• *COLORECTAL CANCER* •

Rectosigmoid findings are not associated with proximal colon cancer: Analysis of 6 196 consecutive cases undergoing total colonoscopy

Makoto Okamoto, Takao Kawabe, Yutaka Yamaji, Jun Kato, Tsuneo Ikenoue, Goichi Togo, Haruhiko Yoshida, Yasushi Shiratori, Masao Omata

Makoto Okamoto, Takao Kawabe, Yutaka Yamaji, Jun Kato, Tsuneo Ikenoue, Goichi Togo, Haruhiko Yoshida, Yasushi Shiratori, Masao Omata, Department of Gastroenterology, Faculty of Medicine, University of Tokyo, Japan
Correspondence to: Makoto Okamoto, MD, Department of Gastroenterology, Faculty of Medicine, University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-8655, Japan. okamoto-2im@h.u-tokyo.ac.jp
Telephone: +81-3-3815-5411-33056   Fax: +81-3-3814-0021
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Abstract

AIM: To review the risk of proximal colon cancer in patients undergoing colonoscopy.

METHODS: We estimated the risk of advanced proximal adenomas and cancers in 6 196 consecutive patients that underwent colonoscopy (mean age 60 years, 65% males, without prior history of colorectal examination). Neoplasms were classified as diminutive adenoma (5 mm or less), small adenoma (6-9 mm), advanced adenoma (10 mm or more, with villous component or high-grade dysplasia) and cancer (invasive adenocarcinoma). The sites of neoplasms were defined as rectosigmoid (rectum and sigmoid colon) and proximal colon (from cecum to descending colon).

RESULTS: The trend of the prevalence of advanced proximal adenoma was to increase with severe rectosigmoid findings, while the prevalence of proximal colon cancer did not increase with severe rectosigmoid findings. Among the 157 patients with proximal colon cancer, 74% had no neoplasm in the rectosigmoid colon. Multivariate logistic-regression analysis revealed that age was the main predictor of proximal colon cancer and existence of rectosigmoid adenoma was not a predictor of proximal colon cancer.

CONCLUSION: Sigmoidoscopy is inadequate for colorectal cancer screening, especially in older populations.

INTRODUCTION

Colorectal cancer is one of the leading causes of cancer death in the USA and Europe. In USA, it was reported in 1998 that there are 144 300 patients with colorectal cancer and approximately 56 600 deaths per year[1]. Recently, the incidence of colorectal cancer has been increasing remarkably in Japan and China, and nearly 37 000 deaths per year occur in Japan[2,3]. In these countries, there is a proximal shift in the subsite distribution of colorectal cancer[4-6], which is associated with increase in age[7-11].

To reduce the high incidence, screening of colorectal cancer in asymptomatic individuals has been advocated[12-14]. Fecal occult blood testing is widely used in colorectal cancer screening and some prospective cohort studies with large populations have shown that this kind of screening can reduce the mortality of colorectal cancer[15-17]. Sigmoidoscopy is an important screening method that has been proposed as an alternative for fecal occult blood test. Endoscopy has a higher sensitivity than fecal occult blood testing, especially for adenoma. Sigmoidoscopy is simpler, faster, and better tolerable than total colonoscopy, but the scope cannot reach the proximal colon segment and therefore, may miss proximal colon cancer. Previous studies reported that polyps in rectosigmoid colon are associated with advanced proximal neoplasms[18-25]. Thus, examination of the proximal colon is recommended for patients with adenomas detected by sigmoidoscopy[13]. On the other hand, studies have reported that patients with proximal advanced neoplasms may have no rectosigmoid adenoma[26-31].

In the present study, we prospectively collected and analyzed the data from a large cohort of consecutive patients who underwent total colonoscopy for specific reasons. Our aim was to investigate the prevalence of advanced proximal adenoma and cancer according to the findings in rectosigmoid colon, and to find their risk factors.

MATERIALS AND METHODS

Patients

Data were collected from 11 520 consecutive patients who

underwent colonoscopic examinations at the Department of Gastroenterology, University of Tokyo, and its affiliated hospitals between January 1997 and December 2002. Any polyp found during the procedure was removed.

The following data were obtained from all patients: age and gender, indication for colonoscopy, history of colorectal cancer resection or polyp excision, colonoscopic findings such as location and size of polyp or tumor, and histopathology of polyp or tumor.

