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Prostate cancer mortality in screen and clinically detected prostate cancer: Estimating the screening benefit

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ABSTRACT

Background: To estimate the benefits of prostate-specific antigen (PSA) screening on prostate cancer (Pca) metastasis and Pca-specific mortality, we compared two populations with a well-defined difference in intensity of screening.

Methods: Between 1997 and 1999, a total of 11,970 men, aged 55–74 years, were included in the intervention arm of the European Randomised Study of Screening for Prostate Cancer (ERSPC) section Rotterdam. Control population consisted of 133,287 men, aged 55–74 years, between 1998 and 1999 in Northern Ireland (NI). Men were followed for Pca incidence, Pca metastasis and cause of death until 31st December 2006.

Results: Median age in both groups was 63 years at study entry ($p = 0.184$). In Rotterdam 94.2% of men and in NI 6% of men underwent PSA testing. In Rotterdam, 1153 men (9.6%) were diagnosed with Pca with median baseline PSA of 5.1 ng/ml. In NI, 3962 men (3.0%, $p < 0.001$) were diagnosed with Pca with median baseline PSA of 18.0 ng/ml ($p < 0.001$). The relative risk of Pca metastasis during observation in the intervention population compared to control population was 0.47 (95% confidence interval (CI), 0.35–0.63; $p < 0.001$). The relative risk of Pca-specific mortality was also lower in the intervention population compared to the control population after a median follow-up of 8.5 years: 0.63 (95% CI, 0.45–0.88; $p = 0.008$); absolute mortality reduction was 1.8 deaths per 1000 men.

Conclusions: A relative reduction in Pca metastasis of 53% and Pca mortality of 37% was observed in the intervention population after 8.5 years of observation. The impact of overdiagnosis, quality of life benefits and cost-effectiveness need to be assessed before population-based PSA screening can be recommended.

1. Introduction

Over the past decade, there has been a marked decline in prostate cancer (Pca) mortality, starting in Northern America and later also observed in many European countries where currently mortality rates are lower than in the pre prostate-specific antigen (PSA) era.[1–3] This decline is likely to be at least in part due to the widespread use of PSA testing and indeed,

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the efficacy of PSA screening in lowering Pca mortality has now been established in a randomised-controlled trial.[4] The European Randomised Study of Screening for Prostate Cancer (ERSPC) demonstrated a 20% relative reduction in Pca mortality due to PSA screening after comparing the number of men who died from Pca in a screened population with that in a control population where screening was not recommended or performed on a systematic basis.[4]

Despite the ERSPC study design recommending no screening in the control population, opportunistic PSA testing occurred in 8–29% of men in the control populations in participating European countries.[5,6] The level of contamination was even higher in the Prostate, Lung, Colorectal and Ovarian (PLCO) trials in the United States (US), with 52% of men in the control population also undergoing PSA screening.[7] The outcomes of both the studies will have been weakened by the considerable level of Pca screening in the control populations, which may have resulted in an underestimation of the true benefits of Pca screening and indeed, may have contributed to the lack of difference in Pca mortality between the two arms of the PLCO study.

One of the possible methods of estimating the true effect of PSA screening is applying a secondary analysis using the Cuzick-method: effect of screening in men actually screened.[8,9] Another method is the selection of a control population with a very low intensity of screening. In Northern Ireland (NI), PSA screening is not recommended and there is a well-documented low level of PSA testing (6% of men >50 years old).[10] Further, 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.[10] In the current study, we compared the characteristics and outcomes of a population participating in the ERSPC, section Rotterdam, with men in Northern Ireland (NI) during a time period when asymptomatic PSA screening was infrequent.[10]

