Capability of four sigmoidoscopy-based screening strategies to predict proximal neoplasia in an asymptomatic Chinese population

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Abstract

Background and Aim: A proper colonoscopy referral criterion is essential for flexible sigmoidoscopy-based colorectal cancer screening. We aimed to compare the predictive capability of four existing criteria to detect proximal neoplasia (PN) and advanced proximal neoplasia (APN) in a Chinese population.

Methods: Asymptomatic Chinese participants aged 50–75 years, who received screening colonoscopy, were consecutively recruited. The four criteria included (i) UK flexible sigmoidoscopy; (ii) Italian Screening for COlon REctum; (iii) NORwegian Colorectal Cancer Prevention trial; and (iv) US clinical index. The sensitivity, specificity, positive/negative predictive value, and the number of subjects needed to screen (NNS)/refer (NNR) to detect one APN/PN were examined. The area under receiver operating characteristic curve was evaluated.

Results: Among 5833 subjects, 749 (12.8%) and 151 (2.6%) cases were found to have PN and APN, respectively. US criteria achieved the highest sensitivity for PN (49%) and APN (66%), while UK criteria attained the highest specificity (93%) for PN/APN. The lowest NNS was required by US criteria for PN (16 vs 19–38) and APN (58 vs 69–86), while the lowest NNR was required by UK criteria for PN (3.2 vs 4.0–4.8) and APN (7 vs 10– 16). The receiver operating characteristic of all four criteria was 0.57–0.61 for PN and 0.68–0.70 for APN.

Conclusions: Among all the four criteria, US criteria had the highest sensitivity and lowest NNS, while UK criteria achieved the highest specificity and lowest NNR. Their limited discriminatory capability highlighted the need for a new score to predict PN/APN in Chinese populations.

Introduction

Colorectal cancer (CRC) is the third most common cancer worldwide and accounts for 10% of all new cancer diagnoses.[1] A substantial body of evidence shows that screening is efficient and cost-effective to reduce CRC-related mortality.[2] Among published studies, several randomized controlled trials of sigmoidoscopy (FS)-based programmes demonstrated a decrease of 22%-30% in CRC-specific mortality.[3-6] In addition, the capability of colonoscopy and FS to detect and remove colorectal adenomas by endoscopic polypectomy places these screening modalities as recommended CRC screening tests, as endorsed by international guidelines and Asia Pacific consensus statements.[7-9] In some countries, these endoscopy-based procedures have been extensively used as primary screening tools.[10] Office-based FS requires a simple bowel preparation without needs for sedation. It could also be performed with promising quality by primary care physicians. Its simplicity and convenience make it a popular CRC screening test in countries which relatively lack colonoscopic capacity.[11] Moreover, the long-term effectiveness of FS screening in population-based programmes[4-6] makes it a feasible approach for a government subsidized screening programmes where CRC imposes a heavy healthcare burden.[12]

However, because FS cannot visualize the proximal colon, its application is preferred for subjects with low risks of advanced proximal neoplasia (APN),[13] especially in the context of proximal shift of CRC[14] and increasing prevalence of isolated proximal neoplasia without distal colorectal lesions in the general populations.[15] The referral criteria for colonoscopy workup after FS is a key determinant of the efficiency and effectiveness of FS-based CRC screening programmes.

Currently, there is no universal consensus on when colonoscopy referral should be initiated based on the distal findings of proximal neoplasia (PN) or APN after FS was performed. Three available scores were devised in European trials and they have been applied in Italy, Norway and UK for

many years based on FS findings.[4-6] Another US APN risk criteria was designed to predict APN based on age, gender and distal findings. Wong et al conducted a similar comparison among the above four criteria in a Chinese population,[16] but its focus is mainly on APN as the outcome from on a cohort of self-referred, asymptomatic individuals, and the authors recommended future research in other Asian populations. Chinese subjects consist of more than one-fifth of the world's population, apart from millions of ethnic Chinese residing in various parts of the globe. There is a scarcity of studies on this population regarding prediction of APN/PN, which bears substantial implications for clinical practice and screening policymaking.

