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Research Article

The Frequency of p53 Mutations in Colorectal Cancer Patients.

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Abstract

One of the cancer types that has seen a rise in occurrence in recent years is colorectal cancer. In the world, it is the second most prevalent cancer in women and the third most common in males. Even if the diagnosis and prevalence are increasing, there is still a low 5-year survival rate. A series of mutations that either activate oncogenes or inactivate tumor suppressor genes cause colorectal cancer. It is generally understood that mutations in the APC, KRAS, and P53 genes lead colorectal cancer to progress. The most often seen genetic changes in colorectal cancer are mutations in the p53 gene, which are thought to be present in 40–70% of colorectal cancer cases.

Mutations in p53 leading to colorectal cancer commonly occur in exons 5 to 8 and mainly in some hot spot codons such as 175, 245, 248 and 282, which code for the amino acids that are extremely important for its DNA binding activity. In this study, we have examined 40 tissues from Libyan colorectal cancer patients admitted to the National Cancer Institute-Misurata for mutations in the p53 gene at exons 5 to 8 using PCR-direct sequencing. We found 75 mutations in 20 cases (50%) and TP53 protein accumulation in 22 cases (55%). The mutation distribution in the exons subjected to analysis was as follows: exon 5 (10.9%), exon 6 (13.3%), exon 7 (54.6%), exon 8 (8%), intron 7 (8%), and splice junction (5.5%). Most of the p53 mutations were substitutions (76.9%) and frameshifts (23.1%). Four mutations were ascribed to hot spot regions: codon 245 and codon 248. Rectal and proximal colorectal cancers were less likely to be mutated than distal colorectal cancers. Overall, our findings supported the reported p53 mutations in colorectal cancer in terms of incidence, type, and associations with TP53 accumulation.

Keywords: colorectal cancer, p53 mutations, PCR, DNA sequencing.

INTRODUCTION

Colorectal cancer is an epithelial tumor. The intestinal tract's glandular or columnar epithelium is the source of both benign and malignant neoplasms known as adenomas and adenocarcinomas. The World Health Organization reported that in 2018, colorectal cancer accounted for 1.8 million new cases and about 862 000 deaths worldwide, making it the second most prevalent cancer in women and the third most common disease in men (1).

The incidence of colorectal cancer varies over ten times by region. Africa and South-Central Asia have the lowest incidence rates, while Europe, North America, Australia, and New Zealand have the highest rates (2). The following factors raise the risk of colorectal cancer: smoking, obesity, inflammatory bowel disease, family history, age, Lynch syndrome, and familial adenomatous polyposis (FAP) (3, 4).

A series of histological, morphological, and genetic alterations occur gradually and are responsible for the majority of colon cancers (5). It is thought that a cascade of genetic alterations that result in increasingly chaotic local DNA replication and faster colonocyte replication are the origin of colorectal cancer(6). The progression of several genetic alterations leads to the change from benign adenoma to severe dysplasia to frank cancer in the mucosa. The identification of accumulating mutations in the APC, KRAS, P53, and BRAF genes suggested a transition from normal mucosa to adenoma to cancer. It is estimated that approximately 15% of sporadic colorectal tumors are caused by mutations in the mismatch repair genes (7).

Since p53 plays a crucial function in controlling normal cell proliferation, mutations in this gene are common in

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malignancies. It has been found that p53 genes are mutated in about 50% of cancer cells (8). Tumor suppressor gene inactivation and oncogene activation play multiple roles in the multifactorial, multistage process that leads to colorectal cancer development (8).

According to Russo et al. (2005) (10), p53 mutations are present in 34% of proximal colon cancers and 45% of distal colorectal tumors in colorectal cancer. Exons 5 to 8 (the DNA binding domain) contain the majority of these mutations, which mostly affect hotspot codons like 175, 245, 248, 273, and 282, which comprise the G to A and C to T transitions, and result in the substitution of a single amino acid in the p53 protein (9). Sequential transactivation and specific DNA binding are disrupted by these alterations, which most frequently cluster in the DNA binding domain (10).

In proximal colon cancer, p53 mutations are linked to lymphatic invasion. In distal colon cancer, they have a strong linkage with both lymphatic and vascular invasions. Compared to colorectal cancer patients with wild-type p53, individuals with mutant p53 exhibit greater chemo-resistance and have a worse prognosis (11). Patients with mutant p53 in exon 5 had a poorer prognosis for proximal colon cancer, according to findings from an international collaborative study on TP53 colorectal cancer. Furthermore, inactivating p53 mutations were linked to a lower chance of survival and were more common in advanced stage cancers (12).

