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Early detection versus prevention in the PLCO flexible sigmoidoscopy screening trial: Which had the greatest impact on mortality?

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Abstract

BACKGROUND—Screening for colorectal cancer (CRC) with flexible sigmoidoscopy (FSG) has been shown to reduce CRC mortality. This study examined whether the observed mortality reduction was primarily due to prevention of incident CRC via removal of adenomatous polyps or to early detection of cancer and improved survival.

METHODS—The Prostate, Lung, Colorectal, and Ovarian (PLCO) cancer screening trial randomized 154,900 men and women age 55–74. Individuals received FSG screening at baseline and 3 or 5 years versus usual-care. CRC-specific survival was analyzed using Kaplan-Meier curves and proportional hazards modeling. We estimated the proportion of CRC deaths averted by early detection versus prevention using a model that applied intervention arm survival rates to usual-care arm CRC cases and vice-versa.

RESULTS—1008 intervention and 1291 usual-care arm CRC cases were observed. Through 13 years of follow-up, there was no significant difference between arms in CRC-specific survival for all CRC (68% intervention vs. 65% usual-care; $p= 0{\cdot}16$) or proximal CRC (68% vs. 62%; $p=0{\cdot}11$); however, distal CRC survival was higher in the intervention arm (77% vs. 66%; $p<0{\cdot}0001$). Within each arm, symptom-detected cases had significantly worse survival than screen-detected cases. Overall, 29–35% of averted CRC deaths were estimated to be due to early detection and 65–71% to prevention.

CONCLUSIONS—CRC-specific survival was similar across arms in PLCO, suggesting a limited role of early detection in preventing CRC deaths. Modeling suggests two-thirds of avoided deaths were due to prevention. Future CRC screening guidelines should emphasize prevention via identification and removal of precursor lesions.

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Author Contributions:
Maryam Doroudi contributed to conceptualization, formal analysis, methodology, software, validation, visualization and writing of the original draft, review and editing. Robert E Schoen contributed to methodology, supervision, review and editing. Paul F Pinsky contributed to conceptualization, formal analysis, methodology, software, validation, visualization, supervision, and writing of the original draft, review and editing.

Keywords

Prostate; Lung; Colorectal; Ovarian Cancer Screening Trial; PLCO; flexible sigmoidoscopy; screening; colorectal cancer; prevention; early detection

Introduction

Colorectal cancer (CRC) is the fourth most common cancer and the second leading cause of cancer death in the United States.[1] Randomized controlled trials have shown that FSG is effective in reducing CRC-specific incidence[2–5] and mortality.[2, 4,5] Studies have not assessed whether the observed mortality reduction is primarily due to primary prevention via removal of adenomatous polyps or due to the effects of early detection, i.e., diagnosing CRC at an earlier stage cancer where mortality from CRC is less likely. This assessment is of importance because it will enhance the scientific understanding of how FSG screening prevents CRC deaths and may further inform future CRC screening recommendations. Some guidelines have stressed favoring screening tests that enable prevention via removal of adenomatous polyps.[6]

The randomized Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial[2] evaluated screening versus usual care (control arm) for effect on cancer-specific incidence and mortality in U.S. subjects. The colorectal component of PLCO included screening with FSG, with a baseline screen and repeat screening at 3 or 5 years.[2] After a median follow-up of 11·9 years, screening with FSG reduced CRC incidence (21% reduction) and mortality (26% reduction) compared to usual care.[2] Two factors may have contributed to the observed reduction in mortality: 1) the reduction in CRC incidence, and 2) the increased proportion of CRCs detected early through screening in the intervention arm compared to usual care.

The objective of this study was to assess whether the observed mortality reduction in PLCO was primarily due to early detection or prevention. A mortality effect due primarily to early detection should demonstrate a substantial survival advantage for CRC cases in the screened versus the control arm. Given the observed reduction in incidence, the absence of a substantial survival difference between arms would provide indirect evidence for the primary effect on mortality was due to prevention, since early detection can only decrease mortality by improving survival. To this end, we analyzed survival by trial arm, as well as cancer stage and mode of detection by arm. Additionally, we developed a quantitative model that estimates the proportion of the mortality reduction that was due to prevention versus early detection, based on the observed incidence and survival in each arm.

Methods

Study Design, Setting, and Participants

The PLCO study design has been described previously.[7] Briefly, PLCO was a large-scale, multi-center, randomized controlled trial designed to evaluate the effect of cancer screening for four types of cancer (ClinicalTrials.gov number NCT00002540).[7] Between 1993 and 2001, PLCO randomized 154,900 men and women to either an intervention or usual care arm.[2] Eligible participants were 55 to 74 years of age at enrollment and had no history of trial cancers and no current treatment for cancer. Intervention arm individuals received screening for all gender-relevant PLCO cancers, including FSG for CRC at baseline and at 3 or 5 years.[2] The median duration of the follow-up was 11·9 years with a maximum of duration of 13 years in each arm. CRC incidence and all-cause mortality data were obtained from participants' medical records released to PLCO.[2] Cause of death was adjudicated by a panel blinded to treatment arm assignment. Participant demographics, screening history, and medical history were collected using a self-administered baseline questionnaire at randomization.[2] The PLCO trial was approved by the institutional review board at each screening center. All participants provided informed consent.

Reason for Detection of Cancer

PLCO abstractors recorded on standardized forms the clinical assessment that led to the diagnosis of CRC for all participants using the categories 'screen detected', 'symptomatic', and 'other'; for "other" a verbatim text in the medical records was recorded. Because abstractors were instructed to select the "screen detected" category only for PLCO protocol screens, and the "surveillance" category (for subjects followed for a history of adenomas) was only used on some versions of the abstracting forms, the verbatim text was reviewed by 2 investigators to identify non-PLCO screen detected cases (including those detected by fecal occult blood testing and screening colonoscopy, as well as FSG) and cases detected because of surveillance. In addition, some cases originally classified as "other" were reassessed by the investigators to be symptomatic, screen-detected or surveillance-detected, based on text review. Details are provided in Supplemental Table 5.

