

Prostate Cancer Screening in the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial: Findings From the Initial Screening Round of a Randomized Trial

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Background: The benefit of screening for prostate cancer using prostate-specific antigen (PSA) testing and digital rectal examination (DRE) is uncertain and is under evaluation in a randomized prospective trial, the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial. Although the final results are several years away, the initial round of screening is complete. We describe the population enrolled in the PLCO trial, their baseline PSA and DRE screening results, and diagnostic follow-up results during the first year of follow-up. **Methods:** A total of 38350 men were randomly assigned to the screening arm of the PLCO trial from November 1993 through June 2001. Men were advised to seek diagnostic follow-up from their primary care provider if their DRE was suspicious for cancer and/or if their serum PSA level was higher than 4 ng/mL. PLCO trial staff obtained records related to diagnostic follow-up. **Results:** Compliance with both screening tests was high (more than 89%). At screening, 7.5% of men had a positive DRE (i.e., suspicious for cancer) and 7.9% had a PSA level higher than 4 ng/mL. Of the men with positive screening tests, 74.2% underwent additional diagnostic testing, and 31.5% underwent a prostatic biopsy within 1 year. Overall, 1.4% of the men in the screening arm were diagnosed with prostate cancer, the majority of whom had clinically localized cancer. These compliance, biopsy, and cancer detection rates appear to be representative of contemporary practice patterns. **Conclusion:** The PLCO trial is evaluating PSA- and DRE-based screening for prostate cancer in a clinically valid manner. Whether such screening will result in a reduction of prostate cancer mortality cannot be answered until the randomized comparison is completed. [J Natl Cancer Inst 2005;97:433–8]

Over the past decade, screening for prostate cancer with serum prostate-specific antigen (PSA) testing and digital rectal examination (DRE) has been the subject of intense scrutiny in the medical community (1–4). Although much has been learned about the performance characteristics of these screening tests, their ability to detect clinically significant prostate cancer when it is still curable is not completely established. The long-term impact of PSA and DRE screening on prostate cancer–specific mortality is unknown. Currently, screening for prostate cancer is recommended by some but not all relevant medical organizations. The American Cancer Society and the American Urological Association recommend PSA and DRE screening beginning at age 50 years in normal-risk men; in contrast, the American Medical Association and the American College of Physicians–American

Society for Internal Medicine do not specifically recommend prostate cancer screening (5). Recently, the United States Preventive Services Task Force concluded that the net benefit of prostate cancer screening with PSA and DRE could not be determined (6).

The prostate component of the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial is designed to determine the impact of annual PSA and DRE screening on prostate cancer–specific mortality by comparing a screened arm with a control arm of men undergoing “routine” medical care (7). The final results of the PLCO trial, in terms of the effect of PSA and DRE screening on prostate cancer mortality, are still several years away. However, the initial screening round of the PLCO trial has now been completed, and the purpose of this article is to characterize the initial experience with prostate cancer screening of men enrolled in the PLCO trial. We describe the demographics and other baseline characteristics of this population, compliance with the initial round of screening, the results of initial PSA and DRE tests, the diagnostic evaluations that occurred as a result of initial positive screens, the rates of prostate cancer, and the characteristics of cancers discovered within 1 year of an initial positive screening test result.

SUBJECTS AND METHODS

The PLCO Cancer Screening Trial (7) is a multicenter, randomized, two-arm trial designed to evaluate the effect of screening for prostate, lung, colorectal, and ovarian cancer on

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disease-specific mortality. Random assignment to the screened or control arm of the PLCO trial began in November 1993 and concluded in June 2001, with 154 942 men and women enrolled. Random assignment and screening procedures were carried out at the following 10 centers: University of Colorado Health Sciences Center, Lombardi Cancer Research Center of Georgetown University, Pacific Health Research Institute, Henry Ford Health System, University of Minnesota School of Public Health/Virginia L. Piper Cancer Institute, Washington University School of Medicine, University of Pittsburgh/Pittsburgh Cancer Institute/Magee-Women's Hospital, University of Utah School of Medicine, Marshfield (Wisconsin) Medical Research and Education Foundation, and the University of Alabama at Birmingham. All laboratory screening tests were performed at a central facility located at the University of California at Los Angeles. All participants signed informed consent documents approved by both the National Cancer Institute and their local institutional review board.

