ORIGINAL ARTICLE

Screening and Prostate-Cancer Mortality in a Randomized European Study

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ABSTRACT

BACKGROUND

The European Randomized Study of Screening for Prostate Cancer was initiated in the early 1990s to evaluate the effect of screening with prostate-specific–antigen (PSA) testing on death rates from prostate cancer.

METHODS

We identified 182,000 men between the ages of 50 and 74 years through registries in seven European countries for inclusion in our study. The men were randomly assigned to a group that was offered PSA screening at an average of once every 4 years or to a control group that did not receive such screening. The predefined core age group for this study included 162,243 men between the ages of 55 and 69 years. The primary outcome was the rate of death from prostate cancer. Mortality follow-up was identical for the two study groups and ended on December 31, 2006.

RESULTS

In the screening group, 82% of men accepted at least one offer of screening. During a median follow-up of 9 years, the cumulative incidence of prostate cancer was 8.2% in the screening group and 4.8% in the control group. The rate ratio for death from prostate cancer in the screening group, as compared with the control group, was 0.80 (95% confidence interval [CI], 0.65 to 0.98; adjusted P=0.04). The absolute risk difference was 0.71 death per 1000 men. This means that 1410 men would need to be screened and 48 additional cases of prostate cancer would need to be treated to prevent one death from prostate cancer. The analysis of men who were actually screened during the first round (excluding subjects with noncompliance) provided a rate ratio for death from prostate cancer of 0.73 (95% CI, 0.56 to 0.90).

CONCLUSIONS

PSA-based screening reduced the rate of death from prostate cancer by 20% but was associated with a high risk of overdiagnosis. (Current Controlled Trials number, ISRCTN49127736.)

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Measurement of serum prostate-specific antigen (PSA), a biomarker for prostate cancer,[1] is useful for the detection of early prostate cancer.[2] Nevertheless, the effect of PSA-based screening on prostate-cancer mortality remains unclear.[3] The European Randomized Study of Screening for Prostate Cancer (ERSPC) was initiated in the early 1990s to determine whether a reduction of 25% in prostate-cancer mortality could be achieved by PSA-based screening.[4] Preliminary data from this study have been published and can be accessed at www.erspc.org. Another randomized screening trial in the United States, the Prostate, Lung, Colon, and Ovarian (PLCO) Cancer Screening Trial, was initiated around the same time, and interim results are also reported in this issue of the *Journal*.[5]

METHODS

STUDY DESIGN

We designed the ERSPC as a randomized, multicenter trial of screening for prostate cancer, with the rate of death from prostate cancer as the primary outcome. An independent data and safety monitoring committee reviewed the trial, and interim analyses were carried out according to a monitoring and evaluation plan in which the outcome of the trial was to be presented to the research group once a statistically significant result corrected for interim analyses was reached.[6,7] The study's protocol was reviewed by local and governmental ethics committees (for details, see Supplementary Appendix 4, available with the full text of this article at NEJM.org).

Recruitment and randomization procedures differed among countries and were developed in accordance with national regulations. In Finland, Sweden, and Italy, the trial subjects were identified from population registries and underwent randomization before written informed consent was provided (population-based effectiveness trial). In the Netherlands, Belgium, Switzerland, and Spain, the target population was also identified from population lists, but when the men were invited to participate in the trial, only those who provided consent underwent randomization (efficacy trial). The results of analyses from two participating countries were not included in this analysis: investigators in Portugal discontinued their participation in October 2000 because they were unable to provide the necessary data, and investigators in France decided to participate in 2001, so data from their analyses were not included because of the short duration of follow-up. Men in whom prostate cancer had been diagnosed (according to data from questionnaires or registries) were ineligible. Within each country, men were assigned to either the screening group or the control group, without the use of blocks of numbers or stratification on the basis of random-number generators (Fig. 1).

