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Preventing colorectal cancer or early diagnosis: Which is best? A re-analysis of the U.S. Preventive Services Task Force Evidence Report☆,☆☆

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ABSTRACT

Flexible sigmoidoscopy (FS) is the only cancer screening test to lower the risk of death compared to usual care in randomized controlled trials (RCTs). We hypothesize that this unique death reduction is more attributable to prevention of colorectal cancer (CRC) than to early diagnosis. The systematic review of the 2016 US Preventive Services Task Force Evidence Report for CRC Screening was used for selection of RCT studies. A random-effects meta-analysis of five FS trials (N = 458,002) and four fecal occult blood test (FOBT) trials (N = 328,767) was performed using intention-to-screen outcomes for death, CRC incidence, and death attributed to CRC; correlation and linear regression analyses explored the relationships between these outcomes. At 10.5–11.9 years of follow-up FS reduces death (relative risk [RR], 0.975; 95% CI, 0.958–0.992 and reduces CRC incidence (RR, 0.79; 95% CI, 0.74–0.84). Within the FS trials death reduction shows a strong linear correlation with CRC incidence reduction (*r*, 0.95; 95% CI 0.42–0.99). At 15.6–30.0 years of follow-up FOBT does not reduce death (RR, 1.001; 95% CI, 0.992–1.010) or CRC incidence (RR, 0.96; 95% CI, 0.89–1.02) but does reduce deaths attributed to CRC (RR, 0.84; 95% CI, 0.78–0.91). Clinical trials of screening FS display a dose-response relationship between the magnitude of CRC prevention and the magnitude of death reduction. Prevention of CRC appears to be the major (or sole) mechanism of action for death reduction by FS in clinical trials. Conversely, early diagnosis of CRC does not appear to reduce death.

1. Introduction

In 2018, colorectal cancer (CRC) is estimated to be the second leading cause of cancer deaths in North America, Europe, and worldwide (Ferlay et al., 2018). Current evidence-based CRC screening guidelines focus upon diagnostic accuracy for early diagnosis of CRC as well as reductions of disease-specific mortality (i.e. death attributed to CRC); these guidelines consider prevention of CRC secondarily and do not consider effects on the risk of actually dying (US Preventive Services Task Force, 2016; European Colorectal Cancer Screening Guidelines Working Group, 2013; Rex et al., 2017). However, disease-specific mortality (DSM) is susceptible to bias due to its critical dependence upon accurate cause-of-death determinations and its potential neglect of harms of screening (Newschaffer et al., 2000; Albertsen, 2000; Gøtzsche and Jørgensen, 2013). Death (i.e. overall mortality) measures all deaths without attempting to ascertain the cause and is therefore less prone to bias and inherently includes any deaths resulting from harms of screening. Indeed, death reduction should be the ultimate goal of cancer screening (Black et al., 2002; Juffs and Tannock, 2002; Penston, 2011; Saquib et al., 2015; Prasad et al., 2016).

Historically, cancer screening has failed to reduce death compared to usual care in clinical trials (Saquib et al., 2015; Prasad et al., 2016). However, we recently showed that the 2016 U.S. Preventive Services Task Force Evidence Report (USPSTF-ER) for Colorectal Cancer Screening (Lin et al., 2016) was confounded by a Simpson's paradox and that correct meta-analysis reveals that flexible sigmoidoscopy (FS) reduces death compared to usual care in clinical trials (Swartz et al., 2017). After more than fifty years of cancer screening trials, FS is the

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Table 1
Characteristics of studies included in the meta-analysis.

Modality/trial	Study	Country	Age range (y)	Intervention	Follow-up duration (y)	Number of participants (screen)	Number of participants (control)	Deaths (screen)	Deaths (control)	Relative risk of death (95% CI)	CRC's (screen)	CRC's (control)	Relative risk of CRC (95% CI)	CRC deaths (screen)	CRC deaths (control)	Relative risk of CRC death (95% CI)	Comments
Flexible sigmoidoscopy																	
PLCO	Schoen et al. (2012)	U.S.	55–74	FS w/repeat at 3–5 y	11.9	77,445	77,455	9390	9627	0.976 (0.950–1.002)	1012	1287	0.79 (0.72–0.85)	252	341	0.74 (0.63–0.87)	ACM data deduced from the article's outcome table and excludes deaths from lung, ovarian, and prostate cancers
SCORE	Segnan et al. (2011)	Italy	55–64	Once-only FS	10.5	17,136	17,136	1202	1233	0.975 (0.903–1.052)	251	306	0.82 (0.70–0.97)	65	83	0.78 (0.57–1.08)	Number of deaths as specified in the article text
UKFSST	Atkin et al. (2010)	U.K.	55–64	Once-only FS	11.2	57,099	112,939	6775	13,768	0.973 (0.947–1.0002)	706	1818	0.77 (0.70–0.84)	221	637	0.69 (0.59–0.80)	
NORCCAP	Holme et al. (2014a, 2014b)	Norway	50–54	Once only FS or FS + FOBT	10.9	6920	37,131	427	2387	0.960 (0.869–1.061)	40	315	0.68 (0.49–0.95)	12	87	0.74 (0.40–1.35)	
NORCCAP	Holme et al. (2014a, 2014b)	Norway	55–64	Once only FS or FS + FOBT	10.9	13,652	41,089	1756	5375	0.983 (0.935–1.034)	213	771	0.83 (0.72–0.97)	59	243	0.73 (0.55–0.97)	
Fecal occult blood test																	
Minnesota	Shaukat et al. (2013), Mandel et al. (2000)	U.S.	50–80	Annual or biennial gFOBT[a] (11 or 6 times, respectively)	30[c],18[d]	31,157	15,394	22,076	10,944	0.997 (0.984, 1.009)	852	507	0.83 (0.75–0.93)	437	295	0.73 (0.63–0.85)	16 y (mortality) and 4 y (CRC incidence) follow-up from screening cessation.
Nottingham	Scholefield et al. (2012)	U.K.	45–74	Biennial gFOBT[a] (3–5 times at 2-year intervals)	19.5	76,056	75,919	40,681	40,550	1.001 (0.992, 1.011)	2279	2354	0.97 (0.91–1.02)	1176	1300	0.90 (0.84–0.98)	15 y follow-up from screening cessation.
Goteborg	Lindholm et al. (2008)	Sweden	60–64	gFOBT[b] two or three times at 1–9 year intervals	15.6	34,144	34,164	10,591	10,432	1.016 (0.993, 1.039)	721	754	0.96 (0.86–1.06)	252	300	0.84 (0.71–0.99)	9 y follow-up from screening cessation.
Funen	Kronborg et al. (2004)	Denmark	45–75	Biennial gFOBT[b] (9 times at 2-	17	30,967	30,966	12,205	12,248	0.996 (0.977, 1.016)	889	874	1.02 (0.93–1.12)	362	431	0.84 (0.73–0.96)	1–17 y follow-up from