2. Materials and methods

2.1. Intervention cohort

Between December 1993 and December 1999, a total of 42,376 men, aged 55–74 years, were randomised in the Rotterdam section of the ERSPC. All men with a prior diagnosis of Pca were excluded. In the current study, men randomised to the intervention arm between 1997 and 1999 were included. This inclusion criterion allowed an equal time of follow-up in the intervention and control populations. Up to May 1997, the men were screened with an interval of 4 years by PSA measurement, digital rectal examination (DRE) and transrectal ultrasound examination (TRUS). Sextant biopsy was initially offered to men with PSA $\geqslant$4.0 ng/ml and/or suspicious finding on DRE and/or TRUS. After November 1997 a biopsy was prompted by PSA $\geqslant$3.0 ng/ml only. Treatment decisions were made by local urologists and individual patient preference. Details of the screening methodology were reviewed by Roobol et al.[11] Cancers diagnosed clinically between the two screens or due to opportunistic screening, transurethral resection of the prostate (TURP) for benign disease and cystoprostatectomy specimens were identified and included in this cohort as interval cancers. These interval cancers were identified by means of a linkage with the national cancer registries. Follow-up in this respect was complete until 31st December 2006. Grading of the cancers was done using the Gleason grading system and classified according to the 1992 TNM classification. When an isotope bone scan was not performed, men with stage T1c disease and serum PSA concentration <10.0 ng/ml at diagnosis were classified as M0 and men with serum PSA concentration $\geqslant$100.0 ng/ml were classified as M1. In men with a PSA >10 ng/ml and <100 ng/ml at diagnosis, the metastatic status was considered as unknown. Pca mortality was based on the consensus of a Causes of Death Committee (CODC).[12] This committee reviewed medical records of all men who were deceased with a Pca using a predefined decision tree.[12]

2.2. Control cohort

Data on 133,287 men, aged 55–74 years between 1st January 1998 and 31st December 1999, in NI were included in the control cohort. Men with a prior diagnosis of any other type of cancer, except non-melanoma skin cancer, were excluded since in the ERSPC almost no men with another type of cancer participated. NI has a stable and homogenous population with little migration (0.7% annually).[10] For this reason the group of men who were extracted from the NI population register was followed up as a cohort. All men diagnosed with Pca in NI are routinely registered by the Northern Ireland Cancer Registry (NICR). Details of the NICR PSA database and matching process have previously been described.[10] Using unique identifiers (name, date of birth and address), the NICR links Pca data to their database of all PSA tests performed throughout Northern Ireland and to the Registrar General's Office (Northern Ireland) database of deaths. Causes of death were obtained from official national death certificates, ICD, 9th revision from 1994 until 2000 and 10th revision onwards (World Health Organisation, 1992).[13] Patients were considered to have died from Pca only if Pca (185 or C61) was coded as the primary cause of death on the death certificate. Grading of the cancers was done using the Gleason grading system. Initial treatment data were extracted from medical charts. Cancers were classified according to the 1992 TNM classification with M0 or M1 status based on the result of isotope bone scans. Where bone scans were not performed, men with serum PSA at diagnosis <10.0 ng/ml were classified as M0, men PSA >10 and <100 ng/ml at diagnosis as unknown, whilst men with serum PSA concentration $\geqslant$100.0 ng/ml at diagnosis were classified as M1. Diagnostic and mortality data were checked until 31st December 2006.

2.3. Validation of cause of death data in Northern Ireland

To validate the cause of death data from death certificates in NI, a random sample of 136 men who had Pca and subsequently died were identified (7.6% of total, median age 77 years). All available information from General Practitioner and hospital charts was extracted and reviewed independently by two authors (P.V.L., D.C.). Using the predefined CODC flowcharts,[12] a cause of death was assigned in each case. In cases where there was a discrepancy in the assigned cause of death, the notes were reassessed until a consensus

was reached. In 119 men (87.5%), the death certificate data matched with that of the performed review. Four men (2.9%) had insufficient information to assign a cause of death. Of the 13 inaccurate recorded causes of death, six were incorrectly recorded as primary cause Pca and seven incorrectly recorded as due to intercurrent disease. This resulted in a death certificate accuracy of 90.4% (SD 2.19).

2.4. *Statistical analysis*

The chi-square (χ^2) and the Mann–Whitney *U* tests were used to assess the relationship between categorical and continuous variables, respectively, between the intervention and the control cohorts. Pca metastasis and mortality risk ratios between the two populations were estimated using a Poisson regression analysis. For both groups the number of man-years were calculated from the date of their study entry up to their date of death or 31st December 2006 when still alive. The Nelson–Aalen analysis was used for the graphical estimation of the Pca mortality and Pca metastasis cumulative hazards,[14] and cumulative survival percentages are presented. In both cohorts the survival time was defined as the time from study entry until Pca death, with censoring at the date of an intercurrent death or 31st December 2006. For Pca metastasis the survival time was defined as the time from study entry until Pca metastasis with censoring at date of death if death occurred prior to a metastasis or 31st December 2006. A two-sided p value <0.05 was considered to be statistically significant. All analyses were performed with STATA: Data Analysis and Statistical Software, version 10.0.

