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ORIGINAL ARTICLE

Risk Factors Such as Male Sex, Smoking, Metabolic Syndrome, Obesity, and Fatty Liver Do Not Justify Screening Colonoscopies Before Age 45

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Abstract
Background Recently, many studies have reported that male sex, smoking, fatty liver, metabolic syndrome (MetS), and obesity are risk factors for colorectal neoplasia (CRN). However, current guidelines recommend that persons at average risk of colorectal cancer begin screening colonoscopy at age 50 years without consideration of those risk factors.
Aim To investigate an appropriate time to start screening colonoscopies in persons with risk factors for CRN.
Methods We performed a cross-sectional study on 27,894 Korean aged ≥30 years who underwent a first colonoscopy as part of a health screening program. To compare the efficacy of colonoscopic screening for the detection of advanced CRN among age groups with risk factors, we calculated the number needed to screen (NNS) to identify 1 patient with advanced CRN.
Results The NNS for those 30–39 years old with all risk factors, male gender, smoking (≥10 pack-years), MetS, obesity, and fatty liver, was higher than that for ≥50-year-old female subjects (55.4 vs. 26.4). The NNS for those 40–44 years old with all risk factors (37.1) was also higher than that for ≥50-year-old female subjects. However, the NNS for those 45–49 years old with risk factors (16.9–22.9) was lower than that for ≥50-year-old women.
Conclusions The efficacy of colonoscopic screening in people 30–44 years old with multiple risk factors is lower than that in ≥50-year-old women. Risk factors such as male sex, smoking, MetS, obesity, and fatty liver do not justify starting screening colonoscopies before age 45.

Keywords Screening colonoscopy · Colorectal neoplasia · Risk factor

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Introduction

Current guidelines recommend that persons at average risk of colorectal cancer (CRC) begin screening colonoscopies at age 50 years [1–3]. Although CRC-associated mortality is effectively reduced by removing precursor lesions [4], the incidence of CRC is still likely to increase in Asian countries, including Korea [5, 6]. Much effort in identifying potentially modifiable risk factors has kept pace with the increase in incidence of CRC. Recently, many studies have reported that male sex, smoking, metabolic syndrome (MetS), obesity, and fatty liver as well as age are risk factors for colorectal neoplasia (CRN) [7–13]. Moreover, several studies have demonstrated that the risk factors for CRN also apply to persons younger than 50 [14–16]. Therefore, some researchers suggest that persons with those risk factors might benefit from starting screening colonoscopies before age 50. Our preceding study found that male sex, smoking, fatty liver, MetS, and obesity were independent risk factors for CRN in people aged 30–49 years and concluded that persons with those risk factors might benefit from a screening colonoscopy before age 50 [17]. However, our preceding study did not establish the age at which such people should be screened, which led us to wonder about the appropriate start time for screening colonoscopy in persons with multiple risk factors.

Because the medical cost for colonoscopy in Korea is very low, Korean people tend to undergo early and frequent colonoscopies. Considering the Korean healthcare environment, the identification of a proper start time for screening colonoscopies in persons with risk factors for CRN is clinically important. Such efforts could reduce unnecessary colonoscopies in persons aged <50 years. Therefore, we conducted a further study to determine whether persons with risk factors for CRN, including male sex, smoking, fatty liver, MetS, and obesity, which were identified in our preceding study, and especially those with multiple risk factors, should start screening colonoscopies in their 30s or 40s.

Patients and Methods

Study Population

We performed this study using the same cohort as in our preceding study [17]. The study population consisted of examinees who had undergone a colonoscopy as part of a comprehensive health screening program at the Total Healthcare Center of Kangbuk Samsung Hospital, Seoul and Suwon, Korea, between 2010 and 2011 ($N = 62{,}171$) [17]. In Korea, the Industrial Safety and Health Law requires employees to participate in annual or biennial health examinations. Approximately 60 % of the participants were employees of various companies or local governmental organizations or their spouses, and the remaining participants registered individually for the program. As part of their welfare policy, companies often subsidize comprehensive health examinations, including colonoscopy, regardless of current guidelines. Thus, our database contains a relatively large group of young people.

