MEDICAL SCIENCE MONITOR

CLINICAL RESEARCH

e-ISSN 1643-3750
© Med Sci Monit, 2019; 25: 5510-5517
DOI: 10.12659/MSM.915335

Received: 2019.01.24
Accepted: 2019.04.05
Published: 2019.07.25

Investigation of Insulin-Like Growth Factor-1 (IGF-1), P53, and Wilms' Tumor 1 (WT1) Expression Levels in the Colon Polyp Subtypes in Colon Cancer

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

AE 1 Ali Aslan
CD 2 Havva Erdem
BC 2 Muruvvet Akcay Celik
AD 3 Arzu Sahin
CD 4 Soner Cankaya

1 Department of Physiology, Faculty of Medicine, Ordu University, Ordu, Turkey
2 Department of Pathology, Faculty of Medicine, Ordu University, Ordu, Turkey
3 Department of Physiology, Faculty of Medicine, Usak University, Usak, Turkey
4 Department of Sports Management, Faculty of Sport Sciences, Ondokuz Mayis University, Samsun, Turkey

Corresponding Author: Ali Aslan, e-mail: draslan@yahoo.com
Source of support: This study was supported by Ordu University Scientific Research Project Unit (Project No: AP-1727)

Background: There is no study in the literature investigating the expression levels of WT1, p53, and IGF-1 in colon polyp subtypes. In this study, we aimed to investigate the expression levels of IGF-1, p53, and WT1 in colon polyp subtypes and to determine whether expression levels are correlated with each other.

Material/Methods: Tissue specimens were obtained from 105 patients (80 men, 25 women; age range, 30–91 years) who underwent surgical resection for colorectal cancer (CRC) at Ordu University School of Medicine, Department of Pathology between January 2015 and 2017. Parameters such as age, sex, region of origin, and pathological diagnosis type were determined. The preparations were immunohistochemically stained with corresponding markers.

Results: The results of the study showed that there was a statistically significant relationship between WT1 expression (negative – positive) in polyps and the place where the sample was taken (P=0.011). There is a positive relationship between P53 staining score (0–3) and positive frequency of IGF-1 (60.9–85.7%). There was a statistically significant change in P53 scores and location (P=0.006, p=0.015, respectively). As the P53 score of the polyps increased (0 to 3), the rate of adenomatous (34.8–78.4%) increased, so a positive relationship was found. WT1 and IGF-1 gene expression was associated with tumor location, p53 staining score, and sex.

Conclusions: WT1 and IGF-1 are appropriate markers for CRC, and WT1 expression in CRC primary tumors especially could be a novel independent marker for prognosis and tumor progression.

MeSH Keywords: Colonic Neoplasms • Genes, p53 • Immunotherapy • Insulin-Like Growth Factor I • Wilms Tumor

Full-text PDF: https://www.medscimonit.com/abstract/index/idArt/915335

2014 6 1 41

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS]

Background

Gastrointestinal polyps are proliferative and neoplastic lesions originating from the mucosa and submucosa epithelium and protruding into the lumen of the gastrointestinal tract. Gastrointestinal (GIS) polyps are more commonly seen in the colorectal region [1]. The polyps detected by the colonoscopic examination may be stemmed or unaltered and their size is variable [2,3]. Colorectal polyps are classified as non-neoplastic polyps {hyperplastic (metaplastic) polyps, hamartomatous polyps (juvenile polyposis, Peutz-Jeghers syndrome, Cronkhite-Canada syndrome, Cowden syndrome), inflammatory polyps}, neoplastic polyps, adenomas (tubular, tubulovillous, villous). Adenomas may include mild, moderate, and severe dysplasia. Tubular adenomas are usually small and show mild dysplasia. As the diameter of polyps increases, dysplasia increases in villous patients. We found 88% mild, 8% moderate, and 4% severe dysplasia in tubular adenomas; 58% mild, 26% moderate, and 16% severe dysplasia in tubulovillous adenomas; and 41% mild, 38% moderate, and 21% severe dysplasia in villous adenomas [4,5]. Insulin-like growth factor-1 (IGF-1) shows the *in vitro* effect either acutely on the anabolic effect on protein and carbohydrate metabolism, or on long-term cell differentiation. IGF-1 stimulates DNA synthesis, and cell replication in cell cycle is a very important effect. It has been shown that cell turnover increases the risk of cellular transformation by the action of IGF-1 receptor [6]. Insulin-like growth factor-1 (IGF-1) and its receptor (IGF-1R) are also thought to play a key role in mitogenesis and tumorigenesis [7,8]. In addition to prognostic factors, histopathological biomarkers such as insulin-like growth factor (IGF), androgen receptor status, microvascular density, Ki-67 index, and p53 gene mutation are also reported to be useful in predicting disease progression [9–11]. P53 stress signals in a somatic cell are involved in apoptosis, cell cycle stop, DNA repair, and aging, and has an important role in translating into classical processes such as "the protector of the genome" [12,13]. Inactivation of the P53 tumor suppressor gene occurs in more than half of all human tumors, meaning that loss of this gene is an important step in the pathogenesis of cancer [14].

