Original Article

Extended Mortality Results for Prostate Cancer Screening in the PLCO Trial With Median Follow-Up of 15 Years

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BACKGROUND: Two large-scale prostate cancer screening trials using prostate-specific antigen (PSA) have given conflicting results in terms of the efficacy of such screening. One of those trials, the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial, previously reported outcomes with 13 years of follow-up. This study presents updated findings from the PLCO trial. **METHODS:** The PLCO trial randomized subjects from 1993 to 2001 to an intervention or control arm. Intervention-arm men received annual PSA tests for 6 years and digital rectal examinations for 4 years. This study used a linkage with the National Death Index to extend mortality follow-up to a maximum of 19 years after randomization. **RESULTS:** Men were randomized to the intervention arm (n = 38,340) or the control arm (n = 38,343). The median follow-up time was 14.8 years (25th/75th, 12.7/16.5 years) in the intervention arm and 14.7 years (25th/75th, 12.6/16.4 years) in the control arm. There were 255 deaths from prostate cancer in the intervention arm and 244 deaths from prostate cancer in the control arm; this meant a rate ratio (RR) of 1.04 (95% confidence interval [CI], 0.87-1.24). The RR for all-cause mortality was 0.977 (95% CI, 0.950-1.004). It was estimated that 86% of the men in the control arm and 99% of the men in the intervention arm received any PSA testing during the trial, and the estimated yearly screening-phase PSA testing rates were 46% and 84%, respectively. **CONCLUSIONS:** Extended follow-up of the PLCO trial over a median of 15 years continues to indicate no reduction in prostate cancer mortality for the intervention arm versus the control arm. Because of the high rate of control-arm PSA testing, this finding can be viewed as showing no benefit of organized screening versus opportunistic screening. *Cancer* 2017;123:592-9. © 2016 American Cancer Society.

KEYWORDS: digital rectal examination (DRE), prostate cancer, prostate-specific antigen (PSA), randomized trial, screening.

INTRODUCTION

Prostate cancer is the second leading cause of cancer death among US men.[1] In addition to improvements in treatment and efforts at primary prevention of prostate cancer, another potential tool to reduce the burden of prostate cancer mortality is early detection. Although screening for prostate cancer with prostate-specific antigen (PSA) has been ongoing for more than 25 years, it is still not clear whether such screening reduces prostate cancer mortality and, if so, whether the benefits outweigh the established harms.[2,3] Because of its frequently indolent nature and the difficulty in distinguishing indolent prostate cancer from potentially fatal prostate cancer, the harms of prostate cancer screening in the form of overdiagnosed and overtreated cases are considerable, as are the financial and medical resource costs. As such, prostate cancer screening has a high bar in terms of the magnitude of mortality reduction required to make screening worthwhile.

This uncertainty about the utility of prostate cancer screening persists even as 2 large-scale, randomized trials of prostate cancer screening have reported their findings. The most recent analysis reported from the European Randomized Study of Screening for Prostate Cancer (ERSPC), with follow-up through 13 years, showed a prostate cancer mortality rate ratio (RR) of 0.79 (95% confidence interval [CI], 0.69-0.91); a prior analysis with a median follow-up of 11 years showed similar findings (RR, 0.79; 95% CI, 0.68-0.91).[4,5] In contrast, the Prostate, Lung, Colorectal, and Ovarian

(PLCO) Cancer Screening Trial did not show any difference between screening and usual care; through up to 13 years of follow-up, the prostate cancer mortality RR was 1.09 (95% CI, 0.87-1.36).[6]

The conflicting results of the trials and the fact that it is not clear whether the harms of screening outweigh the benefits (even if the RR reported from the ERSPC is accepted) led the US Preventive Services Task Force to give prostate cancer screening a D recommendation (ie, a recommendation against screening) for the general US population.[3]

In the current analysis, we update the mortality results of the PLCO trial with follow-up extended to up to 19 years from randomization. In addition to providing a more stable estimate of the risk ratio based on more prostate cancer deaths, this updated analysis also allows an examination of the longer term effects of prostate cancer screening; this is especially relevant because of the natural history of the disease.

