Positive Fecal Immunochemical Test Strongly Predicts Adenomas in Younger Adults With Fatty Liver and Metabolic Syndrome

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INTRODUCTION: **The incidence of early-onset colorectal cancer is increasing. This study explored the feasibility of fecal immunochemical test (FIT) and risk factors for predicting colorectal neoplasm in younger adults.**

METHODS: **This single-center study included 6,457 participants who underwent health examination from 2013 to 2016 including index colonoscopy (3,307 individuals aged 30–49 years as the younger adult group and 3,150 aged ≥50 years as the average-risk group). Primary outcomes were adenoma detection rate (ADR) and advanced ADR (AADR). Findings of younger participants were stratified by the results of FIT and clinical risk factors and were compared with those of the average-risk group.**

RESULTS: **Among participants aged 30–49 years, a positive FIT was associated with significantly higher ADR (28.5% vs 15.5, $P < 0.001$) and AADR (14.5% vs 3.7%, $P < 0.001$) than a negative FIT. Moreover, a positive FIT was associated with higher AADR in younger participants than in average-risk counterparts (14.5% vs 9.8%, $P = 0.028$). Although no single risk factor predicted FIT positivity in younger participants, nonalcoholic fatty liver disease was independently associated with higher ADR (odds ratio = 2.60, 95% confidence interval = 1.27–5.34, $P = 0.001$), and metabolic syndrome was independently predictive of higher AADR in younger participants than in average-risk participants (odds ratio = 3.46, 95% confidence interval = 1.66–7.21, $P = 0.001$).**

DISCUSSION: **A positive FIT in people aged 30–49 years implies a higher risk of colorectal neoplasm, particularly among patients with nonalcoholic fatty liver disease and metabolic syndrome.**

SUPPLEMENTARY MATERIAL accompanies this paper at http://links.lww.com/CTG/A496

INTRODUCTION

Colorectal cancer (CRC) is one of the most common malignancies worldwide (1). In general, the target population of CRC screening is people aged younger than or equal to 50 years because the risk in this population is higher than that in younger people. Although effective screening policies in some countries have led to an overall stability or even decline of CRC incidence, the incidence of early-onset CRC, that is CRC at younger than 50 years of age, seems to be increasing (2,3). By 2030, the incidence of early-onset CRC is expected to double among people aged 20–34 years and increase by approximately 30% among people aged 35–49 years (4).

Few recommendations have been made regarding a screening strategy for early-onset CRC. Although some experts have advocated lowering the age of screening to 45 years (5), this is not endorsed by other experts (6). Moreover, the best screening strategy for the younger population is yet to be determined. The fecal immunochemical test (FIT) is an effective and noninvasive screening method for average-risk people (7,8), but few studies have investigated its efficacy in younger adults. Jung et al. (9) found the FIT useful to detect advanced adenoma in asymptomatic people aged 35–49 years. However, the prevalence of CRC was relatively low (0.027%). Hence, for the younger

population, a risk-based approach, if available, seems reasonable over universal screening.

Several risk factors, including age 40 years or younger, obesity, diabetes mellitus, hypertension, smoking, nonalcoholic fatty liver disease (NAFLD), and metabolic syndrome, are associated with colorectal adenoma in the younger population (10–12). However, little is known about their impact in the presence of a positive FIT. From the perspective of cost-effectiveness, younger adults who present a higher-risk counterpart than average-risk counterparts will benefit most from screening. The study investigated the efficacy of the FIT in healthy younger adults and explored the additional risk factors for colorectal neoplasm in individuals with a positive FIT.

MATERIAL AND METHODS

Study design

This retrospective, single-center study included participants visiting the health examination department of E-Da Hospital, Kaohsiung, Taiwan, between January 2013 and December 2016. It was approved by the Institutional Review Board of E-Da Hospital (No. EMRP40108N). Similar to the previous studies (9,13), participants were asymptomatic people who underwent health checkups at their own expense or following national labor laws requirements.

