Prostate Cancer Screening in the Randomized Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial: Mortality Results after 13 Years of Follow-up


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Correspondence to: Philip C. Prorok, PhD, Biometry Research Group, Division of Cancer Prevention, National Cancer Institute, 6130 Executive Blvd, Ste 3132, Bethesda, MD 20892-7354 (e-mail: prorokp@mail.nih.gov).

Background The prostate component of the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial was undertaken to determine whether there is a reduction in prostate cancer mortality from screening using serum prostate-specific antigen (PSA) testing and digital rectal examination (DRE). Mortality after 7–10 years of follow-up has been reported previously. We report extended follow-up to 13 years after the trial.

Methods A total of 76,685 men, aged 55–74 years, were enrolled at 10 screening centers between November 1993 and July 2001 and randomly assigned to the intervention (organized screening of annual PSA testing for 6 years and annual DRE for 4 years; 38,340 men) and control (usual care, which sometimes included opportunistic screening; 38,345 men) arms. Screening was completed in October 2006. All incident prostate cancers and deaths from prostate cancer through 13 years of follow-up or through December 31, 2009, were ascertained. Relative risks (RRs) were estimated as the ratio of observed rates in the intervention and control arms, and 95% confidence intervals (CIs) were calculated assuming a Poisson distribution for the number of events. Poisson regression modeling was used to examine the interactions with respect to prostate cancer mortality between trial arm and age, comorbidity status, and pretrial PSA testing. All statistical tests were two-sided.

Results Approximately 92% of the study participants were followed to 10 years and 57% to 13 years. At 13 years, 4250 participants had been diagnosed with prostate cancer in the intervention arm compared with 3815 in the control arm. Cumulative incidence rates for prostate cancer in the intervention and control arms were 108.4 and 97.1 per 100,000 person-years, respectively, resulting in a relative increase of 12% in the intervention arm (RR = 1.12, 95% CI = 1.07 to 1.17). After 13 years of follow-up, the cumulative mortality rates from prostate cancer in the intervention and control arms were 3.7 and 3.4 deaths per 10,000 person-years, respectively, resulting in a non-statistically significant difference between the two arms (RR = 1.09, 95% CI = 0.87 to 1.36). No statistically significant interactions with respect to prostate cancer mortality were observed between trial arm and age (Pinteraction = .81), pretrial PSA testing (Pinteraction = .52), and comorbidity (Pinteraction = .68).

Conclusions After 13 years of follow-up, there was no evidence of a mortality benefit for organized annual screening in the PLCO trial compared with opportunistic screening, which forms part of usual care, and there was no apparent interaction with age, baseline comorbidity, or pretrial PSA testing.

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The Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial is a multicenter, randomized two-arm trial designed to evaluate the effect of screening for prostate, lung, colorectal, and ovarian cancer on disease-specific mortality. Randomization began in November 1993 and ended in June 2001, with 154,901 men and women enrolled. The study design has been previously described (1). All participants signed informed consent documents approved by both the National Cancer Institute and local institutional review boards. Men in the intervention arm underwent testing for serum prostate-specific antigen (PSA) and digital rectal examination (DRE) to screen for prostate cancer. The PLCO trial enrolled participants aged 55–74 years who reported no previous personal history of prostate, lung, colorectal, or ovarian cancer. Criteria for exclusion included 1) current...
Random errors in death attribution and bias cannot be ruled out.

Limitation
follow-up.

Study design
Men were randomly assigned to the screening (intervention) arm, where annual serum prostate-specific antigen testing was done for 6 years and annual digital rectal examination for 4 years, and usual care (control) arm, where men sometimes underwent opportunistic screening. In this follow-up report, incident prostate cancers and deaths from prostate cancer were followed through 13 years, and cumulative incidence and mortality rates were calculated.

Contribution
Although a 12% relative increase in the incidence rates of prostate cancer was observed in the intervention arm compared with the control arm, there was no difference in mortality between the two arms.