This comparative study aims to investigate the predictive capability and colonoscopy resources required to detect APN/PN in a large Chinese screening population based on the above four existing criteria. We tested the *a priori* hypothesis that these prediction algorithms could accurately predict APN/PN, as reflected by their concordance statistics.

Patients and methods

Subjects recruitment

The study setting has been described as published elsewhere.[17] Briefly, from January 2013 to December 2015, all asymptomatic Chinese subjects who received screening colonoscopies in a large endoscopy center of Ruijin Hospital North, Shanghai Jiaotong University, were prospectively recruited. The inclusion criteria included: (1) aged 50-75 years; (2) no symptoms of CRC, including rectal bleeding, anorexia or changes in bowel habit in the past 4 weeks, or weight loss of >5 kg in the past 6 months and (3) not having received any CRC colonoscopy screening tests in the past 5 years (16).The exclusion criteria were: (1) incomplete caecal intubation; (2) poor bowel preparation; and (3) diagnosis of other colorectal diseases after colonoscopy test, like inflammatory bowel disease and familial adenomatous polyposis. We recruited a total of 5,833 screening

participants consecutively in this study. All clinical procedures were performed in accordance with the relevant guidelines and regulations. The collection and use of clinical data was approved by the Research Ethics Committee of Ruijing Hospital North. Study details were given to all participants and written informed consent was obtained from all subjects before case enrolment.

Study procedures and definitions

We use routine bowel preparation procedures with total three litters of polyethylene glycol lavage solution in split dosing. Colonoscopy was performed by experienced gastroenterologists in the North Ruijin Hospital. Complete colonoscopy was defined as caecal intubation with photographic evidence of the caecum. The size of a polyp was estimated by open-biopsy forceps before polypectomy was performed. Gastroenterologists performing the colonoscopies were blinded to the study design. They defined the location of all lesions as distal (for lesions located in the rectum, sigmoid, or descending colon) and proximal (those located in the splenic flexure, transverse colon, hepatic flexure, ascending colon, or cecum). Polyps judged as too large for polypectomy and other suspicious lesions were biopsied. All polyp samples were sent for histologic examination in an accredited laboratory. Histologic specimens were reviewed by an experienced team of expert pathologists who were blinded to the colonoscopy reports and the study design throughout the study. The reporting of histology for colorectal neoplasms is classified according to WHO histology reporting criteria.[18] Advanced neoplasia was defined as invasive cancer, an adenoma sized at 10 mm or more, any lesions with at least 25% villous components, an adenoma with high-grade dysplasia, or cancer. Individuals with a pathologic interpretation of carcinoma in situ were classified as subjects with high-grade dysplasia.[19]

Colonoscopy referral criteria

These strategies were: (1) the UK FS criteria: one distal polyp ≥10 mm, of tubullovillous or villous histology, high-grade dysplasia, ≥3 adenomas, CRC or ≥ 20 hyperplastic polyps above the distal

rectum;[6] (2) the Screening for COlon REctum (SCORE) criteria: one distal polyp >5 mm, tubullovillous or villous histology, high-grade dysplasia, ≥3 adenomas or CRC;[4] (3) the NORwegian Colorectal Cancer Prevention (NORCCAP) criteria: one distal polyp ≥10 mm, any adenoma or CRC;[5] and (4) the US APN prediction model.[20] The US criteria employed age (50–54 years: 0; 55–59 years: 1; 60–64 years: 2; 65–70 years: 3); gender (female: 0; male: 1) and distal findings (no polyps: 0; hyperplasia: 1; tubular adenoma <10 mm 2; advanced lesion: 3) as predictors. All eligible participants were assigned an APN risk score with the above three factors and categorized into low ('0–1'), intermediate ('2–3') and high ('4–7') risk group. In present study, we selected the high-risk group (score ≥4) as the criterion for colonoscopy referral, as recommended by the authors of the original study.

