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AIMS AND SCOPE

The primary aim of *World Journal of Gastrointestinal Oncology* (*WJGO*, *World J Gastrointest Oncol*) is to provide scholars and readers from various fields of gastrointestinal oncology with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

WJGO mainly publishes articles reporting research results and findings obtained in the field of gastrointestinal oncology and covering a wide range of topics including liver cell adenoma, gastric neoplasms, appendiceal neoplasms, biliary tract neoplasms, hepatocellular carcinoma, pancreatic carcinoma, cecal neoplasms, colonic neoplasms, colorectal neoplasms, duodenal neoplasms, esophageal neoplasms, gallbladder neoplasms, *etc*.

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ORIGINAL ARTICLE

Observational Study

Effectiveness of fecal DNA syndecan-2 methylation testing for detection of colorectal cancer in a high-risk Chinese population

Wen-Feng Luo, Yu-Ting Jiao, Xiao-Ling Lin, Ying Zhao, Sheng-Bo Wang, Jian Shen, Jie Deng, Yu-Feng Ye, Ze-Ping Han, Fang-Mei Xie, Jin-Hua He, Yu Wan

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Abstract

BACKGROUND

Colorectal cancer (CRC) is among the most prevalent and life-threatening malignancies worldwide. Syndecan-2 methylation (mSDC2) testing has emerged as a widely used biomarker for early detection of CRC in stool and serum samples. Cancer (CRC) is among the most prevalent and life-threatening malignancies worldwide. mSDC2 testing has emerged as a widely used biomarker for early detection of CRC in stool and serum samples.

AIM

To validate the effectiveness of fecal DNA mSDC2 testing in the detection of CRC among a high-risk Chinese population to provide evidence-based data for the development of diagnostic and/or screening guidelines for CRC in China.

METHODS

A high-risk Chinese cohort consisting of 1130 individuals aged 40-79 years was selected for evaluation *via* fecal mSDC2 testing. Sensitivity and specificity for CRC, advanced adenoma (AA) and advanced colorectal neoplasia (ACN) were determined. High-risk factors for the incidence of colorectal lesions were determined and a logistic regression model was constructed to reflect the efficacy of the test.

RESULTS

A total of 1035 high-risk individuals were included in this study according to established criteria. Among them, 16 suffered from CRC (1.55%), 65 from AA (6.28%) and 189 from non-AAs (18.26%); 150 patients were diagnosed with polyps (14.49%). Diagnoses were established based upon colonoscopic and pathological examinations. Sensitivities of the mSDC2 test for CRC and AA were 87.50% and 40.00%, respectively; specificities were 95.61% for other groups. Positive predictive values of the mSDC2 test for CRC, AA and ACN were 16.09%, 29.89% and 45.98%, respectively; the negative predictive value for CRC was 99.79%. After adjusting for other high-risk covariates, mSDC2 test positivity was found to be a significant risk factor for the occurrence of ACN ($P < 0.001$).

CONCLUSION

Our findings confirmed that offering fecal mSDC2 testing and colonoscopy in combination for CRC screening is effective for earlier detection of malignant colorectal lesions in a high-risk Chinese population.

Key Words: Colorectal cancer; Syndecan-2; DNA methylation; Chinese population

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Core Tip: A high-risk Chinese cohort composed of 1130 individuals 40-79 years of age was selected for evaluation using the fecal syndecan-2 methylation (mSDC2) test. Sensitivity and specificity to colorectal cancer (CRC), advanced adenoma and advanced colorectal neoplasia were quantified. High-risk factors for the incidence of colorectal lesions were analyzed; a logistic regression model was subsequently constructed to better reflect the efficacy of fecal mSDC2 testing. The results of this CRC screening study revealed that offering patients a combination of fecal mSDC2 testing and colonoscopy is ideal for facilitating early detection of CRC among a high-risk Chinese population.

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INTRODUCTION

Colorectal cancer (CRC) is a life-threatening malignancy that is highly prevalent in China. Indeed, its incidence and mortality rates have steadily increased. According to data from the International Agency for Research on Cancer, in 2020 alone, China witnessed 555.5 thousand new cases and 283.8 thousand deaths from CRC, ranking second and fifth, respectively, among malignancies[1]. Although CRC incidence is relatively low among individuals aged less than 50 years, incidence markedly increases with age. Importantly, recent data has suggested a rise in early-onset CRC cases[2-4]. Progression from colorectal adenoma to CRC takes approximately a decade on average[5]. Consequently, implementation of screening programs to detect precancerous lesions among average-risk populations is a highly effective strategy for reducing the incidence of CRC.

Currently, several screening methods for CRC include colonoscopy, fecal immunochemical testing (FIT) and serum biomarker evaluation. However, each approach has its limitations. Although colonoscopy remains the gold standard for CRC diagnosis, its invasiveness, complicated intestinal preparation and poor compliance rates have hindered widespread adoption[6]. Importantly, colonoscopy may miss certain lesions[7]. While FIT offers an efficient, non-invasive screening option for the average-risk population, it has modest sensitivity in detecting CRC[7,8]. Levels of certain serum proteins such as carbohydrate antigen 19-9 (CA19-9) and carcinoembryonic antigen (CEA) have been utilized as pan-cancer biomarkers for various malignancies such as those of the pancreas, breast and colon[9-12]. However, their specificity for detecting CRC is limited. Such limitations highlight the need for superior alternative screening methods to improve rates of CRC detection and diagnosis.

