorphism of CYP1A1 gene variants rs4646903 and rs1048943 relation to the incidence of cervical cancer in Chhattisgarh. *Environ Toxicol Pharmacol*, 52 (2017) 188.

5 Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, Parkin DM, Forman D & Bray F, Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. *Int J Cancer*, 136 (2015) E359.

6 Natphopsuk S, Settheetham-Ishida W, Pientong C, Sinawat S, Yuenyao P, Ishida T & Settheetham D, Human papillomavirus genotypes and cervical cancer in northeast Thailand. *Asian Pac J Cancer Prev*, 14 (2013) 6961.

7 Dhillon PK, Dhillon PK, Mathur P, Nandakumar A, Fitzmaurice C, Kumar GA, Mehrotra R, Shukla DK, Rath GK, Gupta PC, Swaminathan R, Thakur JS, Dey S, Allen C, Badwe RA, Dikshit R, Dhaliwal RS, Kaur T, Kataki AC, Visweswara RN, Gangadharan P, Dutta E, Furtado M, Varghese CM, Bhardwaj D, Muraleedharan P, Odell CM, Glenn S, Bal MS, Bapsy PP, Bennett J, Bodal VK, Chakma JK, Chakravarty S, Chaturvedi M, Das P, Deshmane V, Gangane N, Harvey J, Jayalekshmi P, Jerang K, Johnson SC, Julka PK, Kaushik D, Khamo V, Koyande S, Kutz M, Langstieh WB, Lingegowda KB, Mahajan RC, Mahanta J, Majumdar G, Manoharan N, Mathew A, Nene BM, Pati S, Pradhan PK, Raina V, Rama R, Ramesh C, Sathishkumar K, Schelonka K, Sebastian P, Shackelford K, Shah J, Shanta V, Sharma JD, Shrivastava A, Tawsik S, Tyagi BB, Vaitheeswaran K, Vallikad E, Verma Y, Zomawia E, Lim SS, Vos T, Dandona R, Reddy KS, Naghavi M, Murray CJL, Swaminathan S & Dandona L, The burden of cancers and their variations across the states of India: the Global Burden of Disease Study 1990–2016. *Lancet Oncol*, 19 (2018) 1289.

8 Moscicki AB, Impact of HPV infection in adolescent populations. *J Adolesc Health*, 37 (2005) S3.

9 Siegel RL, Miller KD & Jemal A, Cancer statistics, 2019. *CA: Cancer J Clin*, 69 (2019) 7.

10 Chen D & Gyllensten U, Lessons and implications from association studies and post- GWAS analyses of cervical cancer. *Trends Genet*, 31 (2015) 41.

11 Wang X, Huang X & Zhang Y, Involvement of human Papillomaviruses in cervical cancer. *Front Microbiol*, 9 (2018) 2896.

12 Bhatla N, Lal N, Bao YP, Nq T & Qiao YL, A meta-analysis of human papillomavirus type-distribution in women from South Asia: implications for vaccination. *Vaccine*, 26 (2008) 2811.

13 Levine AJ, p53, the cellular gatekeeper for growth and division. *Cell*, 88 (1997) 323.

14 Soussi T & Béroud C, Assessing TP53 status in human tumors to evaluate clinical outcome. *Nat Rev Cancer*, 1 (2001) 233.

15 Scheffner M, Werness BA, Huibregtse JM, Levine AJ & Howley PM, The E6 oncoprotein encoded by human papillomavirus types 16 and 18 promotes the degradation of p53. *Cell*, 63 (1990) 1129.

16 Werness BA, Levine AJ & Howley PM, Association of human papillomavirus types 16 and 18 E6 proteins with p53. *Science*, 248 (1990) 76.

17 Li DB, Wei X, Jiang LH, Wang Y & Xu F, Meta-analysis of epidemiological studies of association of P53 codon 72 polymorphism with bladder cancer. *Genet Mol Res*, 9 (2010) 1599.

18 Alsbeih G, Exploring the causes of the low incidence of cervical cancer in Western Asia. *Asian Pac J Cancer Prev*, 19 (2018) 1425.

19 Koushik A, Platt RW & Franco EL, p53 codon 72 polymorphism and cervical neoplasia: a meta-analysis review. *Cancer Epidemiol Biomarkers Prev*, 13 (2004) 11.

