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Risk of Advanced Proximal Neoplasms According to Distal Colorectal Findings: Comparison of Sigmoidoscopy-Based Strategies

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Background	Screening for colorectal cancer with sigmoidoscopy benefits from the fact that distal findings predict the risk of advanced proximal neoplasms (APNs). This study was aimed at comparing the existing strategies of postsigmoidoscopy referral to colonoscopy in terms of accuracy and resources needed.
Methods	Asymptomatic individuals aged 50–69 years were eligible for a randomized controlled trial designed to compare colonoscopy and fecal immunochemical test. Sigmoidoscopy yield was estimated from results obtained in the colonoscopy arm according to three sets of criteria of colonoscopy referral (from those proposed in the UK Flexible Sigmoidoscopy, Screening for COlon REctum [SCORE], and Norwegian Colorectal Cancer Prevention [NORCCAP] trials). Advanced neoplasm detection rate, sensitivity, specificity, and number of individuals needed to refer for colonoscopy to detect one APN were calculated. Logistic regression analysis was performed to identify distal findings associated with APN. All statistical tests were two-sided.
Results	APN was found in 255 of 5059 (5.0%) individuals. Fulfillment of UK (6.2%), SCORE (12.0%), and NORCCAP (17.9%) criteria varied statistically significantly ($P < .001$). The NORCCAP strategy obtained the highest sensitivity for APN detection (36.9%), and the UK approach reached the highest specificity (94.6%). The number of individuals needed to refer for colonoscopy to detect one APN was 6 (95% confidence interval [CI] = 4 to 7), 8 (95% CI = 6 to 9), and 10 (95% CI = 8 to 12) when the UK, SCORE, and NORCCAP criteria were used, respectively. The logistic regression analysis identified distal adenoma ≥10 mm (odds ratio = 3.77; 95% CI = 2.52 to 5.65) as the strongest independent predictor of APN.
Conclusions	Whereas the NORCCAP criteria achieved the highest sensitivity for APN detection, the UK recommendations benefited from the lowest number of individuals needed to refer for colonoscopy.
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Colorectal cancer (CRC) is the third most common cancer worldwide and the second leading cause of cancer-related death (1). Evidence from several studies has shown that screening is effective (2) and cost-effective (3,4) for CRC prevention in average-risk populations. Indeed, both fecal occult blood testing and flexible sigmoidoscopy have been shown to reduce CRC-specific mortality (5–9) and incidence (8–11) in randomized controlled trials. Accordingly, these two strategies, along with colonoscopy, have been universally accepted and recommended for CRC screening

(2,12). Search for occult blood using the guaiac test and, more recently, the fecal immunochemical test, and sigmoidoscopy have been implemented in Europe (13) and Australia (14), whereas colonoscopy is the dominant modality in North America (2).

Screening for CRC with sigmoidoscopy is based on its capacity to detect neoplastic lesions in the distal colon as well as on the fact that distal findings predict the risk of advanced proximal neoplasms (APNs) (15–18). In that sense, there is general agreement that the magnitude of this risk is related to the histologic features of distal

lesions (ie, villous architecture or high-grade dysplasia), but the association with adenoma size alone is more controversial (15–17). This circumstance has prompted the use of a variety of criteria for referral to colonoscopy among sigmoidoscopy-based screening strategies (8,11,19).

The COLONPREV study, a randomized controlled trial designed to assess the efficacy of one-time colonoscopy and biennial fecal immunochemical test for reducing CRC mortality at 10 years, recently reported the results obtained at baseline screening exam (20). This study constitutes a unique opportunity to estimate the risk of APN according to distal findings in a large cohort of average-risk individuals screened by colonoscopy. More importantly, it allows the comparison of risk estimates by simulating the sigmoidoscopy yield that would have resulted from using the three existing sets of criteria for referral to colonoscopy based on the characteristics of distal lesions (ie, those proposed in the UK Flexible Sigmoidoscopy Trial (8), SCORE Trial (11), and NORCCAP Trial (19)). Therefore, this analysis was aimed at comparing these three sigmoidoscopy-based strategies in terms of accuracy and resources needed to detect one APN, both overall and in age- and sex-specific subgroups. This precise estimation

may contribute to better design of CRC screening programs and tailoring according to population characteristics.

