

# Clinical Features of Fecal Immunochemical Test-Negative Colorectal Lesions based on Colorectal Cancer Screening among Asymptomatic Participants in Their 50s

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## Abstract

**Objective:** To improve the efficacy of colorectal cancer (CRC) screening, decreasing the occurrence of interval cancers is essential. Most interval CRCs develop from fecal immunochemical test (FIT)-negative CRC. This study examined the clinical characteristics of FIT-negative advanced neoplasms (AN) and sessile serrated lesions (SSL), which are main candidate precursors of FIT-negative CRC, and the eligibility criteria for total colonoscopy (TCS) screening following negative FIT. **Methods:** Asymptomatic participants in their 50s were divided into two groups. The FIT-negative group underwent TCS following negative FIT, and the TCS-only group underwent TCS without FIT. One endoscopist reviewed the endoscopic images. Plausible risk factors for colorectal polyps were extracted. The clinical features of AN and SSL were compared between the groups. **Result:** Of 2,437 participants, 56.2% were included in the FIT-negative group. No between-group differences were recorded for the prevalence of different colorectal polyp types. By multivariate analysis, a significantly lower adjusted odds ratio (AOR) of AN was shown in women, and significantly higher AORs of AN were found for aging, smoking, and a family history of CRC. The AOR of SSL was higher for smokers. The proportion of AN in the right colon was higher in the FIT-negative group. No between-group differences were recorded for SSL. **Conclusion:** FIT screening was less likely to detect CRC and certain precancerous lesions in the right colon. Combining annual FIT with TCS for the high-risk population based on a scoring system, may detect FIT-negative CRC and colorectal polyps, thus, reducing interval cancer.

**Keywords:** Colonic polyps- total colonoscopy-early detection of cancer

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## Introduction

In Japan, colorectal cancer (CRC) had the second age-standardized mortality rate in 2019, and the first age-standardized incidence rate in 2017 (Cancer mortality from Vital Statistics in Japan, 1958-2019). Thus, the investigation for effective countermeasures should be

accelerated to address CRC.

Recently, the fecal immunochemical test (FIT) has been widely applied in CRC screening. In Japan, annual two-sample FIT screening has been performed as a CRC screening for people aged  $\geq 40$  years since 1992. A case control study showed that its annual or biennial use reduces CRC mortality by 60% (Saito et al., 1995). However, CRC

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still causes many cancer deaths in Japan. Decreasing the CRC mortality rate in Japan should be examined from three aspects: to advance the screening program's quality control, to improve FIT efficacy, and to add other screening tests to the program. To improve the efficacy of CRC screening, decreasing the occurrence of interval cancer, which is diagnosed after a screening or surveillance examination in which no cancer is detected, and before the date of the next recommended examination (Sanduleanu et al., 2015), is crucial. Interval cancers associated with FIT screening have many common characteristics of FIT-negative CRC (Hasegawa et al., 2020); this is expected because most interval cancers develop from FIT-negative CRC. A precursor of FIT-negative CRC includes sessile serrated lesions (SSL), which become carcinogenic via the serrated pathway (Jass et al., 2002), non-polypoid lesions, which are flat and depressed (Chiu et al., 2013), and adenomas. However, lowering the FIT threshold to detect more of these candidate precursors of FIT-negative CRC may cause an increase in false-positive cases.

Total colonoscopy (TCS) screening for CRC has recently been proposed to reduce interval CRC; additionally, a number of randomized controlled trials of it are currently underway (Quintero et al., 2012; Kaminski et al., 2012; Saito et al., 2020; Dominitz et al., 2017; Fritzell et al., 2020). In the United States, an annual fecal occult blood test, TCS every 10 years, computed tomography colonoscopy or sigmoidoscopy every 5 years, and a stool DNA test every 3 years are recommended for CRC screening (Davidson et al., 2021). However, the implementation of CRC screening with TCS, requires a sufficient number of available endoscopists. A sufficient number of screening tests to cover a target population should be determined, and facilities for diagnostic tests and treatment should be available for cancer patients detected by the screening (Wilson and Jungner, 1968). Therefore, TCS screening in all populations at risk for CRC does not seem to be realistic.