Study Outcomes, Measures, and Statistical Analysis

We estimated CRC-specific survival rates using Kaplan-Meier plots. Losses to-follow up and deaths due to other causes were treated as censored observations.[8] The log-rank test was used to compare survival for different categories of cases, including trial arm, mode of detection and anatomic location. In the analysis related to anatomic location of diagnosed CRC cases, colon anatomy was categorized into either proximal (cecum, ascending colon, hepatic flexure and transverse colon) or distal (splenic flexure, descending colon, sigmoid colon, rectosigmoid and rectum). Proportional hazards modeling was also used to examine the association of survival with study arm, reason that led to cancer detection, and anatomic location. These factors were examined in univariate as well as multivariate analyses; for the latter, the model controlled for age, race, and education. Reason for detection, anatomical location and stage were compared between the trial arms using Chi-square test.

We also attempted to estimate the fraction of avoided CRC deaths in the intervention arm that were due to either early detection or prevention via removal of adenomatous polyps. The underlying premise was to evaluate the expected number of CRC deaths if the observed cases in the usual care arm had the survival of the intervention arm and similarly, the expected number of CRC deaths if the observed cases in the intervention arm had the survival of the usual care arm. The former estimates the number of CRC deaths if only early detection were occurring and the latter the number of CRC deaths if only primary prevention were occurring. Denoting these as D_{ED} and D_{PP} respectively, and the observed CRC deaths in the intervention and usual care arm as D_I and D_{UC}, respectively, the relative numbers of deaths averted due to prevention and early detection can be estimated in two ways. First, since D_{UC} is the number of deaths with neither prevention or early detection, D_{UC} - D_{ED} is the estimated number of deaths averted due to early detection and D_{UC} - D_{PP} is the number of deaths averted due to primary prevention. Alternatively, as D_I is the number of deaths with both prevention and early detection, D_{ED} – D_I is the number of deaths averted due to primary prevention and D_{PP} – D_I is the number averted due to early detection.

To derive D_{ED} and D_{PP}, we calculated Kaplan-Meier CRC-specific survival curves for each trial arm. Then for each arm, the other arm's survival rate curve was applied to its incident CRC cases to estimate expected deaths (see Supplemental Method 1 for details).

Results

Study Population

Of 154,900 individuals enrolled in PLCO, 77,445 and 77,455 were randomized to the intervention and usual care arms, respectively. There were 1,008 CRC cases in the intervention arm and 1291 in the usual care arm. The baseline characteristics of the CRC-diagnosed participants were similar (Table 1). Overall, the mean age at CRC diagnosis was 64 years, more than 50% of cases were male, 85·30% were non-Hispanic white, and greater than 60% of them had college education.

CRC-Specific Survival by Treatment Arm and Anatomic Location

Among those diagnosed with CRC, 253 intervention arm and 351 usual care arm subjects died of CRC. Cumulative CRC-specific survival curves by study arm are depicted in Figure 1A. The 13-year survival rates in the intervention and usual care arms were 68% and 65%, respectively, and not significantly different (p=0·16, log-rank test). Hazard ratios (HRs) - for unadjusted and adjusted Cox regression models are summarized in Table 2. After adjusting for race, age and education, the HR for dying of CRC in the intervention compared to usual care arm was 0·87 (95% CI, 0·73–1·02).

Of 1008 diagnosed intervention arm CRC cases, 478 were distal and 508 were proximal. Among 1291 control arm CRC cases, 669 were distal and 596 proximal. The intervention arm had a significantly higher percentage of proximal CRC cases compare to the usual care arm (51·5% vs 47·1%, p=0·04, Chi-square test) (Supplemental Table 1). CRC-specific survival curves by anatomic location of the tumor are depicted in Figure 1B and C. The 13-year survival rates for individuals diagnosed with distal CRC in the intervention and usual care arms were 77% and 66%, respectively (Figure 1B). Survival curves were significantly different by arm (p<0·0001, log-rank test). However, no significant difference was observed between the survival rates in the intervention (68%) and usual care (62%) arms in subjects diagnosed with proximal CRC (p=0·16, log-rank test) after 13 years of follow up (Figure 1C). In proportional hazards analyses, for distal CRC, intervention arm cases had significantly lower risk of mortality compared to usual care arm cases in both univariate (HR=0·60; 95% CI, 0·46–0·77) and multivariate (HR=0·62; 95% CI, 0·48–0·80) analyses (Table 2) adjusted for age, race, and education. No significant survival difference between arms was observed for proximal CRC cases (HR=1·16; 95% CI, 0·92–1·45) (Table 2).

We also examined how CRC anatomical location and stage distribution varied by trial arm. Stage was categorized into either non-advanced (stages I and II) or advanced (Stages III and IV). The overall proportion of CRC cases that were advanced was similar between the two arms (40·0% in the intervention arm vs. 42·7% in the usual care arm, p=0·20, Chi-square test) (Supplemental Table 2). For distal CRC, intervention arm cases had a significantly lower percentage of advanced cancer compare to usual care arm cases (30·7% vs 39·7%, p=0·002, Chi-square test). However, no differences were observed in proximal cases (p=0·45, Chi-square test). More details on stage distribution and anatomical location by arm are given in Supplemental Table 3.

CRC-Specific Survival by Reason for Detection

Reason for detection of cancer by treatment arm is depicted in Table 3. The intervention arm had a higher percentage of screen-detected cases (31·4% vs 11·0%, p<0·0001, Chi-square test) and a lower percentage of symptom-detected cases (57·5 % vs 76·3%, p<0·0001, Chi-square test) compared to the usual care arm. The proportion of surveillance-detected cases was small (4·0% in the intervention arm vs. 2·2% in the control arm, p=0·02, Chi-square test).