Before each colonoscopy, general practitioners conducted standard interviews to ensure that all participants were asymptomatic. They routinely asked whether the subjects have hematochezia, lower abdominal pain, recent changes in bowel habits or any other intestinal symptoms. Subjects with intestinal symptoms were urged to seek medical care.

Exclusion criteria were as follows: a history of prior colonic examination, colorectal surgery, or colorectal neoplasia ($n = 10{,}421$), a history of inflammatory bowel disease ($n = 173$), a family history of CRC ($n = 1155$), an incomplete colonoscopy because of poor bowel preparation or a colonoscopy in which the cecum was not reached ($n = 5455$), lack of adequate biopsy ($n = 853$), incomplete questionnaire answers ($n = 15{,}992$), missing data on anthropometry ($n = 127$), and persons aged <30 years ($n = 101$). After those exclusions, the total number of eligible subjects was 27,894 (Fig. 1). We excluded the subjects with family history of CRC since they may affect the outcome and they would be screened under current recommendations. Family history of CRC was defined as CRC in one or more first-degree relatives at any age.

This study was approved by the Institutional Review Board of Kangbuk Samsung Hospital, which exempted the requirement for informed consent because we accessed only de-identified data retrospectively.

Measurements and Definitions

Data on medical history and health-related behavior were collected through a self-administered questionnaire, whereas physical measurements and serum biochemical parameters were measured by trained staff. The presence or absence of fatty liver was determined using abdominal ultrasound. MetS was diagnosed if 3 or more of the following criteria were satisfied: abdominal obesity, elevated fasting blood glucose (FBG) levels (≥100 mg/dL) or taking glucose-lowering medications, elevated blood pressure (≥130 mmHg systolic, ≥85 mmHg diastolic) or taking antihypertensive drugs, elevated triglycerides (≥150 mg/dL), and reduced HDL-C levels (<40 mg/dL in men and <50 mg/dL in women) [18]. Because waist circumference measurements were not available for all subjects, we substituted overall obesity for abdominal obesity. Overall obesity was defined as a body mass index ≥25 kg/m^2, the proposed cutoff for the diagnosis of obesity in Asians [19].

Blood samples were taken from the antecubital vein after at least a 10-h fast. Serum levels of total cholesterol and triglycerides were determined using an enzymatic colorimetric assay. Serum fasting glucose levels were measured using the hexokinase method.

Risk factors for CRN were designated as male sex, smoking status (≥10 pack-years), fatty liver, MetS, and obesity based on the results of our preceding study [17].

Colonoscopy and Histologic Examination

Colonoscopy was performed by 1 of 13 experienced gastroenterologists using the EVIS LUCERA CV-260 colonoscope (Olympus). All bowel cleansing was performed using 4 L of polyethylene glycol solution (Taejoon Pharm. Inc., Seoul, Korea). All polypoid lesions were biopsied or removed and histologically assessed by experienced pathologists.

Polyps were classified by number, size, and histologic characteristics (tubular, tubulovillous, or villous adenoma; hyperplastic polyp; sessile serrated adenoma or traditional serrated adenoma). Hyperplastic polyps, inflammatory polyps, or lipoma were considered as normal findings. The

