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Effect of flexible sigmoidoscopy on colorectal cancer incidence and mortality: long-term follow-up of the randomized US PLCO Cancer Screening Trial

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Summary

Background—Screening flexible sigmoidoscopy (FSG) reduces incidence and mortality of colorectal cancer (CRC). Previously reported results from the Prostate, Lung, Colorectal and Ovarian Cancer (PLCO) Screening Trial had a median follow-up of 12 years. Whether the benefit is sustained over the long-term, and remains so in both sexes and all age groupings is uncertain. We report on long-term results after an additional 5 years of follow-up.

Methods—Participants in the PLCO (NCT00002540) were recruited from the general population in the catchment areas of 10 screening centers across the US, without previous diagnosis of a PLCO cancer or current cancer treatment. From 1993-2001, the PLCO randomized men and women aged 55-74 years within blocks stratified by center, age and sex to usual care or FSG at baseline and again at 3 or 5 years. The primary endpoint was cause-specific mortality and secondary endpoints included incidence and tumor staging; cause of death was determined without knowledge of study arm. Using an intent-to-treat analysis, we assessed incidence and mortality rates overall, by time-period, and by combinations of sex, age (55-64; 65-74), location (distal/proximal), and stage.

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Author Contributions

The study design, data interpretation and writing were conducted by EAM, PFP, RES, PCP, and TRC. The data analyses were conducted by EAM, PFP.

ClinicalTrials.gov Identifier: NCT00002540

Conflict of Interest

The authors have no conflicts of interest to declare.

Data Sharing

De-identified PLCO data with extended mortality follow-up and corresponding data dictionaries will be available for researchers to access through the Cancer Data Access System (https://biometry.nci.nih.gov/cdas/plco/). At this time, we are not able to release extended incidence data that includes data linked from cancer registries.

Findings—After a median follow-up of 15·8 years for incidence (25th 13·2 / 75th 18·0) and 16.8 years (14·4 / 18·9) for mortality, the incidence of CRC was significantly lower in the intervention arm (1461 cases; 12·55 per 10000 person-years (PY)) compared to usual care (1761 cases; 15.33 per 10000 PY; relative risk(RR)=0·82; 95% confidence interval (95%CI) 0·76–0·88). Similarly, mortality was lower in the intervention arm (417 deaths; 3·37 per 10000 PY) than the usual care arm (549; 4·48 per 10000 PY RR=0·75; 95%CI 0·66–0·85). The reduction in mortality was limited to the distal colon, with no significant effect in the proximal colon. Reductions in incidence were significantly larger in men than women ($p_{interaction}$=0·04) and reductions in mortality were significantly larger in the older age group (65-74 vs. 55-64 at enrollment; $p_{interaction}$=0·01).

Interpretation—Reduction in CRC incidence and mortality from FSG screening is sustained over the long-term. The benefit is limited to the distal colon, and the benefits are greater in men and in older people. Differences by sex and age should be examined in other ongoing trials of CRC screening to help clarify if different screening strategies would achieve greater risk reduction.

Background

Colorectal cancer is the second leading cause of cancer death for men and women combined in the US but incidence and mortality rates have been decreasing[1] due, in part, to the effectiveness of screening.[2] Randomized clinical trials have consistently shown that both fecal occult blood testing (FOBT) and flexible sigmoidoscopy (FSG) reduce both incidence and mortality of colorectal cancer (CRC).[3–8] A pooled analysis of three FSG trials conducted in the U.S. and Europe found a 21% reduction in CRC incidence and a 27% reduction in CRC-specific mortality after a median follow-up of 10-12 years. The risk reductions were stronger in men than women; among women, reductions were limited to those aged less than 60 years.[9] With the exception of the US-conducted Prostate, Lung, Colorectal and Ovarian Screening Trial (PLCO), reductions in incidence and mortality were limited to the distal colon.

Recently, Atkin et al. (2017) and Holme et al. (2018) reported the results of extended follow-up in the UK Flexible Sigmoidoscopy Screening Trial (UKFSST) and Norwegian Colorectal Cancer Prevention (NORCCAP) study, respectively.[4,8] With a single FSG screening, they found reductions in risk for incidence and mortality were maintained with median follow-up times of 15-17 years. The UKFSST found a 30% reduction in mortality and 26% reduction in incidence. NORCCAP found no significant reduction in women but reductions of 34% and 37% for incidence and mortality, respectively, in men. The PLCO trial included a repeat FSG 3 or 5 years after the study baseline that was found to increase the yield of adenomas by 32%.[10] The most recent report on PLCO, based on a median follow-up of 12 years, found incidence and mortality risk reductions similar to the European trials. Whether longer-term outcomes might differ in PLCO due to the use of two FSG exams and a higher rate of colonoscopy compared to the UK study is unknown. Using PLCO data, we analyzed results overall, and by location, sex and age for a maximum of 21 years of incidence and 22 years of mortality follow-up. Randomized trials of colonoscopy vs. usual care or vs. fecal immunochemical testing [FIT] [11–13] are underway but results are years away. FSG is the only endoscopic screening procedure which has long-term comprehensive follow up of

randomized participants. Exploration of whether the benefit of FSG is sustained over the long-term in both sexes and all age groupings is needed.

Methods

Study design and participants

Details on the design of the PLCO trial (ClinicalTrials.gov: NCT00002540), including power calculations and recruitment methods have been described in depth.[6,14,15] Briefly, the PLCO trial tested the hypothesis that prostate, lung, colorectal, and ovarian cancer screening tests would reduce corresponding cause-specific mortality and enrolled men and women aged 55-74 years between 1993-2001 with no history of prostate, lung, colorectal, or ovarian cancer and not undergoing cancer treatment. Participants were recruited from the general population in the catchment area of 10 clinical centers across the US. Institutional review boards at each institution approved the trial. All participants gave written consent and were given a baseline questionnaire that assessed demographic characteristics, general risk factors and health characteristics, screening history, and family history of cancer.

Randomization and masking

Participants were randomized to an intervention or a usual care arm within blocks stratified by screening center, age and sex. Review of cause of death was conducted without knowledge of participants' study arm.

Procedures

CRC screening in the intervention arm of the trial included FSG at baseline and a second FSG at 3 years for those enrolled before April 1995 or at 5 years for those enrolled after that date. Screening tests were considered positive if a mass or polyp was detected during the procedure, which led to referral to the participant's primary care physician for follow-up. Participants in the usual care arm could be screened under care of their physician.