At all study centers, the core age group included men between the ages of 55 and 69 years at entry. In addition, in Sweden, study investigators included men between the ages of 50 and 54 years, and investigators in the Netherlands, Italy, Belgium, and Spain included men up to the age of 74 years at entry. In Switzerland, men between the ages of 55 and 69 years were included, with screening up to the age of 75 years. In Finland, men were recruited at the ages of 55, 59, 63, and 67 years and were screened until the age of 71 years. Screening was discontinued in all other centers when the chosen upper age limit was reached. The validity of randomization was determined by comparing the age distributions and the rates of death from any cause in the two study groups.

At centers in all countries except Finland, subjects were randomly assigned in a 1:1 ratio to the

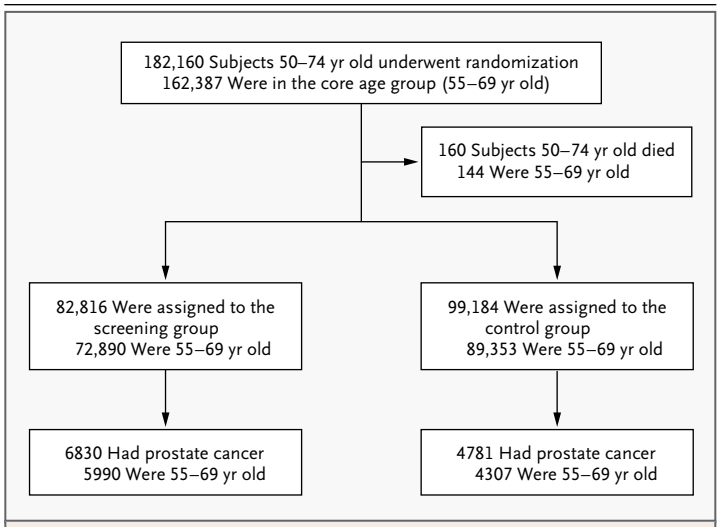

Figure 1. Enrollment and Outcomes, According to Age Group at Randomization. The predefined core age group for this study included 162,243 men between the ages of 55 and 69 years.

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screening group or the control group. In Finland, the size of the screening group was fixed at 32,000 subjects. Because the whole birth cohort underwent randomization, this led to a ratio, for the screening group to the control group, of approximately 1:1.5.

Each center reported data on recruitment, screening, and mortality twice a year to a central data center. Several task forces and working groups were responsible for quality assurance, including an epidemiology committee, a quality-control committee, a pathology committee, and a PSA committee.[7] The data and safety monitoring committee had oversight of the trial, with a mandate to stop the trial on demonstrating a significant difference between the groups or adverse effects of screening. The monitoring committee received reports on the progress of the trial, including prostate-cancer mortality. Causes of death, which were obtained from registries and individual chart review, were assigned according to definitions and procedures developed for the trial. A committee that analyzed causes of death was formed at each center, and an international committee coordinated the work of these national committees.[8,9]

SCREENING TESTS AND INDICATIONS FOR BIOPSY

Total PSA was measured with the use of Hybritech assay systems (Beckman Coulter). From 1994 through 2000, the Tandem E assay was used, and thereafter the Access assay, with the original Hybritech calibration always applied.[10]

Most centers used a PSA cutoff value of 3.0 ng per milliliter as an indication for biopsy. In Finland, a PSA value of 4.0 ng per milliliter or more was defined as positive and the men were referred for biopsy; those with a value of 3.0 to 3.9 ng per milliliter underwent an ancillary test — digital rectal examination until 1998 and calculation of the ratio of the free PSA value to the total PSA value (with a value of ≤0.16) starting in 1999 — and were referred for biopsy if the test was positive. In Italy, a PSA value of 4.0 ng per milliliter or more was defined as positive, but men with a PSA value of 2.5 to 3.9 ng per milliliter also underwent ancillary tests (digital rectal examination and transrectal ultrasonography).