20 Whibley C, Pharoah P & Hollstein M, p53 polymorphisms: cancer implications. *Nat Rev Cancer*, 9 (2009) 95.

21 Bailey LR, Roodi N, Verrier CS, Yee CJ, Dupont WD & Parl FF, Breast cancer and CYP1A1, GSTM1 and GSTT1 polymorphisms: evidence of a lack of association in Caucasians and African Americans. *Cancer Res*, 58 (1998) 65.

22 Tanimoto K, Hayashi S, Yoshiga K & Ichikawa T, Polymorphisms of CYP1A1 and GSTM1 gene involved in oral squamous cell carcinoma in association with a cigarette dose. *Oral Oncol*, 35 (1999) 191.

23 Mitra S, Chatterjee S, Panda CK, Chaudhuri K, Ray K, Bhattacharyya NP, Sengupta A & Roychoudhury S, Haplotype structure of TP53 locus in Indian population and possible association with head and neck cancer. *Ann Hum Genet*, 67 (2003) 26.

24 Liu GC, Zhou YF, Su XC & Zhang J, Interaction between TP53 and XRCC1 increases susceptibility to cervical cancer development: a case control study. *BMC cancer*, 19 (2019) 24.

25 Rosenthal AN, Ryan A, Al-Jehani RM, Storey A, Harwood CA & Jacobs IJ, p53 codon 72 polymorphism and risk of cervical cancer in UK. *Lancet*, 352 (1998) 871.

26 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*, 19 (1999) 1092.

27 Hollstein M & Hainaut P, Massively regulated genes: the example of TP53. *J Pathol*, 220 (2010) 164.

28 Storey A, Thomas M, Kalita A, Harwood C, Gardiol D, Mantovani F, Breuer J, Leigh IM, Matlashewski G & Banks L, Role of a p53 polymorphism in the development of human papillomavirus-associated cancer. *Nature*, 393 (1998) 229.

29 Ciotti M, Coletti A, Giuliani L, Cappiello G, Syrjanen K & Favalli C, The p53 codon 72 arg/arg homozygous women in central Italy are at increased risk for HPV infections. *Anticancer Res*, 26 (2006) 3745.

30 Singhal P, Hussain S, Thakur N, Batra S, Salhan S, Bhambani S & Bharadwaj M, Association of MDM2 and p53 polymorphisms with the advancement of cervical carcinoma. *DNA Cell Biol*, 32 (2013) 19.

31 Nagpal JK, Sahni S & Das BR, p53 codon 72 polymorphism and susceptibility to the development of human papilloma virus-associated cervical cancer in Indian women. *Eur J Clin Invest*, 32 (2002) 943.

32 Saranath D, Khan Z, Tandle AT, Dedhia P, Sharma B, Contractor R, Shrivastava S & Dinshaw K, HPV16/18 prevalence in cervical lesions/cancers and p53 genotypes in cervical cancer patients from India. *Gynecol Oncol*, 86 (2002) 157.

33 Katiyar S, Thelma BK, Murthy NS, Hedau S, Jain N, Gopalkrishna V, Husain SA & Das BC, Polymorphism of the p53 codon 72 Arg/Pro and the risk of HPV type 16/18-associated cervical and oral cancer in India. *Mol Cell Biochem*, 252 (2003) 117.

34 Bhattacharya P & Sengupta S, Lack of evidence that proline homozygosity at codon 72 of p53 and a rare arginine allele at codon 31 of p21, jointly mediate cervical cancer susceptibility among Indian women. *Gynecol Oncol*, 99 (2005) 176.

35 Zhou X, Gu Y & Zhang SL, Association between p53 codon 72 polymorphism and cervical cancer risk among Asians: a huge review and meta-analysis. *Asian Pac J Cancer Prev*, 13 (2012) 4909.

36 El Khair MM, Ennaji MM, El kebbaj R, Mhand RA, Attaleb M & El Mzibri M, p53 codon 72 polymorphism and risk of cervical carcinoma in Moroccan women. *Med Oncol*, 27 (2010) 861.

37 Jiang P, Liu J. Zeng X. Li W & Tanj J, Association of TP53 codon 72 polymorphism with cervical cancer risk in Chinese women. *Cancer Genet Cytogenet*, 197 (2010) 174.

38 Alsbeih GA, Al-harbi NM, Bin Judia SS, Khoja HM, Shoukri MM & Tulbah AM, Reduced rate of human papillomavirus infection and genetic overtransmission of TP53 72C polymorphic variant lower cervical cancer incidence. *Cancer*, 123 (2017) 2459.