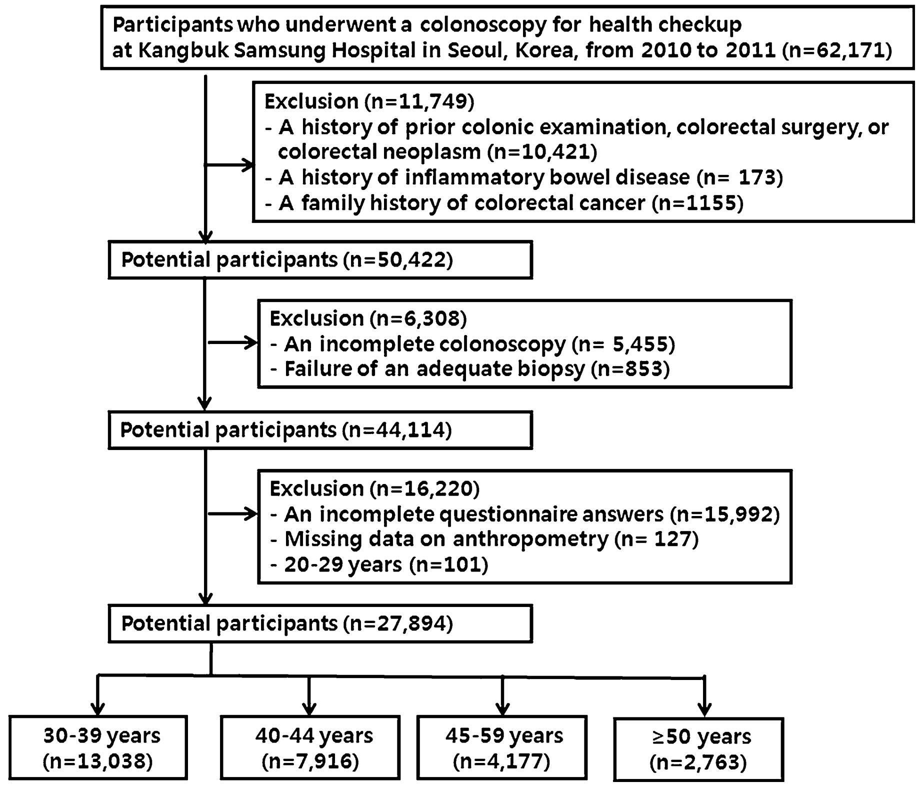

Fig. 1 Flow diagram for selection of study subjects

grade of dysplasia was classified as low or high. An advanced CRN was defined as a cancer or high-risk adenoma (any adenoma larger than 1 cm, 3 or more adenomas, any adenoma with a villous component, or high-grade dysplasia) [20].

Statistical Analysis

Data were stratified by age into four groups (30–39, 40–44, 45–49, and ≥50 years). We used the Chi-square (or Fisher's exact test) or linear-by-linear association tests to compare categorical variables between the groups. To compare the efficacy of colonoscopic screening in detecting advanced CRN among age groups with risk factors, we calculated the number needed to screen (NNS) to identify 1 patient with advanced CRN. For each variable, we report the odds ratios (ORs) and 95 % confidence intervals (CIs) and consider *P* values <0.05 statistically significant. We used the software program SPSS version 18 (SPSS, Inc, Chicago, IL, USA) for statistical analyses.

Results

Basic Characteristics of the Study Population

We analyzed a total of 27,894 participants (Fig. 1). Table 1 shows subjects' clinical characteristics by age group. Male sex was more predominant in the younger age group than in the older age group (*P* for trend = 0.002). The proportions of smokers, MetS, obesity, and fatty liver increased with the age category (*P* for trend <0.001, <0.001, 0.005, and <0.001, respectively).

The Efficacy of Screening Colonoscopy for Detecting Advanced CRN Among Age Groups with Risk Factors

The prevalence of advanced CRN increased with the age category: Among those 30–39, 40–44, 45–49, and ≥50 years old, the occurrence of advanced CRN was 0.7, 1.8, 3.5, and 7.9 %, respectively (*P* for trend <0.001). The NNS to find 1 advanced CRN decreased with increasing age. The NNS among those 30–39, 40–44, 45–49, and ≥50 years old was 148.2, 56.5, 28.4, and 12.7, respectively. The NNS for men was lower than that for women in all age subgroups (Table 2).

We compared the NNS to find 1 advanced CRN in each age subgroup according to risk factors (Table 3). The NNS for the 30–39 years group with all risk factors was 55.4 (95 % CI 32.0–208.5), which was higher than that for ≥50-year-old female subjects (26.4; 95 % CI 19.0–43.5). The NNS for the 40–44 years group with all risk factors (37.1; 95 % CI 24.7–74.0) was also higher than that for ≥50-year-old female subjects. However, the NNS for the