The CRC-specific survival curves by treatment arm by reason for cancer detection are depicted in Figure 2. Hazard ratios from unadjusted and adjusted Cox regression models for risk of death by reason for detection are presented in Table 2. Survival curves were similar regardless of treatment arm for each reason for detection; however, survival was significantly different across reason for detection categories. Within the intervention arm, as compared to the referent group of screen-detected cancers, symptom-detected cases had significantly worse survival in both univariate (HR=4·0; 95% CI, 2·8–5·7) and multivariate (HR=4·8; 95% CI, 2·8–5·8) analyses. Similar results were observed for the usual care arm. There was no significant survival difference between surveillance-detected and screen-detected cases. In the intervention arm, survival curves were not significantly different between non-PLCO screen-detected and PLCO screen-detected cases (p=0·36, log-rank test) (Supplemental Figure 1).

Relative Effect of Early Detection vs. Prevention on Mortality to CRC

The results of the model that attempted to partition CRC deaths attributable to prevention versus those attributable to early detection are displayed in Figure 3. The model estimated that D_{ED} (deaths from early detection alone) was 312 and D_{PP} (deaths from prevention alone) was 277. Subtracting D_{ED} and D_{PP} from the observed usual care arm deaths (D_{UC}=351) gives 39 deaths averted due to early detection and 74 averted due to prevention (Figure 3A). Alternatively, subtracting the observed intervention arm deaths (D_I=253) from D_{ED} and D_{PP}, respectively, gives an estimated 59 deaths averted due to prevention and 24 averted due to early detection (Figure 3B). Therefore, the estimated proportions of deaths averted due to prevention are 65% (39/(39+74)) by the first method and 71% (59/(59+24)) by the second method, with the remainder, 35% and 29%, estimated due to early detection. The total combined estimated deaths prevented, 113 and 84 by the two methods, are reasonably close to the observed number of intervention arm CRC deaths prevented of 98 (i.e., 351–253).

Discussion

Determining the relative effectiveness of prevention versus early detection is of import in elucidating the primary mechanism through which CRC screening tests reduce CRC-specific mortality. Randomized controlled trials have shown that FSG reduces CRC-specific incidence[2–5] and mortality[2, 4, 5]. In the PLCO trial both mortality and incidence reductions were demonstrated, with a mortality relative risk (RR) of 0·74 (95% CI: 0·63 to 0·87) and an incidence RR of 0·79 (95% CI: 0·72 to 0·85).[2] In this study we examined whether the mortality reduction in the intervention arm was primarily due to early detection of CRC or to prevention via removal of adenomatous polyps.

Among 1008 diagnosed CRC cases in the intervention arm, 31% were screen-detected, versus 11% of the 1291 CRC cases in the usual care arm. The relatively low rate of screen detected cancers in the intervention arm suggested a limited contribution of early detection in reducing CRC-specific mortality. In addition, the proportion of CRC cases with advanced stage was similar across arms, again suggesting a limited role for early detection.

Furthermore, CRC-specific survival was relatively comparable across arms. In the intervention arm, the 5 and 13 year CRC-specific survival rates were 75% and 68%, respectively, compared to the corresponding usual care arm rates of 71% (5-year) and 66% (13-year). For overall or proximal CRC, no significant differences were observed in stage distribution or survival by trial arm. For distal colorectal cancers, intervention arm cases had significantly better survival than cases in the usual care arm (77% vs 66%), which is expected, given flexible sigmoidoscopy was the intervention and it examines the distal colon. Despite the 10% improved survival for distal colon cancers in the intervention arm however, this difference is not of sufficient magnitude to explain the overall 26% reduction in CRC-specific mortality.

Thus, early detection does not appear to be the dominant contributor to mortality reduction and a significant role for prevention is suggested. We developed a simple, transparent model to derive quantitative estimates of the relative proportion of CRC deaths averted by early detection versus prevention. The results showed about 65–70% of the reduction due to prevention and 25–30% due to early detection. A limitation of the model is that it did not account for the effect of lead-time or overdiagnosis on the intervention arm survival rates. To the extent that lead-time and/or overdiagnosis were occurring, this would artificially inflate the intervention arm survival rates and therefore overestimate the effect of early detection. However, only around 30% of intervention arm cases were screen detected, and some (11%) usual care arm cases were also screen detected. Further, lead time is estimated to be relatively short (1.6–4.0 years) for CRC and overdiagnosis is not believed to be substantial[9]. Therefore, the quantitative effects of lead-time and overdiagnosis were likely modest.

The model also assumes that the CRCs prevented were similar in prognosis, and would have had similar survival, to those that occurred. To the extent that the less aggressive cancers, with slower adenoma to CRC transition times, were preferentially prevented, this would tend to inflate the estimate of deaths averted due to prevention. While this may have occurred to some extent, an examination of tumor grade shows a similar distribution across arms, with

20.0% (intervention) versus 20.5% (usual care) of tumors being poorly differentiated or undifferentiated and 10.3% (intervention) versus 11.5% (usual care) of tumors being well differentiated.

The present study has several other limitations. In the PLCO population, individuals of black race, Hispanic ethnicity, and lower socioeconomic status are underrepresented. In addition, for the analysis of verbatim text for the method of detection, there was some ambiguity in ascertaining the exact reason for cancer detection in some instances. The study's strengths included its large sample size and excellent long-term follow up of participants.