Outcome indexes and statistical analysis

The predictive capability of all FS based strategies to detect APN /PN was assessed. The outcomes include sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV). Pairwise comparisons among strategies regarding sensitivity and specificity were performed using McNemar test for paired proportions. The analysis of resources was conducted by calculating the number of subjects needed to screen and the number of subjects needed to refer for colonoscopy to detect one APN/PN. These parameters represent the average number of people who need to be screened by FS or to be referred for colonoscopy on the basis of FS results, respectively, to identify one case of APN/PN.[16] To adjust for age and gender, we stratified the participants by different age (50-64 years and 65-75 years) and gender (male vs. female) categories to evaluate the APN/PN performance of the above criteria. The area under the receiver operating characteristics (ROC) curve was also estimated for each criterion in APN/PN respectively.

Data analyses were performed using the SPSS statistical software, version 21.0 (SPSS Inc, Chicago, IL). All statistical tests were two-sided, and all p values less than 0.05 were considered to be

statistically significant.

Results

General characteristic

A total of 5,833 participants were enrolled in our study with an average age of 60.1 years (±6.2) and a female portion of 53.3% (n=3,107). In term of the most advanced colonoscopic findings of the entire cohort, the proportion of subjects having CRC, advanced adenoma, non-advanced adenoma, and hyperplastic polyp was 1.3%, 5.0%, 21.5%, and 11.2%, respectively. The overall advanced colorectal neoplasia (ACN) and APN were detected in 6.3% (n=367) and 2.6% (n=151), respectively. The corresponding prevalence of any colorectal neoplasia (in other words, adenoma detection rate (ADR)) and PN was 27.8% (n=1,620) and 12.8% (n=749) (**Table 1**).

Distribution of APN and PN according to age and gender

Men aged 65-75 years old had the highest prevalence of APN (5.2%) (**Table 2**). Although the prevalence of APN in older age group (65-75 years old) was higher than that in the younger age group (50-64 years old) (p<0.001), there is no difference in APN prevalence between men and women aged 65-75 years (P=0.389). Among the younger age group, the prevalence of APN was much higher in men when compared with women (3.1% vs. 0.7%, p<0.001). The proportion of isolated APN was highest in women aged 65-75 years old (2.9%), and lowest in women aged 50-64 years old (0.6%). There was a significant difference between the prevalence of PN in men and women and across different age groups (all p< 0.001) (**Table 3**). Men aged 65-75 years old had the highest prevalence of PN (23.0%), while women aged 50-64 years old had the lowest prevalence (7.3%). The prevalence of isolated PN was the highest in men aged 65-75 years old (17.9%) and lowest in women aged 50-64 years old (6.3%).

Performance of APN and PN detection among four criteria

The US criteria had the highest sensitivity for APN (0.66, 95% CI 0.59 to 0.74) and the UK criteria had the lowest (0.45, 95% CI 0.37 to 0.53) (**Table 4**). On the contrary, the UK criteria had the highest specificity for APN (0.93, 95% CI 0.92 to 0.93) and the US criteria had the lowest (0.74, 95% CI 0.73 to 0.75). All the criteria had a low PPV (0.06-0.14) but high NPV (0.98-0.99) for APN, and the ROC for APN ranged from 0.68 to 0.70. These observations were similar for PN. Overall, the PPV of PN ranged from 0.21 to 0.32, and the NPV of PN from 0.89 to 0.91. The ROC for PN and APN was 0.57-0.61 and 0.68-0.70.