(*continued on next page*)

Table 1 (*continued*)

Modality/trial	Study	Country	Age range (y)	Intervention	Follow-up duration (y)	Number of participants (screen)	Number of participants (control)	Deaths (screen)	Deaths (control)	Relative risk of death (95% CI)	CRC's (screen)	CRC's (control)	Relative risk of CRC (95% CI)	CRC deaths (screen)	CRC deaths (control)	Relative risk of CRC death (95% CI)	Comments
				year intervals)													screening cessation.
Burgundy	Faivre et al. (2004)	France	45–74	Biennial gFOBT[a] (6 times at 2-year intervals)	11	45,642	45,557	Not reported	Not reported	Not reported	699	696	1.00 (0.90–1.11)	254	304	0.83 (0.71–0.98)	2–3 y follow-up from screening cessation.

Y = years. CRC = colorectal cancer. gFOBT = guaiac-based fecal occult blood test.

[a] Hemoccult.

[b] Hemoccult-II.

[c] Mortality at 30 years.

[d] CRC incidence at 18 years.

first and only screening modality to achieve this landmark outcome.

We hypothesize that FS's unique death reduction may be more attributable to CRC prevention than to early diagnosis. In this study we test this hypothesis by expanding our re-analysis of the 2016 USPSTF-ER to include CRC incidence, death attributed to CRC, and a quantitative comparison of FS outcomes to those of fecal occult blood test (FOBT) from existing RCT data. We then perform correlation and regression analyses to explore the relationships between reductions of death, CRC incidence, and death attributed to CRC in clinical trials.

2. Methods

The 2016 USPSTF-ER systematic review was used for study selection (Lin et al., 2016). The studies specified in Table 1 of the USPSTF-ER were used as data sources for both FS and FOBT trials (Holme et al., 2014a; Schoen et al., 2012; Segnan et al., 2011; Atkin et al., 2010; Shaukat et al., 2013; Mandel et al., 2000; Scholefield et al., 2012; Lindholm et al., 2008; Kronborg et al., 2004; Faivre et al., 2004). Data was extracted from the original articles for total deaths, CRC incidence, and deaths attributed to CRC. The Norwegian Colorectal Cancer Prevention (NORCCAP) FS study reported additional outcomes in a published correspondence-reply (Holme et al., 2014b) and that data was also included in this study. The Burgundy FOBT trial (Faivre et al., 2004) has not reported total deaths or non-CRC deaths and therefore could not be included in the meta-analysis of death.

Only published data and intention-to-screen outcomes were used. The principle summary measures were relative risk and correlation coefficient. Meta-analyses were performed using R version 3.4.1 with the *meta* and *metafor* packages (R Development Core Team, 2010). The Sidik-Jonkman random-effects model was used (both with and without the Hartung-Knapp [HK] adjustment of τ) (Knapp and Hartung, 2003; Röver et al., 2015; Cornell et al., 2014). The criterion for statistical significance was $P < 0.05$ with a two-tailed test. Statistical heterogeneity was assessed via the I^2 statistic. Correlation coefficients were calculated with the R *cor.test* function using Pearson's product-moment coefficient. Linear regression was performed with the R *lmPerm* package. Absolute risk reductions (ARR) were calculated by multiplying the summary relative risk reductions by the risks observed in the study control groups.

3. Results

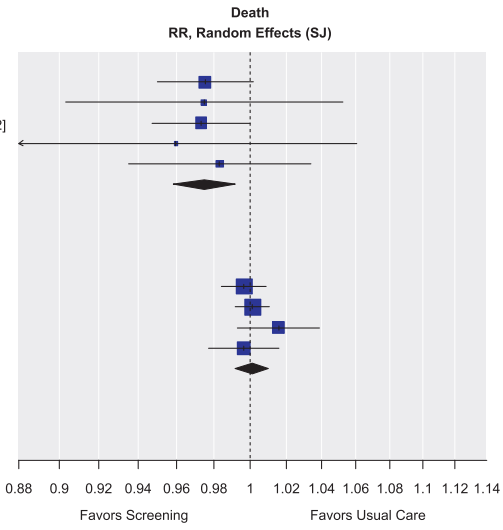
The meta-analysis of death includes five FS trials with a total of 458,002 participants and four FOBT trials with a total of 328,767 participants. The meta-analyses of CRC incidence and death attributed to CRC include the same FS trials but add a fifth FOBT trial for a total of 419,966 participants. Table 1 shows the characteristics of these studies.

