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Mortality Results from a Randomized Prostate-Cancer Screening Trial

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Abstract

BACKGROUND—The effect of screening with prostate-specific-antigen (PSA) testing and digital rectal examination on the rate of death from prostate cancer is unknown. This is the first report from the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial on prostate-cancer mortality.

METHODS—From 1993 through 2001, we randomly assigned 76,693 men at 10 U.S. study centers to receive either annual screening (38,343 subjects) or usual care as the control (38,350 subjects). Men in the screening group were offered annual PSA testing for 6 years and digital rectal examination for 4 years. The subjects and health care providers received the results and decided on the type of follow-up evaluation. Usual care sometimes included screening, as some organizations have recommended. The numbers of all cancers and deaths and causes of death were ascertained.

RESULTS—In the screening group, rates of compliance were 85% for PSA testing and 86% for digital rectal examination. Rates of screening in the control group increased from 40% in the first year to 52% in the sixth year for PSA testing and ranged from 41 to 46% for digital rectal examination. After 7 years of follow-up, the incidence of prostate cancer per 10,000 person-years was 116 (2820 cancers) in the screening group and 95 (2322 cancers) in the control group (rate ratio, 1.22; 95% confidence interval [CI], 1.16 to 1.29). The incidence of death per 10,000 person-years was 2.0 (50 deaths) in the screening group and 1.7 (44 deaths) in the control group (rate ratio, 1.13; 95% CI, 0.75 to 1.70). The data at 10 years were 67% complete and consistent with these overall findings.

CONCLUSIONS—After 7 to 10 years of follow-up, the rate of death from prostate cancer was very low and did not differ significantly between the two study groups.

The benefit of screening for prostate cancer with serum prostate-specific-antigen (PSA) testing, digital rectal examination, or any other screening test is unknown. There has been no comprehensive assessment of the trade-offs between benefits and risks. Despite these uncertainties, PSA screening has been adopted by many patients and physicians in the United

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States and other countries. The use of PSA testing as a screening tool has increased dramatically in the United States since 1988.¹ Numerous observational studies have reported conflicting findings regarding the benefit of screening.² As a result, the screening recommendations of various organizations differ. The American Urological Association and the American Cancer Society recommend offering annual PSA testing and digital rectal examination beginning at the age of 50 years to men with a normal risk of prostate cancer and beginning at an earlier age to men at high risk.^{3,4} The National Comprehensive Cancer Network recommends a risk-based screening algorithm, including family history, race, and age.⁵ In contrast, the U.S. Preventive Services Task Force recently concluded that there was insufficient evidence in men under the age of 75 years to assess the balance between benefits and side effects associated with screening, and the panel recommended against screening men over the age of 75 years.⁶

Evidence from randomized trials would be of great assistance in making decisions about whether to pursue prostate-cancer screening. One randomized trial of PSA-based screening reported a benefit, but the results have been generally discounted because of serious methodologic concerns, including a lack of intention-to-screen analysis.⁷ Two ongoing randomized, controlled trials of prostate-cancer screening are being conducted to determine the effect of screening on prostate-cancer mortality: the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial in the United States and the European Randomized Study of Screening for Prostate Cancer (ERSPC).^{8,9} In the United Kingdom, another ongoing trial, the Comparison Arm for the PROTECT (Prostate Testing for Cancer and Treatment) study (CAP), combines the assessment of screening and treatment.¹⁰

The prostate component of the PLCO trial was designed to determine the effect of annual PSA testing and digital rectal examination on mortality from prostate cancer.¹¹ Previous reports have described the results of the baseline round and three later rounds of screening^{12,13} and the characteristics of men undergoing biopsy¹⁴ in the intervention group. This report provides information on prostate-cancer incidence, staging, and mortality in both study groups during the first 7 to 10 years of the study.

METHODS

SUBJECTS

The design of the PLCO trial has been described previously.¹¹ From 1993 through 2001, men and women between the ages of 55 and 74 years were enrolled at 10 study centers across the United States. Each institution obtained annual approval from its institutional review board to carry out the study, and all subjects provided written informed consent. Individual randomization was performed within blocks stratified according to center, age, and sex. The primary exclusion criteria at study entry were a history of a PLCO cancer, current cancer treatment, and, starting in 1995, having had more than one PSA blood test in the previous 3 years.