The inclusion criteria were individuals aged 20–49 years (younger adult group) who received both FIT and index colonoscopy during the checkup and participants aged younger than or equal to 50 years (average-risk group) who received index colonoscopy, regardless of whether FIT was performed. In either group, colonoscopy within 6 months after FIT was considered in the analysis. The exclusion criteria were as follows: (i) duplicated cases owing to previous checkups, (ii) a history of CRC or colorectal resection, (iii) a history of colonoscopy within 10 years, and (iv) poor colon preparation.

FIT and colonoscopy procedures

The specimen for FIT (OC-Sensor kit; Eiken Chemical, Tokyo, Japan) was obtained and sent to the hospital within 1 week before the examination. The results are expressed in nanograms of hemoglobin per milliliter buffer (ng Hb/mL), and the cutoff value of positivity was set at 100 ng Hb/mL.

All colonoscopies were performed by well-experienced endoscopists who had performed >1,000 colonoscopy examinations, with ≥300 procedures conducted annually, using the EvisLucera CV-260 colonoscope (Olympus Medical Systems, Tokyo, Japan). Bowel preparation regimens were split-dose sodium phosphate or 2 L of polyethylene glycol solution. During the examination, the decision of biopsy, snare polypectomy, or endoscopic mucosal resection for the colorectal neoplasm was at the discretion of the endoscopist. However, the presence of adenoma, advanced adenoma, or CRC was diagnosed through histologic evaluation. In the case of difficult-to-treat polyps, subsequent endoscopic or surgical resection was performed within 6 months after index colonoscopy. Accordingly, polyps and lesions that were not removed at our institute within 6 months of index colonoscopy were not included in the analysis, regardless of endoscopic diagnosis.

Outcome assessment

Primary outcomes were adenoma detection rate (ADR) and advanced ADR (AADR) of younger participants with positive FIT as compared to those with negative FIT and average-risk group. ADR and AADR were calculated as the proportion of cases with detected adenomas and advanced adenomas, respectively, divided by the total number of participants in each group. Advanced adenoma refers to polyps (i) with high-grade dysplasia, carcinoma *in situ*, or intramucosal carcinoma; (ii) ≥1 cm in size; or (iii) with >25% villous component.

Participants' baseline characteristics, including age, sex, underlying disease, laboratory, and endoscopic findings, were thoroughly recorded. Obesity was defined as body mass index >27 kg/m². NAFLD was defined as ultrasonographically detected fatty liver disease in the absence of substantial alcohol intake. Preexisting diagnosis of any metabolic diseases, such as hypertension, diabetes mellitus, dyslipidemia, and metabolic syndrome, was noted. In addition, participants with systolic blood pressure ≥180 mm Hg or diastolic blood pressure ≥120 mm Hg with sustained high-abnormal readings at 2 consecutive examination were considered to have hypertension. Diabetes mellitus was defined as fasting glucose ≥126 mg/dL or glycosylated hemoglobin ≥6.5%. Dyslipidemia was defined as either triglyceride ≥150 mg/dL, total cholesterol ≥200 mg/dL, high-density lipoprotein cholesterol <40 mg/dL in men or <50 mg/dL in women, or low-density lipoprotein cholesterol ≥130 mg/dL.

Metabolic syndrome was defined as the presence of at least 3 of the following findings: central obesity (waist circumference ≥90 cm in men or ≥80 cm in women), elevated blood pressure (systolic blood pressure ≥130 mm Hg or diastolic blood pressure ≥80 mm Hg in 2 consecutive readings), fasting glucose impairment (>100 mg/dL), elevated triglyceride (≥150 mg/dL), and reduced high-density lipoprotein cholesterol (<40 mg/dL in men or <50 mg/dL in women). A family history of CRC was not confined to first-degree relatives.

Statistical analysis

In this study, continuous variables are presented as mean ± SD and were compared using Student t tests. Categorical variables are presented as numbers (percentages) and were compared using the χ^2 test. $P < 0.05$ was considered statistically significant. For the comparison of primary outcomes, odds ratio (OR) with 95% confidence interval (CI) was calculated. All statistical analyses were conducted using SPSS version 26.0 (IBM Corp, Armonk, NY).

To evaluate the impact of FIT results for ADR and AADR, younger adult participants were stratified by age (20–29, 30–39, and 40–49 years) and the FIT results (positive or negative). Because the primary outcomes were not statistically significant for participants aged 20–29 years in the preliminary analysis, further analysis included only participants aged 30–49 years versus the average-risk counterparts.