Implication
Prostate-specific antigen and digital rectal examination screening for prostate cancer has no effect on mortality after 13 years of follow-up.

Limitation
Random errors in death attribution and bias cannot be ruled out.

Methods
Study Subjects and Screening Methods
We have previously described the methods of recruitment for the PLCO trial (ClinicalTrials.gov identifier: NCT00002540), randomization, follow-up, and determination of primary and secondary endpoints (1). The diagram for the participant flow in the trial is presented as Figure 1. In brief, 76,685 men aged 55–74 years were randomly assigned to the intervention arm (38,340 subjects) and to the control (usual care) arm (38,345 subjects) at 10 screening centers (in Birmingham, AL; Denver, CO; Detroit, MI; Honolulu, HI; Marshfield, WI; Minneapolis, MN; Pittsburgh, PA; Salt Lake City, UT; St Louis, MO; and Washington, DC) between 1993 and 2001. Each center obtained annual approval from its institutional review board to carry out the study, and all participants provided written informed consent. Men who were randomly assigned to the intervention arm were offered screening with annual PSA tests for 6 years and DRE for 4 years. Screening was completed in October 2006. A positive test was defined as a PSA value greater than 4 ng/mL or a suspicious DRE. Participants and health-care providers received the results; they decided upon the method by which abnormal screening test results were evaluated. Usual care sometimes included opportunistic screening when a test was requested by a participant or recommended by a doctor. All diagnosed cancers, deaths, and causes of death were ascertained by annual follow-up questionnaire and periodic linkage to the National Death Index. Follow-up was through December 31, 2009, or to 13 years from trial entry. Clinical stage was determined from the clinical assessment of the extent of tumor involvement by using the TNM staging system. Tumor stage was categorized according to the fifth edition of the American Joint Committee on Cancer (AJCC) Cancer Staging Manual (5). Gleason grade was determined using the biopsy Gleason score (range 2–10); high-grade cancer was defined as a Gleason score of 8–10, and non–high-grade cancer as a Gleason score of 2–7. The underlying cause of death was determined in a uniform and unbiased manner from the death certificate and relevant medical records, as has been described in detail previously (6). Subjects completed a baseline questionnaire near the time of enrollment, which inquired about demographics, medical history, and past screening practices.

Assessment of Comorbidity
To assess whether comorbidity status influenced the mortality effect of screening (ie, whether there was an interaction of comorbidity with trial arm), we used the baseline questionnaire responses to calculate a modified Charlson comorbidity score (0 = no comorbidity, ≥1 = one or more comorbid conditions) (7). Because of the scope of the medical history section of the baseline questionnaire, a complete Charlson score could not be determined. The modified Charlson score contained the following conditions found in the Charlson score: myocardial infarction, stroke, diabetes, cancer, pulmonary disease (bronchitis and/or emphysema), and liver disease (cirrhosis and/or hepatitis); not included in the modified score were congestive heart failure, peripheral vascular disease, connective tissue disease, hemiplegia, HIV, renal disease, ulcer disease, and dementia. The modified score is expected to identify the great majority of PLCO subjects with a positive (true) Charlson score at baseline; it has been used previously in PLCO...
The previously reported treatment data \( (1) \) for all clinical cancer stages of prostate cancer (stages I–IV) has also now been updated for all incident prostate cancers through 13 years (Table 2). Within each stage, the distribution of primary treatment of the prostate cancers in each trial arm is displayed. For each stage, the treatment distribution was very similar across trial arms.

### Discussion

This article updates with more person-years of follow-up our previously reported finding of no reduction in mortality from prostate cancer in the intervention arm compared with the control arm to 10 years, with no indication of a reduction in prostate cancer mortality to 13 years. We observed a statistically significant 12% relative increase in the incidence of prostate cancer and a non-statistically
significant decrease in the incidence of high-grade prostate cancer in the intervention arm. There was no apparent prostate cancer mortality interaction of trial arm with age, baseline comorbidity (defined by a modified Charlson index), and pretrial PSA testing.