Men and women in the screened arm of the PLCO trial receive flexible sigmoidoscopy and a chest x-ray. Men in the screened arm also receive DRE and PSA tests, and women in the screened arm also receive CA-125 and transvaginal ultrasound testing. The PLCO trial enrolled participants 55–74 years of age who reported no prior personal history of prostate, lung, colorectal, or ovarian cancer. Criteria for exclusion included 1) current treatment for cancer except basal or squamous cell skin cancer, 2) prior surgical removal of the entire prostate, one lung, or the entire colon, 3) participation in another cancer screening or primary prevention study, and 4) use of finasteride in the previous 6 months. Beginning in April 1995, the PLCO trial also excluded men reporting more than one PSA blood test in the past 3 years and men and women reporting any lower gastrointestinal procedure (proctoscopy, sigmoidoscopy, barium enema, or colonoscopy) in the past 3 years. Additional details about the design of the PLCO Cancer Screening Trial have been published elsewhere (7).

On entry into the study, randomly assigned subjects were given a self-administered baseline questionnaire that included questions about personal sociodemographic characteristics (age, race, sex, marital status, and education), family history of cancer, personal medical history, cigarette smoking history, and cancer screening history within 3 years. The questionnaire covered topics believed to be relevant to risk factors for the PLCO trial cancers.

Baseline PSA tests were performed with a Hybritech Tandem-R assay, currently manufactured by Beckman-Coulter. A PSA level higher than 4 ng/mL was considered suspicious for cancer. DREs were performed by physicians, qualified nurses, or physician assistants. DREs were characterized as positive (i.e., suspicious for cancer) if there was nodularity or induration of the prostate or if the examiner judged the prostate to be suspicious for cancer on the basis of other criteria, including asymmetry. Men with positive PSA or DRE results were notified and advised to see their primary care provider for diagnostic follow-up. Primary care providers were also notified. PLCO trial staff obtained medical records related to diagnostic follow-up of positive screens, and medical record abstractors recorded information on relevant diagnostic and treatment procedures. Certified tumor registrars ascertained the stage, Gleason grade, and type of all diagnosed cases of prostate cancer.

Clinical stage grouping was assigned on the basis of clinical assessment of the extent of tumor involvement by using the TNM

system. Tumor (T) stage was categorized according to the fourth or fifth edition of the AJCC (American Joint Committee on Cancer) Cancer Staging Manual (8,9), depending on the date of diagnosis. Clinical information for nodal (N) and metastatic (M) staging was recorded when available.

Quality Assurance (QA) for the measurement of PSA was done in accordance with the manufacturer's suggested protocol. Specifically, each tray of participant samples included a total of four QA samples consisting of duplicate aliquots from each of two manufacturer-supplied QA samples, one of "low" PSA concentration (3 ng/mL) and one of "high" PSA concentration (40 ng/mL). These QA samples were supplied in solution with bovine protein matrix. During the 8-year QA data collection period (November 16, 1993, to December 29, 2001), a total of 18 lots of QA samples at both concentrations were used. The coefficient of variation (CV), i.e., the mean divided by the standard deviation times 100, was calculated using the residual variation after adjusting for lot-to-lot variability. The CVs were 5.09% (95% confidence interval [CI] = 4.97% to 5.22%) at the lower concentration and 3.30% (95% CI = 3.22% to 3.39%) at the higher concentration. These results are in good agreement with those reported by the manufacturer.