Clinical risk factors, including age, sex, obesity, smoking habits, hypertension, diabetes mellitus, dyslipidemia, metabolic syndrome, and family history of CRC, were analyzed using the χ^2 test to identify factors associated with increased ADR and AADR. Factors that were statistically significant were included in the multivariable binary logistic regression model with backward selection. The diagnostic power of FIT was evaluated using the receiver operating characteristic curve and was displayed as the area under the curve (AUC), and sensitivity analysis was performed to define to best cutoff value, with the highest accuracy (minimal false-negative and false-positive results) determined according to the AUC.

RESULTS

Study participants and baseline characteristics

Overall, 59,413 records were retrieved from the database. The flowchart of participant selection is presented in Figure 1. After applying the exclusion criteria, 6,906 participants (men, 57.2%) were included in the final analysis. Among these participants, 3,756 were younger adults (of whom 3,307 were 30–49 year old), and 3,150 were included in the average-risk group.

The baseline characteristics of each group are summarized in Table 1. Younger adults had a mean age of 40.2 years, and the average-risk group had a mean age of 58.0 years. Slight male predominance was found in the younger adult group (59.5% vs 55.7%, $P < 0.001$). Compared with younger adults, a significantly higher proportion of participants in the average-risk group had adenoma (16.2% vs 28.5%, $P = 0.001$), advanced adenoma (4.3% vs 9.6%, $P < 0.001$), and CRC (0.2% vs 0.8%, $P < 0.001$). Notably, all younger adults with CRC were aged 30–49 years.

In addition, compared with those in the younger adult group, participants in the average-risk group were more likely to have a positive FIT (5.6% vs 8.2%, $P < 0.001$) and metabolic diseases including hypertension (6.3% vs 24.7%, $P < 0.001$), diabetes mellitus (4.2% vs 17.2%, $P < 0.001$), dyslipidemia (64.0% vs 76.1%, $P < 0.001$), metabolic syndrome (24.6% vs 37.5%, $P < 0.001$), and NAFLD (40.0% vs 45.6%, $P < 0.001$). However, a higher proportion of younger adults were current smokers (21.7% vs 15.6%, $P < 0.001$).

Association of ADR and AADR with FIT among different age groups

ADR was compared between younger adult participants with positive and negative FIT results and average-risk group counterparts (Figure 2a). ADR of average-risk participants was 28.5%. ADRs among participants aged 20–29, 30–39, 40–49, and 30–49 years with a positive FIT were 5.6%, 20.8%, 33.9%, and 28.5%, respectively, and with a negative FIT was 3.2% ($P = 0.594$), 9.6% ($P = 0.002$), 20.1% ($P = 0.001$), and 15.5% ($P < 0.001$), respectively.

AADR was 9.6% among average-risk participants. AADR among younger adult participants aged 20–29, 30–39, 40–49, and 30–49 years with positive FITs were 0%, 11.7%, 16.5%, and 14.5%, respectively, and with negative FITs were 0.9%, 1.9%, 5.2%, and 3.7%, respectively (Figure 2b). Similar to the comparative results of ADR, AADR was significantly associated with FIT among participants aged 30–39, 40–49, and 30–49 years (all $P < 0.001$), but not among those aged 20–29 years ($P = 0.681$).

