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Original Article

Balancing the Harms and Benefits of Early Detection of Prostate Cancer

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BACKGROUND: The benefits of prostate cancer screening on an individual level remain unevaluated. **METHODS:** Between 1993 and 1999, a total of 43,987 men, aged 55-74 years, were included in the intervention arm of the European Randomized Study of Screening for Prostate Cancer (ERSPC) section in the Netherlands, Sweden, and Finland. A total of 42,503 men, aged 55-74 years, were included in a clinical population in Northern Ireland. Serum prostate-specific antigen (PSA) <20.0 ng/mL was measured in all men at study entry. All men were followed for prostate cancer incidence and causes of death until December 31, 2006. **RESULTS:** The adjusted absolute difference in prostate cancer specific mortality between the intervention population and the clinical population increased with increasing PSA level at study entry, ie, 0.05 per 10,000 person-years for men who had a serum PSA level of 0.0-1.9 ng/mL and 8.8 per 10,000 person-years for men who had a serum PSA level of 10-19.9 ng/mL. To evaluate the risks of early detection, the number needed to investigate (NNI) and number needed to treat (NNT) to save 1 death from prostate cancer were calculated. Both NNI and NNT were higher for those who had lower PSA levels at study entry. The NNI was 24,642 men for patients who had a serum PSA level of 0.0-1.9 ng/mL and was 133 men for patients who had a serum PSA level of 10-19.9 ng/mL; the NNT was 724 men for patients who had a serum PSA level of 0.0-1.9 ng/mL and was 60 men for patients with a serum PSA level of 10-19.9 ng/mL. **CONCLUSIONS:** For men with a low serum PSA level, the benefits of aggressive investigation and treatment may be limited because they are associated with a large increase in cumulative incidence and potential overtreatment. ***Cancer* 2010;116:4857–65.** © *2010 American Cancer Society.*

KEYWORDS: screening, early detection, prostate cancer, PSA, mortality, ERSPC.

Prostate cancer screening has been subject to much controversy for many years. Recently, the European Randomized Study of Screening for Prostate Cancer (ERSPC) showed a 20% reduction in prostate cancer mortality in the screened population relative to the control population.[1] Secondary analysis of the ERSPC showed that the mortality effect among men was increased to approximately 30% after adjusting for the diluting effect of nonattendance and contamination.[2-3]

The results of the ERSPC did not include individual patient risk stratifications. As blood was not collected at randomization from men in the control group, stratified analysis between the 2 arms of the ERSPC according to serum PSA level on study entry to assess whether the mortality reduction was limited to men with PSA in a particular range was not possible. These analyses are important because the 20% relative reduction in prostate cancer mortality was associated with a considerable increase in the cumulative excess incidence, with screening of 1410 men and treatment of 48 additional cases required to prevent 1 death from prostate cancer.[1]

For this reason, we compared the prostate cancer incidence and prostate cancer specific mortality rates stratified by individual serum PSA level that was measured at study entry in men participating in the intervention arm of the ERSPC and men in Northern Ireland, in whom screening and early detection of prostate cancer was not routinely performed.

MATERIALS AND METHODS

Intervention Population

Between December 1993 and December 1999, a total of 63,153 men, aged 50-74 years, were randomized into the intervention arm of the ERSPC section in the Netherlands, Sweden, and Finland. For the current study, only men aged 55-74

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years, who did not have prostate cancer and were actually screened by PSA, were included. Men with a baseline serum PSA $\geq$ 20.0 ng/mL at study entry were excluded because the main focus of this research was the potential value of early detection. Although legal requirements with respect to randomized trials were different in the Netherlands, Finland, and Sweden, written informed consent was required for those who were randomly assigned to the intervention arm of the study.[4-6]

In the Netherlands, men were screened by PSA measurement, digital rectal examination (DRE) and transrectal ultrasound examination (TRUS) between 1993 and 1997. Sextant biopsy was initially offered to men with PSA $\geq$ 4.0 ng/mL and/or suspicious finding on DRE and/or TRUS. After May 1997, a biopsy was prompted by PSA $\geq$ 3.0 ng/mL only. In Sweden, a sextant biopsy was indicated for men with a level of PSA $\geq$ 3.0 ng/mL. In Finland, men with PSA $\geq$ 4.0 ng/mL were defined as screen positive, and men with PSA = 3.0-3.9 had an ancillary test (DRE until 1998, free/total PSA ratio with a cutoff $\leq$0.16 from 1999 onwards). In Finland, sextant biopsy was initially offered to the screen-positive men; however, in 2002, a biopsy procedure with 10-12 biopsy cores was adopted as a general policy. In Sweden, men were screened at an interval of 2 years until the age of 70 years in contrast to the Netherlands and Finland where men were screened at an interval of 4 years until the ages of 74 years and 71 years, respectively. The screening algorithms used in the centers have been extensively described previously.[4-6]