In the Dutch and Belgian centers, up to February 1997, a combination of digital rectal examination, transrectal ultrasonography, and PSA testing (with a cutoff value of 4.0 ng per milliliter) was used for screening; in 1997, this combination was replaced by PSA testing only.[7,11,12] In Belgium, where the results of a pilot study (from 1991 to 1994) were included in the final data set up to 1995, a PSA cutoff value of 10.0 ng per milliliter was used initially. Most centers used sextant biopsies guided by transrectal ultrasonography. As of June 1996, lateralized sextant biopsies were recommended.[13] In Italy, transperineal sextant biopsies were used. In Finland, a biopsy procedure with 10 to 12 biopsy cores was adopted in 2002 as a general policy for the two study groups.

The screening interval at six of the seven centers was 4 years (accounting for 87% of the subjects); Sweden used a 2-year interval. In Belgium, the interval between the first and second rounds of screening was 7 years because of an interruption in funding.

PATHOLOGICAL EVALUATION

The primary evaluation of specimens from biopsies and radical prostatectomies was performed by local pathologists. Central review of the pathological analyses was not carried out. However, standardization of procedures was coordinated and achieved by the work of the international pathology committee. (For details on the committee and its functions, see Supplementary Appendix 3.)

TREATMENT POLICIES

The treatment of prostate cancer was performed according to local policies and guidelines. The equality of distribution of treatments that were applied to the screening group and the control group has been evaluated, with little indication of differences between the two study groups after adjustment for disease stage, tumor grade, and age (data not shown).[14]

FOLLOW-UP

Follow-up for mortality analyses began at randomization and ended at death, emigration, or a uniform censoring date (December 31, 2006), with identical follow-up in the two study groups. Causes of death were evaluated in a blinded fashion and according to a standard algorithm[9] or, after validation, on the basis of official causes of death. The causes were classified by the independent committees as definite prostate cancer, causes related to screening, probable or possible prostate cancer, and other intercurrent causes (with or without prostate cancer as a contributory factor). Deci-

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sion points that were used for determining the cause of death have been described previously.[9] For this analysis, we have combined the categories of definite and probable prostate cancer and the category of causes related to screening.

OTHER ANALYSES

Aspects of quality of life were evaluated in several study centers. A complete evaluation of all the steps of screening was conducted in the Netherlands (data not shown).[15-21]

STATISTICAL ANALYSIS

The statistical analysis was based on the core age group (including men between the ages of 55 and 69 years at randomization) and on the intention-to-screen principle. Overall mortality was studied to evaluate the correctness of randomization. Poisson regression analysis was used to estimate the ratio of mortality in the intervention group to mortality in the control group, stratified according to study center and age group at randomization. The Nelsen–Aalen method was used for the calculation of cumulative hazard.[22] All P values are two-sided. Interim analyses were conducted for follow-up in 2002, 2004, and 2006, with an alpha spending curve with a division of uneven weights.[23] A preliminary analysis included men who had actually undergone screening in the first round (with adjustment for noncompliance). The number that would need to be screened to prevent one death from prostate cancer was calculated as the inverse of the absolute difference in cumulative mortality from prostate cancer between the two study groups.

The study had a power of 86% to show a statistically significant difference of 25% or more in prostate-cancer mortality with a P value of 0.05 among men who underwent screening, on the basis of follow-up through 2008.[4] The sample-size calculation, which was part of the power calculation, took into account noncompliance in the screening group in each study center and the use of PSA tests outside the protocol assignment in the control group (termed contamination of the control group). On the basis of an overall level of compliance of 82% and 20% contamination in the control group, a 25% reduction in the number of men who underwent screening would be equivalent to a 14% reduction in an intention-to-treat analysis. This assumes that men who were screened and those who were not screened had the same underlying risk and that screening in the control group was as effective as that in the screening group.

RESULTS

SUBJECTS

Figure 1 shows trial enrollment, study-group assignments, and follow-up of all subjects and of the core age group. A total of 162,387 men in the core age group underwent randomization; of these men, 72,952 were assigned to the screening group and 89,435 to the control group. A total of 62 men in the screening group and 82 men in the control group died between identification and randomization.