SCREENING METHODS

Subjects who were assigned to the screening group were offered annual PSA testing for 6 years and annual digital rectal examination for 4 years. PSA tests were analyzed with the Tandem-R PSA assay until January 1, 2004, and with the Access Hybritech PSA after that date (both assays were manufactured by Beckman Coulter). All tests were performed at a single laboratory. As was standard in the United States at the time of the trial's initiation, a serum PSA level of more than 4.0 ng per milliliter was considered to be positive for prostate cancer. Digital rectal examinations were performed by physicians, qualified nurses, or physician assistants. The results of the examinations were deemed to be 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. At study entry, subjects completed a baseline questionnaire that inquired about demographic characteristics and medical and screening histories. In addition, a biorepository for the collection and storage of blood and tissue samples was an integral component of the trial.¹⁵

All men who underwent screening and their health care providers were notified of the PSA value and the results of the digital rectal examination. Men with positive results for the PSA test or suspicious findings on the digital rectal examination were advised to seek diagnostic evaluation. In accordance with standard U.S. practice, diagnostic evaluation was decided by the patients and their primary physicians. Staff members at the PLCO study centers obtained medical records related to diagnostic follow-up of positive screening results, and medical-record abstractors recorded information on relevant diagnostic procedures.

The rate of compliance with screening was calculated as the number of subjects who were screened divided by the number of those who were expected to be screened. Screening outside the trial protocol in the control group was assessed through random surveys. The reasons for and frequency of use of various procedures, including the screening tests under evaluation in the trial, were queried every 1 to 2 years. In each survey, a new random sample of 1% of subjects was chosen. Two groups were identified from responses on the baseline questionnaire: those who had undergone repeated prostate screening in the 3 years before trial entry and those who had not. For the latter, the proportion who reported having had a PSA test as part of a routine physical examination in the previous year was computed; those who had had repeated PSA screenings, who comprised 9.8% of the control group, did not receive the annual surveys during the PLCO study years of screening, and screening was assumed to persist at 100% each year. A weighted average of these two percentages was calculated to provide an estimated overall “contamination” rate for subjects in the control group who underwent screening.

PRIMARY AND SECONDARY END POINTS

Cause-specific mortality for each of the PLCO cancers was the primary end point. In addition, data on PLCO cancer incidence, staging, and survival were collected and monitored as secondary end points. All diagnosed cancers, both PLCO and non-PLCO, and all deaths occurring during the trial were ascertained, primarily by means of a mailed annual questionnaire, which asked about the type of cancer and the date of diagnosis in the previous year. Subjects who did not return the questionnaire were contacted by repeat mailing or telephone.

This active follow-up was supplemented by periodic linkage to the National Death Index to enhance completeness of end-point ascertainment. Clinical stage was determined with the use of the tumor–node–metastasis staging system and categorized according to the fifth edition of the *AJCC* [American Joint Committee on Cancer] *Cancer Staging Manual*.¹⁶ Death certificates were obtained to confirm the death and to provisionally determine the underlying cause. Since the true underlying cause may not always be evident or accurately recorded on the death certificate, the trial used a special end-point adjudication process to assign the cause of death in a uniform and unbiased manner.¹⁷ All deaths from causes that were potentially related to one of the PLCO cancers were reviewed, including any cause of death in which the subject had a PLCO cancer or a possible metastasis from a PLCO cancer and all deaths of unknown or uncertain cause. Reviewers of these deaths were unaware of study-group assignments for deceased subjects.

STATISTICAL ANALYSIS

The primary analysis was an intention-to-screen comparison of prostate-cancer mortality between the two study groups. Event rates were defined as the ratio of the number of events

(cancer diagnoses or deaths) in a given time period to the person-years at risk for the event. Person-years were measured from randomization to the date of diagnosis, death, or data censoring (whichever came first) for incidence rates and to the date of death or censoring (whichever came first) for death rates. Confidence intervals for rate ratios for incidence and mortality were calculated with the use of asymptotic methods, assuming a normal distribution for the logarithm of the ratio and a Poisson distribution for the number of events.¹⁸

