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Meta-analysis on the Diagnostic Value of SDC2 Methylation in Colorectal Cancer Screening Among Chinese

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Abstract. To systematically evaluate the diagnostic value of syndecan-2 (SDC2) gene methylation status in the detection of Colorectal cancer (CRC) and advanced adenomas (AA) through meta-analysis. Databases including PubMed, Web of Science were searched from 2020 to June 14, 2024. Relevant studies were selected based on predefined inclusion and exclusion criteria. The true positive (TP), false positive (FP), false negative (FN), and true negative (TN) results were calculated for each study. The quality of the included studies was assessed using the Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) tool. A bivariate meta-analysis model was used to pool the sensitivity, specificity, diagnostic odds ratio (DOR), positive likelihood ratio (PLR), and negative likelihood ratio (NLR), and a summary receiver operating characteristic (SROC) curve was constructed. Spearman's correlation coefficient, Cochran-Q test, and I^2 test were used to evaluate heterogeneity. Sensitivity analysis was performed to explore the potential sources of heterogeneity. 24 literatures were included for meta-analysis. The pooled sensitivity was 0.77 for CRC and 0.52 for AA, and the pooled specificity was 0.93 for CRC and 0.91 for AA. The pooled PLR was 10.63 for CRC and 5.57 for AA, and the pooled NLR was 0.25 for CRC and 0.53 for AA. The DOR was 43.21 for CRC and 10.47 for AA. The SROC AUC was 0.91 for CRC and 0.83 for AA. The methylation level of the SDC2 gene in stool samples has significant diagnostic value for colorectal cancer and is considered an ideal biomarker for the early detection of this disease.

Keywords: Colorectal cancer; Advanced colorectal adenoma; SDC2 gene methylation; Screening; Meta-analysis.

1. Introduction

CRC is one of the most common malignant tumors of the digestive system, ranking the second in the cancer fatality rate [1]. According to 2020 statistics, the global incidence of CRC was estimated at 1,931,590 new cases, with a standardized incidence rate of 19.5 per 100,000 population. The number of deaths due to CRC was approximately 935,173, with a standardized mortality rate of 9 per 100,000 population. The incidence and mortality of colorectal cancer rank fourth and third among the major malignant tumors in the world, respectively [2]. In China, the age-standardized incidence and mortality rates of CRC are 17.3 and 7.8 per 100,000 population, respectively, and the incidence has been on the rise in recent years due to changes in lifestyle and dietary structure [3, 4]. It has become a malignant tumor with the second and first incidence rate of digestive system in China [5] . It generally takes 5 to 10 years for most sporadic colorectal cancer cases to progress from precancerous lesions (adenomas) to cancer the symptoms of early colorectal cancer patients are hidden and difficult to detect [6]. Therefore, early colonoscopy screening and intervention therapy can reduce the incidence and mortality of colorectal cancer [7] .

At present, colonoscopy biopsy is a common method for the early diagnosis of bowel cancer, and is also the "gold standard" method, but there is a certain rate of missed detection, and this is an invasive examination, with intestinal perforation, bleeding, infection and other risks [8]. Fecal immunochemical test (FIT), carcinoembryonic antigen (CEA), carbohydrate antigen 19-9(carbohydrate antigen) 19-9, CA19-9) test is a commonly used screening method for colorectal cancer in addition to colonoscopy, but FIT is susceptible to interference and has a high false positive rate [9]. CEA and CA19-9 have low specificity and are generally used for efficacy monitoring [10]. Hence, it is crucial to search for a non-invasive colorectal cancer screening and diagnostic technology

with high sensitivity and specificity. Early colorectal cancer often undergoes abnormal methylation, and related methylation markers have been reported. Research results indicate that SDC2 participates in tumor cell activation, tumor angiogenesis, invasion, and metastasis [11, 12].

