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Original Article

Diagnostic value of human fecal SDC2 gene in colorectal cancer

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Abstract: Objective: To explore the clinical value of human fecal Syndecan-2 (SDC2) gene methylation in colorectal cancer screening. Methods: There were 30 patients with colorectal cancer receiving treatment in Zhangjiakou First Hospital from January 2019 to December 2019 collected as the tumor group. There were 30 healthy people determined by a physical examination in 2019 collected as the normal group. The methylation level of fecal SDC2 gene and the level of serum tumor markers including carcinoembryonic antigen (CEA) and Carbohydrate antigen 19-9 (CA19-9) were analyzed. The diagnostic effects of fecal SDC2 methylation and serum tumor markers on colorectal cancer were compared. The area under curve (AUC) of different methods for colorectal cancer diagnosis were evaluated based on the receiver operating characteristic (ROC) curve. Results: There was no distinction between the tumor group and the normal group in clinical basic data, including gender, age, and body mass index ($P > 0.05$), revealing the comparability between the two groups. The level of fecal SDC2 methylation in the tumor group was lower than that in the normal group ($P < 0.05$). CEA and CA19-9 in the tumor group were higher than those in the normal group ($P < 0.05$). Among the 30 colorectal cancers, 28 (93.33%) were positive for SDC2 gene methylation, 18 (60%) were positive for serum CEA, and 19 (63.33%) were positive for serum CA19-9. This indicated that the true positive rate of SDC2 gene methylation was higher than that of serum tumor markers ($P < 0.05$). The AUC of fecal SDC2 gene methylation was 0.981. These were higher than that of serum tumor markers ($P < 0.05$). Conclusions: Fecal SDC2 gene detection has a high sensitivity and specificity for colorectal cancer. It has a very ideal detection effect in detecting colorectal cancer patients in the population.

Keywords: Fecal SDC2 methylation, colorectal cancer, diagnosis

Introduction

Colorectal cancer is a malignant tumor that occurs in the colon and rectum [1]. Among the incidence rate and mortality of malignant tumors in the world, its incidence rate ranks the third and mortality ranks the fourth [2]. As a common tumor, male malignant tumor is the fifth and female malignant tumor is the fourth in China [3]. Among the patients who have been diagnosed with cancer and survived within 5 years in China, the prevalence of colorectal cancer ranks the third in males (the first gastric cancer and the second lung cancer) and the second in females (second only to breast cancer) [4]. It is necessary to improve the diagnostic ability of colorectal cancer in China. Early diagnosis can detect precancerous lesions, improve its survival rate, reduce its incidence rate, and reduce its mortality [5]. Early colorectal cancer is asymptomatic. It is often late when symptoms appear. The 5-year survival rate is 30%. When it is found early, most patients can have it surgically removed, increasing the 5-year survival rate to 97% [6]. Studies have shown that colorectal adenoma and early colorectal cancer can be detected early by screening high-risk groups with symptomatic manifestations. This allows early treatment and removal of polyps before canceration can significantly reduce the incidence rate and mortality [7].

In recent years, the combined detection of tumor markers is more common in clinical appli-

cation to improve the early diagnosis of tumors [8]. A study revealed that the combined detection of serum alpha fetoprotein (AFP), carcinoembryonic antigen (CEA), carbohydrate antigen 19-9 (CA19-9), and carbohydrate antigen 125 (CA125) could significantly improve the positive detection rate of primary liver cancer [9]. As a non-invasive colorectal tumor marker with easy preservation, high detection rate, high sensitivity, and good specificity, fecal gene methylation can detect suspected cases through its positive results. This tumor marker is an important auxiliary means for screening and diagnosing colorectal tumors [10]. The rate of colorectal cell renewal is relatively fast. There are 10^{10} colorectal exfoliated cells every day. Compared with the normal colorectal mucosa, the number of colorectal mucosal exfoliated cells in colorectal cancer is higher [11]. Effective colorectal cancer screening can be carried out by analyzing the status of fecal exfoliated cancer cells and free DNA methylation [12]. Some studies have shown that the change of fecal DNA methylation level is closely related to the occurrence and development of colorectal cancer. Abnormal methylation often occurs in the early stage of colorectal cancer. It has a high accuracy in the detection of proximal and distal colorectal cancer and large adenoma (diameter ≥ 1 cm). Syndecan-2 (SDC2) is a transmembrane proteoglycan located on the cell surface. It plays an important role in colorectal cancer. Through regulating the interaction between cells and microenvironment, it promotes the activation of matrix metalloproteinases to decompose the extracellular matrix; participate in epithelial mesenchymal transition; promote the process of vascular synthesis; and accelerate the growth, diffusion, and metastasis of tumor cells [13]. It was reported that the methylation level of the target region in colorectal cancer tissues was significantly higher than that of the SDC2 target region in paired adjacent non colorectal cancer tissues. Gene mutations often occur in normal human cells. As an early screening for cancer, methylation detection is more advantageous than gene mutation detection.