3. Results

In the intervention cohort, 11,970 men, median age 63 years, were included, with 1153 (9.6%) of these diagnosed with Pca during the follow-up period. In the control cohort 133,287 men were included, with 3962 (3.0%) diagnosed with Pca with identical follow-up. Baseline patient characteristics are presented in Table 1. Median age at inclusion was similar, however the age distribution at inclusion was different for both groups ($p = 0.184$ and $p < 0.001$, respectively). Age at diagnosis was higher in the control cohort (median 70 versus 67 years, $p < 0.001$) with a higher median PSA at diagnosis (18.0 versus 5.1 ng/ml, $p < 0.001$). Median follow-up was 8.53 years in the intervention population and 8.72 years in the control population. In the intervention cohort 100% of Pca diagnoses were confirmed histologically by prostate biopsy (99.7%), cystoprostatectomy specimen (0.1%) or TURP (0.2%). In the control cohort 68.2% of men were diagnosed by prostate biopsy; 18.1% and 13.7% were diagnosed by TURP or on the basis of clinical opinion only (no histological confirmation), respectively.

In the intervention cohort 11 men (0.1% of total) and in control cohort 862 men (0.6% of total) had Pca metastasis at diagnosis ($p < 0.001$). There was a significant reduction of 53% in Pca metastasis during observation in the intervention population relative to the control population: RR 0.47 (95% confidence interval (CI), 0.35–0.63; $p < 0.001$). Pca metastasis cumulative hazard is graphically illustrated in Fig. 1. As shown, the cumulative Pca metastasis hazard starts to differ after 2 years of observation and becomes statistically significant after 5 years. Furthermore, as demonstrated in Fig. 1, this difference in metastatic disease is likely to increase with longer follow-up.

In the intervention cohort 35 (0.29%) men and in the control cohort 627 (0.47%) men died due to Pca or to a Pca intervention-related procedure. This equated to a reduction in Pca mortality of 37% in the intervention population relative to the control population: RR 0.63 (95% CI, 0.45–0.88; $p = 0.008$). The Pca-specific cumulative hazards are graphically illustrated for both cohorts in Fig. 2. The difference in Pca-specific mortality, expressed by a cumulative hazard, becomes statistically significant 6 years after the start of observation. After a median follow-up of 8.5 years, the absolute rate of Pca mortality was 0.36 per 1000 person-years in the intervention cohort compared to 0.58 per 1000 person-years in the control cohort; the absolute risk difference was 1.8 deaths per 1000 men (1.8 per 1000 men = 627 Pca deaths/133,287 men control population – 35 Pca deaths/11,970 men intervention cohort), which correspond to 555 (1000/1.8) men needed to be screened to save one Pca death.[15] Additional Pca diagnosed by screening resulted in an increase in cumulative incidence with respect to the control population of 67 per 1000 men, i.e. 37 (555/1000 * 67) cases had to be treated (NNT) in order to prevent one death from Pca.[15] These estimates are all cumulative and therefore interpreted as the probability, or risk, that an individual will have during the 8.5 years of observation.[16]

During follow-up, 1676 men (14.0% of total) died in the intervention cohort, which was significantly lower than the overall mortality of 27,083 men (20.3% of total) in the control cohort: RR 0.70 (95% CI, 0.66–0.73; $p < 0.001$).

4. Discussion

The ERSPC study demonstrated a 20% decrease in Pca mortality due to PSA screening, whilst the PLCO trial did not find any Pca-specific mortality reduction.[4,7] A weakness in both these trials, more so in the PLCO trial, was the level of opportunistic screening in the control populations. Given the high level of PSA testing and the high rate of screen-detected Pca in many countries throughout the world, any randomised trial will have similar difficulties with contamination of the control population, which may lead to an underestimation of the true value of screening. In the current study, we assessed retrospectively the rate of Pca metastasis and Pca-specific mortality in men who did not undergo systematic screening or early investigation, and compared this with men who were prospectively screened for Pca. Our aim was to estimate the true benefits of PSA screening from a Pca screening trial, when there is a low level of contamination in the control population.