This present study systematically searched databases such as PubMed and Web of Science to collect literature on SDC2 gene methylation and its application in colorectal cancer diagnosis. The aim was to extract and analyze key data including sensitivity, specificity, and detection technology from relevant literature, and to thoroughly evaluate the clinical value of SDC2 gene methylation in colorectal cancer diagnosis through meta-analysis. The ultimate goal of this study was to explore a more precise, convenient, and highly specific colorectal cancer screening method.

2. Methods

2.1. Literature Retrieval

The research team conducted a comprehensive search on VIP Chinese Journal service platform, CNKI.com, Wanfang Data Knowledge Service platform, PubMed and Web of Science databases, and the search time was set to be from 2020 to June 14, 2024. Chinese search keywords include: Colorectal cancer, colorectal cancer, rectal malignancy, colorectal malignancy, colorectal malignancy, fecal gene testing, fecal DNA testing, SDC2 testing, multi-target fecal gene testing, multi-target fecal DNA testing, and SDC2 gene methylation [13-15]. English search keywords are: colorectal neoplasms, colorectal cancer, colorectal tumour, colon neoplasms, colon cancer, colon tumour, rectal neoplasms, multitarget stool DNA-FIT, Multitarget Stool DNA test, stool DNA test, SDC2. In terms of the search strategy, this article adopts the method of free combination of subject words and keywords [16-18].

2.2. Literature Selection

2.2.1. Literature Selection Standards

Inclusion Criteria: (1) Studies focusing on SDC2 methylation screening for CRC and advanced adenomas [19]; (2) Studies with clearly defined study and control groups [20]; (3) Availability of complete 2x2 table data. Exclusion Criteria: (1) Reviews, conferences, lectures, and reports; (2) Control groups consisting of non-healthy populations; (3) Studies on CRC recovery populations using SDC2 screening; (4) Non-human subjects; (5) Incomplete 2x2 table data [21].

2.2.2. Literature Screening and Data Extraction

Following a predefined search strategy, initially screen eligible literature and import into EndNote 20 and CNKI for literature management. Obtain full texts of relevant literature and exclude those inaccessible. Further deduplicate and refine literature selection based on review of titles and abstracts. Proceed with full-text reading to select final literature meeting criteria. Finally, extract data including first author, year, study country, study method, gold standard, sample size, true positives, false positives, true negatives, false negatives, sensitivity, and specificity [22-24].

2.3. Method Introduction

During quality assessment of literature, use the QUADAS-2 tool in Review Manager 5.4 software for visual evaluation of bias risk in selected studies. Calculate Spearman correlation coefficients between the natural logarithm of sensitivity and (1-specificity) using SPSS 27.0 software to detect threshold effects; if $P > 0.05$, no heterogeneity due to threshold effects is indicated [25-27]. Subsequently, this paper uses StataMP 17 software for heterogeneity testing; if $I^2 > 50\%$, significant heterogeneity exists, requiring a random-effects model to combine sensitivity and specificity data and generate forest plots [28-30]. Plus, this paper uses StataMP 17 software to plot receiver operating characteristic (ROC) curves. Conduct sensitivity analysis to explore sources of heterogeneity. Finally, this paper detects potential publication bias by plotting funnel plots [31-33].

3. Results and Discussion

3.1. Screening Results

Based on searches and other sources, a total of 1874 articles were initially identified, of which 538 had PDFs or URLs [33-36]. After removing duplicates, 289 articles remained after initial screening based on titles and abstracts, with 36 articles further selected for full-text review [37, 38]. Ultimately, 25 articles met the inclusion criteria, as depicted in Figure 1. The basic information obtained from the final included literature is shown in Table 1.