Fecal gene detection is based on molecular biology technology. It can detect the changes of cell markers of colorectal tumor detachment in fecal samples to determine whether there is colorectal cancer [14]. It has the advantages of early, non-invasive, and high detection rate. It is a new intestinal cancer detection technology without intestinal preparation [15]. Its high sensitivity and non-invasive characteristics make it the trend of future colorectal cancer screening. Its biological basis is the persistence of cell shedding [16]. In this paper, 30 colorectal cancer patients and 30 healthy people were selected as the research objects to detect the fecal SDC2 methylation level. The content of serum tumor markers, compared the sensitivity and specificity of the two methods in diagnosing colorectal cancer. We explored the clinical value of fecal SDC2 gene methylation detection in the early detection of colorectal cancer.

Materials and methods

Collection of clinical data

There were 30 patients with colorectal cancer who received treatment in Zhangjiakou First Hospital from January 2019 to December 2019 who were collected as the tumor group. There were 30 healthy people who took physical examines in 2019 who were collected as the normal group. The study was approved by the Zhangjiakou First Hospital Ethics Committee.

Inclusion criteria in the tumor group: (1) Patients diagnosed with colorectal cancer by the pathology; (2) The patient's age was between 30~80; (3) There was no evidence of tumor except colorectal cancer; (4) There were detection results of methylation of SDC2 gene, CEA, and CA19-9.

Exclusion criteria: (1) Patients with unclear pathological diagnosis; (2) Patients who received radiotherapy, chemotherapy, and systemic therapy, pregnant women; (3) Patients with other tumors.

Fecal collection and detection methods

Each subject received a specific fecal collection box. The subject took 4.5 g feces in the hospital or at home as required and put them into fecal protection solution. The detection of the changanxin kit included two steps: (1) extraction and transformation and (2) fluorescence PCR. The extraction and transformation step was to extract the SDC2 gene and ACTB gene in human fecal samples by using the magnetic bead capture method, and then using sul-

Table 1. Baseline of the normal and tumor groups

Index	Normal group	tumor group	t/χ^2	P
Age (years old)	52.73±9.42	52.10±8.24	-0.277	0.783
Gender (male, %)	16 (53.33%)	15 (50%)	0.067	0.796
BMI (kg/m^2)	20.45±0.62	20.47±0.6	0.137	0.892
TNM (I, II, III, IV)	-	10, 9, 6, 5	-	-
Tumor diameter (cm)	-	1.84±1.15	-	-
Tumor location (proximal, %)	-	11 (36.67%)	-	-

fite to transform the DNA without methylation. The methylated SDC2 gene will not be transformed by sulfite. The Roche LC480 PCR instrument was used for fluorescent PCR. The steps were to detect the methylated SDC2 gene. The ACTB gene conserved sequences in the same reaction well by using double fluorescent PCR, amplifying the methylated SDC2 gene by specific primers, reporting the amplification signal by FAM labeled fluorescent probes, using the methylated SDC2 gene as a marker for colorectal cancer diagnosis, and amplifying ACTB gene by designing primers in the conserved region. The amplification signal was reported by the Texas Red labeled fluorescent probe. The ACTB gene was used as the internal control gene to evaluate whether the sample DNA was sufficient and whether the sample DNA quality was qualified. The positive and negative quality control products were provided in the kit. Each test reaction was required to be performed simultaneously each time. When the Ct value of ACTB gene was no more than 36, the sample quality was qualified. When the sample quality was qualified, the Ct value of SDC2 gene no more than 38 was selected as the positive result. The Ct value of SDC2 gene more than 38 was selected as the negative result.

