ISSN 1948-9366 (online)

World Journal of *Gastrointestinal Surgery*

World J Gastrointest Surg 2024 July 27; 16(7): 1956-2364

Published by Baishideng Publishing Group Inc

World Journal of Gastrointestinal Surgery

Contents

Monthly Volume 16 Number 7 July 27, 2024

EDITORIAL

REVIEW

ORIGINAL ARTICLE

Case Control Study

Retrospective Cohort Study

World Journal of Gastrointestinal Surgery

Monthly Volume 16 Number 7 July 27, 2024

Contents

Retrospective Study

World Journal of Gastrointestinal Surgery

Monthly Volume 16 Number 7 July 27, 2024

Contents

World Journal of Gastrointestinal Surgery

Monthly Volume 16 Number 7 July 27, 2024

Contents

ABOUT COVER

Peer Reviewer of *World Journal of Gastrointestinal Surgery*, Hideki Aoki, MD, PhD, Chief Doctor, Surgeon, Department of Surgery, Iwakuni Clinical Center, Iwakuni 740-8510, Japan. aoki.hideki.hy@mail.hosp.go.jp

AIMS AND SCOPE

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

WJGS mainly publishes articles reporting research results and findings obtained in the field of gastrointestinal surgery and covering a wide range of topics including biliary tract surgical procedures, biliopancreatic diversion, colectomy, esophagectomy, esophagostomy, pancreas transplantation, and pancreatectomy, *etc.*

INDEXING/ABSTRACTING

The *WJGS* is now abstracted and indexed in Science Citation Index Expanded (SCIE, also known as SciSearch®), Current Contents/Clinical Medicine, Journal Citation Reports/Science Edition, PubMed, PubMed Central, Reference Citation Analysis, China Science and Technology Journal Database, and Superstar Journals Database. The 2024 Edition of Journal Citation Reports® cites the 2023 journal impact factor (JIF) for *WJGS* as 1.8; JIF without journal self cites: 1.7; 5-year JIF: 1.9; JIF Rank: 123/290 in surgery; JIF Quartile: Q2; and 5-year JIF Quartile: Q3.

RESPONSIBLE EDITORS FOR THIS ISSUE

NAME OF JOURNAL
World Journal of Gastrointestinal Surgery

ISSN
ISSN 1948-9366 (online)

LAUNCH DATE
November 30, 2009

FREQUENCY
Monthly

EDITORS-IN-CHIEF
Peter Schemmer

EDITORIAL BOARD MEMBERS
https://www.wjgnet.com/1948-9366/editorialboard.htm

PUBLICATION DATE
July 27, 2024

INSTRUCTIONS TO AUTHORS
https://www.wjgnet.com/bpg/gerinfo/204

GUIDELINES FOR ETHICS DOCUMENTS
https://www.wjgnet.com/bpg/GerInfo/287

GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH
https://www.wjgnet.com/bpg/gerinfo/240

PUBLICATION ETHICS
https://www.wjgnet.com/bpg/GerInfo/288

PUBLICATION MISCONDUCT
https://www.wjgnet.com/bpg/gerinfo/208

ARTICLE PROCESSING CHARGE
https://www.wjgnet.com/bpg/gerinfo/242

STEPS FOR SUBMITTING MANUSCRIPTS
https://www.wjgnet.com/bpg/GerInfo/239

ONLINE SUBMISSION
https://www.f6publishing.com

World Journal of Gastrointestinal Surgery

Submit a Manuscript: https://www.f6publishing.com

World J Gastrointest Surg 2024 July 27; 16(7): 2270-2280

DOI: 10.4240/wjgs.v16.i7.2270

ISSN 1948-9366 (online)

ORIGINAL ARTICLE

Randomized Controlled Trial

Effectiveness of colonoscopy, immune fecal occult blood testing, and risk-graded screening strategies in colorectal cancer screening

Ming Xu, Jing-Yi Yang, Tao Meng

Specialty type: Gastroenterology and hepatology

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's classification

Scientific Quality: Grade B
Novelty: Grade C
Creativity or Innovation: Grade B
Scientific Significance: Grade B

P-Reviewer: Teramoto-Matsubara OT, Mexico

Received: February 14, 2024
Revised: May 15, 2024
Accepted: May 27, 2024
Published online: July 27, 2024
Processing time: 158 Days and 17.6 Hours

Ming Xu, Tao Meng, Department of Colorectal Surgery, Qilu Hospital (Qingdao), Cheeloo College of Medicine, Qingdao 266000, Shandong Province, China

Jing-Yi Yang, Department of Gastrointestinal Surgery, The First Affiliated Hospital of Zhengzhou University, Zhengzhou 450052, Henan Province, China

Corresponding author: Tao Meng, Doctor, Department of Colorectal Surgery, Qilu Hospital (Qingdao), Cheeloo College of Medicine, No. 758 Hefei Road, Qingdao 266000, Shandong Province, China. 18561810550@163.com

Abstract

BACKGROUND

Colorectal cancer (CRC) is one of the most common malignant tumors, and early screening is crucial to improving the survival rate of patients. The combination of colonoscopy and immune fecal occult blood detection has garnered significant attention as a novel method for CRC screening. Colonoscopy and fecal occult blood tests, when combined, can improve screening accuracy and early detection rates, thereby facilitating early intervention and treatment. However, certain risks and costs accompany it, making the establishment of a risk classification model crucial for accurate classification and management of screened subjects.

AIM

To evaluate the feasibility and effectiveness of colonoscopy, immune fecal occult blood test (FIT), and risk-graded screening strategies in CRC screening.

METHODS

Based on the randomized controlled trial of CRC screening in the population conducted by our hospital May 2020 to May 2023, participants who met the requirements were randomly assigned to a colonoscopy group, an FIT group, or a graded screening group at a ratio of 1:2:2 (after risk assessment, the high-risk group received colonoscopy, the low-risk group received an FIT test, and the FIT-positive group received colonoscopy). The three groups received CRC screening with different protocols, among which the colonoscopy group only received baseline screening, and the FIT group and the graded screening group received annual follow-up screening based on baseline screening. The primary outcome was the detection rate of advanced tumors, including CRC and advanced adenoma. The population participation rate, advanced tumor detection rate, and colonoscopy load of the three screening programs were compared.

RESULTS

A total of 19373 subjects who met the inclusion and exclusion criteria were enrolled, including 8082 males (41.7%) and 11291 females (58.3%). The mean age was 60.05 ± 6.5 years. Among them, 3883 patients were enrolled in the colonoscopy group, 7793 in the FIT group, and 7697 in the graded screening group. Two rounds of follow-up screening were completed in the FIT group and the graded screening group. The graded screening group (89.2%) and the colonoscopy group (42.3%) had the lowest overall screening participation rates, while the FIT group had the highest (99.3%). The results of the intentional analysis showed that the detection rate of advanced tumors in the colonoscopy group was greater than that of the FIT group [2.76% *vs* 2.17%, odds ratio (OR) = 1.30, 95% confidence interval (CI): 1.01-1.65, P = 0.037]. There was no significant difference in the detection rate of advanced tumors between the colonoscopy group and the graded screening group (2.76% *vs* 2.35%, OR = 1.9, 95%CI: 0.93-1.51, P = 0.156), as well as between the graded screening group and the FIT group (2.35% *vs* 2.17%, OR = 1.09%, 95%CI: 0.88-1.34, P = 0.440). The number of colonoscopy examinations required for each patient with advanced tumors was used as an index to evaluate the colonoscopy load during population screening. The graded screening group had the highest colonoscopy load (15.4 times), followed by the colonoscopy group (10.2 times), and the FIT group had the lowest (7.8 times).