Resources for screening and colonoscopy referral

Table 5 shows the resources required for screening one APN according to the different colonoscopy referral criteria. The NNS to detect one APN was the highest (n=86) when the UK criteria were used, compared with other criteria. However, the NNR of UK criteria was the lowest (n=7 vs 10–16), indicating that the least resources were required if the UK criteria was adopted. Women aged 50–59 years had much higher NNS and NNR, which is compatible with the relatively low prevalence of APN in this subgroup (0.7%). **Table 6** demonstrates the resources required for screening one PN. Again, the NNS to detect one PN was the lowest (n=16) in the US criteria, while the NNR of US criteria was the highest (n=4.8 vs 3.2-4.0), showing that the most resources were required from US criteria.

Discussion

This study evaluated the performance of four major criteria for colonoscopy referral for FS-based screening strategies in a large population asymptomatic Chinese individuals. As we reported before, there was a substantial difference in the distribution of APN among different age and gender subgroups.[21] In other words, the lower prevalence of APN and isolated APN in women aged 50-64

years old compared to other groups indicated that FS could be a rational option for endoscopic choice for these younger women. Otherwise, 475 (95% CI 195 to 1,305) colonoscopies were needed to detect one APN among this population with a low risk of APN. This similar finding was reported in the study by Imperiale and colleagues.[22] On the contrary, individuals aged 65 years or older had a higher prevalence of APN and isolated APN, who are therefore more suited to receive colonoscopy, or nearly half of APN (45.7%, 16/35) would be missed in women aged 65-75 years old if they only received colonoscopy upon distal lesions detected by FS.

A similar distribution pattern of PN and isolated PN was detected among different age and gender subgroups. The main difference was that the prevalence of PN and isolated PN in men aged 65-75 years old was significantly higher than that of women with the same age range. Over one-fifth of them (23.0%, 95% CI 20.1% to 26.2%) will have neoplasm findings in their proximal colon regardless of the distal findings. Theoretically, over one-fifth of screening participants with false negative results from faecal occult blood test would have precancerous lesions of proximal colon missed if a faecal test is used as procedure primary screening test. Thus, these elderly male individuals should consider receiving colonoscopy as a preferred CRC screening test if there are no contraindications.

Among the four referral criteria, the US criteria had the highest sensitivity and the lowest NNS, while the UK criteria had the highest specificity and the lowest NNR. Because the US criterion was designed for detection of APN, its ROC was the highest (0.70, 95% CI, 0.66 to 0.74) among the four criteria. Nevertheless, regardless of which criteria was applied to this Chinese population, the concordance statistics was modest, implying the need to devise a novel model for prediction of APN/PN in ethnic Chinese.

Our findings were consistent with a previous study performed by Wong et al.[16] In their study to evaluate detection of APN among the same four criteria, the US criteria had the highest sensitivity

and lowest NNS, while the UK score had the highest specificity and the lowest NNR for further colonoscopy. Subjects in the present study were older (60.1 years vs. 57.7 years), had a higher prevalence of ACN (6.3% vs. 6.0%) and a lower prevalence of non-advanced adenoma (21.5% vs. 26.5%). The sample size (5,833 vs. 5,879), gender distribution (proportion of female 53.3% vs. 53.0%) and prevalence of APN (2.6% vs. 2.6%) are similar between the two studies. Both studies were conducted in an asymptomatic Chinese cohort and found only modest performance of the four criteria to predict APN. Among existing validation studies for prediction of APN, both Levitzky et al[23] and Ruco et al[24] utilized US criteria in a Western population, and concluded that it had limited ability to discriminate between low- and intermediate-risk categories.