Mutant p53 is distinct in that its proteins frequently stabilize and build up to extremely high concentrations within tumors (13). For mutant p53 to exercise its effects on carcinogenesis and contribute to the development of more advanced tumors, mutant p53 must accumulate in tumors (a process known as gain-of-function mutations, or GOF) (14). A promising approach to cancer therapy that is presently being actively investigated is destabilizing mutant p53, which can significantly diminish mutant p53 (GOF) in tumorigenesis (15, 16). Mutant p53 protein levels are kept low in normal tissues by MDM2, but certain tumor-related alterations impair MDM2-mediated mutant p53 degradation, which causes mutant p53 protein to build up in tumors (17).

In this study, we examined the p53 gene alterations found in Libyan patients with colorectal cancer. The frequent p53 mutations between exons 5 and 8 were mapped using the direct DNA sequencing technique. We looked into the relationships between the patients' pathological characteristics and the p53 mutations. This study also looked at the accumulation of mutant p53 protein in colorectal cancers.

MATERIALS AND METHODS

Tissue Samples

At the National Cancer Institute, Misurata (NCI), 40 patients with colorectal cancer had curative surgical resections performed between 2016 and 2017. No patient who had undergone chemotherapy or radiation therapy before surgery was included. Every patient had his or her primary tumor removed. New tissues were obtained from the histopathology department, and immediately divided into two halves. One section was paraffin-embedded, placed in 10% neutral-buffered formalin, and periodically processed for histopathologic evaluation. The remaining fraction was immediately stored at -80 °C for molecular testing. The patients signed consent forms, which were authorized by the NCI-Misurata ethical committee.

Patients

The clinical and histological information of the collected tissues was received from the patients' medical records. This information included the patients' age, gender, family history of colorectal cancer, tumor site, degree of tumor differentiation, tumor stage, and histologic types such as common adenocarcinoma.

DNA extraction

Genomic DNA extraction from frozen tumor tissues carried out using a QIAamp DNA Mini Kit, catalog No. 56304 (Qiagen, Hilden, Germany) according to the manufacturer's instructions. Genomic DNA integrity was examined by agarose gel electrophoresis, and the concentration of DNA was measured by spectrophotometer using QIA expert machine (Qiagen Company, Germany).

Polymerase Chain Reaction (PCR)

After extraction of the genomic DNA from the tissue samples, both of the target genes of p53 in exons 5 to 8 and a reference gene (β - globin) were amplified by PCR using the primers shown in table (1). Each PCR reaction had a 20 µl volume in total, and contained: 1X PCR buffer, 2.5mM MgCl2, 0.25 unit of the Taq DNA polymerase (Qiagen Company, catalog No. 201445, 1mM of deoxynucleotide mix (dATP, dCTP, dTTP, dGTP), forward and reverse primers 10 pmol, and 100 ng of extracted genomic DNA. The PCR reaction ran with the following program: step 1, 95°C initial denaturation for activating Taq DNA Polymerase for 5 minutes, step 2, denaturation at 95°C for 30 seconds, step 3, annealing of the primers to the template at 60°C for p53 in exons 5-6 and 7-8, (58°C) for β -globin, for 30 seconds, and step 4: 3 minutes at 72°C for primer extension. Steps 2 to 4 were repeated 35 times followed by a final extension step at 72°C for 5 minutes. The PCR reaction was cooled down to 8°C. The PCR products were checked on an agarose gel 1.5% in TAE buffer 1X (Tris base, Acetic acid, EDTA) and stained with ethidium bromide.

DNA Direct Sequencing

PCR products producing single band at the expected size

on agarose gel, were sent to Macrogen Inc. (Amsterdam, The Netherlands) to be purified then subjected to direct sequencing using the same primers. All mutations were confirmed by sequences originating from reverse primers. The reverse primers of PCR amplification of (p53; exon: 5-6), (p53; exon 7-8) including introns 5 and 7 were used for sequencing, then automatically sequenced through the ABI 3730XL DNA sequencer according to the Big Dye Terminator SANGER method. To ensure the accuracy of sequence results, all the molecular tests and the direct sequencing analysis were performed twice for each sample. PCR products were analyzed using direct sequencing, and their sequences were investigated using Finch TV software to identify mutations in the mutant and wild-type p53 gene. Codon number of the mutant gene and its changed sequence was determined by referring to NCBI/BLAST website.