Excluded from this study were patients with histories of colorectal cancer resection, colorectal polyp excision, hereditary colorectal cancers (familial adenomatous polyposis and hereditary non-polyposis colorectal cancer), inflammatory bowel disease (ulcerative colitis and Crohn's disease), incomplete colonoscopy (unable to reach the cecum), poor bowel preparation, and incomplete polypectomy or unresected polyps. Patients with poor bowel preparation were not included because it was difficult to detect small polyps.

Colonoscopy

Colonoscopy was performed by skilled endoscopists, each with more than 5 years of experience. Examination of the cecum was attempted in each patient. Preparation of colonoscopy consisted of whole-gut lavage with polyethylene glycol-electrolyte solution 3-5 h before the examination. Colonoscopy was performed using a video colonoscope.

Colorectal neoplasms

Histologic diagnosis of adenoma and adenocarcinoma was based on the World Health Organization (WHO) criteria[32] and confirmed by two pathologists. The location and size of all polyps and tumors were recorded at the time of colonoscopy. The location of polyps and tumors was determined by the length of the colonoscope from the anus at the time of examination. The size of polyps was measured with open biopsy forceps at the time of examination.

The location of polyps and tumors was categorized into two groups: rectosigmoid colon (sigmoid colon and rectum) and proximal colon (from cecum to descending colon). In patients with more than one polyp in either the rectosigmoid or proximal segment of the colon, the most advanced lesion in the segment was included in the analysis.

Findings in rectosigmoid and proximal colon were divided into no neoplasm, diminutive, small, and advanced adenomas, and cancer. Diminutive adenoma was defined as tubular adenoma (5 mm or smaller in diameter), small adenoma as tubular adenoma (6-9 mm in diameter), and advanced adenoma as large adenoma (10 mm or larger in diameter) and adenoma with a villous component or high-grade dysplasia[33-35]. Findings such as hyperplastic, inflammatory, and juvenile polyps, or lymphoid aggregation were considered as non-neoplastic lesions and not included in any analyses.

Statistical analysis

Multivariate logistic-regression analysis was used to estimate the odds ratios of proximal advanced adenoma and cancer, categories of age, and gender, indication for colonoscopy, and rectosigmoid findings. Data were analyzed using Bonferroni's method. $P<0.05$ was considered statistically significant.

RESULTS

Patients

During the study period, colonoscopy was performed in 11 520 patients, 5 324 of them were excluded on the basis of the following reasons: history of colorectal polyp excision ($n = 3\ 340$), colorectal cancer resection ($n = 328$), hereditary colorectal cancer ($n = 6$), inflammatory bowel disease ($n = 298$), incomplete polypectomy ($n = 540$), incomplete colonoscopy ($n = 490$), and poor bowel preparation ($n = 322$). The remaining 6 196 patients were included in this study (Table 1).

Among these 6 196 patients, 3 999 (64.5%) were males and 2 197 (35.5%) were females. The mean age of the patients was 60.1 years. The indications for colonoscopy were categorized into asymptomatic, positive FOBT, and symptomatic groups. Asymptomatic group was composed of 575 patients who underwent screening colonoscopy without any abdominal symptom and fecal occult blood test. FOBT group was composed of 2 500 patients who had positive fecal occult blood test in mass screening. Symptomatic group was composed of 3 121 patients who complained of abdominal symptoms (lower gastrointestinal bleeding, lower abdominal pain, altered bowel habit, etc.).

Table 1 **Characteristics of all included patients (n = 6 196)**

Variable	Value (%)
Gender	
Male	3 999 (64.5)
Female	2 197 (35.5)
Age (yr)	
–49	1 166 (18.8)
50–59	1 618 (26.1)
60–69	1 860 (30.0)
70–	1 552 (25.0)
mean±SD	60.1 (13.3)
Indications for colonoscopy	
Asymptomatic	575 (9.3)
Positive for fecal occult blood	2 500 (40.3)
Symptomatic	3 121 (50.4)
Bleeding	922
Lower abdominal pain	861
Altered bowel habit	634
Anemia	261
Elevated CEA	212
Other reasons	231

Findings in rectosigmoid colon

Among the 6 196 patients, 1 951 were positive and 4 245 negative for neoplasms in the rectosigmoid colon. Histology of the neoplasms in the rectosigmoid colon showed that 598 patients had diminutive adenomas, 500 patients had small adenomas, 673 patients had advanced adenomas (466 with tubular adenomas, 76 with adenomas with villous histology, and 131 with adenomas with high-grade dysplasia), and 180 had cancer. One thousand three hundred and twenty-nine patients had a single neoplasm and 622 patients had two or more neoplasms (Table 2).