RESULTS

Demographics

A total of 38 350 men were randomly assigned to the intervention arm of the PLCO trial (Fig. 1). Most of the participants were non-Hispanic white (Table 1). At the time of enrollment, all age groups were well represented, with higher proportions of men in the younger age strata. The population was relatively well educated, with about half having college degrees. About one-quarter of the men reported a history of prostate problems, and 4.3% reported a prior prostate biopsy. In addition, 6.9% had a first-degree relative with prostate cancer.

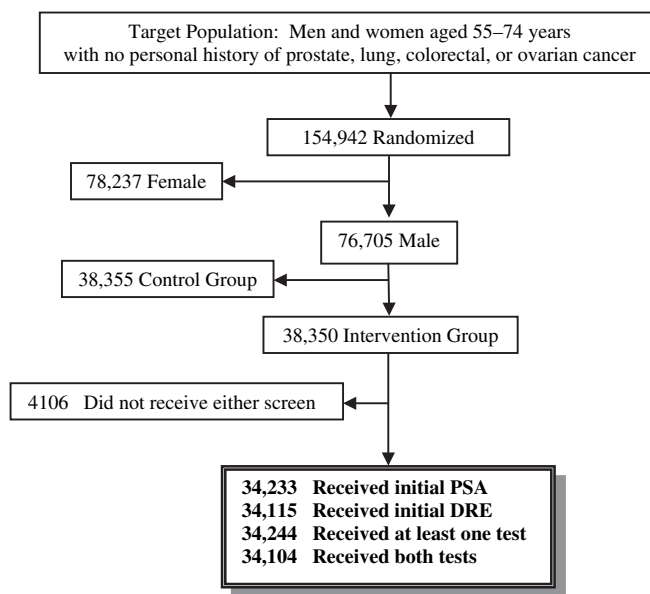


Fig. 1. Flow of participants into the Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial. PRS = prostate-specific antigen; DRE = digital rectal examination.

Table 1. Distribution of baseline demographic and urologic history variables among men in the intervention arm of the Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial

| Baseline variable | % of category (N = 38 350)* |
|--|-----------------------------|
| Race/ethnicity | |
| White, Non-Hispanic | 86.2 |
| Black, Non-Hispanic | 4.5 |
| Hispanic | 2.1 |
| Asian | 4.0 |
| Pacific Islander or American Indian | 0.8 |
| Missing | 2.4 |
| Age | |
| 55–59 years | 32.3 |
| 60–64 years | 31.4 |
| 65–69 years | 23.2 |
| 70–74 years | 13.2 |
| Educational level | |
| Less than high school | 8.1 |
| High school graduate | 29.6 |
| Some college | 19.9 |
| College graduate | 18.3 |
| Postgraduate | 21.5 |
| Unknown | 2.5 |
| Urologic history | |
| Prior prostate biopsy | 4.3 |
| History of enlarged or inflamed prostate or “problems with prostate” | 24.7 |
| First-degree relative with prostate cancer | 6.9 |

*Some categories do not add to 100% because of rounding.

Screening Examination Compliance and Results

A total of 34 244 men underwent an initial PSA and/or DRE screening examination (Fig. 1). Compliance rates for PSA and DRE were roughly equivalent, at 89%. More than 99% of men who underwent screening with either PSA or DRE received both screening tests. As shown in Table 2, compliance with screening did not vary appreciably by age.

The results of the screening tests (Table 3) show that, overall, 7.5% of men undergoing DRE screening were classified as having a positive result. Rates of suspicious DRE results increased with age ($P_{\text{trend}} < .001$). Of men undergoing PSA testing, 7.9% had a positive result (i.e., PSA >4 ng/mL). The probability of a positive PSA result also increased with age ($P_{\text{trend}} < .001$). Of men who underwent both PSA and DRE testing, 1.2% had positive results on both tests, 12.9% had a positive result on only one of the two tests (6.8% with positive PSA and 6.1% with positive DRE), and 85.9% had a negative result on both tests.