Tumor marker detection

A total of 3 ml of fasting venous blood was sampled from the participants and centrifuged at 3800 r/min for 5 min. Serum CEA and CA19-9 were analyzed with an automatic electrochemiluminescence immunoanalyzer and reagents as supporting reagents. Normal reference values are: CEA ≤ 5 ng/ml, CA19-9 ≤ 35 U/ml. The detection reagent of CEA was purchased from Suzhou Fengtai medical supplies Trading Co., Ltd. The detection reagent of CA19-9 was purchased from Beijing Jian'an Biotechnology Co., Ltd. The DJE-9 basic electrophoresis instrument was purchased from Beijing Zhonghui Tiancheng Technology Co., Ltd. The C1000TMPCR instrument and geldoctm ezsystemde were purchased from Bio-Rad company. The full automatic electrochemiluminescence immunoanalyzer (GBI-MAP800) was purchased from Wuhan Huada gene Biomedical Engineering Co., Ltd.

Statistical analysis

SPSS 26.0 statistical software was applied to analyze data. The counted data were described as percentage and analyzed using χ^2 test. The measured data were expressed by mean ± SD, and T-test was adopted for the comparison. ROC curve was utilized to calculate the sensitivity and specificity. When $P < 0.05$, the difference was significant.

Results

Baseline characteristics of the normal and tumor groups

The baseline of the normal and tumor groups were compared in **Table 1**. There were no obvious distinction in the age, gender, and BMI, indicating the comparability between two groups. The tumor related information in the tumor group were shown. Based on the TNM, the number of colorectal cancer patients in I, II, III, and IV was 10, 9, 6, and 5 respectively. The tumor diameter was between (0.27~4.05) cm. The average tumor diameter was (1.84±1.15) cm. There were 11 patients with tumors located at the proximal end and 19 patients at the distal end.

Comparison of tumor serum markers and SDC2 methylation level in the normal and tumor groups

Figure 1 shows that the level of SDC2 methylation in the tumor group was significantly lower than that in the normal group ($P < 0.001$). The average Ct value in the tumor group was 28.83±4.84, and the average Ct value in the normal group was 45.83±4.93. The levels of CEA and CA19-9 in the tumor group were significantly higher than those in the normal group ($P < 0.05$). The average level of CEA in the tumor group and normal group was (5.63±0.78)

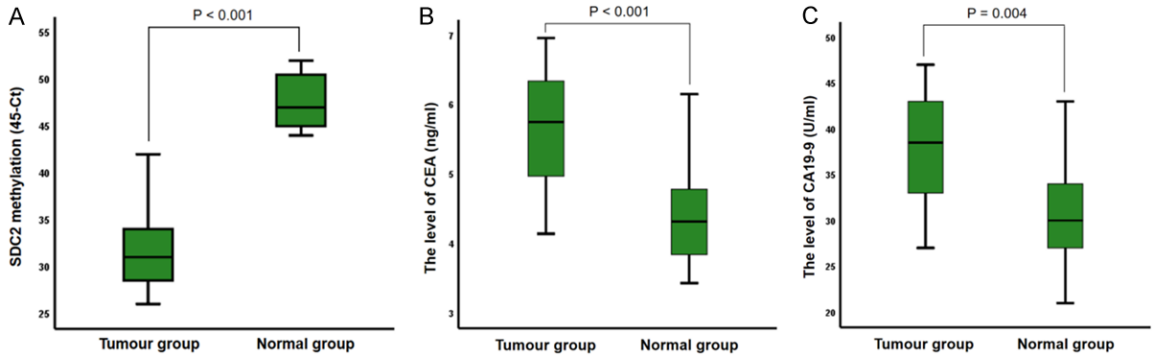

Figure 1. Comparison of Syndecan-2 (SDC2) methylation, carcinoembryonic antigen (CEA), Carbohydrate antigen 19-9 (CA19-9) in two groups.

