Original Investigation

Population-Based Colonoscopy Screening for Colorectal Cancer
A European Randomized Clinical Trial

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IMPORTANCE Although some countries have implemented widespread colonoscopy screening, most European countries have not introduced it because of uncertainty regarding participation rates, procedure-related pain and discomfort, endoscopist performance, and effectiveness. To our knowledge, no randomized trials on colonoscopy screening currently exist.

OBJECTIVE To investigate participation rate, adenoma yield, performance, and adverse events of population-based colonoscopy screening in several European countries.

DESIGN, SETTING, AND POPULATION A randomized clinical population-based trial was conducted among 94 959 men and women aged 55 to 64 years of average risk for colon cancer in Poland, Norway, the Netherlands, and Sweden from June 8, 2009 to June 23, 2014.

INTERVENTIONS Colonoscopy screening or no screening.

MAIN OUTCOMES AND MEASURES Participation in colonoscopy screening, cancer and adenoma yield, and participant experience. Study outcomes were compared by country and endoscopist.

RESULTS Of 31 420 eligible participants randomized to the colonoscopy group, 12 574 (40.0%) underwent screening. Participation rates were 60.7% in Norway (5354 of 8816), 39.8% in Sweden (486 of 1222), 33.0% in Poland (6004 of 18 188), and 22.9% in the Netherlands (730 of 3194) ($P < .001$). The cecum intubation rate was 97.2% (12 217 of 12 574), with 9726 participants (77.4%) not receiving sedation. Of the 12 574 participants undergoing colonoscopy screening, we observed 1 perforation (0.01%), 2 postpolypectomy serosal burns (0.02%), and 18 cases of bleeding owing to polypectomy (0.14%). Sixty-two individuals (0.5%) were diagnosed with colorectal cancer and 3861 (30.7%) had adenomas, of which 1304 (10.4%) were high-risk adenomas. Detection rates were similar in the proximal and distal colon. Performance differed significantly between endoscopists; recommended benchmarks for cecal intubation (95%) and adenoma detection (25%) were not met by 6 (17.1%) and 10 of 35 endoscopists (28.6%), respectively. Moderate or severe abdominal pain after colonoscopy was reported by 601 of 3611 participants (16.7%) examined with standard air insufflation vs 214 of 5144 participants (4.2%) examined with CO_2 insufflation ($P < .001$).

CONCLUSIONS AND RELEVANCE Colonoscopy screening entails high detection rates in the proximal and distal colon. Participation rates and endoscopist performance vary significantly. Postprocedure abdominal pain is common with standard air insufflation and can be significantly reduced by using CO_2.

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Colorectal cancer is the second most common cancer in high-income countries, with more than 730 000 new cases diagnosed globally each year.[1] The disease is expected to also become a large burden for less-developed countries in the near future.[2]

Randomized trials have shown that screening with guaiac fecal occult blood testing reduces colorectal cancer mortality by 15%.[3] One study has also shown an effect of guaiac fecal occult blood testing on colorectal cancer incidence, presumably owing to a high colonoscopy rate after positive test results.[4] Guaiac fecal occult blood testing is being replaced by more sensitive fecal immunochemical testing, but data on colorectal cancer incidence and mortality are lacking.[3]

Because most colorectal cancers develop from benign adenomas, endoscopic screening, which allows detection and removal of adenomas, may have a larger effect on colorectal cancer incidence and mortality than fecal occult blood testing. Four large-scale randomized trials have shown that flexible sigmoidoscopy screening reduces colorectal cancer incidence by 18% to 23% and mortality by 22% to 31%.[5-8]

Because colonoscopy is believed to be more effective than sigmoidoscopy, colonoscopy screening is widely endorsed in the United States and Canada.[9] However, colonoscopy is invasive and expensive, and entails a risk of complications. Large population-based studies investigating patient participation and experience, detection rates for adenomas and cancer, and effectiveness of colonoscopy screening are lacking. To carefully evaluate the balance of the benefits and harms of colonoscopy screening, randomized trials are imperative. Therefore, European guidelines currently do not recommend colonoscopy screening.[10]

The Nordic-European Initiative on Colorectal Cancer (NordICC) study is a multinational, population-based randomized clinical trial to investigate the effectiveness of colonoscopy screening on colorectal cancer incidence and mortality in several European countries. We report on participation, participant experience, adenoma yield, and complications of colonoscopy screening in the different participating countries.