In this study, we compared the clinical features of advanced neoplasm (AN) and SSL between patients who underwent TCS following negative FIT and those who underwent TCS without FIT. There are few reports on TCS screening for FIT-negative individuals, who are generally not offered TCS. We hypothesized that CRC and precancerous lesions were more common in the right colon among FIT-negative individuals and that TCS screening was required as an additional test to detect FIT-negative lesions. The aim of this study was to reveal the clinical characteristics of FIT-negative CRC and colorectal polyps by comparing the clinical characteristics of AN with SSL among those who underwent TCS without FIT results, thus pointing out the eligibility criteria for TCS screening among FIT-negative group.

## Materials and Methods

The data for this study were obtained from the Aomori Colorectal Cancer Screening Project, a health project examining the efficacy of CRC screening with TCS as an organized screening.

### Participants

The participants were residents of Hirosaki or Aomori City, Aomori Prefecture. Those who were 50–59 years of age during the study period (April 2017 to March 2018) and could not be confirmed as having undergone CRC screening by the Aomori prefectural government for the previous 5 years were invited to participate in our study. To identify potential participants, we collated the list of examinees of CRC screening with the list of invited residents of it for five years in Hirosaki and Aomori city and we specified residents who were absent from CRC screening for five years. The exclusion criteria were a history of inflammatory bowel disease, colectomy, or other treatments for CRC. Patients with incomplete colonoscopy results, poor colonoscopy preparation, and imperfect data were also excluded.

The study was approved by the ethics committee of Hirosaki University Graduate School of Medicine (approval number: 2019-1091-1), and this study was funded by Hirosaki University Graduate School of Medicine. Participants understood the aims of the study and agreed to participate in it. Written informed consent was obtained from each participant prior to study initiation.

### Study design

A FIT kit and a TCS invitation were sent to the study participants, who had three options: undergoing FIT only, undergoing both FIT and TCS, or undergoing TCS only. Two-sample FIT (cut-off level: 150 ng/mL) was used in this study. The participants were divided into two groups according to the FIT results. While the FIT-positive participants were offered to consult gastroenterologists, those with negative FIT results (FIT-negative group) then underwent TCS during the same period as those who chose TCS only (TCS-only group). Colonoscopy was performed by expert endoscopists at Hirosaki University Hospital or Aomori Prefectural Central Hospital. Before the colonoscopy, the height and weight of participants were measured, and their body mass index (BMI) was calculated. They also filled out self-administered questionnaires about smoking habits, habitual drinking, family history of CRC, and personal history of TCS or endoscopic treatment for colorectal polyps. Smoking habits were categorized into three statuses: current smoker, past smoker, and non-smoker. A family history of CRC was defined as CRC incidence in first degree relatives or none. BMI and other data obtained from questionnaires were regarded as plausible risk factors for CRC and other neoplasms. One endoscopist reviewed the endoscopic images of all participants after the performance of TCS.

The following characteristics were considered for advanced adenoma (AA): (a)  $\phi \geq 10$  mm, (b) suspected high-grade dysplasia. The AN category included CRC or AA. Adenoma was defined as non-advanced adenoma. We recognized SSL as a pale color lesion, which was flat or only slightly raised, and fulfilled two or more of the following characteristics: (a) covered by mucus (Tadepalli et al., 2011), (b) expanded crypt openings detected with narrow-band imaging (Yamashina et al., 2015), (c) dilated and branching vessels detected with narrow-band imaging (Yamada et al., 2015), and (d) type II-open pit patterns

(Kimura et al., 2012) detected with chromoendoscopy. At the beginning of this study, WHO Classification of Tumors, 5th ed., Vol. 1, Digestive System Tumours (Pai et al., 2019) had not been published, and the “SSL” category was accepted in this paper. Hyperplastic polyp (HP) was a separate category from SSL and defined as a small, flat, and elevated pale color lesion, which shows type II pit patterns detected with chromoendoscopy. Others included traditional serrated adenomas (TSA), non-neoplastic polyps, and submucosal tumors. The right colon represented a part of the colon including the cecum, the ascending and transverse colon, the left descending colon, the sigmoid colon, and the rectum.