In contrast, the ERSPC trial reported a 20% reduction in prostate cancer mortality in their core age group (men aged 55–69 years) that largely occurred after 10 years of follow-up, although a non-statistically significant reduction of 15% was noted in all men (aged 50–74 years) randomly assigned (2). There were major differences between the PLCO and ERSPC trials. One relates to the extent of opportunistic PSA screening that occurred in the control arms. In the PLCO trial, 45% of those randomly assigned had at least one PSA test in the 3 years preceding randomization, and PSA screening in the control arm was estimated to be 52% during the time period of the last round of screening in the intervention arm (1). In a more detailed analysis, the intensity of PSA screening in the control arm was estimated to be approximately half of that in the intervention arm (10). Nevertheless, the level of screening in the intervention arm was substantially greater than that in the control arm throughout the trial screening period. In the ERSPC trial, the degree of contamination was probably less, although details have only been reported from one center (11).

A possible reason for the difference in the mortality results between the PLCO and ERSPC trials is differences in the application of treatment for prostate cancer. In a recent publication from the ERSPC trial investigators, it was reported that men in the screened arm who were diagnosed with prostate cancer were more likely to be treated at an academic center than men who were diagnosed in the control arm (12). The difference in place of treatment favored the screening arm to the extent that outcomes after major surgery are better in major referral centers than in community hospitals. Furthermore, trial arm was associated with treatment choice, especially in men with high-risk localized prostate cancer. Thus, a control arm subject with high-risk prostate cancer was more likely than a screened arm subject to receive radiotherapy (odds ratio [OR] = 1.43, 95% CI = 1.01 to 2.05), expectant management (OR = 2.92, 95% CI = 1.33 to 6.42), or hormonal treatment (OR = 1.77, 95% CI = 1.07 to 2.94) instead of radical prostatectomy (12). These differences are potentially important given a recent report that radical prostatectomy is associated with improved mortality in young men with aggressive cancers (13). In contrast, the policy in the PLCO trial not to mandate specific therapies after screen detection resulted in substantial similarity in initial treatment by stage between the two arms (Table 2). A planned combined evaluation of the PLCO and ERSPC trials, using mathematical models specifically developed with regard to prostate cancer (14–16), may help to resolve some of the current uncertainties.

Improvements in prostate cancer treatment are probably at least in part responsible for declining prostate cancer mortality rates (17). Even if life is only prolonged by therapy, the opportunities for competing causes of death increase, especially among older men.
A statistically significant interaction of trial arm by comorbidity status has recently been reported by Crawford et al. (4) using the PLCO prostate mortality data through 10 years. The reported hazard ratio (intervention vs control arms) was 0.56 (22 deaths in the intervention arm vs 38 deaths in the control arm) among those with no comorbidity vs 1.43 (62 deaths in the intervention arm vs 42 deaths in the control arm) among those with a comorbidity. The primary explanation for the difference in analysis between Crawford et al. (4) and this study lies in the definitions of comorbidity used. Crawford et al. (4) used an expanded definition of comorbidity, which included, in addition to the Charlson conditions, obesity and hypertension (plus a few other comorbid conditions). Hypertension was included as a comorbid condition whether or not it was well controlled. This increased the proportion of

![Figure 3](cumulative_deaths.png)

**Figure 3.** Cumulative deaths from prostate cancer in the intervention and control arms from year 1 to year 13. C = control arm; I = intervention arm; PY = person-years.