From the initiation of the trial, an independent data and safety monitoring board considered reports every 6 months and reviewed the accumulating data. In November 2008, the board unanimously recommended that the current results on prostate-cancer mortality be reported, after notification of study investigators and subjects, on the basis of data showing a continuing lack of a significant difference in the death rate between the two study groups at 10 years (with complete follow-up at 7 years) and information suggesting harm from screening. This recommendation was not the result of crossing a statistical futility boundary but, rather, was triggered by concern that men and their physicians were making decisions on screening on the basis of inadequate information, that the data available from the trial were complete up to 7 years and consistent up to at least 10 years, and that public health considerations dictated that the available results should be made known. However, the monitoring board also supported follow-up of the subjects until all of them had reached at least 13 years of follow-up.

RESULTS

SUBJECTS

The baseline characteristics of the subjects were virtually identical in the two study groups (Table 1). At 7 years, vital status was known for 98% of the men in the two groups (see the Supplementary Appendix, available with the full text of this article at NEJM.org). At 10 years, vital status was known for 67% of the subjects, although 23% had not been enrolled for 10 years. The median duration of follow-up was 11.5 years (range, 7.2 to 14.8) in the two groups.

Compliance with the screening protocol overall was 85% for PSA testing and 86% for digital rectal examination. These findings are similar to the design estimates of 90% for each test. Screening results for the first four rounds were reported previously.¹³ In the control group, the rate of PSA testing was 40% in the first year and increased to 52% in the sixth year; for subjects who reported having undergone no more than one PSA test at baseline (89% of subjects), the rate of PSA testing was 33% in the first year and 46% in the sixth year. The rate of screening by digital rectal examination in the control group ranged from 41 to 46%.

Figure 1A shows the accumulation of cases of prostate cancer in the two study groups. At 7 years, 2 years after the cessation of screening, prostate cancer had been diagnosed in more subjects in the screening group (2820) than in the control group (2322) (rate ratio, 1.22; 95% confidence interval [CI], 1.16 to 1.29). At 10 years, with follow-up complete for 67% of subjects, the excess in the screening group persisted, with 3452 subjects versus 2974 subjects (rate ratio, 1.17; 95% CI, 1.11 to 1.22).

Table 2 shows the characteristics of subjects with prostate cancer in each group, according to the circumstances of detection, through 10 years of follow-up. The large majority of prostate cancers were stage II at diagnosis, regardless of the mode of detection in the screening group; nearly all were adenocarcinomas, and more than 50% had a Gleason score of 5 to 6 (on a scale from 2 to 10, with higher scores indicating more aggressive disease). Overall, the numbers of subjects with advanced (stage III or IV) tumors were similar in the two groups, with 122 in the screening group and 135 in the control group, though the number of subjects with a Gleason score of 8 to 10 was higher in the control group (341 subjects) than in the screening group (289 subjects).

The treatment distributions were similar in the two groups within each tumor stage. For example, among subjects with stage II tumors, as their primary treatment, 44% of the screening group and 40% of the control group underwent prostatectomy, 22% of the screening group and 21% of the control group underwent irradiation alone, and 18% and 21%, respectively, underwent irradiation and hormonal therapy. Among subjects with stage III tumors, 24% of the screening group and 16% of the control group underwent irradiation alone, and 47% and 52%, respectively, underwent irradiation plus hormone therapy. Among subjects with stage IV tumors, 75% of the screening group and 72% of the control group received hormone therapy only. Overall, nearly 11% of the subjects in the screening group and 10% of those in the control group did not undergo any known treatment.

MORTALITY

At 7 years, there were 50 deaths attributed to prostate cancer in the screening group and 44 in the control group (rate ratio, 1.13; 95% CI, 0.75 to 1.70) (Fig. 1B and Table 3). Through year 10, with follow-up complete for 67% of the subjects, the numbers of prostate-cancer deaths were 92 in the screening group and 82 in the control group (rate ratio, 1.11; 95% CI, 0.83 to 1.50). At 10 years, the median follow-up time for subjects with prostate cancer was 6.3 years in the screening group and 5.2 years in the control group.

There was little difference between the two groups in terms of the proportion of deaths according to tumor stage. In the screening group, 60% of the subjects had stage I or II tumors, 2% had stage III tumors, and 36% had stage IV tumors; in the control group, 52% of the subjects had stage I or II tumors, 4% had stage III tumors, and 39% had stage IV tumors.