In conclusion, our study found that CRC-specific survival was comparable across arms in the PLCO trial. There were no statistically significant survival differences between arms for overall CRC and for proximal CRC, and only a small intervention arm survival benefit for distal CRC. Our estimates indicate that about 65–70% of prevented CRC deaths were due to primary prevention, and only 30–35% due to early detection. On the basis of these findings, we believe future recommendations for CRC screening should place greater emphasis on the prevention of incident cases via detection and removal of precursor lesions.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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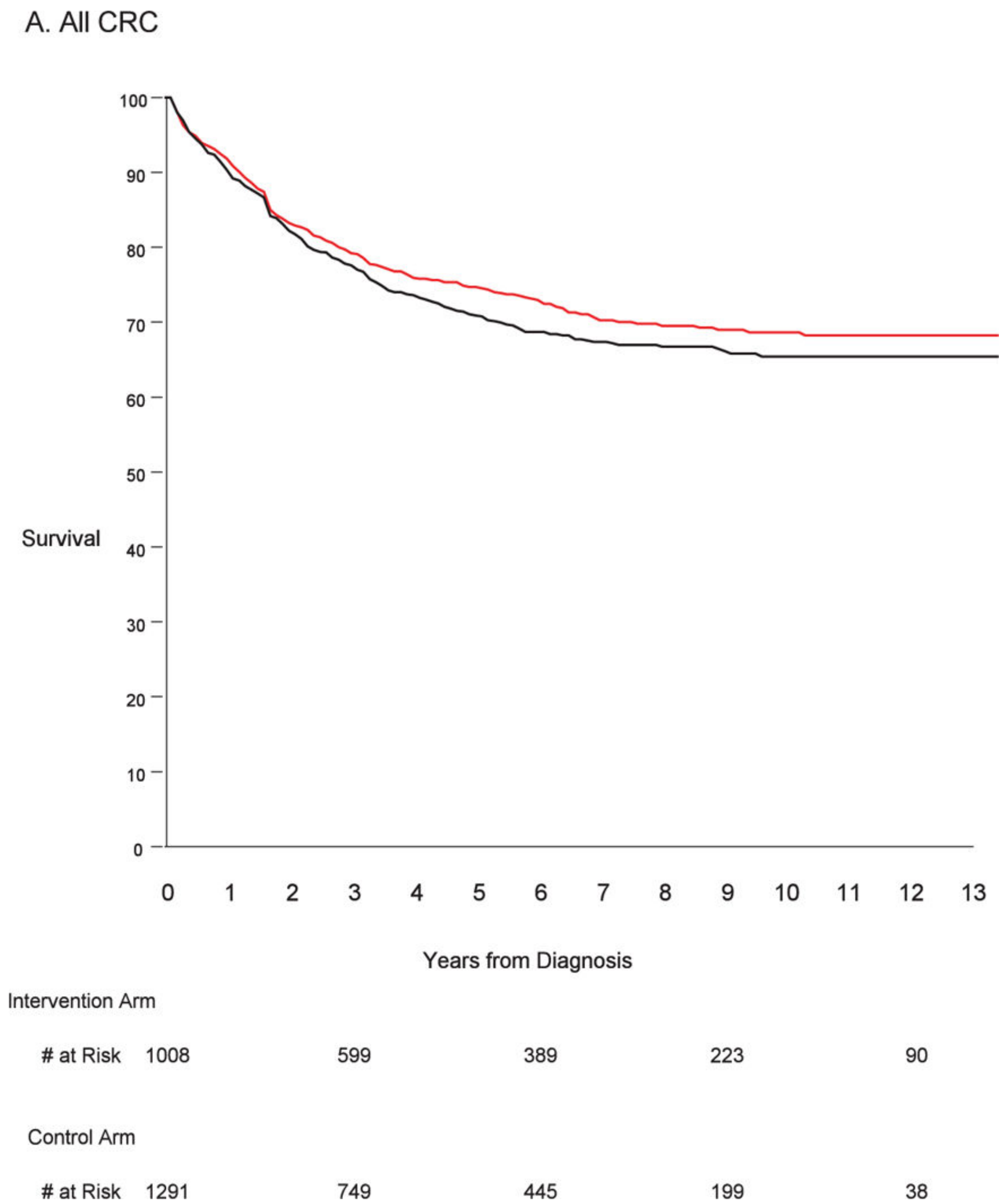
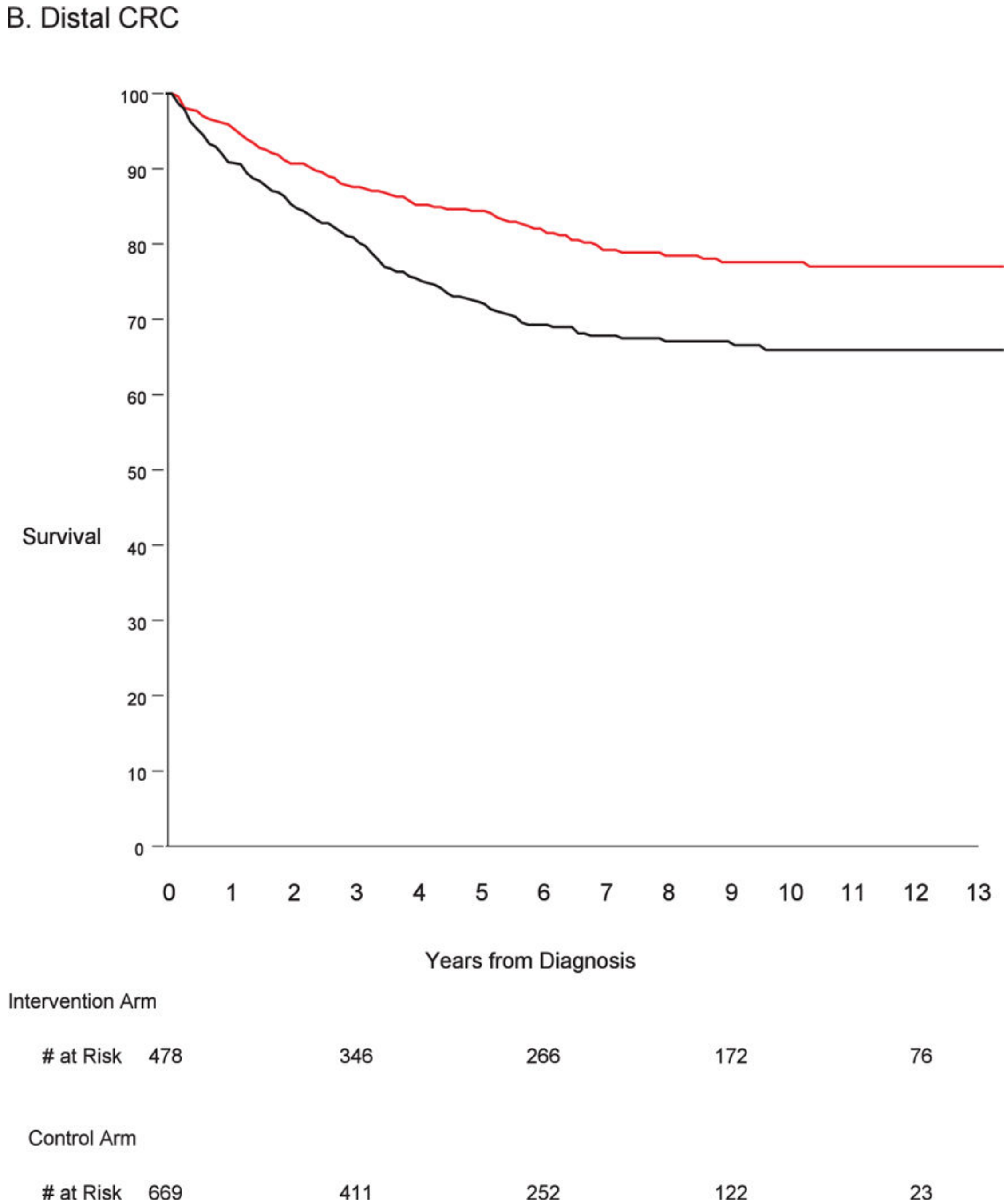
Condensed abstract

