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Reconciling the Effects of Screening on Prostate Cancer Mortality in the ERSPC and PLCO Trials

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Background: The ERSPC (European Randomized Study of Screening for Prostate Cancer) found that screening reduced prostate cancer mortality, but the PLCO (Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial) found no reduction.

Objective: To evaluate whether effects of screening on prostate cancer mortality relative to no screening differed between the ERSPC and PLCO.

Design: Cox regression of prostate cancer death in each trial group, adjusted for age and trial. Extended analyses accounted for increased incidence due to screening and diagnostic work-up in each group via mean lead times (MLTs), which were estimated empirically and using analytic or microsimulation models.

Setting: Randomized controlled trials in Europe and the United States.

Participants: Men aged 55 to 69 (ERSPC) or 55 to 74 (PLCO) years at randomization.

Intervention: Prostate cancer screening.

Measurements: Prostate cancer incidence and survival from randomization; prostate cancer incidence in the United States before screening began.

Results: Estimated MLTs were similar in the ERSPC and PLCO intervention groups but were longer in the PLCO control group than the ERSPC control group. Extended analyses found no evidence that effects of screening differed between trials ($P = 0.37$ to 0.47 [range across MLT estimation approaches]) but strong evidence that benefit increased with MLT ($P = 0.0027$ to 0.0032). Screening was estimated to confer a 7% to 9% reduction in the risk for prostate cancer death per year of MLT. This translated into estimates of 25% to 31% and 27% to 32% lower risk for prostate cancer death with screening as performed in the ERSPC and PLCO intervention groups, respectively, compared with no screening.

Limitation: The MLT is a simple metric of screening and diagnostic work-up.

Conclusion: After differences in implementation and settings are accounted for, the ERSPC and PLCO provide compatible evidence that screening reduces prostate cancer mortality.

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More than 2 decades after prostate-specific antigen (PSA) screening for prostate cancer entered clinical practice, in 2012 the U.S. Preventive Services Task Force (USPSTF) determined that there was "very low probability of preventing a death from prostate cancer in the long term" and recommended against routine use of the test (1). Since then, rates of PSA screening and prostate cancer incidence have decreased significantly in the United States (2, 3).

The USPSTF recommendation relied heavily on results from the ERSPC (European Randomized Study of Screening for Prostate Cancer) (ISRCTN registry number: ISRCTN49127736) and the PLCO (Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial) (ClinicalTrials.gov: NCT00002540). However, the trials had apparently conflicting results, with the ERSPC reporting a 21% reduction in prostate cancer mortality (4–6) and the PLCO finding no difference in mortality between the trial groups (7–9). Interpretation of the trial results is complicated by differences in their implementation (including design and adherence) and practice settings. The PLCO used a shorter screening interval (annual vs. every 2 to 4 years in the ERSPC), had a higher PSA threshold for biopsy referral (4.0 μg/L vs. 3.0 μg/L in most ERSPC centers and rounds), and stopped regular screening after 6 rounds. Prostate cancer incidence was higher in the United States than in Europe before the trials started, reflecting different populations and clinical diagnosis patterns. The U.S. practice setting also contributed to more frequent screening in the PLCO control group and less frequent biopsy than in the ERSPC. Consequently, the PLCO compared the effects of an organized screening program versus opportunistic screening rather than screening versus no screening (8–10). Nonetheless, the PLCO results have been viewed as more relevant to the U.S. setting (11).

The objectives of this study were to formally test whether the effects of screening on prostate cancer

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mortality differed between the ERSPC and PLCO after differences in implementation and practice settings were accounted for and to estimate the effects of screening in both trials relative to no screening.

METHODS

Overview

Our study used individual records from both trials in a collaboration between trial investigators and the prostate cancer working group of the Cancer Intervention and Surveillance Modeling Network. In the intervention groups, these records included age and year of randomization, enrollment center, dates and results of PSA tests and rectal examinations, whether biopsy was performed, date of cancer diagnosis, and date and cause of death. In the control groups, the records included age and year of randomization, enrollment center, date of cancer diagnosis, and date and cause of death. For consistency with prior publications, ERSPC data included men aged 55 to 69 years at randomization (12), and PLCO data included men aged 55 to 74 years at randomization (13).