The unique contribution of our study was that we demonstrated a similar conclusion for prediction of PN estimation as for prediction of APN by the four criteria. To date, very few studies have ever evaluated the accuracy of predicting PN by published scores, and none on Chinese subjects. For instance, in the U.S. national colonoscopy study, Zauber et al concluded that the performance of the UK FS referral algorithm to detect PN/APN was limited, and further steps should be taken to enhance its discriminatory capability.[25]

In addition, distal non-advanced adenoma and ACN, but not distal HP were independent predictors for PN and APN. This is well supported by other studies.[26-28] Since the distal colorectum is exposed to a similar behavioral, environmental and genetic risks level as the proximal colon, distal findings from FS have been regarded by the four criteria as an important predictor for PN/APN. This could also explain why the severer the distal findings were associated with a higher risk for PN and APN.[29] Nevertheless, the newly released prediction tools for APN did not employ distal findings, but other common behavioral or socio-demographic characteristics.[30, 31] The advantage was obvious because no FS test was needed. For example, Imperiale et al[30] included age, sex, cigarette smoking, marital status, metabolic syndrome, use of non-steroidal anti-inflammatory drugs, and physical

activity as independent risk factors. The model was well-calibrated (P = 0.62) and had good discrimination (C-statistic = 0.73). Undoubtedly, more predictors lead to higher c-statistics and better prediction performance, although these are at the expense of reducing practicality in daily clinical practice.

Strengths and limitation

This study has a number of strengths. It is the first study that evaluated the performance of scores predicting both PN and APN based on the most commonly used European and US criteria. The three European referral criteria are derived from well-known clinical trials, [4-6] while the US criteria have been validated in studies on APN.[23, 24] Second, we included a large cohort of asymptomatic, average-risk individuals, which enhances its future application in population-based screening programs. The endoscopists were blinded to the research objectives and determined the location of all colorectal lesions, whilst the pathologists were blinded and independently provided diagnosis based on examination of biopsy samples. These procedures minimized potential information biases. Finally, stringent measures for endoscopic quality were enforced throughout the study, where only experienced gastroenterologists were involved to perform the colonoscopies. The inclusion of colonoscopies where bowel preparations were reported as good or excellent is further enhanced the robustness of the findings. There are however some limitations that should be addressed. Firstly, it did not enroll subjects from a random sampling of the general population. Only one endoscopic center was involved in sampling. Critics would nevertheless argue that a random sampling from multiple centers strategy would not be feasible due to potentially high refusal rates. Also, we estimated APN and PN prediction from the distal findings using simulation from colonoscopy, rather than FS followed by colonoscopy. In the real world, FS were more likely performed by less experienced endoscopists, e.g. primary care professionals, with poorer quality of bowel preparation. Further validation studies using FS as the initial procedure are still required. In addition, the relationship between distal findings and proximal serrated lesions has not been studied due to the

small sample size. Finally, to comprehensively evaluate all four criteria, a cost-effective analysis is warranted- especially under the circumstance that the cost of colonoscopy is relatively low in Asian countries.

Clinical application and future research

The knowledge of prediction criteria for PN and APN deserves more funding for further studies. First, proximal cancer is getting more and more attention because the decrease of CRC mortality was reported to be contributed by reduction of distal, not proximal cancer.[32,33] The limited performance of existing criteria to predict PN/APN highlighted the importance of devising and validating a novel score for FS-based screening programme.

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Table 1 Composition of APN and PN according to distal findings

	Distal Findings				
	AN(%)	NAA(%)	HP(%)	Normal(%)	Total
APN	56(37.1)	27(17.9)	11(7.3)	57(37.7)	151
PN	97(13.0)	202(27.0)	68(9.1)	382(51.0)	749

APN: advanced proximal neoplasia, PN: proximal neoplasia, AN: advanced neoplasia, NAA: non-advanced adenoma, HP: hyperplastic polyp.