Methods

In this simulation comparison, the sigmoidoscopy yield was estimated from results obtained in the colonoscopy arm of the COLONPREV study (ClinicalTrials.gov NCT00906997) (20,21) (Figure 1 and Supplementary Methods, available online) by applying the algorithms of sigmoidoscopy-based strategies to the lesions detected in the rectum and sigmoid colon. Indeed, estimates of individuals referred for colonoscopy were made according to the three existing sets of criteria proposed in the UK Flexible Sigmoidoscopy Trial (hereafter called "UK") (one distal polyp ≥10 mm, tubulovillous or villous histology, high-grade dysplasia, ≥3 adenomas, CRC, or ≥20 hyperplastic polyps above the distal rectum) (8), the SCORE Trial ("SCORE") (one distal polyp >5 mm, tubulovillous or villous histology, high-grade dysplasia, ≥3 adenomas, or CRC) (11), and the NORCCAP Trial ("NORCCAP") (one distal polyp ≥10 mm, any adenoma, or CRC) (19). To minimize any potential bias due to the segments considered
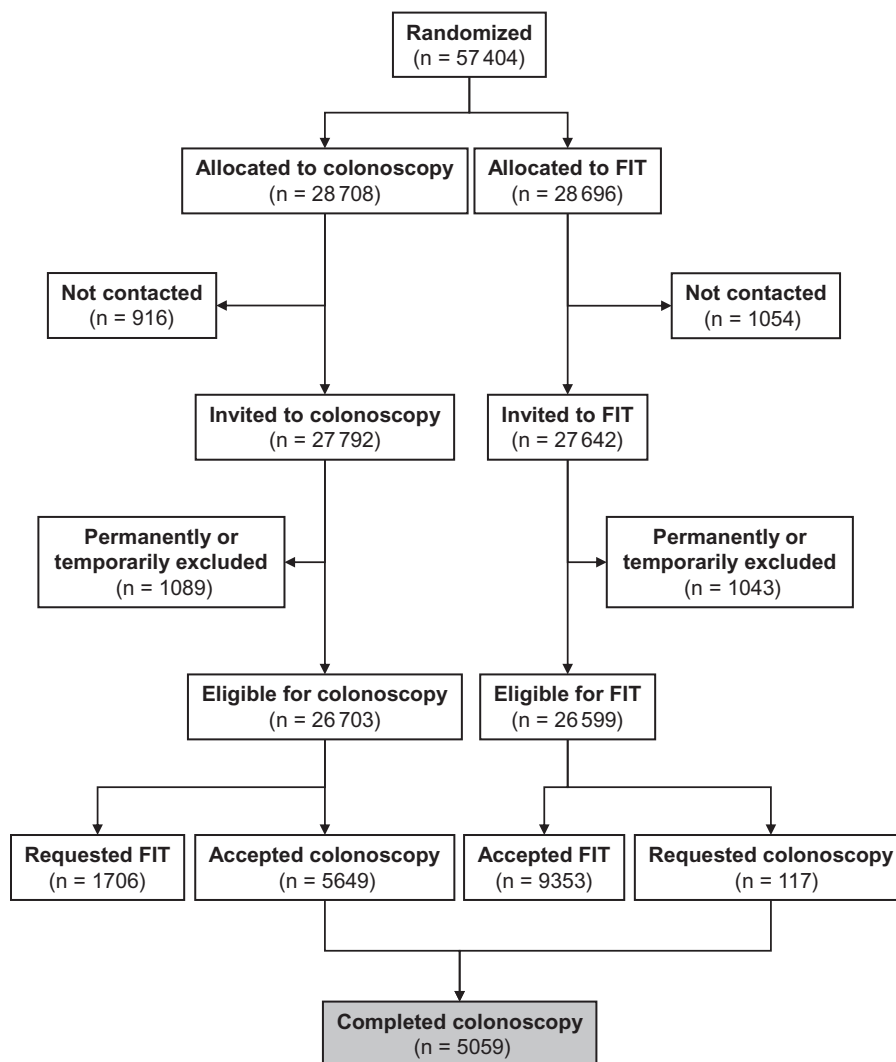

Figure 1. Flow diagram of the analysis. FIT = fecal immunochemical test.

for sigmoidoscopy simulation, a sensitivity analysis was done by including the descending colon in the distal colon.

Advanced neoplasm was defined as advanced adenoma or invasive cancer. Polyp size was usually measured by the pathologist; when it was not possible or the lesion was fragmented, endoscopy size was used. Patients were classified according to the most advanced lesion present in proximal and distal segments.

Statistical Analysis

Detection of APN was the main outcome of this analysis, which was defined as any advanced neoplasm located proximally to colorectal segments considered for the sigmoidoscopy simulation (ie, rectum and sigmoid colon in the primary analysis, and rectum, sigmoid, and descending colon in the sensitivity analysis). Evaluation of the accuracy of each sigmoidoscopy-based strategy with respect to the detection of APN included sensitivity, specificity, and positive and negative predictive values. Pairwise comparisons among strategies regarding sensitivity and specificity were done using McNemar test for paired proportions. Performance characteristics of sigmoidoscopy in detecting any APN were estimated both overall and upon stratifying the whole series in arbitrarily defined subsets of individuals by age (50–59 and 60–69 years) and sex.