Diagnostic Evaluation of Suspicious Screens

Overall, 4801 men had suspicious initial PSA and/or DRE results (Table 4). Of these men, 74% underwent further diagnostic evaluation, and 31.5% underwent prostatic biopsy within 1 year of the screen. Analysis of rates of prostatic biopsy by DRE and PSA results (Table 4) showed that men with higher PSA levels had higher biopsy rates. For example, men with a positive DRE and a PSA level of no more than 4 ng/mL had a biopsy rate of 19.1%, whereas men with a positive DRE and a PSA level higher than 10 ng/mL had a biopsy rate of 85%. Moreover, within each PSA stratum men with suspicious DRE results had higher biopsy rates than men with negative DRE results. Overall, among men with PSA levels higher than 4 ng/mL, the biopsy rate was 40.9%. The biopsy rate was lower for older men (27.1% for men aged

Table 2. Percentage of men in the screening arm of the Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial who were compliant for screening tests, by age*

| Age | Compliant with DRE (%) | Compliant with PSA (%) |
|-------------|------------------------|------------------------|
| 55–59 years | 88.6 | 88.9 |
| 60–64 years | 89.6 | 89.9 |
| 65–69 years | 89.7 | 89.9 |
| 70–74 years | 88.4 | 88.7 |
| All ages | 89.1 | 89.4 |

*Of a total of 38 350 men in the intervention group. DRE = digital rectal examination; PSA = prostate-specific antigen.

70–74 years) than for younger men (33.2% for men aged 55–59 years) (data not shown).

Prostate Cancers Detected Within 1 Year of the Initial Screen

A total of 556 of the 4801 men with suspicious initial PSA and/or DRE screens were diagnosed with prostate cancer within 1 year of their positive screen. As shown in Table 4, prostate cancer diagnosis rates increased as the PSA level increased among both DRE-positive and DRE-negative men. Moreover, within each PSA stratum, men with positive DRE results had higher cancer rates than men with negative DRE results. Among the 397 men with positive DRE results and PSA levels of 4 ng/mL or less who underwent biopsy, 66 (16.6%) were diagnosed with cancer, for an overall cancer diagnosis rate of 3.2% (66/2083). By comparison, among the 77 men with positive DRE and PSA level of more than 10 ng/mL, 69 (90%) had cancer on biopsy, for an overall prostate cancer diagnosis rate of 76% (69/91).

Overall, among the 1112 men with a PSA level of more than 4 ng/mL who underwent biopsy, 489 (44.0%) were diagnosed with cancer, for a diagnosis rate of 18.0% (489/2717). Among the 639 DRE-positive men who underwent biopsy, 219 (34.3%) had a prostate cancer diagnosis. Among all 1510 men who underwent prostate biopsy, cancer was discovered in 556 men (36.8%). The prostate cancer detection rate for all 34 244 men undergoing an initial PSA or DRE screen was 1.6% (556/34 244). The detection rate rose with age, from 1.0% for men aged 55–59 years to 2.5% for men aged 70–74 years ($P_{\text{trend}} < .001$) (data not shown).

Among the 556 cancers diagnosed within 1 year of the initial screen, 10% were Gleason score 2–4, 45% were Gleason score 5 or 6, 31% were Gleason score 7, 12% were Gleason score 8–10, and 2% were of unknown Gleason score (Table 5). The percentage

Table 3. Percentage of men in the Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial with digital rectal examination (DRE) or prostate-specific antigen (PSA) results that were suspicious for cancer, by screening test and age*

| Age | Positive for DRE (%) | Positive for PSA (%) | Positive for both PSA and DRE (%) |
|-------------|----------------------|----------------------|-----------------------------------|
| 55–59 years | 4.9 | 4.1 | 0.5 |
| 60–64 years | 7.2 | 7.2 | 1.1 |
| 65–69 years | 9.4 | 10.8 | 1.8 |
| 70–74 years | 11.5 | 14.0 | 2.2 |
| All ages | 7.5 | 7.9 | 1.2 |

*Percentages are based on the 34 244 men who had at least one of the screening tests. Men were defined as positive for digital rectal examination (DRE) if the test was suspicious for cancer and as positive for prostate-specific antigen (PSA) if the serum PSA level was >4 ng/mL.