CONCLUSION

A hierarchical screening strategy based on CRC risk assessment is feasible for screening for CRC in the population. It can be used as an effective supplement to traditional colonoscopy and FIT screening programs.

Key Words: Colorectal tumor; Immune fecal occult blood testing; Colonoscopy; Hierarchical screening; Risk assessment

Core Tip: A multicenter randomized controlled trial was conducted to investigate the role of colonoscopy combined with immune fecal occult blood test in colorectal cancer screening and establish a risk classification model. The efficacy and safety of the screening methods were evaluated by comparing the colorectal cancer detection rate, early diagnosis rate, and adverse event rate of the screening group and the control group. At the same time, the collected data were used to construct risk classification models for different risk groups, so as to realize individual screening management of subjects.

Citation: Xu M, Yang JY, Meng T. Effectiveness of colonoscopy, immune fecal occult blood testing, and risk-graded screening strategies in colorectal cancer screening. *World J Gastrointest Surg* 2024; 16(7): 2270-2280
URL: https://www.wjgnet.com/1948-9366/full/v16/i7/2270.htm
DOI: https://dx.doi.org/10.4240/wjgs.v16.i7.2270

INTRODUCTION

Colorectal cancer (CRC) is a malignant tumor that occurs in the colon and rectum. According to the Global Cancer Report 2023, there were 555477 new cases of CRC and 286162 related deaths in China[1-3]. The morbidity and mortality of this disease rank third and fifth among the major cancers in China, respectively, with a relatively heavy disease burden[4]. Population-based studies have shown that screening combined with early diagnosis and treatment is an effective means to reduce the incidence and mortality of CRC and improve the survival rate of patients[5]. International and domestic guidelines recommend CRC screening for the general population over the age of 45 or 50 years[6]. Common screening methods include colonoscopy, immune fecal occult blood test (FIT), and multitarget fecal FIT-DNA. Colonoscopy is the gold standard for CRC screening. Endoscopists perform a colorectal examination through visual probes[7-9]. If there are suspicious lesions, a tissue biopsy can be used for pathological diagnosis. Because colonoscopy requires intestinal preparation and is invasive, compliance with mass population screening is not high. In addition, colonoscopy requires professional endoscopists and faces the critical problem of a shortage of experienced endoscopists in mass population screening[10].

The FIT is the most widely used noninvasive screening method for CRC[11]. Compared with traditional chemical methods for fecal occult blood detection, this method has the advantages of high sensitivity and strong specificity. The main technical principle is to detect fecal occult blood by detecting specific human hemoglobin in the stool without the need for dietary or drug restrictions[12-14]. Those who are FIT-positive should undergo a diagnostic colonoscopy to further confirm the diagnosis. In addition, previous studies have successfully built a CRC risk prediction model based on CRC risk factors to assist in CRC high-risk group identification and graded CRC screening, but its effectiveness still needs to be verified[15].

China has a large population and an uneven distribution of medical resources, so it is imperative to explore a suitable screening strategy for the CRC population in China[16-18]. Randomized controlled trials (RCTs) can provide high-level evidence-based medical evidence for the evaluation and analysis of the benefits of different screening strategies in the

population, but there is still a lack of RCTs on CRC screening in the Chinese population.

Based on the first RCT study of CRC screening in China, this study analyzed the feasibility and effectiveness of colonoscopy, FIT, and graded screening based on risk assessment in the Chinese population to provide a theoretical reference for the future development of large-scale screening strategies for the CRC population.

MATERIALS AND METHODS

Research subjects

This study is a national multicenter RCT of CRC screening in the population [TARGET-C study, Chinese Clinical Trial Platform (http://www.chitr.org.cn)]. Participants were recruited from communities and villages according to the uniform inclusion and exclusion criteria.

Inclusion and exclusion criteria

The inclusion criteria for patients were as follows: (1) Had permanent residency in the study area or had resided in the area for ≥ 3 years; (2) Aged 50 to 74 years; and (3) Provided informed consent.

The exclusion criteria were: (1) Had a history of CRC; (2) Had a previous history of colectomy; (3) Had been diagnosed with cancer or had been receiving any cancer-related treatment before enrollment; (4) Had undergone colonoscopy, fibersigmoidoscopy, computed tomography-simulated colonoscopy, or other examinations in the past 5 years; (5) Had received a FIT or FIT-DNA test within the past year; (6) Had symptomatic lower digestive tract diseases or symptoms suggesting the need for diagnostic colonoscopy; and (7) Had severe disease and were not eligible for CRC screening.

Research grouping

The TARGET-C study planned to conduct a single screening in the colonoscopy group, a total of four rounds of annual screening in the FIT and graded screening groups, and long-term follow-up for all enrolled subjects. In this study, eligible subjects were randomly assigned to three intervention groups at a ratio of 1:2:2: (1) Colonoscopy group: Subjects who received a single colonoscopy at baseline screening; (2) FIT group: Subjects who received FIT tests during baseline screening and those who were FIT-positive who received colonoscopies. At the annual follow-up once a year thereafter, FIT testing will continue to be performed on eligible subjects; and (3) Graded screening group: Subjects were assessed for CRC risk at baseline screening, those assessed as high risk received colonoscopy, and those assessed as low risk received FIT (FIT-positive received colonoscopy). At subsequent annual follow-up visits once a year, eligible subjects continue to be offered screening consistent with baseline screening protocols. During the implementation of this project, all screening and testing items were free. All subjects signed informed consent forms, and the First Affiliated Hospital of Zhengzhou University Ethics Committee approved this study (Approval number: 18-013-1619).

Randomization and blinding design

Statistical analysis R 3.5.1 software was used to create random assignment schemes using preset random number seeds, which were imported into the project information management platform. The researchers who created the randomized assignment schemes did not help find field subjects. After completing subject recruitment, the staff of each research center entered the subject information into the project information management platform and conducted a qualification review. When the audit is successful, the project information management platform will relay to the field staff and subjects the group information that the system assigned. The study adopted a single-blind design; that is, the subjects and the staff responsible for the recruitment and management of the subjects were aware of the study grouping information and arranged the corresponding screening interventions, while the doctors providing clinical examination for the subjects were unaware of the subjects' grouping information.

Colonoscopy

The field staff contacted all the subjects who required colonoscopy by phone and made an appointment for them. The project team's designated medical facilities carried out all colonoscopies in accordance with standardized operating procedures. Standardized forms were used to collect colonoscopy (including pathological diagnosis) examination results, which were checked by staff and entered into the project information management platform.