P53 and Wilms' tumor 1 (WT1) are tumor suppressor genes that are expressed everywhere and mutated in a large proportion of human cancers [14]. Changes in WT1 expression have been described in other malignancies and premalignant syndromes [15,16]. Most solid tumor cell lines were examined; WT1 expression was found to be increased in lung, gastric, colon, and breast cancers [17]. There are also studies showing that WT1-expressing leukemia and solid tumor cells are inhibited by the treatment of WT1 antisense oligomers and that the WT1 gene has an oncogenic function in these malignancies [17,18]. These results indicate that WT1 may be a tumor antigen whose expression could be increased for use in immunotherapy against both leukemia and solid tumors [19]. The ability of the WT1 protein to function as a target antigen for immunotherapy has been studied in *in vivo* in rats and *in vitro* in human systems [20–22]. The results showed that WT1 protein may be a promising tumor rejection antigen for cancer immunotherapy [22,23].

There is no study in the literature investigating the expression levels of WT1, p53, and IGF-1 in colon polyp subtypes, and their relationship with age, sex, region of origin, and pathological diagnosis.

In this study, we aimed to investigate the expression levels of IGF-1, p53, and WT1 in colon polyp subtypes and to determine whether expression levels are correlated with each other. However, in order to prevent the occurrence of cancer, we need to maximize the efficacy of immunotherapy in patients after polyp resection.

Material and Methods

Patients and surgical specimens

The experimental protocol was approved by the Institutional Human Ethics Committee of Ordu University (approval no: 2017/46). Tissue specimens were obtained from 105 patients (80 men, 25 women; age range, 30–91 years) who underwent surgical resection for colorectal cancer at Ordu University School of Medicine, Department of Pathology between January 2015 and 2017. Parameters such as age, sex, region of origin, and pathological diagnosis type were determined. The preparations were immunohistochemically stained with corresponding markers.

Immunohistochemical analysis

Kits used in the histochemical analysis are CellMarque 453M-94 p53 (DO7) Conc. 0.1mL (1: 100-500), CellMarque 348M-94 WT1-Wilms' Tumor (6F-H2) Conc. 0.1 mL (1: 100–500), and EMD Millipore CBL52 Insulin-like Growth Factor-I (M23) 100 ug. Immunohistochemical analysis of tissue sections was reviewed by 2 pathologists independently, and a consensus had to be reached in cases of interobserver variation. The pathologists were blinded to the clinicopathological features of the specimens. Specimens were considered immunopositive for P53 when 10% or more of tumor cells showed clear evidence of nuclear staining. Weidner criteria for analysis were used [24]. IGF-1, P53, and WT1 protein staining were analyzed semi-quantitatively. Stained cells were counted under a light microscope (magnification, ×400) and the percentage of stained cells was counted in 5 visual fields. The average was then calculated and divided according to the scoring levels: Without

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS]

positively-stained cells, 0; <25% positively-stained cells, 1; 26–50% positively-stained cells, 2; >50% positively-stained cells, 3.