Due to advancements in biotechnology, molecular diagnostics have attracted rapidly increasing interest among *in vitro* techniques. Importantly, such methods outperform biochemical and immunological diagnostics in terms of accuracy and prognostic worth. Stool-based DNA testing is an emerging CRC screening method that detects tumors by identifying relevant biomarkers in stool samples. Aberrant genetic and epigenetic alterations in the setting of CRC may be tracked by extracting DNA from exfoliated cells[13-15]. In the setting of carcinogenesis, DNA methylation is also highly relevant and considered to be a good biomarker of malignancy[16-18]. Genes such as *Vimentin*, *NDRG4*, *BMP3* and *TFP12* have been

employed as molecular markers to develop sensitive and simple screening approaches for evaluation of DNA methylation[19,20]. Due to its non-invasive, convenient and sensitive characteristics, stool-based DNA testing is predicted to become extensively employed in large-scale screening among average-risk populations. Cologuard® (Exact Sciences, Madison WI) was the first such commercial product authorized for clinical use by the United States Food and Drug Administration. It incorporates fecal hemoglobin immunoassays and quantitative molecular detection of methylated *BMP3*, methylated *NDRG4* and mutant *KRAS*[21]. Furthermore, the United States Preventive Services Task Force initially recommended stool DNA testing as a screening approach for CRC in 2016[22]. In particular, syndecan-2 methylation (mSDC2) testing has emerged as a tool for early detection of CRC in stool and serum samples[23,24]. The *SDC2* gene is a transmembrane heparan sulfate proteoglycan that is a member of the *SDC* proteoglycan family. It is relevant in cell proliferation, angiogenesis and cell migration, and is widely expressed in colonic mesenchymal cells. Zhang *et al*[25] reported that levels of *SDC2* regulatory region methylation are significantly higher in colorectal tumor specimens as compared to paired adjacent non-malignant tissues. Zhao *et al*[26] showed that the methylation level of *SDC2* in tumor tissues surpasses that in corresponding non-cancerous tissues and exceeds levels observed in polyps. As mSDC2 can be detected in both adenomas as well as early carcinogenesis, its methylation is considered to be a gradual process. Relative to normal colorectal tissues and polyps, SDC2 was found to be significantly more methylated in different stages of CRC pathogenesis and advanced intestinal adenoma formation[27,28]. On meta analyses, pooled sensitivity and specificity of mSDC2 testing for CRC was 0.81 [95%confidence interval (CI): 0.74-0.86] and 0.95 (95%CI: 0.93-0.96), respectively[20]. No significant differences in sensitivity (0.82, 95%CI: 0.58-0.94; and 0.83, 95%CI: 0.77-0.88, respectively) or specificity (0.95, 95%CI: 0.91-0.97; and 0.94, 95%CI: 0.90-0.96, respectively) between blood and stool samples were noted.

Here, we aimed to evaluate the efficacy of mSDC2 testing as a screening tool for CRC in a high-risk population. Our primary objective was to assess both sensitivity and specificity of mSDC2 testing for detection of CRC and advanced adenoma (AA). Furthermore, we study aimed to evaluate clinical usefulness of mSDC2 testing as an adjunctive tool for CRC and precancerous lesion identification.

MATERIALS AND METHODS

Study design

From April 2020 to May 2022, CRC screening with stool-based mSDC2 testing was performed at the Panyu Center Hospital of Guangzhou (Guangdong, China) as a primary screening method. Over 1000 high-risk participants were enrolled in this study. Fresh stool was collected from every participant for mSDC2 testing prior to initiating bowel preparation for colonoscopy; subjects subsequently underwent colonoscopy for further diagnostic evaluation. This study was approved by the institutional review board, IRB approval number: No. [2019]62, and written, informed consent was obtained from all study participants.

Inclusion and exclusion criteria

Individual outpatients 40-79 years old completed a high-risk factor questionnaire (HRFQ). A positive HRFQ was defined as: (1) A family history of CRC in first-degree relatives; (2) A history of polyps; and/or (3) A history of two or more of the following: (1) Chronic diarrhea; (2) Chronic constipation; (3) Mucoid bloody feces; (4) Chronic appendicitis or appendectomy; (5) Chronic cholecystitis or cholecystectomy; and (6) Psychiatric trauma (*e.g.*, divorce, death of first-degree relatives)[29-31].

Individuals unsuitable for colonoscopic examination such as those suffering severe cardiac or chronic renal conditions or pregnant patients were excluded from analyses. Participants previously diagnosed with any malignancies, those who had undergone chemo- or immuno-therapy treatments or subjects who were unable or unwilling to provide written, informed consent were also excluded from analyses.