Methods

Study Design

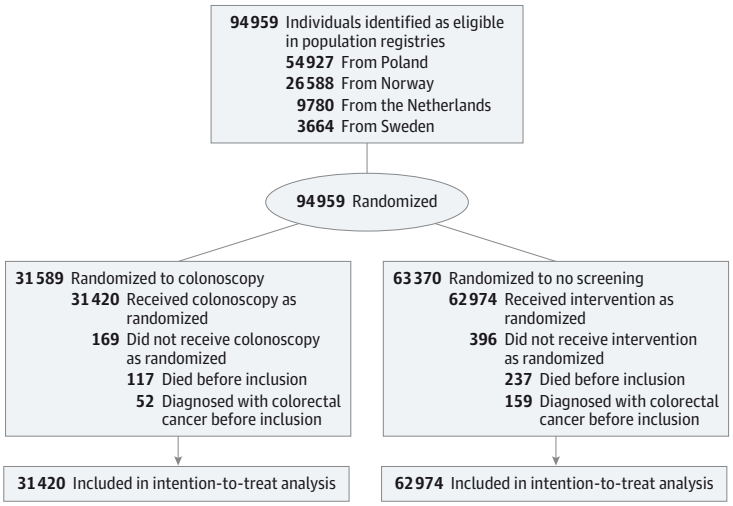
Details of the NordICC trial rationale, its pragmatic (also called management) design, randomization, intervention, and outcomes have been described elsewhere.[11-13] The full study protocol synopsis can be found in Supplement 1. The primary outcome is colorectal cancer incidence and mortality in an intention-to-treat analysis after 15 years of follow-up. Secondary aims include participation rates, participant experience, cancer and adenoma yield, and complications. Eligible individuals were all men and women aged 55 to 64 years living in defined geographical areas in Norway, Poland, Sweden, and the Netherlands. All colonoscopies were performed at dedicated endoscopy centers.

Poland was the only country with an ongoing colorectal cancer screening program,[14] but the individuals recruited for this trial were not part of that program. No other country had organized colorectal cancer screening of any kind in the trial areas.

Randomization and Intervention

Participants were randomly assigned to either the colonoscopy screening group or no screening (control) group in a 1:2 ratio (**Figure 1**). Individuals randomized to the colonoscopy screening group were offered colonoscopy if they did not have any of the prespecified comorbidities.[11] All individuals randomized to the screening group received a personal letter of invitation with an information leaflet about the study, and an informed consent form. An identical information leaflet was used in Norway, Sweden, and Poland, translated into local languages. In the Netherlands, we used a similar, but not entirely identical, leaflet derived for a randomized trial comparing colonoscopy vs computed tomographic colonography.[11] All individuals receiving colonoscopy screening provided written informed consent. Individuals randomized to the control

Figure 1. CONSORT Diagram of Participant Inclusion



group did not receive any intervention and were not contacted at study enrollment.

The study was approved by the ethical committees at all participating centers (Sørlandet Hospital, Kristiansand, Norway; Sørlandet Hospital, Arendal, Norway; The Maria Sklodowska Curie Memorial Cancer Center and Institute of Oncology and Medical Center for Postgraduate Education, Warsaw, Poland; Erasmus Medical Centre, Rotterdam, the Netherlands; Academic Medical Centre, Amsterdam, the Netherlands; University of Uppsala, Uppsala, Sweden; Örebro Hospital, Örebro, Sweden; Vermland Hospital, Karlstad, Sweden; Eskilstuna Hospital, Eskilstuna, Sweden; Falun Hospital, Falun, Sweden; Gävle Hospital, Gävle, Sweden; and Västerås Hospital, Västerås, Sweden). Approvals were also obtained from the National Swedish Ethics Council and from the Dutch National Health Council.

Screening Intervention

Colonoscopy screenings were performed from June 8, 2009 to June 23, 2014. The colonoscopy and the bowel preparation were provided without cost sharing on the part of the participants. No compensation was paid for participation. Trial endoscopists had performed at least 300 colonoscopies before entering the trial and had a minimum workload of 200 colonoscopies per year. Standard video colonoscopes were used for all procedures. All centers were encouraged to use CO_2 insufflation whenever possible; otherwise, standard air insufflation was used. All lesions detected during colonoscopy were removed whenever feasible, and biopsies were performed on all tumors. Data from colonoscopy examinations were registered using an electronic case report form accessible online from the participating centers, and stored at the central trial database (Frontier Science Scotland, Kincraig, UK).