*Statistical analyses*

Plausible risk factors were examined by univariate analyses between the FIT-negative and TCS-only groups. BMI was presented as median (IQR), and other clinical features were expressed as n (%). A difference in BMI was detected using Mann-Whitney U test. The location of lesions and a history of polypectomy were compared using chi-square test. Other features were compared using Fisher’s exact test. To adjust for confounding factors, the

presence of lesions was defined as an objective variable, whereas others were defined as explanatory variables to be examined by logistic regression analysis, thus comparing adjusted odds ratios (AORs). The risk factors for AN and SSL were compared by univariate analysis between the FIT-negative and TCS-only groups. A two-tailed P-value <0.05 was considered statistically significant. Data analyses were performed using SPSS version 21.0 (IBM Corp., Armonk, NY, USA).

**Results**

*Clinical characteristics of the participants*

A total of 2,538 residents from Aomori or Hirosaki City underwent TCS as colorectal screening; of these residents, 101 participants refused participation. Among the participants, 1,370 (56.2%) and 1,067 (43.8%) were included in the FIT-negative and TCS-only groups, respectively (Figure 1a, b). The number of participants who had one or more colorectal polyps was 1,692 (69.5%). Among the FIT-negative group, 63 (4.6%) patients had AN, and 159 (11.6%) had SSL. In the TCS-only group, 55 (5.2%) patients had AN and 136 (12.7%) had SSL. The