Sigmoidoscopy can detect an advanced colorectal neoplasm if there is such a lesion in the distal colon or if there is an advanced neoplasm in the proximal colon along with a sentinel lesion in the distal colon triggering the performance of colonoscopy according to the different sets of criteria for colonoscopy referral. Therefore, the overall advanced neoplasm detection rate represents the likelihood that a patient with an advanced colorectal neoplasm located at any site would have this lesion identified if he/she were to undergo sigmoidoscopy alone. Point estimates of detection rates for each strategy, defined as the number of true positives divided by the number of participating individuals, were compared to the corresponding detection rate in the colonoscopy arm by logistic regression analysis and reported as odds ratios (ORs) with 95% confidence intervals (CIs), adjusted by participating center. Pairwise comparisons among sigmoidoscopy-based strategies were done using the McNemar test for paired proportions.

The analysis of resources was done by calculating the number of individuals needed to screen and the number of individuals needed to refer for colonoscopy to detect one APN. These parameters represent the average number of people who need to be screened by sigmoidoscopy or to be referred for colonoscopy on the basis of sigmoidoscopy results, respectively, to identify one person with such a lesion.

A forward LR, stepwise logistic regression analysis was performed to identify distal findings independently associated with the presence of APN. Variables included were presence of any adenoma, adenoma size, villous histology, high-grade dysplasia, number of small tubular adenomas, and CRC in the distal colon. Patients were classified by the most severe set of polyp characteristics.

Analyses were done using the SPSS statistical software, version 15.0 (SPSS Inc, Chicago, IL). All statistical tests were two-sided, and *P* values less than .05 were considered to be statistically significant.

Results

Within the COLONPREV study, 5059 individuals completed colonoscopy either as initial randomized allocation or after crossover from the fecal immunochemical test arm (20). Demographic characteristics are shown in Table 1. In this cohort, CRC was diagnosed in 27 patients (6 with proximal lesions) and advanced adenomas in 493 patients (249 with proximal lesions). Therefore, 255 of 5059 (5.0%) individuals had any APN.

Colonoscopy Referral Rate

As shown in Table 2, there were statistically significant differences regarding the proportion of individuals who should have

Table 1. Characteristics of individuals included in the analysis

Characteristic	No. (%)
Age, y, mean (SD)	59 ± 5
Sex	
Male	2458 (49.6)
Female	2601 (51.4)
Colorectal cancer	27 (0.5)
Proximal*	5 (0.1)
Distal	21 (0.4)
Both	1 (0.02)
Advanced adenoma	493 (9.7)
Proximal*	207 (4.1)
Distal	244 (4.8)
Both	42 (0.8)
Nonadvanced adenoma	1116 (22.1)
Proximal*	560 (11.1)
Distal	372 (7.4)
Both	184 (3.6)

* Lesions located proximally to the sigmoid colon were accounted as proximal lesions.

Table 2. Individuals referred for colonoscopy according to each sigmoidoscopy-based screening strategy and colorectal segments considered for sigmoidoscopy simulation

Colorectal segments considered for sigmoidoscopy simulation	UK criteria*, No. (%; 95% CI)	SCORE criteria†, No. (%; 95% CI)	NORCCAP criteria‡, No. (%; 95% CI)	*P*§
Rectum and sigmoid colon	317 (6.2; 5.6 to 6.9)	609 (12.0; 11.2 to 12.9)	909 (17.9; 16.9 to 19.1)	<.001
Rectum, sigmoid and descending colon	365 (7.2; 6.5 to 7.9)	717 (14.2; 13.2 to 15.2)	1082 (21.4; 20.3 to 22.5)	<.001

* UK Flexible Sigmoidoscopy Trial (8) criteria: one distal polyp ≥10 mm, tubulovillous or villous histology, high-grade dysplasia, ≥3 adenomas, colorectal cancer, or ≥20 hyperplastic polyps above the distal rectum. CI = confidence interval.

† SCORE Trial (11) criteria: one distal polyp >5 mm, tubulovillous or villous histology, high-grade dysplasia, ≥3 adenomas, or colorectal cancer.

‡ NORCCAP Trial (19) criteria: one distal polyp ≥10 mm, any adenoma, or colorectal cancer.

§ Comparison among all three strategies was done by the χ² test (two-sided).

been referred for colonoscopy depending on the set of criteria employed. Indeed, the number of individuals fulfilling the NORCCAP (17.9%) and SCORE (12.0%) criteria (6.2%) were three-fold and two-fold, respectively, of those fulfilling the UK criteria ($P < .001$). These results were maintained when lesions in the descending colon were also considered for the sigmoidoscopy simulation (Table 2).