FS reduces death (relative risk [RR], 0.975; 95% CI, 0.958–0.992; $P = 0.004$; $I^2 = 0\%$) at 10.5–11.9 years of follow-up (Fig. 1A.1). The corresponding relative risk reduction (RRR) is 2.50% (95% CI, 0.81%–4.15%). The absolute risk reductions (ARR's) observed in the studies varied from 1.6 (95%CI, 0.5–2.7) to 3.3 (95%CI, 1.1–5.4) per 1000 persons invited to screening (see Supplement Table S1 for detailed ARR and number-needed-to-invite [NNI] results for all outcomes). FOBT does not reduce death (RR, 1.001; 95% CI, 0.992–1.010; $P = 0.83$; $I^2 = 0\%$) at 15.6–30.0 years of follow-up (Fig. 1A.2). The difference between the death outcomes of FS and FOBT is statistically significant ($P = 0.008$).

FS reduces CRC incidence (RR, 0.79; 95% CI, 0.74–0.84; $P < 0.001$; $I^2 = 0\%$) at 10.5–11.9 years of follow-up (Fig. 1B.1). The RRR is 21% (95% CI, 17%–25%). The observed ARR's varied from 1.8 (95%CI, 1.4–2.1) to 3.9 (95%CI, 3.2–4.7) per 1000 persons invited to screening. FOBT does not significantly reduce CRC incidence (RR, 0.96; 95% CI, 0.89–1.02; $P = 0.20$; $I^2 = 56\%$) at 11–19.5 years of follow-up (Fig. 1B.2). The difference between the CRC incidence outcomes of FS and FOBT is statistically significant ($P < 0.001$).

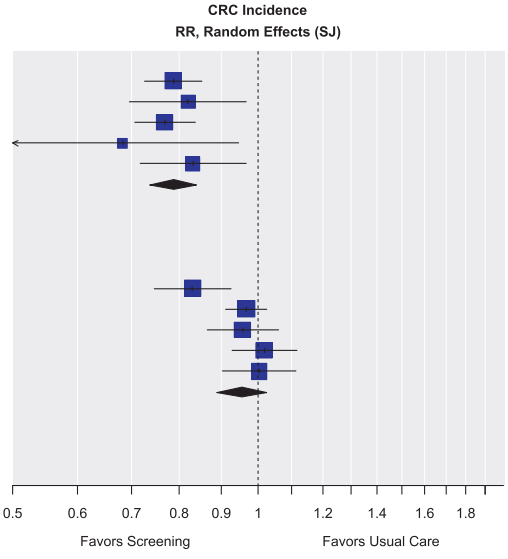
A DEATH

Study (trial, f/u duration)	Screening Deaths	Screening Total	Usual Care Deaths	Usual Care Total	Weight	RR [95% CI]
1. FLEXIBLE SIGMOIDOSCOPY (10.5-11.9y)						
Schoen 2012 (PLCO,11.9y)	9390	77445	9627	77455	10.9%	0.976 [0.950, 1.002]
Segnan 2011 (SCORE,10.5y)	1202	17136	1233	17136	2.1%	0.975 [0.903, 1.052]
Atkin 2010 (UKFSST,11.2y)	6775	57099	13768	112939	10.6%	0.973 [0.947, 1.0002]
Holme 2014a+b (NORCAPP [50-54],11.2y)	427	6920	2387	37131	1.3%	0.960 [0.869, 1.061]
Holme 2014a+b (NORCAPP [55-64],11.2y)	1756	13652	5375	41089	4.4%	0.983 [0.935, 1.034]
Total (95% CI)	**19550**	**172252**	**32390**	**285750**	**29.3%**	**0.975 [0.958, 0.992]**
Heterogeneity: Tau^2 = < 0.0001; Chi^2 = 0.22, df = 4 (P = 0.99); I^2 = 0%						
Test for overall effect: Z = -2.88 (P = 0.0040)						
2. FOBT (15.6-30y)						
Shaukat 2013 (Minnesota,30.0y)	22076	31157	10944	15394	20.2%	0.997 [0.984, 1.009]
Scholefield 2012 (Nottingham,19.5y)	40681	76056	40550	75919	22.4%	1.001 [0.992, 1.011]
Lindholm 2008 (Goteborg,15.6y)	10591	34144	10432	34164	13.1%	1.016 [0.993, 1.039]
Kronborg 2004 (Funen,17.0y)	12205	30967	12248	30966	15.0%	0.996 [0.977, 1.016]
Total (95% CI)	**85553**	**172324**	**74174**	**156443**	**70.7%**	**1.001 [0.992, 1.010]**
Heterogeneity: Tau^2 = < 0.0001; Chi^2 = 2.33, df = 3 (P = 0.51); I^2 = 0%						
Test for overall effect: Z = 0.22 (P = 0.83)						
Test for subgroup differences: Chi^2 = 7.03, df = 1 (P = 0.0080)						