We first conducted a traditional statistical analysis that combined data from both trials and compared hazards of prostate cancer death in the intervention groups versus the control groups, with adjustment for participant age and trial setting. However, this analysis is questionable because of remaining differences in implementation between the trials. To overcome this limitation, we also performed extended analyses that accounted for variable screening and diagnostic work-up (hereafter "screening intensity") in each trial group, which we operationalized using mean lead times (MLTs). The MLTs reflect the magnitude of increased prostate cancer incidence relative to a baseline level expected in the absence of screening, thus capturing differences in both design and adherence (see the next section). We estimated the MLTs both empirically and using analytic or microsimulation models; using multiple approaches allowed us to assess the robustness of results to this uncertain quantity.

Estimating MLTs

The MLT is usually defined as the average time by which diagnosis is advanced by screening relative to the date of diagnosis without screening. Under complete follow-up, where all preclinical cases are eventually diagnosed in the no-screening setting, the MLT corresponds to the difference in areas under 2 "survival curves" (one in the absence of screening minus one in the presence of screening) for time from randomization to diagnosis. Under limited follow-up, we can define a restricted version of the MLT as an analogous difference in areas under survival curves up to a specified time point (14). Restricting the analysis to the duration of the trial recognizes that events after the trial period cannot affect mortality during the trial. To make estimates between trials comparable, follow-up was restricted to 11 years.

Of note, our estimates of the MLTs differ from other estimates in the literature that can be interpreted as the average time by which screening advances diagnosis among cases that would have been clinically diagnosed (15). Our MLTs are designed as proxies for the intensity of screening and diagnosis, with higher values reflecting higher attendance rates at screening examinations, more frequent screening examinations, less conservative criteria for biopsy referral, and/or more frequent biopsy. Thus, accounting for variable MLTs across trial groups captures in a single measure important differences in the trial screening protocols, participant adherence to those protocols in the intervention groups, and control group screening.

We estimated the MLTs empirically, with no model assumptions about cancer progression and diagnosis, and also using 3 models of cancer natural history and diagnosis. The empirical approach estimated the MLTs by calculating the difference between survival curves for observed time from randomization to diagnosis in each trial group relative to an assumed baseline level. The assumed baseline probability of diagnosis in the absence of screening was derived using incidence rates from the SEER (Surveillance, Epidemiology, and End Results) program in 1986—just before PSA screening began in the United States—with adjustment to reflect distributions of age at randomization in each trial. In addition, 1 analytic model (University of Michigan [UMICH]) and 2 simulation models (Fred Hutchinson Cancer Research Center [FHCRC] and Erasmus University Medical Center MIcrosimulation SCreening ANalysis [MISCAN]) estimated times from randomization to diagnosis in the absence and presence of screening based on cancer progression and diagnosis rates, which were estimated using individual-patient data on attendance, screening, and incidence. The fitted models then estimated MLTs as in the empirical approach, but using projected instead of observed incidence rates. Each MLT was then scaled by the corresponding fraction of patients diagnosed within the 11-year follow-up and was projected so that it could be interpreted as an average interval among cancer cases detected in the relevant trial group. Further details are provided in the Supplement (available at Annals.org).

Statistical Analysis

We used Cox regression to model survival from randomization to prostate cancer death, censoring persons who died of other causes or were alive at the last follow-up. We performed both a traditional statistical analysis and extended analyses that incorporated the measure of screening intensity captured by the estimated MLTs. Both types of analysis included participant age at randomization and a trial setting indicator (PLCO vs. ERSPC), which allowed for a different baseline risk for prostate cancer death in the absence of screening between trial settings.

Traditional Statistical Analysis

We first conducted a traditional analysis to test whether the effect of screening differed between trials.

Specifically, we tested the effect of being randomly assigned to the intervention group (relative to the control group) on the risk for prostate cancer death. The exponential of the coefficient for the trial group indicator is the hazard ratio for prostate cancer death in the intervention group relative to the control group; in other words, it reflects the effect of screening on prostate cancer mortality in an intention-to-screen analysis. We fitted this model with and without allowing separate effects of screening in each trial (that is, with and without interaction between the trial group and the trial setting indicator), then used a likelihood ratio test to evaluate evidence of differential effects of screening between trials.

