Association between Tissue Polypeptide Specific Antigen and Vascular Endothelial Growth Factor in Colorectal Cancer Patients and their Relation with P53 Expression and Global DNA Methylation

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Abstract:

Background: Colorectal cancer is a high risk disease with rapidly progression medical problems and high mortality rate. Tissue polypeptide specific antigen can be classified as biomarker candidates in colorectal cancer and other kinds of cancer. Vascular endothelial-derived growth factor has a curial role in the formation of new blood vessels. DNA methylation may decrease invasiveness of cancer.

Objectives: This study was designed to measure the potential role of some serological biomarkers in the progression of colorectal cancer as well as their relations to P53 expression, global 5-methylcytosine.

Patients and Methods: This study involved of 60 patients with colorectal cancer who attended Oncology Teaching Hospital in Baghdad, Iraq and compared with 30 apparently healthy volunteers. All participants were checked for serological biomarker levels using an enzyme-linked immunosorbent assay. Also, DNA and RNA extracted and the levels of 5-methylcytosine and P53 expression were evaluated. The SPSS version 24.0 program was used for all statistical analysis done in this study.

Results: The analysis of serological biomarker data has shown that the mean of tissue polypeptide specific antigen and vascular endothelial growth factor was significantly higher for patients with colorectal cancer, while it was lower for control subjects (356.4 ± 16.9, 139.75 ± 7.31) and (1127.82 ± 65.41, 388.93 ± 35.86), respectively. Also, a significant positive relation between tissue polypeptide specific antigen and vascular endothelial growth factor in the tumor area was significantly associated with control ($P \leq 0.001$). However, there was significant correlation in the levels of P53 expression and global DNA methylation between studied groups as well as tissue polypeptide specific antigen and vascular endothelial growth factor ($P \geq 0.05$).

Conclusion: The serological biomarkers include tissue polypeptide specific antigen and vascular endothelial growth factor and they play a critical role in the development of colorectal cancer. Serum vascular endothelial growth factor is useful in distinguishing colorectal cancer from healthy controls, whereas tissue polypeptide specific antigen is an independent prognostic factor for colorectal cancer proliferation.

Keywords: Colorectal cancer; DNA methylation; P53 expression; Tissue polypeptide antigen;Vascular endothelial growth factor

Introduction

Colorectal cancer (CRC) is considered as the most lethal cancer and the third most prevalent malignant tumor worldwide. However, most cases and deaths are attributed to modifiable risk factor, or infection according to family history (1). Identification suitable biomarkers in the early stages of cancer can create the chances of successful treatment. Tissue polypeptide antigen (TPS) has been categorized as a tumor marker in different kinds of malignant tumor.
It is also used as a monitoring tool for chemotherapy in advanced gastrointestinal cancers (2).

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According to the tumor activity, the concentration of TPS was elevated and this correlated with the tumor action but not tumor size. Detecting the elevation levels of blood TPS very important especially in the early stages of cancer because it has an important role in tumor proliferation. A high level of TPS occurs in about (60–80%) of patients with colorectal cancer (3).

Angiogenesis, new blood vessels formation from existing vessel, and has a vital role in tumor metastasis. Vascular endothelial growth factor (VEGF) is an example of a signal protein. The metastasis of cancer cells from where it originated to another site through via new blood vessels which can grow by the action of vascular endothelial

growth factor (VGEF). VGEF has an additional role as a factor for tumor cell protection by preventing the action of chemotherapy and radiotherapy. Previous functions were named as the autocrine action of VGEF (4).

Epigenetics have gained significant attention since they have added a new dimension to genomic and proteomic research (5). Previous studies investigated that DNA sequence which was enriched with CpG islands became an excellent example for studying the DNA methylation of cancerous colorectal lesions (6). Tumorigenesis can be caused by gene silencing through hypermethylation of the promoter; and this led to DNA mutations and microsatellite instability and these events affected tumor diagnosis and choosing the suitable chemotherapy (7). Epigenetic modifications, such as DNA methylation, histone, miRNAs and lncRNA modifications have shown promise as critical biomarkers for CRC diagnosis, prognosis and treatment (8). Mutations in the tumor suppressor genes or oncogene activation are the main causes of cancer development; and the previous events cause the transformation of normal cells into tumor cells. An example of a frequently mutated gene is TP53 which is a tumor suppressor gene (9). Mutations in the pathways of tumor suppressor genes play an important role for cancer aggressiveness and the poor survival of the patient, such as mutation in the Wnt Family Member 1 (Wnt1) and p53. Previous gene mutations mostly seen in hepatocellular, and colorectal cancer (10). Recent researches suggested choosing genetic and epigenetic changes as a strategy for future medicine but there is insufficient evidence to support the previous use of such changes as biomarkers in CRC diagnosis. Colorectal cancer cells can enter the bloodstream and release noticeable biomarkers in the plasma and these events can be seen in the high stages of CRC (11). Therefore, this study was designed to measure the potential role of TPS, VGEF levels in the progression of CRC as well as their relation to P53 expression, global 5-methylcytosine (5mC) and the biological status of CRC patients including stage, grade, and invasion level.

