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## Prostate-Cancer Mortality at 11 Years of Follow-up

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### ABSTRACT

#### BACKGROUND

Several trials evaluating the effect of prostate-specific antigen (PSA) testing on prostate-cancer mortality have shown conflicting results. We updated prostate-cancer mortality in the European Randomized Study of Screening for Prostate Cancer with 2 additional years of follow-up.

#### METHODS

The study involved 182,160 men between the ages of 50 and 74 years at entry, with a predefined core age group of 162,388 men 55 to 69 years of age. The trial was conducted in eight European countries. Men who were randomly assigned to the screening group were offered PSA-based screening, whereas those in the control group were not offered such screening. The primary outcome was mortality from prostate cancer.

#### RESULTS

After a median follow-up of 11 years in the core age group, the relative reduction in the risk of death from prostate cancer in the screening group was 21% (rate ratio, 0.79; 95% confidence interval [CI], 0.68 to 0.91;  $P=0.001$ ), and 29% after adjustment for noncompliance. The absolute reduction in mortality in the screening group was 0.10 deaths per 1000 person-years or 1.07 deaths per 1000 men who underwent randomization. The rate ratio for death from prostate cancer during follow-up years 10 and 11 was 0.62 (95% CI, 0.45 to 0.85;  $P=0.003$ ). To prevent one death from prostate cancer at 11 years of follow-up, 1055 men would need to be invited for screening and 37 cancers would need to be detected. There was no significant between-group difference in all-cause mortality.

#### CONCLUSIONS

Analyses after 2 additional years of follow-up consolidated our previous finding that PSA-based screening significantly reduced mortality from prostate cancer but did not affect all-cause mortality. (Current Controlled Trials number, ISRCTN49127736.)

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\*Investigators in the European Randomized Study of Screening for Prostate Cancer (ERSPC) are listed in the Supplementary Appendix, available at [NEJM.org](http://NEJM.org).

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SCREENING FOR PROSTATE CANCER HAS remained controversial, despite results showing a significant reduction in the rate of death from prostate cancer (relative reduction, 20%) among men offered screening for prostate-specific antigen (PSA).<sup>1</sup> The European Randomized Study of Screening for Prostate Cancer (ERSPC) is a multicenter trial initiated in 1991 in the Netherlands and in Belgium, with five more European countries (Sweden, Finland, Italy, Spain, and Switzerland) joining between 1994 and 1998. Recruitment was completed in these centers between 1995 and 2003. Later, France also joined, with enrollment in 2000–2005, but data from the French cohort were not included in the present analysis because of a short follow-up period (median, 4.6 years). Here we report mortality results from the ERSPC at 11 years of follow-up, adding 2 more years to the initial analysis.

## METHODS

### STUDY DESIGN

The trial protocol, which has been described previously,<sup>1,2</sup> is available with the full text of this article at NEJM.org. A core age group of men between the ages of 55 and 69 years at entry was defined in the trial protocol in 1994.<sup>3</sup> Screening was carried out at an interval of 4 years (2 years in Sweden).

The principal screening test was measurement of the serum PSA level with the use of the Tandem-R/Tandem-E/Access assay (Hybritech). A positive test result, defined as a PSA value of 3.0 ng per milliliter or higher, was an indication for biopsy in most centers. Sextant prostatic biopsies were recommended for all men with positive test results; lateralized sextant biopsies<sup>4</sup> were adopted in June 1996. Some exceptions to these procedures have been described previously.<sup>1</sup>

### PRIMARY END POINTS

The primary end point of the trial was prostate-cancer mortality. We evaluated deaths among men in both the screening group and the control group in whom prostate cancer was diagnosed (including cases that were first diagnosed at autopsy), regardless of the official cause of death, as described previously.<sup>1,5</sup> Data on overall mortality were collected by linkage to the national registries. Each trial center followed the common core protocol and provided key data to the joint independent data center every 6 months. The independent data monitoring committee received updates every 6 months ac-

ording to a predefined monitoring and evaluation plan.<sup>6</sup>

### STATISTICAL ANALYSIS

We determined the sample size that would be required to show a reduction of 25% in mortality ( $P < 0.05$ ) among men who actually underwent screening, with a power of 80% at 10 years of follow-up.<sup>7</sup> Hence, the primary analysis was planned at the outset on the basis of follow-up of at least 10 years, which was reached with data through 2008. The current analyses include follow-up data through 2008 and follows the third interim monitoring analysis, which showed a significant reduction in mortality from prostate cancer among men undergoing PSA screening.<sup>1</sup> We included the French data in the analysis of PSA test results but not in the analyses of the incidence of prostate cancer or mortality according to time period, since the follow-up period was short in France.

The main analyses were based on the core age group of men between the ages of 55 and 69 years at randomization. Besides the intention-to-screen analysis, we performed a hypothesis-generating secondary analysis, which was limited to men who actually underwent screening and was corrected for selection bias,<sup>8</sup> to show the effect among screened men. We used the Nelson–Aalen method<sup>9</sup> to calculate the cumulative hazard of death from prostate cancer or from any cause. A Forest plot and Kaplan–Meier curves of prostate cancer–specific survival were constructed according to standard techniques. All reported *P* values are two-sided, and there was no adjustment for significance on the basis of previous analyses because the present analysis was not driven by statistical significance but was protocol-based.<sup>10,11</sup> We used Poisson regression analysis to calculate rate ratios, which were adjusted according to center.

We calculated the number of men who would need to be invited (NNI) to undergo screening in order to prevent one death from prostate cancer as the inverse of the absolute risk reduction among men who underwent randomization and for whom follow-up was restricted to 9 and 11 years. Where applicable, we calculated results with the control population for Finland weighted by 1:1.5 to account for the ratio of study-group assignments. We calculated the number of prostate cancers that would need to be detected (NND) in order to prevent one death as the inverse absolute risk reduction multiplied by excess incidence in the screening group for the same time periods, as well

as for all available follow-up data.<sup>1</sup> The terminology was changed from number needed to screen (NNS) and number needed to treat (NNT) because the definitions differed from the previous report and more correctly reflected the choice of data included in the calculations. (NNI is calculated from the intention-to-screen analysis and involves men who were invited but not screened, and NND is different from NNT in treatment trials.)

## RESULTS

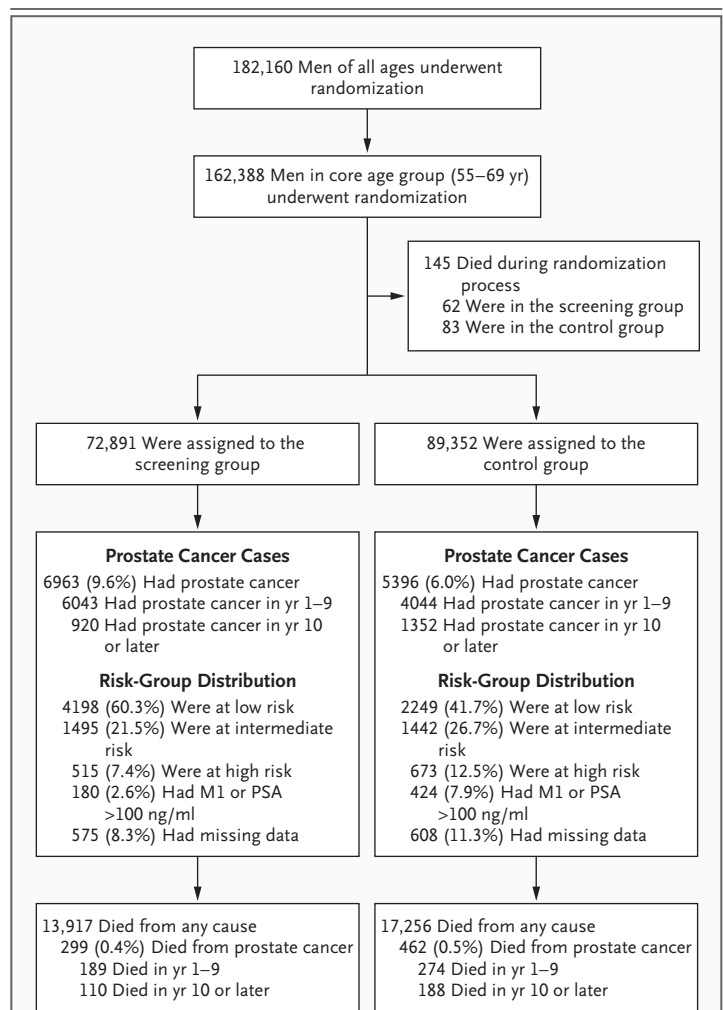
### STUDY SUBJECTS

Recruitment in the ERSPC trial was completed by 2003 in the centers that were included in the mortality analysis, and hence, the number of subjects remained almost unchanged since the first mortality analysis<sup>1</sup> (a total of 182,160 men, of whom 162,388 were in the core age group) (Fig. 1). During the 2 additional years of follow-up, screening continued in the Netherlands, Sweden, Italy, Switzerland, and France but was discontinued after three screening rounds in Belgium, Finland, and Spain (Table 1; and Table 1A in the Supplementary Appendix, available at NEJM.org).

### TEST RESULTS AND INCIDENCE OF PROSTATE CANCER

In the core age group, 136,689 screening tests were performed (average, 2.27 per subject). Of these tests, 16.6% were positive, and 85.9% of the men with positive tests underwent prostate biopsy. The median screening interval was 4.02 years. A total of 6963 prostate cancers were diagnosed in the screening group (cumulative incidence, 9.6%) and 5396 in the control group (cumulative incidence, 6.0%), with approximately 1000 additional cases of prostate cancer in each study group, as compared with our earlier analysis.<sup>1</sup>

With follow-up through 2008, the mean and median durations of follow-up for the core age group were 10.5 and 11.0 years, respectively. The incidence of prostate cancer during the entire follow-up was 9.66 cases per 1000 person-years in the screening group and 5.95 cases per 1000 person-years in the control group (rate ratio in the screening group, 1.63; 95% confidence interval [CI], 1.57 to 1.69), with a rate difference of 3.71 cases per 1000 person-years (95% CI, 3.44 to 3.99) (Table 2). Data for years 0 through 9 are not identical to those in our previous report because continued follow-up in the centers with late entry contributed to the data for this period. The excess



**Figure 1. Enrollment and Outcomes.**

Among subjects in whom prostate cancer was diagnosed, low risk was defined as a tumor stage of either T1 (tumor is present but not detectable clinically or with imaging) or T2 (tumor can be palpated on examination but has not spread outside the prostate) with a Gleason score of 6. Intermediate risk was defined as a tumor stage of T1 or T2 with a Gleason score of 7 or T3 (tumor has spread through the prostatic capsule) with a Gleason score of 7. High risk was defined as a tumor stage of T1, T2, or T3 with a Gleason score of 8 to 10 or T4 (tumor has invaded nearby structures) with any Gleason score. The Gleason score is the sum of the scores for the two most common histologic patterns or grades in a prostate tumor, each of which is graded on a scale of 1 to 5, with 5 being the most histologically aggressive. M1 denotes distant metastasis, and PSA prostate-specific antigen. Additional details regarding prognostic factors are provided in Table 2 in the Supplementary Appendix. Excluded from the total number of subjects were 145 men who submitted their consent forms but died before the randomization process was finalized.

incidence in the screening group was largely due to small, well-differentiated tumors, and the incidence of advanced tumors (stage T3 or T4 or with distant metastasis) and aggressive cancers

**Table 1. Results of Prostate-Cancer Screening in Men 55 to 69 Years of Age, According to Center.\***

Subjects and Screening Results	Netherlands	Belgium	Sweden	Finland
	November 1993– March 2000	June 1991– December 2003	Dec 31, 2004†	January 1996– January 1999
<b>Subjects</b>				
Total no.	34,833	8562	11,852	80,379
Assigned to control group — no. (%)	17,390 (49.9)	4255 (49.7)	5951 (50.2)	48,409 (60.2)
Assigned to screening group — no. (%)	17,443 (50.1)	4307 (50.3)	5901 (49.9)	31,970 (39.8)
Screened at least once — no. (%)	16,502 (94.6)	3908 (90.7)	4484 (76.0)	23,771 (74.4)
Total no. of screenings	37,375	6438	15,474	52,142
Positive tests — no. (%)	8,892 (23.8)	1055 (16.4)	2897 (18.7)	5,925 (11.4)
Biopsies — no. (% with positive results)	7,989 (89.8)	750 (71.1)	2509 (86.6)	5,397 (91.1)
<b>Prostate cancers</b>				
Screening group				
Total no. detected	2028	420	759	2838
No. detected during screening	1730	187	576	1631
No. detected between screenings or in unscreened subjects‡	298	233¶	183	1207
Positive predictive value — %	21.7	24.9	23.0	30.2
Cumulative incidence — %**	11.6	9.8	12.9	8.9
Control group				
Total no. detected	896	311	507	3175
Cumulative incidence — %**	5.2	7.3	8.5	6.6
<b>Follow-up</b>				
Mean — yr	10.7	11.1	12.5	10.4
Median — yr	11.1	12.1	14.0	11.0

\* The cutoff date for listed values was December 31, 2008. Percentages may not total 100 because of rounding.

† In Sweden, all men underwent randomization on the same day.

‡ Excluded from the total were 145 men who submitted their consent forms but died before the randomization process was finalized.

§ This category includes cases of prostate cancer that were clinically detected during the interval between screenings or that were detected in men who declined to undergo screening.

¶ The median screening interval between rounds 1 and 2 was 6 years.

|| The positive predictive value was calculated as the number of cancers that were detected by screening divided by the total number of biopsies that were performed.

\*\* The cumulative incidence was calculated as the total number of cancers detected divided by the total number of men assigned to each study group.

(Gleason score, 8 to 10) was lower in the screening group than in the control group (Table 2 in the Supplementary Appendix). Data on tumor stage and grade distribution and on treatment according to study group are provided in Tables 2 and 9 in the Supplementary Appendix.

#### MORTALITY FROM PROSTATE CANCER

There were 299 deaths from prostate cancer in the screening group and 462 in the control group, with death rates of 0.39 and 0.50 per 1000 person-years, respectively (Table 3). Overall, a rate ratio of

0.79 (95% CI, 0.68 to 0.91;  $P=0.001$ ), corresponding to a relative risk reduction of 21% in favor of screening, was found. The absolute difference in mortality amounted to 0.10 deaths per 1000 person-years, or 1.07 deaths per 1000 men randomized. After correction for selection bias and noncompliance, an adjusted rate ratio of 0.71 (95% CI, 0.58 to 0.86;  $P=0.001$ ) was obtained for screened men, representing a relative risk reduction of 29%. Rate ratios for the period of 1 to 9 years and the period of 1 to 11 years were 0.85 (95% CI, 0.71 to 1.03) and 0.79 (95% CI, 0.67 to 0.92), respectively.

Italy	Spain	Switzerland	Total Excluding France‡	France—Herault	France—Tarn	Total
October 1996–October 2000	February 1996–June 1999	September 1998–August 2003		June 2003–March 2005	December 2000–June 2004	
14,517	2,197	9,903	162,243	57,658	21,356	241,257
7251 (49.9)	1141 (51.9)	4955 (50.0)	89,352 (55.1)	28,866 (50.1)	10,470 (49.0)	128,688 (53.3)
7266 (50.1)	1056 (48.1)	4948 (50.0)	72,891 (44.9)	28,792 (49.9)	10,886 (51.0)	112,569 (46.7)
5730 (78.9)	1056 (100)	4793 (96.9)	60,244 (82.6)	7,164 (24.9)	4,005 (36.8)	71,413 (63.4)
12,731	1846	10,683	136,689	7164	4005	147,858
1443 (11.3)	354 (19.2)	2299 (21.5)	22,865 (16.7)	1,091 (15.2)	614 (15.3)	24,570 (16.6)
902 (62.5)	263 (74.3)	1836 (79.9)	19,646 (85.9)	315 (28.9)	352 (57.3)	20,313 (82.7)
374	69	475	6963	885	497	8345
197	60	376	4757	163	112	5032
177	9	99	2206	722	385	3313
21.8	22.8	20.5	24.2	51.7	31.8	24.8
5.1	6.5	9.6	9.6	3.1	4.6	7.4
257	24	226	5396	782	443	6621
3.5	2.1	4.6	6.0	2.7	4.2	5.1
9.9	10.4	7.9	10.5	4.3	5.5	8.6
10.7	10.7	8.2	11.0	4.4	5.5	9.8

During the 11-year follow-up period, the absolute effect of screening, expressed as the NNI to prevent one death from prostate cancer, was 1055, and the NND was 37. For the nontruncated analysis (which included all available follow-up data for ≥12 years) the NNI was 936, and the NND was 33. The NNI and NND varied considerably according to the period of follow-up at all centers (NNI range, 936 to 2111; NND range, 33 to 80) and at the three largest centers (NNI range, 194 to 1825; NND range, 8 to 42) (Table 3A in the Supplementary Appendix). In Tables 2 and 3, the effect of weighting the control population of Finland by 1:1.5 is also shown.

The Nelson–Aalen curves for the cumulative hazard of death from prostate cancer in the two study groups separate gradually, starting approximately 7 years after randomization (Fig. 2). A steadily increasing mortality with follow-up was found in the two study groups during the various

time periods (Table 3). The rate ratio for the 2 additional years of follow-up (years 10 and 11) was 0.62 (95% CI, 0.45 to 0.85), for a relative risk reduction of 38%. The mortality results according to center are shown in a forest plot (Fig. 1A and Table 4A in the Supplementary Appendix). Kaplan–Meier analyses according to study group and Gleason score are provided in Figure 2A in the Supplementary Appendix.

The total rate ratio for death from prostate cancer among men in the screening group was significantly below 1.00 in the core age group and for all ages. However, in the subgroup analyses, the rate ratio for death from prostate cancer was significant only for men between the ages of 65 and 69 years. The study was powered for analysis of the core age group (Table 5A in the Supplementary Appendix). Only three centers (Finland, the Netherlands, and Sweden) had more than 100 deaths from prostate cancer, and the rate ratio for death



**Table 2. Prostate-Cancer Incidence in Men 55 to 69 Years of Age, According to Study Period.\***

Study Years	Screening Group (N = 72,891)		Control Group (N = 89,352)		Rate Ratio (95% CI)†	Rate Difference per 1000 Person-Yr (95% CI)‡	Rate Difference per 1000 Men‡
	Prostate Cancers no.	Person-Yr	Prostate Cancers no.	Person-Yr			
1-9	6043	580,502	4044	731,204	1.88 (1.81 to 1.96)	4.80 (4.49 to 5.12)	37.6
8-9	1410	113,850	1174	145,293	1.56 (1.44 to 1.69)	4.30 (3.51 to 5.10)	6.2
10-11	541	88,999	916	114,462	0.78 (0.70 to 0.87)	-1.92 (-2.65 to -1.20)	-2.8
1-11	6584	669,501	4960	845,666	1.68 (1.62 to 1.75)	3.97 (3.68 to 4.26)	34.8°
≥12	379	51,141	436	61,726	1.03 (0.90 to 1.19)	0.35 (-0.65 to 1.35)	0.3
Total	6963	720,643	5396	907,392	1.63 (1.57 to 1.69)	3.71 (3.44 to 3.99)	35.1

\* Values are not included for centers in France because of the short follow-up period (median, 4.6 years).

† Rate ratios have been adjusted according to center.

‡ Rate differences are for the screening group as compared with the control group. Values for the control population in Finland were weighted by 1:1.5 to account for the ratio in study-group assignments. With this adjustment, the rate differences per 1000 person-years (95% CI) were as follows: 4.89 (4.56 to 5.21) for 1 to 9 years, 4.54 (3.72 to 5.36) for 8 to 9 years, -1.76 (-2.52 to -0.99) for 10 to 11 years, 4.10 (3.80 to 4.40) for 1 to 11 years, and 0.35 (-0.68 to 1.39) for 12 or more years, for a total between-group difference of 3.84 (3.55 to 1.72). With this adjustment, the rate differences per 1000 men were 38.7 for 1 to 9 years, 6.7 for 8 to 9 years, -2.5 for 10 to 11 years, 36.2 for 1 to 11 years, and 0.1 for 12 or more years, for a total between-group difference of 36.3.

from prostate cancer in the core age group ranged from 0.56 in Sweden to 0.89 in Finland, with significant reductions in Sweden and the Netherlands (Table 4A in the Supplementary Appendix). Figure 3A in the Supplementary Appendix shows the distribution of the 299 deaths in the screening group among men with cancers detected during screening, men with cancers detected between screenings, and men who did not undergo screening. Nearly half the deaths in the screening group occurred among men with cancers detected during screening, and in 74% of these men, the diagnosis was made in the first round of screening. Approximately a quarter of the deaths occurred among men with cancers detected between screenings, with a similar number among unscreened men.

We performed an analysis of the influence of the center by calculating the rate ratios for death from prostate cancer, omitting each center one at a time (Table 6A in the Supplementary Appendix). The overall rate ratios remained significant, with a point estimate of the rate ratio that was close to 0.80, regardless of the exclusion of any of the seven centers. With the omission of Finland, however, the rate ratio approached 0.70. (For details on rates of death from prostate cancer according to center and time period, see Tables 7A1 and 7A2 in the Supplementary Appendix.)

Overall mortality was similar in the two study groups, with 18.2 deaths per 1000 person-years in the screening group and 18.5 per 1000 person-years in the control group (rate ratio, 0.99; 95% CI, 0.97 to 1.01) (Table 5A in the Supplementary Appendix). Data on all-cause mortality according to age group are supplied in Table 8A in the Supplementary Appendix.

## DISCUSSION

The controversy regarding screening for prostate cancer has been renewed by the publication of the draft report of the U.S. Preventive Services Task Force, which after a literature-based analysis of benefits and harms recommended against the use of PSA testing in asymptomatic men.<sup>12</sup> The report has been discussed in several Perspective articles in the *Journal*.<sup>13-15</sup> Clearly, the issue can be resolved only on the basis of evidence that considers both the advantages and disadvantages of screening, data that are not available at this time.

Our study shows that the absolute effect of screening on the risk of death from prostate can-

cer increased in the intention-to-screen analysis from 0.71 to 1.07 deaths per 1000 men at a median of 11 years of follow-up, as compared with the initial results with a shorter follow-up period.<sup>1</sup> Correspondingly, the NNI and NND to avert one death from prostate cancer decreased from 1410 to 936 and from 48 to 33, respectively. These numbers are expected to decrease further with longer follow-up.<sup>16,17</sup> In contrast, the relative reduction in risk remained practically unchanged, at 21%. After correction for noncompliance, there was a relative difference of 29% for screened men.

During years 10 and 11 of follow-up, there was a relative reduction in risk of 38%. However, the reduction in prostate-cancer mortality needs to be balanced against the disadvantages of early detection of prostate cancer, with the proportion of overdiagnosis estimated to be approximately 50% of screening-detected cancers.<sup>18</sup> A review by Loeb et al.<sup>19</sup> showed that septic complications of biopsies increased in line with increasing resistance of large-bowel bacteria to antibiotics. Another important issue is the small effect of radical prostatectomy versus watchful waiting. In the Scandinavian Prostate Cancer Group Study Number 4,<sup>20</sup> there was an absolute reduction in mortality of only 6 percentage points among men who underwent radical prostatectomy. In the Prostate Cancer Intervention Versus Observation Trial (PIVOT; ClinicalTrials.gov number, NCT00007644), there was no significant effect after 12 years of follow-up.<sup>21</sup> In our study, there was no effect on all-cause mortality; an evaluation of the effect on quality of life is pending.

The effect of the extended follow-up is best assessed by comparing the data for follow-up truncated at 9 years with the data for 11 years of follow-up. Both the NNI and the NND were reduced by approximately half on the basis of 11 years of follow-up, as compared with 9 years. These results cannot be directly compared with our earlier analysis on the basis of all available data through 2006, which are not truncated according to follow-up time but by calendar year. The absolute risk reduction is a concrete measure of the effect of screening but depends on the underlying risk in the population and therefore cannot be directly generalized.<sup>22</sup>

The effect of screening on prostate-cancer mortality was significant for the core age group and for all ages. However, there was no indication of a mortality reduction for men 70 years of age or

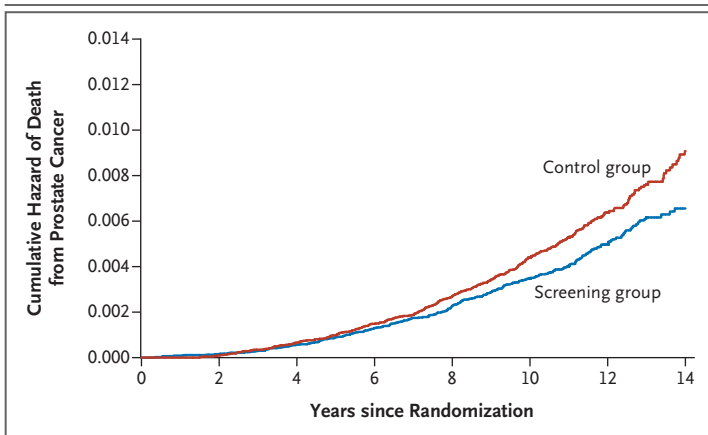
**Table 3. Mortality from Prostate Cancer among Men 55 to 69 Years of Age, According to Study Period.\***

Study Years	Screening Group		Control Group		Rate Ratio (95% CI)†	P Value	Rate Difference per 1000 Person-Yr (95% CI)‡	Rate Difference per 1000 Men‡	
	Deaths from Prostate Cancer	Person-Yr	Rate per 1000 Person-Yr	Deaths from Prostate Cancer					Person-Yr
1-9	189	608,852	0.31	274	0.37	0.85 (0.71 to 1.03)	0.09	-0.06 (-0.12 to 0.01)	-0.47
8-9	71	122,867	0.58	118	0.78	0.74 (0.55 to 0.99)	0.04	-0.20 (-0.40 to 0.00)	-0.35
10-11	56	97,994	0.57	111	0.92	0.62 (0.45 to 0.85)	0.003	-0.35 (-0.57 to -0.12)	-0.47
1-11	245	706,846	0.35	385	0.44	0.79 (0.67 to 0.92)	0.003	-0.10 (-0.16 to -0.04)	-0.95
≥12	54	57,387	0.94	77	1.16	0.80 (0.56 to 1.13)	0.21	-0.22 (-0.58 to 0.14)	-0.12
Total	299	764,233	0.39	462	0.50	0.79 (0.68 to 0.91)	0.001	-0.10 (-0.17 to -0.04)	-1.07

\* Values are not included for centers in France because of the short follow-up period (median, 4.6 years).

† Rate ratios have been adjusted according to center.

‡ Rate differences are for the screening group as compared with the control group. Values for the control population in Finland were weighted by 1:1.5 to account for the ratio in study-group assignments. With this adjustment, the differences in rates per 1000 person-years were as follows: -0.06 (95% CI, -0.12 to 0.00) for 1 to 9 years, -0.20 (95% CI, -0.40 to 0.00) for 8 to 9 years, -0.37 (95% CI, -0.61 to -0.12) for 10 to 11 years, -0.10 (95% CI, -0.17 to -0.03) for 1 to 11 years, and -0.26 (95% CI, -0.64 to 0.12) for 12 or more years, for a total between-group difference of -0.11 (95% CI, -0.18 to 0.04). The corresponding differences in rates per 1000 men were -0.46, -0.33, -0.48, -0.94, and -0.19, for a total between-group difference of -1.13.



**Figure 2. Cumulative Hazard of Death from Prostate Cancer among Men 55 to 69 Years of Age.**

Values are not included for centers in France because of the short follow-up period (median, 4.6 years). The Nelson–Aalen method was used to calculate the cumulative hazard of death from prostate cancer.

older, though the confidence interval was wide for this age group. This upper age limit and life expectancy warrant careful consideration in future screening programs. The Kaplan–Meier analyses of the rate of death from prostate cancer according to Gleason score ( $\leq 6$  vs.  $\geq 7$ ) showed significant differences in the two study groups. This analysis is considered inadequate in the evaluation of randomized screening trials because of lead-time, length, and overdiagnosis biases.<sup>23</sup>

The overall screening effect (in terms of a rate-ratio reduction) was not driven by any single center, as indicated by consistency in the analysis of influence, despite some variation in the screening protocol. Yet the rate ratio was not constant across centers, as also shown in the forest plot (Fig. 1A in the Supplementary Appendix). The screening effect depends on the frequency of cancers that were rendered curable by screening, which may differ according to center because of differences in screening procedures and in underlying risk. However, the screening effect can also be attenuated by contamination (i.e., subjects in the control group who underwent screening). As compared with the entire ERSPC study, the Göteborg screening trial,<sup>24</sup> which evaluated biennial screening during a follow-up period of 14 years, showed a larger mortality reduction and a more favorable NNI and NND, with a higher background rate of death from prostate cancer.

Some biases may have affected the mortality results of our study. Similar treatments need to be

administered for similar disease to ensure that the difference between the two study groups was attributable to screening and not superior management of cases detected by screening. Earlier analyses showed similar treatment approaches in the two study groups according to tumor stage.<sup>25,26</sup> In addition, assignment of causes of death is prone to error, a challenge that is minimized by the use of standardized measures and blinded assignments.<sup>5</sup> Finally, it has been estimated that in the control group, approximately 20% of men per year underwent PSA screening during the early follow-up period.<sup>27,28</sup>

The reasons why the effect of screening did not increase more during the extended follow-up remain unclear at this time. The majority of deaths from prostate cancers that were detected by screening (100 of 136, or 74%) occurred in men whose cancer was diagnosed at the first screening. Natural history studies confirm the need for very long observation periods. Johansson et al.<sup>29</sup> found a large increase in the rate of death from localized prostate cancers during follow-up of 15 to 20 years. The high proportion of prostate cancers that are detected during the intervals between screenings (25.8%) necessitates optimization of screening procedures (Fig. 3A in the Supplementary Appendix). Despite the exclusion of men who had clinically evident prostate cancer at study entry, this high prevalence suggests that a large number of the men in our study probably had latent but aggressive disease, which turned out to be deadly even after prolonged follow-up.

In conclusion, our trial showed a relative risk reduction of 21% in favor of prostate-cancer screening in the intention-to-screen analysis and 29% among screened men after adjustment for noncompliance; the absolute risk reduction was 1.07 deaths per 1000 men at a median follow-up of 11 years. This corresponds to an NNI of 936 and an NND of 33 in order to prevent one death from prostate cancer. During years 10 and 11 of follow-up, the relative risk reduction was 38%. Despite the reduction in the rate of death from prostate cancer, screening had no effect on all-cause mortality. More information on the balance of benefits and adverse effects, as well as the cost-effectiveness, of prostate-cancer screening is needed before general recommendations can be made.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

#### APPENDIX

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