MATERIALS AND METHODS

The design and methods of the PLCO trial have been described.[6,7] Briefly, randomization at 10 US screening centers of subjects aged 55 to 74 years to either an intervention arm or a control arm occurred from 1993 to 2001. The primary exclusion criteria were a history of a PLCO cancer, current cancer treatment, and (beginning in 1995) more than 1 PSA blood test in the prior 3 years. At study entry, participants completed a self-administered baseline questionnaire that included demographics, general risk factors, and screening and medical histories. The trial was approved by the institutional review board at each screening center.

Screening Examinations

Men in the intervention arm underwent PSA blood testing and a digital rectal examination (DRE) at the baseline, a DRE annually for 3 more years (T1-T3), and, generally, PSA testing annually for 5 more years (T1-T5). Men randomized before May 1994 underwent PSA testing only for T1 to T3, and those randomized from June 1994 to May 1995 underwent PSA testing only for T1 to T3 and T5. Participants also underwent chest radiography annually for 4 years and flexible sigmoidoscopy at the baseline and in year 3 or 5. PSA results were classified as abnormal if they were greater than 4 ng/mL. DRE results were considered abnormal if there was nodularity or induration of the prostate or if the examiner judged other criteria to be suspicious for cancer, including asymmetry.

Participants and their physicians were notified in writing of any suspicious abnormality on screening. The diagnostic process after a positive screening was managed by the participants' primary care physicians and was not dictated by the trial.

Ascertainment of Study Endpoints

The primary trial endpoint for the prostate component of the PLCO trial was prostate cancer–specific mortality; secondary endpoints included prostate cancer incidence, cancer stage and Gleason grade, survival, harms of screening, contamination and compliance, and all-cause mortality.

The original analysis period for the PLCO prostate component ran from randomization through 13 years of follow-up or December 31, 2009, whichever came first.[6] Trial endpoints for this period have been described in previous publications. For this original period, incident cancers and deaths were primarily ascertained through a mailed annual study-update questionnaire. Incident cancers reported on the annual study update were verified with medical records and a standardized abstracting process. Next of kin notified the trial of deaths, which were verified with death certificates; National Death Index (NDI) searches were also used. The underlying cause of death was determined in a uniform and unbiased manner from medical records and the death certificate with a blinded endpoint verification process conducted by an independent death review committee.[8]

As has been previously described,[9] after the original analysis period, a structural change in the operation of the PLCO trial affected the ways in which cancer incidence and mortality endpoints were ascertained. Briefly, beginning in mid-2011, PLCO subjects were reconsented with 3 possible options: active follow-up through a central coordinating center, passive follow-up implemented at the screening centers, and refusal of further follow-up. Active participants were eligible for linkages to NDI and state cancer registries and also could be contacted directly to fill out questionnaires or for future specimen collections. Passive participants did not have their personally identifiable information transferred to the central coordinating center but could still be passively followed through NDI and state cancer registries by their local screening centers; those deceased at the time of reconsent were considered passive participants. Finally, refusers had no further active or passive follow-up.

All active and passive subjects were linked to the NDI, and there was complete death information through

the end of 2012. For these subjects, the end of follow-up for mortality for this analysis was December 31, 2012, or the date of death, whichever came first. For refusers, because they had to actively refuse and thus were known to be alive at their refusal date (which ranged from mid-2011 to mid-2012 at 9 centers and to 2014 at 1 center), their end of follow-up was their refusal date or December 31, 2012, whichever came first.

For the extended analysis, the trial ascertained deaths primarily through the NDI, so medical records were not available to perform endpoint verification. Therefore, for deaths occurring after the original cutoff (December 31, 2009), the underlying cause of death from the NDI was used to determine whether deaths were due to prostate cancer or not; for deaths before that date, the endpoint-verified classifications used in the original report were also used here. Alternative analyses were performed to assess the effect of using only death certificate (or NDI) information instead of the endpoint-verified classifications for the originally reported deaths. When all-cause mortality was computed, deaths from lung and colorectal cancer were excluded because trial participants were screened for those cancers, and extended mortality follow-up for these participants is ongoing.