Table 2 Findings in rectosigmoid and proximal colon of all patients (*n* = 6 196)

Findings	Rectosigmoid colon Number of patients (%)	Proximal colon Number of patients (%)
No neoplasm	4 245 (68.5)	3 991 (64.4)
Histology of most advanced lesion		
Diminutive adenoma[1]	598 (9.7)	968 (15.6)
Small adenoma[2]	500 (8.2)	561 (9.1)
Advanced adenoma[3]	673 (10.9)	519 (8.3)
Cancer	180 (2.9)	157 (2.5)
No. of lesions		
One	1 329 (21.4)	1 173 (18.9)
Two or more	622 (10.0)	1 032 (16.7)

[1]Tubular adenoma (5 mm or less in diameter) [2]Tubular adenoma (6–9 mm in diameter) [3]Tubular adenoma (10 mm or more in diameter), villous histology, or severe dysplasia.

Prevalence of advanced proximal adenoma

The prevalence of advanced proximal adenoma was analyzed based on the findings in rectosigmoid colon (Table 3).

The prevalence of advanced proximal adenoma was 6.2% (95% CI, 5.5-6.9) in the 4 245 patients with no rectosigmoid neoplasm, 6.9% (95% CI, 4.8-8.9) in the 598 patients with diminutive rectosigmoid adenomas, 12.0% (95% CI, 9.2-14.8) in the 500 patients with small rectosigmoid adenomas, 18.1% (95% CI, 15.2-21.0) in the 673 patients with advanced rectosigmoid adenomas, and 17.8% (95% CI, 12.2-23.4) in the 180 patients with rectosigmoid cancer.

One hundred and fifty of 1 329 patients with a single neoplasm had advanced proximal adenomas (11.3%, 95% CI, 9.6-13.0), and 105 of 622 patients with two or more rectosigmoid neoplasms had advanced proximal adenomas (16.9%, 95% CI, 13.9-19.8).

The prevalence of advanced proximal adenoma increased with increasingly rectosigmoid findings.

Prevalence of proximal colon cancer

The prevalence of proximal colon cancer was analyzed according to the findings in rectosigmoid colon (Table 3).

The prevalence of proximal cancer was 2.7% (95% CI, 2.2–3.2) in the 4 245 patients without rectosigmoid neoplasm, 1.8% (95% CI, 0.8-2.9) in the 598 patients with diminutive rectosigmoid adenomas, 2.8% (95% CI, 1.4-4.2) in the 500 patients with small rectosigmoid adenomas, 2.2% (95% CI,

1.1-3.3) in the 673 patients with advanced rectosigmoid adenomas, and 0.6% (95% CI, 0.0-1.6) in the 180 patients with rectosigmoid cancer.

Twenty-seven of 1 329 patients with a single neoplasm had proximal cancer (2.0%, 95% CI, 1.3-2.8), and 14 of 622 patients with two or more rectosigmoid neoplasms had proximal cancer (2.3%, 95% CI, 1.1-3.4).

The prevalence of proximal colon cancer was not associated with severe rectosigmoid findings.

Findings in patients with proximal advanced adenoma and cancer

Among the 6 196 patients, 519 patients had proximal advanced adenoma, 264 of these 519 patients had no neoplasm in the rectosigmoid colon (50.9%). Moreover, among 157 patients with proximal colon cancer, 116 had no neoplasm in the rectosigmoid colon (73.9%).

Risk for proximal colon cancer and advanced adenoma

Among the 6 196 patients in this study, multivariate analysis showed that only age was significantly associated with the risk for proximal colon cancer (Table 4). Patients aged 70 years or more showed a markedly increased risk for proximal cancer (odds ratio 35.6; 95% CI 8.7-145.2) compared with patients aged 49 years or less. Gender and rectosigmoid colon findings were not associated with significant differences in the risk for proximal colon cancer.