CRC-specific survival was similar across arms in the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial, suggesting a limited role of early detection in preventing CRC deaths. Modeling suggests two-thirds of averted deaths were due to prevention.


A. All CRC
Survival
100
90
80
70
60
50
40
30
20
10
0
0 1 2 3 4 5 6 7 8 9 10 11 12 13
Years from Diagnosis
Intervention Arm
at Risk 1008 599 389 223 90
Control Arm
at Risk 1291 749 445 199 38


B. Distal CRC
100
90
80
70
60
50
Survival
40
30
20
10
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0 1 2 3 4 5 6 7 8 9 10 11 12 13
Years from Diagnosis
Intervention Arm
at Risk 478 346 266 172 76
Control Arm
at Risk 669 411 252 122 23

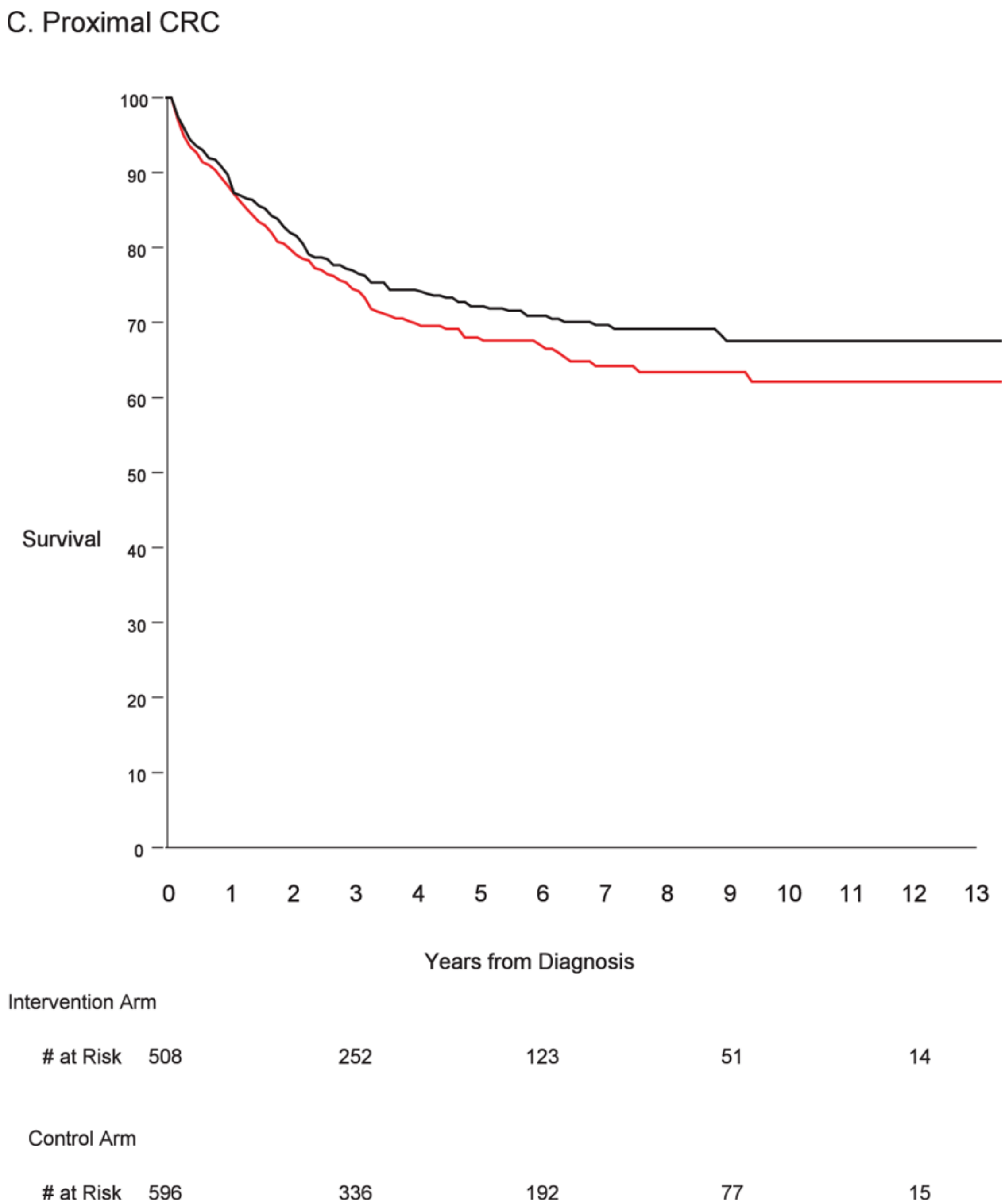
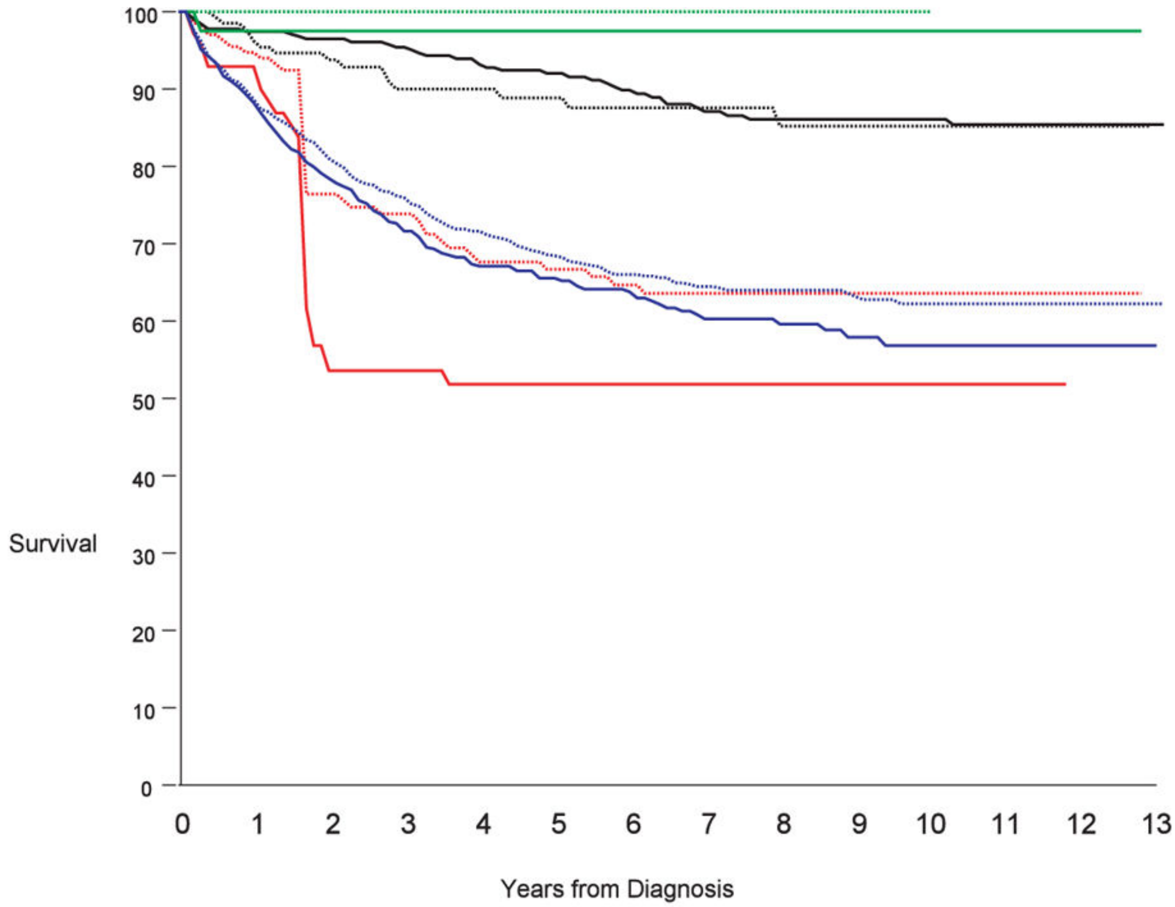


Figure 1. CRC-specific survival rates by trial arm and anatomic location of the tumor

A: All CRC cases by trial arm. P=0·16, long-rank test. B: Distal CRC cases by trial arm. P<0·0001, long-rank test. C: Proximal CRC cases by trial arm. P=0·16, long-rank test. For figures 1A–C, red line represents the intervention arm and black line represents the usual care arm.