To estimate rates of non-study screening activity, a Health Status Questionnaire (HSQ) was administered periodically to a random sample of participants in the usual care arm during the active screening phase of the trial and to a sample of participants from both study arms during the post-screening period.

Outcomes

The primary endpoints for the trial were the cause-specific mortality rates for each of the PLCO cancer sites based on an intent-to-treat analysis. Secondary endpoints for this analysis included overall and tumor stage incidence by study arm. The previous analysis included follow-up through 2009 or 13 years, whichever came first. During that study period, incident cancers were identified primarily through Annual Study Updates (ASU) questionnaires to participants. Cancer diagnoses and tumor characteristics were confirmed through medical record review by certified tumor registrars. Tumors were staged using the TNM staging system based on the fifth edition of the *American Joint Committee on Cancer (AJCC) Cancer Staging Manual*,[16] Deaths were identified through next-of-kin and supplemented through linkage with the National Death Index (NDI). Through 2009, deaths were confirmed

by death certificate and underlying cause of death determined through review of medical records by an independent death review committee.[6,17] After the originally scheduled follow-up period ended, participants were re-consented in 2011 to continue follow-up through a centralized data collection process. Participants had the option to continue active follow-up supplemented with linkage to NDI and statewide cancer registries or to be followed only passively through these linkages. Alternatively, participants could refuse to continue participating in the study. All linkages were probabilistic and based on Social Security Number, name, sex, and date of birth.

Forthis analysis, NDI data were available through 2015, providing up to 22 years of mortality follow-up. Cancer registry data were available through 2014, providing up to 21 years of incidence follow-up. A previous analysis of PLCO's linkage to cancer registries found approximately 87% of CRC's identified by the PLCO matched with the corresponding cancer in cancer registry data.[18] For this analysis, when information was available from both sources, we relied on the active follow-up data unless missing information was available from the registry.

Statistical analysis

We calculated incidence and mortality rates as the number of events divided by the corresponding person-years, which were calculated from the time from randomization to the appropriate end date. For incidence, time was censored on date of death, end-of-file date (December 31, 2014) or December 31, 2009 for those who refused participation after the initial follow-up period. For mortality, participants were censored at date of death by other causes, study refusal date, or end-of-file date (December 31, 2015). Rates were calculated overall, by tumor location (proximal, distal), sex, and age group at baseline (55-64, 65-74 years). We calculated relative risks (RR), person-year (PY) rate differences (RD) and corresponding 95% confidence intervals (CI) by study arm using Poisson regression. The number needed to screen (NNS) to prevent one incident CRC case or CRC death was calculated by taking the reciprocal of the cumulative incidence or mortality risk difference across arms. We included interaction terms for sex and baseline age (55-64; 65-74 years) by study arm to test if RRs significantly differed across subgroups. We compared deaths and incident cases by stage, tumor location, and study arm and calculated the difference in number of cases and deaths and percent change in rates. To assess possible changes in relative risk of CRC over time, we calculated, by arm, 5-year incidence rates from baseline to year 15 and a 6-year incidence rate from year 15 to 21. All analyses were conducted in SAS 9.4.

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Results

Participant characteristics at baseline are presented by study arm (Table 1). Participation status after 2009 differed significantly by study arm, with 10590 of 77444 (17·1%) participants in the usual care arm refusing continued follow-up compared to 8115 of 77443 (13· 0%) in the intervention arm. The median follow-up times were similar by arm for incidence [intervention: 15·9 years (25^{th} 13·5 / 75^{th} 18·1); usual care: 15·7 (12·9/17·9)] and mortality [intervention: 16·9 (14·7/19·0); usual care: 16·7 (14·2/18·9).

The incidence of CRC was significantly lower in the intervention arm compared to usual care (RR=0·82; 95%CI 0·76–0·88) with close to 3 fewer cases diagnosed per 10000 PY (RD=2·78; 95%CI 1·82 – 3·74) (Table 2). Approximately 258 persons would need to be screened to prevent 1 CRC case. By tumor location, the reduction in risk was statically significant for distal tumors (RR=0·71; 95%CI 0·64–0·79), but only modestly reduced and borderline statistically significant for proximal tumors (RR=0·91; 95%CI 0·83–1·00; p=0·05). Compared to usual care, risks of incident CRC in the intervention arm were lower in both men (RR=0·77; 95%CI 0·70–0·84) and women (RR=0·89; 95%CI 0·80–0·99), but the reduction was significantly larger in men ($p_{interaction}$=0’04). For the intervention compared to usual care arm, there were approximately 4 fewer CRC cases per 10000 PY in men (RD=4·28; 95%CI 2·79 – 5·77) but only 1 fewer case per 10000 PY in women (RD=1·34; 95%CI 0·11 – 2·57). The RRs for incidence were similar by age at enrollment; RR=0·79 (95%CI 0·72–0·88) in those aged 65-74 and RR=0·85 (95%CI 0·77–0·93) in those aged 55-64 ($p_{interaction}$=0·35).

For distal tumors, the incidence was significantly reduced in both men (RR=0·65; 95%CI 0·57–0·74) and women (RR=0·83; 95%CI 0·70–0·98) and the reduction was significantly larger in men than women ($P_{interaction}$=0·03) (Table 2). The difference in distal tumors diagnosed comparing the usual care arm to intervention was 3·49 (95%CI 2·43 – 4·55) per 10000 PY in men and 0·87 (95%CI 0·10 – 1·64) per 10000 PY in women. Proximal CRC incidence was not significantly reduced for either men or women. Within age groups, there was no statistical difference in incidence between men and women but for those aged 55-64 at enrollment, the reduced incidence was statistically significant for males (RR=0·79; 95%CI 0·70–0·90) but not for females (RR=0·92; 95%CI 0·80–1·07). However, the interaction term by sex for those aged 55-64 was not statistically significant ($p_{ineraction}$=0·11).