Table 2 Prevalence of APN and IAPN according to age and gender

Age and gender distribution	Prevalence of APN, n(%, 95% CI)	P value	Prevalence of isolated APN, n(%, 95% CI)	P value
Overall (n=5833)	151(2.6,2.2 to 3.0)	*<0.001*	57/4076(1.4,1.1 to 1.8)	*0.034*
Men aged 65-75(n=727)	38(5.2,3.8 to 7.1)	0.389	10/429(2.3, 1.2 to 4.3)	0.367
Women aged 65-75 years(n=734)	35(4.8,3.4 to 6.6)		16/552(2.9,1.8 to 4.7)	
Men aged 50-64 years (n=1999)	61(3.1,2.4 to 3.9)	*<0.001*	20/1199(1.3, 0.8 to 2.2)	*0.003*
Women aged 50-64 years(n=2373)	17(0.7,0.4 to 1.2)		11/1896(0.6, 0.3 to 1.1)	

APN: advanced proximal neoplasia, IAPN: isolated advanced proximal neoplasia, CI: confidence interval.

Table 3 Prevalence of PN and IPN according to age and gender

Age and gender distribution	Prevalence of PN n(%, 95% CI)	P value	Prevalence of IPN n(%, 95% CI)	P value
Overall (n=5833)	749(12.8,12.0 to 13.7)	*<0.001*	382/4076(9.4, 8.5 to 10.3)	*<0.001*
Men aged 65-75(n=727)	167(23.0,20.1 to 26.2)	*<0.001*	77/429(17.9, 14.6 to 21.9)	*<0.001*
Women aged 65-75 years(n=734)	111(15.1,12.7 to 17.9)		60/552(10.9, 8.5 to 13.8)	
Men aged 50-64 years (n=1999)	298(14.9,13.4 to 16.5)	*<0.001*	126/1199(10.5, 8.9 to 12.4)	*<0.001*
Women aged 50-64 years(n=2373)	173(7.3,6.3 to 8.4)		119/1896(6.3, 5.3 to 7.5)	

PN: proximal neoplasia, IPN: isolated proximal neoplasia, CI: confidence interval.

Table 4 Comparison of Performance for PN and APN detection among four criteria (95%CI)

	Category	US criteria	NORCCAP criteria	SCORE criteria	UK criteria
APN n=151 (2.6%)	Se	0.66(0.59,0.74)	0.56(0.48,0.64)	0.47(0.40,0.56)	0.45(0.37,0.53)
	Sp	0.74(0.73,0.75)	0.80(0.79,0.81)	0.88(0.87,0.89)	0.93(0.92,0.93)
	PPV	0.06(0.05,0.07)	0.07(0.06,0.08)	0.10(0.08,0.12)	0.14(0.11,0.17)
	NPV	0.99(0.98,0.99)	0.99(0.98,0.99)	0.98(0.98,0.99)	0.98(0.98,0.99)
	ROC	0.70(0.66,0.74)	0.68(0.63,0.73)	0.68(0.63,0.73)	0.69(0.64,0.74)
PN n=749 (12.8%)	Se	0.49(0.45,0.53)	0.40(0.37,0.44)	0.25(0.22,0.28)	0.20(0.18,0.23)
	Sp	0.73(0.71,0.74)	0.82(0.81,0.83)	0.89(0.88,0.90)	0.93(0.93,0.94)
	PPV	0.21(0.19, 0.23)	0.25(0.20,0.27)	0.25(0.22,0.28)	0.32(0.27,0.36)
	NPV	0.91(0.90, 0.92)	0.90(0.89,0.91)	0.89(0.88,0.90)	0.89(0.88,0.90)
	ROC	0.61(0.59,0.63)	0.61(0.59,0.64)	0.57(0.55,0.59)	0.57(0.55,0.59)

PN: proximal neoplasia, APN: advanced proximal neoplasia, Se: Sensitivity, Sp: Specificity; PPV: positive predictive value; NPV: negative predictive value; ROC: receiver operating characteristics; CI: confidence interval.