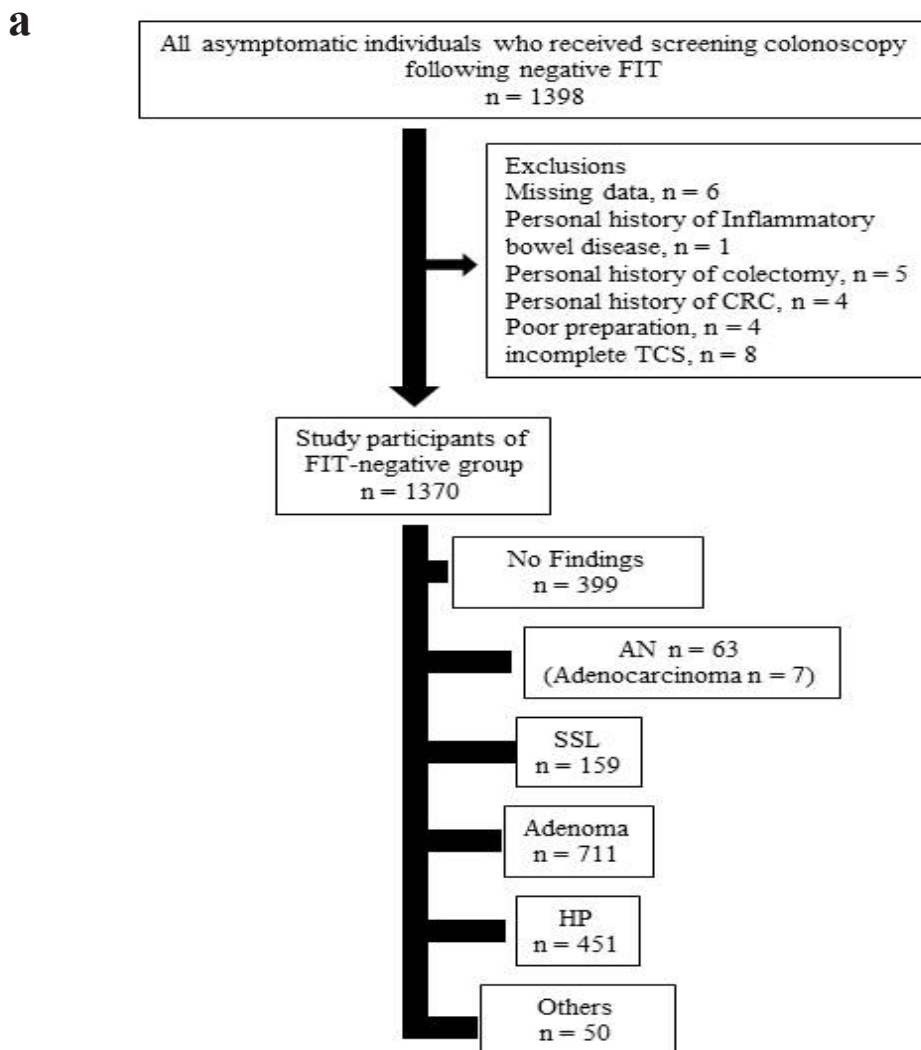


Figure 1. Flow Diagram of the Study. a. FIT-negative group. FIT, fecal immunochemical test; CRC, colorectal cancer; TCS, total colonoscopy; AN, advanced neoplasm; SSL, sessile serrated lesion; HP, hyperplastic polyp

b

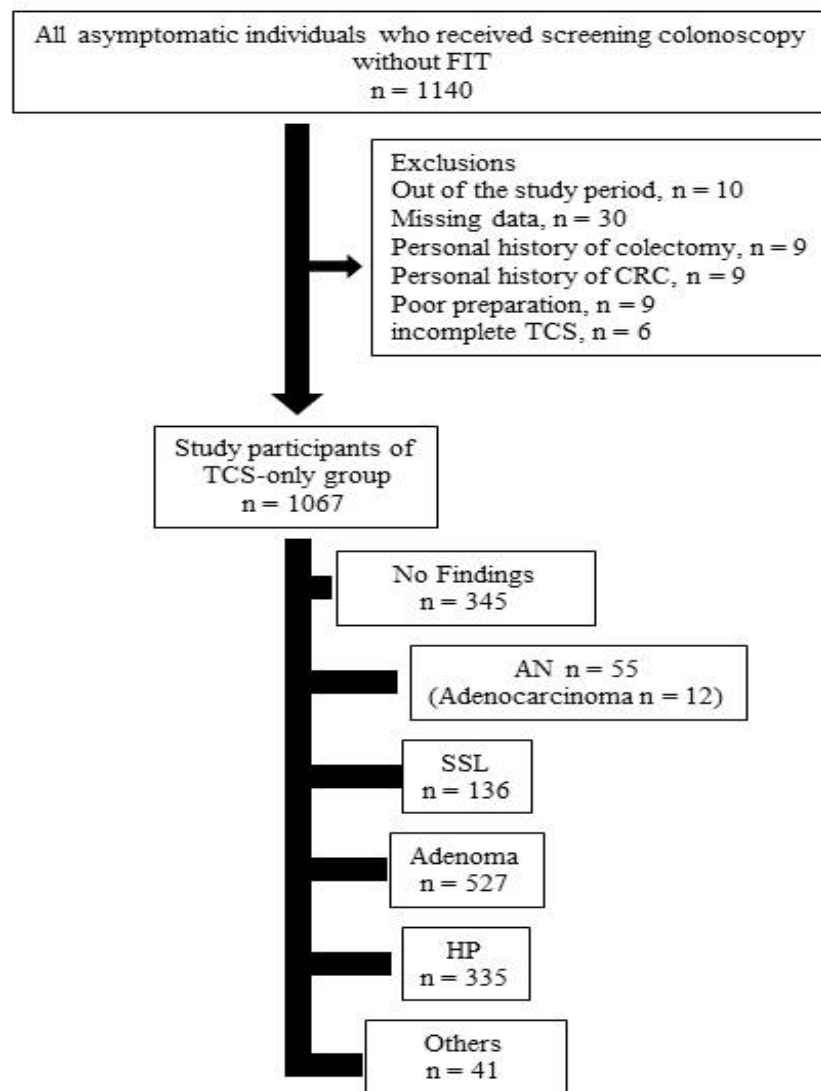


Figure 1. Flow Diagram of the Study. b. TCS-only group. FIT, fecal immunochemical test; CRC, colorectal cancer; TCS, total colonoscopy; AN, advanced neoplasm; SSL, sessile serrated lesion; HP, hyperplastic polyp