B COLORECTAL CANCER INCIDENCE

Study (trial, f/u duration)	Screening CRC	Screening Total	Usual Care CRC	Usual Care Total	Weight	RR [95% CI]
1. FLEXIBLE SIGMOIDOSCOPY (10.5-11.9y)						
Schoen 2012 (PLCO,11.9y)	1012	77445	1287	77455	11.6%	0.79 [0.72, 0.85]
Segnan 2011 (SCORE,10.5y)	251	17136	306	17136	8.3%	0.82 [0.70, 0.97]
Atkin 2010 (UKFSST,11.2y)	706	57099	1818	112939	11.4%	0.77 [0.70, 0.84]
Holme 2014a+b (NORCAPP [50-54],11.2y)	40	6920	315	37131	4.0%	0.68 [0.49, 0.95]
Holme 2014a+b (NORCAPP [55-64],11.2y)	213	13652	771	41089	8.9%	0.83 [0.72, 0.97]
Total (95% CI)	**2222**	**172252**	**4497**	**285750**	**44.2%**	**0.79 [0.74, 0.84]**
Heterogeneity: Tau^2 = 0; Chi^2 = 1.79, df = 4 (P = 0.77); I^2 = 0%						
Test for overall effect: Z = -7.19 (P = 6.5 x 10^{-13})						
2. FOBT (11.0-19.5y)						
Mandel 2000 (Minnesota,18.0y)	852	31082	507	15363	10.6%	0.83 [0.75, 0.93]
Scholefield 2012 (Nottingham,19.5y)	2279	76056	2354	75919	12.4%	0.97 [0.91, 1.02]
Lindholm 2008 (Goteborg,15.6y)	721	34144	754	34164	10.9%	0.96 [0.86, 1.06]
Kronborg 2004 (Funen,17.0y)	889	30967	874	30966	11.2%	1.02 [0.93, 1.12]
Faivre 2004 (Burgundy,11.0y)	699	45642	696	45557	10.7%	1.00 [0.90, 1.11]
Total (95% CI)	**5440**	**217891**	**5185**	**201969**	**55.8%**	**0.96 [0.89, 1.02]**
Heterogeneity: Tau^2 = 0; Chi^2 = 9.11, df = 4 (P = 0.06); I^2 = 56%						
Test for overall effect: Z = -1.28 (P = 0.20)						
Test for subgroup differences: Chi^2 = 15.74, df = 1 (P = 7.3 x 10^{-5})						



C DEATH ATTRIBUTED TO COLORECTAL CANCER

Study (trial, f/u duration)	Screening CRC Deaths	Screening Total	Usual Care CRC Deaths	Usual Care Total	Weight	RR [95% CI]
1. FLEXIBLE SIGMOIDOSCOPY (10.5-11.9y)						
Schoen 2012 (PLCO,11.9y)	252	77445	341	77455	10.9%	0.74 [0.63, 0.87]
Segnan 2011 (SCORE,10.5y)	65	17136	83	17136	3.8%	0.78 [0.57, 1.08]
Atkin 2010 (UKFSST,11.2y)	221	57099	637	112939	11.8%	0.69 [0.59, 0.80]
Holme 2014a+b (NORCAPP [50-54],11.2y)	12	6920	87	37131	1.2%	0.74 [0.40, 1.35]
Holme 2014a+b (NORCAPP [55-64],11.2y)	59	13652	243	41089	4.8%	0.73 [0.55, 0.97]
Total (95% CI)	**609**	**172252**	**1391**	**285750**	**32.5%**	**0.72 [0.65, 0.80]**
Heterogeneity: Tau^2 = 0; Chi^2 = 0.76, df = 4 (P = 0.94); I^2 = 0%						
Test for overall effect: Z = -6.49 (P = 8.6 x 10^{-11})						
2. FOBT (11.0-30.0y)						
Shaukat 2013 (Minnesota,30.0y)	437	31157	295	15394	12.3%	0.73 [0.63, 0.85]
Scholefield 2012 (Nottingham,19.5y)	1176	76056	1300	75919	20.9%	0.90 [0.84, 0.98]
Lindholm 2008 (Goteborg,15.6y)	252	34144	300	34164	10.5%	0.84 [0.71, 0.99]
Kronborg 2004 (Funen,17.0y)	362	30967	431	30966	13.1%	0.84 [0.73, 0.96]
Faivre 2004 (Burgundy,11.0y)	254	45642	304	45557	10.6%	0.83 [0.71, 0.98]
Total (95% CI)	**2481**	**217966**	**2630**	**202000**	**67.5%**	**0.84 [0.78, 0.91]**
Heterogeneity: Tau^2 = 0; Chi^2 = 6.38, df = 4 (P = 0.17); I^2 = 37%						
Test for overall effect: Z = -4.47 (P = 7.8 x 10^{-6})						
Test for subgroup differences: Chi^2 = 5.62, df = 1 (P = 0.018)						

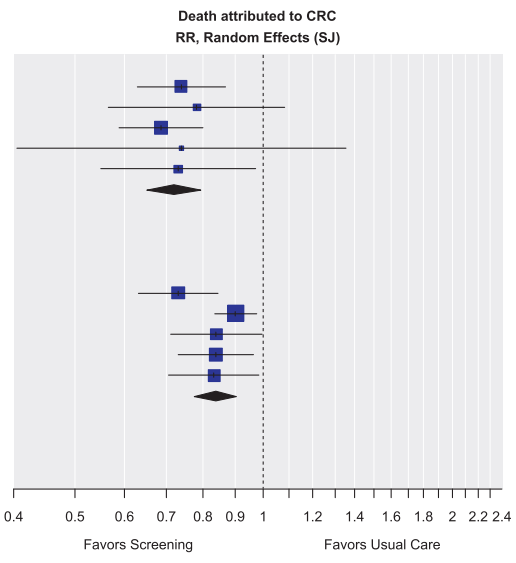


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Fig. 1. Meta-analysis of death, colorectal cancer incidence, and death attributed to colorectal cancer.
f/u = follow-up duration, RR = relative risk, SJ = Sidik-Jonkman random-effects estimator, CI = confidence interval, FOBT = fecal occult blood test, y = years. The FOBT analysis for CRC incidence (1.B.2) uses the outcomes at 18.0 y follow-up from Mandel et al. (2000) because Shaukat et al. (2013) does not report CRC incidence.