Patients and Methods
Subjects
This study involved of 60 patients with colorectal cancer (32 males, 28 females) who attended Oncology Teaching Hospital in Baghdad, Iraq and they were compared with 30 apparently healthy volunteers (12 males, 18 females) from February 2022 to September 2022. All participants in this study provided signed, fully informed consent. The ethical committee of the Department of Biology, College of Science, University of Bagdad, Baghdad,

Iraq gave their approval to this work. The authorization with the reference number (CSEC/1021/0098 on October 29, 2021).

All participants' baseline blood samples were taken in order to estimate the levels of serum TPS and VGEF, gene expression of P53 by RT- PCR and the global 5mC in studied groups. Participants were

staged based on the TNM and grading was based on the World Health Organization. (WHO) also the performance status was estimated based on the ECOG classification (12).

Blood sample
Assay of the immunological analysis of serum TPS and VEGF Each participant in this study had 5ml of blood drawn from the redial vein using disposable syringes. Part of the blood sample (3ml) was placed into gel clot activator vacuum tubes for clotting. Following that, at 3000 rpm for 10 minutes the samples were centrifuged to separate the serum. The serum was then dispensed into Eppendorf tubes using a micropipette, and the tubes were then refrigerated at -20C° for a later immunological investigation of serum TPS, and VEGF levels. The remaining (2 ml) of blood sample was drawn and placed in an EDTA-containing tube to extract the DNA by using (Quick-DNA™ Miniprep Kit; Cat. No. D3024; ZYMO RESEARCH; USA) and the RNA extraction was done using (TRI Reagent®; Cat. No. R2050; ZYMO RESEARCH; USA) for P53 gene expression using real-time PCR, following the manufacturer's instructions.

Extraction of DNA
Human whole blood was used to extract the DNA. A nanodrop spectrophotometer (Thermo, USA) was used to confirm the presence and purity of the extracted DNA and to calculate DNA concentration (ng/μl) and examines DNA purity by measuring the absorbance at (260/280 nm) by staining DNA with ethidium bromide after running it on 1% agarose gels at 80 V for 30 minutes.

Assay of DNA methylation
The 5-methylcytosine (5mC) quantification Kit (Epigentek, USA) was used to estimate the global DNA methylation in whole blood samples .One hundred ng of genomic DNA was used for each sample. According to the manufacturer's instructions, a standard curve was created by using a methylated polynucleotide serving as a positive control that contained 50% of the 5mC provided by the kit. This curve was created by linear regression employing the five concentrations illustrated in (figure 1) and the formula below was used to compute the proportions of 5mC in the entire DNA. Following addition of the standard DNA and sample DNA in their corresponding wells, absorbance was measured using an ELISA reader at 450 nm.

$$5\text{-}mC\ (ng) = \frac{Sample\ OD - Negative\ control\ OD}{Slope\ x\ 2^*}$$

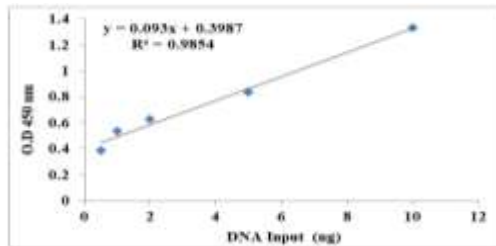$$5\text{-}mC\ \% = \frac{5\text{-}mC\ Amount\ (ng)}{S} \times 100\%$$

Figure (1) Standard curve of this study for determining 5-methylcytosine by the immunoassay. Diagrammatic representation of the linear connection between the quantity of 5-methylcytosine and its absorbance.