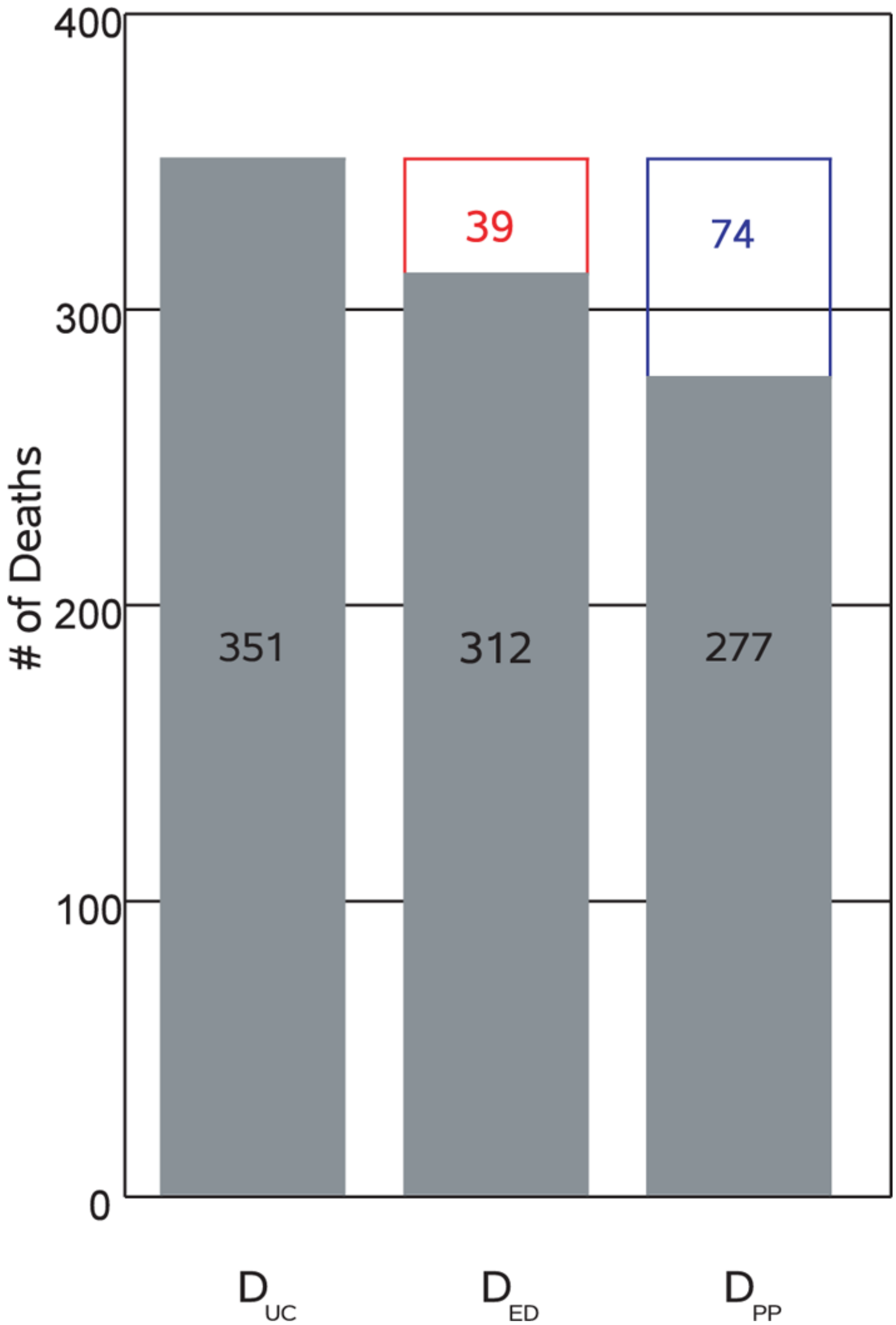


at risk

Scrn_I	316	265	199	154	75
Scrn_C	142	93	57	26	5
Symp_I	577	279	155	56	13
Symp_C	980	558	321	144	31
Surv_I	40	25	15	3	2
Surv_C	29	14	8	3	0
Oth_I	71	30	20	10	0
Oth_C	135	85	59	27	2

Figure 2. CRC-specific survival rates mode of detection

All CRC cases by trial arm and mode of detection. P<0·0001, long-rank test. Color codes: Solid lines represent intervention arm mode of detection subgroups; dotted lines represent usual care arm subgroups. Symptom-detected cases are in blue, screen-detected cases in black, surveillance-detected cases in green and other-detected cases in red. Abbreviations: symptom-detected usual care (control) arm (symp_C), symptom-detected intervention arm (symp_I), screen-detected usual care (control) arm (scrn_C), screen-detected intervention arm (scrn_I), surveillance-detected usual care (control) arm (surv_C), surveillance-detected intervention arm (surv_I), Other usual care (control) arm (oth_C), Other intervention arm (oth_I).