Analyses within strata according to the screening status at baseline showed no indication of any reduction in prostate-cancer mortality in the screening group, as compared with the control group, in any of the subgroups. Thus, at 7 years, among the 34,755 men in the screening group and 34,590 in the control group who reported having undergone no more than one PSA test at baseline, there were 48 prostate-cancer deaths in the screening group and 41 deaths in the control group (rate ratio, 1.16; 95% CI, 0.76 to 1.76); at 10 years, there were 83 deaths in the screening group and 75 in the control group (rate ratio, 1.09; 95% CI, 0.80 to 1.50). Similarly, among 3588 men in the screening group and 3760 men in the control group who reported having had two or more PSA tests in the previous 3 years at baseline, there were two deaths in the screening group and three deaths in the control group at 7 years (rate ratio, 0.70; 95% CI, 0.12 to 4.17) and nine deaths in the screening group and seven in the control group at 10 years (rate ratio, 1.34; 95% CI, 0.50 to 3.59).

At 7 years, the total numbers of deaths (excluding those from prostate, lung, or colorectal cancers) were 2544 in the screening group and 2596 in the control group (rate ratio, 0.98; 95% CI, 0.92 to 1.03); at 10 years, the numbers of such deaths were 3953 and 4058, respectively (rate ratio, 0.97; 95% CI, 0.93 to 1.01). The distribution of the causes of death was similar in the two groups (Table 4).

SCREENING-RELATED RISKS

Risks incurred from a screening process can result from the screening itself or from downstream diagnostic or treatment interventions. In the screening group, the complications associated with screening were mild and infrequent. Digital rectal examination led to very few episodes of bleeding or pain, at a rate of 0.3 per 10,000 screenings. The PSA test led to complications at a rate of 26.2 per 10,000 screenings (primarily dizziness, bruising, and hematoma) and included three episodes of fainting per 10,000 screenings. Medical complications from the diagnostic process occurred in 68 of 10,000 diagnostic evaluations after positive results on screening. These complications were primarily infection, bleeding, clot formation, and urinary

difficulties. Treatment-related complications, which are generally more serious, include infection, incontinence, impotence, and other disorders. Such complications are now being catalogued in a quality-of-life study and are particularly pertinent in cases of overdiagnosis.

DISCUSSION

We are reporting here for the first time on the PLCO trial with respect to prostate-cancer mortality. At 7 years, screening was associated with a relative increase of 22% in the rate of prostate-cancer diagnosis, as compared with the control group. This increase occurred even though the rate of compliance in screening (85%) was slightly below the level we anticipated in the study design (90%) and there was more-than-expected screening in the control group.

Screening was associated with no reduction in prostate-cancer mortality during the first 7 years of the trial (rate ratio, 1.13), with similar results through 10 years, at which time 67% of the data were complete. However, the confidence intervals around these estimates are wide. The results at 7 years were consistent with a reduction in mortality of up to 25% or an increase in mortality of up to 70%; at 10 years, those rates were 17% and 50%, respectively. There was little difference between the two study groups in the number of deaths from other causes. However, among men with prostate cancer at 10 years, 312 in the screening group and 225 in the control group died from causes other than prostate cancer, and the excess in the screening group was possibly associated with overdiagnosis of prostate cancer.

There are several possible explanations for the lack of a reduction in mortality so far in this trial. First, annual screening with the PSA test using the standard U.S. threshold of 4 ng per milliliter and digital rectal examination to trigger diagnostic evaluation may not be effective. In the ERSPC trial, a PSA cutoff level of 3 ng per milliliter was used, with potentially increased sensitivity but reduced specificity. In our trial, a lower cutoff level might have resulted in the diagnosis of more prostate cancers earlier by screening. It has been shown that cancers that are detected by PSA screening at a level of less than 4 ng per milliliter have a favorable prognosis.⁹ Since increased detection of more of such good-prognosis tumors might have increased the rate of overdiagnosis, such a change probably would have had little or no effect on the rate of death from prostate cancer.