SDC2 methylation test

Specimen collection and processing: Each participant was required to provide about 4.5 g of fresh stool for mSDC2 testing using a stool collection device (Creative Biosciences Co. Ltd., Guangzhou, China) at home. Samples stored in preservation buffer were sent to the designated clinical laboratory within two days of collection. Stool specimens were immediately homogenized and centrifuged upon receipt. Supernatants were then aliquoted and frozen at -80 °C until further use. Frozen aliquots were subsequently tested in batches by experienced laboratory technicians using Colosafe® testing reagent kits (Creative Biosciences).

mSDC2 testing: For blind testing, each stool collection device was labeled with a unique code and no other identifying information. Target and control genes [*SDC2* and β-actin (*ACTB*)] were extracted from stool supernatant after centrifugation and subsequently enriched and purified *via* sequence-specific capture technology. Positive and negative controls *SDC2* gene controls were also tested in parallel. Real-time quantitative methylation-specific polymerase chain reaction was employed to quantitatively detect *SDC2* and *ACTB* methylation status in stool samples using a LightCycler 480 II machine (Roche, Basel, Switzerland). *ACTB* was amplified as a reference for DNA input. Primers, probes and amplification conditions in this study were all as previously described[32].

Positive criteria: Stool samples with CT values of *SDC2* ≤ 38 were classified as positive while those with CT values of *SDC2* > 38 were classified as negative under the precondition that CT values of *ACTB* ≤ 36. Stool samples with CT values of *ACTB* > 36 were considered invalid.

Colonoscopy and pathological examination

After mSDC2 testing, all participants were required to undergo colonoscopy. Colonoscopic examinations were performed by gastroenterology specialist sat the endoscopy center of Panyu Center Hospital. After standard bowel preparation, endoscopy with a minimum withdrawal time of 6 min was performed. All lesions noted were measured with opened biopsy forceps and recorded based on size, morphology and localization. Neoplastic lesions observed on colonoscopy were immediately removed and/or biopsied for histologic diagnosis. Individuals suspected of having CRC or polyps that could not be removed endoscopically were referred for surgery. If more than one polyp was noted, the most advanced pathological lesion or largest lesion was considered in analyses.

CRC was staged according to eight edition guidelines of the American Joint Committee on Cancer[33]. AA was defined as an adenomatous lesion with either a diameter of ≥ 10 mm, of ≥ 25% villous character or characterized by high-grade dysplasia[29,30]. Advanced colorectal neoplasia (ACN) was defined as evident CRC and AA lesions. Non-adenomatous polyps (NAP) included inflammatory, hyperplastic and juvenile polyps[29]. Other findings of diagnostic evaluation included completely normal appearance as well as the presence of colitis and colonic diverticulum.

Statistical analyses

All data were represented as numbers and relevant detection rates (DR). Pearson chi-squared or Fisher's exact tests were used, as deemed appropriate, to compare detection data and patient clinicopathological characteristics. A logistic regression model was constructed to compare high-risk factors for colorectal lesions as well as odds ratios and relevant 95%CI to determine exposure risk. Additionally, *P* values of logistic model data were adjusted *via* false discover rate methods to ensure reliability of significance testing. Data analyses were performed using SPSS software version 23.0 (IBM, Armonk, United States). Receiver operating characteristic (ROC) curve and predictive value [sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), area under the curve and relevant 95%CI] analyses were performed using GraphPad Prism version 8.0. $P < 0.05$ was considered statistically significant at $\alpha = 0.05$.

RESULTS

Baseline data

This study enrolled a total of 1130 high-risk subjects who were either outpatients at our hospital's department of gastroenterology or attending well-adult examination sat the health examination center. After excluding 49 persons with inadequate colonoscopy findings and 29 persons who did not complete mSDC2 testing, a total of 1052 subjects were effectively screened and the pass rate was 93.10% (1052/1130). After excluding three patients who lacked pathological data, 10 subjects without qualifying stool samples and four persons who did not meet the age requirement, 1035 cases were finally evaluated in this study (Figure 1). Our studied sample included 502 males and 533 females 40-79 years of age (median age: 52). Most subjects were 50-59 years of age (39.22%); few were 70-79 years of age (4.35%). Statistical data are shown in Table 1. A total of 87 subjects (87/1035, 8.41%) were positive on mSDC2 testing, including 52 males (52/502, 10.36%) and 35 females (35/533, 6.57%); data significantly different among the two groups ($\chi^2 = 4.828$, $P = 0.028$). Furthermore, rates of positivity for different age groups (*i.e.*, 40-49, 50-59, 60-69, 70-79) were 4.02% (15/373), 9.61% (39/406), 11.85% (25/211), and 17.78% (8/45), respectively. Rates of positivity on mSDC2 testing increased with age; rates of positivity significantly differed among age groups ($\chi^2 = 18.454$, $P < 0.001$).

General outcomes of screening

As shown in Figure 1 and Table 1, a total of 420 patients (420/1035, 40.58%) with intestinal lesions of different severity and 615 others (*e.g.*, normal findings on colonoscopy, colitis, colonic diverticulum, *etc.*; 615/1035, 59.42%) were evaluated on colonoscopy. Among all intestinal lesions, 16 cases of CRC diverticulum (16/1035, 1.55%), 65 cases of AA (65/1035, 6.28%), 189 cases of non-AA (189/1035, 18.26%), and 150 cases of polyps (150/1035, 14.49%) were diagnosed. All lesions were verified on histopathology. The DR of intestinal lesions in males was significantly higher than that in females (47.41% *vs* 34.15%, $\chi^2 = 18.862$, $P < 0.001$; Table 2). DR markedly increased with age ($\chi^2 = 55.920$, $P < 0.001$) with the highest rate of positivity among individuals 70-79 years of age (28/45, 62.22%). Pathological CRC characteristics of lesions detected in this study are detailed in Table 3.