Only mortality outcomes are reported here. Linkage with cancer registries to ascertain incident prostate cancers is ongoing, so complete incidence data for the period after December 31, 2009, are not currently available. For those prostate cancers reported from the original analysis period (4250 in the intervention arm and 3815 in the control arm), we computed the proportion of total prostate cancer deaths in the extended analysis that derived from these cases.[6]

A secondary trial endpoint was assessing nonprotocol use of PLCO screening tests. Use of PSA testing outside the trial protocol was assessed through periodic surveys of a sample of trial participants. Surveys were performed for study years 0 to 5 in the control arm only and study years 6 to 17 in both arms. The survey consisted of a self-administered health status questionnaire (HSQ) that inquired about the use of various preventative health procedures, including the PLCO screening tests. For the control arm, the survey asked whether the respondent had ever undergone the test in question and, if so, when the most recent test had been (within the past year, 1-2 years ago, 2-3 years ago, or more than 3 years ago) and what the reason was for the most recent test ("because of a specific health problem," "follow-up of a previous health problem," or "as part of a routine health check-up"). For the intervention arm, the survey asked whether the respon-

TABLE 1. Demographics of the Prostate, Lung, Colorectal, and Ovarian Trial Population

Characteristic	Intervention Arm (n = 38,340)	Control Arm (n = 38,343)
Age, No. (%)		
55-59 y	12,387 (32.3)	12,372 (32.3)
60-64 y	12,012 (31.3)	12,015 (31.3)
65-69 y	8877 (23.2)	8885 (23.2)
70-74 y	5064 (13.2)	5071 (13.2)
Race/ethnicity, No. (%)		
Non-Hispanic white	33,043 (86.2)	32,136 (83.8)
Non-Hispanic black	1713 (4.5)	1657 (4.3)
Hispanic	816 (2.1)	787 (2.1)
Asian	1532 (4.0)	1477 (3.9)
American Indian/Alaska Native	92 (0.2)	96 (0.3)
Education, No. (%)		
<High school	3101 (8.3)	2994 (8.3)
High school	11,347 (30.4)	11,185 (30.9)
Some college	7643 (20.4)	7424 (20.5)
College graduate	7037 (18.8)	6876 (19.0)
Postgraduate study	8257 (22.1)	7780 (21.5)
Family history of prostate cancer, No. (%)	2737 (7.5)	2589 (7.3)
PSA test within past 3 y, No. (%)		
Once	13,252 (38.8)	13,135 (39.5)
More than once	3588 (10.5)	3760 (11.3)

Abbreviation: PSA, prostate-specific antigen.
Except for age, percentages exclude unknowns.
Data on race/ethnicity missing for 1144 (3.0%) intervention and 2190 (5.7%) control arm participants; data on education missing for 955 (2.4%) intervention and 2084 (5.4%) control arm participants; data on family history missing for 1828 (4.8%) intervention and 2872 (7.5%) control arm participants; data on PSA tests missing for 4229 (11.0%) intervention and 5064 (13.2%) control arm participants.

dent ever had the test in question since the date of their last PLCO screen with that test, with the follow-up questions (timing and reason) referring only to tests after that date. The surveys were customized so that a subject's actual last PLCO screening dates were prewritten on the form; if they had no PLCO screens, then the phrase "since their last PLCO screen" was omitted.