FIT

FIT was performed with a self-testing quantization kit (Hangzhou Nuohui Health Technology Co., Ltd.). The staff will take the initiative to contact the subject and issue the FIT kit and explain the FIT operation process in detail; then, the subject will complete the test according to the instructions. The test results (positive, negative, or invalid) were reported to the smartphone app developed by the project team or were actively tracked and followed up by the staff. If the FIT is invalid, it should be tested again. For those who receive an FIT, the program will provide free colonoscopy. The next round of screening will not include members of the FIT and graded screening groups (low-risk individuals) who are FIT-positive and have undergone colonoscopy, while other subjects (FIT-negative or FIT-positive but have not undergone colonoscopy) will undergo follow-up FIT screening in accordance with the study protocol.

Construction of a risk classification model

CRC risk was assessed using the Asia-Pacific CRC Risk Score system. The scoring system assigns different weights based

on age, sex, family history of CRC in first-degree relatives, smoking history, and body mass index, which are then added together to obtain the final score. According to the results of previous studies, this study defined a total APCS score ≥ 4 as a high risk of CRC; otherwise, it was defined as a low risk of CRC. People at high risk should undergo colonoscopy; those at low risk should receive an FIT, and if the FIT is positive, further colonoscopy should be performed. The colonoscopy and FIT procedures were consistent with those described above. Risk assessment was performed at baseline and at the second follow-up screening, and appropriate screening was recommended based on the assessment results and colonoscopy status.

Information collection

All subjects were recruited through an epidemiological questionnaire survey in which basic personal information, lifestyle information, intestinal disease examination history, family cancer history, and other information were collected. The staff checked and entered the data into the project information management platform after collecting all clinical examination information (colonoscopy, pathological examination, *etc.*) through standardized questionnaires.

Study outcomes and definitions

The final diagnosis of the patient was based on a colonoscopy and pathology report. The main outcome indicators of this study were advanced tumors, including CRC and advanced adenoma. The secondary outcome measures were arbitrary colorectal tumors, including rectal carcinoma, progressive adenoma, and nonprogressive adenoma. Advanced adenomas were defined as adenomas with any of the following characteristics: (1) Diameter ≥ 1 cm; (2) Villous adenoma or tubular villous adenoma; (3) High-grade intraepithelial neoplasia; or (4) A serrated adenoma ≥ 1 cm in diameter or with dysplasia. Colorectal adenomas that do not have the characteristics of advanced-stage adenomas were defined as nonadvanced-stage adenomas. Colorectal tumors were categorized by where they were found in the colon. Tumors in the splenic flexure, descending colon, and sigmoid colon were called distal colon tumors. Tumors in the transverse colon, hepatic flexure of the colon, ascending colon, and ileocecal region are called proximal colon tumors.

Data quality control

To ensure the consistency of the pathological diagnosis results among the different research centers, all pathological sections of CRC, advanced adenoma, and nonadvanced adenoma patients included in this study were reviewed by the same pathologist. In cases where the diagnosis is inconsistent, the final diagnosis is discussed by the project expert group. All the data were logically checked and reviewed.

Sample size estimation

The main outcome measure (advanced tumor detection rate) was used to determine the sample size. It was thought that the advanced tumor detection rate in the graded screening group would be approximately the same as that in the colonoscopy group and greater than that in the FIT group. Based on this assumption and compared with previous study data, the expected tumor detection rates in the colonoscopy group, FIT group, and graded screening group were approximately 6.5%, 1.8%, and 5.0%, respectively; the population participation rates were 50%–70%, 60%–90%, and 60%–90%, respectively; and the overall loss to follow-up rate was 10%. When the test level α was 0.05, the degree of assurance (1-β) was 80%, and the detection rate of advanced tumors was 0.05%, the minimum sample sizes required for the colonoscopy group, the FIT group, and the graded screening group were 3417, 6834, and 6834, respectively, according to the 1:2:2 study design.

Statistical analysis

R 4.1.3 software was used to establish the database and carry out the statistical analyses. Age, sex, educational background, and other statistical data are expressed as frequencies, and a chi-square test was used for comparisons between groups. Intention analysis was used to compare the rates of advanced tumor detection and negative colonoscopy results among the three screening programs. A multivariate logistic regression model was used to compare the differences in tumor detection rates in the advanced stages of different screening schemes, and the results are expressed as odds ratios (ORs) with 95% confidence intervals (CIs). The statistical tests used in this paper were bilateral tests, and differences with $P < 0.05$ were considered statistically significant.

RESULTS

General data of patients

The first subject was recruited and enrolled in May 2020; baseline screening (T0) was completed in May 2021; and the first follow-up screening (T1) was completed from June 2021 to May 2022. A second follow-up screening (T2) was completed between June 2022 and May 2023. A total of 19582 subjects who met the inclusion criteria were recruited. There were 3937, 7858, and 7787 patients in the colonoscopy group, FIT group, and graded screening group, respectively. After further qualification checks, 54, 65, and 90 participants were excluded, respectively. A total of 19373 subjects were ultimately included in this study, including 3883 in the mesenteroscopy group, 7793 in the FIT group, and 7697 in the graded screening group. The baseline data for the three groups are shown in Table 1.

Table 1 Comparison of baseline data among 19373 subjects, *n* (%)

Index	Colonoscopy group (*n* = 3883)	FIT group (*n* = 7793)	Graded screening group (*n* = 7697)	*P* value
Gender				0.172
Male	1617 (41.6)	310 (42.5)	3155 (41.0)	
Female	2266 (58.4)	4483 (57.5)	4542 (99.0)	
Age (years)				0.545
50-54	906 (23.3)	1825 (23.4)	1836 (23.9)	
55-59	830 (21.4)	1605 (20.6)	1574 (20.4)	
60-64	992 (25.5)	1924 (24.7)	1886 (24.5)	
65-69	807 (20.8)	1729 (22.2)	1658 (21.5)	
70-74	348 (9.0)	712 (9.1)	743 (9.7)	
Educational background				0.614
Junior high school and below	2701 (73.4)	5605 (72.2)	5595 (72.9)	
High school	696 (18.0)	542 (19.9)	1495 (19.5)	
University and above	281 (7.6)	621 (8.0)	582 (7.6)	
Body mass index (kg/m²)				0.614
< 23	1395 (37.9)	2872 (37.01)	2860 (37.3)	
≥ 23	2283 (62.1)	4896 (63.0)	4812 (62.7)	
Smoking				646
Non-smoking	2978 (81.0)	6269 (80.7)	6154 (80.2)	
Quit smoking	572 (15.6)	1217 (15.7)	1212 (15.8)	
Smoking	28 (3.5)	282 (3.6)	306 (4.0)	
Drinking				0.168
Never	2659 (72.3)	5722 (73.7)	5649 (73.6)	
Occasionally	491 (13.3)	047 (13.5)	983 (12.8)	
Law	528 (14.4)	999 (12.9)	1040 (13.6)	
Family history of colorectal cancer among first-degree relatives				< 0.001
Yes	60 (4.4)	335 (4.3)	473 (6.2)	
No	3427 (93.2)	7277 (93.7)	7018 (91.7)	
Unclear	91 (2.5)	156 (2.0)	161 (2.1)	

FIT: Fecal occult blood test.