demographic and clinical characteristics of the participants are summarized in Table 1. The mean age was 54.4 years (SD  $\pm$  3.3), and 1,250 (51.3%) were men. Although the eligibility criteria included those who could not be confirmed as having undergone colorectal screening, which is usually performed with the FIT two-sample method in Japan, for the past 5 years by the prefectural government, 317 (13.0%) underwent TCS within 5 years. Among them, 171 (7.0%) were treated with polypectomy for colorectal polyps. BMI was significantly higher in the FIT-negative group than in the TCS-only group.

#### *Prevalence and clinical characteristics of colorectal polyps*

The characteristics of each colorectal polyp type are summarized in Table 2. There were no differences in the prevalence of each colorectal polyp type between the FIT-negative and TCS-only groups. The prevalence of AN was higher in men, patients aged 55–60 years, current or past smokers, those with a higher BMI, and those with a family history of CRC. The participants with SSL had a

significantly higher prevalence of current or past smoking.

#### *Multivariate analysis between colorectal polyps and clinical features*

A significantly lower AOR of AN was shown in women (AOR: 0.49, 95% CI: 0.31–0.77), and higher ones in those aged 55–60 years (AOR: 1.72, 95% CI: 1.17–2.52), current or past smokers (AOR: 1.53, 95% CI: 1.01–2.32), and those with a family history of CRC (AOR: 2.18, 95% CI: 1.36–3.51). The prevalence of AN was not associated with BMI (AOR: 1.03, 95% CI: 0.98–10.9). Unlike the AOR of adenoma, that of BMI was not significant, and that of family history of CRC was significant in the participants with AN. TCS only (AOR: 1.18, 95% CI: 0.81–1.72) and habitual drinking (AOR: 0.71, 95% CI: 0.39–1.29) were not associated with the prevalence of AN. The AOR of SSL was higher in current or past smokers (AOR: 1.52, 95% CI: 1.16–1.99), and followed the same trend, as observed in the univariate analysis. TCS only (AOR: 1.13, 95% CI: 0.88–1.45), Sex (AOR: 1.07, 95% CI: 0.81–1.41), Age group (AOR:



Table 1. Demographic and Clinical Characteristics of the Participants

		FIT-negative (n=1370)	TCS-only (n=1067)	P-value
Sex, n (%)	Male	726 (53.0)	524 (49.1)	0.06
	Female	644 (47.0)	543 (50.9)	
Age group, years, n (%)	49–54	686 (50.1)	568 (53.2)	0.13
	55–60	684 (49.9)	499 (46.8)	
Smoking, n (%)	Non-smoker	699 (51.0)	580 (54.4)	0.1
	Smoker	671 (49.0)	487 (45.6)	
Alcohol, n (%)	Non-drinker	1193 (87.1)	947 (88.8)	0.9
	Drinker	177 (12.9)	120 (11.2)	
BMI, kg/m <sup>2</sup> , median (IQR)		23.7 (21.4–26.1)	23.1 (21.2–25.4)	<0.001
Location of the polyps, n (%)	Right	382 (27.9)	280 (26.2)	0.39
	Left	340 (24.8)	255 (23.9)	
	Bilateral	249 (18.2)	187 (17.5)	
Family history of CRC, n (%)	Yes	153 (11.2)	135 (12.7)	0.28
	No	1217 (88.8)	932 (87.3)	
History of Colonoscopy within 5 years, n (%)	Yes	160 (11.7)	157 (14.7)	0.29
	No	1210 (88.3)	910 (85.3)	
History of polypectomy, n (%)	Yes	103 (7.5)	68 (6.4)	<0.001
	No	1263 (92.2)	845 (79.2)	
	Unknown	4 (0.3)	154 (14.4)	