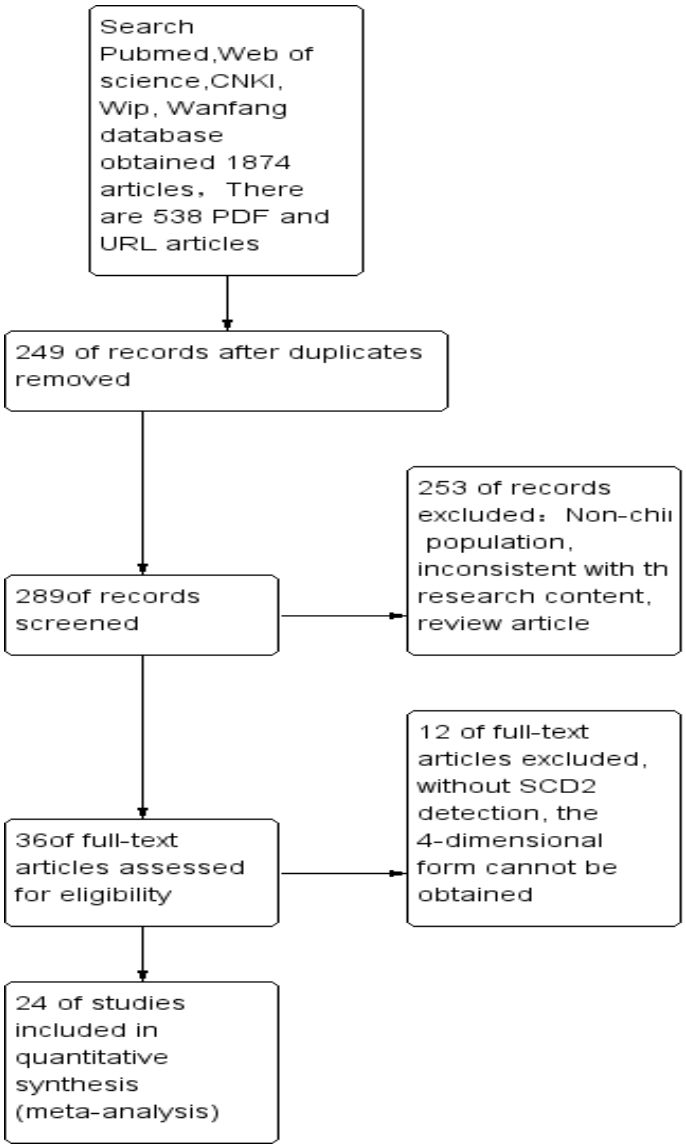

Figure 1. Flowchart of Literature Screening Process

Table 1. Pooled sensitivity and pooled specificity of SDC2 for the diagnosis of CRC and AA

Topic	documents	merge sensitivity	Heterogeneity	Merge specificity	Heterogeneity
CRC	24[15-38]	0.77(0.73~0.81)	70(57.77~78.22)	0.93(0.9~0.95)	72.22(61.88~83.56)
AA	14[15-28]	0.52(0.41~0.62)	78.48(67.67~89.29)	0.91(0.86~0.94)	82.63(74.39~90.87)

This study employed the QUADAS-2 tool in Review Manager 5.4.1 software for systematic evaluation of literature quality. Assessment focused on four dimensions: “patient selection,” “index test,” “reference standard,” and “flow and timing,” aiming to identify potential bias risks. Applicability in clinical settings was considered for the first three dimensions. Evaluation results were visually presented, as detailed in Figure 2 illustrating literature quality assessment results.

Figure 2. Quality Assessment of Included Literature

3.2. Heterogeneity Analysis

3.2.1. Threshold Effect

Using SPSS 27.0 software, the Spearman correlation coefficients between the natural logarithm of sensitivity and the natural logarithm of (1-specificity) for the detection of SDC2 in CRC and advanced adenomas were calculated. The correlation coefficients were -0.182 (P=0.394) and 0.275 (P=0.341) respectively, indicating that there was no threshold effect in this study.