CRC mortality was significantly reduced overall in the intervention compared to usual care arm (RR=0·75; 95% CI 0·66–0·85) (Table 2), due almost exclusively to distal tumors (RR=0·51; 95% CI 0·41–0·63), with no little to no reduction for proximal tumors (RR=0·95; 95%CI 0·79—1 −14). There was approximately 1 fewer death per 10000 PY in the intervention compared to usual care arm for CRC overall (RD=1·11; 95% CI 0·62 – 1·61) and distal tumors (RD=1·05; 95% CI 0·73 – 1·37). It was estimated that 587 (95%CI 401 – 1090) persons would need to be screened to prevent 1 CRC death. Mortality reductions were larger in men (RR=0·68; 95%CI 0·57–0·80) than women (RR=0·87; 95%CI 0·71–1·06) and only statistically significant in men, though the interaction did not reach statistical significance ($p_{interaction}$=0·06). RRs did not differ significantly by sex stratifying by distal and proximal tumors. Both men and women had significantly reduced risks of CRC

mortality from distal tumors in the intervention compared to the usual care arm. Neither sex had a reduced risk of CRC mortality for proximal tumors. Reductions in mortality were statistically significant for those aged 65-74 years at baseline (RR=0·64; 95%CI 0·53–0·77) and larger compared to those aged 55-64 years (RR=0·88; 95%CI 0·73–1·05; $p_{interaction}$=0·01) (Table 2). By sex and age group, CRC mortality was significantly reduced in men but not women aged 55-64, while both men and women aged 65-74 had significantly reduced CRC mortality. There were approximately 3.64 (95% CI 2·00 - 5·28) fewer CRC deaths per 10000 PY among men and 1·46 (95% CI 0·21 - 2·72) fewer among women. However, neither difference by sex was statistically significant within each age group (55-64: $p_{ineraction}$=0·11; 65-74: $p_{interaction}$=0·32).

As expected with the reduced relative risk, the cumulative number of CRC cases has continued to be higher in the usual care arm compared to the intervention arm, overall and for both distal and proximal tumors (Figures 1A-C). Similarly, the cumulative number of CRC deaths remained higher in the usual care arm compared to the intervention arm over 20 years of follow-up (Figures 2A-C). The result is driven by the difference in deaths from distal CRC. For both incidence and mortality from distal CRC, the absolute difference in cases by arm increased from year 10 to year 20.

Examining the relative risk of incident CRC by time-period, it was lowest between 5-10 years (RR=0·72; 95%CI 0·64–0·82) and attenuated towards the null between 15-21 years (RR=0·90; 95%CI 0·72–1·13) (Figure 3). The pattern substantially differed by sex. While the relative risk for men decreased between 5-10 years before attenuating toward the null, there was little change in the relative risk over time for women.

The reduction in incidence was stronger with each advancement in stage, with a 17·0% reduction in stage I tumors and a 29·0% reduction in stage IV tumors (Table 3). Incidence rates in each stage were lower for both distal and proximal tumors in the intervention arm but the magnitude of reduction was much greater for distal tumors. There was no significant difference in the distribution of tumor stage by arm overall or for proximal tumors but there was a significant difference for distal tumors (p=0·02). In the intervention arm, there were higher percentages of stage I/II tumors and lower percentages of stage III/IV tumors compared to the usual care arm. Mortality from CRC was lower for each stage in the intervention arm compared to the usual care arm and the percent reduction increased from 14·7% for stage I tumors to 30·4% for stage IV.

We assessed FSG or colonoscopies received in the past 5 years (for any purpose) during the follow-up period (study years 11-18) to evaluate the effect of testing subsequent to the trial protocol screening on CRC incidence and mortality rates. Between intervention and usual care arms, respectively, the percentage of participants who received a FSG (25·5% vs. 26·3%) or colonoscopy (63·6% vs. 65·3%) did not differ. However, the percentage using either test was modestly higher in the usual care (72·1%) compared to the intervention arm (68·8%). Results by test, age, sex and study year are presented in Supplemental Tables 1 and 2.

Discussion

With extended follow-up for CRC incidence and mortality in the PLCO trial of FSG screening with medians of 16 and 17 years, respectively, there was a reduced risk of 0·75 for CRC mortality and 0·82 for CRC incidence in the intervention compared to usual care arm. These results are similar to the previous report at a median of 12 years of follow-up[6] and indicate sustained, longstanding benefit of the intervention. Incidence and mortality reductions were limited to the distal colon and found to be larger among men than women. The mortality reduction was stronger among older compared to younger participants but the incidence reductions were similar.

Overall, our results are consistent with the long-term follow-up from UKFSST, which found reduced relative risks of 0·74 and 0·70 for incidence and mortality, respectively, after a median follow-up of 17 years.[4] NORCCAP only presented results stratified by sex, and reported a non-significant 0·92 risk reduction in incidence and no effect on mortality in women, and for men a significant 0.66 reduction in incidence and a 0·63 reduction in mortality.[9] In contrast, while the PLCO and NORCCAP found no significant mortality benefit from FSG in women overall, the UKFSST found a significant 0·81 mortality reduction with FSG screening in women. The lower incidence and mortality risk reductions in PLCO observed in women as compared to men are likely explained, at least in part, by women having higher rates of proximal tumors compared to distal tumors. As available from Table 2, in the usual care arm, 59% of tumors in women were proximal compared to only 45% in men. And although there were statistically significant reductions in incidence and mortality among women aged 65-74 years but not 55-64, the ratio of distal to proximal tumors was similar in both age groups. Similarly, studies of screening colonoscopy have demonstrated a higher percentage of cancer precursors in the proximal colon in women than men.[19,20] Alternatively, the PLCO was not powered to detect differences within subgroups and with a lower baseline rate and lower percent risk reduction in women, the study may not have had the power to detect the more modest reduction in women.

The higher proportion of proximal tumors in women might indicate that women would have greater additional benefit from colonoscopy over sigmoidoscopy than men, as colonoscopy examines the entire colon. Although there is currently no colonoscopy trial data available, prospective cohort data from the Nurses Health Study and Health Professionals Follow-up Study found significant reductions in both incidence and mortality for women with colonoscopy.[21] The Nordic-European Initiative on Colorectal Cancer (NordICC) randomized trial of colonoscopy, with over 6000 women receiving screening colonoscopy, may help clarify the benefit of full colonoscopy in women.[22]

The UKFSST and NORCCAP studies were limited to participants up to age 64 at baseline while PLCO included participants up to 74. The pattern of results comparing the PLCO to the other studies was similar when limited to participants aged 55-64 at baseline. However, we found a stronger reduction in mortality rates among those aged 65-74 at enrollment. One potential explanation is that the higher risk of CRC at older ages allows screening older individuals to identify more people with polyps or malignant tumors, and thereby facilitate a larger percent reduction in mortality. Some guidelines have recently changed to recommend

screening beginning at age 45, based on increasing incidence and the assumption of the efficacy of screening in younger age groups.[23] In PLCO, the weaker reduction of CRC mortality by FSG screening in the younger age group suggests that the benefit of screening in younger age groups cannot be assumed.