Table 2
Correlation analysis of flexible sigmoidoscopy outcomes.

Outcome comparison	*r*	95% CI	*P*
Death versus CRC incidence	0.95	0.42–0.99	0.013
Death versus deaths attributed to CRC	−0.024	−0.89–0.88	0.97
Death attributed to CRC versus CRC incidence	0.22	−0.82–0.92	0.72

CRC = colorectal cancer, CI = confidence interval, *r* = Pearson correlation coefficient, *P* = *P*-value.

FS reduces deaths attributed to CRC (RR, 0.72; 95% CI, 0.65–0.80; $P \leq 0.001$; $I^2 = 0\%$) at 10.5–11.9 years of follow-up (Fig. 1C.1), with a RRR of 28% (95% CI, 21%–35%). The observed ARR's varied from 0.7 (95%CI, 0.5–0.8) to 1.7 (95%CI, 1.2–2.1) per 1000 persons invited to screening. FOBT also reduces deaths attributed to CRC (RR, 0.84; 95% CI, 0.78–0.91; $P \leq 0.001$; $I^2 = 37\%$) at 11–30 years of follow-up (Fig. 1C.2), with a RRR of 16% (95% CI, 9%–22%). The observed ARR's varied from 1.1 (95%CI, 0.6–1.5) to 3.1 (95%CI, 1.7–4.2) per 1000 persons invited to screening. The difference between deaths attributed to CRC for FS and FOBT is statistically significant ($P = 0.018$).

In the RCT's, reductions in death from FS show a strong and statistically significant correlation with reductions in CRC incidence (*r*, 0.95; 95% CI, 0.42–0.99; $P = 0.013$). Conversely, death attributed to CRC does *not* correlate with either death (*r*, −0.024; 95% CI, −0.89–0.88; $P = 0.97$) or CRC incidence (*r*, 0.22; 95% CI, −0.82–0.92; $P = 0.72$). See Table 2.

Regression analysis reveals a clear linear relationship between death and associated CRC incidence in FS trials (r^2, 0.90, $P = 0.013$, intercept = 0.87 [95%CI 0.80–0.93], coefficient = 0.14 [95%CI 0.05–0.22], indicating a dose-response relationship (Fig. 2A). Inclusion of the FOBT trial outcomes produces no noticeable change (r^2, 0.75, $P = 0.003$, intercept = 0.87 [95% CI 0.81–0.93], coefficient = 0.14 [95% CI 0.07–0.21]); see Fig. 2B.

The Sidik-Jonkman random effects estimator was used without the Hartung-Knapp (HK) adjustment because of the number of RCTs, as well as the statistical homogeneity of their results. Sensitivity analysis compared the results with and without the HK adjustment (Supplement Table S2). Use of the HK adjustment biases the results in favor of FS (i.e. narrower confidence intervals and smaller *P*-values), therefore meta-analyses were performed without the HK adjustment. This paradoxical effect of the HK adjustment has been previously reported (Wiksten et al., 2016).

The second sensitivity analysis repeated all of the above analyses with a FOBT follow-up duration of 10.0–15.6 years, which is as close as possible to the FS follow-up durations. This produced no meaningful outcome differences (Supplement Fig. S1 and S2), showing that the FS to FOBT comparisons are robust with regard to different FOBT follow-up durations.

The third sensitivity analysis explored the effect of excluding one or two FS trials from the meta-analysis of death. Exclusion of any single trial does not change the magnitude or statistical significance of the death result, and the same is true for most of the two-trial exclusions (Supplement Fig. S3), showing that the FS death reduction is robust with regard to study selection.

4. Discussion

Screening with FS reduces death at 10.5–11.9 years with a homogenous effect across the five large clinical trials. FS also prevents CRC and nearly doubles the reduction in death attributed to CRC compared with FOBT (28% versus 16%). In contrast, FOBT does not significantly reduce the risks of dying or developing CRC, and FS has a statistically significant superiority for all three of these outcomes (death: $P = 0.008$; CRC incidence: $P \leq 0.001$; death attributed to CRC: $P = 0.018$). Though the first FOBT trial did report a reduction of CRC incidence, the four subsequent trials using newer methodology and/or newer fecal tests failed to reproduce that outcome (Fig. 1B.2).

The effect size of the FS death reduction is meaningful despite a relative risk reduction of only 2.50%. Effect size is best conveyed by absolute outcome measures such as absolute risk reduction (ARR) (Jaeschke et al., 2008). The death ARR of 1.6–3.3 deaths prevented per 1000 persons invited to screening compares well to other preventive measures for healthy adults (see Supplement Table S3 for comparison values). The ARR of 1.8–3.9 fewer colorectal cancers per 1000 persons invited to screening is also clinically meaningful. Conversely, relative outcome measures are poor indicators of an individual's likelihood of benefit or harm; therefore, clinical significance should not be inferred from the relative risk reductions.