Table 1 summarizes the characteristics of the subjects according to the center and the results of screening. The mean age at randomization was 60.8 years (range, 59.6 to 63.0), with little variation among the seven countries. In total, 82.2% of the men in the screening group were screened at least once. Compliance was higher in study centers that obtained consent before randomization (88 to 100%) than in those in which subjects underwent randomization before providing consent (62 to 68%) (for details concerning all age groups, see Table 1A in Supplementary Appendix 5).

During the trial, 126,462 PSA-based tests were performed, an average of 2.1 per subject who underwent screening. Overall, 16.2% of all tests were positive, with a range of 11.1 to 22.3% among the centers. The average rate of compliance with biopsy recommendations was 85.8% (range, 65.4 to 90.3). Of the men who underwent biopsy for an elevated PSA value, 13,308 (75.9%) had a false positive result.

We detected 5990 prostate cancers in the screening group and 4307 in the control group. These numbers correspond to a cumulative incidence of 8.2% and 4.8%, respectively. The positive predictive value of a biopsy (the number of cancers detected on screening divided by the number of biopsies expressed as a percentage) was on average 24.1% (range, 18.6 to 29.6). The cumulative incidence of local prostate cancer was higher in the screening group than in the control group (for details about tumor stage, grade distribution, and treatment, see Supplementary Appendixes 6 and 7). For example, the number of men with positive results on a bone scan (or a PSA value of more than 100 ng per milliliter in those without bone-scan results) was 0.23 per 1000

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Table 1. Numbers of Subjects and Results of Screening, According to Study Center.*

Variable	The Netherlands	Belgium	Sweden	Finland	Italy	Spain	Switzerland	Total
	November 1993–March 2000	June 1991–December 2003	June 1991–December 2003	January 1996–January 1999	October 1996–October 2000	February 1996–June 1999	September 1998–August 2003	June 1991–December 2003
Total no. of subjects	34,833	8562	11,852	80,379	14,517	2197	9903	162,243
Screening group — no. (%)	17,443 (50.1)	4307 (50.3)	5,901 (49.9)	31,970 (39.8)	7,265 (50.0)	1056 (48.1)	4948 (50.0)	72,890 (44.9)
Control group — no. (%)	17,390 (49.9)	4255 (49.7)	5,951 (50.1)	48,409 (60.2)	7,252 (50.0)	1141 (51.9)	4955 (50.0)	89,353 (55.1)
Age at randomization — yr								
All subjects								
Mean	61.9	63.0	59.8	59.6	62.2	61.0	61.6	60.8
Median	61.7	63.0	59.7	58.7	61.8	60.4	61.1	60.1
Screening group								
Mean	61.9	63.0	59.8	59.6	62.2	60.5	61.6	60.9
Median	61.7	63.0	59.7	58.7	61.7	59.7	61.0	60.3
Control group								
Mean	62.0	63.0	59.8	59.6	62.2	61.4	61.7	60.7
Median	61.7	63.1	59.7	58.7	61.9	61.1	61.2	59.9
First round of screening — no. (%)	16,502 (94.6)	3795 (88.1)	3,649 (61.8)	20,796 (65.0)	4,961 (68.3)	1056 (100)	4721 (95.4)	55,480 (76.1)
Screening interval — yr	4	4–7	2	4	4	4	4	NA
Screened at least once — no. (%)	16,502 (94.6)	3876 (90.0)	4,466 (75.7)	23,608 (73.8)	5,675 (78.1)	1056 (100)	4740 (95.8)	59,923 (82.2)
No. of screening tests performed	34,526	6042	14,848	48,900	11,377	1846	8923	126,462
Positive PSA tests — no. (%)	7,707 (22.3)	984 (16.3)	2,751 (18.5)	5,528 (11.3)	1,267 (11.1)	354 (19.2)	1846 (20.7)	20,437 (16.2)
Biopsies — no. (%)	6,929 (89.9)	728 (74.0)	2,382 (86.6)	4,991 (90.3)	828 (65.4)	263 (74.3)	1422 (77.0)	17,543 (85.8)
Prostate cancers								
Total detected in screening group — no. (%)	1,736 (10.0)	363 (8.4)	697 (11.8)	2,493 (7.8)	280 (3.9)	68 (6.4)	353 (7.1)	5,990 (8.2)
Detected during screening — no.	1,521	182	550	1,477	180	60	265	4,235
Detected outside of screening protocol — no.	215	181	147	1,016	100	8	88	1,755
Positive predictive value of screening — %†	22.0	25.0	23.1	29.6	21.7	22.8	18.6	24.1
Total detected in control group — no. (%)	685 (3.9)	252 (5.9)	421 (7.1)	2,632 (5.4)	133 (1.8)	24 (2.1)	160 (3.2)	4,307 (4.8)