Statistical Methods

Mortality rates from prostate cancer were defined as deaths from prostate cancer during the follow-up period divided by the person-years of follow-up. The RR for the intervention arm to the control arm was computed as the ratio of the rates in the 2 arms. The 95% CI for the RR was calculated under the assumption of a Poisson distribution of events and with the profile likelihood method; P values were computed on the basis of the normal approximation to the Poisson.[10] We also used Cox proportional hazards regression to estimate the hazard ratio (HR) for prostate cancer death associated with being

TABLE 2. Prostate Cancer and All-Cause Mortality by Arm

Cause of Death	Time Period	No. of Deaths (Rate per 10^5 Person-Years)		Rate Ratio (95% CI)/*P*	Hazard Ratio (95% CI)/*P*
		Intervention Arm (533,014 Person-Years)	Control Arm (529,860 Person-Years)		
Prostate cancer	All	255 (47.8)	244 (46.0)	1.04 (0.87-1.24)/.67	1.03 (0.87-1.23)/.72
	Years 0-8	75 (22.8)	70 (21.3)	1.07 (0.78-1.48)/.68	1.07 (0.77-1.48)/.69
	Years 0-10	113 (28.6)	114 (28.9)	0.99 (0.77-1.29)/.93	0.99 (0.76-1.28)/.99
	Years 0-12	165 (36.2)	164 (36.1)	1.003 (0.81-1.25)/.98	1.001 (0.80-1.25)/.99
All causes[a]	All	9212 (1728.3)	9375 (1769.3)	0.977 (0.950-1.004)/.11	0.973 (0.945-1.001)/.06

Abbreviation: CI, confidence interval.

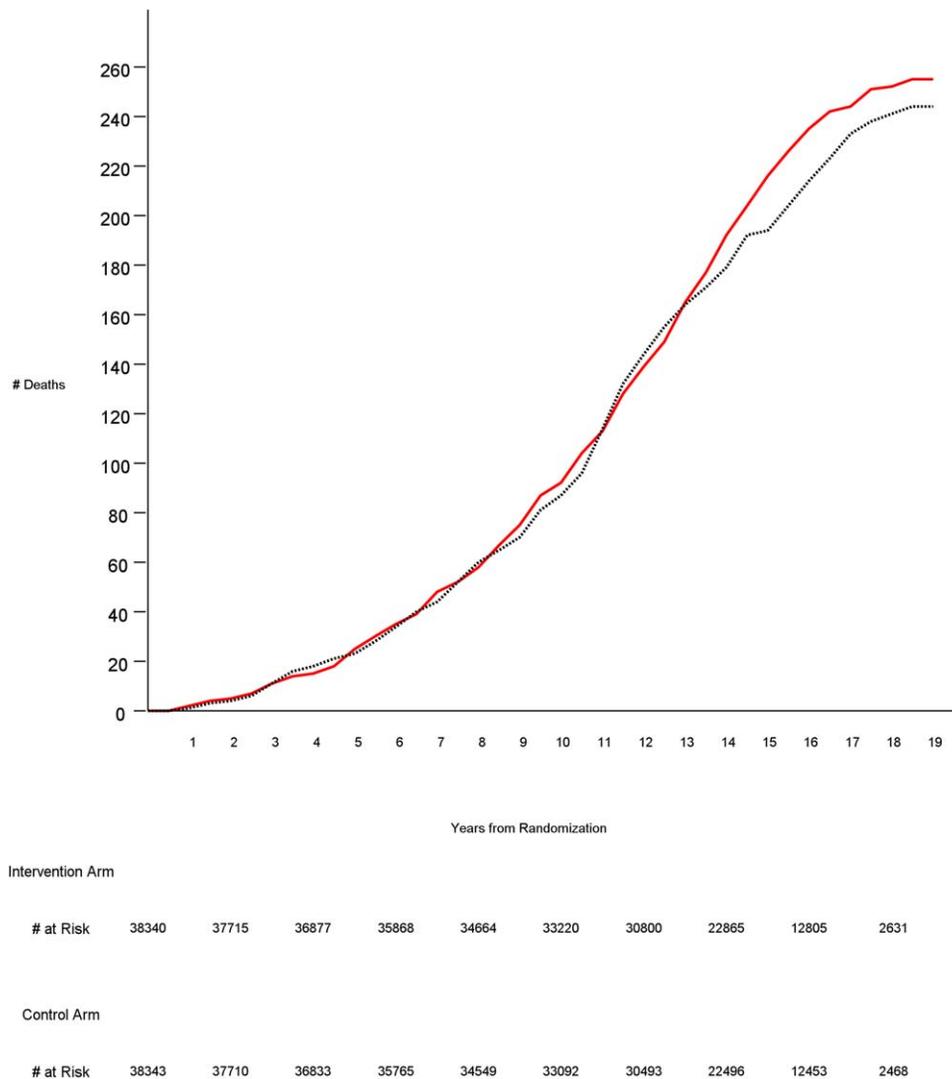[a] Excluding deaths from colorectal cancer and lung cancer.