The main finding is the absolute mortality reduction of 1.8 deaths per 1000 men in favour of the screened population, which corresponds to a relative risk reduction of 37%, after a median follow-up of 8.5 years. These results compare favourably to the ERSPC study that found an absolute mortality reduction of 0.71 per 1000 men after an average follow-up of 8.8 years and a relative reduction of 20%.[4] In the present

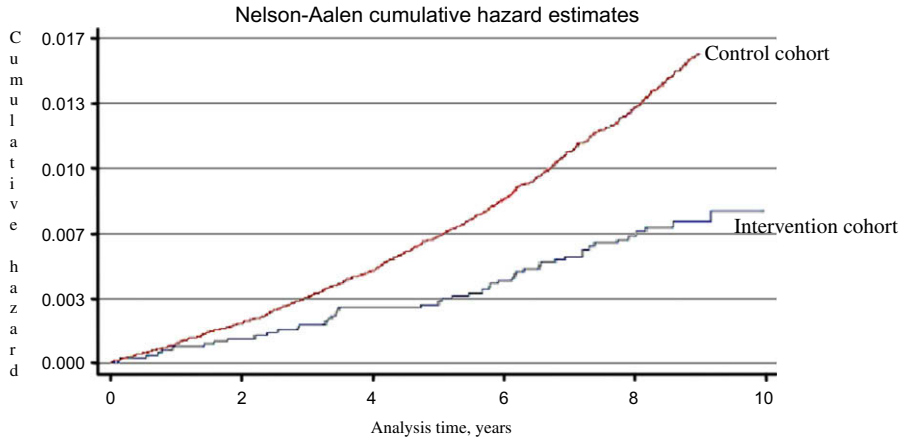
Table 1 – Baseline characteristics at study start, diagnosis and primary treatment modalities. Median follow-up of 8.5 years.

	Control cohort Northern Ireland, N (% of total)	Intervention cohort ERSSC Rotterdam N (% of total)	p Value
Total participants included	133,287	11,970	
Age (year), median	63	63	0.184
55–60	52,104 (39.0)	4310 (36.0)	<0.001
61–65	33,013 (24.8)	3153 (26.3)	
66–70	23,423 (17.6)	2723 (22.7)	
71–74	24,747 (18.6)	1784 (14.9)	
Total patients diagnosed, % of total participants	3962 (3.0)	1153 (9.6)	<0.001
Age (year) at diagnosis, median	70	67	<0.001
55–60	348 (8.8)	175 (15.2)	<0.001
61–65	790 (19.9)	314 (27.2)	
66–70	1069 (27.0)	379 (32.9)	
71–75	1108 (28.0)	265 (23.0)	
⩾76	647 (16.3)	20 (1.7)	
PSA at diagnosis (ng/ml), median	18.0	5.1	<0.001
0.0–2.9	193 (4.9)	134 (11.6)	<0.001
3.0–4.9	168 (4.2)	435 (37.8)	
5.0–9.9	740 (18.7)	361 (31.3)	
10.0–19.9	1003 (25.3)	126 (10.9)	
⩾20.0	1799 (45.4)	89 (7.7)	
Not known or not performed	59 (1.5)	8 (0.7)	
Disease extent			
Not metastasised (M0)	2718 (68.6)	1119 (97.0)	<0.001
Metastasised (M1)	862 (21.8)	11 (1.0)	
Not known or not performed	382 (9.6)	23 (2.0)	
Histological differentiation			
Gleason 2–6	1638 (41.3)	790 (68.6)	<0.001
Gleason 7	850 (21.5)	247 (21.4)	
Gleason 8–10	932 (23.5)	51 (4.4)	
Not known or not performed	542 (13.7)	65 (5.6)	
Initial treatment			
Radical prostatectomy	277 (7.0)	416 (36.1)	<0.001
Radiotherapy	1106 (27.9)	442 (38.3)	
Watchful waiting	419 (10.6)	233 (20.2)	
Androgen-deprivation therapy	1248 (31.5)	48 (4.2)	
Not known or other treatment	912 (23.0)	14 (1.2)	

study, 555 men needed to be screened and an additional 37 men needed treatment to prevent one Pca-related death, which again, is lower than the ERSPC findings (1410 screened and 48 treated, respectively).[4] The trends in prostate-specific mortality in both studies are however similar; there is overlap in the survival curves in the early part of observation, which then diverge with time. In the current study, this divergence happens earlier (4 years versus 7 years in the ERSPC) and becomes more pronounced over time (Fig. 2), leading to a greater overall benefit due to screening, although the mortality difference did not become statistically significant until after 6 years of observation. By the end of observation, the mortality rate rose more slowly in the intervention population and, given the changes noted in the rates of distant metastasis (Fig. 1), this trend is likely to continue with further follow-up. Therefore, there are few benefits of screening in the initial years after PSA testing, but these benefits are likely to increase over time; there is a difference in the rate of distant metastasis in favour of screening after 5 years, which leads to a disease-specific mortality benefit after 6 years of observation. Hence, screening will only be beneficial in men with a life expectancy from at least another 6 to 8 years.