3.2.2. Non-threshold Effect

The meta-analysis was performed using StataMP17, calculating the pooled sensitivity, pooled specificity, and heterogeneity (I2 > 50%), employing a random-effects model. The results showed that the pooled sensitivity of SDC2 for CRC screening was 0.77 (95% CI: 0.73-0.81), the pooled specificity was 0.93 (95% CI: 0.90-0.95), the pooled positive likelihood ratio was 10.63 (95% CI: 7.75-14.57), the pooled negative likelihood ratio was 0.25 (95% CI: 0.21-0.29), the diagnostic odds ratio (DOR) was 43.21 (95% CI: 29.72-62.84), and the area under the summary receiver operating characteristic (SROC) curve (AUC) was 0.91 (95% CI: 0.88-0.93). For the detection of advanced adenomas, the pooled sensitivity was 0.52 (95% CI: 0.41-0.62), the pooled specificity was 0.91 (95% CI: 0.86-0.94), the pooled positive likelihood ratio was 5.57 (95% CI: 3.82-8.82), the pooled negative likelihood ratio was 0.53 (95% CI: 0.43-0.66), the DOR was 10.47 (95% CI: 5.67-19.33), and the SROC AUC was 0.83 (95% CI: 0.80-0.85). The pooled sensitivity, specificity, positive likelihood ratio, negative likelihood ratio, and DOR of SDC2 for the diagnosis of CRC and advanced adenomas are shown in Tables 2-4 and Figure 3, 4.

