

The NEW ENGLAND JOURNAL *of* MEDICINE

ORIGINAL ARTICLE


Effect of Colonoscopy Screening on Risks of Colorectal Cancer and Related Death

M. Bretthauer, M. Løberg, P. Wieszczy, M. Kalager, L. Emilsson, K. Garborg,
M. Rupinski, E. Dekker, M. Spaander, M. Bugajski, Ø. Holme, A.G. Zauber,
N.D. Pilonis, A. Mroz, E.J. Kuipers, J. Shi, M.A. Hernán, H.-O. Adami, J. Regula,
G. Hoff, and M.F. Kaminski, for the NordICC Study Group*

ABSTRACT

26.10.2022, Journal Club Nico Weber

Introduction I

- Colorectal cancer (CRC) is the second leading cause of death from cancer worldwide¹
 -  Attractive screening target for population screening
- Multiple screening options are available²

Background I

- *Preventive screening* (i.e. colonoscopy, pap smear)³
- *Early-detection screening* (i.e. mammography, PSA)³

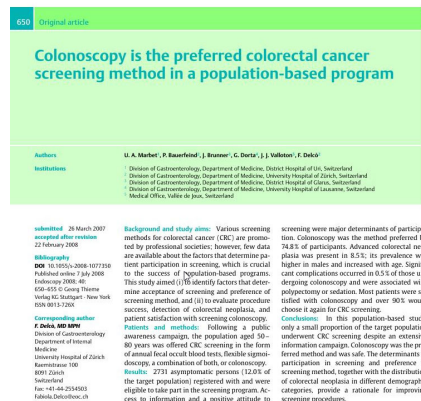


Figure 1

19. Mai 2022 [← Zurück zur Übersicht](#)

Gemeinsame Medienmitteilung des Kantons Bern und der Krebsliga beider Basel

Im Kanton Bern startet breit angelegtes Darmkrebs-Screening-Programm

Das neue Darmkrebs-Screening-Programm im Kanton Bern startet am 1. Juni 2022. Die Krebsliga beider Basel realisiert das Screening-Programm in Zusammenarbeit mit der Gesundheits-, Sozial- und Integrationsdirektion des Kantons Bern (GSI).

Figure 2

Introduction II

- Endoscopic screening may prevent colorectal cancer
→ three randomized trials, incidence up to 25% lower after 10-12 years⁴
- Colonoscopy versus sigmoidoscopy⁵
- *In this current study, they report the results of the Nordic-European initiative on Colorectal Cancer (NordICC)*

Methods I (Trial design)

- The NordICC trial was conducted in Poland, Norway, Sweden and the Netherlands
- Inclusion: Eligible participants were men and women 55 to 64 years of age
- Exclusion: Death or diagnosis of colorectal cancer before trial entry

Methods II (Trial design)

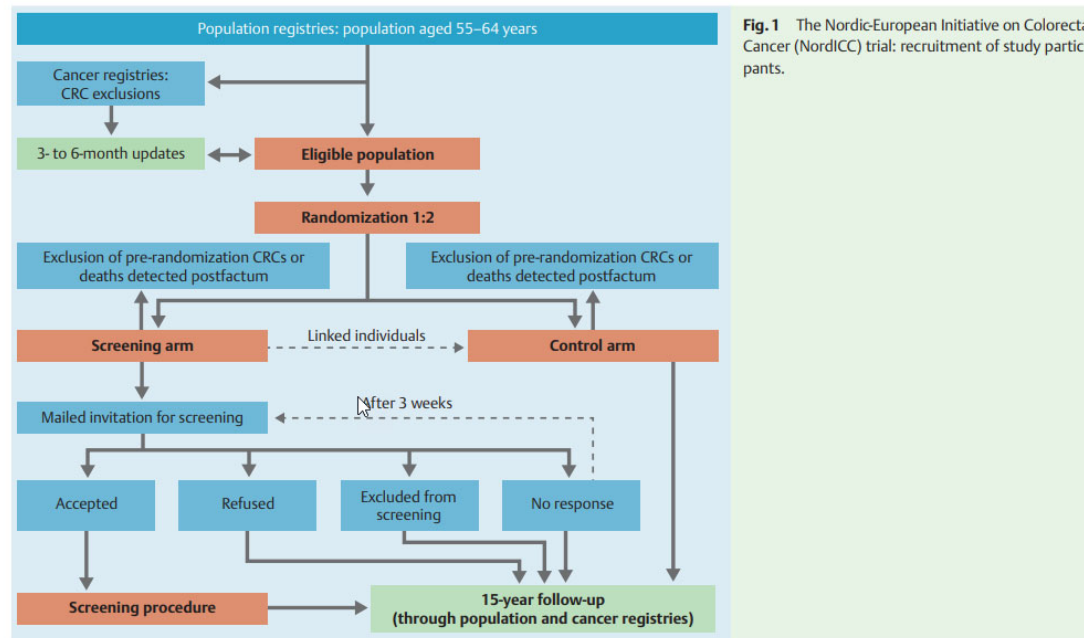


Figure 3

Methods III (Trial design)