Detection Rate

Overall, sigmoidoscopy would have detected 35%–43% fewer individuals with advanced neoplasia than colonoscopy (Table 3). Pairwise comparison of sigmoidoscopy-based strategies with respect to the overall advanced neoplasm detection rate revealed statistically significant differences among all three approaches. Indeed, the detection rate using the NORCCAP criteria was 4.4% higher than the SCORE criteria ($P < .001$), which, in turn, was 7.2% higher than using the UK criteria ($P < .001$) (Table 3). Results obtained in the sensitivity analysis were consistent with those observed in the primary analysis (Supplementary Table 1, available online).

As mentioned, 255 (5.0%) individuals had an APN. Evaluation of accuracy of the three sigmoidoscopy-based strategies for their identification demonstrated an increase in sensitivity (from 22.4% to 36.9%; $P < .001$ for all three pairwise comparisons) associated with an equivalent decrease in specificity (from 94.6% to 83.0%; $P < .001$ for all three pairwise comparison) and positive predictive value (from 18.0% to 10.3%) when passing from the most strict UK criteria to the most generous NORCCAP criteria (Table 4). In fact, the NORCCAP strategy obtained the highest sensitivity for APN detection (36.9%), whereas the UK approach reached the highest specificity (94.6%). Of note, when evaluation was limited to those 27 patients diagnosed with CRC, only 1 of 6 (16.7%) individuals with proximal CRC had distal findings that would have triggered a colonoscopy, regardless of which referral criteria were used. These results were identical when lesions in the descending colon were also considered in the sensitivity analysis.

Sensitivity of sigmoidoscopy-based strategies for the detection of APN was lower in women than in men (age-adjusted χ^2 test, $P < .001$ for any screening strategies), but no statistically significant difference was observed when comparing individuals aged 60–69 years with those aged 50–59 years (sex-adjusted χ^2 test, $P = .12$ for UK, $P = .18$ for SCORE, and $P = 0.35$ for NORCCAP) (Table 4). Interestingly, however, when the prevalence of advanced distal and proximal neoplasms was evaluated (Table 5), women aged 60–69 years had the highest ratio (1.57), indicating a predominance of distal advanced neoplasms; men aged 50–59 years showed the lowest ratio (1.02); and the remaining two subgroups achieved intermediate values (women aged 50–59 years, 1.26; men 60–69 years, 1.21). These differences in the relative proportion of distal and proximal lesions among age and sex subgroups had an impact on the diagnostic yield of sigmoidoscopy-based strategies (Table 3), especially for the most stringent criteria; that is, the overall detection rate was relatively highest in women aged 60–69 years when the UK criteria were used (4.7% with respect to the 7.3% obtained in the colonoscopy).

In the sensitivity analysis, performance characteristics of sigmoidoscopy-based strategies (Supplementary Table 2, available

online) and the differences in the relative proportion of distal and proximal lesions among age and sex subgroups (data not shown) were consistent with those obtained in the primary analysis.

Analysis of Resources

When the UK criteria were used, the number of individuals needed to screen to detect one APN was 65% and 40% higher than when the NORCCAP and SCORE criteria, respectively, were employed (Table 6). This increment in screening resources was, however, counteracted by the number of individuals needed to refer for colonoscopy to find one APN, which was 6 (95% CI = 4–7) for UK, 8 (95% CI = 6–9) for SCORE, and 10 (95% CI = 8–12) for NORCCAP (Table 6), thus representing a 42% and 26% saving when UK criteria were used with respect to NORCCAP and SCORE strategies, respectively.

The number of individuals needed to screen and to refer for colonoscopy increased in those subgroups of individuals with a lower prevalence of APN (Table 6). Interestingly, the above-mentioned saving in the number of individuals needed to refer for colonoscopy using the UK criteria was maintained in men of any age and in women aged 60–69 years, being the largest benefit in the latter subgroup.

Results obtained in the sensitivity analysis were consistent with those observed in the primary analysis (Supplementary Table 3, available online).

Distal Findings Associated With Advanced Proximal Neoplasms

The logistic regression analysis identified the presence of any distal adenoma of 6–9 mm in diameter (OR = 1.84; 95% CI = 1.22–2.78), any distal adenoma ≥10 mm in diameter (OR = 3.77; 95% CI = 2.52–5.65), and any distal adenoma with high-grade dysplasia (OR = 2.83; 95% CI = 1.49–5.36), along with age and sex, as independently associated with the presence of any advanced neoplasm located proximally to the sigmoid colon in the whole series (Table 7).

Distal findings associated with APN varied among age- and sex-specific subgroups (Table 7). Indeed, the presence of any distal adenoma ≥10 mm in diameter was the only polyp characteristic maintaining its predictive value both in men of any age and in women aged 60–69 years. On the other hand, it was not possible to identify any distal finding associated with APN in women aged 50–59 years.