**Table 1.** Relative risk of mortality by age, comorbidity status, and number of PSA tests before enrollment in the PLCO trial*

<table>
<thead>
<tr>
<th>Covariate</th>
<th>Intervention arm</th>
<th>Control arm</th>
<th>RR (95% CI)</th>
<th>P interaction†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of deaths</td>
<td>Deaths per 1000</td>
<td>No. of deaths</td>
<td>Deaths per 1000</td>
</tr>
<tr>
<td></td>
<td>(person-years)</td>
<td>person-years</td>
<td>(person-years)</td>
<td>person-years</td>
</tr>
<tr>
<td>Age, y</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>55–64</td>
<td>65 (276 170)</td>
<td>2.35</td>
<td>54 (274 314)</td>
<td>1.97</td>
</tr>
<tr>
<td>65–74</td>
<td>93 (150 807)</td>
<td>6.17</td>
<td>91 (151 125)</td>
<td>6.02</td>
</tr>
<tr>
<td>Modified Charlson score‡</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>104 (299 994)</td>
<td>3.47</td>
<td>100 (286 992)</td>
<td>3.48</td>
</tr>
<tr>
<td>≥1</td>
<td>44 (116 404)</td>
<td>3.78</td>
<td>39 (114 366)</td>
<td>3.41</td>
</tr>
<tr>
<td>No. of pretrial PSA tests§</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>80 (190 214)</td>
<td>4.21</td>
<td>64 (179 367)</td>
<td>3.57</td>
</tr>
<tr>
<td>≥1</td>
<td>60 (190 924)</td>
<td>3.14</td>
<td>59 (191 082)</td>
<td>3.09</td>
</tr>
</tbody>
</table>

* CI = confidence interval; PLCO = Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial; PSA = prostate-specific antigen; RR = relative risk.
† P values were calculated using a two-sided Wald test in a Poisson regression model.
‡ Score 0 means no comorbid conditions. Score at least 1 means at least one comorbid condition. Sixteen subjects dying from prostate cancer (10 in the intervention arm and six in the control arm) had no comorbidity information available and were excluded from the analysis.
§ PSA test in the 3-year period before entry into the PLCO trial.
subjects classified as having a comorbidity to 64% (4), from the 30% based on the modified Charlson index used in this study. With the 13-year data, the relative risks of mortality in the intervention arm vs control arm were 0.73 and 1.26 for those without and with comorbidity as defined in Crawford et al. (4), ratios both closer to unity than their reported values of 0.56 and 1.43, although the interaction was still statistically significant ($P = .03$).

Furthermore, to validate our observations, we used only the additional deaths and follow-up time through 13 years that were not included in the analysis by Crawford et al. (4). A total of 123 additional prostate cancer deaths were available for this analysis since the 164 deaths reported in the original analysis (4). We found no evidence of interaction between screening arm and comorbidity status because the prostate cancer mortality relative risks comparing trial arms were very similar (RR = 0.99 in the no comorbidity group and RR = 1.06 in the comorbidity group).

In a more detailed exploration of the 13-year data, the highest relative risk of 1.40 was observed for those men with comorbidity according to the definition by Crawford et al. (4) but with a modified Charlson score of 0. This compares to the relative risk of 0.73 for men with no comorbidity according to the definition by Crawford et al. and a relative risk of 1.11 for men with comorbidity according to the definitions of both Crawford et al. and Charlson. Combining the rates from which the 1.40 and the 0.73 rate ratios for the Charlson scores were calculated, 0 men gives the observed ratio of 1.0 for these men. In any case, the biological plausibility of the interaction reported by Crawford et al. (4) seems questionable, because the cohort was relatively healthy to start with (18) and because those men in the 1.40 rate ratio group primarily reported obesity and/or hypertension, which would seem to convey minimal extra risks associated with treatment and minimal differences in treatment options. Thus, the interaction between screening effect and baseline comorbidity is sensitive to the definition of comorbidity. Further, Bach and Vickers (19) concluded that the data do not support the notion that an elevated degree of comorbidity attenuates the benefit of PSA screening in the PLCO study. They advised caution in the interpretation of the analysis of Crawford et al. (4).