Figure 1. Deaths from prostate cancer by arm and years from randomization. The solid red line represents the intervention arm, and the dotted black line represents the control arm. Numbers still at risk at selected time points are listed below the graph.

TABLE 3. Causes of Death by Arm

Cause of Death	Intervention Arm, No. (%)	Control Arm, No. (%)
Prostate cancer	255 (2.8)	244 (2.6)
Other cancer (excluding lung and colorectal cancer)	1933 (21.0)	1882 (20.1)
Ischemic heart disease	1699 (18.4)	1650 (17.6)
Cerebrovascular accident	454 (4.9)	513 (5.5)
Other circulatory disease	1317 (14.3)	1364 (14.6)
Respiratory disease	1028 (11.2)	1069 (11.4)
Digestive disease	302 (3.3)	303 (3.2)
Infectious disease	187 (2.0)	175 (1.9)
Endocrine and metabolic	334 (3.6)	371 (4.0)
Nervous system	438 (4.8)	470 (5.0)
Accidental	463 (5.0)	482 (5.1)
Other	802 (8.7)	852 (9.1)
Total (excluding lung and colorectal cancer)	9212	9375

randomized to the intervention arm versus the control arm; subjects not known to have died of prostate cancer were censored at the end of their follow-up.[11]

For various study periods, we computed HSQ survey rates for PSA tests in the past year for screening, PSA tests in the past year for any reason, PSA tests in the past 3 years for any reason, and PSA tests ever for any reason. Note that it was not possible to estimate the proportion ever undergoing a PSA test for screening because the reason-for-testing question was related only to subjects' most recent test. For the intervention arm, because the survey questions referred only to tests taken after the last PLCO protocol test, the computed rates were adjusted to account for PLCO protocol PSA tests performed within the relevant time period (for PSA tests in the past 3 years) or at any time (for PSA tests ever). Also, as noted previously, for the screening period, the survey excluded so-called baseline contaminated subjects, that is, those who responded on the baseline questionnaire that they had undergone 2 or more PSA tests in the prior 3 years. These were previously assumed, when contamination rates were being calculated, to have undergone screening PSA tests every year during the screening phase. A similar adjustment was performed here, so the displayed rate reflects a weighted average of the survey rates for those without baseline contamination (90%) and the assumed rates for those with baseline contamination.

RESULTS

In all, 38,340 and 38,343 men were randomized to the intervention and control arms, respectively. The demographics and medical histories of the subjects were similar across the arms (Table 1). A total of 88.5% were non-

Hispanic white, and 35% were 65 years old or older at randomization.

With respect to the status of transfer to centralized follow-up, the proportion of refusers was 8.4% in the intervention arm and 11.3% in the usual-care arm ($P < .001$). The median follow-up times were similar for refusers (14.9 years for the intervention arm and 14.8 years for the control arm) and active/passive participants (14.8 years for the intervention arm and 14.7 years for the usual-care arm); note that by definition refusers had to survive at least until the transition time to centralized follow-up, whereas passive participants could have died earlier. Overall, the follow-up time was a median of 14.8 years (25th/75th, 12.7/16.5 years) for the intervention arm and 14.7 years (25th/75th, 12.6/16.4 years) for the control arm. The maximum follow-up was 19.1 years for each arm.