Discussion

This post hoc analysis of the COLONPREV study demonstrated statistically significant differences among all three sigmoidoscopy-based screening strategies. Whereas the NORCCAP criteria (19) achieved the highest overall advanced neoplasm detection rate associated with the highest sensitivity for detecting APN, the set of criteria proposed in the UK Flexible Sigmoidoscopy Trial (8) benefited from the lowest number of individuals needed to refer for colonoscopy associated with the highest specificity.

Identification of reliable distal markers for APN is a critical issue for sigmoidoscopy-based strategies. It is generally accepted that presence of polyps in the distal colon is associated with an increased risk of APN and, more important, that the magnitude of

Table 3. Overall advanced neoplasm detection rate of sigmoidoscopy-based screening strategies relative to colonoscopy

Setting	Colonoscopy Detection rate†, No. (%)	UK criteria*				SCORE criteria*				NORCCAP criteria*			
		Detection rate†, No. (%)	OR‡	95% CI‡	P‡	Detection rate†, No. (%)	OR‡	95% CI‡	P‡	Detection rate†, No. (%)	OR‡	95% CI‡	P‡
Overall (n = 5059)	520 (10.3)	317 (6.3)	0.57	0.49 to 0.67	<.001	340 (6.7)	0.62	0.54 to 0.72	<.001	355 (7.0)	0.65	0.56 to 0.75	<.001
Men aged 60–69 y (n = 1109)	197 (17.8)	124 (11.2)	0.58	0.45 to 0.74	<.001	135 (12.2)	0.64	0.50 to 0.81	<.001	141 (12.7)	0.67	0.53 to 0.85	.001
Men aged 50–59 y (n = 1349)	151 (11.2)	89 (6.6)	0.55	0.42 to 0.73	<.001	98 (7.3)	0.62	0.47 to 0.81	<.001	103 (7.6)	0.65	0.50 to 0.85	.001
Women aged 60–69 y (n = 1194)	87 (7.3)	56 (4.7)	0.62	0.44 to 0.88	.007	57 (4.8)	0.63	0.45 to 0.90	.009	58 (4.8)	0.65	0.46 to 0.91	.01
Women aged 50–59 y (n = 1407)	85 (6.0)	48 (3.4)	0.55	0.38 to 0.79	.001	50 (3.6)	0.57	0.40 to 0.82	.002	53 (3.8)	0.61	0.43 to 0.86	.005

* Rectum and sigmoid colon were considered for sigmoidoscopy simulation. CI = confidence interval; OR = odds ratio.

† Detection rate was calculated as the number of true positives relative to the number of participating individuals.

‡ Detection rate of each sigmoidoscopy-based screening strategy was compared with the detection rate obtained in the colonoscopy by logistic regression analysis; results were adjusted by participating center.

Table 4. Performance characteristics of sigmoidoscopy-based screening strategies in detecting any advanced proximal neoplasm

Setting	Individuals with APN No. (%)	UK criteria*				SCORE criteria*				NORCCAP criteria*			
		Se (95% CI)	Sp (95% CI)	PPV (95% CI)	NPV (95% CI)	Se (95% CI)	Sp (95% CI)	PPV (95% CI)	NPV (95% CI)	Se (95% CI)	Sp (95% CI)	PPV (95% CI)	NPV (95% CI)
Overall (n = 5059)	255 (5.0)	0.22 (0.18 to 0.29)	0.95 (0.94 to 0.95)	0.18 (0.14 to 0.23)	0.96 (0.95 to 0.96)	0.31 (0.26 to 0.37)	0.89 (0.88 to 0.90)	0.13 (0.11 to 0.16)	0.96 (0.95 to 0.97)	0.37 (0.31 to 0.43)	0.83 (0.82 to 0.84)	0.10 (0.08 to 0.12)	0.96 (0.95 to 0.97)
Men aged 60–69 y (n = 1109)	99 (8.9)	0.30 (0.22 to 0.40)	0.91 (0.89 to 0.92)	0.24 (0.17 to 0.32)	0.93 (0.91 to 0.94)	0.41 (0.32 to 0.51)	0.83 (0.81 to 0.85)	0.19 (0.15 to 0.25)	0.93 (0.92 to 0.95)	0.46 (0.37 to 0.56)	0.76 (0.73 to 0.78)	0.16 (0.12 to 0.20)	0.94 (0.92 to 0.95)
Men aged 50–59 y (n = 1349)	83 (6.2)	0.25 (0.17 to 0.36)	0.95 (0.93 to 0.96)	0.24 (0.16 to 0.33)	0.95 (0.94 to 0.96)	0.36 (0.27 to 0.47)	0.88 (0.86 to 0.89)	0.16 (0.12 to 0.23)	0.95 (0.94 to 0.97)	0.42 (0.32 to 0.53)	0.82 (0.80 to 0.84)	0.13 (0.10 to 0.18)	0.96 (0.94 to 0.97)
Women aged 60–69 y (n = 1194)	35 (2.9)	0.14 (0.06 to 0.29)	0.96 (0.94 to 0.97)	0.09 (0.04 to 0.19)	0.97 (0.96 to 0.98)	0.17 (0.08 to 0.33)	0.91 (0.90 to 0.93)	0.06 (0.03 to 0.12)	0.97 (0.96 to 0.98)	0.20 (0.10 to 0.36)	0.86 (0.84 to 0.88)	0.04 (0.02 to 0.08)	0.97 (0.96 to 0.98)
Women aged 50–59 y (n = 1407)	38 (2.7)	0.03 (0.01 to 0.13)	0.97 (0.95 to 0.97)	0.02 (0.01 to 0.11)	0.97 (0.96 to 0.98)	0.08 (0.03 to 0.21)	0.92 (0.91 to 0.93)	0.03 (0.01 to 0.08)	0.97 (0.96 to 0.98)	0.16 (0.07 to 0.30)	0.87 (0.85 to 0.89)	0.03 (0.02 to 0.07)	0.97 (0.96 to 0.98)