Association of ADR and AADR with any clinical factor among younger adults

We explored the association of ADR and AADR (Table 2) with the clinical risk factors according to different age groups among younger adults. For participants aged 20–29 years, no factor significantly affected ADR and AADR. However, for participants aged 30–49 years, ADR was significantly increased in the presence of male sex (20.5% vs 10.0%, $P < 0.001$), obesity (21.8% vs 16.2%, $P < 0.001$), diabetes mellitus (25.0% vs 15.9%, $P = 0.004$), hypertension (21.5% vs 15.9%, $P = 0.032$), and current smoking (28.0% vs 13.0%, $P < 0.001$). AADR was significantly increased in the presence of male sex (5.7% vs 2.2%, $P < 0.001$), obesity (6.3% vs 3.9%, $P = 0.007$), metabolic syndrome (6.1% vs 3.7%, $P = 0.003$), diabetes mellitus (9.3% vs 4.1%, $P = 0.003$), NAFLD (5.4%
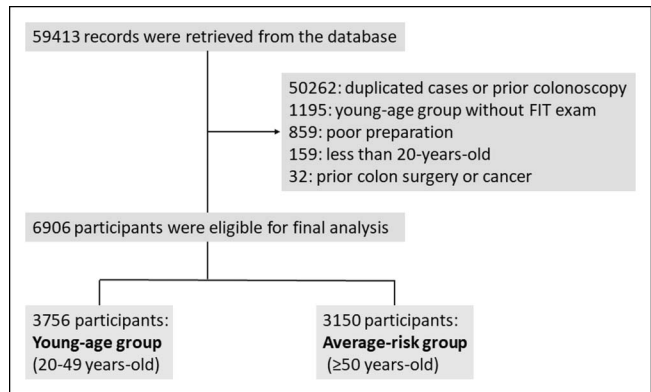
Figure 1. Flowchart of participant selection. FIT, fecal immunochemical test.

vs 3.6%, $P = 0.01$), and current smoking (7.7% vs 3.4%, $P < 0.001$). No single risk factor, including positive FIT, caused the ADR of younger adults to be significantly higher than that of average-risk groups. However, a positive FIT was associated with the significantly higher AADR of the younger adults than average-risk counterparts (14.5% vs 9.8%, $P = 0.028$).

Furthermore, we compared the ADR (Table 3) and AADR (Table 4) of younger, FIT-positive participants with specific clinical factors to that of all average-risk participants. Univariable analysis revealed that male sex (OR = 1.56, 95% CI = 1.04–2.32, $P = 0.028$), obesity (OR = 2.51, 95% CI = 1.22–5.15, $P = 0.012$), metabolic syndrome (OR = 2.11, 95% CI = 1.11–4.09, $P = 0.022$), and NAFLD (OR = 1.91, 95% CI = 1.12–3.05, $P = 0.006$) were associated with a higher ADR in younger adults than in average-risk adults. However, multivariable analysis indicated NAFLD (OR = 2.69, 95% CI = 1.36–5.33, $P = 0.005$) as the only independent risk factor for a higher ADR, and female sex (OR 0.32, 95% CI = 0.16–0.64, $P = 0.001$) was associated with significantly lower ADR.

Univariable analysis revealed the following factors to be associated with higher AADR: male sex (OR = 2.30, 95% CI = 1.40–3.76, $P = 0.001$), obesity (OR = 2.87, 95% CI = 1.22–6.74, $P = 0.016$), metabolic syndrome (OR = 3.49, 95% CI = 1.67–7.28, $P = 0.001$), dyslipidemia (OR = 1.73, 95% CI = 1.00–2.99, $P = 0.048$), NAFLD (OR = 2.52, 95% CI = 1.46–4.33, $P = 0.001$), and current smoking (OR = 2.43, 95% CI = 1.34–5.10, $P = 0.027$). However, multivariable analysis revealed that metabolic syndrome (OR = 3.46, 95% CI = 1.66–7.21, $P = 0.001$) was the only independent risk factor associated with increased AADR among younger adults.

Diagnostic yield of FIT and its association with clinical risk factors in younger adults

In the exploration of the association between FIT positivity and clinical risk factors in the younger adults, no single factor predicted significantly higher FIT positivity (see Supplementary Table 1, Supplementary Digital Content 1, http://links.lww.com/CTG/A496). The presence of dyslipidemia was associated with a lower proportion of FIT positivity (4.9% vs 6.8%, $P = 0.02$).