In all centers, the treatment decisions were made by a local urologist and based on individual patient preference. Cancers diagnosed between the 2 screening intervals or after the maximal screening age clinically or due to opportunistic screening, transurethral resection of the prostate (TURP) for benign disease, and cystoprostatectomy specimens were considered as well and defined as interval cancers. These interval cancers were routinely identified by means of linkage to the national cancer registry. Cancers were classified according to the 1992 Tumor, Node, Metastasis (TNM) classification system. Men with stage T1c disease and serum PSA concentration of $<$10.0 ng/mL were classified as M0, and men with serum PSA concentration of $\geq$100.0 ng/mL were classified as M1, when an isotope bone scan was not performed. In men with a PSA $\geq$ 10.0 and $<$100.0 ng/mL in whom an isotope bone scan was not performed, the metastatic status was considered unknown. Prostate cancer mortality was based on the consensus of an independent Causes of Death Committee (CODC) in Sweden and the Netherlands and on accurately validated official causes of death certificates in Finland.[7-8] Diagnostic and mortality data was available until December 31, 2006.

Clinical Population

In Northern Ireland, data on men aged 55-74 years who had a first serum PSA measurement between January 1994 and December 1999 were included. Men with a prior diagnosis of prostate cancer or a baseline serum PSA $\geq$ 20.0 ng/mL at study entry were excluded. Data were retrospective and were obtained from a population-based database of the Northern Ireland Cancer Registry (NICR) that included all routinely performed PSA tests since 1994. The NICR maintains this confidential electronic database of all PSA results for prostate cancer surveillance purposes. No personal nor identifiable information was removed from the database, and no patient contact was made during this study. During the years of observation, the clinical population was not systematically screened because in Northern Ireland, early detection and screening was not recommended, and the population had a well documented low level of PSA testing (6% of men aged $>$50 years).[9] Furthermore, men tended not to proceed to prostate biopsy until PSA levels were $>$10.0 ng/mL, with few men with low PSA levels having a prostate biopsy.[9] There was no available individual data on the reason for PSA testing, but recent evidence showed that between 1994-1998 $<$20% of PSA testing was in asymptomatic men.[10] The NICR registers all prostate cancer cases and links these to their PSA data. Causes of death were obtained from accurately validated official national death certificates, the World Health Organization's International Classification of Diseases ICD-9 from 1994 until 2000 and the ICD-10 onwards.[3,11] Cancers were classified according to the 1992 TNM classification system with M0 or M1 based on the result of isotope bone scans. Where bone scans were not performed, men with a serum PSA concentration $<$10.0 ng/mL were classified as M0, whereas men with serum PSA concentration $\geq$100.0 ng/mL were classified as M1. In men with a PSA $\geq$ 10.0 and $<$100.0 ng/mL at diagnosis in whom an isotope bone scan was not performed, the metastatic status was considered unknown. Diagnostic and mortality data was available until December 31, 2006.

Statistical Analysis

For both groups the time of follow-up was measured from the date of their first PSA test up to their date of death or

Table 1. Characteristics of Men at Study Entry

	Intervention Group No. (% of Total)	Clinical Group No. (% of Total)	*P*
Total participants included	43,987	42,503	
Age, y, median	61	65	<.001[a]
PSA at study entry, ng/mL			
Median	1.18	1.60	<.001[a]
0.00-1.99	32,035 (72.8)	25,555 (60.1)	<.001[b]
2.00-3.99	7467 (17.0)	8703 (20.5)	
4.00- 9.99	3927 (8.9)	6493 (15.3)	
10.00-19.99	558 (1.3)	1752 (4.1)	

[a] Mann-Whitney *U* test.
[b] Chi-square test.