* Rectum and sigmoid colon were considered for sigmoidoscopy simulation. UK = UK Flexible Sigmoidoscopy Trial (8); SCORE = SCORE Trial (11); NORCCAP = NORCCAP Trial (19). APN = advanced proximal neoplasm (ie, cancer or advanced adenoma) with respect to the sigmoid colon; CI = confidence interval; NPV = negative predictive value; PPV = positive predictive value; Se = sensitivity; Sp = specificity.

Table 5. Distribution of distal and proximal advanced neoplasms according to age and sex*

Sex and age distribution	Prevalence of advanced distal neoplasm, No. (%; 95% CI)	Prevalence of APN, No. (%; 95% CI)	Ratio distal/proximal advanced neoplasm
Overall (n = 5059)	308 (6.1; 5.5 to 6.8)	255 (5.0; 4.5 to 5.7)	1.21
Men aged 60–69 y (n = 1109)	120 (10.8; 9.1 to 12.8)	99 (8.9; 7.4 to 10.7)	1.21
Men aged 50–59 y (n = 1349)	85 (6.3; 5.1 to 7.7)	83 (6.2; 5.0 to 7.6)	1.02
Women aged 60–69 y (n = 1194)	55 (4.6; 3.6 to 5.9)	35 (2.9; 2.1 to 4.1)	1.57
Women aged 50–59 y (n = 1407)	48 (3.4; 2.6 to 4.5)	38 (2.7; 2.0 to 3.7)	1.26

* APN = advanced proximal neoplasm (ie, cancer or advanced adenoma) with respect to the sigmoid colon; CI = confidence interval.

Table 6. Number of individuals needed to screen and to refer for colonoscopy to detect one advanced proximal neoplasm according to each sigmoidoscopy-based screening strategy

Sex and age distribution	UK criteria*, No. (95% CI)	SCORE criteria*, No. (95% CI)	NORCCAP criteria*, No. (95% CI)
Number needed to screen with sigmoidoscopy to detect one advanced proximal neoplasm			
Overall	89 (69 to 115)	63 (51 to 79)	54 (44 to 66)
Men aged 60–69 y	37 (26 to 53)	27 (20 to 37)	24 (18 to 32)
Men aged 50–59 y	64 (42 to 98)	45 (32 to 64)	39 (28 to 53)
Women aged 60–69 y	239 (102 to 559)	199 (92 to 434)	171 (83 to 352)
Women aged 50–59 y	1407 (249 to 7970)	469 (160 to 1379)	235 (108 to 511)
Number needed to refer for colonoscopy to detect one advanced proximal neoplasm			
Overall	6 (4 to 7)	8 (6 to 9)	10 (8 to 12)
Men aged 60–69 y	4 (3 to 6)	5 (4 to 7)	6 (5 to 8)
Men aged 50–59 y	4 (3 to 6)	6 (4 to 8)	8 (6 to 10)
Women aged 60–69 y	11 (5 to 26)	18 (8 to 32)	24 (12 to 49)
Women aged 50–59 y	48 (9 to 271)	37 (13 to 107)	31 (14 to 67)

* Rectum and sigmoid colon were considered for sigmoidoscopy simulation. CI = confidence interval; UK = UK Flexible Sigmoidoscopy Trial (8); SCORE = SCORE Trial (11); NORCCAP = NORCCAP Trial (19).