For the diagnostic ability of FIT, the sensitivities of FIT for adenoma detection among participants aged 30–39, 40–49, and ≥50 years were 10.8%, 9.5%, and 14.0%, respectively, and the specificities were 95.3%, 95.1%, and 94.1%, respectively; for advanced adenoma

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Table 1. Baseline characteristics of the included patients

Group (years-old)	Young-age group				Average-risk	P value
	20–29	30–39	40–49	30–49	≥50	
No. of patients	449	1,450	1857	3,307	3,150	
Age (mean ± SD)	26.2 ± 2.5	35.3 ± 2.7	44.3 ± 2.8	40.2 ± 5.3	58.0 ± 6.1	<0.001[a]
Male sex, n (%)	228 (50.8)	789 (54.4)	1,179 (63.5)	1968 (59.5)	1755 (55.7)	0.002[a]
Body mass index (kg/m^2, mean ± SD)	22.7 ± 4.6	23.5 ± 4.1	24.2 ± 3.6	23.9 ± 3.8	24.4 ± 3.4	<0.001[a]
Obesity, n (%)	67 (14.9)	248 (17.1)	370 (19.9)	618 (18.7)	614 (19.5)	0.400
Smoking habits						<0.001[a]
Current smoker, n (%)	75 (16.7)	284 (19.7)	430 (23.2)	714 (21.7)	488 (15.6)	<0.001[a]
Ex-smoker, n (%)	9 (2.0)	47 (3.3)	103 (5.6)	150 (4.6)	198 (6.3)	0.015[a]
Hypertension, n (%)	1 (0.2)	39 (2.7)	170 (9.2)	209 (6.3)	778 (24.7)	<0.001[a]
Diabetes mellitus, n (%)	4 (0.9)	20 (1.4)	120 (6.5)	140 (4.2)	541 (17.2)	<0.001[a]
Fasting sugar (mg/dL, mean ± SD)	90.8 ± 9.4	95.1 ± 14.4	101.5 ± 22.2	98.7 ± 19.4	108.7 ± 28.7	<0.001[a]
HbA1C (%, mean ± SD)	5.2 ± 0.4	5.3 ± 0.5	5.5 ± 0.7	5.4 ± 0.7	5.9 ± 1.0	<0.001[a]
Dyslipidemia, n (%)	178 (39.6)	818 (56.6)	1,289 (69.7)	2,107 (64.0)	2,333 (76.1)	<0.001[a]
Metabolic syndrome (%)	42 (9.4)	271 (18.7)	544 (29.4)	815 (24.6)	1,181 (37.5)	<0.001[a]
AST (IU/ml, mean ± SD)	23.4 ± 12.2	26.3 ± 15.7	28.1 ± 15.6	27.3 ± 15.7	30.4 ± 27.9	<0.001[a]
ALT (IU/ml, mean ± SD)	23.4 ± 20.9	31.4 ± 29.7	32.9 ± 25.6	32.3 ± 27.5	31.6 ± 39.9	0.447
NAFLD	77 (17.1)	466 (32.1)	857 (46.2)	1,323 (40.0)	1,435 (45.6)	<0.001[a]
Positive FIT	18 (4.0%)	77 (5.3%)	109 (5.9%)	186 (5.6)	207 (8.2%)[b]	<0.001[a]
CRC family history	36 (8.0)	117 (8.1)	118 (6.4)	235 (7.1)	209 (6.6)	0.454
Adenoma (%)	15 (3.3)	148 (10.2)	389 (20.9)	537 (16.2)	897 (28.5)	<0.001[a]
Advanced adenoma (%)	4 (0.9)	35 (2.4)	108 (5.8)	143 (4.3)	302 (9.6)	<0.001[a]
Serrated adenoma (%)	4 (0.9)	32 (2.2)	54 (2.9)	86 (2.6)	83 (2.6)	0.929
CRC (%)	0	3 (0.2)	5 (0.3)	8 (0.1)	24 (0.8)	0.003[a]

Data were compared between the younger adults and the average-risk group.
AST, aspartate aminotransferase; ALT, alanine aminotransferase; CRC, colorectal cancer; FIT, fecal immunochemical study; NAFLD, nonalcoholic fatty liver disease.
[a]$P < 0.05$.
[b]Only 2,518 participants in the average-risk group received FIT.

detection, the sensitivities were 11.7%, 16.5%, and 25.9%, respectively, and the specificities were 95.2%, 94.8%, and 93.7%, respectively. For participants aged 30–49 years, the sensitivity, specificity, and positive and negative predictive values were 9.9%, 95.2%, 28.5%, and 84.5%, respectively, for adenoma and 18.9%, 95.0%, 14.5%, and 96.3%, respectively, for advanced adenoma.