* The results are for the predefined core age group for this study, which included men between the ages of 55 and 69 years. The dates that are listed for each country are the periods in which subjects underwent randomization. NA denotes not applicable, and PSA prostate-specific antigen.
† The positive predictive value of biopsy was calculated as the number of screen-detected cancers divided by the number of biopsies.

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person-years in the screening group, as compared with 0.39 per 1000 person-years in the control group, a 41% reduction in the screening group (P<0.001). The proportions of men who had a Gleason score of 6 or less were 72.2% in the screening group and 54.8% in the control group, and the proportions with a Gleason score of 7 or more were 27.8% in the screening group and 45.2% in the control group.

PROSTATE-CANCER MORTALITY

As of December 31, 2006, with average and median follow-up times of 8.8 and 9.0 years in the screening and control groups, respectively, there were 214 prostate-cancer deaths in the screening group and 326 in the control group in the core age group. Deaths that were associated with prostate-cancer–related interventions were categorized as deaths from prostate cancer. The unadjusted rate ratio for death from prostate cancer in the screening group was 0.80 (95% confidence interval [CI], 0.67 to 0.95; P=0.01); after adjustment for sequential testing with alpha spending due to two previous interim analyses (based on Poisson regression analysis), the rate ratio was 0.80 (95% CI, 0.65 to 0.98; P=0.04). The rates of death in the two study groups began to diverge after 7 to 8 years and continued to diverge further over time (Fig. 2). Overall mortality results at 30 days are summarized in Supplementary Appendix 8.

In the intention-to-screen analysis, the absolute difference between the screening group and the control group was 0.71 prostate-cancer death per 1000 men. This means that in order to prevent one prostate-cancer death, the number of men who would need to be screened would be 1410 (95% CI, 1142 to 1721), with an average of 1.7 screening visits per subject during a 9-year period. The additional prostate cancers diagnosed by screening resulted in an increase in cumulative incidence of 34 per 1000 men, as compared with the control group. In other words, 48 additional subjects (1410÷1000×34) would need to be treated to prevent one death from prostate cancer.

In an analysis of men who were actually screened during the first round (which was adjusted for noncompliance), the rate ratio for prostate-cancer death after 9 years was 0.73 (95% CI, 0.56 to 0.90), which meant that 1068 men would need to be screened and 48 would need to be treated to prevent one death from prostate cancer. The number of men who would need to be treated (48) remained unchanged in the per-protocol analysis because the same number of deaths were prevented and the same number of additional cases were diagnosed in men who actually underwent screening.