On the other hand, age and gender were significantly associated with the risk of advanced proximal adenoma. Male patients showed increased risk of advanced proximal adenoma (odds ratio 2.1; 95% CI, 1.7-2.6) compared with female patients, and patients aged 70 years or more showed increased risk for proximal cancer (odds ratio 3.5; 95% CI, 2.4-5.1) compared with patients aged 49 years or less. Patients with diminutive adenomas in the rectosigmoid colon were not associated with significantly increased risk for proximal advanced adenoma (odds ratio 0.9: 95% CI, 0.6-1.3) compared with patients without rectosigmoid neoplasm.

DISCUSSION

In developed countries, the incidence of proximal colon cancer increases with a time trend[4-6]. Furthermore, proximal shift of colorectal cancer is observed in the aged population[7-11]. With the aged population increase in developed countries,

Table 3 Prevalence of proximal advanced adenoma and cancer

Rectosigmoid findings	Number of pts	Proximal findings					
		Advanced adenoma			Cancer		
		Number of pts	(%)	(95% CI)	Number of pts	(%)	(95% CI)
No neoplasm	4 245	264	(6.2)	(5.5–6.9)	116	(2.7)	(2.2-3.2)
Histology of most advanced neoplasm							
Diminutive adenoma	598	41	(6.9)	(4.8–8.9)	11	(1.8)	(0.8–2.9)
Small adenoma	500	60	(12.0)	(9.2–14.8)	14	(2.8)	(1.4–4.2)
Advanced adenoma	673	122	(18.1)	(15.2–21.0)	15	(2.2)	(1.1–3.3)
Cancer	180	32	(17.8)	(12.2–23.4)	1	(0.6)	(0.0–1.6)
No. of neoplasms							
One	1 329	150	(11.3)	(9.6–13.0)	27	(2.0)	(1.3–2.8)
Two or more	622	105	(16.9)	(13.9–19.8)	14	(2.3)	(1.1–3.4)

Table 4 Risk of proximal advanced adenoma and cancer according to gender, age, and rectosigmoid findings (multivariate analysis)

| Variables | No. of pts | Proximal colon | | | | | |
| | | Advanced adenoma | | | Cancer | | |
		Odds ratio	(95%CI)	P	Odds ratio	(95%CI)	P
Gender							
Female	2 197	1	(Referent)		1	(Referent)	
Male	3 999	2.1	(1.7–2.6)	<0.0001	0.9	(0.6–1.3)	0.5287
Age (yr)							
–49	1 166	1	(Referent)		1	(Referent)	
50–59	1 618	2.5	(1.7–3.6)	<0.0001	10.0	(2.4–42.4)	0.0018
60–69	1 860	3.1	(2.12–4.5)	<0.0001	13.8	(3.3–57.2)	0.0003
70–	1 552	3.5	(2.4–5.1)	<0.0001	35.6	(8.7–145.2)	<0.0001
Findings of rectosigmoid colon							
No neoplasm	4 245	1	(Referent)		1	(Referent)	
Diminutive adenoma	598	0.9	(0.6–1.3)	0.4995	0.7	(0.3–1.2)	0.1881
Small adenoma	500	1.6	(1.2–2.2)	0.0019	1.0	(0.6–1.8)	0.9731
Advanced adenoma	673	2.5	(2.0–3.2)	<0.0001	0.8	(0.5–1.4)	0.4577
Cancer	180	2.6	(1.7–3.8)	<0.0001	0.2	(0.0–1.2)	0.0726

proximal colon cancer has had more significance. Therefore it is of great significance to review the risk factor for the proximal colon cancer.

Sigmoidoscopy is a vital procedure for screening colorectal cancer[12-14]. If there was a reliable rectosigmoid marker for the presence of clinically important proximal neoplasms or if normal findings in the rectosigmoid colon were a reliable marker for their absence, then sigmoidoscopic examination could determine which patients should undergo total colonoscopy.

The principal findings in this study are as follows: patients with no rectosigmoid adenoma could indeed have proximal colon cancer, which was not associated with rectosigmoid findings. It is clear that a substantial number of colorectal cancers would be missed if only sigmoidoscopy was performed. In addition, old age is an important risk factor for proximal colon cancer.