In the pooled analysis of 3 FSG trials (PLCO, NORCCAP and SCORE), the authors found significantly reduced incidence and mortality from screening in women aged 55-59 years but no effect in women aged 60-64 or ≥60 years.[9] These results seemingly conflict with the results in the current analysis where we found significant reductions for incidence and mortality in women aged 65-74 but not those aged 55-64 years. The discrepancy may arise from collapsing the 5-year age groups into 10-year age groups in our study. There was evidence of heterogeneity in the results between those aged 55-59 and 60-64 years in the pooled analysis, including results presented only for PLCO.

It is important to note that although the PLCO included a repeat FSG at 3 or 5 years, the magnitude of risk reduction for incidence and mortality was not larger compared to NORCCAP and UKFSST, which used a single exam. This is surprising since the additional round of screening identified approximately 30% more advanced adenomas.[10] However, with the high rate of endoscopic testing in the usual care arm, and only 50% of participants in the intervention arm receiving a second screening test,[10] the additional cases and deaths prevented due to repeat testing may not have been large enough to demonstrate a difference from the other trials.

Although the cumulative incidence difference by study arm continued to the end of follow-up, examining the relative risks for incidence by time-period provides evidence that the reduced risk may attenuate after 10 years. However, this was driven by the effect in men. It will be important to determine if there are differences in short and long-term outcomes by sex with the use of colonoscopy, which is now more commonly used for screening. Differences could suggest a need to adjust screening schedules and strategies by sex and age. Holme *et al.* (2017) also suggested a potential need to individualize screening regimens by sex and age based on their pooled analysis.[9] Alternatively, the increasing use of lower endoscopy in the usual care arm over time[24] could possibly account for attenuation but we did not see evidence of a differential effect by sex (Supplemental Table 2).

This investigation has several limitations. When the follow-up process switched from active participant contact to passive linkage, collection of detailed medical records was no longer possible. As a result, cause of death was obtained from the death certificate instead of a blinded death review process. While this could introduce bias, previous investigations comparing death certificate to death review have found little difference.[17,25] In addition, the change in follow-up procedures after the original study period created the potential for bias since the refusal rates were significantly different by arm, albeit modestly. However, we feel the modest difference is unlikely to have much impact. Comparisons of mortality over time can be influenced by treatment differences within stage between trial arms. However, data in earlier reports indicate comparable treatment distributions between arms within stage.[24] Endoscopic contamination (FSG or colonoscopy) was close to 50% during the screening phase of the trial in the usual care arm[6] and any use of endoscopy increased to

approximately 65% for both arms during the extended follow-up time-period. The high rate of contamination during the trial and follow-up limits the ability to assess the true reduction in risk from FSG.

Follow-up of PLCO participants for up to 22 years demonstrates a sustained, long-term reduction in CRC incidence and mortality with FSG. The benefit is primarily limited to the distal colon, and the benefits are greater in men and in older people. A critical focus in ongoing screening trials such as the NordICC study[22] and in studies comparing fecal immunochemical testing to colonoscopy[26] will be to examine results within sex and age groups, to further clarify whether more personalized screening recommendations are needed to achieve the maximal impact in reducing colorectal cancer incidence and mortality.

Research in context

Evidence before the study

Articles on clinical trials for colorectal cancer screening were obtained from 2016 evidence review published by the US Preventive Services Task Force (USPSTF) and by searching PubMed from Jan 1, 1995 to June 30, 2018. Most relevant to our analysis were the recent extended results from previous randomized trials of flexible sigmoidoscopy (FSG) from the UK and Norway, as well as the original follow-ups of those studies and of the Prostate, Lung, Colorectal, and Ovarian (PLCO) Screening Trial. All 3 of the trials found significant reductions in colorectal cancer incidence and mortality during the original follow-up periods. The UK trial found continued risk reduction with extended follow-up but the reduction in NORCCAP was limited to men.

Added value of this study

The studies conducted in the UK and Norway included a single screening test while the PLCO included a follow-up test. It is unknown if there is a greater reduction in risk with the follow-up test. It is also important to assess if the risk reductions are consistent across populations with different healthcare systems and follow-up experiences. The PLCO provides results comparing an intervention FSG group to a usual care group, which includes a higher utilization of screening with colonoscopy in the general population than the European trials. The results of the extended analysis indicate that the reductions in risk from FSG screening can be sustained long-term and may differ by age group and sex.