BMI, body mass index; IQR, interquartile range; CRC, colorectal cancer; FIT, fecal immunochemical test; TCS, total colonoscopy

0.97, 95% CI: 0.76–1.24), habitual drinking (AOR: 1.10, 95% CI: 0.77–1.59), BMI (AOR: 1.01, 95% CI: 0.98–1.05), and Family history of CRC (AOR: 1.26, 95% CI: 0.88–1.80) were not associated with the prevalence of SSL. A significantly lower AOR of Adenoma was shown in women (AOR: 0.54, 95% CI: 0.45–0.65), and higher ones in those aged 55–60 years (AOR: 1.47, 95% CI: 1.25–1.73), current or past smokers (AOR: 1.43, 95% CI: 1.20–1.70), and BMI (AOR: 1.03, 95% CI: 1.01–1.06). The prevalence of Adenoma was not associated with TCS only (AOR: 0.96, 95% CI: 0.81–1.13), habitual drinking (AOR: 1.21, 95% CI: 0.94–1.57), and Family history of CRC (AOR: 1.22, 95% CI: 0.95–1.57). A significantly higher AOR of hyperplastic polyp was shown in Current or past smoker (AOR: 1.69, 95% CI: 1.40–2.04), habitual drinker (AOR: 1.57, 95% CI: 1.22–2.03). BMI was also associated with the prevalence of hyperplastic polyp (AOR: 1.07, 95% CI: 1.04–1.09). The prevalence of it was not associated with TCS only (AOR: 0.99, 95% CI: 0.83–1.18), Sex (AOR: 0.90, 95% CI: 0.74–1.10), Age group (AOR: 1.16, 95% CI: 0.98–1.39), and Family history of CRC (AOR: 1.02, 95% CI: 0.78–1.33). A significantly higher AOR of others was shown in BMI (AOR: 1.08, 95% CI: 1.02–1.14). Other clinical features were not associated with the prevalence of it.

#### Comparisons in clinical features of AN and SSL

A univariate analysis was performed to compare the clinical characteristics of AN and SSL between the FIT-negative and TCS-only groups (Table 4). As for AN, the proportion of a family history of CRC was significantly higher in the TCS-only group than in the FIT-negative

group, and the proportion of the right colon was higher in the FIT-negative group than in the TCS-only group. There were no significant differences in sex, age, smoking, and BMI between the FIT-negative and TCS-only groups. SSL did not show any significant differences in clinical features or polyp positions.

## Discussion

Our results showed that AN was more frequent in the right colon in the FIT-negative group than in the TCS-only group, and there were no significant differences in SSL between the two groups. These findings suggested that FIT screening was less likely to detect CRC and certain precancerous lesions in the right colon.

These results may be attributed to the fact that ANs in the right colon were more likely detected by TCS than FIT. A previous study reported that the sensitivity of FIT to AN in the proximal colon was lower than that of the distal colon (Morikawa et al., 2005). This may be because patients presenting left-sided AN had higher fecal hemoglobin concentration than those presenting right-sided AN (Navarro et al., 2019). Additionally, polyps in the right colon are small and flat and are often non-tubular adenomas (Brenner et al., 2015), in which bleeding is less common. Contrarily, the sensitivity of SSL, which was reported to be 6.2–16.3% (Cock et al., 2019; Chang et al., 2017), seemed to be lower than that of AN. In this study, there was no significant difference in the number of SSLs between the left and right colon in both groups, showing the low detection rate of SSL by FIT.

The Asia-Pacific Colorectal Screening (APCS) score

Table 3. Association of the FIT-negative and TCS-only Groups for AN and SSL with Clinical Features