A report of follow-up through 14 years of the Goteborg component of ERSPC included findings from some subjects who were not part of the ERSPC analysis (20). Comparing the earlier ERSPC report (2) with this report, it seems that 60% of the Goteborg cohort was included in the core age group (55–69 years) of ERSPC. Of the 122 deaths from prostate cancer reported in the Goteborg trial, 109 (89%) occurred in those aged 55–69 years at entry. Although the extent of the overlap in deaths is unclear, it seems reasonable to assume that most or all of these 109 were included in the core group analysis of the ERSPC. Indeed, the overall ERSPC result without the Goteborg (Swedish) component did not quite reach statistical significance (RR = 0.84, 95% CI = 0.70 to 1.01) (2). Thus, we conclude that the major finding of the Goteborg study (20) concerning reduction in prostate cancer mortality from screening seems largely derived from previously reported data from the ERSPC trial. Furthermore, as the control...
group in the Goteborg trial was followed passively, it is possible that differences in treatment had an impact on the reported results.

This study has certain limitations. For example, the borderline statistically significant lower all-cause (excluding PLCO cancers) mortality in the intervention arm compared with the control arm raises the question as to whether a reduction in prostate cancer mortality in the present analysis has somehow been masked by problems in death attribution, the sticking diagnosis effect (21), even though a death review process has been in operation throughout the trial (6). There is no single cause of death that could account for the difference in all-cause mortality. The deaths in excess in the control arm are from cerebrovascular accidents, other circulatory diseases; respiratory illnesses; infectious diseases; endocrine, nutritional, metabolic and immune diseases; diseases of the nervous system; accidents; and other causes. The deaths in excess in the intervention arm are from non-PLCO neoplasms, ischemic heart disease, and digestive diseases. As anticipated, the majority of those diagnosed with prostate cancer died of other causes. Of the 4250 prostate cancer case patients diagnosed in the intervention arm, 455 (10.7%) had died of causes other than prostate, lung, and colorectal cancer by 13 years, the corresponding numbers for the usual care arm being 3815 prostate cancer case patients and 377 deaths (9.9%), respectively. Thus, a higher percentage of deaths from other causes rather than a deficit occurred among the prostate cancer patients diagnosed in the intervention arm, an indication of the overdiagnosis associated with PSA screen detection (14). We conclude that error in cause of death attribution does not account for the excess in prostate cancer deaths in the intervention arm; random errors and bias cannot be ruled out as explanations for the discrepant outcomes.

A systematic review and meta-analysis of all randomized screening trials for prostate cancer has been reported (22), including the data from PLCO (1) and ERSPC (2) trials in 2009, data from the Goteborg and French components that were not part of the ERSPC 2009 report, and the earlier Quebec and Norwegian trials. In this meta-analysis, there was no statistically significant effect of screening on prostate cancer mortality (RR = 0.88, 95% CI = 0.71 to 1.09) and no effect on overall mortality (RR = 0.99, 95% CI = 0.97 to 1.01).

We plan to update the mortality findings from the prostate component of the PLCO when follow-up data through 15 years are available. In PLCO, the screening that occurred in the usual care arm was not enough to eliminate the expected impacts of the annual screening in the intervention arm, such as earlier diagnosis and a persistent excess of cases. Therefore, the trial was evaluating the effect of adding an organized component of annual screening to the opportunistic screening already in place, and as far as the follow-up has continued to date (13 years), there is no evidence of a benefit. Indeed, there is evidence of harms, in part associated with the false-positive tests, but also with the overdiagnosis inseparable from PSA screening, especially in older men.

Caution is required in determining whether the efficacy of screening is influenced by comorbidity in the relatively healthy population of men that is generally targeted for screening. Using an approach to classify comorbidity as has been previously applied in the trial, we did not find any evidence for an interaction of comorbidity with trial arm, in contrast to what has been recently reported.

Appendix

The following persons are either current or former members of the Data and Safety Monitoring Board of the PLCO Cancer Screening Trial. The following persons are either current or former members of the endpoint verification team.