Implications of all the available evidence

The results from this study, in combination with the other screening trials, can help inform future colorectal cancer screening guidelines.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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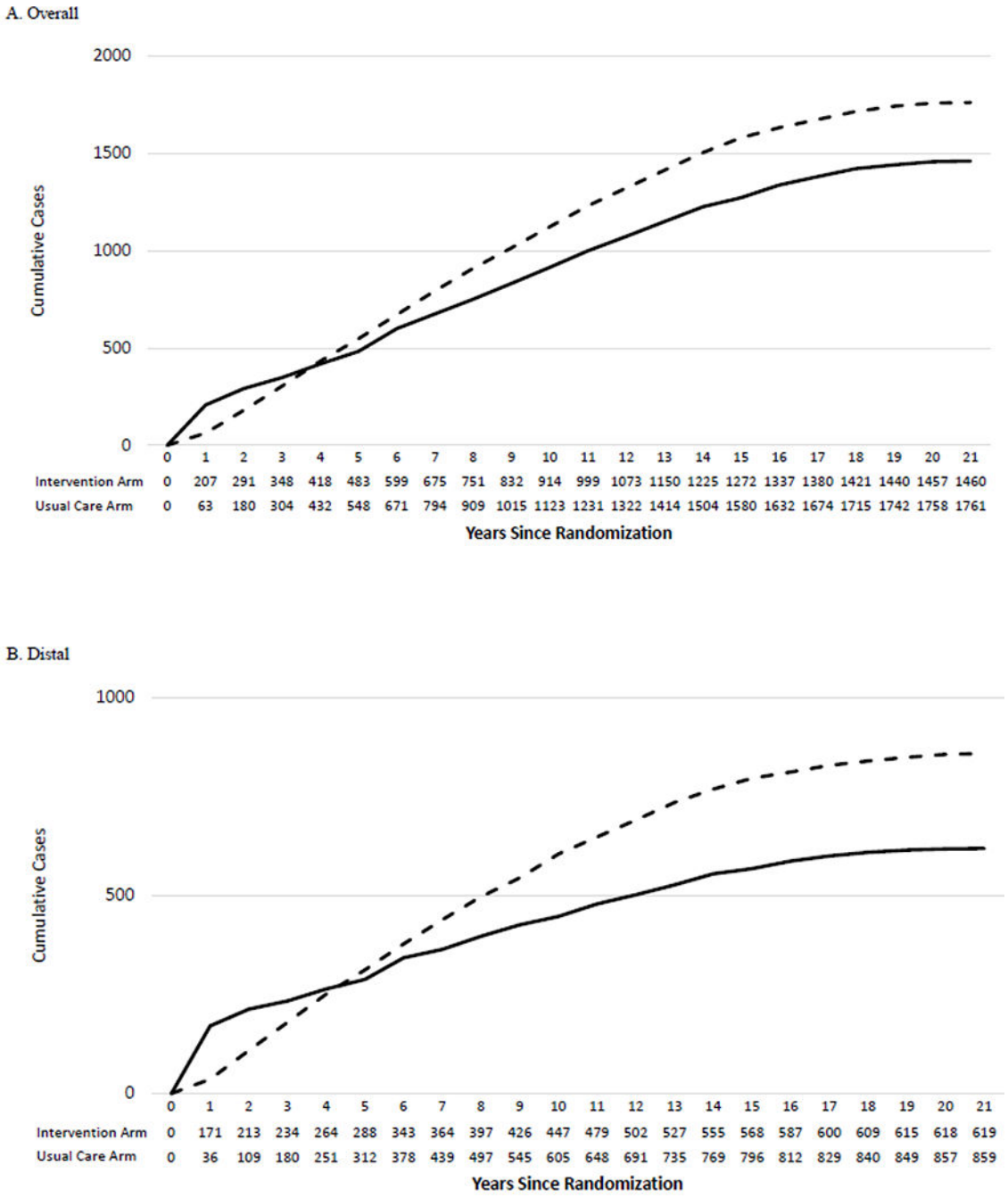
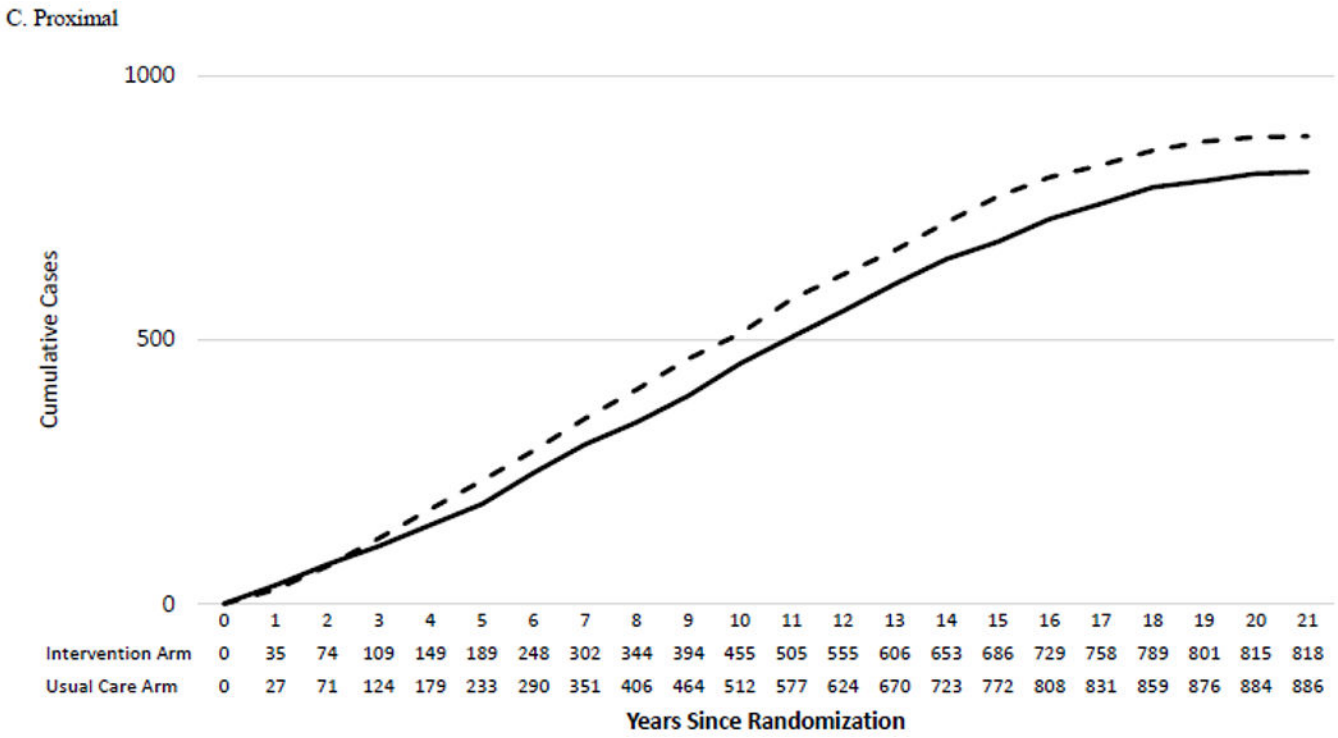
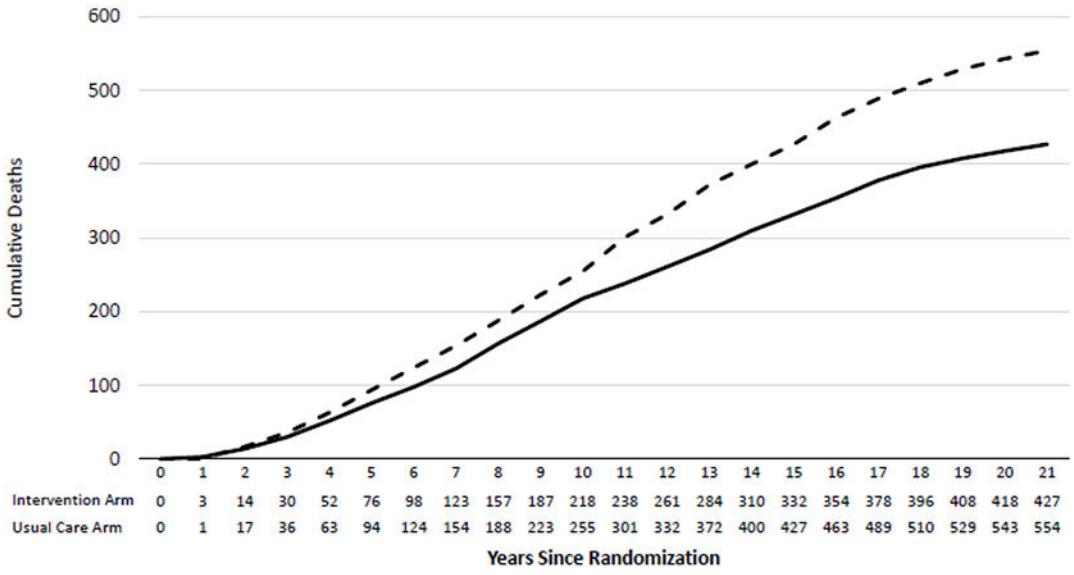