Table 4. Biopsy and prostate cancer yield in the Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial by prostate-specific antigen (PSA)/digital rectal examination (DRE) stratum

| Serum PSA level | DRE* | Total no. | Biopsies | | Prostate cancers | | |
|--|------|-----------|----------|------------|------------------|------------|---------------|
| | | | No. | % of total | No. | % of total | % of biopsies |
| ≤4 ng/mL | + | 2083 | 397 | 19.1 | 66 | 3.2 | 16.6 |
| 4–7 ng/mL | + | 236 | 116 | 49.2 | 55 | 23.3 | 47.4 |
| | – | 1594 | 485 | 30.4 | 151 | 9.5 | 31.1 |
| 7–10 ng/mL | + | 71 | 48 | 68 | 28 | 39 | 58 |
| | – | 366 | 183 | 50.0 | 63 | 17.2 | 34.4 |
| >10 ng/mL | + | 91 | 77 | 85 | 69 | 76 | 90 |
| | – | 247 | 158 | 64.0 | 102 | 41.3 | 64.6 |
| >4 ng/mL | Any | 2717 | 1112 | 40.9 | 489 | 18.0 | 44.0 |
| Any | + | 2482 | 639 | 25.7 | 219 | 8.8 | 34.3 |
| Either test positive (PSA >4 ng/mL or DRE +) | | 4801 | 1510 | 31.5 | 556 | 11.6 | 36.8 |

*+ = suspicious for cancer; – = not suspicious for cancer.

of men with Gleason score 7 or higher increased with the PSA level and, for each PSA stratum, was higher in DRE-positive men than in DRE-negative men. Of the men with positive DRE results, 28% of those with low PSA (≤4 ng/mL) had Gleason scores of 7 or higher compared with 66% of men with high PSA (>10 ng/mL).

Overall, 83% of the men diagnosed with prostate cancer had clinical T1 or T2 cancers (stage I or II) and 6% had T3 cancers (stage III) (Table 5), all without known nodal or metastatic involvement. Four percent had either T4 lesions or evidence of nodal or metastatic disease (stage IV). The proportion of T3 and T4 cancers or cancer with nodal or metastatic involvement was highest for men with PSA levels higher than 10 ng/mL. Among men with PSA levels in this highest stratum, 32% of DRE-positive but only 11% of DRE-negative men had clinical evidence of locally advanced or metastatic disease at the time of diagnosis. Among men with PSA levels between 4 and 10 ng/mL who were diagnosed with prostate cancer, 88% had clinically localized disease (T1/T2, N0/NX, M0/NX).

DISCUSSION

We have presented the results of the baseline round of prostate cancer screening in the PLCO trial and the cancer detection rates

during the first year of follow-up. Compliance with both the PSA and the DRE screening tests was high (89%). Positivity rates for PSA and/or DRE tests increased with age, and prostate cancer detection rates among men with positive screens increased with PSA stratum and DRE findings.

These observations are similar to those reported elsewhere among cohorts of men undergoing initial PSA and DRE screening. For example, rates of positive PSA and DRE tests in the current study were 7.9% and 7.5%, respectively. Crawford et al. (3) reported a PSA positivity rate (using the same cutoff, 4 ng/mL) of 9.7% and a DRE positivity rate of 11.6% among 31 953 men aged 50 years and older who took part in initial testing during Prostate Awareness Week in hundreds of sites across the United States in 1993. Smith et al. (10) reported a PSA positivity rate (again, using the same cutoff) of 9.3% and a DRE positivity rate of 9.4% among 19 476 men aged 50 years and older who took part in the initial round of the PSA-2 study in the St. Louis area.