Dedicated pathologists were responsible for histopathologic classification according to the World Health Organization.[15] Polyps were categorized as adenomas, serrated polyps (including hyperplastic polyps, sessile serrated polyps, and traditional serrated adenomas), inflammatory polyps, neuroendocrine polyps, or other. Adenomas measuring 10 mm or more in diameter, or with villous architecture or high-grade dysplasia, were classified as advanced adenomas. Participants with advanced adenomas or 3 or more adenomas were classified as high risk. We defined lesions with submucosal invasion as cancer. Participants were classified according to the most advanced lesion detected at screening.

We assessed participants' abdominal pain during the colonoscopy and in the 24 hours after the colonoscopy using a validated patient questionnaire in Norway, Poland, and Sweden.[11] Participants scored abdominal pain on a 4-point visual rating scale as either none, light, moderate, or severe. Similar questions were applied for pain during the colonoscopy and for the 24-hour period after the procedure. All participants in Norway, Poland, and Sweden were asked to respond to the questionnaire 24 hours after the screening examination and return it to the central secretariat. Thirty-day morbidity and mortality after screening was assessed from the electronic case report forms and by linkage to patient registries in the participating countries.

Statistical Analysis

For this report, we assessed study outcomes for the whole cohort, and for the comparison of participating countries. Colonoscopy yield and participant satisfaction was compared between participating 32 endoscopists who had performed at least 30 colonoscopies in the trial. Participants' abdominal pain scores during and after the colonoscopy were dichotomized for analyses (none or slight pain vs moderate or severe pain). Adenoma yield per endoscopist is defined as the percentage of participants with at least 1 adenoma (corresponding to what is commonly called *adenoma detection rate*). Differences between the groups in baseline variables that could influence study outcomes were adjusted for age and sex by multiple logistic regression analyses and reported as odds ratios with 95% CIs. We fitted a logistic regression model to estimate the association between country, sedation, and insufflation gas (air or CO_2) and abdominal pain, and tested country-wise heterogeneity by including a product (interaction) term between sedation and country. We estimated mean performance indicators and 95% CIs using a random-effects model to account for clustering at the endoscopist level.

For questionnaire data, we present percentages among those who responded to the particular questions. All analyses were performed with the use of Stata statistical software, version 14.0 (StataCorp).

Results

Study Population

At study start, 94 959 individuals were identified as eligible in the population registries. During the course of the screening period, 169 individuals assigned to the screening group and 369 individuals assigned to the control group were excluded because they were dead or diagnosed with colorectal cancer before study entry (but not yet identified as such in the registries) (Figure 1). Thus, our analyses are based on 94 394 individuals: 31 420 in the screening group and 62 974 in the control group; 47 135 (49.9%) women and 47 259 (50.1%) men, with a median age of 60.0 years.

Screening Participation

Among the 31 420 participants who were assigned to the colonoscopy group, 12 574 (40.0%) underwent screening. A total of 662 individuals did not undergo colonoscopy owing to 1 or several comorbidities that precluded screening[11] (these individuals are included in the estimates of participation, according to the intention-to-treat principle). Participation rates were slightly higher in men than women (6493 of 15 744 [41.2%] vs 6081 of 15 676 [38.8%]), and among those aged 60 to 64 years vs those aged 55 to 59 years (6333 of 15 454 [41.0%] vs 6241 of 15 966 [39.1%]) (**Table 1**). Participation varied substantially between the participating countries: 60.7% in Norway (5354 of 8816), 39.8% in Sweden (486 of 1222), 33.0% in Poland (6004 of 18 188), and 22.9% in the Netherlands (730 of 3194) ($P < .001$).

Table 1. Baseline and Procedural Characteristics, and Screening Colonoscopy Acceptance