Table 1 Baseline characteristics stratified by age group

	30–39 years ($n = 13{,}038$)	40–44 years ($n = 7916$)	45–49 years ($n = 4177$)	≥50 years ($n = 2763$)	*P* value for trend
Male sex	10,599 (81.3)	6410 (81.0)	3435 (82.2)	2129 (77.1)	0.002
Smoking ≥10 pack-years	2393 (17.6)	2995 (37.8)	1780 (42.6)	1138 (41.2)	<0.001
Metabolic syndrome	1889 (14.5)	1565 (19.8)	931 (22.3)	660 (23.9)	<0.001
Obesity[a]	4556 (34.9)	2909 (36.7)	1592 (38.1)	994 (36.0)	0.005
BP ≥ 130/85 mmHg	3313 (25.4)	2613 (33.0)	1616 (38.7)	1349 (48.8)	<0.001
FBG ≥ 100 mg/dL	2472 (19.0)	1951 (24.6)	1236 (29.6)	971 (35.1)	<0.001
Low HDL-C levels[b]	1609 (12.3)	1099 (13.9)	617 (14.8)	426 (15.4)	<0.001
TG ≥ 150 mg/dL	2727 (20.9)	2123 (26.8)	1143 (27.4)	693 (25.1)	<0.001
Fatty liver	4321 (33.1)	3089 (39.0)	1698 (40.7)	1076 (38.9)	<0.001

BP blood pressure, *FBG* fasting blood glucose, *HDL-C* high-density lipoprotein cholesterol, *TG* triglyceride

[a] Body mass index ≥25.0 kg/m^2

[b] HDL-C <40 mg/dL in men or <50 mg/dL in women

Table 2 Number needed to screen to find 1 advanced neoplasm in 4 age groups

	Total no. screen/no. patients with advanced neoplasm (%)	*P* value	NNS to find 1 advanced neoplasm (95 % CI)
30–39 years group	13,038/88 (0.7)		148.2 (122.6–187.1)
Men	10,599/75 (0.7)	0.342	141.3 (115.3–182.5)
Women	2439/13 (0.5)		187.6 (121.7–409.8)
40–44 years group	7916/140 (1.8)		56.5 (48.6–67.6)
Men	6410/124 (1.9)	0.021	51.7 (44.0–62.6)
Women	1506/16 (1.1)		94.1 (63.3–183.6)
45–49 years group	4177/147 (3.5)		28.4 (24.5–33.8)
Men	3435/140 (4.1)	<0.001	24.5 (21.1–29.3)
Women	742/7 (0.9)		106.0 (61.0–403.5)
≥50 years group	2763/218 (7.9)		12.7 (11.2–14.5)
Men	2129/194 (9.1)	<0.001	11.0 (9.7–12.7)
Women	634/24 (3.8)		26.4 (19.0–43.5)

CI confidence interval, *NNS* number needed to screen

45–49 years group with all risk factors (18.4; 95 % CI 12.6–34.1) was lower than that for ≥50-year-old female subjects.

The NNS for women aged 50–54 years without risk factors (34.3; 95 % CI 19.2–162.3) was higher than that for the 45–49 years group with risk factors (16.9–22.9), whereas the NNS for women without risk factors aged 55–59 years (21.3; 95 % CI 10.9–490.3) was similar to that for the 45–49 years group with risk factors.

Discussion

In this large cross-sectional study, we found that the NNS for the 30–44 years group with multiple risk factors was higher than that for ≥50-year-old female subjects. On the other hand, the NNS for the 45–49 years group with risk factors was lower than that for ≥50-year-old female subjects (16.9–22.9 vs. 26.4).

Recently, a few studies, including our preceding study, have investigated risk factors for CRN in people <50 years old [14–17]. In a Korean study, advanced adenoma was found in 0.7 % of the 30–39 years group and 2.7 % of the 40–49 years group, and in the 40–49 years group, male sex and current smoking habits showed associations with advanced adenoma [15]. However, that study did not compare the efficacy of colonoscopic screening for the detection of advanced adenoma among age groups with risk factors and thus did not indicate whether it is reasonable for persons with risk factors to start screening colonoscopies before age 50. Another Korean study demonstrated that in the 40–49 years group, an increased

Table 3 Number needed to screen to find 1 advanced neoplasm in each age subgroup according to risk factors