Table 2. Diagnosis of colorectal cancer based on SDC2 methylation and tumor serum markers

	SDC2	CEA	CA19-9	$\chi^2_{SDC2\text{-}CEA}$	$P_{SDC2\text{-}CEA}$	$\chi^2_{SDC2\text{-}CA19\text{-}9}$	$P_{SDC2\text{-}CA19\text{-}9}$
tumor group (n=30)	28 (93.33%)	18 (60%)	19 (63.33%)	9.317	0.002	7.954	0.005
Normal group (n=30)	3 (10%)	7 (23.33%)	7 (23.33%)	1.920	0.166	1.920	0.166

Note: SDC2, syndecan-2, CEA, carcinoembryonic antigen, CA19-9, Carbohydrate antigen 19-9.

ng/ml, and (4.52±0.82) ng/ml respectively. The average level of CA19-9 in the tumor group and normal group was (37.83±5.50) U/ml and (32.5±7.87) U/ml, respectively.

Diagnosis of colorectal cancer based on SDC2 methylation and tumor serum markers

All the patients in the tumor group had colorectal cancer. The true positive rate of diagnosis by SDC2 methylation was significantly better than that by CEA CA19-9 ($P < 0.05$). All the people in the normal group were healthy. The false positive rate of diagnosis by SDC2 methylation was lower than that by CEA and CA19-9. There was no significant difference ($P > 0.05$) (**Table 2**).

AUC analysis of colorectal cancer diagnosis by SDC2 methylation and serum tumor markers

As shown in **Table 3** and **Figure 2**, ROC showed that the AUC of SDC2, CEA, and CA19-9 was 0.981, 0.839, and 0.735 respectively. The AUC of SDC2 was higher than that of serum tumor markers. The sensitivity and specificity of SDC2 were 0.933 and 0.933 ($P < 0.001$). The result indicated that the diagnostic effect of SDC2 was higher than that of serum tumor markers.

Discussion

The number of new cases of rectal cancer and the number of death cases are the third and second among all malignant tumors respectively [17]. Colonoscopy is the most important examination for early detection of colon cancer, and its sensitivity and specificity are the best [18]. As an invasive examination, colonoscopy requires patients to make bowel preparation and exposes privacy. This makes it difficult to be widely used in screening [19]. There are some detection methods such as fecal occult blood test, rectal digital examination, tumor marker detection, and colon CT, all of which have low sensitivity and low specificity [20]. CEA and CA19-9 serological tumor markers are common methods in clinical auxiliary diagnosis and prognosis judgment of colorectal cancer, but their specificity is not high, which makes their value in clinical diagnosis not high [21].

The guidelines for colorectal cancer screening published in recent years point out that fecal DNA testing is the recommended screening technology. Oncogenes related to colorectal cancer have been detected in feces, such as Ras and c-myc [22]. Tumor suppressor genes include P53, APC, and DCC [23]. Genes related to colorectal cancer metastasis include CD44 and nm23 [24]. Several fecal gene markers have been reported, such as AGATA4/5, VIM methylation, TFPI2, BMP3, NDRG4, SFRP2, mgmt, p16INK4A, and ECAD genes [25]. DNA methylation is the most well-known epigenetic

Table 3. AUC analysis of colorectal cancer diagnosis by SDC2 methylation and serum tumor markers

Index	AUC	95% CI	Sensitivity	Specificity	P
SDC2 methylation	0.981	0.953~1.000	0.933	0.933	< 0.001
CEA (ng/ml)	0.839	0.738~0.940	0.733	0.767	< 0.001
CA19-9 (U/ml)	0.735	0.598~0.872	0.733	0.767	0.002