Statistical analysis

All statistical analyses were performed using SPSS Statistics 25 (IBM SPSS, NY, USA). The gene expression levels in cancer tissue were compared with those in adjacent normal mucosa using the Wilcoxon signed-rank test. The associations between gene expression and potential explanatory variables (including age, sex, tumor location, histological type, expression levels, and staining scores) were evaluated using the chi-square test. A p-value of <0.05 was considered significant.

Results

There was no significant difference between the age distribution of the patients in terms of the presence of WT1 expression (P=0.974) (Table 1).

Histochemical staining of p53, IGF-1, and WT1 is shown in Figure 1. Nuclear staining with p53 in HP, membrane staining with IGF-1 in AP, and cytoplasmic/membranous staining with WT1 in HP are shown in Figure 1. The results of the study showed that there was a statistically significant relationship between WT1 expression (negative-positive) in polyps and the place where the sample was taken (P=0.011). WT1-positive staining was strongest in samples taken from the pre-transverse colon section and weakest in samples taken from the post-transverse colon (Table 2). There was no statistically significant relationship between WT1 expression in the polyps and sex, diagnostic IGF, or P53 staining scores, but there were clinically significant differences in OR (odds ratio) values. Positive staining according to hyper-polyposis (HP) was 1.609 times (OR=4.308) higher in the adenomatous polyposis (AP), 1.393 times (OR=1.393) higher in the women compared to men, and those with IGF-positive staining were 2.103 times (OR=2.103) higher than in those with IGF-negative staining. In addition, we found a positive relationship between P53 staining score (0–3) and WT1 positive frequency (39.1–64.3%). In other words, as the P53 staining score increased, the rate of WT1 staining increased.

There was no statistically significant relationship between IGF-1 expression (negative-positive) and P53 staining scores (P=0.062). The IGF-1 positive staining rate was highest in the samples with the most severe staining (Table 3). However, there was a positive relationship between P53 staining score (0–3) and positive frequency of IGF1 (60.9–85.7%). In other words, the P53 staining score increased as the staining rate increased. Our findings showed that there was no relationship between sex, WT1, and IGF-1 staining in cases where the samples were hyperplastic and adenomatous after pathological diagnosis. We found that there was no relationship between sex, WT1, and IGF-1 staining in patients with hyperplastic and adenomatous lesions after pathological diagnosis. However, there was a statistically significant change in P53 scores and location (P=0.006, p=0.015, respectively). As the P53 score of the polyps increased (0–3), the rate of adenomas (34.8–78.6%) increased, so a positive relationship was found. The rate of AP pathological diagnosis was 88.2% in the samples taken from the transverse colon. No statistically significant difference was found between the mean age of the patients diagnosed with AP and HP (P = 0.060). Although there was no significant relationship between pathologic diagnosis and sex, in terms of OR values, the rate of adenomatous pathologic diagnosis was 2.60 times higher than hyperplastic pathologic diagnosis, 2.69 times higher in men compared to women, and 2.075 times higher in patients with IGF-1 staining than in negative ones (Table 4).

The results of the study revealed that there was no significant relationship between P53 status and WT1 (P=0.473) and IGF-1 (P=0.740) staining status in the samples (Table 5).

There was no statistically significant correlation between P53-IGF-1-WT1 status and AP and HP status (P=0.088). However, AP and HP incidence rates were significantly higher in P53-positive patients than in others (Table 6). In the P53-positive group, IGF-1 positivity was higher in patients with IGF-1-positivity than in those with IGF-1-positivity, but negative or positive WT1 status was not associated with AP and HP distribution (Table 6).

Discussion

We found that that the colon location in the colon polyps affected the WT1 positivity and the adenomatous polyp ratio, and that the p53 staining score, WT1, and IGF-1 positivity increased in adenomatous polyps. However, as the p53 score increased, WT1 and IGF-1 positivity increased. In addition, the WT1 positivity rate was 2.371 times higher in females, and in men the adenomatous polyp ratio was 1.609 times and IGF-1 was 2.075 times higher.