Second, the level of screening in the control group could have been substantial enough to dilute any modest effect of annual screening in the screening group. Although the estimated rate of screening in the control group was higher than the original design estimate of 20%, it was similar to the 38% level anticipated in the protocol revision in 1998.¹¹ To be included in our definition of “PSA contamination,” a subject in the control group needed to have had a PSA test within the past year as part of a routine physical examination. It was thought that such a situation would most closely represent the experience of PSA screening among compliant men in the screening group. However, this definition could be overly restrictive, since PSA testing that occurred outside these measures could still have had an effect on prostate-cancer incidence and mortality in the control group. Nonetheless, in the early years of the study, the level of testing in the screening group was substantially higher than that in the control group, and although the difference lessened later, testing levels remained distinctly higher in the screening group. The screening that occurred in the control group was not enough to eliminate the expected effects of annual screening — such as earlier diagnosis and a persistent excess of cases, largely due to overdiagnosis — in the screening group.

Third, approximately 44% of the men in each study group had undergone one or more PSA tests at baseline, which would have eliminated some cancers detectable on screening from the randomized population, especially in health-conscious men (who tend to be screened more often, a form of selection bias); thus, the cumulative death rate from prostate cancer at 10 years

in the two groups combined was 25% lower in those who had undergone two or more PSA tests at baseline than in those who had not been tested.

Fourth, and potentially most important, improvement in therapy for prostate cancer during the course of the trial probably resulted in fewer prostate-cancer deaths in the two study groups, which blunted any potential benefits of screening.^{19,20} It is important to note that our policy of not mandating specific therapies after cancer detection on screening resulted in substantial similarities in treatment according to tumor stage between the two study groups.

Finally, the follow-up may not yet be long enough for benefit from the earlier detection of an increased number of prostate cancers in the screening group to emerge. Data are accruing on the natural history of screen-detected prostate cancer. Thus, a report from the Rotterdam component of the ERSPC trial suggests a lead time of 12.3 years at the age of 55 years and 6 years at the age of 75 years, with estimated overdiagnosis rates of 27% and 56%, respectively.²¹ Wider application of improvements in prostate-cancer treatment is probably at least in part responsible for declining death rates from prostate cancer in most countries.²² For example, if a patient's life is prolonged by the use of hormone therapy, the opportunities for competing causes of death increase, especially among older men. Computations of lead time provide little information on prognosis, except to the extent that patients with long lead times are likely to have a better prognosis than those with short lead times. In our study, the average lead time achieved by increased early diagnosis through screening was approximately 2 years (Fig. 1A). At 7 years, 73% of prostate cancers had been screen-detected in the screening group. In addition, the possibly emerging reduction in the incidence of tumors with a Gleason score of 8 to 10 in the screening group might portend a future reduction in mortality.

However, we now know that prostate-cancer screening provided no reduction in death rates at 7 years and that no indication of a benefit appeared with 67% of the subjects having completed 10 years of follow-up. Thus, our results support the validity of the recent recommendations of the U.S. Preventive Services Task Force, especially against screening all men over the age of 75 years.⁶

Risks incurred by screening, diagnosis,^{23,24} and resulting treatment^{25–31} of prostate cancer are both substantial and well documented in the literature. To the extent that overdiagnosis occurs with prostate-cancer screening, many of these risks occur in men in whom prostate cancer would not have been detected in their lifetime had it not been for screening. The effect of screening on quality of life is a subject of an ongoing substudy and should be completed within the next several years. Follow-up in the PLCO trial is planned to continue until all subjects reach at least 13 years. A final report will be presented once the planned duration of follow-up is completed.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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APPENDIX