- Opportunistic screening program for CRC in some geographic areas, but not in the area where the trial was conducted
 - New screening programs; by the time the programs were introduced the trial participants were too old to be eligible
- none of the participants were eligible for any screening programs outside the trial

Methods IV (Interventions)

- Randomly assigned
 - One-time screening colonoscopy or no invitation
- Standard bowel preparation
- Lesions were removed (if feasible), tumors were biopsied

Methods V (Trial endpoints)

- Primary endpoint
 - Risks of CRC and death from CRC after median follow-up of 10 to 15 years
- Secondary endpoint
 - Death from any cause

Methods VI (Statistical analysis)

- Estimated effect of screening in CRC mortality depends primarily on three variables;
 - Attendance for screening
 - Efficacy of examination
 - Screening contamination in the control group

Methods VII (Statistical analysis)

- Main hypothesis;
 - *25% difference* in the CRC mortality
- To detect *25% difference* with 80% power (at significance level of 5%) they calculated;
 - 22`800 participants in the invited group
 - 45`600 participants in the usual-care group

Results I

Table 1. Characteristics of the Trial Participants.

Characteristic	All Participants (N = 84,585)	Participants in Norway (N = 26,411)	Participants in Poland (N = 54,258)	Participants in Sweden (N = 3646)
Group — no.				
Invited	28,220	8,815	18,184	1221
Usual care	56,365	17,596	36,344	2425
Sex — no.				
Female	42,186	13,194	27,330	1662
Male	42,399	13,217	27,198	1984
Age at randomization — no.				
55–59 yr	43,100	12,524	28,792	1784
60–64 yr	41,485	13,887	25,736	1862
Screening participation — no./total no. (%)				
Women and men	11,843/28,220 (42.0)	5354/8815 (60.7)	6003/18,184 (33.0)	486/1221 (39.8)
Women	5,724/14,066 (40.7)	2580/4390 (58.8)	2918/9117 (32.0)	226/559 (40.4)
Men	6,119/14,154 (43.2)	2774/4425 (62.7)	3085/9067 (34.0)	260/662 (39.3)
55–59 yr	5,877/14,369 (40.9)	2497/4174 (59.8)	3173/9599 (33.1)	207/596 (34.7)
60–64 yr	5,966/13,851 (43.1)	2857/4641 (61.6)	2830/8585 (33.0)	279/625 (44.6)
Screening performance — no./total no. (%)				
Good or very good bowel preparation ^a	110,610/11,635 (91.2)	4739/5174 (91.6)	5445/5979 (90.8)	426/462 (92.2)
Cecum intubation	11,470/11,843 (96.8)	5130/5354 (95.8)	5868/6003 (97.8)	472/486 (97.1)
Adenoma detection	3,634/11,843 (30.7)	1453/5354 (27.1)	2111/6003 (35.2)	70/486 (14.4)
Screening-related adverse events — no./total no. (%)				
Perforation [†]	0	0	0	0
Major bleeding [‡]	15/11,843 (0.13)	8/5354 (0.15)	7/6003 (0.12)	0

^a Data in this category were missing for 208 participants, including some for whom data on the bowel preparation regimen were missing and others for whom data on the quality of bowel preparation were missing.

[†] One perforation that occurred in a participant in the Netherlands was not included in these analyses.⁴

[‡] Major bleeding was defined as bleeding that warranted treatment. All cases of major bleeding were treated endoscopically, and further therapy was not warranted.