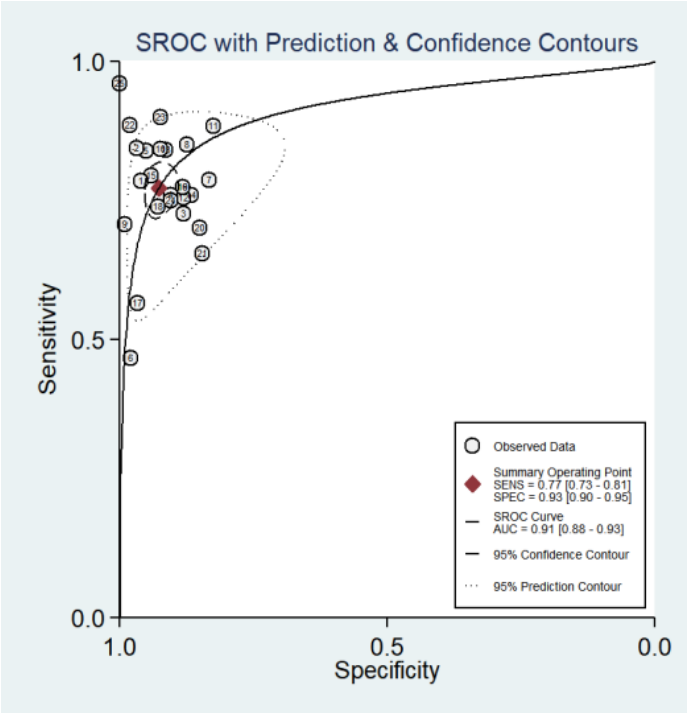

Figure 3. SDC2 Diagnostic ROC Curves for CRC

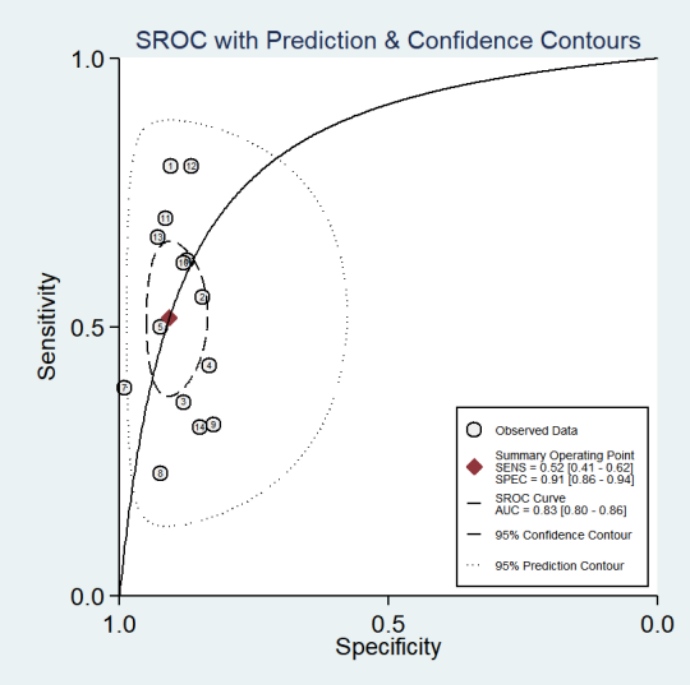

Figure 4. SDC2 Diagnostic ROC Curves for AA

Table 2. Co-positive Likelihood Ratio and Co-negative Likelihood Ratio (95% CI) for SCD2 Diagnosis of CRC and AA

topic	documents	Pooled positive likelihood ratio	Heterogeneity	Pooled nagetive likelihood ratio	Heterogeneity
CRC	24[15-38]	10.63(7.75~14.57)	58.30(58.30%~82.39%)	0.25(0.21~0.29)	72.22(63.92%~84.24%)
AA	14[15-28]	5.57(3.82~8.82)	71.86(71.86%~90.25%)	0.53(0.43~0.66)	82.83(74.71%~90.95%)

Table 3. SDC2 Diagnosis of CRC and AA pooled DOR (95% CI)

topics	documents	Merge DOR	Heterogeneity
CRC	24[15-38]	43.21(95%CI:29.72~62.84)	100.00(95%CI: %~100%)
AA	14[15-28]2	10.47(95%CI:5.67~19.33)	100.00(95%CI: %~100%)

Table 4. Basic Information Included in the Study

Author	Year	n	True positive number	False positive number	False nagetive number	True nagetive number	Research methods
Zhong[29]	2024	120	55	2	15	48	retrospective
Zhang[3]	2023	96	27	2	5	62	retrospective
Zhang[21]	2022	101	37	6	14	44	retrospective
Wu[16]	2023	46	19	2	6	19	prospective
Wang[31]	2023	66	21	2	4	39	retrospective
Tan[32]	2023	80	14	1	16	49	retrospective
Pan[17]	2020	55	19	4	10	22	retrospective
Niu[34]	2023	86	31	1	4	50	retrospective
Bud A[20]	2023	59	37	2	10	10	retrospective
Cai[18]	2021	23	9	1	1	12	retrospective
Chen[19]	2024	80	34	5	6	35	retrospective
Chu[22]	2023	441	75	3	31	332	retrospective
Gong[33]	2022	90	43	3	8	36	retrospective
Jin[23]	2021	38	12	2	4	19	retrospective
Li[24]	2020	112	23	15	3	71	retrospective
Li[35]	2023	30	24	0	1	5	retrospective
Li[25]	2023	78	40	3	13	22	retrospective
Lin[26]	2022	204	74	10	14	106	retrospective
Wu[15]	2022	40	19	2	6	13	retrospective
Dai[36]	2022	431	194	11	50	176	retrospective
Zhao[37]	2021	213	69	3	53	88	retrospective
Long[28]	2024	166	102	2	36	26	retrospective
Su[38]	2021	138	48	9	14	67	retrospective
Zhan[27]	2023	887	312	66	133	376	retrospective

3.2.3. Publication Bias

Deek's funnel plot was made by linear regression to assess potential publication bias in the included literature. The results showed that the deek funnel plot for SDC2 diagnosis of CRC literature was P

= 0.27, and the deek funnel plot for SDC2 diagnosis of AA literature was P = 0.75, indicating no publication bias (Figure 5, 6).