Assay of P53 gene expression

The master mix was prepared for all the samples in a final volume of 20 ul containing RT buffer. The (TRI Reagent®; Cat. No. R2050; ZYMO RESEARCH; USA) reagent was supplied as a 2X master mix with integrated Kapa Sybr Fast qPCR Master Mix (2X) Universal, forward primer, reverse primer, nuclease-free water and the template DNA sample volume. Reverse transcriptase was activated at 50 °C for 30 min. Then, activated at 95 °C for 15 min and it was denatured at 95 °C for 1 min. Followed by 39 denaturation cycles at 95 °C, annealing at 55 °C and an extension at 72 °C for 1 min before a final elongation step at 72 °C for 10 min. The P53 primer sequence for cDNA amplification is Forward primer AGA GTC TAT AGG CCC ACC CC Reverse primer GCT CGA CGC TAG GAT CTG AC (13), while the GAPDH sequence was used as a reference gene is Forward primer AATGGGCAGCCGTTAGGAAA, GAPDH Reverse primer GCGCCCAATACGACCAAATC (14).

Statistical analysis:

The SPSS version 24.0 program was used for all statistical analysis. The mean ± SE were presented for all of the numerical parameters. The three or more parameters were compared using the ANOVA test. The Student's t-test were additionally utilized to compare two numerical or categorical parameters. The P Value < 0.05 was accepted as statistically significant.

Results:

Evaluation of serum TPS and VEGF levels

Table1 showed the variation in serum levels of TPS and VEGF between cases and control group. Results showed that serum levels of TPS in CRC patients were significantly increased as compared to the control group (P≤ 0.001). Also, the results showed increases in VEGF levels in CRC patients as compared the control group with highly significant differences (P≤ 0.001).

Table (1) Serum levels of TPS and VEGF in colorectal cancer patients and healthy controls.

Parameters	CRC patients	Healthy Controls	P-value
	Mean ± SE		
TPS (pg/ml)	356.4±16.9	139.75±7.31	0.001
VEGF (pg/ml)	1127.82±65.41	388.93±35.86	0.001

Relationship between TPS, and VEGF and different parameters in the study groups:

The results revealed significant differences in the mean serum levels of TPS and VEGF in CRC patients with low and high stage diseases (P≤ 0.001) (Table 2), according to the histopathological parameters that were used to classify the grades of CRC, and no significant increases in the level of TPS in low and high grades tumors was observed. In contrast, noticeable differences in the mean serum levels of VGEF were recorded between high and low level grades and there was a significant difference (P ≤ 0.001). The current study also compared the levels of TPS and VEGF in CRC patients with low and high invasion tumors and the results showed that no significant difference was observed (P ≥ 0.05).

Table (2) TPS and VGEF in colorectal cancer patients in relation to clinical-pathological variables of tumor

Variables	TPS (pg/ml)	VGEF (pg/ml)
	TNM Stage	
Low level (I+II)	350.88±26.95	1138.09±111.24
High level (III+ IV)	358.95±21.55	1123.05±81.57
P-value	0.001	0.001
	Grading	
Grade 1-2	364.44±27.87	1370.52± 82.58
Grade 3-4	371.22± 41.00	1087.22± 112.89
	Tissue invasion	
Low invasion T1+T2	304.62± 35.80	1190.85± 122.02
High invasion T3+T4	377.20 ± 28.90	1164.92± 119.92
Low invasion T1+T2	304.62± 35.80	1190.85± 122.02
P-value	0.123	0.884
The results are presented as mean ± standard error (SE		

Relationship between TPS, VEGF and gender in the study groups

The study included 60 CRC patients (33 men and 27 women), the serum levels of TPS and VEGF were tested as shows in (Table 3). Results showed that TPS and VEGF levels were high in females in both low and high level of disease progress and there were significant differences (P≤0.001).

Table (3) Statistical analysis, according to the age groups, of TPS and VGEF levels in CRC patients in relation to clinico-pathological variables the tumor

Variable	Gender	TPS (pg/ml)	
Low L. (I+II)	Male	331.85±33.75 a	
	Female	383.51±45.34 a	1459.45±188.88 a
High L.(III+ IV)	Male	359.11±33.56 b	810.22±83.68 a
	Female	358.78±27.58 b	1451.53±99.44 b
P-value		0.001	0.001

The results are presented as mean ± standard error (SE).
*Different letters mean there are significant differences between genders.

