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# European Study of Prostate Cancer Screening — 23-Year Follow-up

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## ABSTRACT

### BACKGROUND

The European Randomized Study of Screening for Prostate Cancer (ERSPC) was initiated in 1993 to assess the effect of prostate-specific antigen (PSA) testing on prostate cancer mortality. Because deaths from prostate cancer are expected to rise worldwide owing to increased life expectancy and population growth, a final analysis of the long-term outcomes of prostate cancer screening is essential to understanding the benefits and harms of PSA testing.

### METHODS

We updated the findings from ERSPC, a multicenter, randomized study conducted across eight European countries with a focus on a predefined core age group of 162,236 men who were 55 to 69 years of age at the time of randomization. Participants were randomly assigned to the screening group and offered repeated PSA testing or to the control group and not invited for screening. The primary outcome was prostate cancer mortality.

### RESULTS

After a median follow-up of 23 years, prostate cancer mortality was 13% lower in the screening group (rate ratio, 0.87; 95% confidence interval [CI], 0.80 to 0.95), and the absolute risk reduction was 0.22% (95% CI, 0.10 to 0.34). The cumulative incidence of prostate cancer was higher in the screening group than in the control group (rate ratio, 1.30; 95% CI, 1.26 to 1.33). At a median of 23 years of follow-up, one death from prostate cancer was prevented for every 456 men (95% CI, 306 to 943) who were invited for screening, and one death from prostate cancer was averted for every 12 men (95% CI, 8 to 26) in whom prostate cancer was diagnosed, as compared with one death from prostate cancer prevented for every 628 men (95% CI, 419 to 1481) and one death averted for every 18 men (95% CI, 12 to 45) at 16 years of follow-up.

### CONCLUSIONS

Long-term follow-up confirms a sustained reduction in deaths from prostate cancer with PSA testing, alongside an improved harm–benefit ratio. Future screening strategies should adopt risk-based approaches to minimize overdiagnosis while maintaining clinical benefits. (Funded by the Dutch Cancer Society and others; ERSPC ISRCTN registry number, ISRCTN49127736.)

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*A list of the ERSPC investigators is provided in the Supplementary Appendix, available at NEJM.org.

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A Quick Take is available at NEJM.org

Prostate cancer mortality is projected to double worldwide by 2040 owing to increased life expectancy and population growth. Therefore, the role of early detection and treatment to counter this burden remains a public health priority.[1] The European Randomized Study of Screening for Prostate Cancer (ERSPC) was undertaken in 1993 to assess whether population-based prostate-specific antigen (PSA) screening reduces prostate cancer mortality. Previous findings showed a significant relative reduction of 20% in prostate cancer mortality in favor of screening after a median follow-up of 16 years.[2-5] However, this benefit was counterbalanced by overdiagnosis and overtreatment of screening-detected tumors that were unlikely to have caused symptoms or death, thereby reducing the overall ratio of benefit to harm.

Given the typically slow progression of prostate cancer and the competing risk of death from other causes, current guidelines recommend against routine PSA screening in men over 70 years of age or those with a life expectancy of less than 15 years.[6,7] Nonetheless, up to 40% of men 75 years of age or older continue to undergo PSA screening.[8] Now that the prespecified screening in ERSPC of participants between the ages of 55 and 74 years concluded at least a decade ago for the vast majority, reassessment of the long-term outcomes is important for understanding how the effect of screening evolves, especially among participants who were screened but who had not received a diagnosis of prostate cancer by the end of the active screening phase. These data may contribute to ongoing discussions around when to stop screenings and in whom continued screening may be beneficial.

This update of the ERSPC, three decades after its initiation, aims to assess the long-term effect of PSA-based prostate cancer screening, with special attention focused on the evaluation of prostate cancer mortality among participants after the prespecified screening period ended. This report marks the final update of the primary outcome of the ERSPC as a unified cohort, because new European privacy regulations restrict data sharing from centers that used Zelen randomization (i.e., consent after randomization).

## METHODS

### STUDY DESIGN AND PARTICIPANTS

The ERSPC is a multicenter, randomized study that was initiated in 1993 in the Netherlands and Belgium (Fig. 1) and spanned eight European countries. Centers in Sweden, Finland, Italy, Spain, and Switzerland joined the study between 1994 and 1998, followed by two French centers in 2000 and 2003.

The study was designed by three of the authors. Data were gathered by investigators at the participating centers, and analyses were conducted

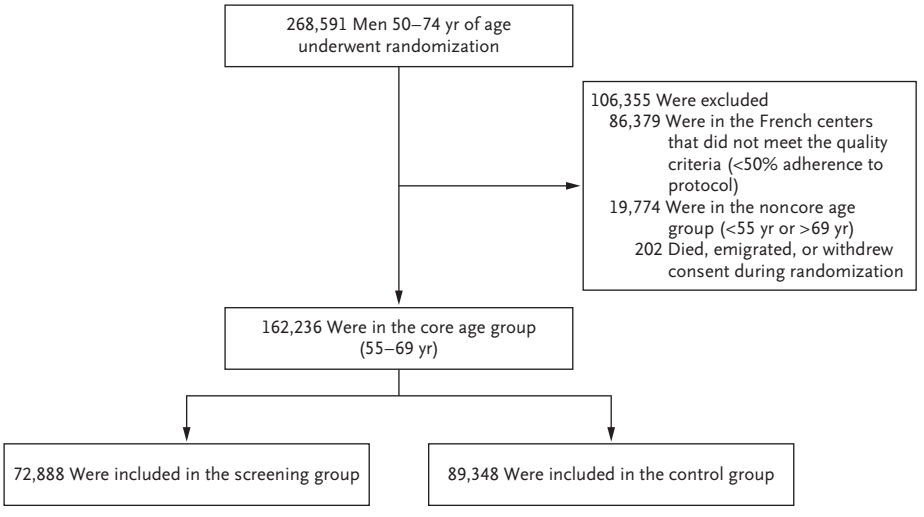



**Figure 1. Randomization of Overall Study Population and Core Age Group.**

by four of the authors. The first two authors of this report wrote the first draft of the manuscript, and all the authors contributed to subsequent revisions and approved submitting the manuscript for publication. Safety assessments were conducted by an independent data monitoring committee.[9] Oversight of data quality and adherence to the protocol (available with the full text of this article at NEJM.org) was performed by the Quality Control Committee.[10] The authors vouch for the accuracy and completeness of the data and the fidelity of the study to the protocol. The sponsors had no role in the design of the study, data collection, data analysis, manuscript preparation, or the decision to submit the manuscript for publication. No confidentiality agreements were made that preclude the publication of study findings.

The protocol has been described previously.[2-5] The primary aim of the study was to assess prostate cancer mortality in an intervention group consisting of participants who were invited to screening as compared with a control group in which no intervention was offered. Men between the ages of 50 and 74 years were eligible for the study, with each center defining its own specific age range within this span, but all centers included a predefined core age group of participants between the ages of 55 and 69 years.

Randomization was performed in a 1:1 ratio except in Finland, where a fixed number of 8000 men were randomly assigned to the screening group each year, with the remainder forming the control group, resulting in an approximate ratio of 1:1.5. On the basis of local regulations, two randomization approaches were used — in Sweden, Finland, and Italy, participants underwent randomization before providing consent (population-based Zelen-type effectiveness design[11]); in other centers, randomization occurred after consent was provided (volunteer-based efficacy design). Each participating center obtained its own ethical approval for the study.

### SCREENING PROTOCOL

All centers used PSA testing, standardized with the use of the Hybritech assay systems (Beckman Coulter), as the primary screening test. Men who had a positive result on the PSA test underwent transrectal-ultrasound–guided systematic prostate biopsies (with the number of cores taken during biopsy increasing from 6 in the early years of the study to 12 in later years). Most centers used a PSA level of 3.0 ng per milliliter as the cutoff for biopsy. In Finland, a PSA level of more than 4.0 ng per milliliter was considered to be positive, whereas PSA levels between 3.0 and 3.9 ng per millimeter required ancillary tests (a digital rectal exam until 1998, then a ratio of free PSA to total PSA of ≤0.16). Centers in Italy also used a cutoff of 4.0 ng per milliliter, with PSA levels of 2.5 to 3.9 ng per milliliter requiring additional tests (a digital rectal exam and transrectal ultrasound). Participants in the core age group were offered a minimum of two and a maximum of eight screening invitations, with most centers implementing a 4-year interval between screenings. Sweden and France, however, used a 2-year interval, and Belgium applied a 7-year interval. The upper age limit for screening invitations ranged from 71 to 74 years depending on the center.

### OUTCOMES

The primary outcome of the study was prostate cancer mortality. To assess this outcome, local committees whose members were not involved in the study and were unaware of study-group assignments determined the cause of death using a standardized algorithm to review all deaths among men in either group who had received a diagnosis of prostate cancer.[12] When the local committees could not reach consensus, the international cause-of-death committee was consulted. In Finland and Sweden, death certificates were used to establish the cause of death after a high concordance with committee determinations was established.[13-16]

The secondary outcome was the incidence of prostate cancer, stratified according to the European Association for Urology risk classification at the time of diagnosis. Advanced prostate cancer was defined as the presence of lymph-node or bone metastasis, or a PSA level greater than 100 ng per milliliter. All participants were linked to national cancer registries to track cancer diagnoses and overall mortality, with data reported biannually to a central database. No information was available regarding emigration in our data, so prostate cancer diagnoses and deaths among men who subsequently emigrated might be missing. However, we assume that the proportion of men who emigrated to be of approximately equal size in the two study groups. This assumption is supported by emigration data from Finland and

Sweden, where emigration rates were low (1.4% and 2.1%, respectively) and evenly distributed between the screening and control groups, indicating that any missingness is unlikely to introduce bias in relative comparisons. Data regarding tumor–node–metastasis stages, PSA levels, and Gleason scores were obtained from medical records. On the basis of these data, participants were assigned to European Association of Urology risk groups.[7] Participants for whom one or more of these tumor characteristics were missing were classified according to the remaining available clinical factors in accordance with the hierarchical structure of the risk classification system.

### STATISTICAL ANALYSIS

The primary analysis assessed prostate cancer diagnosis and mortality with follow-up truncated to either December 31, 2020, or 23 years after randomization, whichever occurred first. The cumulative incidence of a prostate cancer diagnosis or death from prostate cancer for each study group was calculated with the use of a competing-risks method, with death from other causes as a competing event. Poisson regression analysis was used to calculate the rate ratios (ratio of incidence per person-year) of prostate cancer diagnosis and death from prostate cancer in the study groups. The Finnish control group was weighted at a ratio of 1:1.5, as agreed upon when Finland joined the study. Rate ratios were calculated according to the intention-to-screen principle, which provides that randomized groups are compared regardless of screening compliance. In addition, a prespecified rate ratio was calculated for men who attended at least one screening round, with adjustment for nonparticipation made with the use of Cuzick's method (Fig. S1 in the Supplementary Appendix, available at NEJM.org).[17]

The number needed to invite for screening to prevent one death from prostate cancer was calculated as the inverse of the absolute risk difference between the groups in prostate cancer mortality. The number needed to diagnose was calculated by multiplying the number needed to invite by the excess incidence of prostate cancer in the screening group. The excess incidence was defined as the between-group difference in the proportion of participants diagnosed with prostate cancer. Confidence intervals for absolute risk difference, number needed to invite, and number needed to diagnose were calculated with the use of 200 bootstrap samples. Confidence intervals are presented without adjustment for multiplicity and should not be used to infer definitive significance or for formal hypothesis testing.

The additional analysis assessed prostate cancer mortality among men who underwent screening but did not receive a diagnosis during the active screening phase. For this post hoc analysis, men from both the screening group and the control group who were alive and without a prostate cancer diagnosis at the time of the center-specific upper age limit of the screening protocol were included. The center-specific upper age limit was 74 years for men in the Netherlands, Spain, Switzerland, Belgium, and Italy and 71 years for men in Sweden and Finland. Because a small percentage of participants were screened just after they passed the upper age limit, the age limit for this analysis was defined as the one described in the screening protocol plus 1 year. The cumulative prostate cancer mortality was estimated by means of a competing-risks analysis. Follow-up time was defined as the period from the upper age limit of the screening protocol to either the date of death or date of data censoring (December 31, 2020).

To assess how the effect of screening on prostate cancer mortality evolved over time after cessation of screening, we applied a time-dependent Cox proportional-hazards regression model with an interaction term between the study group and the time since passing the upper age limit. Natural spline functions were used to flexibly model the time interaction. We evaluated models with three, four, and five knots, located at quantiles informed by the distribution of follow-up time. Model selection was based on the Akaike Information Criterion, with the three-knot model shown to be the best fit. The estimated hazard ratios over time were plotted with corresponding pointwise 95% confidence intervals, providing a continuous view of the change in risk of death in the two groups across the follow-up period.

This report is restricted to men in the predefined core age group (55 to 69 years of age at the time of randomization). As in previous ERSPC reports, data from the French centers are excluded because they did not meet the predefined quality criteria for inclusion — specifically, owing to participation in the screening group involving

less than 50% of the participants and poor compliance with the biopsy protocol after positive results on PSA tests.[18] In addition, the later start of recruitment in France (2001–2005) resulted in substantially shorter follow-up, limiting the ability to assess long-term mortality. A sensitivity analysis that included the French centers, with follow-up truncated at their median of 17 years, was performed to assess the risk ratio for prostate cancer mortality. All statistical analyses were performed with the use of R Statistical Software, version 4.4.0.

## RESULTS

### PARTICIPANTS

A total of 162,236 men were included in the present analysis, with 72,888 assigned to the screening group and 89,348 assigned to the control group (Fig. 1). The median age at the time of randomization was 60 years (interquartile range, 57 to 64). The median follow-up among participants who were still alive was 23 years (interquartile range, 22 to 23) in the two groups; the median among all participants was 21 years (interquartile range, 14 to 23) in each group. Men who were assigned to the screening group underwent an average of two screenings, with 60,259 men (83%) receiving at least one screening (Table 1). Among those who participated, 28% had at least one positive screening result. Compliance with undergoing a prostate biopsy after a positive result was 89%.

### INCIDENCE OF PROSTATE CANCER

At follow-up 23 years after randomization, the cumulative prostate cancer incidence was 14% in the screening group and 12% in the control group (Fig. 2A), resulting in an overall risk ratio of 1.30 (95% confidence interval [CI], 1.26 to 1.33). The absolute excess incidence was 27 cases of prostate cancer (95% CI, 23 to 30) per 1000 men. After stratification according to risk category at the time of diagnosis, the risk ratios were 2.14 (95% CI, 2.04 to 2.25) for low risk, 1.10 (95% CI, 1.04 to 1.17) for intermediate risk, 0.95 (95% CI, 0.89 to 1.01) for high risk, and 0.66 (95% CI, 0.60 to 0.74) for advanced prostate cancer (Fig. S2). The distribution of tumor characteristics according to European Association of Urology risk groups is shown in Table S1. Risk-group classification was not possible in 316 men (1.6%) owing to missing variables for tumor characteristics. Center-specific risk ratios and cumulative incidence of prostate cancer are provided in Table S2 and Figure S3, respectively.

### PROSTATE CANCER MORTALITY

The cumulative prostate cancer mortality at 23 years was 1.4% in the screening group and 1.6% in the control group (Fig. 2B). This result corresponds to a risk ratio of 0.87 (95% CI, 0.80 to 0.95), with cumulative prostate cancer mortality and risk ratio according to center shown in Figure S4 and Table S3, respectively. After correction for nonattendance, the risk ratio was 0.84 (95% CI, 0.76 to 0.92) for men attending at least one screening round. Sensitivity analyses including the French centers showed a risk ratio of 0.84 (95% CI, 0.76 to 0.93) after a median follow-up of 17 years, which is consistent with previously published results based on a similar length of follow-up.[5] The absolute risk reduction in prostate cancer mortality was 0.22% (95% CI, 0.10 to 0.34), corresponding to a number needed to invite of 456 (95% CI, 306 to 943) and a number needed to diagnose of 12 (95% CI, 8 to 26) to prevent one prostate cancer death. Prostate cancer mortality data across varying follow-up periods are shown in Table 2. Cumulative other-cause mortality at 23 years was 49% in each of the two groups (risk ratio, 1.00; 95% CI, 0.98 to 1.01) (Fig. 2C).

### ADDITIONAL ANALYSIS

At the time they reached the upper age limit of the screening protocol (median age, 72 years [interquartile ratio, 72 to 74]), 72% of the participants in the screening group (52,252 men) and 75% in the control group (67,098 men) were still alive and had not received a diagnosis of prostate cancer. Among those in the screening group, 3040 men (5.8%) had never participated in screening within the study, 3874 men (7.4%) had undergone one screening, 13,554 men (26%) had undergone two screenings, and 31,784 men (61%) had undergone three or more screenings. The median follow-up after the screening intervention ended was 8 years (interquartile range, 5 to 12).

At 12 years after prespecified screening, the cumulative prostate cancer incidence among men without a diagnosis at the end of the active screening phase was 0.71% in the screening group and 0.87% in the control group (Fig. S5), with an absolute risk reduction of 0.17% (95% CI, 0.04 to 0.29).

**Table 1. Characteristics of the Study Population Overall (Excluding France) and According to Center.***

| | Belgium (N=8562) | Finland (N=80,379) | Italy (N=14,514) | Netherlands (N=34,831) | Spain (N=2197) | Sweden (N=11,850) | Switzerland (N=9903) | Overall, Excluding France (N=162,236) | France, Herault (N=58,536) | France, Tarn (N=21,363) |
|---|---|---|---|---|---|---|---|---|---|---|
| Median age at randomization (IQR) — yr | 63 (60 to 66) | 58 (54 to 62) | 61 (58 to 65) | 61 (58 to 65) | 60 (57 to 64) | 59 (57 to 62) | 61 (57 to 65) | 60 (57 to 64) | 61 (57 to 66) | 61 (58 to 65) |
| Median duration of follow-up of men still alive (IQR) — yr | 23 (19 to 23) | 23 (22 to 23) | 21 (11 to 22) | 23 (23 to 23) | 23 (23 to 23) | 23 (23 to 23) | 22 (20 to 23) | 23 (22 to 23) | 17 (16 to 17) | 18 (17 to 18) |
| Assigned to control group — no. (%) | 4255 (50) | 48,409 (60) | 7250 (50) | 17,389 (50) | 1141 (52) | 5949 (50) | 4955 (50) | 89,348 (55) | 29,311 (50) | 10,479 (49) |
| Assigned to screening group — no. (%) | 4307 (50) | 31,970 (40) | 7264 (50) | 17,442 (50) | 1056 (48) | 5901 (50) | 4948 (50) | 72,888 (45) | 29,225 (50) | 10,884 (51) |
| Total no. of screenings | 6446±1.5 | 52,142±1.6 | 12,728±1.8 | 42,001±2.4 | 1846±1.7 | 15,476±2.6 | 12,068±2.4 | 142,707±2.0 | 10,060±1.2 | 5358±1.3 |
| Positive tests — no./total no. (%)† | 1058/6446 (16) | 5925/52,142 (11) | 1443/12,728 (11) | 9932/42,001 (24) | 354/1846 (19) | 2708/15,476 (17) | 2599/12,068 (22) | 24,019/142,707 (17) | 1627/10,060 (16) | 821/5358 (15) |
| Biopsies — no./total no. (%)‡ | 754/1058 (71) | 5467/5925 (92) | 1019/1443 (71) | 9279/9932 (93) | 343/354 (97) | 2551/2708 (94) | 2031/2599 (78) | 21,444/24,019 (89) | 657/1627 (40) | 446/821 (54) |
| Positive biopsies — no./total no. (%)§ | 197/754 (26) | 1604/5467 (29) | 205/1019 (20) | 1985/9279 (21) | 60/343 (17) | 576/2551 (23) | 437/2031 (22) | 5064/21,444 (24) | 242/657 (37) | 128/446 (29) |
| Screened at least once — no./total no. (%)¶ | 3908/4307 (91) | 23,771/31,970 (74) | 5729/7264 (79) | 16,501/17,442 (95) | 1056/1056 (100) | 4484/5901 (76) | 4810/4948 (97) | 60,259/72,888 (83) | 8121/29,225 (28) | 4143/10,884 (38) |
| ≥1 positive test — no./total no. (%)‖ | 914/3908 (23) | 4635/23,771 (19) | 1054/5729 (18) | 6937/16,501 (42) | 326/1056 (31) | 1482/4484 (33) | 1729/4810 (36) | 17,077/60,259 (28) | 1560/8121 (19) | 760/4143 (18) |
| ≥1 biopsy — no./total no. (%)‖ | 684/3908 (18) | 4380/23,771 (18) | 812/5729 (14) | 6325/16,501 (38) | 256/1056 (24) | 1435/4484 (32) | 1496/4810 (31) | 15,388/60,259 (26) | 657/8121 (8) | 438/4143 (11) |

* Plus–minus values are means ±SD. Data from France were excluded from the overall analysis because they did not meet the predefined quality criteria for inclusion.
† Total no. is the number of screenings.
‡ Total no. is the number of positive tests.
§ Total no. is the number of biopsies.
¶ Total no. is the number of men assigned to the screening group at that center.
‖ Total no. is the number of men who had at least one screening test or biopsy.

The between-group hazard ratio for death from prostate cancer gradually increased, with the upper boundary of the confidence interval crossing 1.0 approximately 6 years after the upper age limit of the screening protocol (Fig. 3). The incidence of prostate cancer after prespecified screening, stratified according to risk category at the time of diagnosis, is shown in Figure S6.

## DISCUSSION

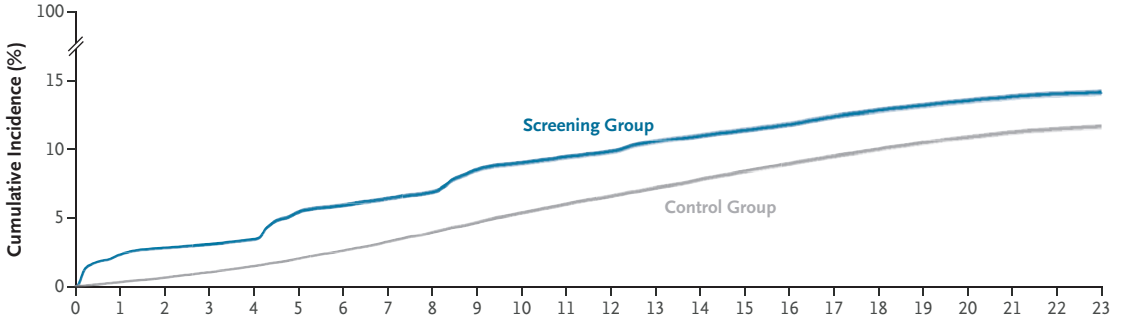
Understanding the long-term outcomes of an organized prostate cancer screening program is essential to addressing the growing global burden of this disease. Over the past decades, the ERSPC has been evaluating the benefits and harms of population-based PSA screening, thereby shaping global discussions and guidelines on early detection. This final report of the primary outcome, including more than two decades of follow-up, shows a reduction in prostate cancer mortality of 13% in favor of screening. Although the relative reduction has decreased from the previously reported 20% with shorter follow-up, this update shows that the absolute between-group risk reduction for death from prostate cancer continues to rise (0.22% at 23 years vs. 0.14% at 16 years). Together with a decreasing excess incidence of prostate cancer in the screening group (27 vs. 31 extra cases per 1000 men), the increased absolute reduction results in a more favorable harm-to-benefit profile than previously estimated, which is reflected in the reduction of the number needed to invite (from 628 to 456 men) and number needed to diagnose (from 18 to 12 men) in this follow-up as compared with the 16-year follow-up.

Nonetheless, the harms associated with PSA-based screening, including unnecessary testing, biopsies, overdiagnosis, and subsequent overtreatment, remain a critical concern. With only 16% of PSA tests yielding elevated results and merely 24% of the subsequent biopsies confirming prostate cancer, a considerable number of these tests and procedures may have been unnecessary. More important, considerable harm arises from the overdiagnosis and subsequent overtreatment of tumors that are unlikely to cause prostate cancer illness or death, as indicated by the excess incidence of prostate cancer of 27 cases per 1000 men and, in particular, the doubling in detection of low-risk cancers in the screening group. These findings highlight the need for a more targeted strategy for prostate cancer screening that focuses on identifying population subgroups that are most likely to benefit from early detection while reducing unnecessary interventions for those with the highest risk of overdiagnosis.

A stepwise, risk-based approach, guided by risk stratification tools such as risk calculators and magnetic resonance imaging, limits biopsies to men with a confirmed elevated risk, a strategy that breaks the traditional link between elevated PSA and immediate biopsy.[19] Several ongoing, population-based, randomized screening trials that incorporate a risk-based screening approach have shown a reduction in unnecessary biopsies and detection of low-grade prostate cancer while maintaining detection of high-grade cancers.[20-22] This improved ratio of the detection of high-grade to indolent cancers, as compared with traditional PSA-based screening, suggests a substantial reduction in overdiagnosis. However, long-term outcomes such as metastatic disease rates and prostate cancer mortality must be evaluated to confirm the true effect of risk-based screening. In addition, the frequency of PSA screening plays a key role in balancing benefits and harms — more frequent PSA screening, such as annual testing, is associated with greater potential benefit but also with increased risk of harm.[23] Although the optimal screening interval remains debatable, unnecessary repeated screening may be reduced by limiting screening in men with very low PSA levels at baseline or a PSA value of 1 or less at age 60, both of which indicate a very low risk of death from prostate cancer.[24-26]

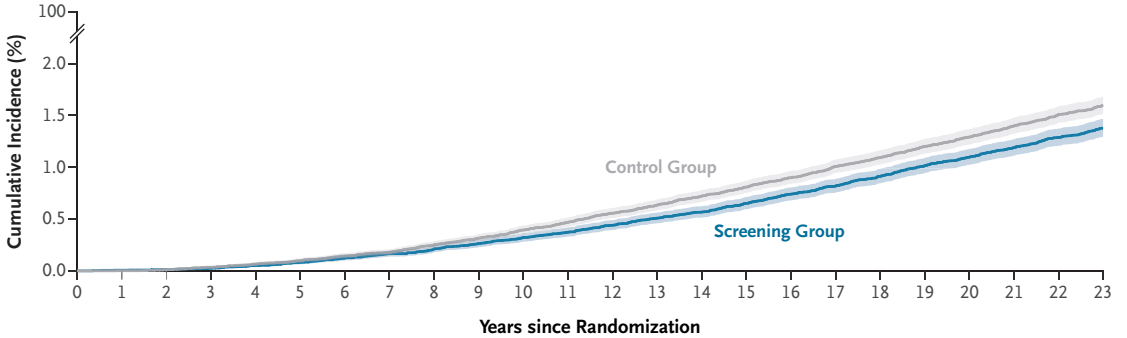
Given the strong association between age and the prevalence of prostate cancer, particularly high-risk disease,[27] as well as the global rise in life expectancy,[28] determining the appropriate age range for screening is a key question. To address this question, we evaluated the duration of the reduction in prostate cancer mortality among men who were screened but not diagnosed at the upper age limit of the screening protocol (median age, 72 years). In this subgroup, the hazard ratio for death from prostate cancer favored the screening group, indicating a sustained protective effect, although the benefit gradually waned as the duration since the last screening increased. At 12 years after screening ended, cumulative prostate cancer mortality in this subgroup was 0.71%, slightly higher than the 0.55% observed

**A** Prostate Cancer Diagnosis




| No. at Risk (no. of events) | | | | | | |
|---|---|---|---|---|---|---|
| Screening group | 72,888 (0) | 64,312 (3929) | 55,870 (6533) | 46,834 (8292) | 27,657 (9748) | 11,843 (9995) |
| Control group | 89,348 (0) | 81,494 (1800) | 71,036 (4777) | 59,344 (7462) | 32,961 (9529) | 12,306 (9870) |

**B** Prostate Cancer–Specific Mortality




| No. at Risk (no. of events) | | | | | | |
|---|---|---|---|---|---|---|
| Screening group | 72,888 (0) | 68,052 (60) | 61,574 (233) | 53,239 (475) | 41,639 (796) | 26,069 (969) |
| Control group | 89,348 (0) | 83,131 (87) | 75,068 (352) | 64,954 (722) | 51,054 (1150) | 31,634 (1385) |

**C** Other-Cause Mortality


| No. at Risk (no. of events) | | | | | | |
|---|---|---|---|---|---|---|
| Screening group | 72,888 (1) | 68,052 (4776) | 61,574 (11,081) | 53,239 (19,174) | 41,639 (28,911) | 26,069 (34,493) |
| Control group | 89,348 (2) | 83,131 (6130) | 75,068 (13,928) | 64,954 (23,672) | 51,054 (35,588) | 31,634 (42,444) |

**Figure 2 (facing page). Incidence of Prostate Cancer Diagnosis, Prostate Cancer–Specific Mortality, and Other-Cause Mortality.**

Shaded areas represent pointwise 95% confidence intervals. Confidence intervals are presented without adjustment for multiplicity and should not be used to infer definitive statistical significance or for formal hypothesis testing.

in the control group of the overall cohort at the same time point. However, other-cause mortality in this subgroup was substantially higher (approximately 45% vs. 20% in the full cohort), highlighting the limited life expectancy in this subgroup.

It should be noted that the findings of this exploratory analysis are potentially subject to confounding and should therefore be interpreted with caution. Nonetheless, given the low absolute risk of death from prostate cancer, the high competing risk of death from other causes in these older men, and the limited potential for life-years gained as compared with earlier screening, the benefit of extending screening appears marginal. This conclusion is further supported by the prostate cancer mortality curves in the overall cohort, which show that the absolute benefit of screening is minimal during the first 10 years but increases thereafter, showing the importance of life expectancy in achieving a decrease in mortality. Furthermore, extending screening would also coincide with higher risks of overdiagnosis, because older men more often have tumors that will not result in illness or death.[29,30] Continued screening may still be considered on an individual basis for older men who have a long life expectancy, although evidence for this consideration is scarce.

Two other large-scale, population-based PSA screening trials were initiated in the 1990s. The Prostate, Lung, Colorectal and Ovarian (PLCO) trial in the United States did not show a significant reduction in prostate cancer–specific mortality despite sharing similarities to the ERSPC in design, including multicenter recruitment and repeated PSA testing.[31] This result was largely due to contamination of more than 80% of PSA testing in the control group during the trial, a factor that thereby obscured any substantial effect of the intervention in the screening group.[32] A modeling exercise estimated that with lower contamination, the PLCO trial was consistent with a 27 to 32% reduction in prostate cancer–specific mortality in favor of screening.[33] The Cluster Randomized Trial of PSA Testing for Prostate Cancer (CAP) in the United Kingdom evaluated prostate cancer mortality in participants 15 years after a single invitation to undergo PSA testing in the intervention group.[34] The results showed only a modestly significant relative reduction of 8% and an absolute reduction of 0.09% in prostate cancer mortality. Together with the low participation rate of 40% in the intervention group, these data suggest that higher compliance and repeated testing are necessary to achieve a more substantial mortality benefit.

At the time of this analysis, half the ERSPC cohort had died and the median age of survivors was 82 years. Nevertheless, the prostate cancer mortality in the control group remained below population-based estimates of 2 to 3%, having reached only 1.5%. This result probably reflects

**Table 2. Prostate Cancer Mortality According to Length of Follow-up.***

| Length of Follow-up | Rate Ratio (95% CI) | Relative Risk Reduction | Absolute Risk Difference (95% CI) | No. Needed to Invite (95% CI) | No. Needed to Diagnose (95% CI) |
|---|---|---|---|---|---|
| | | *percent* | | | |
| 9 yr | 0.83 (0.69–1.01) | 17 | 0.05 (0.00–0.09) | 1919 (903–14308) | 73 (34–567) |
| 11 yr | 0.79 (0.67–0.93) | 21 | 0.10 (0.03–0.15) | 1041 (679–3486) | 36 (22–118) |
| 13 yr | 0.80 (0.70–0.91) | 20 | 0.12 (0.05–0.19) | 803 (538–1927) | 27 (18–62) |
| 16 yr | 0.82 (0.73–0.92) | 18 | 0.16 (0.07–0.24) | 628 (419–1481) | 18 (12–45) |
| 23 yr | 0.87 (0.80–0.95) | 13 | 0.22 (0.11–0.33) | 456 (306–943) | 12 (8–26) |

* Confidence intervals (CIs) are presented without adjustment for multiplicity and should not be used to infer definitive statistical significance or for formal hypothesis testing.

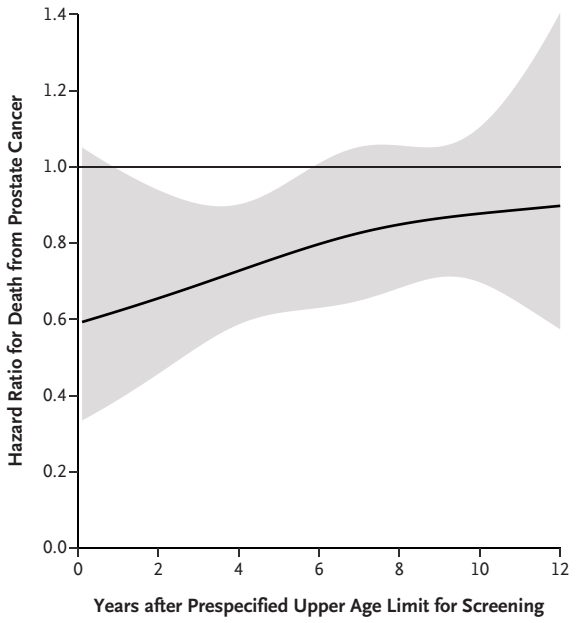



**Figure 3. Hazard Ratio for Death from Prostate Cancer after the Prespecified Upper Age Limit among Men without a Screening Diagnosis.**

The between-group hazard ratio for death from prostate cancer gradually increased with time, with the upper boundary of the confidence interval (shaded area) crossing 1.0 approximately 6 years after the age limit of the screening protocol. Confidence intervals are presented without adjustment for multiplicity and should not be used to infer definitive statistical significance or for formal hypothesis testing.

the fact that many of the youngest participants of the cohort have not yet reached the age of 80 years, after which prostate cancer mortality typically rises. This fact indicates that the true long-term effect of PSA-based screening may still be underestimated, given that modeling data from the Swedish section of the ERSPC suggest screening in this younger age group provides the greatest reduction in prostate cancer mortality,[35] along with the continued decline in the number needed to invite and number needed to diagnose with extended follow-up. Although this report represents the final update of the primary outcome from the ERSPC as a whole, individual centers will continue independent analyses, further contributing to our understanding of the long-term outcomes of PSA-based screening.

Our study has limitations. First, differences in population characteristics, baseline prostate cancer risks, and slight variations in protocols across centers might have affected the results.[36] In addition, data from France were excluded because they did not meet the predefined quality criteria for inclusion.[2,10] Nevertheless, the large, multicenter design still ensures a broad representation of European populations, enhancing generalizability. Furthermore, although data regarding off-study PSA testing are not systematically collected, previous analyses of data from the Finnish, Dutch, and Swedish centers showed that the prevalence of opportunistic PSA screening across the control groups could have partly underestimated the true benefit of organized screening.[37-39] Finally, advances in diagnostics and treatment since the study was initiated may limit the applicability of its findings to current practice. However, many of these improvements, such as greater diagnostic accuracy with MRI and reduced treatment-related harm owing to active surveillance and nerve-sparing surgery, primarily benefit patients with localized disease — the category of disease most often diagnosed through early detection. These developments may therefore enhance, rather than reduce, the potential benefits of screening.

This final analysis of the primary outcome of the ERSPC underscores the importance of long-term outcomes in evaluating the effectiveness of prostate cancer screening. Although our study has shown that PSA-based screening has been beneficial in reducing prostate cancer mortality and in increasing the favorability of the harm-versus-benefit profile over extended follow-up, the associated risks of overdiagnosis and unnecessary interventions remain considerable. Future screening strategies should focus on risk-based approaches to minimize these harms while maintaining the benefits.

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