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Retrospective Study

Should we go backward to sigmoidoscope for screening colorectal cancer in people under 45 years?

Sigmoidoscope for primary screening CRC

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Abstract

BACKGROUND

The strategy for preventing colorectal cancer is screening by colonoscopy, which offers a direct way for detection and removal of adenomatous polyps (AP). American College of Gastroenterology (ACG) guideline recommended people beyond 45-year-old should perform an initial colonoscopy, however, how to deal with people under 45 years is still unknown.

AIM

To compare the prevalence of AP and high-grade neoplasia between left-sided and right-sided colon in patients under 45 years.

METHODS

A retrospective observational study was conducted at a single tertiary III hospital in China. This study included patients aged 18-45 years with undergoing first colonoscopy dissection and pathological diagnosis AP or and high-grade neoplasia between

February 2014 and January 2021. The number of AP in the whole colon while screening and post-polypectomy surveillance in following 1-3 years were further evaluated.

RESULTS

A total of 3,053 cases were included. The prevalence of AP in left-sided and right-sided colon were 55.0% and 41.6%, respectively (ORs 1.7, 95% CIs 1.6-2.4; $p < 0.05$). For AP with high-grade neoplasia, the prevalence was 2.7% and 0.9%, respectively (ORs 3.0, 95% CIs 2.0-4.6; $p < 0.05$). Therefore, the prevalence of both AP and high-grade neoplasia in left-sided colon were significantly higher than those of right-sided colon under 45 years. There were 327 cases voluntarily participated in post-polypectomy surveillance, in which AP were found 216 cases (66.1%); among them, 170 cases had 1-3 polyps (52.0%) while 46 cases more than 3 polyps (14.1%) (ORs 0.3, 95% CIs 0.1-0.6; $p < 0.05$).

CONCLUSION

This study suggests that flexible sigmoidoscopy would be an optimal approach for the initial screening in population under 45 years, which will be a more cost-effective and safety strategy.

Key Words: Adenomatous polyps; High-grade neoplasia; Colonoscopy; Flexible sigmoidoscope

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Core Tip: This is a retrospective observational study to investigate the prevalence of AP and high-grade neoplasia and find out the significant difference between left-sided and right-sided colon in patients under 45 years. The prevalence of both AP and high-grade neoplasia in left-sided colon were significantly higher than those of right-sided colon

under 45 years. Given that, it is reasonable that flexible sigmoidoscopy would be an optimal approach for the initial screening in population under 45 years, which is a more cost-effective and safety strategy; and colonoscopy for post-polypectomy surveillance could be an appropriate interval of around 3 years.

INTRODUCTION

Colorectal cancer (CRC) is not only the third most common cancer but also the third cause of cancer mortality worldwide with more than 1.85 million cases and 850,000 deaths annually [1]. The incidence of CRC is increasing nowadays in both developed and developing regions and countries since the lifestyle of more people especially the young shifts to western high-fat and high-calories diet with less exercises, along with obesity and metabolic syndrome are prevalent [2, 3]. Till now, several studies indicated that the incidence of CRCs at aged under 50 years was increasing in recent years [4, 5]. There are about 70% of sporadic CRCs developing from adenomatous polyps (AP) through the adenoma-carcinoma sequence [6, 7]. Newly American College of Gastroenterology (ACG) guidelines suggested CRC screening in average-risk individuals beyond 45-year-old to reduce incidence of advanced adenoma, CRC, and mortality from CRC in the 2021 [8].

Colonoscopy with pathological examination is considered the most effective strategy of CRCs screening since it can directly remove polyps and pathological diagnosis of adenoma, high-grade neoplasia, or early-stage CRCs. However, colonoscopy need experienced doctors, sedation or anesthesia, better bowel preparation and longer examination time; besides, it may increase medical consumption, the potential for patient discomfort and the risk of complications [9, 10].

Since the newly ACG guideline recommended coloscopy screening performs in population beyond 45 years, how to deal with people under 45 years is still questionable, whether they still need colonoscopy screening or not is unanswered. Our study aimed to compare and statistically analyze the prevalence of AP and high-grade neoplasia between left-sided (including rectal, sigmoid, descending colon and spleen flexure) and right-sided (including transverse, ascending, hepatic flexure, cecum, and

ileocecal) colon in patients under 45 years visiting our out-patient clinic in order to identify whether flexible sigmoidoscopy would be an optimal approach for their initial CRC screening. In addition, the numbers of AP in the whole colon when post-polypectomy surveillance in following 1-3 years were further evaluated to provide an appropriate interval of follow-up recommendation.