Prostate cancer deaths by arm are shown in Table 2. A total of 255 prostate cancer deaths (rate, 47.8 per 100,000 person-years) were observed in the intervention arm, and 244 (rate, 46.0 per 100,000 person-years) were observed in the control arm. The RR was 1.04 in favor of the control arm (95% CI, 0.87-1.24). Proportional hazards modeling showed that the HR was essentially identical to the RR with similar CI and P values (Table 2). Figure 1 displays cumulative prostate cancer deaths by the study time. RRs and HRs varied little by the cumulative study time period. The RRs were 1.07 (95% CI, 0.78-1.48), 0.99 (95% CI, 0.77-1.29), and 1.00 (95% CI, 0.81-1.25) for the study periods of 0 to 8, 0 to 10, and 0 to 12 years, respectively; the HRs were similar (Table 2).

For the newly determined deaths (occurring after December 31, 2009), endpoint verification was not performed because of a lack of collected medical records. We examined the potential impact of this by reperforming the analysis with only death certificate or NDI underlying-cause data for all deaths. The RR increased slightly to 1.06 (95% CI, 0.89-1.26) and the HR increased slightly to 1.05 in favor of the control arm (95% CI, 0.88-1.26).

The previously reported analysis of cases occurring through the end of 2009 and within 13 years of randomization, for which the median follow-up for the cohort was 11.9 years, showed a total of 4250 intervention-arm prostate cancer cases and 3815 control-arm prostate cancer cases. Of these, 2539 intervention-arm cases (60%) and 1996 control-arm cases (52%) were diagnosed during the screening phase (first 6 trial years); the incidence RR during the screening phase was 1.27 (95% CI, 1.20-1.35). Of the currently reported 255 intervention-arm prostate

TABLE 4. PSA Testing Rates From Health Status Questionnaire Surveys

Time Period	Trial Arm	Total Surveyed, No.[a]	PSA Test Within Past Year for Screening, %	PSA Test Within Past Year for Any Purpose, %	PSA Test Within Past 3 y for Any Purpose, %[b]	PSA Test Ever for Any Purpose, %[b]
Study years 0-5[c]	Control	2214	46.0	52.5	67.9	78.9
Study years 6-9	Intervention	861	47.6	54.4	88.9	98.8
	Control	1068	45.6	54.6	78.4	83.6
Study years 10-13	Intervention	702	43.7	53.1	73.7	98.9
	Control	807	47.5	56.4	80.2	88.1
Study years 14-17	Intervention	294	40.5	45.6	71.1	99.3
	Control	339	43.1	50.2	76.4	87.9
All postscreening study years (6-17)	Intervention	1857	45.0	52.5	80.3	98.9
	Control	2214	45.9	54.6	78.7	85.9

Abbreviations: PLCO, Prostate, Lung, Colorectal, and Ovarian; PSA, prostate-specific antigen.

[a] The total surveyed group excludes unknowns and those with a prior prostate cancer diagnosis. Percentages exclude both groups. Over all survey years, 168 intervention and 363 control arm participants had unknown responses; 227 intervention and 364 control arm participants had a prior prostate cancer diagnosis.

[b] For the intervention arm, rates include PLCO protocol screening tests performed in the relevant time period (for tests within the past 3 years) or at any time (for PSA tests ever). Note the intervention-arm health status questionnaire survey asked only about PSA tests taken outside the PLCO protocol.

[c] This was adjusted to included baseline contaminated subjects. See the text for details.

cancer deaths, 88.6% came from these previously reported 4250 cases, and 61.6% came from the 2539 screening phase cases. The figures were comparable for the control arm (244 currently reported prostate cancer deaths): 88.9% and 58.6%.

The all-cause mortality rates were 1728 and 1769 per 100,000 person-years in the intervention and control arms, respectively (Table 2). The HR was 0.973 (95% CI, 0.945-1.001), which was borderline statistically significant in favor of the intervention arm ($P = .06$); the RR was similar (RR, 0.977; 95% CI, 0.950-1.004), although the P value was slightly higher ($P = .11$). Table 3 shows the distribution of all-cause mortality. The proportions for the various causes of death were generally similar across arms.