Characteristic	Value[a]				
	Total Participants	Norway	Poland	Sweden	Netherlands
Total participants, No.	94 394	26 417	54 533	3664	9780
Screening group	31 420 (33.3)	8816 (33.4)	18 188 (33.4)	1222 (33.4)	3194 (32.7)
Control group	62 974 (66.7)	17 601 (66.6)	36 345 (66.6)	2442 (66.4)	6586 (67.3)
Sex					
Women	47 135 (49.9)	13 195 (49.9)	27 334 (50.1)	1671 (45.6)	4935 (50.5)
Men	47 259 (50.1)	13 222 (50.1)	27 199 (49.9)	1993 (54.4)	4845 (49.5)
Age at study entry, y					
55-59	48 024 (50.9)	12 526 (47.4)	28 794 (52.8)	1791 (48.9)	4913 (50.2)
60-64	46 370 (49.1)	13 891 (52.3)	25 739 (47.2)	1873 (51.1)	4867 (49.8)
Screening participation					
Total	12 574 (40.0)	5354 (60.7)	6004 (33.0)	486 (39.8)	730 (22.9)
Women	6081/15 676 (38.8)	2580/4391 (58.8)	2919/9120 (32.0)	226/560 (40.4)	356/1605 (22.2)
Men	6493/15 744 (41.2)	2774/4425 (62.7)	3085/9068 (34.0)	260/662 (39.3)	374/1589 (23.5)
55-59 y	6241/15 966 (39.1)	2497/4175 (59.8)	3174/9601 (33.1)	207/597 (34.7)	363/1593 (22.8)
60-64 y	6333/15 454 (41.0)	2857/4641 (61.6)	2830/8587 (33.0)	279/625 (44.6)	367/1601 (22.9)
Procedure performed					
Cecum intubation	12 217 (97.2)	5157 (96.3)	5869 (97.8)	472 (97.1)	719 (98.5)
Sedation given	2848 (22.7)	579 (10.8)	1389 (23.1)	223 (45.9)	657 (90.0)
Withdrawal time[b], median (IQR)	10 (8-15)	10 (8-15)		8 (6-12)	11 (9-17)
Adverse events					
Perforations	1 (0.01)	0	0	0	1 (0.14)
Major bleedings	18 (0.14)	8 (0.15)	7 (0.12)	0	3 (0.41)
Vasovagal reactions	51 (0.41)	28 (0.52)	14 (0.23)	2 (0.41)	7 (0.96)

Abbreviation: IQR, interquartile range.

[a] Data are presented as number (percentage) of patients unless otherwise indicated.

[b] Given cecum intubation (calculated as total procedure time – time to reach cecum).

Overall Performance and Diagnostic Yield

The overall cecum intubation rate was 97.2% (12 217 of 12 574), and the median withdrawal time was 10 minutes (interquartile range, 8-15 minutes) (Table 1). Reflecting differences in performance of colonoscopy procedures in the different countries, sedation was administered to 10.8% of participants (579 of 5354) in Norway, 23.1% (1389 of 6004) in Poland , 45.9% (223 of 486) in Sweden, and in 90.0% (657 of 730) in the Netherlands. The most commonly used drugs were propofol (1433 individuals [11.4%]), midazolam (2126 [16.9%]), and a combination of midazolam and fentanyl (2398 [19.1%]). The quality of bowel preparation was judged as very good or good in more than 90% of colonoscopies (**Table 2**).

Sixty-two individuals (0.5%) were diagnosed with colorectal cancer at screening (Table 2). Of these, 14 (0.1%) had tumors in the proximal colon (cecum, ascending or transverse colon, or splenic flexure) and 50 (0.4%) had distal tumors (descending or sigmoid colon or rectum). The overall prevalence of colorectal polyps was 48.1% (6049 individuals); 3861 participants (30.7%) had adenomas, and, of these, 1304 (10.4%) were high risk. The adenoma yield was similar in the distal and proximal colon (Table 2). In total, 3095 individuals (24.6%) were diagnosed with serrated polyps; 285 (2.3%) with a size of 10 mm or larger. Two hundred twenty-one participants had large (≥10 mm) serrated polyps in the proximal colon and 73 in the distal colon. During screening colonoscopy, 58 participants were diagnosed with previously unknown inflammatory bowel disease and 7 participants had neuroendocrine tumors removed.

Adverse Events

One participant (0.01%) experienced colonoscopy perforation. The individual returned to the hospital the evening after the colonoscopy with abdominal pain and fever. Results of a computed tomographic scan revealed free air; laparotomy with surgical suture of the perforation was performed, after which the participant fully recovered. Two individuals (0.02%) experienced postpolypectomy serosal burns, both of which resolved without intervention. Eighteen participants (0.14%) developed bleeding owing to polypectomy, all of which were treated endoscopically. No deaths or other major complications related to the screening intervention occurred within 30 days after screening. Fifty-one participants (0.41%) experienced minor vasovagal reactions during colonoscopy screen-

