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# Colonoscopy Reduces CRC Incidence and CRC-Related Morality…If You Get It!

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## STRUCTURED ABSTRACT

**Question**: Does a mailed letter invitation for colonoscopy improve colorectal cancer (CRC) incidence or colorectal cancer associated mortality, compared to those who do not get a mailed invitation?

**Study Design**: The Nordic-European Initiative on Colorectal Cancer (NordiCC) trial is a pragmatic multi-center randomized controlled trial.

**Setting**: Poland, Norway, Sweden. Although the Netherlands was part of the original trial, due to Dutch law, the Netherlands investigators were unable to share outcome data on those randomized to the usual care arm.

**Participants:** Individuals between ages 55-64 who had not had prior CRC screening were eligible and identified from population registries. Those with a history of CRC were excluded. There were 10,374 patients from the Netherlands not included in this report because of inability to share data. Overall, 84,585 participants (64.1% Polish, 31.2% Norwegian, 4.3% Swedish) between 2009-2014 were included in this analysis, 49.9% of all

participants were female and 50.1% were ages 55-59.

**Intervention:** Study patients were randomized 1:2 to get a personal letter of invitation for screening colonoscopy by mail with an information leaflet about the study vs usual care (i.e., no mailed invitation sent and not informed about their enrollment in the trial at inclusion or during follow-up). Patients in the invitation group also received an informed consent to complete if they chose to participate.

**Outcomes:** Primary outcomes were risk of CRC and death from CRC with an initial analysis after 10 years and a follow-up analysis after 15 years.[1] The current publication reports results after median 10 years of follow-up. Secondary outcome was all-cause mortality.

**Data Analysis:** Intention-to-screen analysis where usual care participants were compared to study participants who were mailed an invitation to colonoscopy, regardless of whether or not these individuals underwent colonoscopy. A separate adjusted per-protocol analysis was performed only using study participants who completed a colonoscopy. Kaplan-Meier estimates were calculated to assess the cumulative 10-year risks of CRC and CRC-related deaths.

**Results:** Of the 28,220 individuals who were sent a mailed invitation, 11,843 (42%) completed a colonoscopy and 259 were diagnosed with CRC over median follow-up of 10.0 years (IQR: 9.9-10.0; maximum follow-up=10.0 years). Of the 56,365 participants in the usual care arm, 622 were diagnosed with CRC over 10-year follow up. In the intention-to-screen analysis of participants who were mailed an invitation to colonoscopy (regardless of whether or not colonoscopy was performed) vs usual care, the risk ratio (RR) for CRC incidence was 0.82 (95% confidence interval [CI], 0.70-0.93, **Figure 1**) and the RR for CRC-related mortality was 0.90 (95% CI 0.64-1.16). In an adjusted per-protocol analysis that compared invited patients who actually underwent colonoscopy vs usual care, the RR for CRC incidence was 0.69 (95% CI 0.55 to 0.83) and CRC-related mortality was 0.50 (95% CI 0.27 to 0.77). There was no difference in all-cause mortality. Of the 11,843 individuals who had a colonoscopy, there were no perforations and 15 (0.13%) had clinically significant bleeding.

Quality indicators for colonoscopy were also reported: good/very good bowel

preparation (91.2%), cecal intubation (96.8%), and adenoma detection rate (ADR) (30.7%). It's unclear from this report if patients with poor prep or failed cecal intubation had repeat colonoscopy. Although mean ADR of study endoscopists was 30.7%, the mean ADR varied from 14.4% in Sweden to 27.1% in Norway to 35.2% in Poland, and prior reports[1] noted that 29% of study endoscopists had an ADR below the recommended minimum threshold of 25%. No data on performance of colon polyp surveillance colonoscopy is available for the study population.

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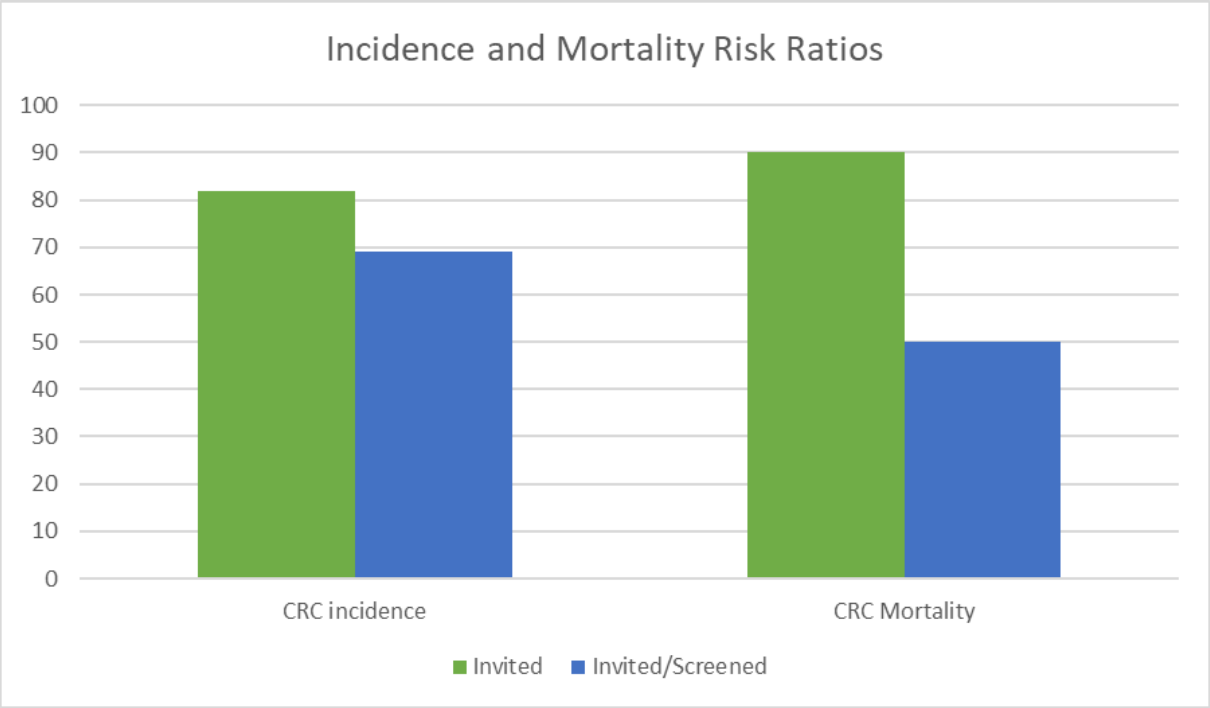