Table 4 shows the results of the HSQ surveys on nonprotocol PSA testing. For the entire postscreening period, rates were similar across arms for testing within the past year both for screening (45.0% and 45.9% for the intervention and control arms, respectively) and for any reason (52.5% and 54.6% for the intervention and control arms, respectively). These rates varied little over the study time periods in the postscreening phase (Table 4). The corresponding rates during the screening phase in the control arm were slightly lower (40.1% and 47.3% for screening and testing for any reason, respectively). Ever PSA testing rates during the postscreening phase were 99% for the intervention arm and 86% for the control arm.

In the intervention arm, compliance rates for PSA screening were 89.4%, 87.2%, 86.4%, 85.1%, 78.4%, and 78.3% for study years 0 to 5 (average, 84.1%). By protocol, 80.0% of the intervention-arm men were sched-

uled to receive all 6 PSA tests, 16.4% were scheduled to receive 5 PSA tests, and 3.6% were scheduled to receive 4 PSA tests according to their randomization date. A total of 93.6% of the intervention-arm men underwent at least 1 protocol PSA screening.

DISCUSSION

In this extended follow-up of the prostate component of the PLCO trial, the median follow-up increased by approximately 3 years, the maximum follow-up increased by 6 years, and prostate cancer deaths increased by 65% from the prior analysis. The rate ratio (intervention arm vs usual-care arm) for prostate cancer mortality remained slightly above 1 with a value of 1.04 (95% CI, 0.87-1.24); this was down from 1.09 in the prior analysis (the lower 95% confidence limit remained unchanged at 0.87).

With a median follow-up of almost 15 years, the majority of deaths from prostate cancer (approximately 60% in each arm) still occurred in cases diagnosed during the screening phase of the trial (first 6 years). This indicates the need for long-term follow-up, perhaps even longer than 15 years, to fully capture the potential mortality effects of PSA screening.

As with any null trial, statistical power is a critical issue. The original power analysis performed near the start of the trial showed 90% power for a 20% mortality reduction across arms.[12] This power value was based on estimated event rates (for control-arm prostate cancer deaths), predicted compliance and contamination rates, and an estimated true mortality effect of screening with perfect compliance and no contamination. A revised analysis, based in part on longer follow-up (13 years instead of

10 years), showed similar 90% power with the assumption of a 38% contamination rate (specifically, 38% of the control-arm men received yearly screening), 90% compliance (averaged over screening rounds), and the same true mortality effect (27%).[13] A common critique of the PLCO prostate trial has been that the original (and revised) power estimate was too high because it was based on both higher levels of contamination and lower numbers of events than predicted. With extended follow-up and approximately 65% more prostate cancer deaths in the current analysis, the second factor has been mitigated to some extent.

With respect to contamination, with the original trial definition (screening PSA test in the past year), the rate reported here of 46% in the screening phase is only modestly higher than the aforementioned rate of 38%. However, the effect on the power of nonyearly testing during the screening phase, reflected, for example, in the 67.9% rate of PSA testing in the past 3 years, and the effect of high (even if equal across arms) control-arm screening in the postscreening phase are not clear. The model used for the aforementioned power computations assumed no control-arm PSA testing outside the 38% undergoing yearly screening and no postscreening phase testing in either arm.[12] More complex modeling is needed to assess the effect on the trial power of the observed pattern of nonprotocol control- (and intervention-) arm use of PSA testing. The average 84% compliance rate for PSA screening in the intervention arm was substantially greater than the 46% comparable screening-phase control-arm rate, and the prostate cancer incidence risk ratio of 1.27 during that phase clearly shows more screening in the intervention arm than the control arm during that period. On the other hand, with most control-arm men (86%) undergoing some PSA testing during the trial and with almost half undergoing annual screening, the dilution of power due to contamination is likely to have been substantial.