MATERIALS AND METHODS

Study Design

To retrospectively evaluate the distribution characteristics of adenomatous polyps (AP) and compare the prevalence of neoplasia in left and right-sided colon of patients in out-patient clinic at the University of Hongkong-Shenzhen hospital, a tertiary III hospital located Southern China. The data were collected from the database of our endoscope center and pathology department spanning from February 2014 to January 2021. All colonoscopies were performed by experienced eligible endoscopists with the time of coloscopy pull-out time over 9 minutes and adequate bowel cleanliness which Boston Bowel preparation scale (BBPS) over 6 scores in all 3 segments as well as the ability to detect polyps >5 mm in size [11, 12]. Tissue specimens were evaluated by two gastrointestinal pathologists. The histopathological diagnosis was based on the morphological features on hematoxylin and eosin staining.

Participant Selection and Data Collection

All patients (aged 18-45 years) conducted first colonoscopy as opportunistic examination according to specialist's medical recommendation for gastrointestinal symptoms or patient initiative instead of colorectal cancer screening according to guidelines. Their pathological diagnosis with polyps included polypoid mucosa, inflammatory polyps (pseudopolyp), hyperplastic polyps (HP), sessile serrated polyps (SSP), adenomatous polyps (AP), and adenomatous polyps with high-grade neoplasia from 1st February 2014 to 31st January 2021. A total of 3,053 independent cases were included (colonoscopies which examination time at the interval of less 6 months were considered as the same cases in our research statistics strategy). The exclusion criteria

were patients who were aged under 18 years, and over 45 years; or histopathological diagnosis was colorectal cancer. A retrospective chart review of electronic medical records, electronic colonoscopy and histopathological reports of included patients was performed to collect data on patient demographics, colonoscopy and colonic location, and pathological classification of all polyps were recorded.

Study outcome and definitions

The study outcome was the prevalence of adenomatous polyp in left-sided and right-sided colon. Polypoid mucosa, inflammatory polyps, and hyperplastic polyps (HP) were defined as non-adenomatous polyps. In addition, AP with high-grade neoplasia were included polyps with high-grade intraepithelial tumor and high-grade dysplasia. The term of “left-sided colon” included rectum, sigmoid, descending colon, and splenic flexure; otherwise, “right-sided colon” included transverse, ascending colon, hepatic flexure, cecum and ileocecal. Our primary analysis focused on the rates between left and right-sided colon. We also studied cases voluntarily follow-up in 1-3 years for post-polypectomy surveillance. The recurrent rates of AP were measured during the follow-up period.

Statistical analysis

All the analyses were conducted using SAS software version 9.4 (SAS Institute Inc, Cary, NC) and GraphPad Prism 8 (GraphPad software, San Diego, CA). Categorical variables are summarized as percentages, and continuous variables are summarized as means \pm standard deviations. Between group comparisons were evaluated using Chi-square test or Fisher's exact test, and estimated odds ratios (ORs), and 95% confidence intervals (CIs). A Two-sided P-value of 0.05 or less were considered statistically significant.

RESULTS

1. Baseline characteristics

A total of 66,008 cases underwent colonoscopies for all adult patients from 1st February 2014 to 31st January 2021 in our hospital; and 31,485 cases (about 47.7%) underwent

colonoscopy at the age under 45 years. Among them, there were 3,265 cases (2,747 participants) with biopsy histological diagnosis of non-cancerous lesions and 3,053 cases as independent cases were included for final analyses of which 2,138 cases were male (70%) with the average age of 38.33 ± 5.15 years. For histopathological diagnosis in whole colon, 2,652 cases (86.9%) were AP and 106 cases (3.5%) were AP with high-grade neoplasia. In addition, there were 19 cases both AP and high-grade neoplasia in whole colon. 314 cases were non-adenomatous polyps. The demographic characteristics are shown in Table 1.

2. Prevalence and distribution of adenomatous polyps

To assess the characteristics of AP, we analyzed the relation between the position. The cases of AP in left-sided colon, right-sided colon and both colons were 1,679, 1,271, and 298, respectively. The prevalence of left-sided colon and right-sided colon were 55% and 41.6%, respectively (ORs 1.7, 95% CIs 1.6-2.4; $p < 0.05$). For AP with high-grade neoplasia, the cases of those lesions in left-sided colon, right-sided colon and both colons were 82, 28, and 4, respectively. The prevalence of left-sided colon and right-sided colon were 2.7% and 0.9%, respectively (ORs 3.0, 95% CIs 2.0-4.6; $p < 0.05$). Compared to right-sided colon, AP, and AP with high-grade neoplasia in left-sided colon were significantly higher (see Table 2 and Supplementary Table 1). Surprisingly, the similar results were found in under 40 years which were included 1,659 cases (1,400 participants), but there was no significant difference between under 45 years and under 40 years either left-sided colon or whole colon (see Supplementary Table 2).