December 31, 2006. Baseline serum PSA levels were stratified into 4 categories, PSA of 0.0-1.9, 2.0-3.9, 4.0-9.9, and 10.0-19.9 ng/mL. A multivariate Poisson regression analysis was used with the time of follow-up (divided into 2-years intervals) until either the event of interest or censoring occurred. The following model was used:

$$Log\ (E(Y)) = log(exp) + \beta_0 + \beta_1 x_1 + \cdots\cdots + \beta_5 x_5$$

This is a generalized linear model with log-link function and Poisson distributed errors where $E(Y)$ is expected number of prostate cancer deaths, $log(exp)$ is the logarithm of the follow-up time, $(x_1, x_2, \ldots, x_p)^T$ are the predictive variables, ie, PSA (categories), age (continue), study population, and the time interval since first screening visit (2-years intervals). The βi is the coefficient corresponding to x_i. The term $log(exp)$ was an offset with the parameter estimate constrained to 1, which enables the interpretation of the parameter estimates as rate ratios.

Comparisons between the observed and predicted data of this multivariate model showed the predictions to be accurate. In addition, the number needed to investigate (NNI) and the number needed to treat (NNT) to save 1 death from prostate cancer were calculated[12] on the basis of the adjusted absolute rate differences. In both populations, baseline serum PSA levels and age-adjusted cumulative hazards were graphically estimated for different PSA categories at study entry by using a cumulative hazard method. All analyses were performed with the commercially available STATA package: Data Analysis and Statistical Software, version 10.0 (StataCorp, College Station, Tex), and the cumulative hazard figures were obtained with Statistical Package for the Social Sciences software, version 16.0 (SPSS, Chicago, Ill).

RESULTS

Baseline Characteristics

A total of 42,503 men were included in the clinical population, and a total of 43,987 men were included in the intervention population. Participants had statistically significant differences in their baseline characteristics at study entry (Table 1); the median age and baseline serum PSA level were higher in the clinical population. The median follow-up time was 8.8 years (standard error of the mean [SE], 3.1 years) and 9.1 years (SE, 2.2 years) for the clinical and intervention population, respectively.

Prostate Cancer Diagnosis

Prostate cancer was diagnosed in 1522 (3.6%) men in the clinical population and in 4339 (9.9%) men in the intervention population (adjusted rate ratio [RR], 4.61; 95% confidence interval [CI], 4.33-4.91). Patients in the clinical population were diagnosed at an older age and with a higher median serum PSA level (Table 2). The number of men with a positive result on an isotope bone scan (or a PSA value of more than 100.0 ng/mL in those without bone scan results) at diagnosis was 6.1 per 1000 men in the clinical group and 1.2 per 1000 men in the intervention group ($P < .001$). The median time to a prostate cancer diagnosis was lower in the intervention group than in the clinical group, 4.1 versus 5.3 years, respectively, $P < .001$.

The prostate cancer incidence rates increased with increasing baseline PSA level in both study populations

Table 2. Patient Characteristics at Diagnosis

	Intervention Group No. (% of Total Participants)	Clinical Group No. (% of Total Participants)	*P*
Total patients diagnosed	4339 (9.9)	1522 (3.6)	<.001[a]
Age, y, at diagnosis, median	66	71	<.001[b]
PSA at diagnosis, ng/mL, median	5.0	12.8	<.001[b]
Disease extent at diagnosis			
Not metastasized, M0	4285 (9.8)	1129 (2.7)	<.001[a]
Metastasized, M1	54 (0.1)	261 (0.6)	
Not known	0 (0)	124 (0.3)	

PSA indicates prostate-specific antigen.
[a] Chi-square test.
[b] Mann-Whitney *U* test.

Table 3. Adjusted Rate Ratio of Prostate Cancer Incidence for Serum PSA at Study Entry

	Intervention Population				Clinical Population			
PSA at Baseline	No. at Risk	No. Diagnosed	Rate Ratio (95%CI)	*P*	No. at Risk	No. Diagnosed	Rate Ratio (95%CI)	*P*
0.0-1.99	32,009	980	*		25,555	243	[a]	
2.0-3.99	7467	1553	6.80 (6.27-7.37)	<.001	8703	313	3.66 (3.09-4.33)	<.001
4.0-9.99	3889	1472	12.62 (11.62-13.71)	<.001	6493	611	9.56 (8.22-11.12)	<.001
10.0-19.99	539	334	21.67 (19.09-24.59)	<.001	1752	355	21.48 (18.18-25.38)	<.001

PSA indicates prostate-specific cancer; No., observed number of men at risk.
[a] Reference group to which other groups are compared. The reference group by definition has a rate ratio of 1.

(Table 3). The adjusted absolute rate differences on a cancer diagnosis between the intervention group and the clinical group increased with increasing baseline PSA levels (Table 4).