Sensitivity analysis was performed by comparing the AUC for advanced adenoma for participants aged 30–49 years with different cutoff values of FIT. These cutoff values selected were 50, 100, and 200 ng Hb/mL. When the cutoff was set at 100 ng Hb/mL, the AUC for advanced adenoma of FIT was 0.569. However, the AUC was not significantly different when the cutoff value was set at either 50 ng Hb/mL (0.570, $P = 0.957$) or 150 ng Hb/mL (0.557, $P = 0.204$). In addition, the presence of metabolic syndrome did not improve the AUC (0.573 vs 0.517, $P = 0.330$).

DISCUSSION

Nearly 10%–20% of CRC cases are diagnosed before the age of 50 years (14,15), and early-onset CRC has become a leading cause of cancer death in that population (16). Although the effectiveness of screening tests is largely unknown in the younger population, it

is reasonable to screen at-risk younger adults. The incidence of CRC is low in this population, and studies have suggested that younger adults with advanced adenoma have a similar risk of metachronous advanced neoplasia as the average-risk counterparts (17,18); therefore, the current study used both ADR and AADR as the primary outcomes of evaluation.

Our findings revealed that a positive FIT in people aged 30–49 was predictive of significantly higher ADR and AADR with the index colonoscopy and that the risk of advanced adenoma was even higher in people aged 40–49 years. Moreover, we found that NAFLD and metabolic syndrome were independent risk factors for higher ADR and AADR, respectively. The first part of the findings is similar to the results of Jung et al. (9) although they used the age of 35–49 years as the cutoff point. However, they did not explore parameters other than male sex and smoking, such as metabolic diseases, which were considered in the present study.

Similar to CRC in average-risk people, diabetes mellitus, obesity, and metabolic syndrome are risk factors for early-onset CRC, and insulin resistance is probably the mutual pathophysiology. NAFLD, however, is a precursor of metabolic syndrome and diabetes mellitus (19), and there has been some evidence
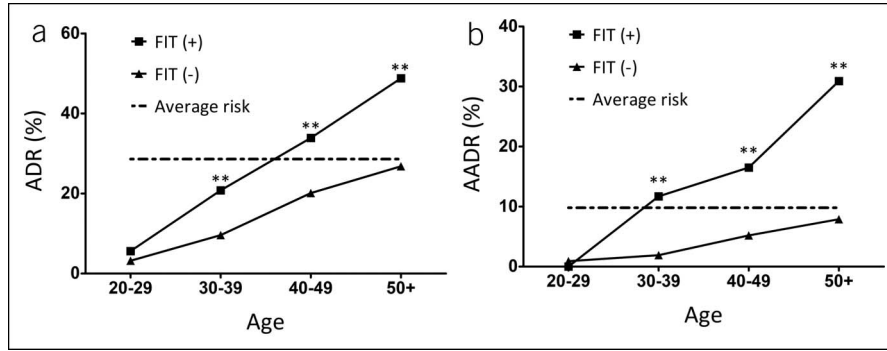
Figure 2. (**a**) Comparison of ADR based on the results of FIT among different age groups. **$P < 0.01$. (**b**) Comparison of AADR based on the results of the FIT among different age groups. **$P < 0.01$. ADR, adenoma detection rate; AADR, advanced ADR; FIT, fecal immunochemical test.

linking its presence to colorectal neoplasms (20–22). Although diabetes mellitus and family history of CRC are established risk factors (5,6), we did not find the association between them and the risk of adenoma in younger FIT-positive adults. This may be explained by the low prevalence of diabetes mellitus in this subgroup (8/182, 4.3%). Similarly, family history of CRC was also not significant in this cohort likely because the family history in the database was not confined to first-degree relatives.