Population participation rates for three screening regimens

At the baseline screening, a total of 1644 colonoscopy patients in the colonoscopy group completed colonoscopy according to the protocol, with a population participation rate of 42.3% (1644/3883). A total of 7327 participants in the FIT group completed the FIT examination according to the scheme, and the population participation rate was 94.0% (7327/7793). In the graded screening group, 25 patients did not complete the risk assessment, and 1453 of the remaining 7672 patients who were assessed as high risk were required to undergo colonoscopy; 712 of these patients completed the examination, and the colonoscopy screening population participation rate was 49.0% (712/1453). According to the protocol, 6219 people who were considered low risk had to undergo an FIT. Of those, 5845 completed the test, giving the graded screening group an overall participation rate of 85.2% (6557/6219) and a population participation rate of 94.0% (5845/6219). Overall, after three screenings, the overall population participation rates (total number of subjects or screening groups who completed at least one round of screening in accordance with the study protocol) in the colonoscopy, FIT, and graded screening groups were 42.3% (1644/3883), 99.3% (7740/7793), and 89.2% (6865/7697), respectively ($P < 0.05$), as shown in Figure 1.

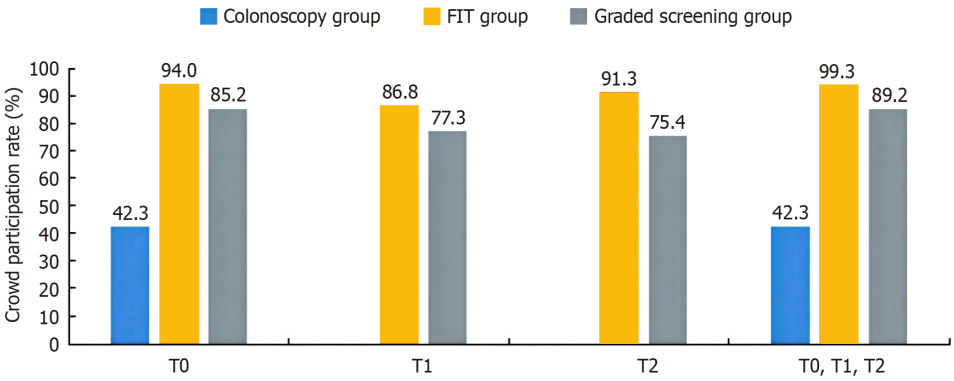

Figure 1 Population participation rate analysis of three groups of screening programs. FIT: Fecal occult blood test.

Rates of positive FIT results and colonoscopy compliance in FIT and graded screening groups

As shown in Table 2, at the baseline screening, the first follow-up screening, and the second follow-up screening, the percentages of positive FIT results among the subjects in the FIT group were 13.7%, 5.6%, and 5.5%, respectively. The compliance rates of colonoscopy in the FIT-positive population were 76.3%, 75.7%, and 71.7%, respectively. In the graded screening group, the FIT-positive rates of the low-risk group were 10.2%, 3.8%, and 2.7%, and the colonoscopy compliance rates of the FIT-positive group were 76.9%, 74.6%, and 60.1%, respectively. The high risk rates for the three screenings were 18.9% (1453/7697), 11.6% (737/6352), and 14.9% (915/6131), respectively. The compliance rates of colonoscopy in the high-risk groups were 49.0% (712/1453), 6.4% (47/737), and 10.5% (96/915), respectively.

Rates of advanced tumor detection by three screening programs

The results of the intentional analysis showed that the detection rate for advanced tumors by single colonoscopy was 2.76%. In the FIT group, the cumulative detection rates at baseline, first follow-up screening, and second follow-up screening were 1.15%, 1.67%, and 2.17%, respectively. The cumulative detection rates of advanced tumors at baseline, first follow-up, and second follow-up were 1.65%, 1.91%, and 2.35%, respectively. After three screenings, the detection rate of advanced adenoma in the colonoscopy group was greater than that of the FIT group (OR = 1.30, 95%CI: 1.01-1.65, P = 0.037); there was no significant difference in the detection rate of advanced tumors between the colonoscopy group and the graded screening group (OR = 1.9, 95%CI: 0.93-1.51, P = 0.156), as well as between the graded screening group and the FIT group (OR = 1.09, 95%CI: 0.88-1.34, P = 0.440). Among the three screening programs, the detection rate of advanced tumors in the distal colon or rectum was greater than that in the proximal colon (P < 0.05), as shown in Table 3.

Colonoscopy load analysis

The intentional analysis showed that the colonoscopy load was 15.4 times and 4.1 times greater in the colonoscopy group for the detection of advanced tumors and arbitrary colorectal tumors, respectively. In the FIT group, the colonoscopy loads for detecting advanced tumors at baseline screening and ,first and second follow-up screening stages were 9.1, 8.3, and 7.8, respectively. The colonoscopy loads for detecting any colorectal tumor were 3.2, 3.1, and 3.0, respectively. The colonoscopy loads for advanced tumors detected at baseline screening, first follow-up screening, and second follow-up screening were 10.3 times, 10.5 times, and 10.2 times, respectively. The colonoscopy loads for detecting any colorectal tumor were 3.5, 3.4, and 3.5, respectively. The colonoscopy load for detecting lesions in the female population was greater than that in the male population in the three screening regimen groups (P < 0.05 for all), as shown in Tables 4 and 5.

DISCUSSION

This study is the first large-scale multicenter RCT of CRC screening in China[19]. By conducting multicenter population-based CRC screening, the feasibility and effectiveness of three different protocols for population CRC screening were compared in parallel, providing high-level evidence-based medical evidence for exploring suitable strategies for CRC screening in the Chinese population[20]. In addition to single colonoscopy screening and the once-a-year FIT screening strategy, this study also evaluated a hierarchical screening strategy based on risk assessment, which is the first one at home and abroad[21-23]. The results of this study suggest that after three screening sessions, the overall population participation rate of the graded screening group was significantly greater than that of the colonoscopy group (89.2% *vs* 42.3%), but the overall population participation rate was not significantly different from that of the FIT group (89.2% *vs* 99.3%)[24]. The results of the intentional analysis showed that the graded screening group achieved better results than did the colonoscopy group (OR = 1.19, 95%CI: 0.93–1.51, P = 0.156) and the FIT group (OR = 1.09, 95%CI: 0.88-1.34, P = 0.440), similar to the detection rate of advanced tumors[25-27]. The colonoscopy load for detecting advanced tumors was the highest in the colonoscopy group (15.4 times), moderate in the graded screening group (10.2 times), and lowest in the FIT group (7.8 times)[28]. In conclusion, the graded screening strategy based on risk assessment has good feasibility and high screening efficiency in the screening of CRC in the population and can significantly reduce the burden of endoscopic

Table 2 Comparison of fecal occult blood test positivity rate and colonoscopy compliance rate between fecal occult blood test group and graded screening group

Screening plan	Baseline screening		First follow-up screening		Second follow-up screening	
	FIT positivity rate	Colonoscopy compliance rate	FIT positivity rate	Colonoscopy compliance rate	FIT positivity rate	Colonoscopy compliance rate
FIT group	13.7 (1071/7793)	76.3 (817/1071)	5.6 (341/6048)	75.7 (258/341)	5.5 (339/6113)	71.7 (2431339)
Graded screening group (Low-risk)	10.2 (782/7697)	76.9 (601/782)	3.8 (244/6352)	74.6 (182/244)	2.7 (163/6131)	0.1 (98/163)

FIT: Fecal occult blood test.