Table 2. Bowel Preparation Quality and Diagnostic Yield at Screening Colonoscopy

Characteristic	Total Participants, No. (%)	Sex, No. (%)		Age Group, No. (%)	
		Women	Men	55-59 y	60-64 y
Split dose bowel preparation[a]	9845 (100)	4316 (100)	5529 (100)	4868 (100)	4977 (100)
Very good cleansing	6643 (67.5)	3078 (71.3)	3565 (64.5)	3245 (66.7)	3398 (68.3)
Good cleansing	2289 (23.3)	899 (20.8)	1390 (25.1)	1162 (23.9)	1127 (22.6)
Partially poor cleansing	301 (3.1)	129 (3.0)	172 (3.1)	143 (2.9)	158 (3.2)
Generally poor cleansing	534 (5.4)	173 (4.0)	361 (6.5)	287 (5.9)	247 (5.0)
Day before bowel preparation[a]	2332	1549	783	1205	1127
Very good cleansing	1252 (53.7)	898 (58.0)	354 (45.2)	654 (54.3)	598 (53.1)
Good cleansing	855 (36.7)	532 (34.3)	323 (41.3)	441 (36.6)	414 (36.7)
Partially poor cleansing	93 (4.0)	44 (2.8)	49 (6.3)	45 (3.7)	48 (4.3)
Generally poor cleansing	126 (5.4)	71 (4.6)	55 (7.0)	61 (5.1)	65 (5.8)
Participants	12 574 (100)	6081 (100)	6493 (100)	6241 (100)	6333 (100)
Polyps	6049 (48.1)	2535 (41.7)	3514 (54.1)	2958 (47.4)	3091 (48.8)
Proximal[b]	3341 (26.6)	1356 (22.3)	1985 (30.6)	1571 (25.2)	1770 (28.0)
Distal[b]	4402 (35.0)	1776 (29.2)	2626 (40.4)	2174 (34.8)	2228 (35.2)
Adenomas	3861 (30.7)	1490 (24.5)	2371 (36.5)	1836 (29.4)	2025 (32.0)
Proximal	2273 (18.1)	818 (13.5)	1455 (22.4)	1035 (16.6)	1238 (19.6)
Distal	2407 (19.1)	907 (14.9)	1500 (23.1)	1143 (18.3)	1264 (20.0)
High-risk adenomas	1304 (10.4)	430 (7.1)	874 (13.5)	566 (9.1)	738 (11.7)
Proximal	562 (4.5)	176 (2.9)	386 (5.9)	230 (3.7)	332 (5.2)
Distal	725 (5.8)	255 (4.2)	470 (7.2)	312 (5.0)	413 (6.5)
Serrated polyps	3095 (24.6)	1325 (21.8)	1770 (27.3)	1507 (24.2)	1588 (25.1)
Proximal	1078 (8.6)	510 (8.4)	568 (8.8)	503 (8.1)	575 (9.1)
Distal	2439 (19.4)	998 (16.4)	1441 (22.2)	1211 (19.4)	1228 (19.4)
Colorectal cancer	62 (0.5)	23 (0.4)	39 (0.6)	29 (0.5)	33 (0.5)
Proximal	14 (0.1)	4 (0.1)	10 (0.2)	7 (0.1)	7 (0.1)
Distal	50 (0.4)	19 (0.3)	31 (0.5)	24 (0.4)	26 (0.4)
Neuroendocrine tumor	7 (0.06)	4 (0.07)	3 (0.05)	3 (0.05)	4 (0.06)
Proximal	1 (0.008)	1 (0.02)	0	0	1 (0.02)
Distal	6 (0.05)	3 (0.05)	3 (0.05)	3 (0.05)	3 (0.05)

[a] Cleansing regimen missing for 124 participants and cleansing quality missing for 190 participants.

[b] Proximal colon defined as cecum to splenic flexure; distal colon defined as descending colon to rectum. The total number of subjects with proximal and distal lesions may exceed the total number of subjects because subjects could have lesions in both locations.