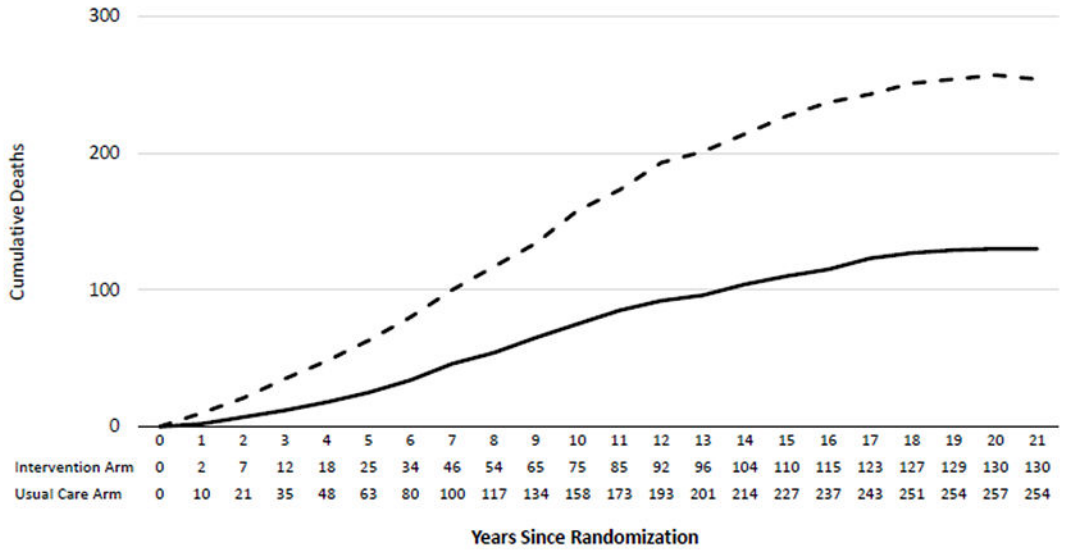
Figures 1A-C.

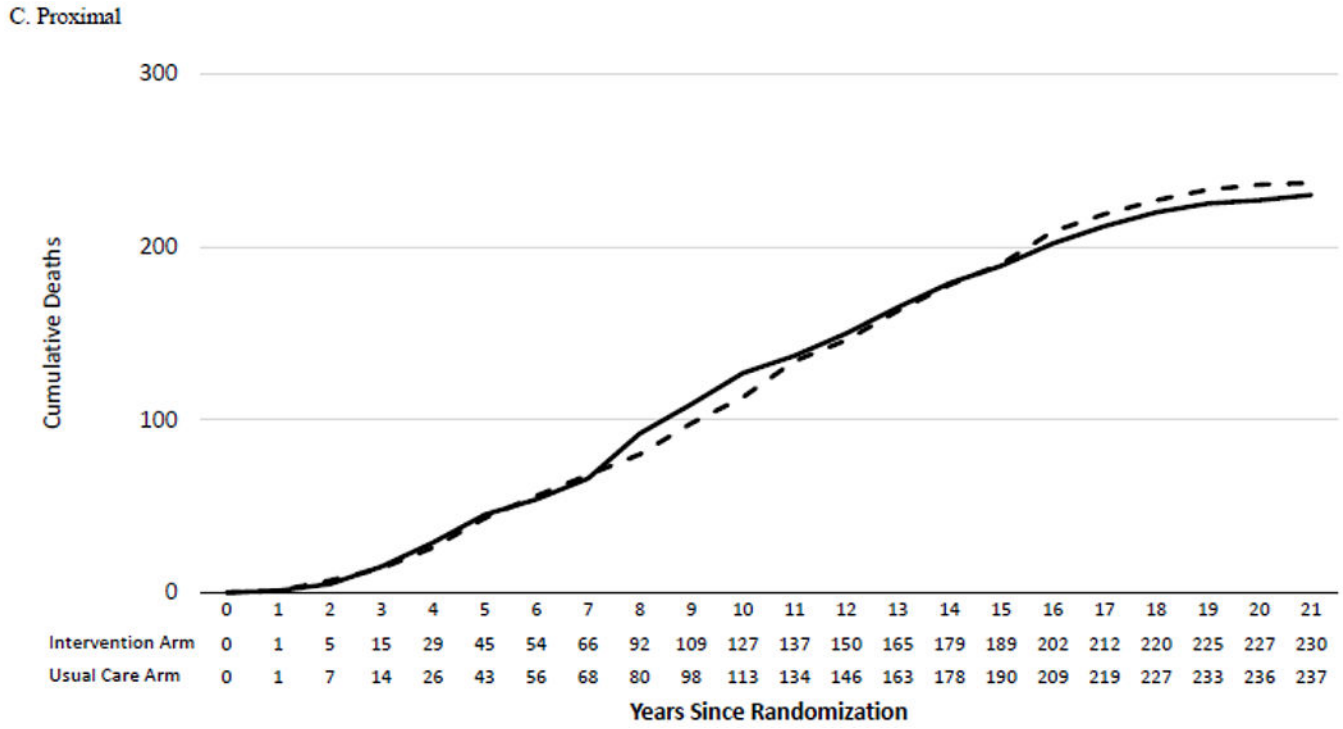
Cumulative incidence of colorectal cancer by study arm and tumor location. Intervention arm is the solid line and usual care arm is the dashed line.

A. Overall



B. Distal





Figures 2A-C.

Cumulative mortality of colorectal cancer by study arm and tumor location. Intervention arm is the solid line and usual care arm is the dashed line.