	Total no. screen/no. patients with advanced neoplasm (%)	NNS to find 1 advanced neoplasm (95 % CI)
Subgroup according to risk factors in 30–39 years group		
Male, ≥10 pack-years	2274/29 (1.3)	78.4 (57.6–122.8)
Male, ≥10 pack-years, MetS	566/9 (1.6)	62.9 (38.2–178.7)
Male, ≥10 pack-years, obesity	1079/19 (1.8)	56.5 (39.3–102.4)
Male, ≥10 pack-years, fatty liver	999/15 (1.5)	66.6 (44.3–133.8)
Male, ≥10 pack-years, MetS, fatty liver	414/7 (1.7)	59.1 (34.1–222.8)
Male, ≥10 pack-years, obesity, fatty liver	702/12 (1.7)	58.5 (37.5–133.2)
Male, ≥10 pack-years, MetS, obesity, fatty liver	388/7 (1.8)	55.4 (32.0–208.5)
Subgroup according to risk factors in 40–44 years group		
Male, ≥10 pack-years	2983/55 (1.8)	54.2 (43.0–73.5)
Male, ≥10 pack-years, MetS	830/20 (2.4)	41.5 (29.0–73.2)
Male, ≥10 pack-years, obesity	1373/27 (2.0)	50.9 (37.0–81.2)
Male, ≥10 pack-years, fatty liver	1430/34 (2.4)	42.1 (31.6–63.0)
Male, ≥10 pack-years, MetS, fatty liver	629/16 (2.5)	39.3 (26.5–76.1)
Male, ≥10 pack-years, obesity, fatty liver	943/19 (2.0)	49.6 (34.3–89.4)
Male, ≥10 pack-years, MetS, obesity, fatty liver	556/15 (2.7)	37.1 (24.7–74.0)
Subgroup according to risk factors in 45–49 years group		
Male, ≥10 pack-years	1771/87 (4.9)	20.4 (16.9–25.6)
Male, ≥10 pack-years, MetS	508/30 (5.9)	16.9 (12.6–25.9)
Male, ≥10 pack-years, obesity	800/42 (5.3)	19.0 (14.7–27.0)
Male, ≥10 pack-years, fatty liver	823/36 (4.4)	22.9 (17.3–33.6)
Male, ≥10 pack-years, MetS, fatty liver	365/18 (4.9)	20.3 (14.0–36.9)
Male, ≥10 pack-years, obesity, fatty liver	532/24 (4.5)	22.2 (15.9–36.4)
Male, ≥10 pack-years, MetS, obesity, fatty liver	312/17 (5.4)	18.4 (12.6–34.1)
Subgroup according to risk factors in ≥50 years group		
Male, ≥10 pack-years	1123/124 (11.0)	9.1 (7.8–10.9)
Male, ≥10 pack-years, MetS	302/40 (13.2)	7.6 (5.9–10.6)
Male, ≥10 pack-years, obesity	413/45 (10.9)	9.2 (7.2–12.7)
Male, ≥10 pack-years, fatty liver	467/52 (11.1)	9.0 (7.1–12.1)
Male, ≥10 pack-years, MetS, fatty liver	190/25 (13.2)	7.6 (5.6–12.0)
Male, ≥10 pack-years, obesity, fatty liver	251/30 (12.0)	8.4 (6.3–12.6)
Male, ≥10 pack-years, MetS, obesity, fatty liver	152/20 (13.2)	7.6 (5.4–12.8)
Women without risk factors aged 50–54 years	206/6 (2.9)	34.3 (19.2–162.3)
Women without risk factors aged 55–59 years	85/4 (4.7)	21.3 (10.9–490.3)

CI confidence interval, *NNS* number needed to screen

risk of CRN was associated with age ≥45 years, male sex, presence of abdominal obesity, and MetS and therefore concluded that men with abdominal obesity or metabolic syndrome might benefit from screening colonoscopy starting at 45 years of age [14]. That study also reported that because the NNS for 45- to 49-year-old persons with MetS is lower than that for average-risk 50- to –59-year-old persons (14.7 vs. 23.0), it might be reasonable to offer colonoscopic screening to those individuals. However, that study did not provide data on 30- to 39-year-old persons or persons with multiple risk factors. More recently, a Taiwanese study showed that the prevalence of advanced neoplasms with concurrent MetS and smoking (6.2 %) or smoking alone (3.8 %) among men aged 40–49 years was higher than that of average-risk women aged 50–59 years (2.1 %) and found that the NNS to detect 1 advanced neoplasm in men aged 40–49 years with concurrent MetS and smoking, smoking, MetS, and women aged 50–59 years was, respectively, 14.6, 24.8, 39.8, and 47.4 [16]. Therefore, that study suggested that MetS and smoking could justify earlier CRC screening in men.