Correlation between TPS, VEGF and Age Groups in the Study groups: The group of 60 CRC patients were matched based on age (<40, 40-60, 61-80 years) and serum levels of TPS and VEGF, and evaluated (Table 4). According to the serum level of TPS, the highest level was recorded in the age group (<40) years in the low level of CRC stage, while the highest level of VEGF was recorded in the age group (61-80) years in the low level of CRC stage, and there were statically significant differences (P≤0.001). In regard to the high level stages (III+ IV), TPS and VEGF recorded the highest mean levels in the age group (61-80) years and there was a significant difference between the two levels (P≤0.001).

Table (4) Statistical analysis, according to the age groups, of TPS and VEGF levels values in CRC patients in relation to clinico-pathological variables of the tumor.

Variable	Age group/ year	TPS (pg/ml)	VGEF (pg/ml)
Low L. (I+II)	<40	463.69±0.00 a	901.65±0.00 a
	40-60	334.35±34.38 a, b	1020.57±139.57 a, b
	61-80	357.44±47.49 a, b	1314.55±190.67 b
High L.(III+ IV)	<40	292.34±34.49 b. c	950.78±199:89 b
	40-60	369.03±37.08 b, c	1121.88±116.34 b
	61-80	376.30±33.23 c	1195.16±139.00 b
P-value		0.001	0.001

The results are presented as mean ± standard error (SE).
*Different letters mean there are significant differences among age groups.

The current study was done using the Pearson correlation to evaluate the strength of the relationship and the percentages are presented as medians or individually as individual dots. The results of figure (2) (A) shown that VGEF and P53 expression in the tumor area showed no correlation and are significantly associated with control (P ≤ 0.001). Also, a negative correlation was found between VGEF and DNA methylation in the tumor area and was not significantly associated with control as shown in figure1 (B). There was no correlation between TPS and P53 expression in the

tumor area (Figure 1- C). Also, figure (1-D) showed that there was no correlation between TPS and DNA methylation in the tumor area (P ≥ 0.05). The results of figure1 (E) showed a positive relation between TPS and VGEF in the tumor area and they were significantly associated with control (P≤ 0.001).
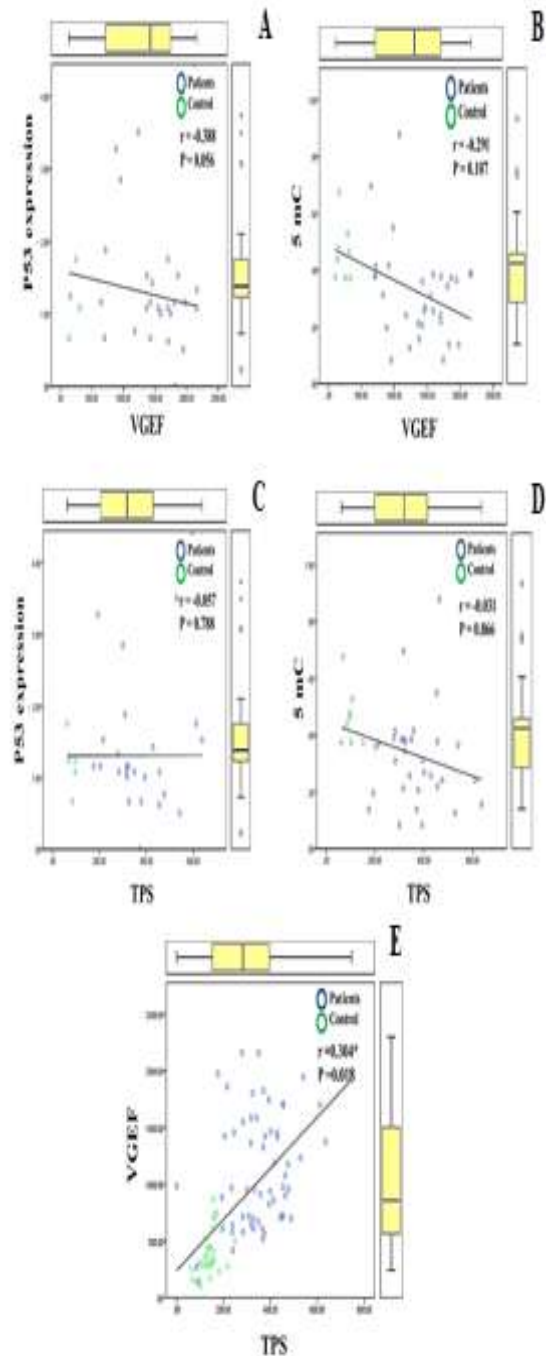