Importantly, mSDC2 test positivity, sex, age, a family history of CRC and a history of polyps were all significant risk factors for the development of ACN (*i.e.*, CRC and AA). Otherwise, chronic diarrhea, constipation, appendicitis and cholecystitis, as well as hematochezia and a history of psychiatric trauma, were not significant risk factors for CRC (Table 4).

Efficacy of the mSDC2 test for the screening of colorectal neoplasms

To assess the performance of the mSDC2 test in identifying intestinal malignancies, an ROC curve was constructed (Figure 2). The value of the area under the ROC curve (AUC) in regards to detecting *SDC2* gene methylation in CRC cases was 0.914 (95%CI: 0.807-1.000), highlighting the capacity of this test to accurately distinguish CRC lesions from non-advanced or benign tissue (Figure 2A). For AAs, the AUC value decreased to 0.707 (95%CI: 0.631-0.782), indicating relatively standard test efficacy in detection of precancerous lesions (Figure 2B). For ACN, the AUC value was 0.756 (95%CI: 0.689-0.823; Figure 2C). Furthermore, compared with fecal occult blood testing, mSDC2 testing exhibited significantly improved diagnostic sensitivity, specificity and AUC values for CRC, AA and ACN, suggesting that mSDC2 is effective for use in the early diagnosis of malignancy. Although the price of mSDC2 testing far exceeds that of fecal

Table 1 Baseline data of subjects evaluated

Characteristics	Cases (*N*%)	mSDC2 (*N*%)		*P* value
		(+) *n* = 87	(-) *n* = 948	
Gender				0.028[a]
Male	502 (48.50)	52 (5.02)	450 (43.48)	
Female	533 (51.50)	35 (3.38)	498 (48.12)	
Age				< 0.001[b]
40-49	373 (36.04)	15 (1.45)	358 (34.59)	
50-59	406 (39.22)	39 (3.77)	367 (35.46)	
60-69	211 (20.39)	25 (2.42)	186 (17.97)	
70-79	45 (4.35)	8 (0.77)	37 (3.57)	
Family history of CRC				< 0.001[b]
Yes	99 (9.57)	18 (1.74)	81 (7.83)	
No	936 (90.43)	69 (6.67)	867 (83.77)	
History of colorectal polyps				0.406
Yes	252 (24.35)	18 (1.74)	234 (22.61)	
No	783 (75.65)	69 (6.67)	714 (68.99)	
History of chronic diarrhea				0.108
Yes	342 (33.04)	22 (2.13)	320 (30.92)	
No	693 (66.96)	65 (6.28)	628 (60.68)	
History of chronic constipation				0.747
Yes	493 (47.63)	40 (3.86)	453 (43.77)	
No	542 (52.37)	47 (4.54)	495 (47.83)	
History of hematochezia				0.692
Yes	580 (56.04)	47 (4.54)	533 (51.50)	
No	455 (43.96)	40 (3.86)	415 (40.10)	
History of appendicitis				0.243
Yes	66 (6.38)	3 (0.29)	63 (6.09)	
No	969 (93.62)	84 (8.12)	885 (85.51)	
History of cholecystitis				0.836
Yes	66 (6.38)	6 (0.58)	60 (5.80)	
No	969 (93.62)	81 (7.83)	888 (85.80)	
History of psychiatric trauma				0.890
Yes	63 (6.09)	5 (0.48)	58 (5.60)	
No	972 (93.91)	82 (7.92)	890 (85.99)	
Pathological classification				< 0.001[b]
CRC	16 (1.55)	14 (1.35)	2 (0.19)	
AA	65 (6.28)	26 (2.51)	39 (3.77)	
NAA	189 (18.26)	8 (0.77)	181 (17.49)	
Polyps	150 (14.49)	12 (1.16)	138 (13.33)	
Others	615 (59.42)	27 (2.61)	588 (56.81)	

[a]$P < 0.05$.

[b]*P* < 0.001.

mSDC: Syndecan-2 methylation; CRC: Colorectal cancer; AA: Advanced adenoma; NAA: Non-advanced adenoma; Polyps: Non-adenomatous polyps; Others: Totally normal colonoscopy, colitis and colonic diverticulum, *etc*.

Table 2 Primary outcomes of pathological findings on screening

Characteristics	Intestinal lesions (*N*%)				Others (*N*%)	*P* value
	CRC	AA	NAA	Polyps		
Gender						< 0.001[a]
Male	9 (0.87)	43 (4.15)	109 (10.53)	77 (7.44)	264 (25.51)	
Female	7 (0.68)	22 (2.13)	80 (7.73)	73 (7.05)	351 (33.91)	
Age (yr)						< 0.001[a]
40-49	3 (0.29)	8 (0.77)	48(4.64)	46 (4.44)	268 (25.89)	
50-59	5 (0.48)	30 (2.90)	73 (7.05)	59 (5.70)	239 (23.09)	
60-69	7 (0.68)	18 (1.74)	57 (5.51)	38 (3.67)	91 (8.79)	
70-79	1 (0.10)	9 (0.87)	11 (1.06)	7 (0.68)	17 (1.64)	
mSDC2						< 0.001[a]
Positive	14 (1.35)	26 (2.51)	8 (0.77)	12 (1.16)	27 (2.61)	
Negative	2 (0.19)	39 (3.77)	181 (17.49)	138 (13.33)	588 (56.81)	

[a]*P* < 0.001.

mSDC: Syndecan-2 methylation; CRC: Colorectal cancer; AA: Advanced adenoma; NAA: Non-advanced adenoma; Polyps: Non-adenomatous polyps; Others: Totally normal colonoscopy, colitis and colonic diverticulum, *etc*.