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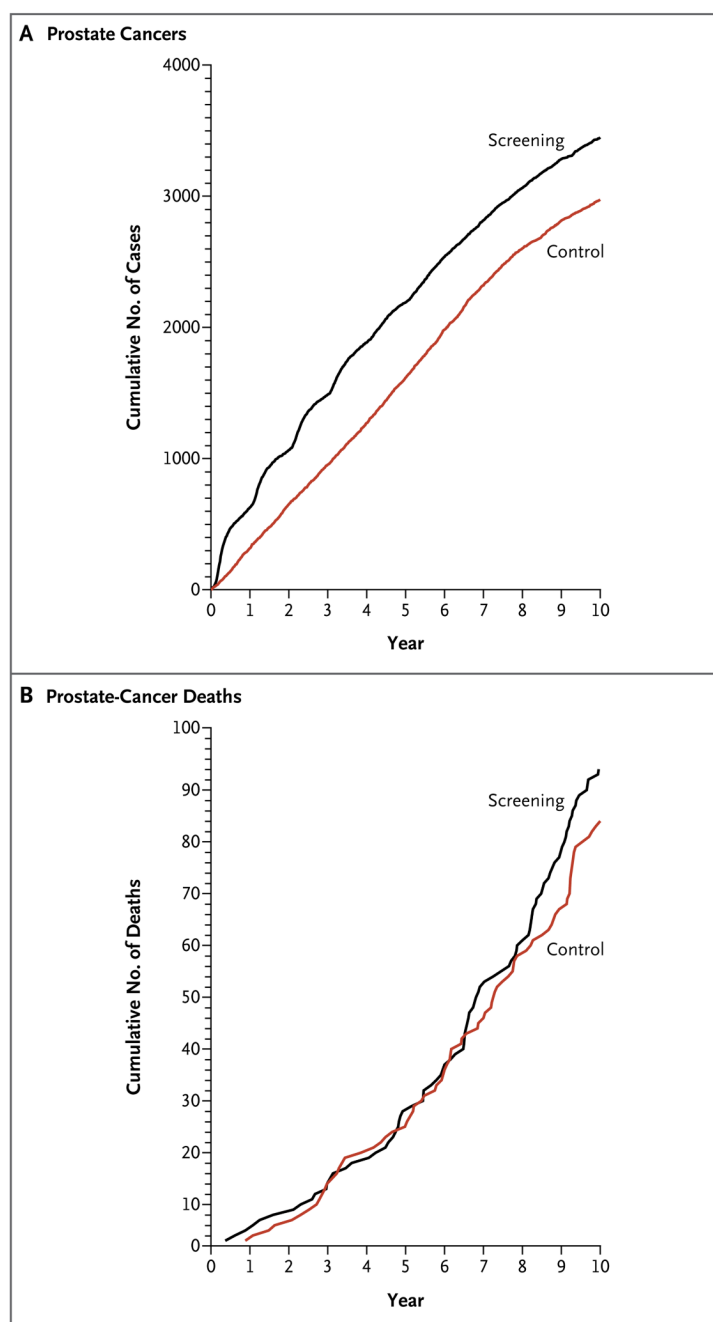


Figure 1. Number of Diagnoses of All Prostate Cancers (Panel A) and Number of Prostate-Cancer Deaths (Panel B).

Table 1

Characteristics of the Subjects at Baseline.*

	Screening Group	Control Group
Variable	(N = 38,343)	(N = 38,350)
<i>percent</i>		
Age		
55–59 yr	32.3	32.3
60–64 yr	31.3	31.3
65–69 yr	23.2	23.2
70–74 yr	13.2	13.2
Race or ethnic group [†]		
Non-Hispanic white	86.2	83.8
Non-Hispanic black	4.5	4.3
Hispanic	2.1	2.1
Asian	4.0	3.9
Other	0.8	0.9
Missing data	2.4	5.0
Enlarged prostate or benign prostatic hyperplasia	21.4	20.5
Previous prostate biopsy	4.3	4.3
Family history of prostate cancer	7.1	6.7
PSA test within past 3 yr		
Once	34.6	34.3
Two or more times	9.4	9.8
Digital rectal examination within past 3 yr		
Once	32.8	31.9
Two or more times	22.2	22.0

* PSA denotes prostate-specific antigen.

[†] Race or ethnic group was self-reported.

Table 2

Tumor Stage, Histopathological Type, and Gleason Score for All Prostate Cancers at 10 Years, According to Method of Detection and Time of Diagnosis.*