Table 3 Comparison of detection rates of advanced tumors

Screening stage	Progressive tumors (%, 95%CI)			Colonoscopy group/FIT group	
	Colonoscopy group	FIT group	Graded screening group	OR (95%CI)	*P* value
Baseline screening					
Overall	2.76 (2.29-3.32)	0.15 (0.94-1.42)	0.65 (1.39-1.96)	2.45 (1.84-3.26)	< 0.001
Proximal colon	1.36 (1.05-1.78)	0.53(0.39-0.71)	0.62 (0.47-0.83)	2.62 (1.74-3.97)	< 0.001
Distal colon and rectum	1.73 (1.36-2.19)	0.80 (0.62-1.02)	0.17 (0.95-1.43)	2.19 (1.54-3.12)	< 0.001
Baseline screening + 1st follow-up screening					
Overall	2.76 (2.29-3.32)	0.67 (1.41-1.98)	0.91 (1.63-2.24	1.68 (1.29-2.18)	< 0.001
Proximal colon	1.36 (1.05-1.78)	0.72 (0.55-0.95)	0.73 (0.56-0.94)	1.91 (1.30-2.79)	0.001
Distal colon and rectum	1.73 (1.36-2.19)	1.15 (0.94-1.42	1.35 (1.12-1.63)	0.50 (1.08-2.06)	0.014
Baseline screening + 1st follow-up screening + 2nd follow-up screening					
Overall	2.76 (2.29-3.32)	2.17 (1.87-2.52)	2.35 (2.04-2.71)	0.30 (1.01-1.65)	0.037
Proximal colon	1.36 (1.05-1.78)	0.96 (0.77-1.20)	0.90 (0.71-1.13)	1.46 (1.05-2.05)	0.031
Distal colon and rectum	1.76 (1.45-2.18)	1.48 (1.23-1.77)	1.65 (1.39-1.96)	1.19 (0.88-1.61)	0.244
Screening stage	**Colonoscopy group compared to grading screening group**			**Graded screening group/FIT group**	
	OR (95%CI)		***P* value**	**OR (95%CI)**	***P* value**
Baseline screening					
Overall	1.69 (1.29-2.20)		< 0.001	1.45 (1.11-1.92)	0.008
Proximal colon	2.21 (1.49-3.28)		0.001	1.19 (0.79-1.82)	0.409
Distal colon and rectum	1.46 (1.06-2.02)		0.021	1.49 (1.08-2.08)	0.017
Baseline screening + 1st follow-up screening					
Overall	1.45 (1.12-1.87)		0.004	1.15 (0.91-1.47)	0.245
Proximal colon	1.9 (1.29-2.76)		0.001	1.01 (0.70-1.47)	0.941
Distal colon and rectum	1.26 (0.92-1.72)		0.148	1.18 (0.88-1.57)	0.266
Baseline screening + 1st follow-up screening + 2nd follow-up screening					
Overall	1.19 (0.93-1.51)		0.156	1.09 (0.88-1.34)	0.440
Proximal colon	1.56 (1.10-2.20)		0.012	0.94 (0.68-1.29)	0.681
Distal colon and rectum	1.06 (0.79-1.42)		0.680	1.12 (0.87-1.44)	0.384

FIT: Fecal occult blood test; CI: Confidence interval.

Table 4 Comparison of colonoscopy load for detecting advanced tumors

Screening phase	Advanced tumors (*n*, 95%CI)		
	Colonoscopy group	FIT group	Graded screening group
Baseline screening			
Overall	15.4 (12.8-18.5)	9.1 (7.5-11.1)	10.3 (8.8-12.2)
Male	10.7 (8.5-13.5)	6.5 (5.2-8.3)	8.0 (6.7-9.5)
Female	22.9 (17.0-30.9)	14.7 (10.4-21.1)	22.4 (14.9-34.0)
Baseline screening + 1st follow-up screening			
Overall	15.4 (12.8-18.5)	8.3 (7.1-9.7)	10.5 (9.0-12.2)
Male	10.7 (8.5-13.5)	6.2 (5.1-7.5)	8.2 (6.9-9.8)
Female	22.9 (17.0-30.9)	12.5 (9.4-16.7)	18.6 (13.4-26.1)
Baseline screening + 1st follow-up screening + 2nd follow-up screening			
Overall	15.4 (12.8-18.5)	7.8 (6.8-9.0)	10.2 (8.9-11.8)
Male	10.7 (8.5-13.5)	5.9 (5.0-7.0)	8.3 (7.1-9.8)
Female	22.9 (17.0-30.9)	11.4 (8.9-14.5)	15.3 (11.8-20.1)

FIT: Fecal occult blood test; CI: Confidence interval.

Table 5 Comparison of colonoscopy load in random colorectal tumors

Screening phase	Random colorectal tumors (*n*, 95%CI)		
	Colonoscopy group	FIT group	Graded screening group
Baseline screening			
Overall	4.1 (3.8-4.5)	3.2 (2.9-3.5)	3.5 (3.2-3.8)
Male	3.0 (2.7-3.4)	2.5 (2.2-2.8)	2.8 (2.6-3.1)
Female	5.6 (4.9-6.4)	4.5 (3.8-5.4)	5.9 (4.9-7.3)
Baseline screening + 1st follow-up screening			
Overall	4.1 (3.8-4.5)	3.1 (2.9-3.4)	3.4 (3.2-3.7)
Male	3.0 (2.7-3.4)	2.5 (2.3-2.8)	2.9 (2.6-3.1)
Female	5.6 (4.9-6.4)	4.2 (3.6-4.9)	5.1 (4.3-6.0)
Baseline screening + 1st follow-up screening + 2nd follow-up screening			
Overall	4.1 (3.8-4.5)	3.0 (2.8-3.3)	3.5 (3.2-3.7)
Male	3.0 (2.7-3.4)	2.5 (2.3-2.7)	2.9 (2.7-3.1)
Female	5.6 (4.9-6.4)	3.9 (3.5-4.5)	4.9 (4.3-5.6)

FIT: Fecal occult blood test; CI: Confidence interval.

resources in the screening of the population, which has positive significance for areas with limited medical and health resources[29].

The population participation rate is one of the most important indicators affecting screening efficacy[30]. Colonoscopy, the gold standard for CRC screening, is invasive and requires intestinal preparation, resulting in low acceptance and participation rates[31-33]. A multicenter study based on the Chinese Urban Population Cancer Screening Program included 1381561 participants recruited from 16 provinces in China from 2012 to 2015[34]. After risk assessment, 182927 subjects were considered to be at high risk of CRC and recommended for colonoscopy, and follow-up screening revealed that 25593 subjects underwent colonoscopy as recommended, for a participation rate of only 14.0%. A study of CRC screening in four countries in Europe showed that colonoscopy screening population participation rates ranged from 22.9% to 60.7%[35-37]. The colonoscopy screening population participation rate in the colonoscopy group in this study was 42.3%, which was higher than the national average but still relatively low overall, with great room for improvement.