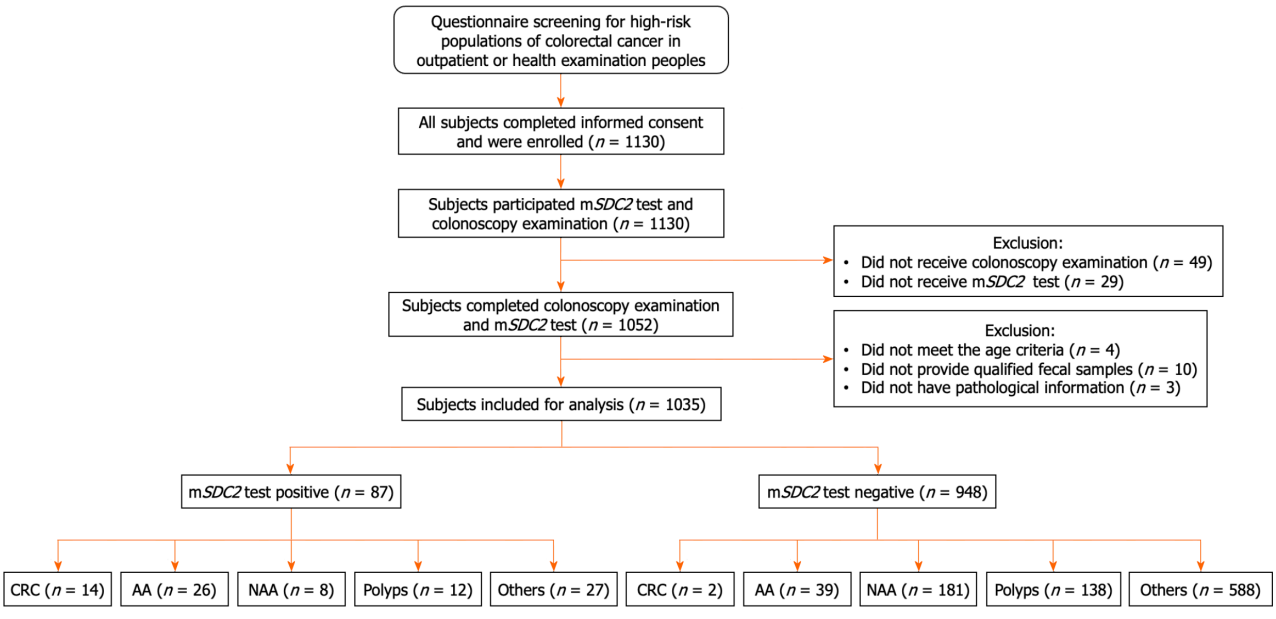

Figure 1 Screening process flow chart. mSDC: Syndecan-2 methylation; CRC: Colorectal cancer; AA: Advanced adenoma; NAA: Non-advanced adenoma; Polyps: Non-adenomatous polyps; Others: Totally normal colonoscopy, colitis and colonic diverticulum, *etc*.

occult blood testing, early detection of CRC has the potential to save lives and direct more effective clinical intervention. As such, the long-term benefits of mSDC2 testing warrant its use in clinic.

In this study, as shown in Tables 1, 2 and 5, the mSDC2 test was able to identify 14 out of 16 CRC cases with a sensitivity of 87.50% (95%CI: 60.41-97.80). For AA cases, sensitivity was 40.00% (95%CI: 28.28-52.90). The specificity of the mSDC2 test for detecting other conditions was 95.61% (95%CI: 93.59-97.03) among 615 individuals. For 954 subjects who were diagnosed with conditions other than AA or CRC, mSDC2 test specificity was 95.07% (95%CI: 93.45-96.32).

Table 3 Characteristics of colorectal cancer detected on screening

Characteristics	Colonoscopy (*N* = 16)	mSDC2 (*N*%)	
		Positive (*n* = 14)	Negative (*n* = 2)
Gender			
Male	9 (56.25)	8 (50.00)	1 (6.25)
Female	7 (43.75)	6 (37.50)	1 (6.25)
Age (yr)			
40-49	3 (18.75)	2 (12.50)	1 (6.25)
50-59	5 (31.25)	5 (31.25)	0 (0)
60-69	7 (43.75)	7 (43.75)	0 (0)
70-79	1 (6.25)	0 (0)	1 (6.25)
TNM stage			
0/I/II	8 (50.00)	6 (43.7)	2 (12.50)
III/IV	5 (31.25)	5 (31.25)	0 (0)
Unknown	3 (18.75)	3 (18.75)	0 (0)
Tumor location			
Proximal	3 (18.75)	3 (18.75)	0 (0)
Distal	13 (81.25)	11 (68.75)	2 (12.50)
Tumor size (mm)			
≤ 30	9 (56.25)	7 (43.75)	2 (12.50)
> 30	7 (43.75)	7 (43.75)	0 (0)
Dysplasia			
Low	0 (0)	0 (0)	0 (0)
Median	12 (75.00)	12 (75.00)	0 (0)
High	4 (25.00)	2 (12.50)	2 (12.50)

mSDC: Syndecan-2 methylation.