Variable	Screening Group				Control Group	
	According to Method of Detection				All Subjects (N = 3452)	All Subjects (N = 2974)
	Never Screened (N = 154)	After Screening (N = 875)	Outside of Screening Protocol (N = 374)	Screen Detected at Baseline (N = 549)	Screen Detected at Yr 1-Yr 5 (N = 1500)	
	number (percent)					
Clinical stage						
I	1 (0.6)	5 (0.6)	8 (2.1)	2 (0.4)	2 (0.1)	15 (0.5)
II	138 (89.6)	838 (95.8)	347 (92.8)	516 (94.0)	1458 (97.2)	2790 (93.8)
III	5 (3.2)	7 (0.8)	3 (0.8)	12 (2.2)	22 (1.5)	56 (1.9)
IV	10 (6.5)	20 (2.3)	9 (2.4)	19 (3.5)	15 (1.0)	79 (2.7)
Unknown	0	5 (0.6)	7 (1.9)	0	3 (0.2)	34 (1.1)
Histopathological type						
Adenocarcinoma						
Any	144 (93.5)	824 (94.2)	346 (92.5)	511 (93.1)	1375 (91.7)	2802 (94.2)
Acinar	9 (5.8)	48 (5.5)	25 (6.7)	36 (6.6)	124 (8.3)	158 (5.3)
Other	1 (0.6)	3 (0.3)	3 (0.8)	2 (0.4)	1 (0.1)	14 (0.5)
Gleason score on biopsy [†]						
2-4	11 (7.1)	1.7 (1.9)	36 (9.6)	64 (11.7)	94 (6.3)	137 (4.6)
5-6	78 (50.6)	500 (57.1)	228 (61.0)	278 (50.6)	963 (64.2)	1656 (55.7)
7	39 (25.3)	252 (28.8)	74 (19.8)	132 (24.0)	318 (21.2)	779 (26.2)
8-10	16 (10.4)	95 (10.9)	25 (6.7)	55 (10.0)	98 (6.5)	289 (8.4)
Unknown	10 (6.5)	11 (1.3)	11 (2.9)	20 (3.6)	27 (1.8)	61 (2.1)

* Subjects with available data for tumor staging but not for nodal status or the presence or absence of metastasis were classified as having stage II disease. Percentages may not total 100 because of rounding.

[†] The Gleason score ranges from 2 to 10, with higher scores indicating more aggressive disease.

Table 3

Death Rates from Prostate Cancer per 10,000 Person-Years at 10 Years.*

Variable	Years after Randomization									
	1	2	3	4	5	6	7	8	9	10
Screening group										
Cumulative deaths — no.	3	6	12	16	26	35	50	59	76	92
Cumulative person-yr— no.	37,864	75,292	112,234	148,635	184,490	219,752	254,295	287,196	316,244	340,230
Death rate	0.8	0.8	1.1	1.1	1.4	1.6	2.0	2.1	2.4	2.7
Control group										
Cumulative deaths — no.	1	4	12	18	23	34	44	56	65	82
Cumulative person-yr— no.	37,838	75,231	112,123	148,444	184,154	219,135	253,317	285,777	314,463	338,083
Death rate	0.3	0.5	1.1	1.2	1.2	1.6	1.7	2.0	2.1	2.4
Rate ratio (95% CI)	3.00 (0.31–28.82)	1.50 (0.42–5.31)	1.00 (0.45–2.22)	0.89 (0.45–1.74)	1.13 (0.64–1.98)	1.03 (0.64–1.65)	1.13 (0.75–1.70)	1.05 (0.73–1.51)	1.16 (0.83–1.62)	1.11 (0.83–1.50)

* Rate ratios are the rates of death in the screening group divided by those in the control group.

Table 4

Causes of Death at 10-Year Follow-up.*

Cause	Screening Group	Control Group
<i>no (%)</i>		
Any [†]	3953 (100.0)	4058 (100.0)
Cancer [†]	916 (23.2)	918 (22.6)
Ischemic heart disease	857 (21.7)	843 (20.8)
Stroke	107 (2.7)	109 (2.7)
Other circulatory disease	684 (17.3)	723 (17.8)
Respiratory disease	415 (10.5)	416 (10.3)
Digestive disease	141 (3.6)	133 (3.3)
Infectious disease	74 (1.9)	85 (2.1)
Endocrine or metabolic disease or immune disorder	155 (3.9)	188 (4.6)
Nervous system disease	128 (3.2)	113 (2.8)
Accident	238 (6.0)	235 (5.8)
Other	238 (6.0)	295 (7.3)

* Causes of death were determined by death certificate.

[†] Causes of death from any cause and cancer do not include prostate, lung, and colorectal cancer.