Extended Statistical Analysis

Next, we replaced the trial group indicator with the corresponding MLT, which was estimated empirically or using a model-based approach. The exponential of the coefficient for the MLT represents the hazard ratio for prostate cancer death per additional year of MLT; in other words, it reflects screening efficacy standardized by screening intensity. As in the traditional analysis, we fitted this model with and without allowing separate effects of screening on prostate cancer mortality in each trial (that is, with and without interaction between the MLT and the trial setting indicator), then used a likelihood ratio test to evaluate evidence of differential effects of screening between trials.

Our extended analyses are consistent with the analyses in the trial publications (4, 7), with 2 important differences. First, rather than relying on an intention-to-treat effect of screening determined by the assigned group in a single trial, we explicitly included a covariate (MLT) to capture the intensity of screening in each group. This represents a transition from thinking about screening as "all or nothing" (corresponding to an intervention and control group) to a continuous metric of screening intensity, with resulting coefficient estimates interpreted relative to a no-screening setting (where the MLT equals zero). Second, we used combined data from both trials in a single analysis, adding an indicator for trial to capture differences between trials in baseline cancer-specific survival without screening and an interaction term to test whether screening efficacy (per year of MLT) differed between trials.

Role of the Funding Source

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RESULTS

Table 1 summarizes participant characteristics, follow-up, and prostate cancer cases and deaths in the 2 trials under all available follow-up and restricted to 11 years of follow-up. The data under all available follow-up differ modestly from published results (5, 8) because of cleaning and updating. Nonetheless, the cleaned and updated data restricted to 11 years of follow-up yielded values similar to published prostate cancer incidence rate ratios (PLCO: 1.12 vs. 1.12; ERSPC: 1.68 vs. 1.63) and mortality rate ratios (PLCO: 1.02 vs. 1.09; ERSPC: 0.79 vs. 0.79) and preserved the greater effects of screening on prostate cancer incidence and mortality rates in the ERSPC relative to the PLCO.

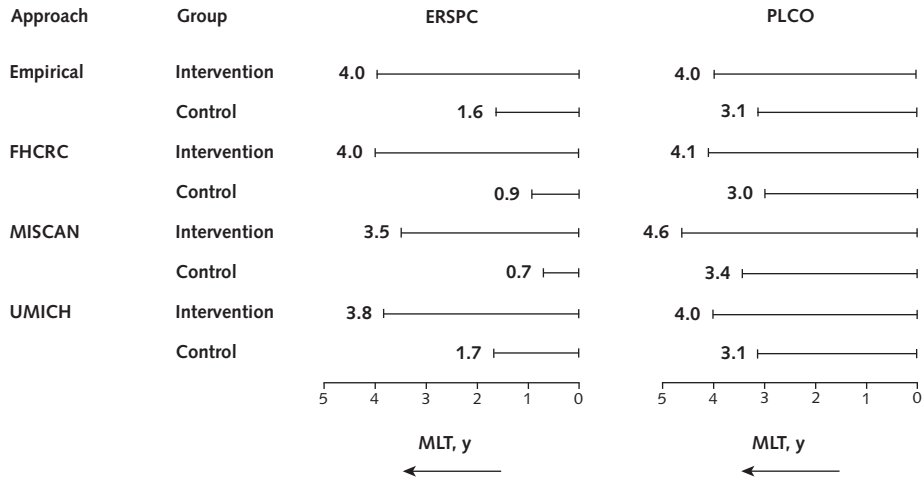
To compare screening intensity in the intervention and control groups of the trials, Figure 1 illustrates MLTs estimated empirically or using a model-based approach. All estimation approaches found similar ordering and relative magnitudes of MLTs across groups. The ERSPC and PLCO intervention groups had similar

Table 1. Summary of Participant Characteristics, Follow-up, and Prostate Cancer Cases and Deaths in the ERSPC and PLCO, Under All Available Follow-up and Restricted to 11 Years of Follow-up