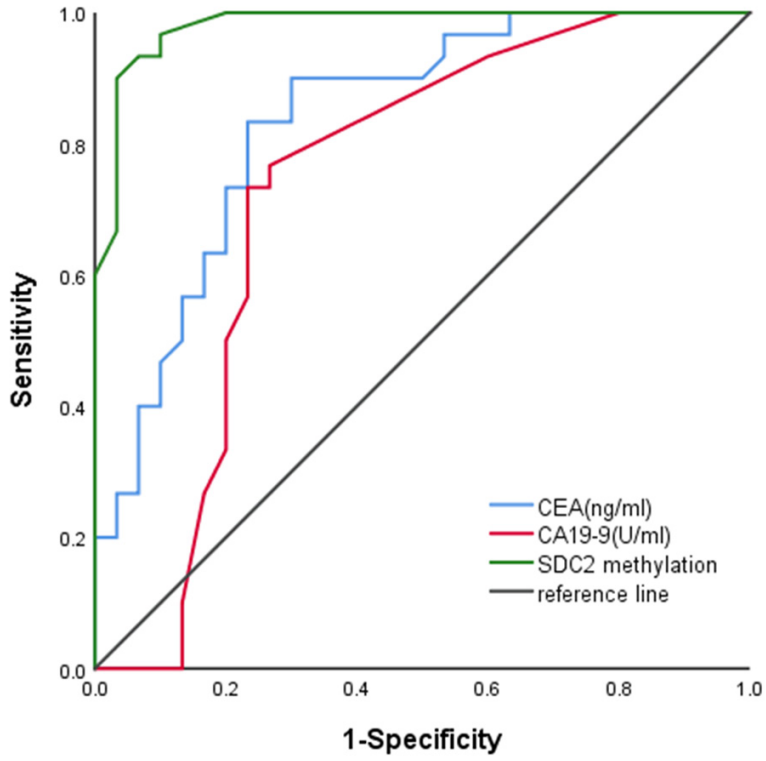

Figure 2. AUC analysis of colorectal cancer diagnosis by SDC2 methylation and serum tumor markers.

mode. Abnormal methylation of GpG island is an epigenetic change. This is more common in the development of cancer. During the occurrence of colorectal cancer, gene methylation changes are common early events in the process of cell carcinogenesis [26]. Methylation changes of some genes, such as P16, SFRP2, TFPI2, MGMT, and Vimentin, have been detected in colorectal cancer. These have a great value in the early diagnosis of colorectal cancer [27]. Some studies have shown that the detection of methylation changes of a single gene in stool in the same countries has a sensitivity of 42%~77% in diagnosing colorectal cancer, a sensitivity of 31%~67% in diagnosing adenoma, and a specificity of 63%~100% [28].

We evaluated the diagnostic effect of colorectal cancer by SDC2 methylation. The level of fecal SDC2 methylation in the tumor group were higher than that in the normal group. This was in agreement with Fan's study [29]. SDC2 belongs to transforming growth factor β Pathway related genes. These are closely related to immune monitoring, and metastasis. In colorectal cancer, SDC2 regulates the interaction between cells and tumor microenvironment, activates matrix metalloproteinases, and decomposes extracellular matrix [30]. SDC2 participates in biological processes such as mesenchymal epithelial transformation and promotes the proliferation and metastasis of tumor cells. Some studies have found that the methylation of SDC2 gene is related to colorectal cancer and has a good application prospect [31]. We found that the positive rates of fecal SDC2 gene methylation in colorectal cancer patients were 93.33%, significantly higher than the positive rates of serum CEA and CA19-9. It was suggested that fecal SDC2 gene methylation detection has a good application value in colorectal cancer screening. We found that the AUC of fecal SDC2 methylation was 0.981. This was significantly better than the current commonly used clinical indicators (CEA and CA19-9). It was suggested that the methylation of fecal SDC2 gene has a good application prospect in colorectal cancer screening. This may be related to the involvement of SDC2 in tumor growth, invasion, and metastasis.

The disadvantage of this study is that the number of participants is small. This may be related to the fact that the fecal sample retention method used for the methylation detection of SDC2 gene is different from the general fecal routine. The patient still needs an acceptance process. It is believed that with more extensive publicity and the improvement of patient acceptance, the advantages of non-invasive, simple,

and accurate methylation detection of fecal SDC2 gene will be reflected.

Fecal SDC2 DNA methylation detection has the advantages of high sensitivity, convenient sampling, non-invasive, and rapid detection in colorectal cancer diagnosis. Compared with serum CEA detection, it can improve the diagnostic efficiency of colorectal cancer. If the sample size can be expanded and through long-term follow-up, it is expected to play an important role in the early screening of colorectal tumors.

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Disclosure of conflict of interest

None.

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