3. Post-polypectomy surveillance after screening

A total of 430 cases (14.1%, 346 participants) follow-up for twice or more colonoscopies and 327 cases (76.1%, 282 participants), who conducted repeated colonoscopy in the following period in an interval of more 6-month considered as post-polypectomy surveillance, were follow-up in 1-3 years. Among them, AP were 216 cases (66.1%) and non-adenomatous polyps were 111 cases (33.9%) in whole colon. For AP, there were 170 cases detected 1-3 polyps (52.0%) while 46 cases were more than 3 polyps (14.1%); In

addition, among non-adenomatous polyps, 104 cases had 1-3 polyps (31.8%) and 7 cases were more than 3 polyps (2.1%) (ORs 0.3, 95% CIs 0.1-0.6; $p < 0.05$) (see Table 3).

DISCUSSION

Colorectal cancer remains a common cancer worldwide and a critical public health burden. With an increasing steadily incidence and mortality associated with CRC in adults younger than 50 years, the guideline update recommends that individuals aged 45 years and older with an average-risk of CRC undergo tailored screening [8, 13, 14]. To our known, none of the studies have shown the screening recommendations and strategies for individuals aged 45 and younger. Our study shows that the prevalence of AP in left-sided colon is significantly higher than right-sided colon whether with high-grade neoplasm or not and the recurrence of more than 3 adenomatous polyps is less 15% in 1-3 years follow-up. The results suggest that the sigmoidoscopy for primary screening would be a potential approach and colonoscopy for surveillance following polypectomy would be in 3 years in the population under 45 years, which would be a more efficient strategy with cost-effective, less risky for colorectal cancer screening under 45 years.

Early-onset CRC (EOCRC), defined as CRC diagnosed in aged younger 50 years, is a highly heterogeneous disease and almost two-thirds of them occurring between the ages of 40 and 49 [5, 15]. Recent data from SEER (Surveillance, Epidemiology, and End Results) and National Program of Cancer Registries databases found that about 42% of tumor was in the rectum [16]. Most of EOCRC are identified through screening because of presenting with high-risk and red flag symptoms such as anemia without apparent cause, hematochezia, change in bowel habits, and abdominal pain; thus, they tend to experience longer duration to diagnosis than individuals older than 50 years [17-19]. AP is the precursors for aggressive CRCs and approximately 60-70% of sporadic CRCs would develop from AP through the adenoma-carcinoma pathway *via* a multistep over several years or even a decade [6, 7, 20, 21]. Early detection and resection of precancerous polyps are critical to interrupt the adenoma-carcinoma process preventing the development of

CRC. However, given the EOCRC characteristics, Laiyemo and Pinsky also suggested that widespread use of colonoscopy among young persons may be leading to over detection and insurance consumption in the United States [22].

Accordingly, CRC screening program has contributed to reduce the CRC-related morbidity and mortality through the detection and removal of AP and other precancerous lesions, but clinicians have to weigh against the benefits, risk, cost and insurance burden. The CRC screening approaches include colonoscopy, flexible sigmoidoscopy (FS), computed tomography colonography (CTC), colon capsule endoscopy (CCE), fecal immunochemical test (FIT), multitarget stool DNA test, and blood Septin 9, each of which has advantages and limitations [8, 14]. The first-four is structural examination for screening which allow the operator a visual inspection of the bowel. CTC and CCE, despite non-invasive screening and emerging technologies, are required to follow-up with timely colonoscopy for further evaluation or biopsy if positive test result [9, 23]. Moreover, CTC is not good at detection flat adenomatous or serrated polyp lesions well, due to its dependence on morphology as well as requirement full bowel cleansing preparation and radiation exposure. Notably, there is no empirical evidence to demonstrate that CT colonography can reduce CRC incidence or related mortality [9, 12]. On the contrary, colonoscopy and flexible sigmoidoscopy, though invasive examination, offer the optimize direct detection of precancerous lesion as well as the ability of removal lesions simultaneously that provide long-term protection against CRC morbidity and mortality [10, 24]. However, colonoscopy requires better adequate bowel preparation and the adenoma detection rate is positive correlated with the quality of cleansing and the withdrawal time. Additionally, it needs experienced endoscopists who are well trained, better under conscious sedation or anesthesia, thus much risky for complications and higher costs [12, 23, 25, 26]. Flexible sigmoidoscopy (FS), an endoscopy reaching the splenic flexure or about 60cm from the anal dentate line with less invasive and lower risk of complications, has over 95% sensitivity for CRCs and 70% sensitivity for adenomatous polyps which is the same as colonoscopy for distal colon [27, 28]. Besides, the advantages of flexible sigmoidoscopy

were less time for preoperative preparation and lower cost without any sedation or anesthesia [29, 30]. In four large randomized controlled trials with 11-17 years of follow-up, the intention-to-treat analysis reported a 27% reduction in the incidence of CRC and a 21% reduction in mortality; moreover, the per-protocol analyses reported 31-33% reduction in the incidence and 38-43% reduction in mortality with screening by FS [31-34]. Furthermore, recent studies demonstrated that the effect of FS is similar to colonoscopy in the distal colon [9, 35]. Compared with right-sided colon, there were 1.7-fold increase in AP and 3-fold increase in AP with high-grade neoplasia in left-sided colon, respectively ($p < 0.05$) (see Table 2). Our findings are consistent with prior studies of SEER national database reported that incidence of EOCRC tend to more commonly present with left-sided CRC as well as more likely to occur rectal cancer [36].