Studies reported that prevalence of advanced proximal adenoma is related to sigmoidoscopic findings in total colonoscopy[18-31]. According to these studies, the prevalence of advanced proximal adenoma increases with rectosigmoid findings. But the prevalence of proximal colon cancer in association with rectosigmoid findings is rarely reported[28]. Levin et al[28], reported that the prevalence of proximal cancer is not associated with rectosigmoid findings. But in their study, the number of proximal cancer cases was less. We used a large number of patients undergoing total colonoscopy and analyzed the prevalence of both advanced proximal adenoma and cancer. We found that the prevalence of advanced proximal adenoma increased in association with rectosigmoid findings. On the other hand, the prevalence of proximal colon cancer did not show such a tendency.

Studies reported that the prevalence of rectosigmoid adenoma in cases of proximal colon cancer is not associated with rectosigmoid neoplasms[36-38]. Rex et al[39], carried out a prospective study on the prevalence of distal adenoma in cases of proximal colon cancer, and reported that 66% of the proximal cancer cases have no distal adenoma. In our present study, 74% of the proximal colon cancer cases lacked rectosigmoid adenoma, which is consistent with what was reported in previous studies[36-39]. Moreover, about

3% of the patients with no rectosigmoid adenoma in our cohort had proximal colon cancer.

Imperiale et al[27], reported that distal polyps, older age, and male sex were the risk factors of advanced proximal neoplasia including advanced adenoma and invasive cancer. However, the risk for proximal cancer alone was not addressed. In the present study, multivariate logistic-regression analysis revealed that old age, male sex and rectosigmoid small or advanced adenoma were risk factors for advanced proximal adenoma. On the other hand, only old age was a risk factor, but not the male sex or rectosigmoid findings for proximal cancer. These results suggest that sigmoidoscopy is an insufficient screening procedure for detecting proximal cancer, especially in older subjects. Our previous study[7] reported that with advancing age, there is a tendency of a proximal shift of colon cancer, but the distribution of adenoma is not associated with age. This difference between proximal cancer and advanced proximal adenoma may provide some information concerning the carcinogenesis of proximal colon cancer, as it seems that a certain number of proximal colon cancers are not associated with adenoma. This topic, especially from the aspect of molecular biology, requires further extensive studies. Microsatellite instability frequently occurs in the proximal colon cancer, especially in aged patients[40-43], but it is rare in adenoma[44]. This difference between proximal colon cancer and adenoma might be reflected in the difference of the risk factor for proximal colon cancer and adenoma as observed in our study.

Interpretation of our findings requires careful consideration of several methodological issues. First, our data may have been affected by selection bias, because our study population included patients with various indications for colonoscopy To adjust the confounding effect caused by the indications for colonoscopy, multivariate analyses were adjusted according to indications for colonoscopy. Moreover, among the 6 196 patients, 575 asymptomatic patients underwent colonoscopy. Three, of these 575 patients, had proximal colon cancer two patients had no rectosigmoid adenoma, and only one had small adenoma in rectosigmoid colon.

Second, "proximal colon" generally means the colon

proximal to the splenic flexure. But flexible sigmoidoscopy reaches the splenic flexure in only 16% of the cases, and usually reaches up to the sigmoid-descending junction[45]. Thus, in general, neoplasms proximal to the sigmoid colon cannot be visualized by sigmoidoscopy. We defined the proximal colon as proximal to the sigmoid colon in this study.

Third, hyperplastic polyp is a non-neoplastic lesion, and the significance of hyperplastic polyps in the rectosigmoid colon has been controversial. Some studies reported that hyperplastic polyps are a marker of proximal colon neoplasms[23,25,27], whereas other studies showed that hyperplastic polyps in the rectosigmoid colon have no relation with proximal colon neoplasms[24,26,30]. In the present study, patients with hyperplastic polyps in the rectosigmoid colon were considered normal.