The PPVs of the mSDC2 test for CRC, AA and ACN were 16.09% (14/87) (95%CI: 9.38-25.87), 29.89% (26/87) (95%CI: 20.78-40.79) and 45.98% (40/87) (95%CI: 35.36-56.96), respectively. The NPVs of this test for CRC, AA, and ACN were 99.79% (946/948) (95%CI: 99.15-99.96), 95.89% (909/948) (95%CI: 94.37-97.02) and 95.68% (907/948) (95%CI: 94.13-96.84), respectively.

DISCUSSION

The risk factors questionnaire is a cost-effective and easily administered tool, but its high rate of false positivity and subjectivity have resulted in low compliance with colonoscopy among patients it identifies as indicated to undergo the procedure. Consequently, the effectiveness of large-scale population screening remains effectively compromised. To address such limitations, this study evaluated the efficacy, specificity and sensitivity of mSDC2 testing for detection of intestinal malignancies. Our findings indicate that mSDC2 testing is a valuable complementary approach for large-scale population screening. Furthermore, mSDC2 testing can enhance patient compliance with colonoscopy, more precisely identify patients indicated to undergo colonoscopy, conserve medical resources, and improve screening efficiency.

Importantly, mSDC2 testing can also miss diagnoses. Based on our study as well as previous literature, the rate of missed diagnosis for CRC was estimated to be 10%-15%. Missed diagnoses can occur for several reasons. Firstly, as this is a self-sampling product, test accuracy may be influenced by factors such as adherence to proper sampling technique by subjects and timely sample transportation to the laboratory. Secondly, while mSDC2 is a reliable marker for CRC detection, there may be a small number of patients who do not exhibit abnormal mSDC2. To minimize missed diagnoses, it is beneficial to combine mSDC2 testing with other methods such as questionnaires and fecal occult blood tests to enhance overall disease detection. Additionally, regular and repeated testing can also effectively reduce missed diagnoses.

Table 4 Risk factors for detection of advanced colorectal neoplasia

Characteristics	B	SE	Wald	df	*P* value	OR	95%CI	
							Lower limit	Upper limit
Gender								
Male	-0.768	0.294	6.816	1	0.009[b]	0.464	0.261	0.826
Age								
40-49			22.792	3	< 0.001[c]			
50-59	-2.627	0.567	21.459	1	< 0.001[c]	0.072	0.024	0.220
60-69	-1.612	0.499	10.422	1	0.001[c]	0.200	0.075	0.531
70-79	-1.266	0.516	6.010	1	0.014[a]	0.282	0.102	0.776
mSDC2								
Positive	-2.798	0.320	76.308	1	< 0.001[c]	0.061	0.033	0.114
Family history of CRC								
Yes	-1.674	0.530	9.958	1	0.002[b]	0.188	0.066	0.530
History of colorectal polyps								
Yes	2.055	0.580	12.560	1	< 0.001[c]	7.809	2.506	24.335
History of chronic diarrhea								
Yes	0.077	0.405	0.036	1	0.850	1.080	0.488	2.388
History of chronic constipation								
Yes	0.417	0.399	1.090	1	0.296	1.518	0.694	3.320
History of hematochezia								
Yes	0.322	0.442	0.529	1	0.467	1.380	0.580	3.284
History of appendicitis								
Yes	0.860	0.818	1.105	1	0.293	2.362	0.476	11.729
History of cholecystitis								
Yes	-0.306	0.555	0.305	1	0.581	0.736	0.248	2.183
History of psychiatric trauma								
Yes	1.287	0.912	1.991	1	0.158	3.621	0.606	21.633

[a]$P < 0.05$.
[b]$P < 0.01$.
[c]$P < 0.001$.
CI: Confidence interval; B: Beta; SE: Standard error; df: Degree of freedom; OR: Odds ratio; CRC: Colorectal cancer; mSDC: Syndecan-2 methylation.

Despite the excellent efficacy of mSDC2 testing, its price currently remains high, thus limiting its accessibility and popularity among the general public. Many individuals are unaware of this product or even lack knowledge concerning the importance of CRC screening in general. As such, there is an urgent need to raise awareness among the general patient population. Continuous product optimization is also essential, focusing on enhancing sampling success and simplifying laboratory testing. Such improvements are bound to contribute towards expanding mSDC2 utilization worldwide.

Usually, CRC develops from adenomas and certain genes relevant for CRC pathogenesis undergo alterations in methylation levels during the adenomatous stage. Most gene promoters associated with CRC contain CpG islands; abnormal methylation of cytosine within these sequences can result in gene inactivation. As disease progresses, gene methylation increases and the number of malignant cells with methylation mutations increases. One such relevant gene is *SDC2*, which encodes a transmembrane proteoglycan that influences CRC cell proliferation, migration and invasive capabilities. Methylation of SDC2 leads to the silencing of DNA transcription, disrupting cell growth and differentiation, promoting tumor cell proliferation and enhancing invasive and metastatic characteristics. Interestingly, levels of mSDC2 in CRC are higher as compared to AA tissue.