Statistical Analysis

The Chi-squared test was used to determine the significance of differences between patients and p53 accumulation with and without p53 mutations in terms of categorical characteristics such gender, age, tumor localization, and stages. The statistical program SPSS version 20.0 was used to process the acquired data. p- value < 0.05 were deemed to signify a statistically significant variation.

RESULTS

DNA Extraction

All tissue samples in the study group (40 cases) had a histological diagnosis of adenocarcinoma of the colon and rectum. The extracted genomic DNA from tumour tissues was examined its quality by loading 5 µl of DNA on 1% agarose gel to check the integrity of DNA. the amplification of the studied samples of exons 5 to 6 of p53 gene using the specific primers showed a band of 456 bp, while the same samples showed an amplification of exons 7 to 8 of p53 gene in a band of 655 bp.

The frequency of Tp53 mutatioms

The p53 mutational status of the 40 colorectal cancers was determined by sequencing analysis of the amplified fragments. The p53 mutation analysis spanned exons 5 to 6 and exons 7 to 8 including two introns 5 and 7. Mutations were detected in 20/40 cases(50%), which included 11/20 cases with one mutation, 3/20 cases with two mutations and 6/20 cases with multi-mutations. The total of mutations in the studied exons and introns from 5 to 8 were 75 mutations. The mutations located in exon 5 were 8/75 (10.7 %) , in exon 6: 10/75(13.3%); in exon 7: 41/75(54.6%), and in exon 8: 6/75 (8 %). The mutations in intron 7 were 6/75(8%), and in splice junction were 4/75 (5.5 %). The somatic mutations were 65/75 (86.7 %) in the target region in our study (Exons 5,6,7 and 8), and 10/75 (13.3 %) in out site target region in intron 7 and splice junction(**Table 1**).

Table 1. Primers' sequences for the target gene p53 in exons 5-8, and the reference gene (β-globin).

Genes	Sequence		PCR product
Tp53-exon 5-6	Forward	3' – CTCTGTCTCCTTCCTCTTCC-5'	456 bp
	Reverse	3'– ACTGACAACCACCCTTAACC-5'	
Tp53-exon 7-8	Forward	3' – CAGGTCTCCCCAAGGCGCAC-5'	655 bp
	Reverse	3'– GTGAATCTGAGGCATAACTG 5'	
β-globin	Forward	3' –ACACAACTGTGTTCACTAGC-5'	110 bp
	Reverse	3'– CAACTTCATCCACGTTCACC-5'	

The Types of p53 mutations

The types of mutations in the exons 5 to 8 were substitutions 50/65 (76.9%), and all were missenses. The substitutions were 26/50 (52 %) transversion, and 24/50 (48%) transition. The other mutations were frameshift 15/65 (23.1 %) which included 11/15 (73.33%) deletions, and 4/15(26.67%) insertions. We found 4 mutations were attributed to hot spot regions of p53 gene: 2 at codon 245, and 2 at codon 248. The splice site mutation was observed in 4 samples (**Table 2**). Most mutations were base substitutions among which (18/50) G: C transversions, (10/50) C: T transitions, (5/50) A:C transversions , (5/50) G:A transitions, and CpG site dinucleotide were 6/65 (9.2%)(**Table 3**).

Table 2. The types of p53 mutations in the studied colorectal cancer patients.

Characteristics	Number	Percentage %
Tissue Samples	40	
Wild-type p53	20	50%
Mutant p53	20	50%
Total mutations	75	
Mutations in the target region exons: 5-8	65/75	
Mutations in out-site	10/75	
Mutation type		
Substitutions	50/65	76.9%
Missense	50	100%
Nonsense	0	0%
Transition	24/50	48%
Transversion	26/50	52 %
GpC- site	6/65	9.2 %
Frameshift	15/65	23.1 %
Deletion	11/15	73.33 %
Insertion	4/15	26.67 %
Distribution of the mutations on the exons		
Exon 5	8/75	10.7 %
Exon 6	10/75	13.3 %
Exon 7	41/75	54.6 %
Exon 8	6/75	8 %
Intron 7	6/75	8 %
Splice junction	4/75	5.5 %
Total	4	100 %

Table 3. Types of p53 mutations

bEEI4.5: Exon	Codon	Codon change	Nucleotide change	Amino acid change
5	173	GTG >TT G	G > T	Val > Leu
6	210	AAC > GAC	A > G	Asn > Asp
7	240	AGT > ACC	T > C	Ser > Thr
7	242	TGT > TCC	GT > CC	Cys > Ser
7	245	GGC > CGC	G > C	Gly > Arg
7	248	CGG > CAG	G > A	Arg > Gln
8	305	AAG > ACA	A > C	Lys > Thr

TP53 mutations and protein accumulation

All the 40 cases analyzed for p53 mutations were immuno-stained for TP53 detection. Overall 22/40 cases (55%) scored positive for TP53 nuclear accumulation: three were weekly (+), 8 moderately (++), and 11 strong positive (+++) for TP53 protein expression. The other 18 cases were negative for TP53 accumulation (**Table 4**). There was a general concordance between protein accumulation and mutation status (p-value=0.011). The specificity of TP53 accumulation was 65% (13/20 negative by IHC) with no evidence of p53 mutation. While, the sensitivity of TP53 accumulation was 75% (15/20 positive by IHC of mutated cases). Five of the 18 cases (27.7%) with detected p53 mutations did not show TP53 accumulation.

Table 4. TP53 mutations and p53 protein accumulation.

TP53 Status	IHC Test		Total
	Positive	Negative	
Wild-Type	7	13	20
Mutant	15	5	20
Total	22	18	40

Tp53 Mutations and Histopathological Analysis

P53 mutation was identified in 20/40 (50%) of the studied colorectal tumors. The Age of the patients was found to be a potential risk factor in the study group with p53 mutation. Statistical analysis of the sequencing results showed that the mutations of p53 gene were correlated with the advanced age of patients >50 years 11/20(55%), but they were also in ages ≤ 50 years 9/20(45%) (p-value = 0.013). **Table 5** shows the frequency and association of clinicopathological features of interest in patients who harbored the mutant and wild-type p53 tumors. 17/20(85%) of the patients with mutant p53 tumors presented with stage B, C, and D of the disease. This indicates that patients with mutant p53 tumors are more likely to present with the advanced stage of the disease, but they were also in early stage of the disease 2/20 (10%). There was a trend for a relatively higher frequency of mutant status in male gender11/20 (55%) compared to female gender 9/20 (45%). However, this did not translate to statistical significance (p-value = 0.752). Tumor differentiation was not statistically significant predictor for p53 status (p-value = 0.717). The gender of patients and the stage at diagnosis were not statistically correlated to p53 status. Concerning the location of the colorectal cancer, we found that p53 mutations in distal colon were 10/20(50%), and in rectal colon were 6/20(30%), and in proximal colon were 4/20(20%). The location of tumor was not statistically significant predictors for Tp53 mutation. (p-value= 0.311), (**Table 5**).

Table 5. Distribution of tumor characteristics according to p53 mutation status

	p53 mutation status	**p-value**			
			Overall	**Mutation**	**Wild type**
Number of patients			40	20	20
Gender		0. .752			
	Male		21	11	10
	Female		19	9	10
Age (years)		0 .013*			
	≤ 50		29	11	18
	> 50		11	9	2
Localization		0.311			
	distal		16	10	6
	proximal		12	4	8
	Rectal		12	6	6
Differentiation		0.717			
	High		15	7	8
	Moderate		17	9	8

DISCUSSION

The most frequent genetic changes that are known to occur in a variety of human malignancies are mutations of p53 gene (18, 19). In this case, we identified p53 gene alterations in 50% of the studied cases. This result was consistent with other research that found rates ranging from 50% to 70%. P53 mutation rates were 59.6% in Tunisia (20), 52.5% in the Arabian Gulf (21), 61.3% in the United Kingdom (22), 45.4% in the United States (23), 44.4% in Iran (24), and 32, 2% in Egypt (25). The discrepancies in the observed frequency of p53 mutations can be attributed to a wide range of factors, including sample selection and population differences. The primary functional domain responsible for DNA binding, exons 5–8 (codons 126-306), is where the mutations found. Exons 7, 6, and 5 had higher rates of mutations than exons 8. Furthermore, we found alterations in intron 7 and the splice site that are not present in the p53 coding region. There were two types of mutations: 76.9% were missense mutations, and 23.1% were frame shift mutations. In this investigation, we only discovered mutations in codons 245 and 248 that were situated in the hot spot locations. Transversions made up 62% (31/50) and transitions made up 38% (19/50) of the mutation types. The most found transversion type was G to C (35.5%), and the transition type was C to T (16.1%). These results were in line with those from earlier studies (20, 21). It should be mentioned that the TP53 protein's domains III–V contained mutations in the hotspot codons containing CpG sites (codons 245, 248). These orientations appear to be typical of colorectal carcinomas and were consistent with those in the previous investigations (24, 25, 26).