The P53 gene is a proven tumor suppressor gene, is downregulated in colon cancer patients, and is consistent with malignant transformation, as reported in the literature. Hundreds of target genes have been associated with p53, including WT1 and IGF-1 [25–30].

The WT1 protein was shown to be expressed in cancer cells derived from various kinds of cancers, including colon cancer, breast cancer, primary leukemia, bone and soft-tissue sarcoma, lung cancer, and head and neck squamous cell

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS]

Table 1. Age distribution by WT1 staining status.

WT1 staining status	n	Mean	SD	*P*-value
No	56	60.95	11.09	0.974
Yes	48	61.02	11.88	

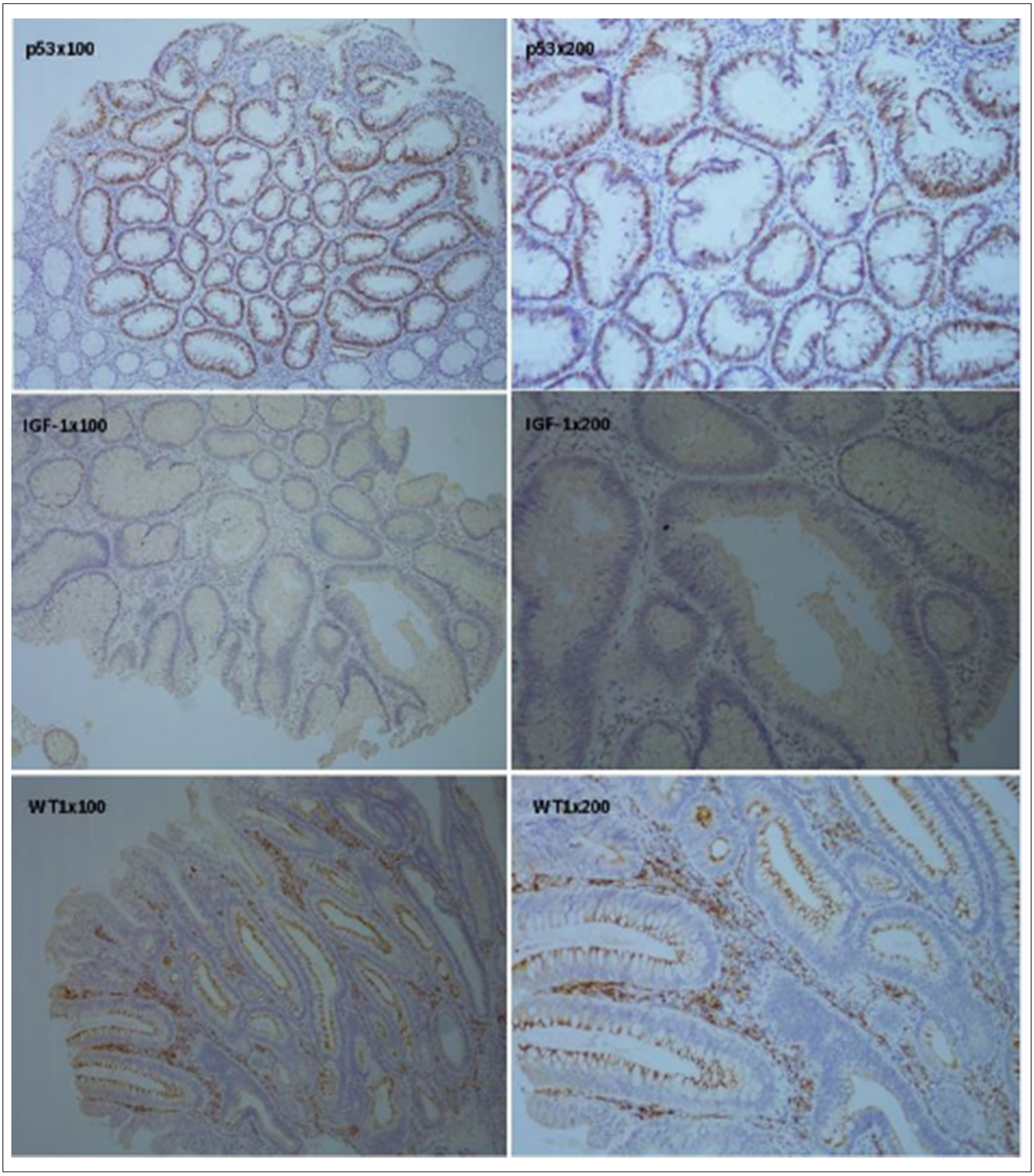

Figure 1. Histochemical staining of p53, IGF-1, and WT1. Nuclear staining with p53 in HP. Membrane staining with IGF-1 in AP and cytoplasmic/membranous staining with WT1 in HP.

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS]

Table 2. Sex, pathological diagnosis, location of sample, and WT1 distribution according to IGF and P53.

Features	WT1 status				χ^2-value	*P*-value
	Negative n (%)		Positive n (%)			
Sex						
Men	45	(56.3)	35	(43.8)	0.522	0.470
Women	12	(48.0)	13	(52.0)		
Pathological diagnosis						
Hyper-polyposis (HP)	28	(60.9)	18	(39.1)	1.430	0.232
Adenomatous polyposis (AP)	29	(49.2)	30	(50.8)		
Location of sample						
Before transverse colon	5	(27.8)	13	(72.2)	9.095	0.011
Transverse colon	7	(41.2)	10	(58.8)		
After Transverse colon	45	(64.3)	25	(35.7)		
IGF-1						
No	25	(65.8)	13	(34.2)	3.176	0.075
Yes	32	(47.8)	35	(52.2)		
P53 staining score						
None (0)	14	(60.9)	9	(39.1)	2.448	0.485
Mild (1)	22	(55.0)	18	(45.0)		
Moderate (2)	16	(57.1)	12	(42.9)		
Severe (3)	5	(35.7)	9	(64.3)		