In this study, our findings suggest that positive FIT is correlated with higher colorectal neoplasms especially for younger

Table 2. Adenoma and advanced adenoma detection rate in the presence and absence of the clinical risk factors

	Adenoma detection rate in each age group, %									
	20–29		30–39		40–49		30–49		50+	
Risk factor	+	−	+	−	+	−	+	−	+	−
Male	4.4	2.3	12.0[a]	8.0[a]	26.1[a]	11.9[a]	20.5[a]	10.0[a]	35[a].5	19.6[a]
FIT	5.6	3.2	20.8[a]	9.6[a]	33.9[a]	20.1[a]	28.5[a]	15.5[a]	48.8[a]	26.8[a]
Obesity	6.0	2.9	8.5	10.6	30.8[a]	18.5[a]	21.8[a]	16.2[a]	33.6[a]	27.3[a]
MS	4.8	3.2	12.2	9.8	27.2[a]	18.4[a]	22.2	14.3	33.3[a]	25.6[a]
Dyslipidemia	4.5	2.6	11.1	8.6	22.5[a]	17.1[a]	18.1	12.6	28.6	27.9
Diabetes mellitus	0	3.4	20	10.1	25.8	20.6	25.0[a]	15.9[a]	30.2	28.0
Hypertension	0	3.3	7.7	10.3	24.7	20.6	21.5[a]	15.9[a]	33.3[a]	26.9[a]
NAFLD	6.5	2.7	10.9	9.9	25.0[a]	17.4[a]	20.0	13.7	31.7[a]	25.7[a]
Family history	0	3.6	6.8	10.5	27.1	20.5	17.0	16.2	31.1	28.3
Current smoker	4.0	3.2	19.7[a]	7.8[a]	33.5[a]	17.2[a]	28.0[a]	13.0[a]	39.8[a]	26.4[a]

	Advanced adenoma detection rate in each age group, %									
	20–29		30–39		40–49		30–49		50+	
Risk factor	+	−	+	−	+	−	+	−	+	−
Male	1.8*	0*	2.9	1.8	9.6[a]	2.7[a]	5.7[a]	2.2[a]	12.5[a]	5.9[a]
FIT	0	0.9	11.7[a]	1.9[a]	16.5[a]	5.2[a]	14.5[a]	3.7[a]	30.9[a]	7.9[a]
Obesity	1.5	0.8	2.0	2.5	9.2[a]	5.0[a]	6.3[a]	3.9[a]	12.5[a]	8.9[a]
MS	0	1.0	2.6	2.4	7.9[a]	5.0[a]	6.1[a]	3.7[a]	12.4[a]	7.9[a]
Dyslipidemia	1.1	0.7	2.2	2.6	6.3	4.6	4.7	3.5	9.5	9.8
Diabetes mellitus	0	0.9	5.0	2.4	10[a]	5.5[a]	9.3[a]	4.1[a]	10.9	9.3
Hypertension	0	0.9	0	2.5	7.6	5.6	6.2	4.2	12.9[a]	8.5[a]
NAFLD	2.6	0.5	3.2	2.0	6.7	5.1	5.4[a]	3.6[a]	11.4[a]	8.1[a]
Family history	0	0.9	2.6	2.4	9.3	5.6	6.0	4.2	7.7	9.7
Current smoker	0	1.1	3.9	2.2	10.2	4.5	7.7	3.4	16.4[a]	8.4[a]

FIT, fecal immunochemical study; MS, metabolic syndrome; NAFLD, nonalcoholic fatty liver disease.
[a]Statistically significant (P value < 0.05) for the difference of rate between the specific positive and negative clinical risk factors in the same-age group.

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Table 3. Adenoma detection rate in younger participants (30–49 years of age) with a positive FIT with any specific risk factor versus average-risk counterparts

Risk factor	ADR, %	OR (95% CI): 30–49 year-old FIT (+) vs average risk			
		Univariable analysis	P value	Multivariable analysis[b]	P value
Male	38.3	1.56 (1.04–2.32)	0.028[a]	0.91 (0.52–1.61)	0.768
Obesity	50	2.51 (1.22–5.15)	0.012[a]	1.84 (0.76–4.44)	0.175
Metabolic syndrome	45.9	2.13 (1.11–4.09)	0.022[a]	1.30 (0.51–3.31)	0.577
Dyslipidemia	31.1	1.13 (0.74–1.73)	0.567		
Diabetes mellitus	50	2.51 (0.62–10.06)	0.193		
Hypertension	50	2.51 (0.87–7.18)	0.086		
NAFLD	43.2	1.91 (1.20–3.05)	0.006[a]	2.69 (1.36–5.33)	0.005[a]
Family history	30.8	1.11 (0.34–3.63)	0.855		
Current smoker	35.9	1.40 (0.72–2.71)	0.310		
Average-risk	28.5	1 (reference)		1 (reference)	