Table 5 NNS and NNR to detect one APN according to different criteria (n, 95% CI)

	US criteria		NORCCP criteria		SCORE criteria		UK criteria	
NNS with sigmoidoscopy to detect one APN								
Overall (n=5833)	58	(48 to 71)	69	(56 to 85)	81	(64 to 102)	86	(68 to 109)
Men aged 65-75 years(n=727)	19	(14 to 26)	28	(19 to 41)	30	(20 to 45)	32	(21 to 48)
Women aged 65-75 years(n=734)	39	(25 to 61)	46	(28 to 75)	46	(28 to 75)	52	(31 to 90)
Men aged 50-64 years (n=1999)	53	(38 to 72)	53	(38 to 72)	71	(49 to 104)	74	(51 to 108)
Women aged 50-64 years(n=2373)	475	(195 to 1305)	475	(195 to 1305)	593	(220 to 1972)	593	(220 to 1972)
NNR for colonoscopy to detect one APN								
Overall (n=5833)	16	(13 to 19)	14	(12 to 18)	10	(8 to 13)	7	(6 to 9)
Men aged 65-75 years(n=727)	19	(14 to 26)	9	(6 to 12)	6	(4 to 8)	4	(3 to 6)
Women aged 65-75 years(n=734)	10	(6 to 15)	8	(5 to 12)	5	(3 to 6)	4	(3 to 7)
Men aged 50-64 years (n=1999)	14	(10 to 19)	14	(10 to 19)	13	(9 to 18)	8	(6 to 12)
Women aged 50-64 years(n=2373)	31	(13 to 83)	67	(28 to 180)	41	(16 to 132)	26	(10 to 80)

NNS: number need to screen, the total number of subjects in each subgroup divided by the number of subjects referred for colonoscopy and detected as having APN, according to each sigmoidoscopy-based screening strategy.

NNR: number need to refer, the number of subjects referred for colonoscopy divided by the number of subjects referred for colonoscopy and detected as having APN.

APN: advanced proximal neoplasia, CI: confidence interval.

Table 6 NNS and NNR to detect one PN according to different criteria (n, 95% CI)

	US criteria	NORCCP criteria	SCORE criteria	UK criteria
NNS with sigmoidoscopy to detect one PN				
Overall (n=5833)	16 (14 to 18)	19(17 to 21)	32(28 to 36)	38(33 to 45)
Men aged 65-75 years(n=727)	8 (7 to 10)	10(8 to 12)	15(11 to 20)	17(13 to 23)
Women aged 65-75 years(n=734)	14 (11 to 19)	18(13 to 24)	29(20 to 43)	35(23 to 54)
Men aged 50-64 years (n=1999)	12 (10 to 13)	14(12 to 17)	23(18 to 28)	29(23 to 36)
Women aged 50-64 years(n=2373)	44 (34 to 57)	55(41 to 74)	103(68 to 156)	132(83 to 211)
NNR for colonoscopy to detect one PN				
Overall (n=5833)	4.8 (4.4 to 5.2)	4.0(3.6 to 4.4)	4.0(3.5 to 4.5)	3.2(2.8 to 3.6)
Men aged 65-75 years(n=727)	3.4 (2.9 to 4.1)	2.9(2.5 to 3.5)	2.8(2.3 to 3.5)	2.3(1.9 to 3.0)
Women aged 65-75 years(n=734)	3.6 (2.9 to 4.5)	3.0(2.4 to 3.9)	3.2(2.4 to 4.6)	2.7(2.0 to 3.9)
Men aged 50-64 years (n=1999)	4.7 (4.1 to 5.3)	3.8(3.3 to 4.4)	4.0(3.4 to 4.9)	3.2(2.7 to 3.9)
Women aged 50-64 years(n=2373)	8.8 (6.9 to 11)	7.7(5.9 to 10.3)	7.2(5.0 to 10.6)	5.7(3.8 to 8.8)

NNS: number need to screen, the total number of subjects in each subgroup divided by the number of subjects referred for colonoscopy and detected as having PN, according to each sigmoidoscopy-based screening strategy.

NNR: number need to refer, the number of subjects referred for colonoscopy divided by the number of subjects referred for colonoscopy and detected as having PN.

PN: proximal neoplasia, CI: confidence interval.