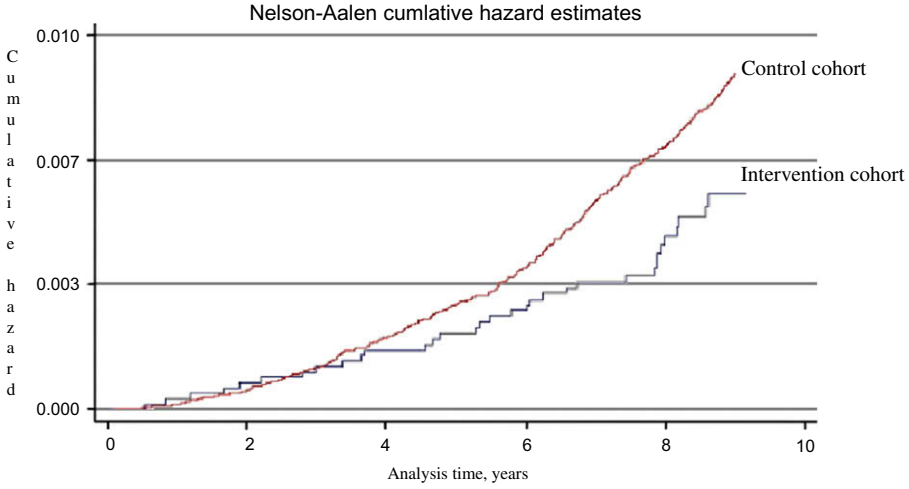
Although the absolute benefit in terms of deaths prevented by screening might increase after longer follow-up, the life years saved per death prevented might tend to be smaller after more years of follow-up. Based on the data of current study we assume an average of 5 years saved per death prevented in current study. Consequently, we expect that the benefit in terms of the number of life years gained will become smaller after longer follow-up when the patients become older and will have limited life expectancies. However, for evaluation of the screening studies, these estimates are less used because they are confusing and difficult to understand. Furthermore, the life years gained should be corrected for quality of life, making it quality of life adjusted life years (QALY's) gained.

Another important observation is the screening induced increase in the Pca incidence. The intervention cohort had a 3.2-fold increased rate of Pca diagnosis, with a cumulative incidence increase of 67 per 1000 men. These results compare



Years	0	2	4	6	8	10
Intervention cohort						
N at risk	11 970	11 701	11 324	10 912	7315	0
Cumulative N Pca metastasis (survival rate %)	0 (100)	9 (99.9)	20 (99.8)	29 (99.8)	43 (99.7)	47 (99.6)
Control cohort						
N at risk	133 287	127 872	122 567	116 501	104050	0
Cumulative N Pca metastasis (survival rate %)	0 (100)	162 (99.9)	363 (99.7)	631 (99.5)	956 (99.3)	1 126 (99.2)

Fig. 1 – Incidence of prostate cancer distant metastasis in the intervention and control populations.



Years	0	2	4	6	8	10
Intervention cohort						
N at risk	11 970	11 706	11 333	10 923	7326	0
Cumulative N Pca specific death (survival rate %)	0 (100)	5 100)	11 (99.9)	19 (99.8)	29 (99.8)	35 (99.7)
Control cohort						
N at risk	133 287	127 972	122 706	116 689	104 226	0
Cumulative N Pca specific death (survival rate %)	0 (100)	39 (100)	145 (99.9)	285 (99.8)	508 (99.6)	627 (99.5)

Fig. 2 – Prostate cancer-specific mortality in the intervention and control populations.

to 34 per 1000 men in the ERSPC and 12.5 per 1000 men in the PLCO studies, again highlighting the degree of contamination in the control arms of these studies and the advantages of the control population in the present study.[4,7] In the current study, the increased incidence rate was much greater than the observed decrease in mortality between the two groups (67 versus 1.8 per 1000 men, respectively), leading to the potential for overdiagnosis (and overtreatment) of the majority of men diagnosed by screening. As the life expectancy of men at the end of observation is approximately 10 years, further follow-up will determine how many additional men are diagnosed with Pca and how many die from Pca or concurrent

disease, giving more definitive data on overdiagnosis due to PSA screening.