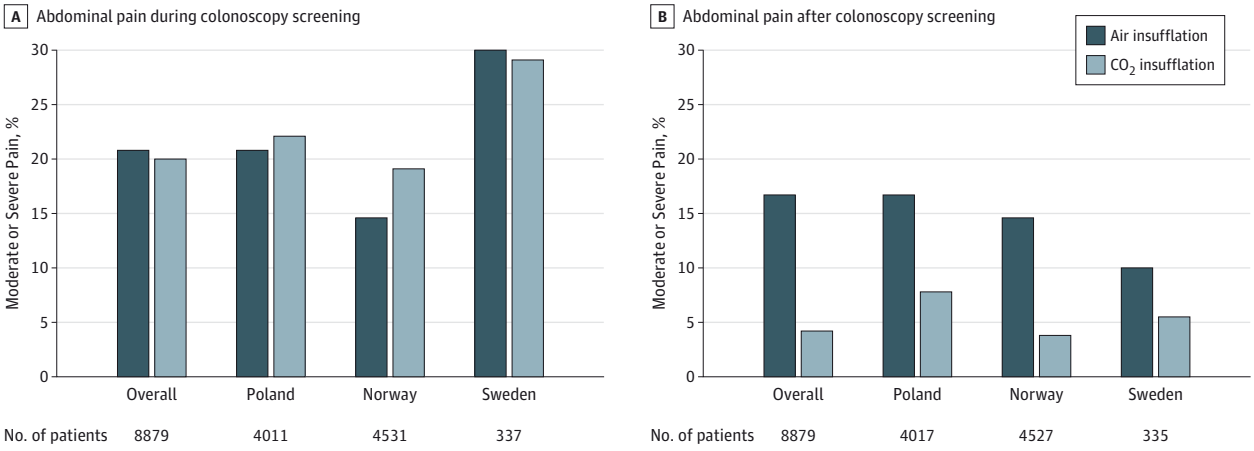
ing. All of these reactions were short term, without need of extra measures after the procedure.

Participant Pain and Satisfaction

Participant pain and satisfaction questionnaires were used in Norway, Poland, and Sweden. Overall, 10 907 questionnaires were issued (92.1% of 11 844 participants in those 3 countries), and 9201 individuals (84.4%) returned the questionnaire; 8285 of 8375 participants (98.9%) indicated they were generally satisfied with the screening intervention. **Figure 2**A shows participant pain during colonoscopy; 7291 individuals (79.7%) had no pain or slight abdominal pain during colonoscopy (no pain, 4161 [45.5%]; slight pain, 3130 [34.2%]), while 1855 [20.3%] reported moderate or severe pain (moderate pain, 1141 [12.5%]; severe pain, 714 [7.8%]). The association of participant pain with sedation and insufflation gas used in the different countries is shown in eFigure 1 and eTable 1 in Supplement 2. Overall, pain during colonoscopy was not significantly associated with the use of sedation (adjusted odds ratio, 0.91; 95% CI, 0.61-1.35), but there were differences between the countries owing to variation in clinical practice. There was no difference in participant pain during the procedure between the 2 insufflation gases used, but significant differences were observed between countries ($P < .001$). A higher proportion of women than men experienced moderate or severe pain (1160 [26.4%] vs 695 [14.6%]; $P < .001$).

During the 24 hours after colonoscopy, 859 participants (9.4%) experienced moderate or severe abdominal pain (moderate pain, 592 [6.5%]; severe pain, 267 [2.9%]). A 4-fold higher proportion of individuals examined with air insufflation reported abdominal pain compared with those examined with CO_2 insufflation (602 [16.7%] vs 223 [4.2%]; $P < .001$) (Figure 2B). Severe pain after colonoscopy was reported by 55 participants (1.0%) examined with CO_2 insufflation compared with 203 (5.6%) of those examined with air insufflation. This finding did not change after adjustment for country, and there was no significant heterogeneity between countries.

Figure 2. Participants' Self-Reported Abdominal Pain During and After Colonoscopy Screening



A, Participants' self-reported moderate or severe abdominal pain during colonoscopy screening ($P < .001$ for difference between countries; $P = .40$ for difference between insufflation gases after adjustment for country).

B, Participants' self-reported moderate or severe abdominal pain after screening colonoscopy ($P < .001$ for difference between insufflation gas after adjustment for country).