Characteristic	ERSPC		PLCO	
	Control	Screening	Control	Screening
Participants, *n*	88 921	72 473	38 343	38 340
Median age at randomization (range), *y*	59 (55–69)	60 (55–69)	62 (55–74)	62 (55–74)
All available follow-up				
Median follow-up from randomization (range), *y*	11.0 (0.4–17.5)	11.1 (0.4–17.3)	12.5 (0–13.0)	12.5 (0–13.0)
Prostate cancer cases, *n*	5398	6967	4040	4430
Person-years of follow-up for incidence	933 854	740 775	403 955	400 008
Deaths, *n*	17 019	13 652	7149	6940
Other causes	16 557	13 353	7003	6788
Prostate cancer	462	299	146	152
Person-years of follow-up for mortality	990 678	827 148	426 720	427 824
Restricted to 11 y of follow-up				
Median follow-up from randomization (range), *y*	11.0 (0.4–11.0)	11.0 (0.4–11.0)	11.0 (0–11.0)	11.0 (0–11.0)
Prostate cancer cases, *n*	4961	6586	3641	4038
Person-years of follow-up for incidence	868 834	686 766	368 844	365 129
Deaths, *n*	13 207	10 397	5880	5798
Other causes	12 822	10 150	5771	5687
Prostate cancer	385	247	109	111
Person-years of follow-up for mortality	890 581	725 997	387 027	387 861

ERSPC = European Randomized Study of Screening for Prostate Cancer; PLCO = Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial.

Figure 1. Estimated MLTs in the intervention and control groups of the ERSPC and PLCO relative to a hypothetical no-screening setting (where MLT equals zero).



Estimated MLTs are visualized as increasing to the left to suggest the extent to which prostate cancer diagnosis is advanced by more intensive screening and diagnostic work-up. ERSPC = European Randomized Study of Screening for Prostate Cancer; FHCRC = Fred Hutchinson Cancer Research Center; MISCAN = Erasmus University Medical Center MIcrosimulation SCreening ANalysis; MLT = mean lead time; PLCO = Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial; UMICH = University of Michigan.

MLTs, but the PLCO control group had substantially longer MLTs than the ERSPC control group, which is consistent with more intensive screening (that is, greater "contamination") in the PLCO control group.

Table 2 shows results of the traditional analysis. A likelihood ratio test associated with this analysis suggested marginal evidence of different effects of screening on mortality between trials (P for interaction = 0.087). Under a common effect of screening, screening was estimated to reduce the risk for prostate cancer death by 16% (95% CI, 4% to 27%; P = 0.010) after we accounted for different baseline risks for prostate cancer death in the PLCO setting relative to the ERSPC setting and participant age at randomization. This result essentially corresponds to a weighted average of the effect in each trial, with the relative sizes of the trials as weights.

Table 2 also presents our extended analyses, which account for the MLT in each trial group, estimated empirically or using a model-based approach. The analyses are highly consistent and indicate no evidence of different effects of screening on mortality between trials (P for interaction = 0.37 to 0.47 [range across estimation approaches]). Under a common effect of screening, all approaches indicated strong evidence that a longer MLT was associated with a lower risk for prostate cancer death after differential baseline risks for prostate cancer death between trial settings and participant age at randomization were accounted for (P = 0.0027 to 0.0032). These analyses estimated that screening conferred a 7% to 9% lower risk for prostate cancer death per year of MLT. Using the formula $1 - (\text{hazard ratio})^{MLT}$, this would translate into estimated 25% to 31% and 27% to 32% reductions in the expected risk for prostate cancer death in the setting of screening as performed in the ERSPC and PLCO intervention groups, respectively, over 11 years of follow-up relative to no screening.

Figure 2 shows prostate cancer survival from randomization in each trial group, obtained by Kaplan–Meier estimation and predicted under a common effect of screening given MLTs estimated by the empirical approach. Predictions obtained using MLTs estimated by the model-based approaches (not shown) are similar. The predicted curves closely reproduce observed differences in prostate cancer survival between the intervention and control groups in both trials, showing that screening intensity as captured by the MLT is highly informative about between-group differences in risks for prostate cancer death in both trials.

DISCUSSION

The USPSTF is currently updating its recommendations about PSA screening and has previously used the ERSPC and PLCO as its main sources of evidence about screening benefit. Primary publications from these high-quality randomized controlled trials are indispensable for evaluating causal effects of screening for prostate cancer. Yet, analyses like the one in this article that attempt to overcome limitations of traditional statistical analyses complement the empirical trial findings by providing information about whether the evidence from the trials is compatible and about the expected reduction in prostate cancer mortality relative to no screening.

Rather than comparing the trial groups as if they represented screened and nonscreened populations, this study estimated the intensity of screening in each group relative to no screening. This allowed us to formally assess whether screening effects differed between the trials when we accounted for differential

screening intensity between groups in each trial. By decoupling screening intensity from trial group labels and investigating how benefit depends on screening intensity, we concluded that differences between the ERSPC and PLCO results are largely attributable to differences in screening intensities between groups within each trial. After finding no evidence of different effects of screening on prostate cancer mortality between trials given the screening intensities, we estimated a common effect of screening on mortality using pooled data on 19 226 prostate cancer cases. The pooled estimate showed a highly significant benefit of screening. This is the first time that data from both trials have been harnessed to estimate screening benefit.