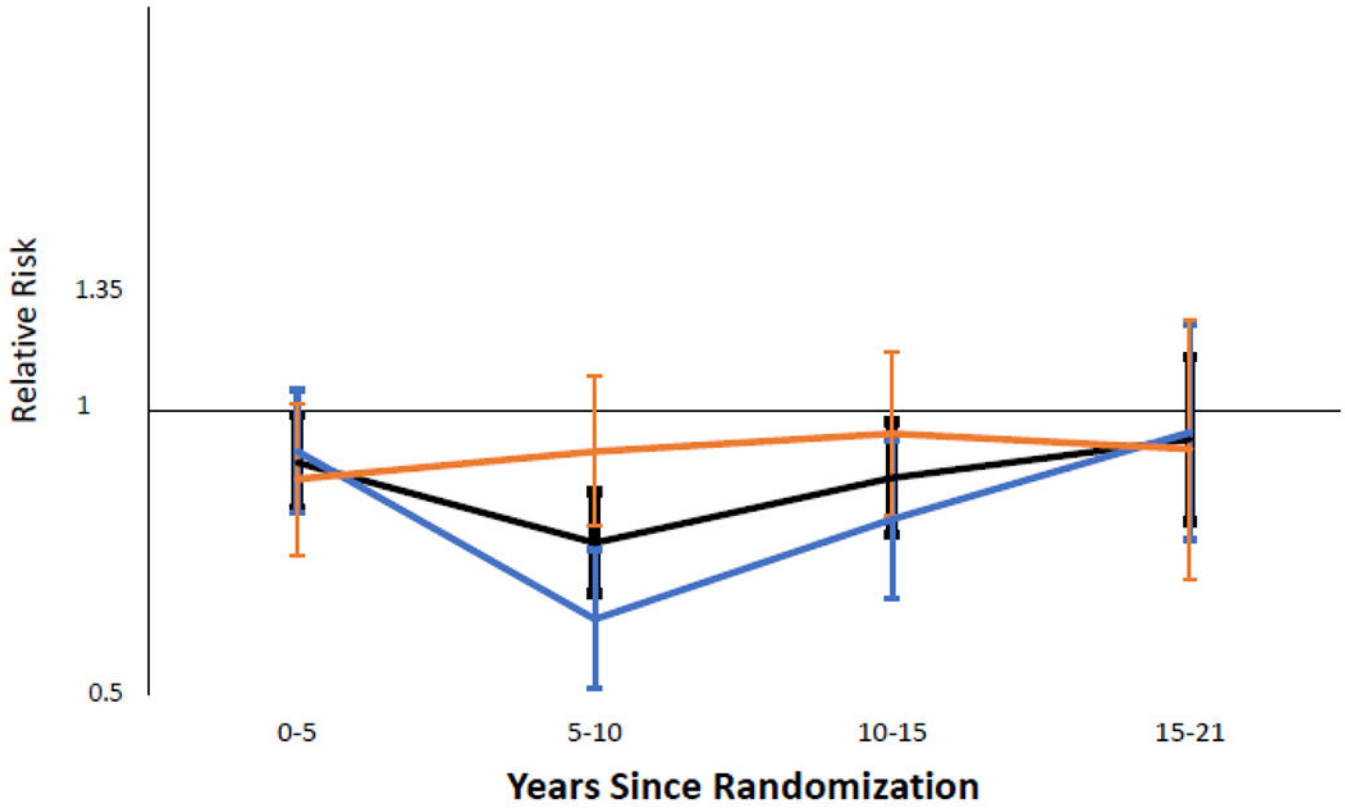


Figure 3.

Relative risks of incident colorectal cancer by time-period and sex. Overall relative risk is the solid line, males the dotted line, and females the dashed line.

Table 1.

Distribution of PLCO participants at baseline.

	Intervention Arm (n=77443)	Usual-Care Arm (n=77444)
Sex	**n (%)**	**n (%)**
Male	38340 (49·5)	38338 (49·5)
Female	39103 (50·5)	39106 (50·5)
Age		
55-59 Years	25849 (33·4)	25838 (33·4)
60-64	23783 (30·7)	23765 (30·7)
65-69	17454 (22·5)	17469 (22·6)
70-74	10357 (13·4)	10372 (13·4)
Race/Ethnicity		
White non-Hispanic	66872 (86·4)	65700 (84·8)
Black non-Hispanic	3883 (5·0)	3825 (4·9)
Hispanic	1421 (1·8)	1397 (1·8)
Asian	2791 (3·6)	2784 (3·6)
Other/unknown	2476 (3·2)	3738 (4·8)
Educational Level		
High-school graduate or less	22892 (29·6)	22583 (29·2)
Some college	25935 (33·5)	25584 (33·0)
College graduate	26658 (34·4)	25914 (33·5)
Unknown	1959 (2·5)	3372 (4·3)
First-degree Relative with Colorectal Cancer	7641 (9·9)	7320 (9·5)
Daily Use of Aspirin or Ibuprofen in Past 12 Months	24822 (32·1)	23948 (30·9)
Participation Status After 2009[1]		
Continued Participation	54197 (87·0)	51495 (82·9)
Refused Further Participation	8115 (13·0)	10590 (17·1)

[1]Distribution by arm is significantly different (p<0.001). Does not add up to the total because it is limited to those alive after 2009.

Table 2.

Colorectal cancer mortality and incidence rates by intervention arm.

Incidence	Intervention Arm		Usual Care Arm		RR (95% CI)	RD (95% CI) per 10000	P-value for Interaction	NNS
	N	rate per 10000	n	rate per 10000				
All CRC cases[1]	1461	12·55	1761	15·33	0·82 (0·76 – 0·88)	2·78 (1·82 – 3·74)		258 (188 – 411)
Distal	619	5·32	857	7·46	0·71 (0·64 – 0·79)	2·14(1·49 – 2·79)		
Proximal	818	7·03	886	7·71	0·91 (0·83 – 1·00)	0·68 (−0·02 – 1·38)		
Male	803	14·13	1031	18·41	0·77 (0·70 – 0·84)	4·28 (2·79 – 5·77)	0·04	168 (123 – 266)
Female	658	11·05	730	12·39	0·89 (0·80 – 0·99)	1·34 (0·11 – 2·57)		543 (270 – ∞)
55-64 Years	784	10·21	912	12·06	0·85 (0·77 – 0·93)	1·85 (0·79 – 2·91)	0·35	386 (237 – 1036)
65-74	677	17·10	848	21·59	0·79 (0·72 – 0·88)	4·49 (2·55 – 6·43)		163 (113 – 297)
55-64								
Male	428	11·41	532	14·44	0·79 (0·69 – 0·90)	3·03 (1·39 – 4·66)	0·11	233 (148 – 559)
Female	356	9·07	380	9·80	0·92 (0·80 – 1·07)	0·73 (−0·63 – 2·09)		1040 (326 - ∞)
65-74								
Male	375	19·43	498	25·99	0·75 (0·65 – 0·85)	6·56 (3·55 – 9·57)	0·20	114(77 – 216)
Female	302	14·89	350	17·40	0·85 (0·73 – 1.00)	2·51 (0·03 – 4·99)		292 (142 – ∞)
Distal								
Male	371	6·53	561	10·02	0·65 (0·57 – 0·74)	3·49 (2·43 – 4·55)	0·03	
Female	248	4·16	296	5·03	0·83 (0·70 – 0·98)	0·87 (0·10 – 1·64)		
Proximal								
Male	414	7·28	457	8·16	0·90 (0·79 – 1·02)	0·88 (−0·14 – 1·90)	0·71	
Female	404	6·78	429	7·28	0·93 (0·81 – 1·06)	0·50 (−0·45 – 1·45)		
Mortality								
All CRC deaths[1]	417	3·37	549	4·48	0·75 (0·66 – 0·85)	1·11 (0·62 – 1·61)		587 (401 – 1090)
Distal	135	1·09	262	2·14	0·51 (0·41 – 0·63)	1·05 (0·73 – 1·37)		
Proximal	233	1·88	242	1·97	0·95 (0·79 – 1·14)	0·09 (−0·25 – 0·44)		
Male	234	3·88	341	5·73	0·68 (0·57 – 0·80)	1·84 (1·06 – 2·63)	0·06	358 (248 – 639)
Female	183	2·88	208	3·30	0·87 (0·71 – 1·06)	0·42 (−0·19 – 1 03)		1565 (613 - ∞)
55-64 Years	230	2·81	259	3·20	0·88 (0·73 – 1·05)	0·40 (−0·14 – 0·93)	0·01	1701 (684 -)