Although the threshold of NNS to reflect the cost-effectiveness of CRC screening has not been well established, previous studies have looked at analogous measures such as the NNS to detect cancer or advanced neoplasm by screening or surveillance colonoscopy [21, 22]. Imperiale et al. [21] reported that the NNS to detect an advanced neoplasm and recommend colonoscopy after sigmoidoscopy was 9, with an upper 95 % CI value of 25. Based on those reports, a Korean study suggested an NNS value of 25 or lower as a satisfactory threshold to recommend colonoscopy for detection of an advanced neoplasm [14]. Because we found the NNS to identify 1 patient with an advanced CRN in the 30–39 years group with all risk factors and the 40–44 years group with all risk factors to be 55.4 and 37.1, respectively, we cannot advocate screening colonoscopy in those age groups despite the multiple risk factors. However, we found that the NNS for the 45–49 years group with risk factors was 16.9–22.9, which was lower than that for ≥50-year-old female subjects (23.6). Therefore, it could be reasonable to offer colonoscopic screening to men aged 45–49 years who have other risk factors for CRN. On the other hand, the NNS for women without risk factors aged 50–54 years was 34.3, which was higher than that for the 45–49 years group with risk factors. Therefore, it might also be reasonable to offer later colonoscopic screening to women without risk factors. A previous study reported that in average-risk Koreans, the prevalence of advanced neoplasms in men of a specific age group was similar to that of women in the 10-year age group and thus the optimal starting age to start screening in Korean women might be higher than that in men by 10 years [23]. However, the study did not consider other risk factors for CRN.

Based on our results, we carefully suggest that the optimal starting age for screening colonoscopies in men with risk factors such as smoking, MetS, obesity, and fatty liver could be 45 years of age, whereas the optimal starting age for screening colonoscopies in women without those risk factors could be 55 years of age. The current guidelines for CRC screening need to be reconsidered to provide customized screening recommendations by gender and other risk factors as well as by age.

On the other hand, our results suggest that risk factors such as male sex, smoking, MetS, obesity, and fatty liver cannot justify starting screening colonoscopies before age 45. Korean people tend to undergo earlier colonoscopies than people in other countries because they are not economically burdensome to Korean people. Screening colonoscopies among people in their 30s or 40s, excluding 45- to 49-year-old men with risk factors, should be discouraged, and unnecessary colonoscopies in the young population need to be reduced. Recently, a study compared colonoscopy findings in symptomatic patients between 18 and 49 years against those of asymptomatic patients between 50 and 54 years and found that the prevalence of advanced CRN in younger patients with rectal bleeding was comparable with that found by screening older controls (5.9 vs. 6.9 %, $P = 0.459$) [24]. Thus, symptoms such as rectal bleeding could justify diagnostic colonoscopy in young population.

Our study has a few limitations. It was not population based but a cross-sectional study that included individuals who had been seen for a regular health maintenance examination in two centers with a cohort composed of ethnic Korean individuals. Moreover, the cost-effectiveness of screening colonoscopies could be different in each nation because medical costs vary in each nation. Therefore, interpretation of our results requires careful consideration when applied to populations with different ethnicities and healthcare environments. In addition, because most of the study subjects were male (about 80 %), our data from female subjects might have insufficient power to reach a decisive conclusion.

In conclusion, the efficacy of colonoscopic screening for the detection of advanced CRN among people 30–44 years old with multiple risk factors was lower than that among ≥50-year-old women. Our study thus suggests that risk factors such as male sex, smoking, MetS, obesity, and fatty liver cannot justify starting screening colonoscopies before age 45.

Compliance with ethical standards

Conflict of interest There was no conflict of interest.

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