Table 3. IGF distribution by P53 staining score.

P53 staining score	IGF-1 status				χ^2-value	*P*-value
	Negative n (%)		Positive n (%)			
None (0)	9	(39.1)	14	(60.9)	7.332	0.062
Mild (1)	12	(30.0)	28	(70.0)		
Moderate (2)	15	(53.6)	13	(46.4)		
Severe (3)	2	(14.3)	12	(85.7)		

carcinoma [31–34]. A study by Miyata et al. found that WT1 expression was increased in colorectal cancers. Furthermore, WT1 expression was reported to be correlated with tumor progression, lymph node metastasis, and clinical staging [35]. Oji et al. [32] showed that WT1 expression in colon cancer was significantly higher than that in normal-appearing colorectal tissues, with no significant correlations between WT1 expression and clinical factors and TNM stages. In the present study, WT1 gene expression was found to be associated with tumor location, p53 staining score, and sex.

A number of previous studies have compared the expression levels of the IGF-1, IGF-2, IGF-1R, and IGFBP-3 genes in colon cancer tissue and adjoining normal mucosa. Zhang et al. [36] showed that there was identifiable IGF-1 mRNA in malignant human colonic tissue. The mRNA expression levels of the IGF-1R gene were reported to be higher in adenocarcinoma tissue of the colon compared to adjoining normal mucosa [37]. Another study demonstrated that mRNA expression of the IGF-IR gene was detected liver metastasis in CRC tissue specimens but was undetectable in adjoining normal mucosa [38]. Keku et al. [5] demonstrated that the mRNA expression level of the IGF-1R gene was higher in CRC tissue compared with adjoining normal

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS]

Table 4. According to the pathological diagnosis (hyperplastic and adenomatous) WT1, IGF-1, and P53 distribution.