This analysis may have had insufficient power to detect a significant difference in screening efficacy between trials. Thus, although there is no evidence of different screening efficacies, we cannot unequivocally conclude that they were identical. Nevertheless, our combined analysis of both trials allowed the most powerful examination of this question to date.

Our analysis indicated that the baseline risk for prostate cancer death differed between trials. This could be due to different incidence, stage distributions, and treatment patterns in the trial populations in the absence of screening. Lower-than-expected mortality (relative to survival in the pre–PSA screening era) was observed in the PLCO, which may reflect healthier participants or an era with improved disease-specific survival (16). By quantifying screening efficacy as a function of intensity, we projected that screening decreased the expected risk for prostate cancer death in both PLCO groups.

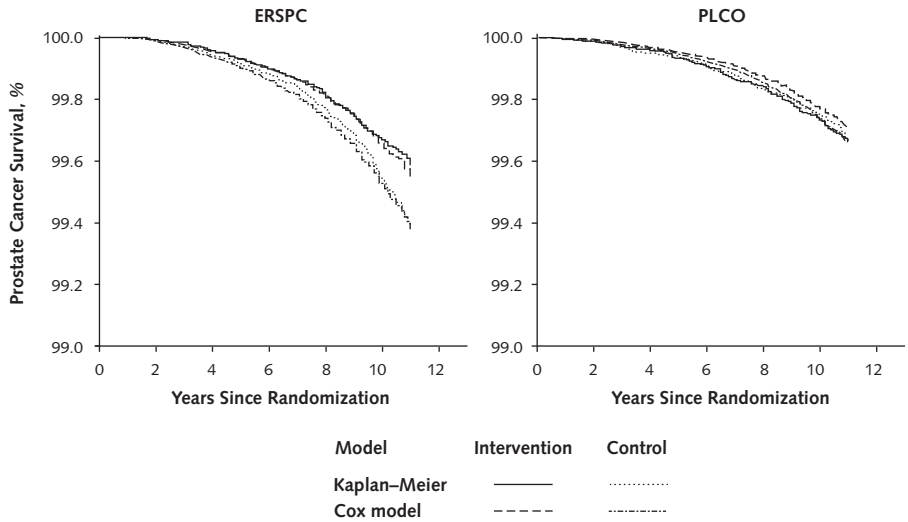
We used several approaches to estimate screening intensity. The empirical approach reflected catchall differences in the risk for prostate cancer diagnosis between groups and calculated the MLT most consistent with incidence in each group relative to a common baseline level. In contrast, the model-based approaches explicitly accounted for trial protocols and practice setting details that were known or could be quantified, such as age distributions, enrollment and attendance patterns, and screening and biopsy frequencies within each ERSPC center. As expected, the estimates were shorter than in other studies (15) owing to the different estimation approach and because we restricted our analyses to 11 years of follow-up. In general, results were highly consistent across estimation approaches and suggest robustness of our conclusions to these ways of estimating screening intensity. Although quantifying the screening intensity using the MLT was simple and natural for our problem, other more complicated measures are possible. These include various standardized measures derived from an excess hazard of cancer diagnosis in a screened population versus an unscreened population, using recent methods (17) and earlier literature on relative survival analysis.

Table 2. Results of Traditional and Extended Cox Regression Analyses of Death From Prostate Cancer and Estimated Mortality Reductions in the ERSPC and PLCO Intervention Groups Relative to No Screening