Table 1

Results II

Table 2. Primary and Secondary End Points.						
End Point	Invited Group		Usual-Care Group		Risk Difference (95% CI)	Risk Ratio (95% CI)
	Participants	10-Yr Risk (95% CI)	Participants	10-Yr Risk (95% CI)		
	<i>number</i>	<i>percent</i>	<i>number</i>	<i>percent</i>	<i>percentage points</i>	
Colorectal cancer	259	0.98 (0.86 to 1.09)	622	1.20 (1.10 to 1.29)	–0.22 (–0.37 to –0.07)	0.82 (0.70 to 0.93)
Death						
From colorectal cancer	72	0.28 (0.21 to 0.34)	157	0.31 (0.26 to 0.35)	–0.03 (–0.11 to 0.05)	0.90 (0.64 to 1.16)
From any cause	3036	11.03 (10.66 to 11.40)	6079	11.04 (10.78 to 11.30)	–0.01 (–0.47 to 0.44)	0.99 (0.96 to 1.04)

Table 2

Results III (intent-to-screen)

- Cumulative incidence of CRC was significantly lower in the invited group (0.98% vs. 1.20%), likely due to removal of precancerous polyps⁷
- CRC-related mortality at 10 years was not significantly different in the two groups (0.28% vs. 0.31%)⁷
- All-cause mortality at 10 years was identical in the two groups (11.0%)⁷

Results IV (pre-protocol)

- Risk of CRC at 10 years was decreased from 1.22% to 0.84%
- CRC-related mortality reached significance (0.15% in the invited group versus 0.30% in the usual-care group)

Discussion I

- Risk of CRC ↓
- Risk of CRC-related death ?
- (Low?) screening rate of 42% in the invited group
- Colonoscopy versus sigmoidoscopy – similar results ?
 - Risk reduction of CRC 23% - 34% in intention-to-treat⁶
 - Risk reduction of CRC 33% - 40% in pre-protocol analysis⁶

Discussion II

- Positive effect of screening colonoscopy with respect of CRC earlier than to deaths related to CRC
- Current data show lower risk reduction compared to previous trials⁸
 - Declining risk of CRC, better treatment options

Discussion III

- Limitations
 - Lower-than-expected participation
 - Consent after randomization ?
 - No analyses of distal compared with proximal cancer
 - Low adenoma detection rate (29% of the endoscopists had an rate below 25%)

Discussion IV

- Outlook⁹
 - Ongoing SCREESCO (Screening of Swedish Colons) trial
 - Randomized trial comparing colonoscopy with either FIT or usual care (no screening)
 - CAVE: preliminary report low rates undergoing colonoscopy, low adenoma detection rates

References

1. Sung H, Ferlay J, Siegel RL, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 2021; 71: 209-49.
2. Helsing LM, Kalager M. Colorectal cancer screening — approach, evidence, and future directions. *N Engl J Med Evid* 2022. DOI: 10.1056/EVIDra2100035
3. Lise M. Helsingen, M.D. Colorectal Cancer Screening — Approach, Evidence, and Future Directions January 10, 2022 *NEJM Evid* 2022; 1 (1)
4. Holme Ø, Schoen RE, Senore C, et al. Effectiveness of flexible sigmoidoscopy screening in men and women and different age groups: pooled analysis of randomized trials. *BMJ* 2017; 356: i6673.
5. Lauby-Secretan B, Vilahur N, Bianchini F, Guha N, et al. The IARC perspective on colorectal cancer screening. *N Engl J Med* 2018; 378: 1734-40.
6. Holme Ø, Løberg M, Kalager M, et al. Effect of flexible sigmoidoscopy screening on colorectal cancer incidence and mortality: a randomized clinical trial. *JAMA* 2014; 312: 606-15.
7. Allan S. Brett, reviewing Bretthauer M et al. *N Engl J Med* 2022 Oct 9
8. Holme Ø, Løberg M, Kalager M, et al. Effect of flexible sigmoidoscopy screening on colorectal cancer incidence and mortality: a randomized clinical trial. *JAMA* 2014; 312: 606-15.
9. Jason A. Dominitz, Understanding the results of a randomized trial of screening colonoscopy. *N Engl J Med* 2022 Oct 21

Figures and Tables

Figure 1: Marbet UA et al. Colonoscopy is the preferred colorectal cancer screening method¼ Endoscopy 2008; 40: 650±655

Figure 2: 19. Mai 2022 Gemeinsame Medienmitteilung des Kantons Bern und der Krebsliga beider Basel

Figure 3: Kaminski MF et al. Randomized trial on colonoscopy screening for colorectal cancer... Endoscopy 2012; 44: 695–702

Table 1: M. Bretthauer Effect of Colonoscopy Screening on Risks of Colorectal Cancer and Related DeathDOI: 10.1056/NEJMoa2208375

Table 2: M. Bretthauer Effect of Colonoscopy Screening on Risks of Colorectal Cancer and Related DeathDOI: 10.1056/NEJMoa2208375



Thank you for your attention