Figure 1. Cumulative risk of colorectal cancer in participants invited vs those invited who underwent colonoscopy.

## COMMENTARY

### *Why Is This Important?*

Until this study was published, we have relied on prospective cohort studies to understand the effectiveness of colonoscopy, which estimated a 40-69% reduction in CRC incidence and 29-88% reduction in death from CRC.[2] This is the first RCT to evaluate the long-term effectiveness of a population-based screening program in reducing CRC incidence and CRC-related mortality.

### *Key Study Findings*

The screening program rolled out in Poland, Norway and Sweden, consisting of sending a mailed colonoscopy invitation to random individuals in the population, was not effective. Only 42% of those invited actually completed a colonoscopy.

In the adjusted per-protocol analysis of screening patients who actually had colonoscopy, the procedure was effective; there was a 31% decrease in CRC incidence and a 50% decrease in risk of death from CRC over 10 years of follow up.

Colonoscopy was also very safe with 0 perforations and a 0.13% risk of serious bleeding.

***Caution***

This study shows that mailing random people an invitation to complete a colonoscopy does not work. This is important information for countries that have a population-based approach to screening, where these results will likely promote multimodal ways of reaching/educating patients and hopefully promote the multiple screening options available, since a simple snail mailer about colonoscopy did not work.

It is important to note that this is not how screening is approached in the United States, where medical professionals serve the key role of educating individuals and helping them make personalized decisions about cancer screening. Thus, the effectiveness of this screening program is not applicable to how we provide care in the US.

It is very encouraging that that the colonoscopy procedures in this study were effective. With that said, the magnitude of benefit was less than prior cohort studies conducted in the US. We know that the protective effect of colonoscopy depends on careful inspection to identify and remove precancerous lesions. For every 1% increase in ADR, there is a 3% decrease in CRC incidence and 5% decrease in CRC mortality with continued inverse association as ADR increases up to at least 40%.[3] Approximately 29% of endoscopists in the NordICC trial had an ADR below the recommended minimum threshold of 25% and the highest ADR reported was 40%.[1] It is unclear why ADRs were lower among these endoscopists, but possibilities include that most exams were performed without sedation with over 20% of patients reporting "moderate or severe" pain during the procedure. This may have hastened the examination. Overall, colonoscopy seems to be a different procedure in these countries compared to the US where the average ADR for screening colonoscopies has increased in recent years to 39%[4], which is probably due to factors including use of high-definition white light colonoscopy, a well-publicized effort to educate US endoscopists about ADR, and offering sedation to most patients to facilitate a careful inspection.

Also, more follow up time may be needed to see to the full protective benefit of colonoscopy. A recent study from the Polish investigators who contributed to the NordICC study showed that a high-quality negative screening colonoscopy can be protective of CRC for 17 years.[5] Investigators will report outcomes after 15 years, which was also a planned analysis.[1]

***My Practice***

This study does not change my practice with regards to CRC screening. I will explain to my patients and colleagues that this study shows that the best screening test is the one that gets done and that colonoscopy is highly safe and highly effective in decreasing risk of CRC and death from CRC. I will continue to offer and perform high-quality colonoscopy as a primary screening test or as a follow up after a positive fecal immunochemical test. I will strive for top notch quality, including pristine bowel preparations, adequate sedation to allow for thorough inspection, and optimizing lumen exposure and lesion recognition by incorporating new technologies, such as artificial intelligence, as they emerge.

***For Future Research***

There are multiple RCTs comparing colonoscopy to fecal immunochemical test that are currently underway currently underway[6] in different health settings, including the CONFIRM trial being conducted at US VA Medical Centers. These studies will undoubtedly provide more comprehensive data about the long-term effects of colonoscopy on CRC incidence and mortality.

With that said, it is important to place results from any study into context and assess how generalizable those results will be to a particular health setting. Bretthauer and colleagues should be commended for conducting a rigorous RCT with an intention-to-screen analysis that was a better fit for health care in Poland, Norway, Sweden, and the Netherlands. Their data demonstrates that performance of population-based CRC screening based on a mailed invitation for colonoscopy is not effective, largely because the majority of these individuals never got colonoscopy. That is useful information, but it's not generalizable to the US setting despite some sensationalized lay media coverage in the US. Finally, we should also remember that studies which measure long-term outcomes, like CRC incidence and mortality, will be outdated when results are reported because of contemporary advances and innovations in colonoscopy quality.

***Conflicts of Interest***

Dr. Patel reports no conflicts of interest.

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