As a noninvasive screening technique, the FIT has good initial screening compliance. In this study, the participation rate of the baseline screening population in the FIT group was 94.0%; in the graded screening group, the participation rate of the low-risk group was significantly greater in the baseline screening population in the FIT, and the participation rate of the colonoscopy group was greater in the high-risk group (94.0% *vs* 49.0%)[38]. Both the FIT group and the graded screening group maintained a high population participation rate in the first and second follow-up screenings, suggesting that FIT as a preliminary screening can not only effectively improve the population participation rate of baseline screening but also play a positive role in ensuring the participation rate of follow-up screening. In addition, in the FIT group, compliance with colonoscopy was significantly improved (> 70%), suggesting that in mass population screening, efficient and easy noninvasive screening technology should be used as a primary screening method to identify high-risk groups for CRC patients. This strategy can significantly improve population screening participation rates and colonoscopy compliance rates in high-risk populations[39].

An efficient and accurate risk prediction model is the core of a hierarchical screening strategy[40]. The APCS score data collected in this study included five parameters, namely, age, sex, body mass index, smoking history, and family history of CRC in first-degree relatives[41]. Risk assessment could be conducted based on aspects such as individual basic characteristics, lifestyle, family history, *etc.* High-risk groups had higher detection rates of CRC and precancerous lesions. It can be used as a priority group for CRC screening[42]. However, this risk score did not include biomarkers related to CRC, so there is still much room for improvement in the efficiency of CRC risk prediction. At present, researchers have developed polygenic risk scores for CRC-related genetic variants based on clinical data combined with genetic information, which can further improve the ability of these models to predict CRC compared with traditional models[43]. In future studies, noninvasive screening techniques will be combined with accurate risk prediction models to further improve the population screening effect of graded screening strategies[44].

This study has several limitations: (1) Due to the overall follow-up time, this study could not evaluate the mortality rate of patients with CRC in the three screening programs, but long-term follow-up of the cohort population is still being carried out, and it is expected that the effects of different screening programs in reducing CRC mortality will be compared in the future; (2) Compliance with diagnostic colonoscopy in FIT-positive patients is still not ideal. The nonconformists were mainly elderly people with other diseases, which indirectly indicated that the feasibility of colonoscopy in a large-scale elderly population was not high; and (3) The study did not provide alternative screening modalities for high-risk individuals in the graded screening group who refused colonoscopy, which may affect screening participation rates.

This large-scale RCT study from multiple centers across the country confirmed that the new risk-assessment-based hierarchical screening strategy is more practical and effective for screening for CRC than traditional colonoscopy and FIT. This is especially true in remote areas where medical resources are limited. Hierarchical screening is an effective screening strategy for CRC.

CONCLUSION

This study validated the efficacy of colonoscopy combined with immune fecal occult blood testing in CRC screening through a multicenter RCT. The results showed that the combined application of these two methods could significantly improve the detection rate of early CRC and precancerous lesions, and reduce the rate of missed diagnosis. At the same time, the risk classification model constructed by us provides an effective tool for risk stratification of screening populations, which helps to improve the individualization and accuracy of screening strategies. The study found that high-risk patients can be diagnosed and treated in time after screening through this model, which significantly improves the treatment effect and quality of life of patients with CRC.

FOOTNOTES

Author contributions: Xu M wrote the manuscript; Yang JY collected the data; Meng T guided the study. All authors reviewed, edited, and approved the final manuscript and revised it critically for important intellectual content, gave final approval of the version to be published, and agreed to be accountable for all aspects of the work.

Institutional review board statement: This study was approved by the Medical Ethics Committee of The First Affiliated Hospital of Zhengzhou University.

Clinical trial registration statement: This study is a national multicenter RCT of colorectal cancer screening in the population [TARGET-C study, Chinese Clinical Trial Platform (http://www.chitr.org.cn)].

Informed consent statement: Informed consent was obtained from all the patients for this study.

Conflict-of-interest statement: The authors declare no conflicts of interest for this article.

Data sharing statement: The data in this study support the principles of transparent science, and the corresponding data sets can be shared with the scientific community upon reasonable request. For detailed data access and usage rules, please contact the person in charge of this study: jingyi_yang1613@163.com.

CONSORT 2010 statement: The authors have read the CONSORT 2010 Statement, and the manuscript was prepared and revised

according to the CONSORT 2010 Statement.

Country of origin: China

ORCID number: Tao Meng 0009-0008-0895-4403.

S-Editor: Fan JR
L-Editor: Wang TQ
P-Editor: Zhao YQ

REFERENCES

1 **Bretthauer M**, Løberg M, Wieszczy P, Kalager M, Emilsson L, Garborg K, Rupinski M, Dekker E, Spaander M, Bugajski M, Holme Ø, Zauber AG, Pilonis ND, Mroz A, Kuipers EJ, Shi J, Hernán MA, Adami HO, Regula J, Hoff G, Kaminski MF; NordICC Study Group. Effect of Colonoscopy Screening on Risks of Colorectal Cancer and Related Death. *N Engl J Med* 2022; **387**: 1547-1556 [PMID: 36214590 DOI: 10.1056/NEJMoa2208375]

2 **Burnett-Hartman AN**, Lee JK, Demb J, Gupta S. An Update on the Epidemiology, Molecular Characterization, Diagnosis, and Screening Strategies for Early-Onset Colorectal Cancer. *Gastroenterology* 2021; **160**: 1041-1049 [PMID: 33417940 DOI: 10.1053/j.gastro.2020.12.068]

3 **Ladabaum U**, Dominitz JA, Kahi C, Schoen RE. Strategies for Colorectal Cancer Screening. *Gastroenterology* 2020; **158**: 418-432 [PMID: 31394083 DOI: 10.1053/j.gastro.2019.06.043]

4 **Champion VL**, Christy SM, Rakowski W, Lairson DR, Monahan PO, Gathirua-Mwangi WG, Stump TE, Biederman EB, Kettler CD, Rawl SM. An RCT to Increase Breast and Colorectal Cancer Screening. *Am J Prev Med* 2020; **59**: e69-e78 [PMID: 32690203 DOI: 10.1016/j.amepre.2020.03.008]

5 **Mannucci A**, Zuppardo RA, Rosati R, Leo MD, Perea J, Cavestro GM. Colorectal cancer screening from 45 years of age: Thesis, antithesis and synthesis. *World J Gastroenterol* 2019; **25**: 2565-2580 [PMID: 31210710 DOI: 10.3748/wjg.v25.i21.2565]

6 **Bailey JR**, Aggarwal A, Imperiale TF. Colorectal Cancer Screening: Stool DNA and Other Noninvasive Modalities. *Gut Liver* 2016; **10**: 204-211 [PMID: 26934885 DOI: 10.5009/gnl15420]