Figure (2): Pearson correlation was used to evaluate the strength relationship between parameters studied and the percentages are presented as median of individual dots. The results of correlation are significant at the level of 0.05

Discussion

The link between CRC outcomes and growth factor (VEFG) is questionable. Thus, the results of this study showed that the circulating level of TPS and VGEF increased in CRC patients. Some studies demonstrated that the poor prognosis of VEGF and VEGF receptors in colorectal cancer patients is associated with their overexpression (4). Other studies described VGEF as a prognostic marker in cancer patients without clarifying the relationship between serum VEGF and VEGF receptors levels (4). Findings of this study showed that the circulating level of TPS increased in the high level stage, grade and invasion while the circulating level of VEGF increased in the low level stage, grade and invasion of CRC patients. Recent studies concluded that a higher percentage of advanced stage rectal cancer was recorded in young patients compared to older patients and they suggested numerous reasons such as: young patients are having worse health care and they need more complex treatment to preserve fertility and sexual function and this takes a long time and has late effects, including subsequent primary malignancies (15). According to results of this study, the highest mean levels of TPS were shown in age group (<40) years while the highest level of VEGF was shown in the age group (61-80) years. In the high level disease progression, the TPS and VGEF recorded the highest mean levels in the age group (61-80) years. Many patients in the early-stages belonging to the age group (18-49) years received adjuvant therapy for the early disease stages (II, III) but with no improved survival in comparison to an age of (65–75) years (16). Cancer societies recommend improving CRC survival by start screening at the age of 45 years old. However, colonoscopy is considered an expensive tool for CRC screening, so it's recommended to use new screening tools instead (17). According to apoptosis and necrosis DNA molecules in tumor cells are released into the blood stream as cell-free tumor DNA (ctDNA) and this process can be used for cancer detection where the DNA methylation of (ctDNA) is different between patients and healthy individuals (18). Previous studies showed that patients in advanced stages of breast cancer and those with a poor prognosis experienced low levels of vitamin B12 and 5mC (19). Angiogenesis is key for the development of tumors. During angiogenesis, VEGF promotes cell proliferation, migration and angiogenesis (20). Previous results showed that age, sex, tumor size, location, lymph node metastasis, TNM stage, vascular tumor thrombosis or the neurological invasion of CRC patients was not significantly associated with the expression of some markers such as VEGF-A (17). Our results showed no correlation between 5mC, TPS, and VEGF and no significant association with control. Gorenjak et al., 2020 showed significant associations between DNA methylation and VEGF-A concentrations (21). Pancreatic ductal adenocarcinoma (PDAC) is an aggressive type of tumor which used TPS as a

biomarker in pre-diagnostic PDAC while an elevated level of TPS was observed in the metastatic stage of CRC and this had a role in identifying the recurrence of the disease (22). However, the previous study showed that at the different stages of PDAC there is no difference in plasma TPS levels and that's why TPS is considered a controversial biomarker in PDAC (2). However, Xiao et al., 2022 investigated on how increased TPS levels were associated with lymph nodes and metastasized cancer such as breast cancer and CRC (23) and these results disagree with our study. Increases in the levels of TPS occurred very late in the development of PDAC (2). The TP53 gene is classified as an onco-suppressor gene which is responsible for the repair of damaged DNA, blocking the cellular cycle until repair and apoptosis. The finding of previous studies showed no correlation between VEGF and P53 expression in the tumor area but it was significantly associated with control (P $\leq$ 0.001) while no correlation was found between TPS and P53 in the tumor area and control. According to many studies, P53 mutations have been examined in CRC patients and the results have shown a prognostic value in some studies and while some results contradict (24). Moreover, gene expression may not relate to the disease progression as a recent study detected that the reduction in BRCA1 expression was negatively associated with the disease's grades, in the advanced stage III of the breast cancer patients (25). Its alterations are frequent at early stage in the natural history of many cancers. This is its strength and its weakness since it determines its lack of specificity (26). Due to the increased cancer cells' cycle activity, changes in the metabolic pathways of organic compounds are expected (27). Studies suggested that infection with serious diseases may be linked to the patient's medical state, the severity of the adverse effects and other influencing factors (28).

