Long-term effects of a flexible sigmoidoscopy screening after 17 years of follow up

Atkin W, Wooldrage K, Parkin DM, et al. Long term effects of once-only flexible sigmoidoscopy screening after 17 years of follow-up: the UK Flexible Sigmoidoscopy Screening randomised controlled trial. Lancet 2017; 389: 1299-311.

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Colorectal cancer is a preventable disease. Screening programs have been initiated to reduce the incidence of colorectal cancer in many countries. One of the recent articles presented by Atkin et al. (1) in Lancet was 'Long term effects of once-only flexible sigmoidoscopy screening after 17 years of follow up: the UK Flexible Sigmoidoscopy Screening randomised controlled trial'. Two studies presented by the same group showed that the colorectal cancer incidence was reduced by 33%, distal colorectal cancer incidence by 50%, and colorectal cancer mortality by 43% (2-3). The aim of this study was to investigate the efficacy of a single sigmoidoscopy in reducing colorectal cancer incidence and mortality rates after a median follow-up of 17 years.

Participants aged from 55 to 64 years, either men or women, were recruited from 14 UK general serving hospitals between November 14, 1994, and March 30, 1999. The exclusion criteria were a history of colorectal cancer, adenomas, or inflammatory bowel disease; life expectancy of <5 years; flexible sigmoidoscopy or colonoscopy procedure within the previous 3 years, or were unable to provide informed consent. Appropriate participants were requested to complete a questionnaire regarding whether they were interested in undergoing a single flexible sigmoidoscopy screen. All participants interested in undergoing a flexible sigmoidoscopy were randomized to the control group or intervention group (2:1). If high risk polyps (≥1 cm; ≥3 adenomas; tubulovillous or villous histology; severe dysplasia or malignant disease) were present in patients in the intervention group, then participants underwent a pancolonoscopy after a sigmoidoscopy. On the other hand, there was no contact for pancolonoscopy in control group. Primary end points were colorectal incidence and mortality rate and secondary end points were distal (rectum and sigmoid) and proximal colon cancer incidence and mortality, all-cause and non-colorectal cancer mortality, and number needed to screen (NNS) for preventing one colorectal cancer diagnosis and death. Overall, 375744 men and women aged 55-64 years were found eligible but 7602 of them were excluded by their general practitioner. After exclusion, 368142 people were provided the questionnaire on interest in undergoing a flexible sigmoidoscopy for screening. In total, 194726 people were interested in flexible sigmoidoscopy screen, but 8280 people were considered inappropriate. Of these, 16014 people were excluded because the trial was funded for only 40000 participants. Finally, 170432 people were randomly assigned as 113195 people for the control group and 57237 people for the intervention group. In both groups, the mean age was 60 years, and 51% of the group included women. In the intervention group, 38525 participants were discharged with the absence or low-risk polyps, whereas 2131 were referred for colonoscopy because of high-risk polyps and 18 were referred to surgery without undergoing a colonoscopy before. Cohort analysis included 170034 participants: 112936 in the control group and 57098 in the intervention group. In the intervention group (n=57098), 40621 participants were screened through a flexible sigmoidoscopy, whereas 16477 were not screened. The median follow-up time from randomization to death, immigration and loss to follow-up was 17.1 years. During screening and follow-up, 4483 people were diagnosed with colorectal cancer (1230 in the intervention group and 3253 in the control group). Overall, 1987 people were diagnosed with distal colorectal cancer in the control group and 592 people in the intervention group of whom 126 were detected during screening. In total, 1255 people were diagnosed with proximal colorectal cancer in the control group and 612 in the intervention group of whom 14 were detected during screening. In the intention-to-treat analysis, it was found that the incidence of all-site colorectal cancer was reduced by 26% ($p<0.001$) and distal colorectal cancer incidence

was reduced by 41% (p<0.001). No risk reduction was found in proximal colorectal cancers (p=0.436). In the per-protocol analysis, which examined the effectiveness in those individuals undergoing a flexible sigmoidoscopy screening, colorectal cancer incidence was reduced by 35% for all-site colorectal cancer and by 56% for distal colorectal cancers; there was no significant effect on proximal colorectal cancer incidence.

During the first 4 years after screening, it was observed that the incidence of all-site and distal colorectal cancers were higher in the intervention group compared to the control group because of detecting already located colorectal cancers during screening. After the first 4 years, the incidence of colorectal cancers was higher in the control group compared to the intervention group. As expected, proximal colon cancer incidence did not significantly change in both control and intervention groups. The estimated NNS to prevent one colorectal cancer during median 17 years was 98; this number was <191, which was found in the previous study during the follow-up of 11 years (3). There was no difference between sex in reducing distal colorectal cancer either in the intention-to-treat analysis (42% for men vs 40% for women) or in the per-protocol analysis (56% for men and women). There was no effect of a flexible sigmoidoscopy screen on the reduction in proximal colon cancer incidence in either men or women; however, there was a slight statistically significant difference between sex in the reduction in all-site colorectal cancers in both intention-to-treat analysis (19% for women vs 30% for men; p=0.0497) and per-protocol analysis (27% for women vs 40% for men; p=0.0480). The NNS to prevent one colorectal cancer was significantly higher in women than in men (165 for women vs 70 for men), probably because women had more proximal colon cancers than did men. When it was examined whether there was an effect of one flexible sigmoidoscopy screen between those aged 55-59 years and those aged 60-64 years for incidence of all colorectal cancers, no difference was found between ages in the intention-to-treat analysis or per-protocol analysis for both men and women.

All-site colorectal cancer mortality was reduced by 30%, distal colorectal cancer mortality by 46%, and proximal colon cancer mortality by a nonsignificant 9%. In the per-protocol analysis, the reduction in colorectal cancer mortality in the screened group was 41%. Distal colorectal cancer mortality was reduced by 66%. There was a reduction in the proximal colon cancer mortality by 12% although it did not reach a statistical significance. The NNS to prevent one death from colorectal cancer during 17 years of follow-up was 220 which was <489 that was found in the previous study (3). However, the NNS to prevent one colorectal cancer death was higher for women than for men. There was no effect of one flexible sigmoidoscopy screen on colorectal cancer mortality when two categories of ages were examined.

The investigators showed that the incidence of colorectal cancer at all sites in screened patients was reduced by 35%, and distal colorectal cancer incidence was reduced by 56% during 17 years of follow-up. The NNS to provide one colorectal cancer diagnosis was almost half (98) of the number (191) that was found in the previous study whose follow-up time was 11 years. This means that a single flexible sigmoidoscopy screen continues to provide long-lasting protection for colorectal cancer. The investigators found that the reduction in distal colorectal cancer incidence after a single flexible sigmoidoscopy was similar in men and women (56%). However, the effect of one single flexible sigmoidoscopy on all-site colorectal cancer incidence was weaker in women than in men; this was because the rates of proximal colorectal cancer in all colorectal cancers was higher in women than in men, particularly in older population in UK. Analyzing the study data by age showed consistent and significant reductions for all-site and distal colorectal cancer incidences and mortality in both the younger and older age categories when men and women were considered together and within each sex.

This study had several strengths. This study was the first trial with a follow-up time as long as 17 years, which showed the protective effect of one flexible sigmoidoscopy. The other strength was that this trial collected the data from national datasets resulting with a very little loss to follow-up the patients, even though some of them migrated in the UK. The limitation of the study was that the cohort was selected based on their interest in attending screening. In conclusion, the investigators claimed that this study showed the effectiveness of one flexible sigmoidoscopy to protect people from colorectal cancer for a long time, at least 17 years.

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