7 **Wolf AMD**, Fontham ETH, Church TR, Flowers CR, Guerra CE, LaMonte SJ, Etzioni R, McKenna MT, Oeffinger KC, Shih YT, Walter LC, Andrews KS, Brawley OW, Brooks D, Fedewa SA, Manassaram-Baptiste D, Siegel RL, Wender RC, Smith RA. Colorectal cancer screening for average-risk adults: 2018 guideline update from the American Cancer Society. *CA Cancer J Clin* 2018; **68**: 250-281 [PMID: 29846947 DOI: 10.3322/caac.21457]

8 **Emile SH**, Barsom SH, Wexner SD. An updated review of the methods, guidelines of, and controversies on screening for colorectal cancer. *Am J Surg* 2022; **224**: 339-347 [PMID: 35367029 DOI: 10.1016/j.amjsurg.2022.03.034]

9 **Gupta S**, Sussman DA, Doubeni CA, Anderson DS, Day L, Deshpande AR, Elmunzer BJ, Laiyemo AO, Mendez J, Somsouk M, Allison J, Bhuket T, Geng Z, Green BB, Itzkowitz SH, Martinez ME. Challenges and possible solutions to colorectal cancer screening for the underserved. *J Natl Cancer Inst* 2014; **106**: dju032 [PMID: 24681602 DOI: 10.1093/jnci/dju032]

10 **Murphy CC**, Halm EA, Zaki T, Johnson C, Yekkaluri S, Quirk L, Singal AG. Colorectal Cancer Screening and Yield in a Mailed Outreach Program in a Safety-Net Healthcare System. *Dig Dis Sci* 2022; **67**: 4403-4409 [PMID: 34800219 DOI: 10.1007/s10620-021-07313-7]

11 **Holden DJ**, Harris R, Porterfield DS, Jonas DE, Morgan LC, Reuland D, Gilchrist M, Viswanathan M, Lohr KN, Lyda-McDonald B. Enhancing the use and quality of colorectal cancer screening. *Evid Rep Technol Assess (Full Rep)* 2010; 1-195, v [PMID: 20726624]

12 **Wu L**, Zheng Y, Liu J, Luo R, Wu D, Xu P, Wu D, Li X. Comprehensive evaluation of the efficacy and safety of LPV/r drugs in the treatment of SARS and MERS to provide potential treatment options for COVID-19. *Aging (Albany NY)* 2021; **13**: 10833-10852 [PMID: 33879634 DOI: 10.18632/aging.202860]

13 **Wheeler SB**, Leeman J, Hassmiller Lich K, Tangka FKL, Davis MM, Richardson LC. Data-Powered Participatory Decision Making: Leveraging Systems Thinking and Simulation to Guide Selection and Implementation of Evidence-Based Colorectal Cancer Screening Interventions. *Cancer J* 2018; **24**: 136-143 [PMID: 29794539 DOI: 10.1097/PPO.0000000000000317]

14 **Berger BM**, Ahlquist DA. Stool DNA screening for colorectal neoplasia: biological and technical basis for high detection rates. *Pathology* 2012; **44**: 80-88 [PMID: 22198259 DOI: 10.1097/PAT.0b013e3283502fdf]

15 **Randel KR**, Schult AL, Botteri E, Hoff G, Bretthauer M, Ursin G, Natvig E, Berstad P, Jørgensen A, Sandvei PK, Olsen ME, Frigstad SO, Darre-Næss O, Norvard ER, Bolstad N, Kørner H, Wibe A, Wensaas KA, de Lange T, Holme Ø. Colorectal Cancer Screening With Repeated Fecal Immunochemical Test Versus Sigmoidoscopy: Baseline Results From a Randomized Trial. *Gastroenterology* 2021; **160**: 1085-1096.e5 [PMID: 33227280 DOI: 10.1053/j.gastro.2020.11.037]

16 **Wu L**, Zhong Y, Wu D, Xu P, Ruan X, Yan J, Liu J, Li X. Immunomodulatory Factor TIM3 of Cytolytic Active Genes Affected the Survival and Prognosis of Lung Adenocarcinoma Patients by Multi-Omics Analysis. *Biomedicines* 2022; **10** [PMID: 36140350 DOI: 10.3390/biomedicines10092248]

17 **Kisiel JB**, Eckmann JD, Limburg PJ. Multitarget Stool DNA for Average Risk Colorectal Cancer Screening: Major Achievements and Future Directions. *Gastrointest Endosc Clin N Am* 2020; **30**: 553-568 [PMID: 32439088 DOI: 10.1016/j.giec.2020.02.008]

18 **Dodou D**, de Winter JC. Agreement between self-reported and registered colorectal cancer screening: a meta-analysis. *Eur J Cancer Care (Engl)* 2015; **24**: 286-298 [PMID: 24754544 DOI: 10.1111/ecc.12204]

19 **Williams CD**, Grady WM, Zullig LL. Use of NCCN Guidelines, Other Guidelines, and Biomarkers for Colorectal Cancer Screening. *J Natl Compr Canc Netw* 2016; **14**: 1479-1485 [PMID: 27799515 DOI: 10.6004/jnccn.2016.0154]

20 **Pettit N**, Ceppa D, Monahan P. Low Rates of Lung and Colorectal Cancer Screening Uptake Among a Safety-net Emergency Department Population. *West J Emerg Med* 2022; **23**: 739-745 [PMID: 36205665 DOI: 10.5811/westjem.2022.5.55351]

21 **Brandhof SD**, Fagerlin A, Hawley S, Toes-Zoutendijk E, Trevena L, McCaffery K, Korfage IJ. Colorectal cancer screening: Associations between information provision, attitudes and intended participation. *Patient Educ Couns* 2018; **101**: 546-550 [PMID: 28899711 DOI: 10.1016/j.pec.2017.08.021]

22 **Wu L**, Liu Q, Ruan X, Luan X, Zhong Y, Liu J, Yan J, Li X. Multiple Omics Analysis of the Role of RBM10 Gene Instability in Immune Regulation and Drug Sensitivity in Patients with Lung Adenocarcinoma (LUAD). *Biomedicines* 2023; **11** [PMID: 37509501 DOI: 10.3390/biomedicines11071861]

23 **Zhu X**, Weiser E, Jacobson DJ, Griffin JM, Limburg PJ, Finney Rutten LJ. Patient preferences on general health and colorectal cancer screening decision-making: Results from a national survey. *Patient Educ Couns* 2022; **105**: 1034-1040 [PMID: 34340846 DOI: 10.1016/j.pec.2021.07.033]

24 **Ameen S**, Wong MC, Yee KC, Nøhr C, Turner P. AI Diagnostic Technologies and the Gap in Colorectal Cancer Screening Participation. *Stud Health Technol Inform* 2022; **294**: 803-804 [PMID: 35612208 DOI: 10.3233/SHTI220588]

25 **Coronado GD**, Nielson CM, Keast EM, Petrik AF, Suls JM. The influence of multi-morbidities on colorectal cancer screening recommendations and completion. *Cancer Causes Control* 2021; **32**: 555-565 [PMID: 33687606 DOI: 10.1007/s10552-021-01408-2]