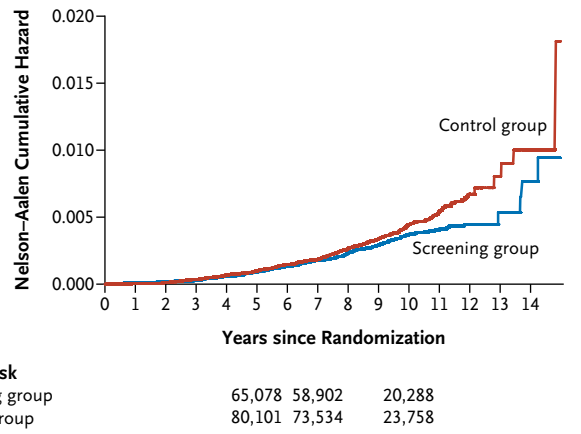

Figure 2. Cumulative Risk of Death from Prostate Cancer.
As of December 31, 2006, with an average follow-up time of 8.8 years, there were 214 prostate-cancer deaths in the screening group and 326 in the control group. Deaths that were associated with interventions were categorized as being due to prostate cancer. The adjusted rate ratio for death from prostate cancer in the screening group was 0.80 (95% CI, 0.65 to 0.98; P=0.04). The Nelsen–Aalen method was used for the calculation of cumulative hazard.

EFFECT OF AGE ON MORTALITY

In an exploratory analysis of mortality according to age group, there was no evidence of heterogeneity among age groups (Table 2). Among men between the ages of 50 and 54 years at baseline, the number of events was small, with no obvious screening effect.

HETEROGENEITY OF RATE RATIOS

In an exploratory analysis of heterogeneity according to study center (which was carried out in accordance with the monitoring plan[6]), the decrease in the rate of death from prostate cancer in the screening group could not be attributed to any single center, as evidenced by rate ratios ranging between 0.74 and 0.84 after the exclusion of each center, one at a time. There was no significant difference in overall mortality (Table 3).

ADVERSE EVENTS

No deaths were reported as a direct complication (e.g., septicemia or bleeding) associated with a

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Table 2. Death from Prostate Cancer, According to the Age at Randomization.*

Age at Randomization	Screening Group		Control Group		Rate Ratio (95% CI)†
	No. of Deaths	Person-Yr (Death Rate per 1000 Person-Yr)	No. of Deaths	Person-Yr (Death Rate per 1000 Person-Yr)	
All subjects	261	737,397 (0.35)	363	878,547 (0.41)	0.85 (0.73–1.00)
Age group					
50–54 yr	6	55,241 (0.11)	4	53,734 (0.07)	1.47 (0.41–5.19)
55–59 yr	60	316,389 (0.19)	102	402,062 (0.25)	0.73 (0.53–1.00)
60–64 yr	76	191,542 (0.40)	95	221,113 (0.43)	0.94 (0.69–1.27)
65–69 yr	78	135,470 (0.58)	129	162,410 (0.79)	0.74 (0.56–0.99)
70–74 yr	41	38,755 (1.06)	33	39,228 (0.84)	1.26 (0.80–1.99)

* The result of the chi-square test for heterogeneity among subjects in the core age group (55 to 69 years) was 2.44 (P=0.49).
† Rate ratios were calculated with the use of Poisson regression and compare the rate of death from prostate cancer in the screening group with the rate in the control group.

biopsy procedure. Complications associated with screening procedures (including prostate biopsy) have been reported previously.[24,25]

DISCUSSION

In an intention-to-screen analysis of data from seven European centers, PSA screening was associated with a significant absolute reduction of 0.71 prostate-cancer death per 1000 men after an average follow-up of 8.8 years (median, 9.0). This finding corresponds to a relative reduction of 20% in the rate of death from prostate cancer among men between the ages of 55 and 69 years at study entry, given an average screening interval of 4 years and a compliance rate of 82% of those who accepted the offer of screening (rate ratio, 0.80; adjusted P=0.04). To prevent one prostate-cancer death, 1410 men (or 1068 men who actually underwent screening) would have to be screened, and an additional 48 men would have to be treated. The high number of men who would need to be treated could be improved by avoiding the diagnosis and treatment of indolent cancers during screening or by improving treatment in the remaining men with cancer. The number needed to screen in our study is similar to that in studies of mammographic screening for breast cancer and fecal occult-blood testing for colorectal cancer.[26,27]

Our analysis shows that the results were generally similar in all participating study centers considered individually (Table 3). The trial was not powered to evaluate mortality differences between centers or for age subgroups. The results were based on a combined analysis of data from centers sharing a common core protocol, which defined the minimal criteria for inclusion and the scope of the primary analysis but allowed wider age ranges or shorter screening intervals. Because of various recruitment approaches, the estimate of a 20% reduction in prostate-cancer mortality does not represent the effect of a screening program at the population level or the effect on individual subjects but instead represents a mixture of such estimates. Despite some variation in screening procedures, the results from each center were compatible with the main result: a lowering of the death rate from prostate cancer associated with screening.