Features	Pathological diagnosis				χ^2-value	*P*-value
	Negative n (%)		Positive n (%)			
Sex						
Men	31	(38.8)	49	(61.3)	3.494	0.062
Women	15	(60.0)	10	(40.0)		
WT1						
Negative	28	(49.1)	29	(50.9)	1.430	0.232
Positive	18	(37.5)	30	(62.5)		
IGF-1						
No	21	(55.3)	17	(44.7)	3.174	0.075
Yes	25	(37.3)	42	(62.7)		
P53 staining score						
None (0)	15	(65.2)	8	(34.8)	22.382	**0.006**
Mild (1)	21	(52.5)	19	(47.5)		
Moderate (2)	7	(25.0)	21	(75.0)		
Severe (3)	3	(21.4)	11	(78.6)		
Location of sample						
Before transverse colon	9	(50.0)	9	(50.0)	8.461	**0.015**
Transverse colon	2	(11.8)	15	(88.2)		
After transverse colon	35	(50.0)	35	(50.0)		
					t-value	*P*-value
Age*	58.9	(9.11)	62.8	(12.7)	–1.90	0.060

* Age values were given as mean (std deviation) according to pathological diagnosis groups.

Table 5. Distribution of P53 according to IGF-1 and WT1 status.

Features	P53 staining				χ^2-value	*P*-value
	Negative n (%)		Positive n (%)			
WT1 status						
Negative	14	(24.6)	43	(75.4)	0.514	0.473
Positive	9	(18.8)	39	(81.3)		
IGF status						
Negative	9	(23.7)	29	(76.3)	0.110	0.740
Positive	14	(20.9)	53	(79.1)		

mucosa. However, the mRNA expression levels of the IGF-1 gene were reduced in cancer tissue compared with adjoining normal mucosa. Peters et al. [39] showed that IGF-1 gene expression was not associated with any clinic-pathological characteristic in CRC, while Shiratsuchi et al. [40] reported that IGF-1 gene expression in CRC was associated with tumor size, depth of tumor invasion, lymphatic invasion, and venous invasion in CRC. Increased postoperative tumor growth and the presence of liver metastasis were associated with significantly elevated IGF-1R gene expression in gastrinoma [40,41]. In the present study, IGF-1 gene expression was associated with tumor location, p53 staining score, and sex.

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS]

Table 6. Comparison of P53-IGF-1-WT1 and AP-HP distribution.

P53	IGF-1	WT1	AP		HP		χ^2-value	*P*-value
–	–	–	2	(1.90)	5	(4.76)	11.830	0.088
		+	0	(0.00)	2	(1.90)		
	+	–	3	(2.86)	4	(3.81)		
		+	3	(2.86)	4	(3.81)		
+	–	–	10	(9.52)	8	(7.62)		
		+	5	(4.76)	6	(5.71)		
	+	–	14	(13.33)	11	(10.48)		
		+	22	(20.95)	6	(5.71)		

We acknowledge that there are some limitations in our study. These include a small sample size, the relatively small proportion of high-grade and advanced-stage lesions, and lack of survival data. Despite these limitations, the WT1 and IGF-1 expressions may reflect tumor progression and metastatic activity. These analyses of WT1 and IGF-1 will increase our understanding of CRC pathogenesis, and could further lead to novel treatment and early diagnostic tools and offer new strategies for immunotherapies in CRC.

Conclusions

WT1 and IGF-1 are appropriate markers for CRC, and WT1 expression in CRC primary tumors especially could be a novel independent marker for prognosis and tumor progression.

Conflict of interests

None.

References:

1. Lian J, Ma L, Yang J, Xu L: Aberrant gene expression profile of unaffected colon mucosa from patients with unifocal colon polyp. Med Sci Monit, 2015; 21: 3935–40
2. Dölek Y, Karabulut YY, Topal F, Kurşun N: [Gastrointestinal poliplerin boyut, lokalizasyon ve histopatolojik tipleriyle değerlendirilmesi.] Endoskopi Dergisi, 2013; 21 [in Turkish]
3. Yao S, Sun C, Wang T et al: Is it necessary to intubate the cecum to examine the whole colorectum during endoscopic polypectomy? Med Sci Monit, 2018; 24: 4324–29
4. Ucmak F, Tuncel ET: Relationship between lesions in adenomatous polyp-dysplasia-colorectal cancer sequence and neutrophil-to-lymphocyte ratio. Med Sci Monit, 2016; 22: 4536–41
5. Keku TO, Sandler RS, Simmons JG et al: Local IGFBP-3 mRNA expression. apoptosis and risk of colorectal adenomas. BMC Cancer, 2008; 8: 143
6. Giovannucci E: Insulin, insulin-like growth factors, and colon cancer: A review of the evidence. J Nutr, 2001; 131: 3109S–20S
7. Robbins DH, Itzkowitz SH: The molecular and genetic basis of colon cancer. Med Clin North Am, 2002; 86: 1467–95
8. Topalak Ö, Çolakoğlu Ö, Özkara E et al: [Kolorektal tümör gelişiminde insülin benzeri büyüme Faktörü-1 reseptör sunumunun rolü.] Akademik Gastroenteroloji Dergisi, 2003; 2 [in Turkish]
9. Augoff K, Rabczynski J, Tabola R et al: Immunohistochemical study of decorin expression in polyps and carcinomas of the colon. Med Sci Monit, 2008; 14: CR530–35
10. Wu L, Han T, Fan X et al: Serum C-reactive protein as a possible marker to predict delayed hemorrhage after colonoscopic polypectomy. Med Sci Monit, 2012; 18: CR480–85
11. Sy E: [Prostat kanseri doğal seyri. prognostik faktörler ve nomogramlar. Üroonkoloji Kitabı Üroonkoloji Derneği; Ankara.] Ertem Basım Yayın, 2007; 593–603 [in Turkish]
12. Lane DP: Cancer. p53, guardian of the genome. Nature, 1992; 358: 15–16
13. Aloni-Grinstein R, Shetzer Y, Kaufman T, Rotter V: p53: The barrier to cancer stem cell formation. FEBS Lett, 2014; 588: 2580–89
14. Miyashita T, Reed JC: Tumor suppressor p53 is a direct transcriptional activator of the human bax gene. Cell, 1995; 80: 293–300
15. Scharnhorst V, van der Eb AJ, Jochemsen AG: WT1 proteins: Functions in growth and differentiation. Gene, 2001; 273: 141–61
16. Sugiyama H: WT1 (Wilms' tumor gene 1): Biology and cancer immunotherapy. Jpn J Clin Oncol, 2010; 40: 377–87
17. Oji Y, Ogawa H, Tamaki H et al: Expression of the Wilms' tumor gene WT1 in solid tumors and its involvement in tumor cell growth. Jpn J Cancer Res, 1999; 90: 194–204
18. Yamagami T, Sugiyama H, Inoue K et al: Growth inhibition of human leukemic cells by WT1 (Wilms tumor gene) antisense oligodeoxynucleotides: Implications for the involvement of WT1 in leukemogenesis. Blood, 1996; 87: 2878–84
19. Tsuboi A, Oka Y, Osaki T et al: WT1 peptide-based immunotherapy for patients with lung cancer: report of two cases. Microbiol Immunol, 2004; 48: 175–84
20. Oka Y, Udaka K, Tsuboi A et al: Cancer immunotherapy targeting Wilms' tumor gene WT1 product. J Immunol, 2000; 164: 1873–80
21. Tsuboi A, Oka Y, Ogawa H et al: Cytotoxic T-lymphocyte responses elicited to Wilms' tumor gene WT1 product by DNA vaccination. J Clin Immunol, 2000; 20: 195–202
22. Oka Y, Tsuboi A, Elisseeva OA et al: WT1 as a novel target antigen for cancer immunotherapy. Curr Cancer Drug Rargets, 2002; 2: 45–54
23. Sugiyama H: Cancer immunotherapy targeting WT1 protein. Int J Hematol, 2002; 76: 127–32
24. Weidner N: Tumor angiogenesis: Review of current applications in tumor prognostication. Semin Diagn Pathol, 1993; 10: 302–13
25. Attias Z, Werner H, Vaisman N: Folic acid and its metabolites modulate IGF-I receptor gene expression in colon cancer cells in a p53-dependent manner. Endocr Relat Cancer, 2006; 13: 571–81
26. Feng Z, Hu W, de Stanchina E et al: The regulation of AMPK beta1. TSC2. and PTEN expression by p53: Stress, cell and tissue specificity, and the role of these gene products in modulating the IGF-1-AKT-mTOR pathways. Cancer Res, 2007; 67: 3043–53
27. Lee H, Kim N, Yoo YJ et al: beta-catenin/TCF activity regulates IGF-1R tyrosine kinase inhibitor sensitivity in colon cancer. Oncogene, 2018; 37: 5466–75