The rates of cancer diagnosed in biopsied men in our study were also similar to those of Crawford et al. (3) and Smith et al. (10). We found cancer yields for prostate cancer among men undergoing biopsy of 44.0% for those with suspicious PSA results, 34.3% for men with suspicious DRE results, and 16.6% for men with suspicious DRE and normal PSA results. For participants in

Table 5. Gleason score and stage distribution of prostate cancers in the Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial by prostate-specific antigen (PSA)/digital rectal examination (DRE) stratum

| PSA | DRE* | Number of cancers | Gleason score (%) | | | | | Clinical stage (%)† | | | |
|--|-------|-------------------|-------------------|-----|----|------|---------|---------------------|-----|----|-------------------------|
| | | | 2–4 | 5–6 | 7 | 8–10 | Unknown | I/II | III | IV | Clinical T not recorded |
| ≤4 ng/mL | + | 66 | 17 | 55 | 23 | 5 | 2 | 91 | 0 | 3 | 6 |
| 4–7 ng/mL | + | 53 | 11 | 47 | 36 | 4 | 2 | 81 | 4 | 0 | 15 |
| | – | 150 | 12 | 49 | 34 | 3 | 1 | 91 | 4 | 1 | 5 |
| 7–10 ng/mL | + | 30 | 7 | 37 | 30 | 20 | 7 | 90 | 7 | 3 | 0 |
| | – | 64 | 11 | 50 | 27 | 11 | 2 | 86 | 6 | 2 | 6 |
| >10 ng/mL | + | 69 | 6 | 22 | 36 | 30 | 6 | 64 | 13 | 19 | 4 |
| | – | 102 | 7 | 46 | 28 | 19 | 0 | 78 | 7 | 4 | 10 |
| >4 ng/mL | (Any) | 489 | 10 | 43 | 32 | 13 | 2 | 82 | 6 | 4 | 7 |
| Any | + | 219 | 11 | 40 | 32 | 15 | 4 | 80 | 6 | 7 | 7 |
| Either test positive (PSA >4 ng/mL or DRE +) | | 556 | 10 | 45 | 31 | 12 | 2 | 83 | 6 | 4 | 7 |

*+ = suspicious for cancer; – = not suspicious for cancer.

†Stage I/II = T1/T2 with N0/NX and M0/MX, stage III = T3 with N0/NX and M0/MX, stage IV = T4 or M1 or N1 or N2 (8,9).

the initial screening round of Prostate Cancer Awareness Week, cancer yields among men receiving biopsy were 31.6% (for men with PSA >4 ng/mL), 25.5% (for men with abnormal DRE), and 14.6% (for men with abnormal DRE and PSA ≤4 ng/mL) (3). For participants in the PSA-2 study initial round, cancer yields among men who underwent biopsy were 35% and 23% for men with abnormal PSA (>4 ng/mL) and abnormal DRE, respectively (10).

As shown in Table 5, the majority (464 men, or 83%) of the 556 men with cancer were diagnosed with clinically localized prostate cancer (T1/T2). Six percent were found to have locally advanced (T3) disease without evidence of nodal or metastatic spread. Four percent were found to have locally advanced (T4) or metastatic (M1 or N1 or N2) disease. The percentage of men with stage III or IV disease increased with increasing PSA level and was generally higher among men with suspicious DRE results. This difference by DRE result was especially pronounced in men with a PSA level higher than 10 ng/mL. These patterns are similar to those found in previous studies. Crawford et al. (3) reported that 89% of cancers diagnosed in men who participated in Prostate Cancer Awareness Week were clinically localized. In that study, as in the PLCO trial, the rate of advanced cancers was higher in men with PSA levels higher than 4 ng/mL. In the PSA-2 study, fewer than 6% of cancers were clinically advanced (T3/T4) at the time of diagnosis (11).