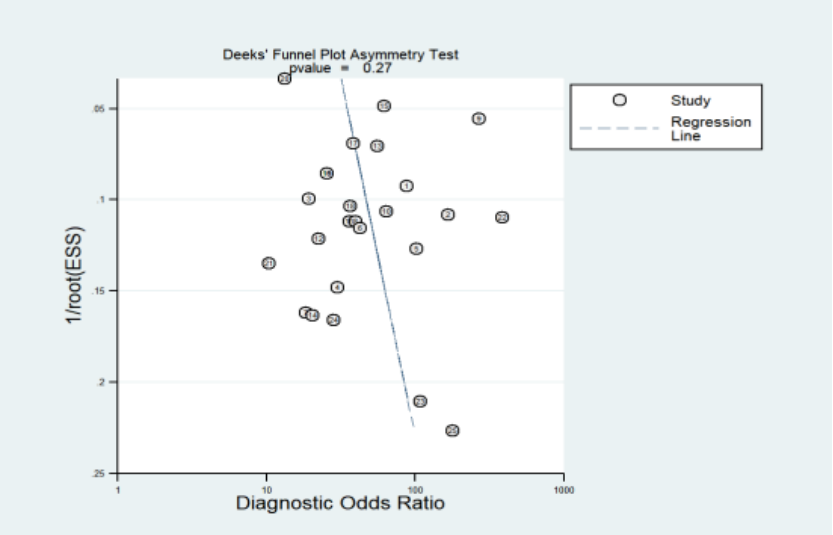

Figure 5. Deek Funnel Diagram of SDC2 for CRC (A)

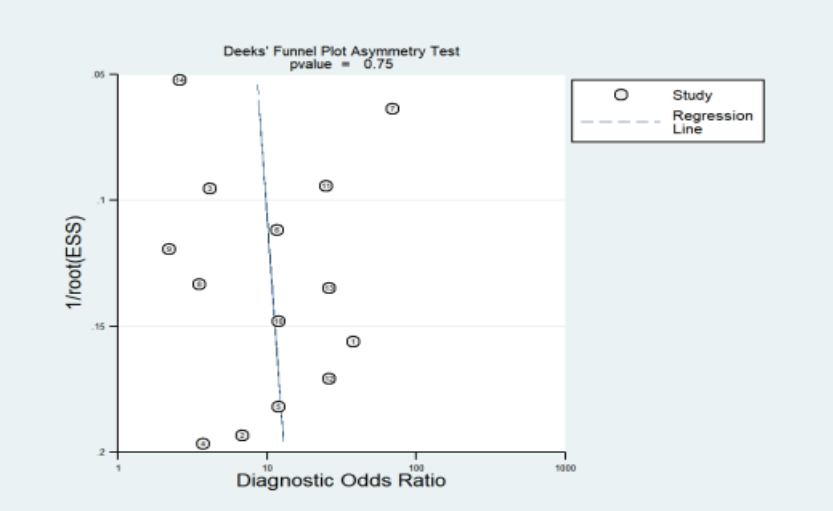

Figure 6. Deek Funnel Diagram of SDC2 for AA (B)

3.3. Discussion

CRC is a malignant tumor originating from the epithelial and glandular tissues of the colon mucosa. Its typical developmental pathway includes: normal colonic epithelium → adenoma → colorectal cancer [12], a process that generally spans over 10 years. Adenomas are categorized into non-advanced adenomas (NAA) and AA. AA, as a critical precursor lesion to cancer, is defined by: adenoma diameter ≥1 cm, containing ≥25% villous tissue, or displaying high-grade dysplasia (meeting either criterion) [13]. Intervening before the AA stage not only significantly reduces patient financial burden but also improves prognosis, potentially without impacting survival. Hence, developing a convenient, low-cost, and highly accurate screening method is paramount. However, traditional diagnostic methods such as colonoscopy and fecal occult blood tests (FOBT) are not widely applied in screening, partly due to their limitations. While colonoscopy remains the gold standard for diagnosing colorectal cancer, its invasiveness leads to lower compliance in screening. In addition, given the relative scarcity of gastrointestinal endoscopists in the country and a high-risk population of over 100 million individuals aged 50 and above, it is impractical to perform colonoscopy screening for all high-risk groups under current medical resource conditions. Despite its simplicity and low cost, FOBT accuracy is affected by factors like diet and hemorrhoids, resulting in relatively lower accuracy.