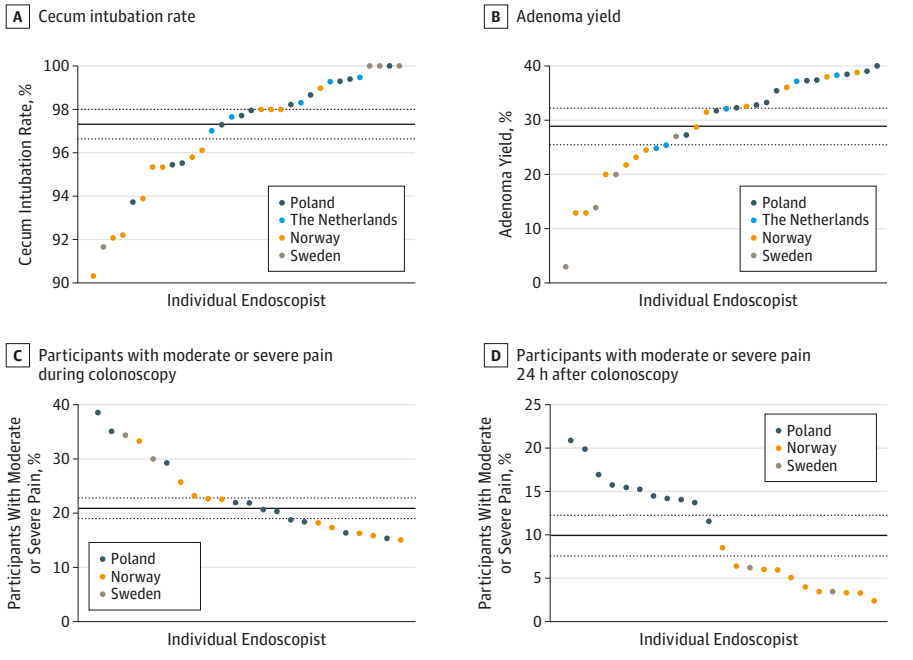
Individual Performance and Diagnostic Yield

We found substantial variations in individual endoscopist performance regarding cecum intubation rate, adenoma yield, and participant pain and discomfort during and after colonoscopy (**Figure 3**C and Figure 3D). There was also a significant difference in adenoma yield between the participating countries ($P < .001$) (eTable 2 in Supplement 2).

Discussion

In this randomized, population-based trial of colonoscopy screening, we found satisfactory participation, performance, and adenoma yield for both distal and proximal polyps, but with large differences between endoscopists. We further found

Figure 3. Individual Endoscopist Performance in Colonoscopy Screening



Performance indicators for endoscopists who performed at least 30 examinations in the Nordic-European Initiative on Colorectal Cancer trial. The horizontal lines represent the mean value (solid) with 95% CIs (dashed). These are estimated with a random effects model to account for clustering at the endoscopist level. A, Cecum intubation rate. B, Adenoma yield. C, Percentage of participants with moderate or severe pain during colonoscopy. D, Percentage of participants with moderate or severe pain 24 hours after colonoscopy.

that postprocedural abdominal pain is common when using standard air insufflation, but that it can be significantly reduced by using CO_2.

Although many Americans regularly undergo colonoscopy screening, no randomized trials have been performed to quantify the effectiveness of such screening on colorectal cancer incidence and mortality. The NordICC trial is the first, to our knowledge, to investigate the effectiveness of colonoscopy screening vs no screening. The main results are expected in 15 years.

The overall performance of colonoscopy screening was well above thresholds for adenoma detection and cecum intubation. This is reassuring with regards to future achievement of the trial endpoints. However, as Figure 3 shows, there was considerable variation between endoscopists. Recommended benchmarks for cecum intubation rate (95%) and adenoma yield (25% adenoma detection rate) were not met by 6 (17.1%) and 10 of 35 endoscopists (28.6%), respectively. Future analysis will reveal if endoscopist performance is related to differences in ultimate outcomes. Furthermore, although high adenoma yield is desirable, most nonadvanced adenomas do not harbor a large risk of transformation to a malignant neoplasm, but detection of adenomas leads to a larger number of surveillance colonoscopies. Future analysis may reveal if the effect on colorectal cancer incidence and death outweighs the increased burden in colonoscopy capacity owing to high adenoma yield.

The rate of major adverse events (bleeding and perforations) was 0.15%, which we consider acceptable. Our rate is lower than that observed in a population-based trial comparing colonoscopy with fecal immunochemical testing in Spain (0.51%).[16] The higher adverse event rate may be related to the higher sedation rate in the Spanish trial (96% sedation rate) as compared with ours.

Some studies[17] have suggested a smaller effect of colonoscopy in the proximal as compared with the distal colon. In our study, detection rates for low-risk and high-risk adenomas were as high in the proximal as in the distal colon. This finding is in accordance with the Spanish colonoscopy screening trial.[16] The high adenoma yield in the proximal colon may translate into higher effectiveness of colonoscopy screening vs sigmoidoscopy for prevention of proximal cancer. Site-specific age-categorized colorectal cancer incidence and mortality will be investigated during follow-up, but to be able to achieve sufficient power, data pooling from the 4 currently ongoing randomized colonoscopy trials will be necessary.[17]