Prostate Cancer Mortality

By the end of 2006, the overall mortality was 25.5% in the clinical group and 14.5% in the intervention group (adjusted RR, 0.79; 95% CI, 0.77-0.82). In total, 236 (0.6%) men died from a prostate cancer-related cause of death in the clinical population, and 109 (0.2%) men died from a prostate cancer-related cause of death in the intervention population. This resulted in an age and baseline serum PSA level adjusted, nonsignificant, relative reduction in prostate cancer specific mortality of 20% in the intervention population relative to the clinical population (RR, 0.80; 95% CI, 0.63-1.02).

The prostate cancer mortality rates increased with increasing baseline PSA level in both groups (Table 5). Relative to the men with a baseline serum PSA<2.0 ng/mL at study entry, men with a higher baseline serum PSA level had a significant, increased, adjusted RR of dying from prostate cancer in both groups. The absolute difference in prostate cancer specific mortality was 0.05 per 10,000 person years in men with a baseline serum PSA level of 0-1.9 ng/mL and 8.88 per 10,000 person years in men with a baseline serum PSA of 10-19.9 ng/mL, increasing with the increasing baseline PSA level (Table 6).

Table 4. Adjusted Absolute Difference in Prostate Cancer Incidence Between the Intervention Population and the Clinical Population

PSA at Baseline	Observed Pca Incidence Intervention	Observed Pca Incidence Clinical	Absolute Difference PC Incidence
0.0-1.99	23.47	11.52	35.59
2.0-3.99	235.95	43.21	214.32
4.0-9.99	431.29	144.71	377.40
10.0-19.99	709.80	253.04	561.76

Pca indicates prostate cancer. Pca incidence in rates per 10,000 man-years. Absolute difference, statistically adjusted, defined as rate per 10,000 man-years.

The age-adjusted cumulative hazard graphs for prostate cancer specific death by baseline PSA and study group are presented in Figures 1-4. Relative to the lowest PSA category, the main absolute difference in prostate cancer mortality was observed for the PSA categories 4.0-9.9 ng/mL and 10.0-19.9 ng/mL at study entry.

Table 5. Adjusted Rate Ratio of Prostate Cancer Specific Mortality for Serum PSA at Study Entry

	Intervention Population				Clinical Population			
PSA at Baseline	No. at Risk	No. Pca Deaths	Relative Risk (95%CI)	*P*	No. at Risk	No. Pca Deaths	Relative Risk (95%CI)	*P*
0.0-1.99	32,009	26	[a]		25555	29	*	
2.0-3.99	7467	26	3.97 (2.29-6.87)	<.001	8703	44	3.39 (2.5-6.29)	<.001
4.0-9.99	3889	38	10.78 (6.46-17.99)	<.001	6493	89	10.09 (6.59-15.43)	<.001
10.0-19.99	539	19	37.17 (20.13-68.62)	<.001	1752	74	31.05 (20.03-48.11)	<.001

No. indicates observed number of men at risk.
[a] Reference group to which other groups are compared. The reference group by definition has a RR of 1.

Table 6. Adjusted Absolute Difference of Prostate Cancer Specific Deaths Between the Clinical Population and the Intervention Population, Adjusted NNI And NNT to Save One Man From Prostate Cancer Death

PSA at Baseline	Proportion of Study Population	Median Follow-up, y	Observed Pca Deaths Intervention	Observed Pca Deaths Clinical	Absolute Difference Pca Mortality	NNI	NNT
0.0-1.99	66.6%	8.9	0.92	1.37	0.05	24,642	724
2.0-3.99	18.7%	9.0	3.95	6.07	0.47	2393	427
4.0-9.99	12.0%	8.9	11.13	16.71	2.34	492	152
10.0-19.99	2.7%	8.7	40.38	52.75	8.88	133	60

NNI indicates number needed to investigate to save one death from prostate cancer; NNT, number needed to treat to save one death from prostate cancer. Pca deaths in rates per 10,000 man-years. Absolute difference, statistically adjusted, defined as rate per 10,000 man-years.