Incidence	Intervention Arm		Usual Care Arm		RR (95% CI)	RD (95% CI) per 10000	P-value for Interaction	NNS
	N	rate per 10000	n	rate per 10000				
65-74	186	4·44	290	6·96	0·64 (0·53 – 0·77)	2·52 (1·49 – 3·54)		268 (190 – 456)
55-64								
Male	127	3·18	161	4·10	0·78 (0·61 – 0·98)	0·91 (0·75 – 1·76)	0·11	715 (362 – 28944)
Female	103	2·45	98	2·36	1·04 (0·79 – 1·37)	−0·09 (−0·76 – 0·57)		--
65-74								
Male	107	5·27	180	8·91	0·59 (0·47 – 0·75)	3·64 (2·00 – 5·28)	0·32	191 (131 – 352)
Female	79	3·67	110	5·13	0·71 (0·53 – 0·95)	1·46 (0·21 – 2·72)		449 (240 – 3526)
Distal								
Male	90	1·49	182	3·06	0·49 (0·38 – 0·63)	1·56 (1·02 – 2·10)	0·56	
Female	45	0·71	80	1·27	0·56 (0·39 – 0·80)	0·56 (0·21 – 0·91)		
Proximal								
Male	117	1·94	130	2·18	0·89 (0·69 – 1·14)	0·24 (−0·27 – 0·76)	0·43	
Female	116	1·83	112	1·79	1·03 (0·79 – 1·33)	−0·05 (−0·52 – 0·42)		

[1] Total number of cases and deaths is greater than sum of deaths by tumor location because of unspecified tumor location.

RR=relative risk; RD=risk difference; NNS=number needed to screen and is calculated as the reciprocal of the difference across arms in cumulative incidence or mortality.

Table 3.

Distribution of colorectal cancer (CRC) deaths and rates by stage and tumor location

	Stage				Chi-Square P-Value
	I	II	III	IV	
Incidence					
All CRC cases					
Intervention arm					
N (%)	448 (34·3)	340 (26·0)	331 (25·3)	187 (14·3)	0·65
Rate per 10000	3·85	2·92	2·84	1·61	
Usual care arm					
N (%)	537 (33·0)	413 (25·4)	418(25·7)	258 (15·9)	
Rate per 10000	4·67	3.59	3·64	2·24	
Difference - N (% reduction)	**89 (17·6)**	**73 (18·7)**	**87 (22·0)**	**71 (28·1)**	
Distal					
Intervention arm					
N (%)	238 (44·4)	128 (23·9)	112 (20·9)	58 (10·8)	0·02
Rate per 10000	2·04	1·10	0·96	0·50	
Usual care arm					
N (%)	311 (39·8)	163 (20·8)	181 (23·1)	127 (16·2)	
Rate per 10000	2·71	1·42	1·57	1·10	
Difference - N (% reduction)	**73 (24·7)**	**35 (22·5)**	**69 (38·9)**	**69 (54·5)**	
Proximal					
Intervention arm					
N (%)	207 (27·2)	211 (27·8)	219 (28·8)	123 (16·2)	0·80
Rate per 10000	1·78	1·81	1·88	1·06	
Usual care arm					
N (%)	225 (26·9)	250 (29.9)	236 (28·2)	126 (15·0)	
Rate per 10000	1·96	2·18	2·05	1·10	
Difference - N (% reduction)	**18 (9·2)**	**39 (17·0)**	**17 (8·3)**	**3 (3·6)**	
Mortality					
All CRC Deaths					
Intervention arm					
N (%)	36 (10·0)	47 (13·1)	120 (33·4)	156 (43·5)	0·77
Rate per 10000	0·29	0·38	0·97	1·26	
Usual care arm					
N (%)	42 (8·8)	56 (11·8)	155 (32·6)	222 (46·7)	
Rate per 10000	0·34	0·46	1·27	1·81	
Difference - N (% reduction)	**6 (14·7)**	**9 (17·4)**	**35 (23·6)**	**66 (30·4)**	
Distal					
Intervention arm					
N (%)	19 (14·4)	23 (17·4)	43 (32·6)	47 (35·6)	0·40

	Stage				Chi-Square P-Value
	I	II	III	IV	
Rate per 10000	0·15	0·18	0·34	0·38	
Usual care arm					
N (%)	29 (11·6)	37 (14·9)	72 (28·9)	111 (44·6)	
Rate per 10000	0·24	0·30	0·60	0·93	
Difference - N (% reduction)	**10 (37·5)**	**14 (36·7)**	**29 (40·7)**	**64 (58·2)**	
Proximal					
Intervention arm					
N (%)	17 (7·6)	24 (10·8)	77 (34·5)	105 (47·1)	0·72
Rate per 10000	0·14	0·18	0·63	0·88	
Usual care arm					
N (%)	13 (5·9)	19 (8·6)	83 (37·4)	107 (48·2)	
Rate per 10000	0·10	0·15	0·68	0·90	
Difference - N (% reduction)	**−4 (−27·3)**	**−5 (−26·7)**	**6 (8·8)**	**2 (2·3)**	