Current Members: J. E. Buring (chair), Brigham and Women’s Hospital; D. Alberts, Arizona Cancer Center; H. B. Carter, Johns Hopkins School of Medicine; G. Chodak, Midwest Prostate and Urology Health Center; E. Hawk, M.D. Anderson Cancer Center; H. Malin, Loyola University; R. J. Mayer, Dana–Farber Cancer Institute; S. Piantadosi, Cedars–Sinai Medical Center; G. A. Silvestri, Medical University of South Carolina; I. M. Thompson, University of Texas Health Sciences Center at San Antonio; C. L. Westhoff, Columbia University. Former Members: J. P. Kahn, Medical College of Wisconsin; B. Levin, M.D. Anderson Cancer Center; D. DeMets, University of Wisconsin; J. R. O’Fallon, Mayo Clinic; A. T. Porter, Harper Hospital; M. M. Ashton, Edina, MN; W. C. Black, Dartmouth–Hitchcock Medical Center.

Current Members: P. C. Albertsen (chair), University of Connecticut Health Center; J. H. Edmonson, Rochester, MN; W. Lawrence, Medical College of Virginia; R. Fontana, Rochester, MN; A. Rajput, Roswell Park Cancer Institute. Former Members: A. B. Miller, University of Toronto; M. Eisenberger, Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins; I. Jatoi, National Naval Medical Center; E. Glatstein, University of Pennsylvania Medical Center; H. G. Welch, Dartmouth Medical School.

References


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**Notes**

Conflict of interest declarations: G. L. Andriole serves as a Consultant/Advisor for Amgen, Augmenix, Bayer, Cambridge Endo, Caris, France Foundation, GenProbe, GlaxoSmithKline, Myriad Genetics, Steba Biotech, and Ortho Clinical Diagnostics. He serves as Medical Director of Envisioneering Medical and Viking Medical. He is the recipient of grant support from the National Cancer Institute and the National Institute of Diabetes and Digestive and Kidney Diseases. R. L. Grubb conducts research sponsored by GlaxoSmithKline. J. D. Clapp has a financial interest in Human Genome Sciences, Inc, which conducts research and development in the treatment of hepatitis, lupus, and cancer. The Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial is a federally funded registered clinical trial (ClinicalTrials.gov identifier NCT00002540). We thank the study participants for their contributions in making this study possible. The authors are solely responsible for the study design, data collection, analysis and interpretation of the data, writing the article, and decision to submit the article for publication.

**Affiliations of authors:** Division of Urologic Surgery, Washington University School of Medicine, St Louis, MO (GLA, RLG); Anschutz Cancer Pavilion, University of Colorado, Denver, CO (EDC); Huntsman Cancer Institute at the University of Utah Health Sciences Center, Salt Lake City, UT (SSB); University of California Los Angeles Immunogenetics Center, Los Angeles, CA (DC); University of Minnesota School of Public Health, Minneapolis, MN (TRC); University of Alabama at Birmingham, School of Medicine, Birmingham, AL (EP, MNF); Lombardi Cancer Center, Georgetown University, Washington, DC (CI); Henry Ford Health System, Detroit, MI (PA.K); Marshfield Clinic Research Foundation, Marshfield, WI (DJR); University of Pittsburgh Medical Center Cancer Pavilion, Pittsburgh, PA (J.LW); Pacific Health Research Institute, Honolulu, HI (LAY); Westat, Inc, Rockville, MD (BO’B, LRR); Information Management Services, Rockville, MD (JDC, JMR, TLR); Division of Cancer Epidemiology and Genetics (AWH), National Cancer Institute, National Institutes of Health, Bethesda, MD (AWH); Biometry Research Group (GI, PCP) and Early Detection Research Group (FPF), Division of Cancer Prevention, National Cancer Institute, National Institutes of Health, Bethesda, MD and Office of the Director (BSK); Dalla Lana School of Public Health, University of Toronto, Toronto, ON, Canada (ABM); Office of Disease Prevention, National Institutes of Health, Bethesda, MD (JKG).