	FIT-negative (n=63)		TCS-only (n=55)		P-value	FIT-negative (n=159)		TCS-only		P-value
Sex, n (%)	Male	47 (74.6)	37 (67.3)	0.42		87 (54.7)	72 (52.9)		0.82	
	Female	16 (25.4)	18 (32.7)			72 (45.3)	64 (47.1)			
Age group, years, n (%)	49-54	24 (38.1)	21 (38.2)	0.99		75 (47.2)	78 (57.4)		0.1	
	55-60	39 (61.9)	34 (61.8)			84 (52.8)	58 (42.6)			
Smoking, n (%)	Never	21 (33.3)	22 (40.0)	0.57		69 (43.4)	60 (44.1)		0.91	
	Current or past	42 (66.7)	33 (60.0)			90 (56.6)	76 (55.9)			
Alcohol, n (%)	Non-drinker	57 (90.5)	48 (87.3)	0.77		137 (86.2)	118 (86.8)		0.99	
	Drinker	6 (9.5)	7 (12.7)			22 (13.8)	18 (13.2)			
BMI, kg/m <sup>2</sup> , median (IQR)		24.0 (22.4-26.4)	24.3 (22.4-25.4)	0.57		24.1 (21.1-26.7)	23.3 (21.3-26.1)		0.36	
Family history of CRC, n (%)	Yes	8 (12.7)	16 (29.1)	0.04		20 (12.6)	21 (15.4)		0.5	
	No	55 (87.3)	39 (70.9)			139 (87.4)	115 (84.6)			
Location of the polyps, n (%)	Right	31 (49.2)	15 (27.3)	0.02		114 (71.7)	101 (74.3)		0.2	
	Left	26 (41.3)	37 (67.3)			35 (22.0)	21 (15.4)			
	Bilateral	6 (9.5)	3 (5.5)			10 (6.3)	14 (10.3)			

BMI, body mass index; IQR, interquartile range; CRC, colorectal cancer; AN, advanced neoplasm; SSL, sessile serrated lesion; FIT, fecal immunochemical test; TCS, total colonoscopy

Table 2. Prevalence of Colorectal Polyps according to Clinical Features in the Study

	All subjects		AN (n=118)		SSL (n=295)		Adenoma (n=1238)		HP (n=786)		Others (n=91)	
				P-value		P-value		P-value		P-value		P-value
FIT, n (%)	Negative	1370 (56.2)	63 (4.6)	0.568	159 (11.6)	0.416	711 (51.9)	0.221	451 (32.9)	0.432	50 (3.6)	0.83
	TCS-only	1067 (43.8)	55 (5.2)		136 (12.7)		527 (49.4)		335 (31.4)		41 (3.8)	
Sex, n (%)	Male	1250 (51.3)	84 (6.7)	<0.001	159 (12.7)	0.352	761 (60.9)	<0.001	465 (37.2)	<0.001	57 (4.6)	0.032
	Female	1187 (48.7)	34 (2.9)		136 (11.5)		477 (40.2)		321 (27)		34 (2.9)	
Age group (years), n (%)	49-54	1254 (51.5)	45 (3.6)	0.003	153 (12.2)	0.901	573 (45.7)	<0.001	381 (30.4)	0.046	38 (3)	0.069
	55-60	1183 (48.5)	73 (6.2)		142 (12)		665 (56.2)		405 (34.2)		53 (4.5)	
Smoking, n (%)	Never	1279 (52.5)	43 (3.4)	<0.001	129 (10.1)	0.001	555 (43.4)	<0.001	329 (25.7)	<0.001	44 (3.4)	0.455
	Current or past	1158 (47.5)	75 (6.5)		166 (14.3)		683 (59)		457 (39.5)		47 (4.1)	
Alcohol, n (%)	Non-drinker	2140 (87.8)	105 (4.9)	0.774	255 (11.9)	0.448	1060 (49.5)	0.001	657 (30.7)	<0.001	79 (3.7)	0.329
	Drinker	297 (12.2)	13 (4.4)		40 (13.5)		178 (59.9)		129 (43.4)		12 (4)	
BMI, kg/m <sup>2</sup> , median (IQR)		23.4 (21.3-25.8)	24.3 (22.4-25.8)	0.022	23.8 (21.3-26.4)	0.375	23.9 (21.8-26.1)	<0.001	24 (21.9-26.6)	<0.001	24.8 (22.9-27.2)	<0.001
Family history of CRC, n (%)	Yes	288 (11.8)	24 (8.3)	0.008	41 (14.2)	0.248	153 (53.1)	0.415	90 (31.3)	0.737	12 (4.2)	0.622
	No	2149 (88.2)	94 (4.4)		254 (11.8)		1085 (50.5)		696 (32.4)		79 (3.7)	