this risk is proportional to histologic features of the distal lesion (15,22). However, there is less agreement about whether such a risk is related to the size of distal adenomas, this circumstance being translated into different criteria of postsigmoidoscopy referral to colonoscopy (ie, the UK criteria consider any polyp ≥10 mm, the SCORE criteria consider any polyp >5 mm, and the NORCCAP criteria consider any polyp ≥10 mm and any adenoma regardless of size) (8,11,19). According to the results of our analysis, the NORCCAP criteria were associated with a modest but statistically significant increase in the overall advanced neoplasm detection rate, paralleling their high sensitivity for detecting APN. On the other hand, the UK criteria achieved the highest specificity, which is clinically relevant because of the relatively low prevalence of advanced neoplasms in a screening setting. Interestingly, the multivariable analysis of distal findings associated with APN identified adenoma size and presence of high-grade dysplasia as independent predictive characteristics; distal adenoma of ≥10 mm in diameter was the strongest predictor in the whole series as well as the only parameter that prevailed in three of four age- and sex-specific subsets of individuals, thus supporting the UK algorithm in which this adenoma size was considered. The fact that it was not possible to identify any predictor in the fourth subgroup probably reflects a sample size limitation in the subset of women aged 50–59 years. More importantly, the UK recommendations were associated with a saving on the number of individuals needed to refer for colonoscopy to find one APN with respect to the NORCCAP and SCORE criteria, thus favoring the former strategy in terms of resources needed.

It is beyond the scope of our analysis to compare the efficacy of sigmoidoscopy with respect to colonoscopy. Indeed, sigmoidoscopy has been demonstrated to reduce CRC-specific mortality (8,9) and incidence (8,9,11) in randomized controlled trials and, accordingly, has received full recognition as an effective CRC screening strategy (2,12,13). It is also certain, however, that sigmoidoscopy has long been criticized because of its lower ability to detect APN lesions with respect to colonoscopy (15,23,24). In that sense, our analysis indicates that sigmoidoscopy-based strategies detected 35%–43% fewer individuals with advanced neoplasms than did colonoscopy, with a sensitivity for identifying APN of 22%–37%, similar to results of previous studies (15,24). A potential approach to further improve the efficacy of sigmoidoscopy could be to repeat it periodically, rather than performing this examination only once, although results on participation, diagnostic yield, and complication rate of this approach cannot be anticipated.

Performance of sigmoidoscopy-based strategies depending on age and sex deserve some comments. As expected, both parameters were independent predictors of APN, given that the prevalence of such lesions was lower in women than in men, as well as in individuals aged 50–59 years than in those aged 60–69 years. Because prevalence of proximal lesions could parallel the prevalence of colorectal lesions at any site, it was reasonable to evaluate the relative distribution of both proximal and distal neoplasms in each age- and sex-specific subgroup. Accordingly, it has been suggested that as a consequence of an aging and increasingly female population, the epidemiology of CRC has changed in recent decades, with patients having fewer distal and more proximal neoplasms

Table 7. Characteristics independently associated with the presence of any advanced proximal neoplasm*

Characteristic	Overall			Male, 60–69 y			Male, 50–59 y			Female, 60–69 y			Female, 50–59 y		
	ORt	95% CI	P	ORt	95% CI	P	ORt	95% CI	P	ORt	95% CI	P	ORt	95% CI	P
Sex, male	2.52	1.89 to 3.34	<.001	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Age	1.05	1.02 to 1.07	<.001	1.10	1.03 to 1.18	.009	1.10	1.01 to 1.20	.03	1.19	1.05 to 1.34	.006	—	—	—
Distal adenoma of 6–9 mm in diameter	1.84	1.22 to 2.78	.004	—	—	—	2.45	1.28 to 4.69	.007	—	—	—	—	—	—
Distal adenoma of ≥10 mm in diameter	3.77	2.52 to 5.65	<.001	4.07	2.29 to 726	<.001	4.26	2.07 to 8.79	<.001	3.88	1.28 to 11.73	.02	—	—	—
Distal adenoma with high-grade dysplasia	2.83	1.49 to 5.36	.001	3.22	1.23 to 8.44	.02	5.48	1.86 to 15.97	.002	—	—	—	—	—	—

* Advanced proximal neoplasm was defined as any advanced neoplasm (ie, cancer or advanced adenoma) located proximally to the sigmoid colon. To facilitate the interpretation of data, only variables achieving statistical significance were shown (otherwise, a dash is depicted). CI = confidence interval; OR = odds ratio; NA = not applicable.

† A Forward LR, stepwise logistic regression analysis was performed to identify distal findings independently associated with the presence of advanced proximal neoplasm; results were adjusted by participating center.

over time (25). This leads to the assumption that sigmoidoscopy should not be recommended in older individuals, especially women (18). According to our results, however, women aged 60–69 years would benefit the most from sigmoidoscopy-based screening as they had the highest predominance of distal advanced neoplasms, in concordance with the results obtained in the SCORE trial (11) and in another recent study (26). This information, along with the overall performance of sigmoidoscopy in terms of detection rate and resources needed in each age- and sex-specific subgroup, may contribute to the tailoring of CRC screening based on population characteristics (27–29).