Because of the high control-arm use of PSA testing, the PLCO trial has often been described as a trial of organized screening versus opportunistic screening. When the trial is viewed in this light, the assumed reduction in prostate cancer mortality in the intervention arm versus the control arm would be considerably less than the 27% true mortality reduction cited previously because both arms would be undergoing some screening but there would be, by definition, no contamination. The actual power of the trial is the same whichever way the trial is regarded, but in this interpretation, the power is reduced because the postulated expected mortality reduction between arms is lowered. Therefore, the trial can be viewed as showing no

mortality benefit from organized screening versus opportunistic screening, with somewhat low power due to an expected modest difference in prostate cancer mortality between arms.

In addition to power, another important consideration for null trials is the width of the CI for the primary endpoint. With this extended follow-up, the lower bound of the 95% CI for the mortality rate ratio was unchanged from the prior analysis at 0.87. Even though the width of the entire CI was narrowed by the larger number of events, the point estimate was decreased toward 1.0, and this resulted in an unchanged lower 95% CI bound. It is important to interpret this lower limit correctly. Because of the high contamination rate, it should not be considered to be the lower 95% bound of the true mortality effect (as defined previously) of prostate screening. Rather, under the interpretation of the PLCO trial as a trial of an organized screening program versus opportunistic screening, the lower 95% bound should be interpreted in that context. In other words, organized screening versus opportunistic screening could give a mortality benefit as high as 13% (or harm as high as 24%).

An analysis by non-PLCO investigators suggested that a higher percentage of the PLCO control-arm men versus the PLCO intervention-arm men underwent any PSA tests.[14] This is not correct because the analysis neglected to take into account the fact that the HSQ survey data for the intervention arm concerned only non-PLCO protocol PSA tests.[15] As seen here and reported elsewhere, the true rate of ever PSA testing was 99% in the intervention arm and 86% in the control arm.[15]

Recently, the results of the Prostate Testing for Cancer and Treatment (PROTECT) trial, which compared curative treatment (surgery and radiotherapy) with active monitoring in men with screen-detected localized prostate cancer, were reported.[16] Deaths from prostate cancer over a median 10 years of follow-up were very low in each arm, at most 1.5%, and no significant difference was observed between the active-monitoring and curative-treatment arms. The incidence of metastases was statistically significantly higher in the active monitoring arm, although the overall rate (6%) was low. Because the efficacy of screening is premised on the assumption that earlier treatment leads to reduced prostate cancer deaths, the PROTECT results raise provocative questions about the timing and magnitude of any effect of screening on prostate cancer mortality.

An intriguing finding was the borderline significant reduction in all-cause mortality in the intervention arm (P values of .06 and .11 for the risk ratio and the HR,

respectively). This borderline association was also reported in a prior analysis of the PLCO trial with follow-up through 13 years.[6] It is possible that the increased contact with medical professionals brought on by screening (not just for prostate cancer but also for lung and colorectal cancer as well) might have resulted in decreased mortality. However, this is more likely a chance finding, especially because an examination of the causes of death showed no clear pattern by trial arm.

In conclusion, extended follow-up of the PLCO trial (up to 19 years) continues to show no prostate cancer mortality benefit of screening with PSA and DRE for the intervention arm versus the control arm. Because of the high rate of control-arm PSA testing, this finding can be viewed as showing no benefit of organized screening versus opportunistic screening with PSA.

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AUTHOR CONTRIBUTIONS

Paul F. Pinsky: Conceptualization, methodology, validation, formal analysis, data curation, writing–original draft, writing–review and editing, visualization, supervision, and project administration. **Philip C. Prorok**: Conceptualization, methodology, validation, formal analysis, data curation, writing–original draft, writing–review and editing, and visualization. **Kelly Yu**: Investigation, data curation, and writing–review and editing. **Barnett S. Kramer**: Conceptualization, writing–review and editing, supervision, and project administration. **Amanda Black**: Investigation, data curation, and writing–review and editing. **John Gohagan**: Conceptualization, writing–review and editing, supervision, project administration, and funding acquisition. **E. David Crawford**: Investigation, writing–review and editing, and funding acquisition. **Robert Grubb**: Investigation and writing–review and editing. **Gerald Andriole**: Conceptualization, investigation, writing–review and editing, project administration, and funding acquisition.

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