Our trial randomized individuals directly from the population registries. The intention-to-treat estimates obtained with this design are more helpful to assess population effectiveness than to inform individual decision making because the magnitude of the effect depends on the proportion of participants who choose to undergo colonoscopy screening. Participation rates differed considerably between the different countries. This may be grounded in differences in cultural settings and beliefs, as well as expectations regarding endoscopic procedures. We used the same information and invitation routines in Poland, Sweden, and Norway. The Netherlands used a slightly different invitation brochure, and owing to national requirements, individuals were invited to an outpatient visit before the colonoscopy for verbal information on participation in the trial, the colonoscopy procedure, and its preparation at the hospital before the date of the colonoscopy. Although this may explain the lower participation rate in the Netherlands, observed rates were also significantly different between the other 3 countries. Thus, we cannot fully explain the difference in participation between the 4 countries by different approaches within the study organization. We believe that cultural differences, such as public awareness of or shame about colorectal disease, or perception about colonoscopy as painful or uncomfortable, may play a role in the observed differences. Although the high participation rate in Norway (60.7%) correlates with the previous participation rates for flexible sigmoidoscopy screening,[8] the low participation rate in the Netherlands (22.9%) contrasts with the 70% uptake in fecal immunochemical screening in that country. High cecum intubation rates were achieved in our study with a low sedation rate.

The overall participation rate (40.0%) was somewhat lower than expected, but is higher than in other population-based trials: 24.6% (6581 of 26 703) for colonoscopy and 34.2% (9089 of 26 599) for fecal immunochemical screening in the Spanish randomized trial,[16] and 33.6% (982 of 2920) for computed tomographic colonography in the Dutch Colonoscopy or Colonography for Screening trial.[18] As shown in eFigure 2 of Supplement 2, the NordICC trial will likely have sufficient power to detect differences in colorectal cancer mortality with the achieved participation.

Pain and discomfort may be a major barrier for participation in screening colonoscopy. We found that 79.7% of participants reported no pain or only light pain during the procedure, whereas 20.3% reported moderate or severe pain. This is comparable with reported patient pain in screening trials of flexible sigmoidoscopy.[19,20] About 16% of participants experienced moderate or severe pain after colonoscopy using standard air insufflation. The use of CO_2 insufflation reduced the absolute risk of postcolonoscopy abdominal pain significantly to 4% (Figure 2). It is important to separate the effects of CO_2 from the effects of sedation; while the main effect of CO_2 occurs after the examination (in the hours after the colonoscopy has ended, often after the patient is discharged from the endoscopy unit), sedation relates to pain and discomfort during the colonoscopy. Furthermore, while pain and discomfort during colonoscopy often is short, pain after colonoscopy lasts longer (for up to 24 hours) and may affect patient compliance more than intraprocedural pain. Thus, CO_2 is equally relevant to use in sedated and nonsedated patients. Therefore, CO_2 insufflation is also beneficial in countries in which colonoscopy is performed with sedation, such as the United States.

The profound effect of CO_2 at reducing postcolonoscopy pain and discomfort is intriguing, although not novel. Our observation is in accordance with previous evidence from smaller randomized trials.[21] Furthermore, CO_2 eliminates the risk of explosion during polypectomy. Although explosion during polypectomy is very rare event with air insufflation, cases have been reported in the literature until recently.[22] However, despite strong evidence for the superiority of insufflation with

CO_2, air insufflation is still the standard gas used around the world. The lack of implementation of CO_2 insufflation is a concern for patient safety and comfort. Abdominal pain after colonoscopy may also be an ignored cause for poor participation in endoscopic screening.

We found no significant correlation between participant pain and the use of sedation, but found different patterns in the participating countries (eFigure 2 in Supplement 2). This finding is in accordance with previous evidence and suggests that pain and discomfort during colonoscopy is more related to local practice, endoscopist training, and patient characteristics.[23,24] Colonoscopy without sedation is performed differently than it is with sedation, and local traditions for training are guiding local practice. Colonoscopy without sedation and with sedation both have advantages and disadvantages.[23] For many patients, colonoscopy without sedation is feasible. However, some patient groups (eg, women who have undergone previous abdominal surgery) have a higher risk of experiencing pain during colonoscopy, and unsedated colonoscopy may be more challenging.[24]

Our study is limited in that it is designed to estimate the effectiveness but not the efficacy of colonoscopy screening. A further limitation of the trial is that the control group is not subjected to any comparative intervention.

Conclusions

We found satisfactory participation, high adenoma yield, and adequate performance for colonoscopy screening in the NordICC trial. The observed large differences between countries and individual endoscopists deserve further investigation. Air insufflation should be abandoned in favor of insufflation with CO_2 in colonoscopy screening.

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