Covariate	Cox Regression Analysis		Estimated Mortality Reduction Relative to No Screening			
	Hazard Ratio (95% CI)	*P* Value	ERSPC Intervention Group		PLCO Intervention Group	
			MLT, *y*	Reduction (95% CI), %	MLT, *y*	Reduction (95% CI), %
Traditional analysis						
PLCO setting*	0.53 (0.45–0.62)	<0.001	–	–	–	–
Participant age at randomization†	1.13 (1.11–1.14)	<0.001	–	–	–	–
Randomization to intervention group	0.84 (0.73–0.96)	0.0099	NA	16 (4–27)	NA	16 (4–27)
Extended analyses						
Empirical						
PLCO setting*	0.57 (0.48–0.67)	<0.001	–	–	–	–
Participant age at randomization†	1.13 (1.11–1.14)	<0.001	–	–	–	–
MLT†	0.92 (0.87–0.97)	0.0027	3.96	29 (11–43)	4.02	29 (11–44)
FHCRC						
PLCO setting*	0.58 (0.49–0.69)	<0.001	–	–	–	–
Participant age at randomization†	1.13 (1.11–1.14)	<0.001	–	–	–	–
MLT†	0.93 (0.88–0.97)	0.0029	4.00	27 (10–40)	4.10	27 (10–41)
MISCAN						
PLCO setting*	0.63 (0.51–0.77)	<0.001	–	–	–	–
Participant age at randomization†	1.13 (1.11–1.14)	<0.001	–	–	–	–
MLT†	0.92 (0.87–0.97)	0.0032	3.49	25 (9–38)	4.62	32 (12–47)
UMICH						
PLCO setting*	0.57 (0.48–0.68)	<0.001	–	–	–	–
Participant age at randomization†	1.13 (1.11–1.14)	<0.001	–	–	–	–
MLT†	0.91 (0.85–0.97)	0.0029	3.83	31 (12–45)	4.01	32 (12–47)

ERSPC = European Randomized Study of Screening for Prostate Cancer; FHCRC = Fred Hutchinson Cancer Research Center; MISCAN = Erasmus University Medical Center MIcrosimulation SCreening ANalysis; MLT = mean lead time; NA = not applicable; PLCO = Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial; UMICH = University of Michigan.
* Relative to the ERSPC setting to account for differential baseline risk for prostate cancer death.
† Continuous covariate.

Figure 2. Prostate cancer survival from randomization in the ERSPC and PLCO, estimated by Kaplan–Meier or Cox regression model using mean lead time estimated with the empirical approach.



ERSPC = European Randomized Study of Screening for Prostate Cancer; PLCO = Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial.

The finding that effects of screening on mortality seemed consistent between trials after differences in implementation and practice setting were accounted for corroborates results from other analyses. For example, a prior investigation of the PLCO found that control group screening substantially limited the power of that trial to detect a clinically important reduction in prostate cancer mortality (18). However, that study did not formally evaluate whether effects of screening on prostate cancer mortality differed between the ERSPC and PLCO when implementation and setting details are taken into account.

A limitation of this study is that we did not explicitly account for differences between trials in characteristics of cancer cases (for example, clinical stage or Gleason score) or primary treatments. Any differences in these factors between trials are accounted for in the trial-specific baseline risks for prostate cancer death. Also, the model-based approaches to estimate MLTs assume that cancer cases are progressive, although they allow heterogeneity of risk for progression across patients. It is impossible to know whether some cancer cases could remain indolent indefinitely or regress spontaneously and permanently. However, all estimation approaches closely matched incidence trends in each trial group. We also assumed that incidence in the absence of screening was constant across calendar years before and after the trials began, which is a simplification. We considered only the MLT as a surrogate for screening intensity. Other metrics could have associations with risk for prostate cancer death that differ from those we found. Finally, the estimated mortality reduction in each trial group was based on the assumption that the risk for death from any cause is small during follow-up.

In conclusion, taken together, the data from the ERSPC and PLCO do not provide evidence that screening efficacy (relative to no screening) differed between the trials after we accounted for differences in implementation and setting. Our estimation of the common effect of screening suggests that it can significantly reduce the risk for prostate cancer death. However, as for all interventions, the benefit of screening must be weighed against its potential harms for informed clinical and shared decision making.

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Reproducible Research Statement: *Study protocol:* Not available. *Statistical code:* Source code or runs using the FHCRC model are available from Mr. Gulati (e-mail, rgulati@fredhutch.org), runs using the MISCAN model are available from Dr. Heijnsdijk (e-mail, e.heijnsdijk@erasmusmc.nl), and source code or runs using the UMICH model are available from Dr. Tsodikov (e-mail, tsodikov@umich.edu). *Data set:* PLCO data are available from the National Cancer Institute Cancer Data Access System (https://biometry.nci.nih.gov/cdas). ERSPC data may be available from Dr. Moss (e-mail, s.moss@qmul.ac.uk).

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