The most important outcome of this study is the identification of an apparent dose-response relationship between the magnitude of CRC prevention and the magnitude of death reduction. The observed reductions of death display a strong, statistically significant linear correlation with observed reductions of CRC incidence. This correlation is so strong among the FS trials that it is easily seen in the similar forest plot shapes for death and CRC incidence (Fig. 1A.1 and B.1). Though this is an observational finding (i.e. the amount of CRC prevention was not experimentally controlled), the high plausibility makes this a powerful argument for causality, satisfying nearly all of the Hill criteria (Hill, 1965). Therefore the results of this study appear to confirm our hypothesis that CRC prevention is the major mechanism of action for the death reduction produced by screening with FS in clinical trials. In fact, the death versus CRC incidence regression line indicates that when there is no change in CRC incidence, there is no death reduction (Fig. 2A and B). This indicates that early diagnosis of CRC appears to have had no detectable effect on death in these trials. However, we note that the lower 95% CI of the regression line does not rule out a small early diagnosis effect (see Supplement Fig. S4). This correlation/regression analysis of clinical trial outcomes is novel and yields evidence with substantial implications for the rationale underlying screening recommendations.

This study has several strengths. First, use of a previously published systematic review minimizes our researcher degrees of freedom and therefore minimizes the chance of biased study/outcome selection. Second, compared with disease-specific mortality, death (i.e. overall mortality) is less prone to bias because it is both dichotomous and unequivocal. The occurrence of death is far simpler to assess than the cause, especially in older persons where deaths are often multifactorial with multiple chronic and acute comorbidities contributing to death. Third, overall mortality inherently includes any deaths resulting from screening in any way, whether or not the researchers correctly attribute the cause. And fourth, this study's focus on clinical trials, intention-to-screen outcomes, death, and CRC incidence avoids the numerous biases (such as selection bias, lead-time bias, overdiagnosis bias, and others) which frequently undermine the validity of cancer screening studies and make harms (such as overdiagnosis) appear to be benefits (such as improved survival and/or staging) (Wegwarth et al., 2012). This study focuses upon the most objective and patient-important outcomes rather than the most optimistic ones.

The major difference between this study and the USPSTF-ER is the inclusion of the individual NORCCAP cohorts as opposed to the