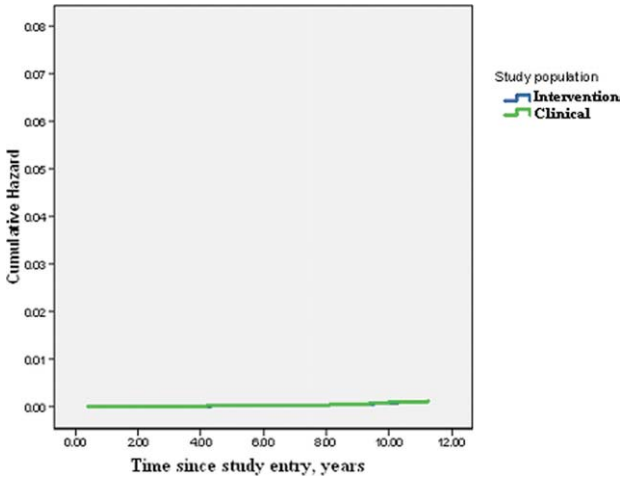

Figure 1. Prostate cancer specific death in men with serum PSA of 0.0-1.99 ng/mL at study entry.

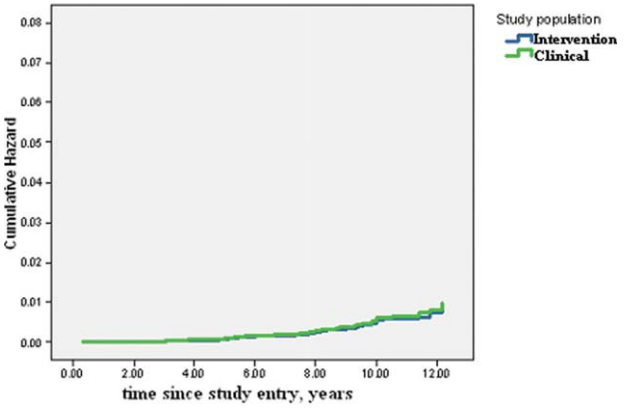

Figure 2. Prostate cancer specific death in men with serum PSA of 2.0-3.99 ng/mL at study entry.

Furthermore, a negligible difference in the cumulative hazard in prostate cancer death was observed for men with PSAs of 0.0-1.9 ng/mL and 2.0-3.9 ng/mL at study entry.

Potential Harms of Early Detection

Table 6 summarized the adjusted magnitude of early detection and treatment for the baseline PSA categories in terms of the NNI and NNT to save 1 man from prostate cancer death. NNI and NNT decreased with increasing baseline PSA level. NNI varied from 24,642 men to 133 men for patients with a baseline serum PSA of 0.0-1.9 ng/mL versus patients with a baseline serum PSA of 10.0-19.9 ng/mL, respectively. NNT varied from 724 men to 60 men for patients with a baseline serum PSA 0.0-1.9 ng/mL versus those with a baseline serum PSA of 10.0-19.9 ng/mL, respectively.

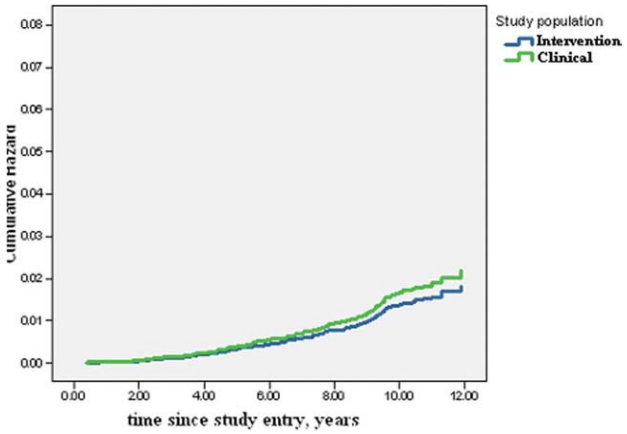

Figure 3. Prostate cancer specific death in men with serum PSA of 4.0-9.99 ng/mL at study entry.

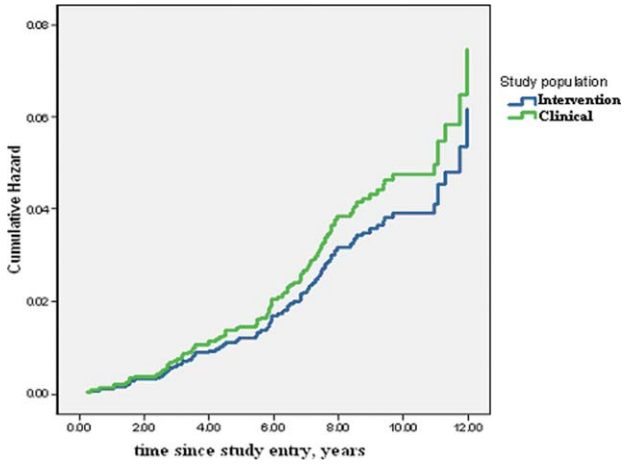

Figure 4. Prostate cancer specific death in men with serum PSA of 10.0-19.99 ng/mL at study entry.

DISCUSSION

Early detection and screening for prostate cancer has potential harms. Prostate cancer screening increases incidence, which may cause needless worry and expense for a lot of men who may be getting treatment for tumors growing too slowly to do any harm.[13] However, screening and early detection has potential benefits as well. These benefits are a reduction in prostate cancer mortality and a decrease in the number of men that suffer from the complications of advanced disease.[1,3] In the current study, the potential balance between these harms and benefits is demonstrated by using the measures NNI and NNT. The NNI equals 1 divided by the absolute mortality reduction, and the NNT equals 1 divided by the absolute mortality reduction multiplied by the excess prostate cancer incidence. Consequently, the NNI and NNT show, on the one hand the effectiveness of early detection in terms of the reduction in prostate cancer mortality, and on the other hand, the harms of early detection in terms of the percentage of men who are diagnosed with a potential overdiagnosed prostate cancer.

This study provides additional information on how the harms and benefits of screening, early detection, and treatment are distributed in relation to baseline PSA levels. It has demonstrated that the yield of prostate cancer increased with the increasing baseline serum PSA level at study entry. The benefits of early detection may be small for men with a baseline serum PSA of 0-3.9 ng/mL at study entry. Despite the short follow-up, especially for men with a baseline serum PSA $<$ 2.0 ng/mL at study entry, aggressive investigation and treatment yielded little or no mortality reduction, whereas a significant increase in the cumulative incidence of prostate cancer was observed. These observations are in line with studies that show a strong correlation between the lower baseline PSA values and the detection of cancers with potential indolent tumor characteristics.[9,14-16] These results were confirmed in the current study; men with relatively low serum PSA levels at study entry were more often diagnosed with prostate cancer and favorable tumor stage and pathological characteristics (data not shown).

The main purpose of this study was to add information to the existing results of the ERSPC by providing a PSA risk stratification that would avoid misuse and maximization of PSA testing. Our results suggest that, assuming that the risk distribution according to the different PSA levels in this study was similar to the ERSPC, most of the absolute reduction in prostate cancer mortality is achieved in men who had a moderately elevated PSA at study entry. In other words, the greatest benefits of early detection programs may be when men, aged 55-74 years, are diagnosed and treated when their serum PSA level is in the range of 4.0 ng/mL to 9.9 ng/mL or 10.0 ng/mL to 19.9 ng/mL. Furthermore, the practice of following research that recommends more intensive PSA-based screening by lowering the PSA level cutoff may greatly increase the number of men who need additional investigations and treatment while having little effect on the reduction of prostate cancer mortality.

Our second main observation is that a large, cumulative, excess incidence was observed in men with a low

baseline serum PSA level at study entry in the intervention group. For men with a baseline serum PSA of 0.0-1.99 ng/mL at study entry, the increased risk of being diagnosed with prostate cancer was increased more than 4 fold. In contrast, the prostate cancer specific mortality difference was small, meaning that the potential harms were greater. The NNTs to save 1 human from prostate cancer death were 724 and 427, respectively, when the baseline serum PSA level was in the range of 0.0 ng/mL to 1.9 ng/mL or 2.0 ng/mL to 3.9 ng/mL at study entry, respectively. Consequently, in these men, aggressive investigation and treatment was associated with extensive overtreatment and increase in costs. Furthermore, these observations suggest that for men with lower PSA levels, a screening protocol, as currently performed in the ERSPC, may not be a proper tool to reduce prostate cancer mortality. A simultaneous decrease in the quality of life may result. However, because all results are cumulative, and the overall mortality is still low, longer follow-up is needed to confirm this early conclusion.

The significant, excess, incidence rates were mainly a result of repeated systematic screening using a lateralized sextant biopsy technique. A recent review showed that sextant biopsy, either classic or lateralized, will miss 23% or 19% of biopsy-detectable prostate cancer with extended biopsy schemes, respectively.[17] Therefore, the excess incidence could be even higher if the current, clinically acceptable, extended biopsy schemes are used for repeated screening.

The observations of the present study can be compared with the results of the Scandinavian Control Group Prostate (SCGP-4) study because current data included the effect of early detection as well as the effect of early aggressive treatment. The SCGP-4 study showed that radical prostatectomy decreased prostate cancer mortality compared with expected management for men with favorable, localized, clinically diagnosed disease after a median follow-up of 10 years.[18] In the SCGP-4 study, 52% of the patients who were diagnosed with prostate cancer had PSA $\leq$ 10 ng/mL. In patients with PSA $\leq$ 10 ng/mL at diagnosis, the difference in the cumulative incidence of prostate cancer death between radical prostatectomy and watchful waiting was smaller and was observed after more years of follow-up than in the patients diagnosed with PSA $>$ 10 ng/mL.[19] Although the present study is not a randomized controlled trial, the trends in prostate cancer mortality of our study compars equal to the SCGP-4 study. In the current study, the difference in the cumulative risk of death from prostate cancer was observed earlier for men with a baseline serum PSA level of 10.0-19.9 ng/mL at study entry (Fig. 4). Furthermore, for men included in the intervention and clinical cohort, an overlap in the cumulative hazard curves during the first 5 years was observed for men with baseline serum PSA of 4.0-9.9 ng/mL and 8 years for men with baseline serum PSA of 2.0-3.9 ng/mL at study entry (Figs. 2 and 3).

The main limitation of this study is the absence of randomization, which necessarily results in different patient characteristics at study entry. Statistical adjustment was needed for the difference in age and serum PSA level at study entry. Furthermore, the large difference in all-cause mortality might have biased the outcomes. Obviously, the optimal study design would be the comparative evaluation of the intervention and control arm of the ERSPC. However, because serum PSA was not collected nor was PSA measured at study entry in the control arm of the ERSPC, the present study design is an alternative method.

Furthermore, different treatments in both cohorts might have affected the outcomes, with men diagnosed and treated with curative intent at an earlier stage likely to have a better outcome.[18,20-21] In both groups, after diagnosis, men were free to choose treatment in collaboration with their local urologist. As outlined in Table 2, men in Northern Ireland had higher PSA levels at diagnosis and a higher rate of metastatic disease; they were, therefore, less likely to undergo prostatectomy and more likely to have androgen deprivation therapy.[3] These differences in treatment are inherent to any study with a large difference in the intensity of screening and early detection. The distribution of different treatments in the 2 study groups were published earlier.[3]

Another limitation that might have biased the study is the different PSA assays used. Several assays were used in Northern Ireland, which differs from the same PSA assay used in the ERSPC. Cluster analyses that were performed for the different laboratories in Northern Ireland showed that there was no systematic difference in PSA values provided by the different laboratories and that the laboratory of origin did not affect the results. Finally, it could be argued that this study is plagued by a methodological bias, ie, lead time. Generally, lead time is defined as the time between the detection by screening and the clinical diagnosis when there had been no screening. However, as in current study, the observation time is defined as the time difference between the time of death and the time of first PSA measurement; thus, lead time is unlikely to have influenced outcomes. Nevertheless, it

remains unknown whether men with a specific age and PSA level in a screening population compares equally to men with the same age and PSA level in the selected clinical population.

The strong aspect of this study is the risk stratification based on baseline PSA level and age. To the best of our knowledge, our study is the first report on a population-based study cohort that showed the prostate cancer incidence and mortality in 2 populations with a different intensity of screening and early detection stratified by baseline age and PSA level. Currently, the interpretation of the balance between the risks and benefits is subjective, meaning it is a matter of personal judgement for which PSA level the benefits outweigh the harm. However, the final purpose of the current study design is to stratify men by risk at baseline (based on age and PSA) into groups that require no further screening or that have a higher risk of prostate cancer mortality and should continue screening and early treatment. Currently, longer follow-up is needed to provide clinical recommendations.

Conclusions

Baseline serum PSA level before diagnosis is a strong predictor for prostate cancer mortality in screen-detected and clinically detected prostate cancer. In the absence of standardized early detection programs, PSA level can be used for a risk assessment that balances the harms and benefits of early detection in men aged 55-74 years. Current analyses suggest that the significant reduction in disease-specific mortality with screening and early detection may be limited to men with baseline elevated PSA levels. In men with a low baseline serum PSA, the benefits of continued aggressive investigation and treatment may be limited, and they are associated with a large increase in cumulative incidence, overtreatment, and costs.

CONFLICT OF INTEREST DISCLOSURES

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REFERENCES

1. Schroder FH, Hugosson J, Roobol MJ, et al. Screening and prostate-cancer mortality in a randomized European study. *N Engl J Med*. 2009;360:1320-1328,.
2. Roobol MJ, Kerkhof M, Schroder FH, et al. Prostate cancer mortality reduction by prostate-specific antigen-based screening adjusted for nonattendance and contamination in the European Randomised Study of Screening for Prostate Cancer (ERSPC). *Eur Urol*. 2009;56:584-591.
3. van Leeuwen PJ, Connolly D, Gavin A, et al. Prostate cancer mortality in screen and clinically detected prostate cancer: estimating the screening benefit. *Eur J Cancer*. 2010;46: 377-383.
4. Roobol MJ, Schroder FH. European Randomized Study of Screening for Prostate Cancer: achievements and presentation. *BJU Int*. 2003;92(suppl 2):117-122.
5. Finne P, Stenman UH, Maattanen L, et al. The Finnish trial of prostate cancer screening: where are we now? *BJU Int*. 2003;92(suppl 2):22-26.
6. Hugosson J, Aus G, Bergdahl S, et al. Population-based screening for prostate cancer by measuring free and total serum prostate-specific antigen in Sweden. *BJU Int*. 2003; 92(suppl 2):39-43.
7. De Koning HJ, Blom J, Merkelbach JW, et al. Determining the cause of death in randomized screening trial(s) for prostate cancer. *BJU Int*. 2003;92(suppl 2):71-78.
8. Makinen T, Karhunen P, Aro J, Lahtela J, Maattanen L, Auvinen A. Assessment of causes of death in a prostate cancer screening trial. *Int J Cancer*. 2008;122:413-417.
9. Connolly D, Black A, Gavin A, Keane PF, Murray LJ. Baseline prostate-specific antigen level and risk of prostate cancer and prostate-specific mortality: diagnosis is dependent on the intensity of investigation. *Cancer Epidemiol Biomarkers Prev*. 2008;17:271-278.
10. Connolly D. Long term follow-up of men with elevated prostate specific antigen levels: a population based study. MD Thesis. Belfast: Queen's University Belfast. 2007.
11. World Health Organization. International statistical classification of diseases and related health problems. 10th revision. Geneva: WHO; 1992:1.
12. Rembold CM. Number needed to screen: development of a statistic for disease screening. *BMJ*. 1998;317:307-312.
13. Draisma G, Boer R, Otto SJ, et al. Lead times and overdetection due to prostate-specific antigen screening: estimates from the European Randomized Study of Screening for Prostate Cancer. *J Natl Cancer Inst*. 2003;95:868-878.
14. Gann PH, Hennekens CH, Stampfer MJ. A prospective evaluation of plasma prostate-specific antigen for detection of prostatic cancer. *JAMA*. 1995;273:289-294.
15. Fang J, Metter EJ, Landis P, Chan DW, Morrell CH, Carter HB. Low levels of prostate-specific antigen predict long-term risk of prostate cancer: results from the Baltimore Longitudinal Study of Aging. *Urology*. 2001;58:411-416.

16. Loeb S, Roehl KA, Antenor JA, Catalona WJ, Suarez BK, Nadler RB. Baseline prostate-specific antigen compared with median prostate-specific antigen for age group as predictor of prostate cancer risk in men younger than 60 years old. *Urology*. 2006;67:316-320.
17. Schroder FH, van den Bergh RC, Wolters T, et al. Eleven-year outcome of patients with prostate cancers diagnosed during screening after initial negative sextant biopsies. *Eur Urol*. 2010;57:256-266.
18. Bill-Axelson A, Holmberg L, Ruutu M, et al. Radical prostatectomy versus watchful waiting in early prostate cancer. *N Engl J Med*. 2005;352:1977-1984.
19. Holmberg L, Bill-Axelson A, Garmo H, et al. Prognostic markers under watchful waiting and radical prostatectomy. *Hematol Oncol Clin North Am*. 2006;20:845-855.
20. Messing EM, Manola J, Yao J, et al. Immediate versus deferred androgen deprivation treatment in patients with node-positive prostate cancer after radical prostatectomy and pelvic lymphadenectomy. *Lancet Oncol*. 2006;7:472-479.
21. Bolla M, Collette L, Blank L, et al. Long-term results with immediate androgen suppression and external irradiation in patients with locally advanced prostate cancer (an EORTC study): a phase III randomised trial. *Lancet*. 2002;360:103-106.