The screening interval of 4 years was chosen on the basis of the mean lead time of 5 to 10 years in PSA-based screening.[28,29] However, the lead time of aggressive cancers, which may be the most important target of screening, is likely to be much shorter.

The benefit of screening was restricted to the core age group of subjects who were between the ages of 55 and 69 years at the time of randomization. The results that were seen in other age groups are preliminary and inconclusive. Our findings are early results of the trial, and continued follow-up will provide further information. Adjustment for noncompliance resulted in a greater effect among men who actually underwent screening, and after adjustment for both noncompliance and contamination, the effect of screening in the intention-to-screen analysis is likely to be further enhanced.

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Table 3. Rate Ratios for Death from Any Cause and Death from Prostate Cancer, with Exclusions According to Location of Study Center.*

Variable	Rate Ratio (95% CI)	P Value†
All deaths from any cause	0.99 (0.97–1.02)	0.50
All deaths from prostate cancer	0.80 (0.67–0.95)	0.01
Excluding the Netherlands	0.81 (0.67–0.99)	0.04
Excluding Finland	0.74 (0.58–0.94)	0.01
Excluding Sweden	0.84 (0.70–1.01)	0.06
Excluding Belgium	0.79 (0.66–0.94)	0.01
Excluding Spain	0.79 (0.67–0.94)	0.01
Excluding Italy	0.79 (0.66–0.94)	0.01
Excluding Switzerland	0.80 (0.68–0.96)	0.02

* Rate ratios, which were calculated with the use of Poisson regression, compare the rate of death from prostate cancer in the screening group with the rate in the control group. The calculations were restricted to men in the core age group (55 to 69 years).

† P values have not been corrected for multiple testing.

The rate of overdiagnosis of prostate cancer (defined as the diagnosis in men who would not have clinical symptoms during their lifetime) has been estimated to be as high as 50% in the screening group.[30] Consistent estimates of overdiagnosis (a third of cancers detected on screening) have also been obtained by identifying potentially indolent prostate cancers on the basis of clinical and pathological characteristics.[31-33] Overdiagnosis and overtreatment are probably the most important adverse effects of prostate-cancer screening and are vastly more common than in screening for breast, colorectal, or cervical cancer.[34]

Although the results of our trial indicate a reduction in prostate-cancer mortality associated with PSA screening, the introduction of population-based screening must take into account population coverage, overdiagnosis, overtreatment, quality of life, cost, and cost-effectiveness. The ratio of benefits to risks that is achievable with more frequent screening or a lower PSA threshold than we used remains unknown. Further analyses are needed to determine the optimal screening interval in consideration of the PSA value at the first screening and of previously negative results on biopsy.[35-38]

A video roundtable and comments on the value of PSA screening are available at NEJM.org

Supported by grants from Europe Against Cancer and the fifth and sixth framework program of the European Union, by grants from agencies or health authorities in the participating countries, and by unconditional grants from Beckman Coulter. The studies in each national center were funded by numerous local grants (see Supplementary Appendix 2).

Dr. Hugosson reports receiving lecture fees from GlaxoSmithKline; Dr. Tammela, receiving consulting or lecture fees from GlaxoSmithKline, Pfizer, AstraZeneca, Leiras, and Novartis; and Dr. Lilja, holding a patent for an assay for free PSA. No other potential conflict of interest relevant to this article was reported.

APPENDIX

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