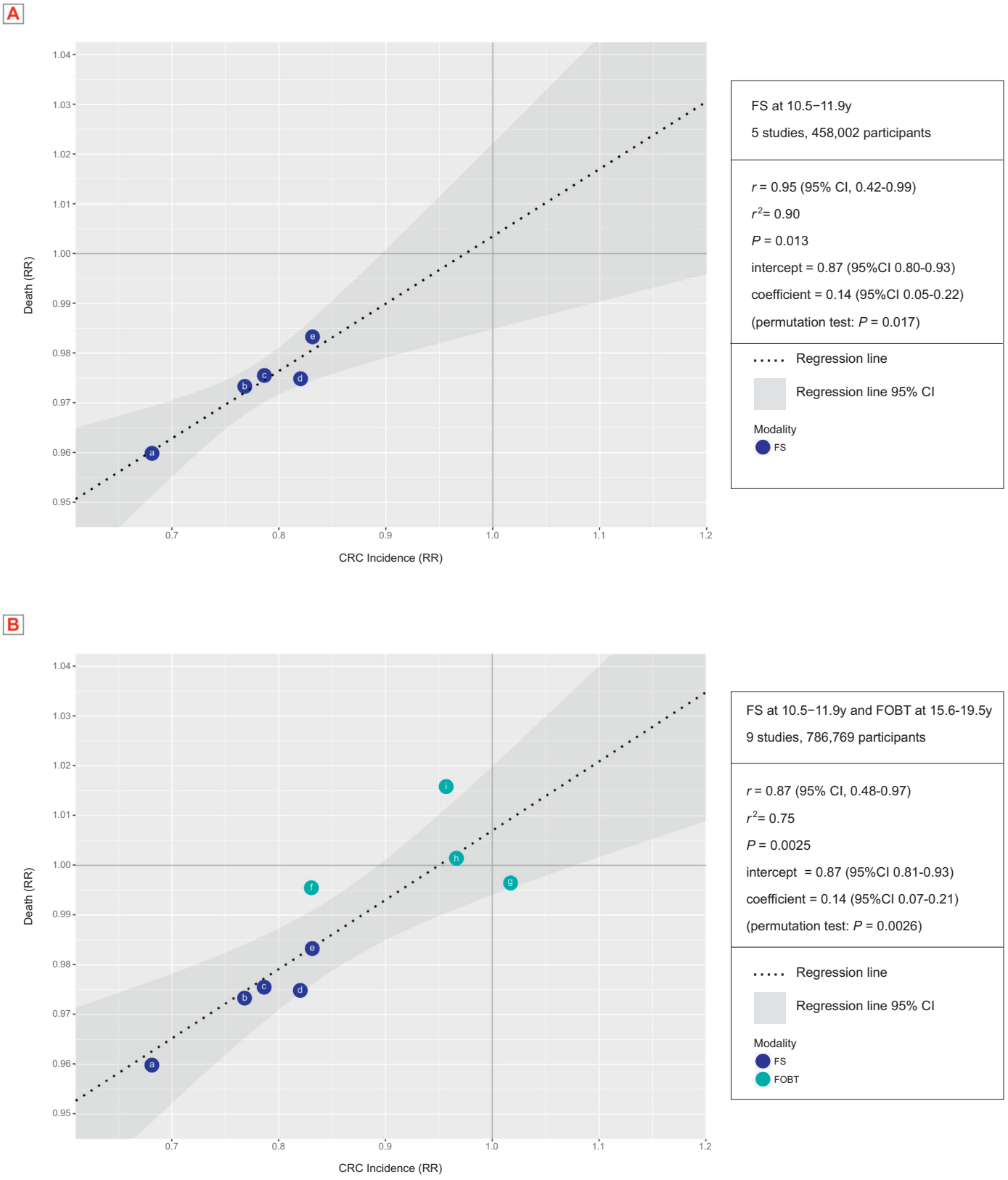

Fig. 2. Correlation and regression analysis of the relationship between observed reductions of CRC incidence and death in randomized controlled trials.
CRC = colorectal cancer, RR = relative risk, FS = flexible sigmoidoscopy, FOBT = fecal occult blood test, y = years, RCT = randomized controlled trial. A. RCT's of flexible sigmoidoscopy. B. RCT's of fecal occult blood test results are added. For the Minnesota FOBT trial, the 30 year study (Shaukat et al., 2013) does not report CRC incidence, therefore both CRC incidence and death are at 18 years follow-up (Mandel et al., 1999, 2000).
Key to trials/studies: a = NORCAPP [ages 50–54] (Holme et al., 2014a, 2014b), b = UKFSST (Atkin et al., 2010), c = PLCO (Schoen et al., 2012), d = SCORE (Segnan et al., 2011), e = NORCAPP [ages 55–64] (Holme et al., 2014a, 2014b), f = Minnesota (Mandel et al., 1999, 2000), g = Funen (Kronborg et al., 2004), h = Nottingham (Scholefield et al., 2012), i = Goteborg (Lindholm et al., 2008).

aggregate outcome initially published for the NORCCAP trial (Holme et al., 2014a; Holme et al., 2014b). The two NORCCAP cohorts were recruited separately and had markedly different screen-to-control ratios (Bretthauer et al., 2002). Therefore, as we previously reported, NORCCAP should be treated as two independent trials in meta-analysis (Swartz et al., 2017). Though aggregating the two cohorts into one is appealing, it produces erroneous results. This phenomenon, known as Simpson's paradox, occurs when combining studies with different sizes, screen-to-control ratios, and/or event rates; it is the main reason that meta-analysis combines studies via weighted means rather than simple aggregation (Julious and Mullee, 1994; Altman and Deeks, 2002). The use of the aggregate NORCCAP outcome caused the USPSTF-ER meta-analysis to conclude that no CRC screening modality reduces death (Swartz et al., 2017). The Simpson's paradox also affected the USPSTF-ER FS meta-analyses for CRC incidence and death attributed to CRC, but the magnitude of the effect was smaller and less consequential for these outcomes. This study is the first to report the correct meta-analysis results for all three of these FS outcomes (death, CRC incidence, and death attributed to CRC) or to make quantitative comparisons to the respective FOBT outcomes.

This study has several potential weaknesses. First, the screening protocol varied somewhat among the trials and this clinical heterogeneity could bias the results. Specifically, the PLCO screened twice whereas the other trials screened only once. The trials also included slightly different age ranges and had variable follow-up durations. Despite these minor clinical differences, the statistical measure of heterogeneity ($I^2 = 0\%$) supports the appropriateness of the study grouping, and previously published meta-analyses have concluded that the clinical heterogeneity of these trials is low enough to warrant grouping for both mortality and incidence outcomes (Littlejohn et al., 2012; Elmunzer et al., 2012; Holme et al., 2013; Brenner and Stock, 2014; Shroff et al., 2014).

A second potential weakness is that the Burgundy FOBT trial is excluded from the FS versus FOBT comparison of death because that outcome data has not been published. Though that data would not change the FS result, it could potentially affect the FS versus FOBT comparison for death.

A third potential weakness is that the FS outcome at 10.5–11.9 years is compared to FOBT outcome at 15.6–30.0 years. The FS follow-up is shorter (10.5–11.9 years), yet all but one of the studies used a single screen and thus the screening ended when it started. While the FOBT follow-up was 15.6–30.0 years, this is from the initiation of a recurring screening that lasted up to 16 years. The entire rationale for a recurring screening is that additional benefit accrues over time. Thus the most appropriate comparison may be based upon duration from the end of screening rather than the start. In the FOBT studies, the duration of follow-up from cessation varied from 9 to 16 years in three of the studies, and within the remaining study the range was 1–17 years (the protocol was that non-attendees at any screening round received no subsequent invitations). Given the expected 10-year lead-time between a screening intervention and a demonstrable reduction of mortality, these follow-up durations seem reasonable (and possibly optimal) for comparing these modalities. Nonetheless, sensitivity analysis repeated the comparisons using FOBT outcomes at 10–15.6 years follow-up; this yielded no meaningful outcome differences (Supplement Figs. S1 and S2). Again, this potentially affects the FS to FOBT comparison but cannot affect the FS results.

A clear limitation of this study is that it does not address differences of cost, cost-effectiveness, or patient preference between the screening modalities. These are important issues which must be taken into account when making both individual and population screening decisions.