FIT, fecal immunochemical test; BMI, body mass index; IQR, interquartile range; CRC, colorectal cancer; TCS, total colonoscopy; AN, advanced neoplasm; SSL, sessile serrated lesion; HP, Hyperplastic polyp

is a risk scoring system for AN in asymptomatic Asian patients (Yeoh et al., 2011). In this scoring system, age, sex, family history of CRC, and smoking habits are included as score factors, and the risk factors for AN were similar to the score factors described above; therefore, the risk factors for AN in Japanese people in their 50s were presumed to be similar to those in previous reports. Although a risk scoring system for SSL has not yet been developed, a meta-analysis reported smoking habits, habitual drinking, and high BMI as risk factors for SSL (Bailie et al., 2017). In this study, the smoking rate was higher in those with SSL than in those without SSL.

CRC screening adding TCS to FIT screening has been suggested as a combined screening method that may detect more instances of FIT-negative CRC, as compared to each screening on its own. Sekiguchi et al., (2016) revealed that TCS-based screening was the most cost-effective method. Nonetheless, considering the safety and capacity of TCS, they proposed undergoing TCS once within the 45–55-year age range as well as annual FIT-based screening. Moreover, a previous study examined risk stratification by combining the conventional risk scores of AN with FIT among patients aged  $\geq 40$  years and showed that high sensitivity to invasive CRC and AN could be achieved by performing TCS in patients with those at risk for high APCS scores, even with negative FIT results (Chiu et al., 2016).

Despite the aforementioned favorable results, offering TCS screening to all members of an at-risk population is extremely demanding because of the limited examination capacity. After applying the APCS score to the participants of this study, 43.2% (592) of patients in the FIT-negative group were at high risk for AN. If TCS was offered to those aged  $\geq 40$  years with negative FIT results and at risk for having high APCS scores, the number of TCS procedures would considerably increase. SSL was significantly high in patients who had a smoking habit. The combined rate of current smokers and past smokers in this study was 49.0% (671). Thus, TCS screening for smokers among FIT-negative subjects was also considered not realistic.

In CRC screening, an annual FIT should be combined with TCS performed once for patients aged 50 years onward (or at their first CRC screening after the age of 50 years), evaluated as being at high risk of developing CRC based on their APCS scores. With this methodology, the screening program shall be carried out within the capacity to perform examinations.

This study had several limitations. First, the participants could not be confirmed as having undergone CRC screening for the previous 5 years perfectly. A certain number of individuals who underwent FIT screening or TCS within 5 years might have been included. Second, the proportion of participants with high health consciousness might be high, and the prevalence of colorectal polyps could be lower than that expected in the general population. Third, the prevalence of SSL was high; because the well-trained endoscopist who performed TCS in this study might have detected more SSLs than other studies. Furthermore, the prevalence of TSA was extremely low; thus, the lesions were included in others, and we could not investigate specific characteristics in detail. Some types of TSA

should have been included in adenoma, but they were not considered to significantly affect the results of this study because of their small number.

In conclusion, by combining annual FIT with TCS for the population at high risk of CRC according to a scoring system, FIT-negative CRC and colorectal polyps may be detected, and the occurrence of interval cancers may be reduced.

## Author Contribution Statement

Conception and design, all authors; Data analysis and interpretation, SS, MM; Drafting of the article, SS; Critical revision of the article for important intellectual content, SS, MM; Final approval of the article, all authors.

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### Ethical Approval

The study was approved by the ethics committee of Hirosaki University Graduate School of Medicine (approval number: 2019-1091-1)

### Data availability statement

Due to the nature of this research, participants of this study did not agree for their data to be shared publicly, so supporting data is not available.

### Conflicts of interest

The Authors declare that there is no conflict of interest.

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