400
300
200
100
0
# of Deaths
351
312
39
277
74
D UC
D ED
D PP

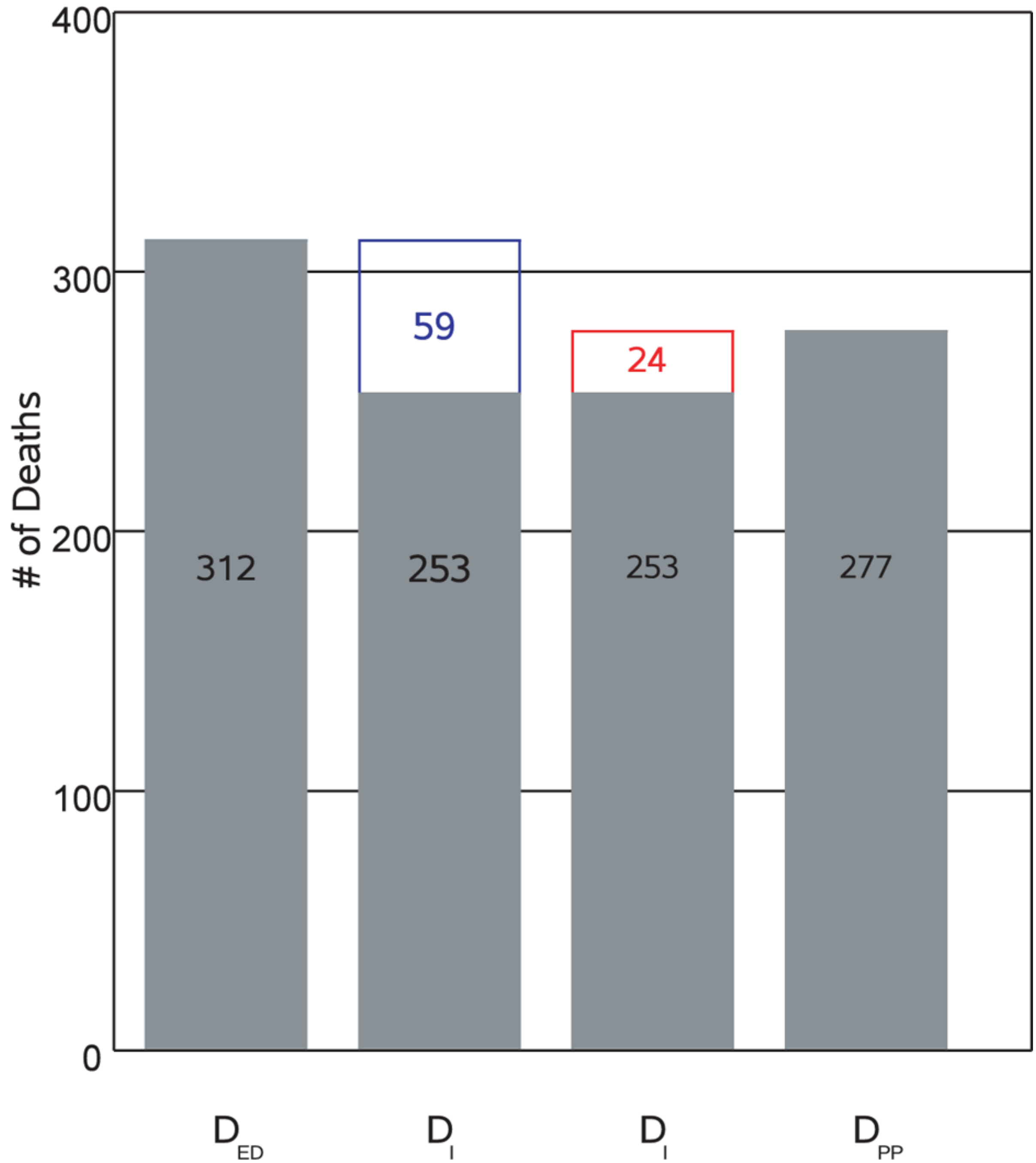


Figure 3.
The estimated numbers of CRC deaths averted by early detection and prevention. In Figure 3A, estimated deaths due to early detection and primary prevention are computed as D_{UC}- D_{ED} (red box) and D_{UC}- D_{PP} (purple box), respectively, where D_{UC}, D_{PP}, and D_{ED} are observed usual care arm deaths, estimated deaths with prevention only and estimated deaths with early detection only, respectively. In 3B, estimated deaths due to early detection and

prevention are estimated as D_{ED}-D_I (red box) and D_{PP} -D_I (purple box), respectively, where D_I is observed intervention arm deaths.

Table 1

Demographics of CRC cases in PLCO

Characteristics	Intervention arm (n= 1008 cases) # (%) of Cases	Usual care arm (n= 1291 cases) # (%) of Cases
Sex		
Female	444 (44·1)	518 (40·1)
Male	564(55·9)	773 (59·9)
Age		
55–64 yr	241 (23·9)	254 (19·7)
65–74 yr	535 (53·1)	719 (55·7)
75+ yr	232 (23·0)	318 (24·6)
Race		
White, Non-Hispanic	854 (84·7)	1107 (85·7)
Black, Non-Hispanic	77 (7·6)	63 (4·9)
Asian	35 (3·5)	48 (3·7)
Other or Unknown	42 (4·2)	73 (5·7)
Education		
High-school graduate or less	353 (35·0)	421 (32·6)
Some College	327 (32·4)	432 (33·5)
College graduate	302 (30·0)	390 (30·2)
Unknown	26 (2·6)	48 (3·7)

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Table 2

Proportional Hazard Models of CRC-specific Survival.

	Univariate	Multivariate
Arm	**HR (95% CI)**	**HR (95% CI)[a]**
Overall		
Usual care arm	Referent	Referent
Intervention arm	0·88 (0·74–1·03)	0·87 (0·73–1·02)
Distal		
Usual care arm	Referent	Referent
Intervention arm	0·60 (0·46–0·77)	0·62 (0·48–0·80)
Proximal		
Usual care arm	Referent	Referent
Intervention arm	1·18 (0·94–1·48)	1·16 (0·92–1·45)
Mode of Detection, Usual care arm		
Screen-detected	Referent	Referent
Symptom-detected	3·1 (1·8–5·2)	3·1 (1·8–5·2)
Surveillance-detected	NC	NC
Other	3·1 (1·7–5·6)	3·1 (1·7–5·5)
Mode of Detection, Intervention Arm		
Screen-detected	Referent	Referent
Symptom-detected	4·0 (2·8–5·7)	4·0 (2·8–5·8)
Surveillance-detected	0·3 (0·04–2·0)	0·3 (0·04–2·1)
Other	5·6 (3·5–9·0)	5·6 (3·5–9·1)

[a]Multivariate model is controlled for black race, age and education.

NC: Not calculable due to no deaths in this group

Table 3

Distributions of CRC Modes of Detection by Trial Arm.

Mode of Detection	Intervention arm (n=1008)[a] # (%)			Usual care arm (n=1291)[a] # (%)		
	Total	**Distal**	**Proximal**	**Total**	**Distal**	**Proximal**
	1008 (100)	**478 (48·5)**	**508 (51·5)**	**1291 (100)**	**669 (52·9)**	**596 (47·1)**
Screen-detected	316[b] (31·4)	219 (45·8)	95 (18·7)	142 (11·0)	81 (12·1)	61 (10·2)
Symptom-detected	580 (57·5)	224 (46·9)	354 (69·7)	985 (76·3)	513 (76·7)	465 (78·0)
Surveillance-detected	40 (4·0)	18 (3·8)	21 (4·1)	29 (2·2)	12 (1·8)	17 (2·9)
Other	72 (7·1)	17 (3·5)	38 (7·5)	135 (10·5)	63 (9·4)	53 (8·9)

[a] 22 cases in the intervention and 26 in the usual care arm had unknown location.

[b] of 316 cases, 224 were PLCO screen detected and 92 were non-PLCO screen detected.