Sigmoidoscopy is the method widely used for screening colorectal cancer[12-14], and has led to increased detection of benign diminutive adenomas in the rectosigmoid colon. The need for colonoscopy in individuals with diminutive tubular adenomas found in sigmoidoscopy is an important but controversial issue in screening for colorectal cancer. Some studies reported that adenomas of the rectosigmoid colon, regardless of size, are markers of neoplasms in the colon, and colonoscopy is thus advocated for such patients[13,18,21,22,25,29]. However, other studies reported that the discovery rate of advanced proximal neoplasm in such patients is low and colonoscopy is not indicated[19,28]. According to our study, diminutive adenomas in the rectosigmoid colon might be a useful marker of advanced proximal adenoma, but its prevalence does not differ between patients with no rectosigmoid adenoma and those with rectosigmoid diminutive adenomas. Moreover, neither diminutive adenoma in the rectosigmoid colon nor any other type of rectosigmoid adenoma could be a marker of proximal colon cancer. Even if colonoscopy was performed for any distal adenoma in our study cohort, nearly three-quarters of the patients with proximal invasive cancer and half of the patients with advanced proximal adenoma would have been missed, indicating that a substantial number of proximal cancers and advanced adenomas are not associated with any distal neoplasms.

In conclusion, sigmoidoscopy might be an inadequate method for colorectal cancer screening, especially in older people. The current strategy of deciding who should undergo colonoscopy on the basis of sigmoidoscopy needs to be reconsidered.

REFERENCES

1   **Jemal A,** Thomas A, Murray T, Thun M. Cancer statistics, 2002. *CA Cancer J Clin* 2002; **52**: 23-47
2   Statistics and Information Department. Ministry of Health and Welfare in Japan. Vital statistics of Japan 2001. Tokyo: Kosei Tokei Kyokai, 2003 (in Japanese)
3   **Zhang YL,** Zhang ZS, Wu BP, Zhou DY. Early diagnosis for colorectal cancer in China. *World J Gastroenterol* 2002; **8**: 21-25
4   **Rhodes JB,** Holmes FF, Clark GM. Changing distribution of primary cancers in the large bowel. *JAMA* 1977; **238**: 1641-1643
5   **Levi F,** Randimbison L, La Vecchia C. Trends in subsite distribution of colorectal cancers and polyps from the Vaud Cancer Registry. *Cancer* 1993; **72**: 46-50
6   **Takada H,** Ohsawa T, Iwamoto S, Yoshida R, Nakano M, Imada S, Yoshioka K, Okuno M, Masuya Y, Hasegawa K, Kamano N, Hioki K, Muto T, Koyama Y. Changing site distribution of colorectal cancer in Japan. *Dis Colon Rectum* 2002; **45**: 1249-1254
7   **Okamoto M,** Shiratori Y, Yamaji Y, Kato J, Ikenoue T, Togo G, Yoshida H, Kawabe T, Omata M. Relationship between age and site of colorectal cancer based on colonoscopy findings. *Gastrointest Endosc* 2002; **55**: 548-551
8   **Griffin PM,** Liff JM, Greenberg RS, Clark WS. Adenocarcinomas of the colon and rectum in persons under 40 years old. A population-based study. *Gastroenterology* 1991; **100**: 1033-1040
9   **Nelson RL,** Dollear T, Freels S, Persky V. The relation of age, race, and gender to the subsite location of colorectal carcinoma. *Cancer* 1997; **80**: 193-197
10   **Fante R,** Benatti P, di Gregorio C, De Pietri S, Pedroni M, Tamassia MG, Percesepe A, Rossi G, Losi L, Roncucci L, Ponz de Leon M. Colorectal carcinoma in different age groups: a population-based investigation. *Am J Gastroenterol* 1997; **92**: 1505-1509
11   **Jass JR.** Subsite distribution and incidence of colorectal cancer in New Zealand, 1974-1983. *Dis Colon Rectum* 1991; **34**: 56-59
12   **Winawer S,** Fletcher R, Rex D, Bond J, Burt R, Ferrucci J, Ganiats T, Levin T, Woolf S, Johnson D, Kirk L, Litin S, Simmang C. Colorectal cancer screening and surveillance: clinical guidelines and rationale-Update based on new evidence. *Gastroenterology* 2003; **124**: 544-560
13   **Byers T,** Levin B, Rothenberger D, Dodd GD, Smith RA. American Cancer Society guidelines for screening and surveillance for early detection of colorectal polyps and cancer: update 1997. American Cancer Society Detection and Treatment Advisory Group on Colorectal Cancer. *CA Cancer J Clin* 1997; **47**: 154-160
14   **Rosen L,** Abel ME, Gordon PH, Denstman FJ, Fleshman JW, Hicks TC, Huber PJ, Kennedy HL, Levin SE, Nicholson JD. Practice parameters for the detection of colorectal neoplasms-supporting documentation. The Standards Task Force. AmericanSociety of Colon and Rectal Surgeons. *Dis Colon Rectum* 1992; **35**: 391-394
15   **Mandel JS,** Bond JH, Church TR, Snover DC, Bradley GM, Schuman LM, Ederer F. Reducing mortality from colorectal cancer by screening for fecal occult blood. Minnesota Colon Cancer Control Study. *N Engl J Med* 1993; **328**: 1365-1371
16   **Kronborg O,** Fenger C, Olsen J, Jorgensen OD, Sondergaard O. Randomised study of screening for colorectal cancer with faecal-occult-blood test. *Lancet* 1996; **348**: 1467-1471
17   **Hardcastle JD,** Chamberlain JO, Robinson MH, Moss SM, Amar SS, Balfour TW, James PD, Mangham CM. Randomised controlled trial of faecal-occult blood screening for colorectal cancer. *Lancet* 1996; **348**: 1472-1477
18   **Read TE,** Read JD, Butterly LF. Importance of adenomas 5 mm or less in diameter that are detected by sigmoidoscopy. *N Engl J Med* 1997; **336**: 8-12
19   **Zarchy TM,** Ershoff D. Do characteristics of adenomas on flexible sigmoidoscopy predict advanced lesions on baseline colonoscopy? *Gastroenterology* 1994; **106**: 1501-1504
20   **Papatheodoridis GV,** Triantafyllou K, Tzouvala M, Paspatis G, Xourgias V, Karamanolis DG. Characteristics of rectosigmoid adenomas as predictors of synchronous advanced proximal colon neoplasms. *Am J Gastroenterol* 1996; **91**: 1809-1813
21   **Schoen RE,** Corle D, Cranston L, Weissfeld JL, Lance P, Burt R, Iber F, Shike M, Kikendall JW, Hasson M, Lewin KJ, Appelman HD, Paskett E, Selby JV, Lanza E, Schatzkin A. Is colonoscopy needed for the nonadvanced adenoma found on sigmoidoscopy? The Polyp Prevention Trial. *Gastroenterology* 1998; **115**: 533-541
22   **Wallace MB,** Kemp JA, Trnka YM, Donovan JM, Farraye FA. Is colonoscopy indicated for small adenomas found by screening flexible sigmoidoscopy? *Ann Intern Med* 1998; **129**: 273-278
23   **Blue MG,** Sivak MV, Achkar E, Matzen R, Stahl RR. Hyper-