Recently, enteroscopy was reported to not be a suitable method for large-scale population screening[34]. Considering China's large population as well as an uneven distribution of medical technology across different geographic regions, comprehensive colorectal screening poses significant challenges. As such, optimization of CRC screening methods and

Table 5 Performance characteristics of the syndecan-2 methylation test regarding detection of colorectal neoplasia

Category	Colonoscopy (*N* = 1035)	mSDC2 test (*N* = 1035)		PPV % (95%CI)	NPV % (95%CI)
		Positive (*n* = 87)	Sensitivity % (95%CI)		
Colorectal cancer	16	14	87.50 (60.41-97.80)	16.09 (9.38-25.87)	99.79 (99.15-99.96)
Advanced adenoma	65	26	40.00 (28.28-52.90)	29.89 (20.78-40.79)	95.89 (94.37-97.02)
Advanced colorectal neoplasia	81	40	49.38 (38.19-60.64)	45.98 (35.36-56.96)	95.68 (94.13-96.84)
		Negative (*n* = 948)	**Specificity % (95%CI)**		
Others	615	588	95.61 (93.59-97.03)		
Others, polyps and NAA	954	907	95.07 (93.45-96.32)		
Normal	552	527	95.47 (93.29-96.99)		

mSDC: Syndecan-2 methylation; CI: Confidence interval; PPV: Positive predictive value; NPV: Negative predictive value; Others: Totally normal colonoscopy, colitis and colonic diverticulum, *etc.*; Polyps: Non-adenomatous polyps; NAA: Non-advanced adenoma; Normal: Totally normal colonoscopy.

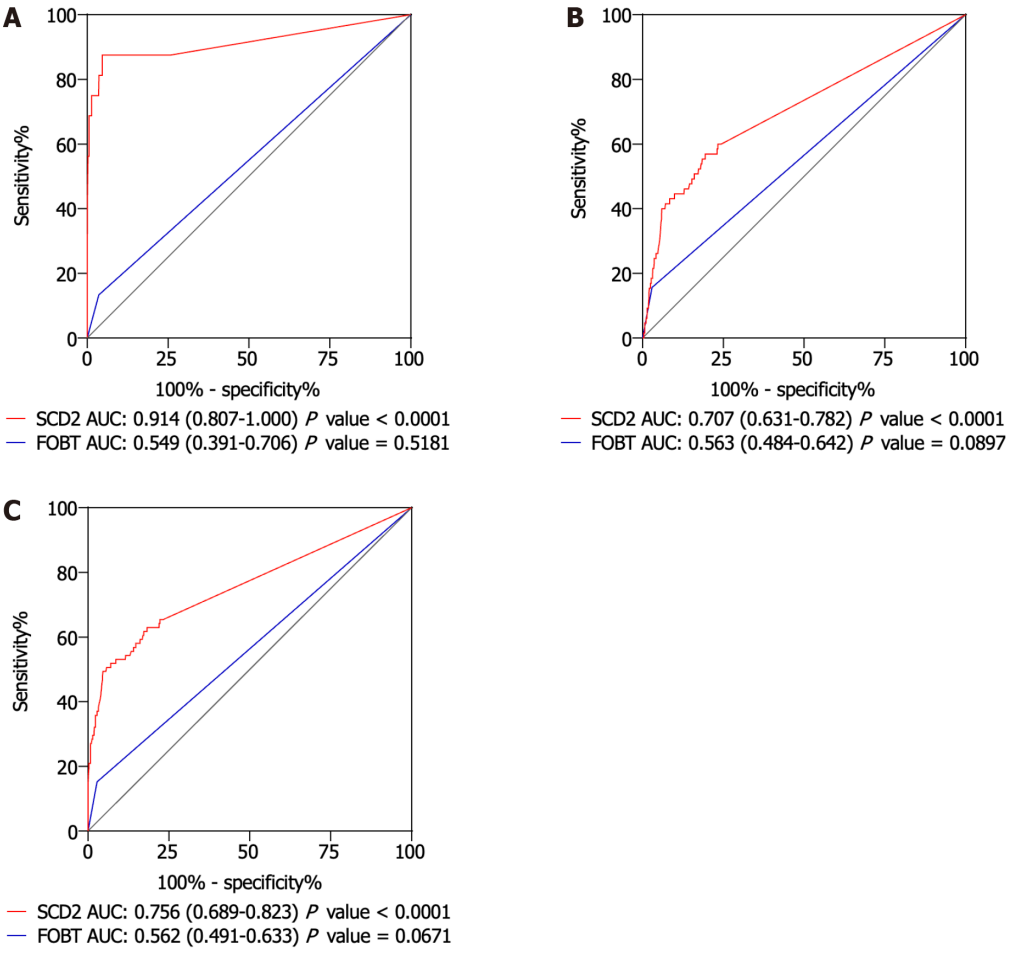

Figure 2 Receiver operating characteristic curve of fecal occult-blood and syndecan-2 methylation tests for detection of colorectal cancer, advanced adenoma and advanced colorectal neoplasia. A: Colorectal cancer; B: Advanced adenoma; C: Advanced colorectal neoplasia. SCD2: Syndecan-2; FOBT: Fecal occult-blood; AUC: Area under the receiver operating characteristic curve.

efficiency is urgently warranted.