Conclusion

The serological biomarkers including TPS and VEGF may play a critical role in the development of CRC, and they can be used as prognostic factors in differentiating CRC patients and healthy controls. Serum VGEF is useful in the prediction of the stage and grade of patients and also in distinguishing CRC from healthy controls whereas TPS is an independent prognostic factor for CRC proliferation.

Authors' contributions:

Dalya F. Ahmed and Rakad M. Kh AL-Jumaily as a researcher, samples and data collectors.

Author Declaration

We confirm that all the Figures and Tables in the manuscript are ours. Written informed consents were obtained from all subjects and the study was ap-proved by Ethical Committee (Ref.: CSEC/1021/0098 in October 29, 2021), Department

of Biology, College of Science, University of Baghdad.

Conflicts of interest: None.

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الارتباط بين مُسْتَضِدٍّ متعدد الببتايد الخاص بالنَّسيج و عامل نمو بطانة الأوعية الدموية في مرضى سرطان القولون والمستقيم وعلاقتهم بتعبير جين P53 ومثيلة الحمض النووي DNA

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الاستاذ المساعد الدكتور ركاد الجميلي/ جامعة يغداد / كلية العلوم/ قسم البايولوجي

خلفية البحث: سرطان القولون والمستقيم (CRC) هو مرض شديد الخطورة يتسبب في مشاكل طبية سريعة التطور وله معدل وفيات مرتفع. يمكن تصنيف مُسْتَضِدٍّ مُنَاوِغٌ للنَّسيج (TPS) كمؤشر حيوي في سرطان القولون والمستقيم وأنواع أخرى من السرطانات. لوحظ ان لعامل نمو بطانة الأوعية الدموية (VEGF) دور علاجي في تكوين أوعية دموية جديدة. قد تساهم مثيلة الحمض النووي بتقليل انتشار السرطان .

اهداف البحث: تم تصميم هذه الدراسة لقياس الدور المحتمل لبعض المؤشرات المصلية في تطور مرض سرطان قولون المستقيم وكذلك علاقته مع تعبير جين P53 ومثيلة السايتوسين. (mC5)

المرضى وطرق العمل: تم اجراء دراسة مقطعية مستعرضة شملت 60 مريضًا بسرطان القولون والمستقيم ارتادوا مستشفى الأورام التعليمي في بغداد ، العراق وتمت المقارنة مع 30 متطوعًا يتمتعون بصحة جيدة. تم فحص المؤشرات الحيوية المصلية لجميع المشاركين باستخدام تقنية الامتزاز المرتبط بالإنزيم. تم استخدام برنامج SPSS الإصدار 24.0 لجميع التحليلات التي أجريت في هذه الدراسة.

النتائج: أظهر تحليل بيانات المؤشرات الحيوية المصلية أن متوسط مستضد الأنسجة النوعي متعدد الببتيد (TPS) وعامل النمو البطاني الوعائي (VEGF)كان أعلى معنويًا لمرضى سرطان القولون والمستقيم ، بينما كان أقل بالنسبة لمجموعة السيطرة (16.9 ± 356.4 ، 139.75 ± 7.31) و (65.41 ± 1127.82 ، 388.93 ± 35.86) ، على التوالي. أيضا ، تم ايجاد علاقة موجبة معنوية بين TPS و VEGF في منطقة الورم مع مجموعة السيطرة (0.001 ≥P). لا يوجد ارتباط معنوي في مستويات التعبير53P ، و مثيلة الحمض النووي بين المجموعات المدروسة وكذلك بي TPS و (0.05 ≤ P). و VEGF (P ≥ 0.05).

الاستنتاجات: في الختام ، فإن المؤشرات الحيوية المصلية TPS و VEGF قد تلعب دورًا مهمًا في تطوير سرطان القولون والمستقيم. يعتبر مستوى عامل نمو بطانة الأوعية الدمويةVGEF في مصل الدم مفيدًا في التمييز بين مرضى القوقون والمستقيم ومجموعة السيطرة ، في حين أن مستوى المُسْتَضِدٍّ المُنَاوِغٌ للنَّسيج TPS هو عامل تنبؤي مستقل لتطور واستمرار مرض سرطان القوقون والمستقيم.

الكلمات المفتاحية: سرطان القولون والمستقيم ، مثيلة الحمض النووي, تعبير جين P53, مُسْتَضِدٍّ مُنَاوِغٌ للنَّسيج ، عامل نمو بطانة الأوعية الدموية