We revealed no correlation between the incidences of colorectal cancer clinicopathological variables with the exception of the relationship between p53 mutations and advanced age. Ages ≥ 50 years showed a tendency toward a comparatively greater frequency of p53 mutant status (55%, p, value = 0.013). This result deviates from other research, while it is in line with certain earlier results (10, 21, 23, 24). Although

colorectal cancer can strike younger individuals, it is far more likely after the age of 50. Numerous risk factors contribute to colorectal cancer; of these, the interplay between hereditary and environmental factors is of special interest. According to Parkin et al. (2005) (27) people older than 50 accounted for more than 90% of newly diagnosed cases of colorectal cancer. Similar findings were observed in this study, which showed that persons over 40 years old had a higher incidence of colorectal cancer (90.5%). According to other studies, colorectal cancer incidence is still comparatively low in people under 40 years (28, 29). Our data found that 57.4 years was the average age at colorectal cancer diagnosis. Similar findings have been reported in previous investigations, such as those carried out in Tunisia, Arabian Gulf, and Egypt (20, 21, 25).

It is unclear, therefore, why males are more likely than women to get colorectal cancer. According to one study, the higher frequency of colorectal cancer in men than in women may be caused by variables such food, body size, physical activity, hormones, and family history of the disease (30).

There was no obvious correlation between the location of the tumor and p53 mutations. This was not the case for the data published by other researchers, which indicated that p53 mutations were more common in rectal and left-sided cancers (31, 32). P53 mutations were also more common in proximal, rectal, and distal cancers, while the difference was not statistically significant. This result was consistent with other research conducted in Tunisia and in Iran (20, 24). This discrepancy is most likely caused by the possibility that these cancers developed more frequently because of carcinogen exposure than the tumors on the colon's right side. Overall, in line with the majority of other research (24, 31), there was no discernible correlation between p53 mutations and the tumor's differentiation.

According to McDermott et al. (2002) (33) p53 mutations are frequently linked to protein accumulation in the nucleus and may lengthen the half-life of proteins. TP53 was immunostained in each of the 40 tissues that were examined for p53 mutations. In total, 22 patients (or 55%) had positive TP53 nuclear accumulation results. With 65% specificity and 75% sensitivity, there was a general agreement between protein accumulation and mutation status (p- value = 0.011). The range of findings described in the literature (34, 35) is represented by these results. Out of the 18 cases where TP53 mutations were found, five cases (27.7%) did not exhibit TP53 accumulation. Lastly, it is possible that the overexpression of the p53 protein is a result of the apoptotic and DNA-repairing mechanisms triggered in malignant cells with damaged DNA (36). We also found that, with the exception of a strong correlation between p53 protein increase and age, there was no association between the clinicopathological features of colorectal cancer tumors and changes in the p53 protein or gene.

In conclusion, we have found that 50% of the studied patients with colorectal cancer have p53 gene alterations. The mutations were found in exons 5 through 8. Compared to exon 8, they were more commonly detected in exons 7, 6, and 5, as well as intron 7 and the splice junction. All of the mutations were missenses, with transversions accounting for 52% of the type and transitions accounting for 48%. With the exception of the age of CRC patients, we found no correlation between the existence of p53 mutations and any clinical or pathological criteria. Furthermore, we found a strong association (p- value = 0.011) between TP53 protein increase and p53 mutations. To confirm our findings in a large number of colorectal cancer patients, more research is required.

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Authors' Contributions(CRidT)

Alqawi O: supervision, methodology, writing; Allelish A: methodology; Emaetig F: methodology, formal analysis; Agoob M: formal analysis, data curation; Aljahamie F: writing, methodology, formal analysis.

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No funding was received concerning this study.

Conflict of Interest

The authors have no conflict of interest for this study.

Data Availability Statement

The data of this study is available upon requested.

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