Here, we found that men and older individuals were more likely to possess intestinal lesions as compared to women and younger individuals, respectively. Based on known data, most specialists recommend that individuals over the age of 40 undergo screening for CRC. If no precancerous lesions such as polyps are detected during initial screening, subsequent screening should be performed five years later.

It is important to note that the sample used in this study was primarily native to Guangzhou, China, which naturally imposes geographic and ethnic limitations. In the future, large-scale studies that clinically validate mSDC2 while considering possible ethnic and geographic differences within a studied population will be necessary. Finally, combinations of stool mSDC2 methylation analysis with other tumor markers, such as combined mSDC2 and serum CEA detection[35], stool mSDC2 and *TFPI2* methylation detection[36], or stool mSDC2 and *NDRG4* methylation detection[37], significantly enhance both sensitivity and diagnostic accuracy of CRC. Further investigation relevant to this topic is urgently warranted to develop novel simple, accurate and efficacious CRC screening methods.

CONCLUSION

In summary, stool mSDC2 testing carries a sensitivity of 87.50% for the detection of CRC among high-risk populations, underscoring its clinical value in early cancer screening. Importantly, mSDC2 serves as a reliable biomarker for CRC diagnosis. Use of stool samples for analyses offers a simpler and less invasive approach, minimizing patient discomfort and promoting patient compliance.

Here, we solely focused on evaluating SDC2 from the perspective of a diagnostic biomarker; as such, our study was not without its limitations. Multi-target fecal DNA testing, which includes markers such as *WIF*, *NAP*, *PENK*, *SETP9*, is described in literature as relevant to the diagnosis of CRC. Use of multiple fecal DNA biomarkers in combination was reported to enhance CRC DR, better identify early intestinal lesions and enable patients to receive treatment earlier, thereby reducing the case fatality rate. Thus, future research should consider incorporating multi-target fecal DNA testing in analyses to improve CRC screening accuracy and efficiency.

ARTICLE HIGHLIGHTS

Research background

Colorectal cancer (CRC) is a prevalent and life-threatening malignant tumor affecting the digestive system globally. Testing for syndecan-2 methylation (mSDC2) has emerged as a widely used screening tool for early detection of CRC in stool and serum samples.

Research motivation

Our findings provide evidence-based data concerning diagnostic and screening methods relevant to a Chinese population at high-risk population for CRC.

Research objectives

To validate the effectiveness of fecal mSDC2 testing in the detection of CRC among a high-risk Chinese population.

Research methods

A high-risk Chinese cohort composed of 1130 individuals 40-79 years of age was selected for evaluation using the fecal mSDC2 test. Sensitivity and specificity to CRC, advanced adenoma (AA) and advanced colorectal neoplasia (ACN) were quantified. High-risk factors for the incidence of colorectal lesions were analyzed; a logistic regression model was subsequently constructed to better reflect the efficacy of fecal mSDC2 testing.

Research results

According to criteria previously established, 1035 high-risk individuals were included in analyses. Among them, 16 CRC cases (1.55%), 65 AA cases (6.28%), 189 non-advanced adenoma cases (18.26%), and 150 cases of polyps (14.49%) were successfully identified on colonoscopy and pathological examination. The sensitivities of mSDC2 testing for CRC and AA were 87.50% and 40.00%, respectively; the specificity for subjects in the "others" group was 95.61%. The positive predictive values of mSDC2 testing for CRC, AA, and ACN were 16.09%, 29.89% and 45.98%, respectively. In addition, negative predictive value of mSDC2 testing for CRC was 99.79%. Positivity on mSDC2 testing is a significant risk factor for the development of ACN ($P < 0.001$) after adjusting for other high-risk covariates.

Research conclusions

The results of this CRC screening study revealed that offering patients a combination of fecal mSDC2 testing and colonoscopy is ideal for facilitating early detection of CRC among a high-risk Chinese population. CRC screening study revealed that offering patients a combination of fecal mSDC2 testing and colonoscopy is ideal for facilitating early detection of CRC among a high-risk Chinese population.

Research perspectives

Detection of stool mSDC2 offers great promise for early and effective CRC screening.

FOOTNOTES

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Co-corresponding authors: Wen-Feng Luo and Yu Wan.

Author contributions: Luo WF and Jiao YT contributed equally to this work; Luo WF and Wan Y were co-corresponding authors; Luo WF, Jiao YT, and Wan Y contributed to conceptualization, visualization, initial draft writing, funding acquisition, review and editing; Luo WF, Jiao YT, Wang SB, and Deng J proposed and designed the study; Lin XL, Shen J, and Xie FM performed analyses; Zhao Y, Han ZP, and Han ZP wrote the initial draft; Jiao YT, Ye YF, He JH, and Wan Y revised the manuscript; and all authors read and approved the final manuscript.

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Informed consent statement: The informed consent was obtained from all study participants.

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