Syndecan-2 (SDC2) is a transmembrane heparan sulfate proteoglycan involved in cell proliferation, migration, and interactions with the extracellular matrix. In colorectal adenocarcinoma, its expression is elevated compared to normal epithelial cells, playing a crucial role in tumorigenic activity. It regulates cancer cell adhesion, promotes proliferation and tumorigenic activity, and interacts with various ligands and matrix proteins such as MMP-7. Activated MMP-7 enhances SDC2 shedding; soluble SDC2 promotes angiogenesis, thereby supporting cancer cell growth and metastasis.

Increasing research indicates that DNA methylation changes are a common epigenetic modification in the occurrence and development of colorectal cancer. Recently, SDC2 gene methylation in feces has been used as an early screening tool for colorectal cancer; however, its diagnostic value varies across studies. Therefore, this study systematically evaluates the comprehensive diagnostic performance of SDC2 methylation in colorectal cancer using meta-analysis methods. The results demonstrate that SDC2 gene methylation has high overall accuracy in diagnosing colorectal cancer, particularly excelling in specificity, thus serving as a valuable exclusion test when negative. Septin-9 gene methylation testing is currently a widely used method in CRC screening, praised for its simplicity and non-invasiveness. Zhao et al. conducted a systematic meta-analysis assessing the value of Septin-9 gene methylation testing in colorectal cancer diagnosis, revealing a pooled sensitivity of 0.74 and specificity of 0.81 [14]. This finding suggests that compared to Septin-9 gene methylation, SDC2 gene methylation testing demonstrates higher sensitivity and specificity in colorectal cancer diagnosis. The Diagnostic Odds Ratio (DOR), an indicator of diagnostic test effectiveness ranging from 0 to ∞ (>1 indicates diagnostic value; higher values indicate higher accuracy).

4. Conclusion

This study used a systematic meta-analysis method to evaluate the comprehensive test efficacy of SDC2 methylation in the diagnosis of colorectal cancer. The results show that SDC2 gene methylation has a high overall accuracy in the diagnosis of colorectal cancer, especially in terms of specificity, and is of great value as a negative exclusion testIn this present study DOR was 43.21, indicating that SDC2 gene methylation testing holds high diagnostic value for colorectal cancer. Plus, the pooled positive likelihood ratio was 10.63, indicating that individuals testing positive for fecal SDC2 have a 10.63 times higher probability of having colorectal cancer than those testing negative. The pooled negative likelihood ratio was 0.25, suggesting a 25% chance of false negatives among all negative test results. Heterogeneity testing is crucial in meta-analysis. In this study, the Spearman correlation coefficient was -0.182 (P=0.394), indicating no threshold effect-induced heterogeneity. Further Cochran-Q test: (Q=48.193, P=0.002) and I^2 test: (I^2=52.28%) revealed heterogeneity not attributable to threshold effects. Nonetheless, overall heterogeneity affects the accuracy of the pooled effect size, indicating limitations in this meta-analysis. In addition, there are other limitations. First, some included studies did not provide a threshold value for analyzing diagnostic value, so the potential impact of different cutoff values on diagnostic outcomes cannot be ruled out. Second, the included studies showed significant heterogeneity in sensitivity and specificity, which may affect the reliability of the conclusions. Third, the sample size of the included literature was too different between the experimental group and the control group. Fourth, the included studies did not consider the effect of colorectal cancer risk factors such as age sex smoking diet and genetic factors on the results, which may weaken the robustness of the conclusions. Therefore, these results should be interpreted with caution.

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