plastic polyps seen at sigmoidoscopy are markers for additional adenomas seen at colonoscopy. *Gastroenterology* 1991; **100**: 564-566

24   **Provenzale D,** Garrett JW, Condon SE, Sandler RS. Risk for colon adenomas in patients with rectosigmoid hyperplastic polyps. *Ann Intern Med* 1990; **113**: 760-763

25   **Achkar E,** Carey W. Small polyps found during fiberoptic sigmoidoscopy in asymptomatic patients. *Ann Intern Med* 1988; **109**: 880-883

26   **Lieberman DA,** Weiss DG, Bond JH, Ahnen DJ, Garewal H, Chejfec G. Use of colonoscopy to screen asymptomatic adults for colorectal cancer. Veterans Affairs Cooperative Study Group 380. *N Engl J Med* 2000; **343**: 162-168

27   **Imperiale TF,** Wagner DR, Lin CY, Larkin GN, Rogge JD, Ransohoff DF. Risk of advanced proximal neoplasms in asymptomatic adults according to the distal colorectal findings. *N Engl J Med* 2000; **343**: 169-174

28   **Levin TR,** Palitz A, Grossman S, Conell C, Finkler L, Ackerson L, Rumore G, Selby JV. Predicting advanced proximal colonic neoplasia with screening sigmoidoscopy. *JAMA* 1999; **281**: 1611-1617

29   **Sciallero S,** Bonelli L, Aste H, Casetti T, Bertinelli E, Bartolini S, Parri R, Castiglione G, Mantellini P, Costantini M, Naldoni C, Bruzzi P. Do patients with rectosigmoid adenomas 5 mm or less in diameter need total colonoscopy? *Gastrointest Endosc* 1999; **50**: 314-321