The main limitation is the lack of randomisation, meaning the current study is more akin to studies which have compared rates of prostate cancer diagnosis and prostate-specific mortality in areas with high and low rates of PSA screening and radical treatment, such as in Seattle–Connecticut[17] and in the Tyrol region of Austria.[18] The current study has advantages over previous studies as the difference in PSA testing and treatment is more pronounced in the current populations and will more accurately estimate the potential benefits of PSA screening. Further, as there are individualised data in each population in the current study, survival analyses can also be performed as opposed to simply assessing differences in prostate cancer incidence and mortality rates.

Due to the lack of randomisation, the rates of Pca or Pca mortality may have been different in both groups at the beginning of the observation. At inclusion, the incidence of Pca in both countries was very different (86 versus 62 per 100,000 persons in the Netherlands and NI, respectively).[19,20] This difference was mainly due to the early use of PSA testing in the Netherlands, with Pca rates increasing significantly from a baseline of 62 per 100,000 persons in the end-1980s to over 90 per 100,000 by 2002.[19,20] In NI, there was an equal baseline incidence of 63 per 100,000 persons, but this remained stable until 2000, when the rates started to increase. In contrast, the Pca mortality rates in both countries were remarkably similar, with a slow increase in mortality until its peak in 1995 (34.4 per 100,000 persons in Netherlands versus 28.5 in NI),[19,20] with a subsequent decrease in both countries. As men in both populations had similar ethnic backgrounds (virtually all white) and had an equivalent median age at inclusion (63 years), they should have a similar baseline risk of Pca. However, the higher level of PSA testing in the Dutch general population before 1995 means that many men have been pre-screened using PSA and will have already been diagnosed with Pca, especially more advanced Pca, and so will not have been offered inclusion into the screen-detected population. This and the fact that many more men in the Dutch population had undergone PSA testing prior to inclusion in the study population (on average 14% versus 4%) will bias outcomes in favour of the screened group. Further, it is likely that a small number of men in the NI population may also have undergone PSA screening (9.1% of cancers diagnosed with PSA <5.0 ng/ml). There is therefore some degree of contamination in the control population of the present study, although the magnitude of this will be much less than in the ERSPC and PLCO studies.[4,7] The method of inclusion, i.e. men in Rotterdam signing informed consent whilst those in NI being identified retrospectively, also resulted in a healthy screening bias with generally healthier men of higher socio demographic level agreeing to participate in the ERSPC.[21] This resulted in a large difference in overall mortality: RR 0.75 (95% CI, 0.73–0.76; $p < 0.001$) in favour of the intervention group. As men in the control cohort died sooner, they were more likely to die from a co-morbid cause as opposed to Pca, decreasing the Pca mortality relative to that in the intervention group. Finally, different treatments in both cohorts will have affected outcomes, with men diagnosed and treated with curative intent at an earlier stage likely to have a better outcome.[22–24] In both groups, following diagnosis, men were free to choose treatment in collaboration with their local urologist. As outlined in Table 1, men in NI had a higher PSA 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. These differences in treatment are inherent in any study with a wide difference in the intensity of screening.

A number of criteria must be met before population-based screening can be justified.[25] Little is known about the screening risks, side-effects of overtreatment and health-related quality of life benefits of earlier treatment. Further, given the very large number needed to screen and needed to treat, it seems likely that cost of population-based PSA screening will be considered prohibitive in many countries.

5. Conclusion

Men undergoing systematic PSA screening had a 3.2-fold increased diagnosis of Pca. After 8.5 years, the rate of Pca metastasis was 53% lower in the intervention population. Further, a significant reduction in Pca-specific mortality of 37% was observed in the intervention cohort, however, 555 men needed to be screened and 37 men needed treatment to prevent one Pca-related death. Longer follow-up is likely to demonstrate an increasing mortality benefit in favour of PSA screening, although the impact of overdiagnosis, quality of life benefits and cost-effectiveness need to be assessed before population-based PSA screening can be recommended.

Conflict of interest statement

Fritz H. Schröder is consultant to Ferring Ltd., GlaxoSmith Kline, Bayer Schering and Genprobe.

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