Given that the EOCRC incidence is alarming increased, the 2018 American Cancer Society (ACS) and 2021 ACG guideline recommend lowering the CRC screening initiation age from 50 to 45 years to decrease in subsequent CRC incidence and cost-effectiveness [8, 13]. Some research studied initiating screening at age down to 40 years [36, 37]. In our study, there were not significantly different between aged ≤ 45 years and < 40 years cohorts in the prevalence of AP or AP with high-grade neoplasia either left-sided colon or whole colon. Hence, these results imply that lower aged at 40 years would not provide more benefit than aged ≤ 45 years (see Supplementary Table 2).

Multiple societies and organizations have issued surveillance guidelines for patients who were screening or post-polypectomy surveillance. The current guidelines suggest that flexible sigmoidoscopy should be repeated every 5 years in asymptomatic individuals with no previous history of colon polyps [14, 38]. After positive findings, there is recommended repeated colonoscopy and frequent surveillance. The majority of people with polypectomy would receive surveillance colonoscopy about every 1, 3, 5, or 10 years depending on the polyp characteristics including size, number, and histologic features [8, 25]. According to risk stratification for colorectal adenomatous polyps, the regular surveillance intervals are recommended every 3-5 years for patients with high-risk and every 5-10 years patients with low risk [13, 25]. In our cohort, we found that

recurrent adenomatous polyps were about one tenth followers for screening or postresection surveillance in 1-3 years. Among them, approximately two thirds were adenomatous polyps in whole colon; moreover, there was lower recurrence of more than 3 adenomatous polyps observed compared with 1-3 polyps (14% *vs* 52.0%, see Table 3). Therefore, we suggest that colonoscopy for postresection surveillance would be adequate longer intervals around 3 years to reduce body invasiveness and improve cost-effectiveness.

We acknowledge that there are limitations. First, this is a single central retrospective observational study which is prone to selection bias. Second, our study did not show any correlation between smoking, moderate alcohol consumption, obesity, red meats, processed meats, and diabetes/metabolic syndrome, which are considered high-risk factors for EOCRC as well as family history of CRC and polyps **because it was not CRC screening in average-risk individuals** [2, 19]. Additionally, the presence or absence of symptoms such as pain, bleeding, or altered bowel habits was not also recorded [19]. Third, although all endoscopists met the eligibility requirements for endoscopic procedures, they were randomly arranged irrespective of their experience. This could lead to an underestimation of the true prevalence. Finally, the determine post-polypectomy surveillance periods in the research was depended on the patient voluntary prefer, **including gastrointestinal symptoms or individual willing**. Moreover, due to insurance status, financial motivations, and personal or working reasons to move out of city of Shenzhen *etc.*, some patients would choose other hospitals or lost to follow-up, which could influence the outcome of postresection follow-up.

CONCLUSION

This retrospective study suggests that flexible sigmoidoscopy would be an optimal **primary** approach for CRC screening in people younger 45 years; **and** post-polypectomy surveillance could be in 3 years. However, there is still a need for prospective, **multiple-center research** for further confirmation.

ARTICLE HIGHLIGHTS

Research background

EOCRC has been an increasing steadily incidence and mortality so that the update guidelines recommend individuals aged 45 years and older with an average-risk of CRC undergo screening. However, whether people under 45 years need colonoscopy screening or other tailored screening is unknown.

Research motivation

What is the better approach of CRC screening for people under 45 years.

Research objectives

This study aimed to investigate the prevalence of AP and high-grade neoplasia as well as compare and find out the significant difference between left-sided and right-sided colon in patients under 45 years.

Research methods

A retrospective observational study was conducted patients (aged 18-45 years) who underwent first colonoscopy from February 2014 to January 2021 at the tertiary III hospital in China.

Research results

The prevalence of both AP and high-grade neoplasia in left-sided colon were significantly higher than those of right-sided colon under 45 years. The recurrence of more than 3 adenomatous polyps is less 15% in 1-3 years follow-up.

Research conclusions

Flexible sigmoidoscopy would be an optimal approach for the initial screening in population under 45 years, which will be a more cost-effective and safety strategy.

Research perspectives

Further multi-center, large-sample clinical and prospective studies are still needed to verify the results of the present study and investigate in CRC average-risk individuals under 45 years.