26 **Heisser T**, Hoffmeister M, Brenner H. Effects of screening for colorectal cancer: Development, documentation and validation of a multistate Markov model. *Int J Cancer* 2021; **148**: 1973-1981 [PMID: 33320964 DOI: 10.1002/ijc.33437]

27 **Wu L**, Zheng Y, Ruan X, Wu D, Xu P, Liu J, Wu D, Li X. Long-chain noncoding ribonucleic acids affect the survival and prognosis of patients with esophageal adenocarcinoma through the autophagy pathway: construction of a prognostic model. *Anticancer Drugs* 2022; **33**: e590-e603 [PMID: 34338240 DOI: 10.1097/CAD.0000000000001189]

28 **Van Gossum A**. Guidelines for colorectal cancer screening--a puzzle of tests and strategies. *Acta Clin Belg* 2010; **65**: 433-436 [PMID: 21268961 DOI: 10.1179/acb.2010.65.6.012]

29 **Harper DM**, Tariq M, Alhawli A, Syed N, Patel M, Resnicow K. Cancer risk perception and physician communication behaviors on cervical cancer and colorectal cancer screening. *Elife* 2021; **10** [PMID: 34427182 DOI: 10.7554/eLife.70003]

30 **Bonafede MM**, Miller JD, Pohlman SK, Troeger KA, Sprague BL, Herschorn SD, Winer IH. Breast, Cervical, and Colorectal Cancer Screening: Patterns Among Women With Medicaid and Commercial Insurance. *Am J Prev Med* 2019; **57**: 394-402 [PMID: 31377088 DOI: 10.1016/j.amepre.2019.04.010]

31 **Ladabaum U**, Mannalithara A, Mitani A, Desai M. Clinical and Economic Impact of Tailoring Screening to Predicted Colorectal Cancer Risk: A Decision Analytic Modeling Study. *Cancer Epidemiol Biomarkers Prev* 2020; **29**: 318-328 [PMID: 31796524 DOI: 10.1158/1055-9965.EPI-19-0949]

32 **Wu L**, Li H, Liu Y, Fan Z, Xu J, Li N, Qian X, Lin Z, Li X, Yan J. Research progress of 3D-bioprinted functional pancreas and *in vitro* tumor models. *IJB* 2024; **10**: 1256 [DOI: 10.36922/ijb.1256]

33 **Joseph DA**, Meester RG, Zauber AG, Manninen DL, Winges L, Dong FB, Peaker B, van Ballegooijen M. Colorectal cancer screening: Estimated future colonoscopy need and current volume and capacity. *Cancer* 2016; **122**: 2479-2486 [PMID: 27200481 DOI: 10.1002/cncr.30070]

34 **Sekiguchi M**, Igarashi A, Sakamoto T, Saito Y, Esaki M, Matsuda T. Cost-effectiveness analysis of colorectal cancer screening using colonoscopy, fecal immunochemical test, and risk score. *J Gastroenterol Hepatol* 2020; **35**: 1555-1561 [PMID: 32167186 DOI: 10.1111/jgh.15033]

35 **Ylitalo KR**, Camp BG, Umstattd Meyer MR, Barron LA, Benavidez G, Hess B, Laschober R, Griggs JO. Barriers and Facilitators of Colorectal Cancer Screening in a Federally Qualified Health Center (FQHC). *J Am Board Fam Med* 2019; **32**: 180-190 [PMID: 30850454 DOI: 10.3122/jabfm.2019.02.180205]

36 **Wu L**, Zhong Y, Yu X, Wu D, Xu P, Lv L, Ruan X, Liu Q, Feng Y, Liu J, Li X. Selective poly adenylation predicts the efficacy of immunotherapy in patients with lung adenocarcinoma by multiple omics research. *Anticancer Drugs* 2022; **33**: 943-959 [PMID: 35946526 DOI: 10.1097/CAD.0000000000001319]

37 **Hardin V**, Tangka FKL, Wood T, Boisseau B, Hoover S, DeGroff A, Boehm J, Subramanian S. The Effectiveness and Cost to Improve Colorectal Cancer Screening in a Federally Qualified Homeless Clinic in Eastern Kentucky. *Health Promot Pract* 2020; **21**: 905-909 [PMID: 32990049 DOI: 10.1177/1524839920954165]

38 **Mojica CM**, Vargas N, Bradley S, Parra-Medina D. Barriers and Facilitators of Colonoscopy Screening Among Latino Men in a Colorectal Cancer Screening Promotion Program. *Am J Mens Health* 2023; **17**: 15579883231179325 [PMID: 37287187 DOI: 10.1177/15579883231179325]

39 **Soodejani MT**, Mirzaei H, Manesh MM, Tabatabaei SM, Ghaderi A. Incidence of Colorectal Cancer and Adenomatous Polyps After a Two-Step Screening in Isfahan Province, Iran in 2018. *J Gastrointest Cancer* 2020; **51**: 850-854 [PMID: 31656018 DOI: 10.1007/s12029-019-00313-x]

40 **Wu L**, Li X, Qian X, Wang S, Liu J, Yan J. Lipid Nanoparticle (LNP) Delivery Carrier-Assisted Targeted Controlled Release mRNA Vaccines in Tumor Immunity. *Vaccines (Basel)* 2024; **12** [PMID: 38400169 DOI: 10.3390/vaccines12020186]

41 **Clark GR**, Digby J, Fraser CG, Strachan JA, Steele RJ. Faecal haemoglobin concentrations in women and men diagnosed with colorectal cancer in a national screening programme. *J Med Screen* 2022; **29**: 26-31 [PMID: 34806935 DOI: 10.1177/09691413211056970]

42 **Wu L**, Chen X, Zeng Q, Lai Z, Fan Z, Ruan X, Li X, Yan J. NR5A2 gene affects the overall survival of LUAD patients by regulating the activity of CSCs through SNP pathway by OCLR algorithm and immune score. *Heliyon* 2024; **10**: e28282 [PMID: 38601554 DOI: 10.1016/j.heliyon.2024.e28282]

43 **Davis MM**, Coury J, Larson JH, Gunn R, Towey EG, Ketelhut A, Patzel M, Ramsey K, Coronado GD. Improving colorectal cancer screening in rural primary care: Preliminary effectiveness and implementation of a collaborative mailed fecal immunochemical test pilot. *J Rural Health* 2023; **39**: 279-290 [PMID: 35703582 DOI: 10.1111/jrh.12685]

44 **Krul MF**, Elferink MAG, Kok NFM, Dekker E, Lansdorp-Vogelaar I, Meijer GA, Nagtegaal ID, Breekveldt ECH, Ruers TJM, van Leerdam ME, Kuhlmann KFD. Initial Impact of National CRC Screening on Incidence and Advanced Colorectal Cancer. *Clin Gastroenterol Hepatol* 2023; **21**: 797-807.e3 [PMID: 36116753 DOI: 10.1016/j.cgh.2022.08.046]

Published by **Baishideng Publishing Group Inc**
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
Telephone: +1-925-3991568
E-mail: office@baishideng.com
Help Desk: https://www.f6publishing.com/helpdesk
https://www.wjgnet.com