This study has several strengths. First, it is based on the results of a large, prospective, multicenter, nationwide, randomized controlled trial, in which a strict quality assurance program was followed (20,21), thus ensuring the reliability of data. Second, it represents the first study in which the three strategies of postsigmoidoscopy referral to colonoscopy were compared, thus providing valuable information for an accurate estimation of human, economic, and logistical needs with unequivocal impact on public health policies. Third, the analysis of results both overall and after stratifying by age and sex permits a more accurate ascertainment of usefulness of screening strategies and, consequently, facilitates a more efficient implementation in a population-based setting. In that sense, it is important to mention that although there was a discrepancy in age groups between the UK and SCORE trials and the COLONPREV study (ie, 55–64 years vs 50–69 years, respectively), results obtained in our analysis in the subset of individuals aged 55–64 did not differ from those observed in the whole series (data not shown).

We are aware, however, of some limitations of the study. First, data on the sigmoidoscopy yield were extrapolated from colonoscopy results, thus introducing some degree of uncertainty because of the unreliability of endoscopist assessment on the real polyp location. This potential bias, however, was minimized by performing a sensitivity analysis in which the descending colon was included in the distal colon. As shown, both estimations were consistent with respect to any evaluated parameter, thus reinforcing the conclusions of the study. Moreover, extrapolation of sigmoidoscopy data from colonoscopy results, an approach also employed in similar studies (15,18,24), has the additional advantage of establishing the real accuracy of sigmoidoscopy for APN, which cannot be fully ascertained in a real flexible sigmoidoscopy setting (in which colonoscopy is not routinely performed in individuals without distal lesions). It is also important to mention that our results did not differ from those observed in a sigmoidoscopy scenario (16), including the only randomized controlled trial comparing directly the performance of colonoscopy and sigmoidoscopy (30), or from studies of similar characteristics (15,18,24,26). Finally, the regression analysis of distal lesion characteristics associated with APN contributed to a better understanding of the main reasons for the observed differences among strategies. A second limitation of this analysis was the low acceptance rate for colonoscopy in the COLONPREV study, which was lower than expected according to colonoscopy-based strategies in the United States but similar to the results obtained in other trials performed in a similar setting (30). Although this circumstance could potentially represent a selection bias, the analysis of baseline characteristics of patients included in

our study (20) makes this possibility unlikely and confirms that the colonoscopy cohort is representative of the screening population.

In conclusion, the NORCCAP criteria (19) benefit from the highest overall advanced neoplasm detection rate whereas criteria proposed in the UK Flexible Sigmoidoscopy Trial (8) seem to be the most appropriate in terms of saving resources. Confirmation of these results, as well as those observed in the prevalence of APN and effectiveness of sigmoidoscopy among age- and sex-specific subgroups in an independent dataset, may contribute to further expansion and tailoring of CRC screening strategies in average-risk populations.

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Notes

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Specific contributions of investigators:

Antoni Castells, Xavier Bessa, Enrique Quintero, and Montserrat Andreu designed the analysis; Cristina Hernández gathered the data; Antoni Castells, Xavier Bessa, Enrique Quintero, and Montserrat Andreu analyzed the data; Antoni Castells, Xavier Bessa, Enrique Quintero, Montserrat Andreu, Luis Bujanda, Joaquín Cubiella, Dolores Salas, Ángel Lanas, Fernando Carballo, Juan Diego Morillas, and Rodrigo Jover vouch for the data and the analysis, and made the decision to publish the paper; Antoni Castells, Xavier Bessa, Enrique Quintero, and Montserrat Andreu wrote the paper. Ángel Lanas, María-Pilar Roncales, and Francisca González-Rubio were responsible for the development of the study in Aragón; Luis Bujanda, Isabel Montalvo, Juan Arenas, and Ángel Cosme in the Basque Country; Enrique Quintero, Inmaculada Alonso-Abreu, Marta Carrillo-Palau, and Mariola de la Vega-Prieto in Canarias; Montserrat Andreu, Antoni Castells, Xavier Bessa, Agustín Seoane-Urgorri, Jaume Grau, Maria Pellisé, and Anna Serradesanferm in Catalonia; Joaquín Cubiella, Vicent Hernández, Begoña Iglesias, Lucía Cid, and Inés Castro in Galicia; Juan Diego Morillas, Rosario Iglesias, Javier Amador, José Manuel Blanco, Rocio Sastre, Juan Ferrándiz, and Mª José González-Hernández in Madrid; Fernando Carballo, Akiko Ono, José Cruzado, and Francisco Pérez-Riquelme in Murcia; Dolores Salas, Teresa Sala, Marta Ponce, Mercedes Andrés, Gloria Teruel, and Antonio Peris in Valencia. Rodrigo Jover chaired the Quality Committee of the study.

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