30   **Sciallero S,** Costantini M, Bertinelli E, Castiglione G, Onofri P, Aste H, Casetti T, Mantellini P, Bucchi L, Parri R, Boni L, Bonelli L, Gatteschi B, Lanzanova G, Rinaldi P, Giannini A, Naldoni C, Bruzzi P. Distal hyperplastic polyps do not predict proximal adenomas: results from a multicentric study of colorectal adenomas. *Gastrointest Endosc* 1997; **46**: 124-130

31   **Kadakia SC,** Wrobleski CS, Kadakia AS, Meier NJ. Prevalence of proximal colonic polyps in average-risk asymptomatic patients with negative fecal occult blood tests and flexible sigmoidoscopy. *Gastrointest Endosc* 1996; **44**: 112-117

32   **Morson BC,** Sobin LC. Histologic typing of intestinal tumours. In: Intestinal histological classification of tumors. Vol. 15. Geneva: World Health Organization;1976

33   **Grossman S,** Milos ML, Tekawa IS, Jewell NP. Colonoscopic screening of persons with suspected risk factors for colon cancer: II. Past history of colorectal neoplasms. *Gastroenterology* 1989; **96**: 299-306

34   **Stryker SJ,** Wolff BG, Culp CE, Libbe SD, Ilstrup DM, MacCarty RL. Natural history of untreated colonic polyps. *Gastroenterology* 1987; **93**: 1009-1013

35   **DiSario JA,** Foutch PG, Mai HD, Pardy K, Manne RK. Prevalence and malignant potential of colorectal polyps in asymptomatic, average-risk men. *Am J Gastroenterol* 1991; **86**: 941-945

36   **Dinning JP,** Hixson LJ, Clark LC. Prevalence of distal colonic neoplasia associated with proximal colon cancers. *Arch Intern Med* 1994; **154**: 853-856

37   **Lemmel GT,** Haseman JH, Rex DK, Rahmani E. Neoplasia distal to the splenic flexure in patients with proximal colon cancer. *Gastrointest Endosc* 1996; **44**: 109-111

38   **Castiglione G,** Ciatto S, Mazzotta A, Grazzini G. Sensitivity of screening sigmoidoscopy for proximal colorectal tumours. *Lancet* 1995; **345**: 726-727

39   **Rex DK,** Chak A, Vasudeva R, Gross T, Lieberman D, Bhattacharya I, Sack E, Wiersema M, Farraye F, Wallace M, Barrido D, Cravens E, Zeabart L, Bjorkman D, Lemmel T, Buckley S. Prospective determination of distal colon findings in average-risk patients with proximal colon cancer. *Gastrointest Endosc* 1999; **49**: 727-730

40   **Thibodeau SN,** Bren G, Schaid D. Microsatellite instability in cancer of the proximal colon. *Science* 1993; **260**: 816-819

41   **Ionov Y,** Peinado MA, Malkhosyan S, Shibata D, Perucho M. Ubiquitous somatic mutations in simple repeated sequences reveal a new mechanism for colonic carcinogenesis. *Nature* 1993; **363**: 558-561

42   **Togo G,** Toda N, Kanai F, Kato N, Shiratori Y, Kishi K, Imazeki F, Makuuchi M, Omata M. A transforming growth factor beta type II receptor gene mutation common in sporadic cecum cancer with microsatellite instability. *Cancer Res* 1996; **56**: 5620-5623

43   **Togo G,** Shiratori Y, Okamoto M, Yamaji Y, Matsumura M, Sano T, Motojima T, Omata M. Relationship between grade of microsatellite instability and target genes of mismatch repair pathways in sporadic colorectal carcinoma. *Dig Dis Sci* 2001; **46**: 1615-1622

44   **Togo G,** Okamoto M, Shiratori Y, Yamaji H, Kato J, Matsumura M, Sano T, Motojima T, Omata M. Does mutation of transforming growth factor-beta type II receptor gene play an important role in colorectal polyps? *Dig Dis Sci* 1999; **44**: 1803-1809

45   **Lehman GA,** Buchner DM, Lappas JC. Anatomical extent of fiberoptic sigmoidoscopy. *Gastroenterology* 1983; **84**: 803-808

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