FIT, fecal immunochemical study; NAFLD, nonalcoholic fatty liver disease.
[a]$P < 0.05$.
[b]Binary logistic regression.

adults with NAFLD and metabolic syndrome. As demonstrated in the results, for most younger adults who had a negative FIT, the risk of colorectal adenoma was generally low. Although individuals with multiple clinical risk factors may remain at a high risk of developing adenoma (11), most of them do not require early colonoscopy. Interestingly, a cost-effective model by Wong et al. (23) also suggested FIT rather than colonoscopy as the screening tool for younger adults with NAFLD. In addition to the lower cost, FIT is also more convenient and less invasive than colonoscopy. Despite the several advantages of FIT, more studies are necessary to evaluate the utility of FIT as the screening tool for the younger patients, and the comparison versus colonoscopy in the cost and efficacy also has to be performed to determine the optimal screening strategy.

The study has some limitations. First, this was a retrospective study. Second, we did not consider the effectiveness of previous FIT, and the surveillance interval for a negative FIT remains unclear. Third, we did not include the location and numbers of lesions in the analysis. Although a fecal occult blood test is traditionally believed to be more sensitive for distal colon lesions traditionally, one study found FIT to be equally sensitive for proximal and distal colon neoplasia (24). Fourth, we did not analyze sessile serrated adenomas owing to the generally low prevalence in this cohort. Finally, the clinical risk factors evaluated in this study might have cofounding effects on each other even in multivariable analysis. For example, patients with obesity are more likely to have fatty liver and metabolic syndrome, and

Table 4. Advanced adenoma detection rate in younger participants (30–49 years of age) with positive FIT with any specific risk factor versus average-risk counterparts

Risk factor	AADR, %	OR (95% CI): 30-49 year-old FIT (+) vs average risk			
		Univariable analysis	P value	Multivariable analysis[b]	P value
Male	13.6	2.30 (1.40–3.76)	0.001[a]	1.74 (0.95–3.17)	0.068
Obesity	23.3	2.87 (1.22–6.74)	0.016[a]	0.85 (0.25–2.85)	0.802
Metabolic syndrome	27.0	3.49 (1.67–7.28)	0.001[a]	3.46 (1.66–7.21)	0.001[a]
Dyslipidemia	15.5	1.73 (1.00–2.99)	0.048[a]	0.66 (0.26–1.69)	0.389
Diabetes mellitus	12.5	1.34 (0.16–10.98)	0.781		
Hypertension	21.4	2.57 (0.71–9.27)	0.149		
NAFLD	21.6	2.60 (1.47–4.58)	0.001[a]	1.69 (0.82–4.23)	0.255
Family history	23.1	2.82 (0.77–10.33)	0.116		
Current smoker	20.5	2.43 (1.34–5.10)	0.027[a]	0.98 (0.35–2.74)	0.972
Average-risk	9.6	1 (reference)		1 (reference)	

FIT, fecal immunochemical study; NAFLD, nonalcoholic fatty liver disease.
[a]$P < 0.05$.
[b]Binary logistic regression.

metabolic syndrome is associated with diabetes mellitus occurrence owing to underlying insulin resistance. Further research is necessary to validate our findings and develop a prediction model to more accurately identify younger adults who would be candidates for FIT.

In conclusion, a positive FIT in individuals aged 30–49 years may imply a higher risk of colorectal neoplasm, especially for patients with NAFLD and metabolic syndrome. Future studies are warranted to determine the utility of FIT and optimal time interval of surveillance with an initially negative test.

Study Highlights

WHAT IS KNOWN

✓ Early onset CRC has become more frequent.
✓ FIT predicts colorectal adenoma in younger adults.
✓ The performance of FIT in different risk groups are largely unknown.

WHAT IS NEW HERE

✓ FIT is the strongest factor to predict advanced adenomas in younger adults.
✓ Positive FIT is associated with higher risk in adults aged 30 and more.
✓ Metabolic syndrome and fatty liver with positive FIT are among highest risk.

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