The somewhat lower rate of clinically localized disease found in our study (83%) than in the Prostate Cancer Awareness Week study (89%) may reflect our use of N and M staging, rather than only T staging, to define disease extent. That is, we included men with NX or MX designations along with men with N0 or M0 designations in the T1/T2 and T3 groups because many men, especially those with PSA levels of 4 ng/mL or less and DRE results suggestive of clinically localized disease, did not undergo definitive staging examinations. Men with radiographic evidence of metastatic (M1) or nodal (N1 or N2) disease at the time of diagnosis were classified as such. We feel that the approach of including men with the NX or MX designation in clinically localized groups is justified because radiographic staging studies are often negative and are generally not recommended in these men (12). The fact that, in the PLCO trial, the diagnostic workup was done at the discretion of the subjects' clinicians may also explain why our results (e.g., biopsy rates and the rate of advanced cancers) are different from those of other studies, such as that by Smith et al. (10), which included specific staging protocols.

In the current study, the percentage of prostate cancers with Gleason scores of 7–10 was 47% for men with positive DRE results only, 45% for men with abnormal PSA results only, 54% for men with abnormal results on both tests, and 43% overall. These results are slightly higher than those found in other studies. For example, in a study of men referred for biopsy due to abnormal DRE or PSA test results, Fowler et al. (13,14) found that the percentage of prostate cancers with Gleason scores of 7–10 was 34% in white men with an abnormal DRE and PSA levels of 4 ng/mL or less and 27% in white men with PSA levels higher than 4 ng/mL; blacks had somewhat higher percentages. Among men in the Rotterdam section of the European Randomized Study of Screening for Prostate Cancer (ERSPC) trial with prostate cancer diagnosed at the first round, 36% had Gleason scores of 7–10; in this study, recommendation for biopsy was on the basis of PSA levels higher than 4 ng/mL or an abnormal DRE or ultrasound result (15). The slightly higher rate of cancers with Gleason scores of 7–10 discovered in the first year of the PLCO trial compared with rates in the other two studies could reflect the absence

of a central pathologist and/or differences in prestudy testing rates of men enrolled in the PLCO trial.

Our study results differ from those of some other studies mainly with respect to the percentage of men with positive screens undergoing biopsy and the overall prostate cancer yield. In the Rotterdam section of the ERSPC trial, the prostate cancer diagnosis rate was 4.2% among 4133 men undergoing first-round screening (15). In the PSA-2 study, the detection rate in the initial round of screening was 3.2% among 19 746 white and black volunteers undergoing PSA and DRE screening (10).

The higher detection rate in these studies compared with the initial round of the PLCO trial (1.4%) may be reflected to the higher biopsy rates in these studies (91% for the ERSPC and 78% for the PSA-2 study) than in the PLCO trial (31.5%). Such differences in biopsy rates are to be expected due to the differences in study design across these trials. In the ERSPC trial, follow-up of positive screening results is specified in the protocol; in the PLCO trial, by contrast, men are notified of results and referred to their private health care providers for decisions about subsequent diagnostic workup. Results in the PLCO trial may therefore be more reflective of the medical community's practice patterns with regard to PSA and DRE screening. Nevertheless, because of a potential concern about what might appear to be low biopsy rates in the PLCO trial, a thorough analysis of factors related to prostate biopsy during the first 3 years of follow-up in the PLCO trial has been performed (16). That analysis reinforces the conclusion that contemporary medical judgment is being applied to the diagnostic follow-up of the PLCO trial population because it shows that biopsy rates of PLCO trial participants varied by age in accordance with previously reported strategies to adjust PSA reference ranges by age (17). That analysis also shows that PSA and DRE tests were often repeated at diagnostic follow-up, with the decision for biopsy depending on the results of the repeated tests, a practice recommended in a recent report showing considerable fluctuation of PSA levels (18). Finally, for many men the diagnostic process stretched beyond the 1-year interval covered in the analyses presented here. Within 3 years of a baseline suspicious screen, 64% of men in the PLCO trial underwent biopsy. Thus, in the aggregate, these considerations suggest that men in the PLCO Cancer Screening Trial are being evaluated by contemporary standards within the medical community, indicating that the long-term hypothesis of the trial—that PSA and DRE screening will reduce prostate cancer-specific mortality—is being evaluated in a clinically robust manner. However, the question of reduction in prostate cancer mortality as a result of screening cannot be answered at this early stage in the PLCO trial.

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NOTES

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