These results have several important implications. First, a demonstrable reduction in the risk of death is an achievable goal in clinical trials of cancer screening. Though the effect might be too small to be statistically significant in individual trials, meta-analysis can overcome this limitation. Indeed, combining as few as two of the FS trials yields a statistically significant death reduction (Supplement Fig. S3). Consequently, we should question why the disease-specific mortality reductions of many modalities of cancer screening fail to produce even a non-significant trend towards fewer deaths (Saquib et al., 2015). Black et al. (2002) have described several biases in cause-of-death determinations where DSM reductions merely reflect mortality *shifting* (i.e. changing the cause-of-death without changing the occurrence of death) rather than mortality reduction, a phenomenon that has been reported with prostate cancer (Newschaffer et al., 2000; Albertsen, 2000). Although FOBT is effective at diagnosing CRC early and reducing deaths attributed to CRC, it lacks even a small, non-significant trend towards fewer overall deaths (RR = 1.001) with meta-analysis of four large clinical trials. This result appears more consistent with mortality shifting than with a death reduction that is statistically non-significant due to inadequate sample size (Fig. 1A.2 and C.2). This may indicate that a reduction of a certain type of death is an inadequate surrogate for a reduction of the occurrence of death in these types of screening trials. Additionally, the lack of *any* positive correlation ($r = -0.024$; 95% CI −0.89–0.88; $P = 0.97$) between death and death attributed to CRC in the FS RCT's highlights this discrepancy, especially in comparison to the strong, statistically significant correlation between reductions of death and reductions of CRC incidence ($r = 0.95$; 95% CI 0.42–0.99; $P = 0.013$). Future research should reassess the validity of using disease-specific deaths as the primary outcome in these types of screening trials.

The second implication is that *prevention* of cancer appears to be far more effective than early diagnosis. FOBT works mainly via early diagnosis of CRC, whereas FS adds an additional mechanism of action — the prevention of CRC by polyp detection and removal — thereby arresting the proposed polyp–dysplasia–cancer sequence. All five FS trials show a consistent reduction of both CRC incidence and death, effects notably absent from FOBT (Fig. 2B). The magnitudes of these reductions display a clear and statistically significant dose-response relationship and the resultant regression line is most consistent with CRC prevention being the only mechanism of action for death reduction in these trials. This implies that early diagnosis of CRC had little or no effect upon death. This result is corroborated by a recent similar finding in a study that examined this issue from a completely different perspective. Doroudi et al. compared the CRC-specific survival between the screening and control arms of the PLCO trial and found no difference, which they interpreted as suggesting that the effect of FS was mostly attributable to primary prevention of CRC and that early diagnosis of CRC had a “limited role” (Doroudi et al., 2017).

Even if prevention and early diagnosis of CRC were equally effective, prevention has considerable advantages. When CRC is prevented, the only associated subsequent medical care is surveillance colonoscopy, which frequently is not required until three to five years later (Lieberman et al., 2012). Conversely, early diagnosis of CRC usually involves costly surgery, chemotherapy, radiation therapy, and all of the morbidities that accompany these therapies (Cunningham et al., 2010; Damin and Lazzaron, 2014). Early diagnosis also carries all of the emotional and financial burdens of cancer diagnosis and treatment, while prevention completely avoids these. Therefore even if the mortality effects of prevention and early diagnosis were equal, prevention would be greatly preferable. Both cancer prevention and death reduction are patient-oriented outcomes by themselves. Conversely, early diagnosis of cancer and reduction of a specific *type* of death could both be considered disease-oriented outcomes that are of questionable value if they fail to affect whether a patient lives or dies.

Though many areas have advanced to screening with colonoscopy and/or fecal immunochemical tests (FIT), the results of this study have implications for these newer modalities. Given the identical mechanism of action, colonoscopy can clearly be expected to have equal or better CRC prevention than FS, though a superiority has not been proven in randomized controlled trials to date, and observational studies have not

consistently demonstrated additional benefit over FS (Neugut and Lebwohl, 2010). But given that FOBT does not prevent cancer, it is unclear if FIT should be expected to achieve this outcome. FIT's diagnostic superiority over FOBT is mostly in its sensitivity for colorectal cancer detection rather than for adenoma detection (Quintero et al., 2012). Future research should evaluate if FIT can prevent CRC and/or reduces death compared to usual care in RCT's using intention-to-screen analysis.

5. Conclusions

The results of this meta-analysis of over three-quarters of a million participants in randomized controlled trials of FS and FOBT indicate that, within these trials, FS uniquely and consistently reduced death. In the FS trials, reduction of death and prevention of CRC display a strong, linear, dose-response relationship, which is a powerful indicator that the death reduction is attributable to the CRC prevention. Regression analysis indicates that prevention of CRC is most likely the sole mechanism of action, implying that early diagnosis of CRC did not have an effect on whether or not patients died.

This study's focus upon death and CRC incidence means that the benefits reported here cannot be attributed to artifacts of screening (such as overdiagnosis creating the illusion of improved survival and staging).

The outcomes of this study suggest that CRC screening recommendations warrant reassessment. Current recommendations are based upon reduction of deaths attributed to CRC and do not consider differing effects on the risk of actually dying. For example, the USPSTF life-years gained model predicts that FS is the *least* effective modality of colorectal screening, ranking it well below FOBT (US Preventive Services Task Force, 2016). Yet the SORT Grade A evidence (Ebell et al., 2004) from this study indicates that FS is the only modality of colorectal screening to reduce death in clinical trials and that FOBT has no detectable effect on this outcome; this discrepancy warrants reconciliation. Additionally, current guidelines do not clearly differentiate between early diagnosis of CRC and prevention. Yet the results of this study indicate that CRC prevention is the major (and likely sole) mechanism of action for death reduction in clinical trials of colorectal screening. Thus we should consider shifting the focus of screening from early diagnosis of CRC to prevention of CRC; or more explicitly, prioritizing diagnostic accuracy for adenomatous polyps over diagnostic accuracy for cancer. At present, direct mucosal visualization, whether by FS or colonoscopy, may be the only way to achieve an adenoma sensitivity that is adequate to yield the CRC prevention produced by FS in clinical trials.

Preventing cancer and reducing death are the two most patient-important outcomes that colorectal screening can achieve. The results of this study indicate that both outcomes are achievable if the focus is CRC prevention.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ypmed.2018.10.014.

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