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS]

28. Lyu Y, Lou J, Yang Y et al: Dysfunction of the WT1-MEG3 signaling promotes AML leukemogenesis via p53-dependent and -independent pathways. Leukemia, 2017; 31: 2543–51
29. Matalka I, Obeidat B, Mohtaseb A, Awamleh A: The significance of Wilms Tumor Gene (WT1) and p53 expression in curettage specimens of patients with endometrial carcinomas. Pathol Res Pract, 2013; 209: 19–23
30. Nahor I, Abramovitch S, Engeland K, Werner H: The p53-family members p63 and p73 inhibit insulin-like growth factor-I receptor gene expression in colon cancer cells. Growth Horm IGF Res, 2005; 15: 388–96
31. Aslan A, Erdem H, Çelik MA et al: [Kolon poliplerinde WT1 ekspresyonunun incelenmesi.] Anatolian Clinic the Journal of Medical Sciences, 2018; 23: 79–83 [in Turkish]
32. Oji Y, Yamamoto H, Nomura M et al: Overexpression of the Wilms' tumor gene WT1 in colorectal adenocarcinoma. Cancer Sci, 2003; 94: 712–17
33. Miyoshi Y, Ando A, Egawa C et al: High expression of Wilms' tumor suppressor gene predicts poor prognosis in breast cancer patients. Clin Cancer Res, 2002; 8: 1167–71
34. Oji Y, Miyoshi S, Maeda H et al: Overexpression of the Wilms' tumor gene WT1 in *de novo* lung cancers. Int J Cancer, 2002; 100: 297–303
35. Miyata Y, Kumagai K, Nagaoka T et al: Clinicopathological significance and prognostic value of Wilms' tumor gene expression in colorectal cancer. Cancer Biomark, 2015; 15: 789–97
36. Zhang R, Xu GL, Li Y et al: The role of insulin-like growth factor 1 and its receptor in the formation and development of colorectal carcinoma. J Int Med Res, 2013; 41: 1228–35
37. Han L, Zhang GF, Cheng YH, Zhao QC: Correlations of insulin-like growth factor I and insulin-like growth factor I receptor with the clinicopathological features and prognosis of patients with colon cancer. Jpn J Clin Oncol, 2016; 46: 1127–34
38. Chu PC, Lin PC, Wu HY et al: Mutant KRAS promotes liver metastasis of colorectal cancer. in part. by upregulating the MEK-Sp1-DNMT1-miR-137-YB-1-IGF-IR signaling pathway. Oncogene, 2018; 37: 3440–55
39. Peters G, Gongoll S, Langner C et al: IGF-1R. IGF-1 and IGF-2 expression as potential prognostic and predictive markers in colorectal-cancer. Virchows Archiv, 2003; 443: 139–45
40. Shiratsuchi I, Akagi Y, Kawahara A et al: Expression of IGF-1 and IGF-1R and their relation to clinicopathological factors in colorectal cancer. Anticancer Res, 2011; 31: 2541–45
41. Yamamoto N, Oshima T, Yoshihara K et al: Clinicopathological significance and impact on outcomes of the gene expression levels of IGF-1. IGF-2 and IGF-1R. IGFBP-3 in patients with colorectal cancer: Overexpression of the IGFBP-3 gene is an effective predictor of outcomes in patients with colorectal cancer. Oncol Lett, 2017; 13: 3958–66

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS]