

Prostate specific antigen concentration at age 60 and death or metastasis from prostate cancer: case-control study

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ABSTRACT

Objective To determine the relation between concentrations of prostate specific antigen at age 60 and subsequent diagnosis of clinically relevant prostate cancer in an unscreened population to evaluate whether screening for prostate cancer and chemoprevention could be stratified by risk.

Design Case-control study with 1:3 matching nested within a highly representative population based cohort study.

Setting General population of Sweden taking part in the Malmö Preventive Project. Cancer registry at the National Board of Health and Welfare.

Participants 1167 men aged 60 who provided blood samples in 1981 and were followed up to age 85.

Main outcome measures Metastasis or death from prostate cancer.

Results The rate of screening during the course of the study was low. There were 43 cases of metastasis and 35 deaths from prostate cancer. Concentration of prostate specific antigen at age 60 was associated with prostate cancer metastasis (area under the curve 0.86, 95% confidence interval 0.79 to 0.92; $P < 0.001$) and death from prostate cancer (0.90, 0.84 to 0.96; $P < 0.001$). The greater the number for the area under the curve (values from 0 to 1) the better the test. Although only a minority of the men with concentrations in the top quarter (> 2 ng/ml) develop fatal prostate cancer, 90% (78% to 100%) of deaths from prostate cancer occurred in these men. Conversely, men aged 60 with concentrations at the median or lower (≤ 1 ng/ml) were unlikely to have clinically relevant prostate cancer (0.5% risk of metastasis by age 85 and 0.2% risk of death from prostate cancer).

Conclusions The concentration of prostate specific antigen at age 60 predicts lifetime risk of metastasis and death from prostate cancer. Though men aged 60 with concentrations below the median (≤ 1 ng/ml) might harbour prostate cancer, it is unlikely to become life threatening. Such men could be exempted from further screening, which should instead focus on men with higher concentrations.

INTRODUCTION

Testing for prostate specific antigen is widely used for the early detection of prostate cancer. Even before randomised evidence as to the effects of screening on mortality became available,^{1,2} about half of age appropriate men in the United States presented for regular tests.³

The operating characteristics of the prostate specific antigen test have been determined by comparing concentrations with the result of prostate biopsy.⁴⁻⁶ A notable feature of such studies is that men with concentrations below commonly used biopsy thresholds, such as 4 ng/ml, have a substantial risk of cancer detectable at biopsy.⁷ Yet it has been established from autopsy studies that many men dying of causes other than prostate cancer none the less harbour prostate tumours. A typical estimate is that close to 40% of 70 year old men have detectable cancer in the prostate at autopsy.⁸ This figure is reflected in the widely recognised problem of overdiagnosis,^{9,10} with the European randomised trial suggesting that 48 men with screen detected cancer need to be treated for one death from prostate cancer to be avoided at nine years.²

Accordingly, the key question is not whether a man has prostate cancer but whether that cancer is likely to cause symptoms or shorten his life. In 1981-2, a highly representative cohort of 60 year old Swedish men provided blood samples for cardiovascular studies as part of the Malmö Preventive Project.^{11,12} We have been able to match these samples to cancer registries updated on 31 December 2006, when participants had either died or reached their 85th birthday. The rate of prostate specific antigen screening in Sweden during this time was low,¹³ and men in this cohort would have been too old to be eligible for screening by the time the screening test became available in Sweden in the 1990s. As such, the study provides a natural experiment to determine the association between prostate specific antigen concentrations, taken at an age typical for a man undergoing screening, and lifetime risk of clinically detected prostate cancer, prostate cancer metastasis, and death from prostate cancer.

METHODS

Study participants

The Malmö Preventive Project has been previously described.^{11,12} The cohort reported here includes 1167 men born in 1921, constituting 71% of the eligible population, who gave blood and completed medical history and lifestyle questionnaires in 1981-2. Records of participants were linked to the cancer registry at the National Board of Health and Welfare in Sweden to identify men diagnosed with prostate cancer up to 31 December 2006. This registry has been shown to be highly accurate.¹⁴ We excluded five men diagnosed with prostate cancer before the date of their baseline blood sample. Medical charts were available for 101 of 126 men (80%) with a diagnosis of prostate cancer, including 73 of 88 men (83%) who subsequently died. One urologist (DU), blinded to baseline prostate specific antigen data, reviewed charts, which were also independently reviewed for cause of death (by TB). When medical charts were not available, data on metastasis were taken from National Cancer Registry data on stage at diagnosis (14 patients, six with metastasis); cause of death was obtained from the Causes of Death Registry at the National Board of Health and Welfare in Sweden (n=15, six deaths from prostate cancer).

We used a nested case-control design to analyse data from the cohort. Separate matches were conducted for each of the three study events: clinically diagnosed prostate cancer, prostate cancer metastasis, and death from prostate cancer. A metastasis event included metastases documented at the time of diagnosis of prostate cancer as well as those metastases documented subsequently. Men who died from prostate cancer without previous clinical documentation of metastasis were defined as having been diagnosed with metastasis at the date of death. For each end point, we selected three controls at random from the group of men alive and event-free at the time of the event in the affected patient (the case) during follow-up. Controls were matched on date of birth and date of baseline blood

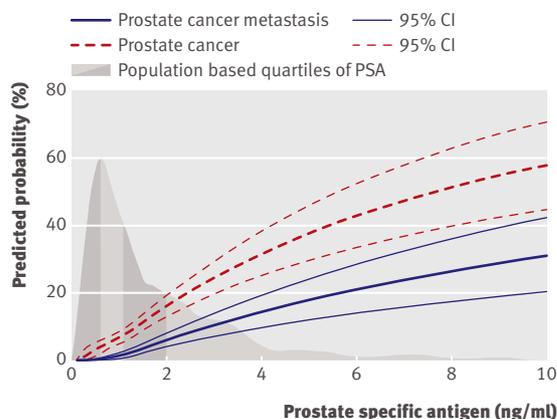


Fig 1 | Lifetime risk of clinically diagnosed prostate cancer or prostate cancer metastasis. Shaded region represents population based distribution of prostate specific antigen. Curves for risk of death from prostate cancer nearly overlap with curves for prostate cancer metastasis and are not shown

Table 1 | Characteristics of entire study cohort (n=1162) at 31 December 2006. Figures are numbers (percentages) unless stated otherwise

	Data
Alive at age 85:	
Without prostate cancer	360 (31)
With non-metastatic prostate cancer	38 (3)
With metastatic prostate cancer	0 (0)
Died from other causes:	
Without prostate cancer	668 (57)
With non-metastatic prostate cancer	45 (4)
With metastatic prostate cancer	8 (1)
Died from prostate cancer	35 (3)
Emigrated	8 (1)
Median (IQR) PSA at age 60 (ng/ml)*	1.06 (0.65-1.92)

IQR=interquartile range; PSA=prostate specific antigen.
*Imputed to whole population from case-control data.

sample, with a window of three months. Using this algorithm, we successfully matched three controls to each case for all of the study end points.

Laboratory methods

Total prostate specific antigen was assayed in anti-coagulated blood plasma stored at -20°C for up to 27 years. We have shown that prostate specific antigen is not significantly labile when stored under these conditions.¹⁵ Levels of total prostate specific antigen (plus free prostate specific antigen and kallikrein related peptidase 2 (hK2)) were determined as previously reported^{16,17} and conducted in accordance with World Health Organization calibration standards at Lund University.

Statistical methods

We used conditional logistic regression to test the association between prostate specific antigen concentrations and study end points. The area under the receiver operating characteristic curve was calculated directly from the concentrations, with confidence intervals obtained by the method of DeLong et al.¹⁸ The area under the curve is a simple quantitative summary value of whether the continuous measure (in this case prostate specific antigen) is a good diagnostic tool. Values can lie between 0.5 and 1, with higher values showing greater diagnostic power. All statistical analyses were conducted with Stata 10.1 (StataCorp LP, College Station, TX).

To estimate the risk of the prostate cancer outcomes for a given concentration, we used locally weighted scatterplot smoothing (LOWESS)¹⁹ to allow for a non-linear relation between prostate specific antigen and outcome. To obtain population based estimates of risk, we first imputed concentrations for participants without measured prostate specific antigen—623 men without a diagnosis of prostate cancer who were not selected as controls—by randomly sampling concentrations with replacement from cancer-free controls. We then used LOWESS to estimate risk; the imputation and estimation was repeated 200 times, with the

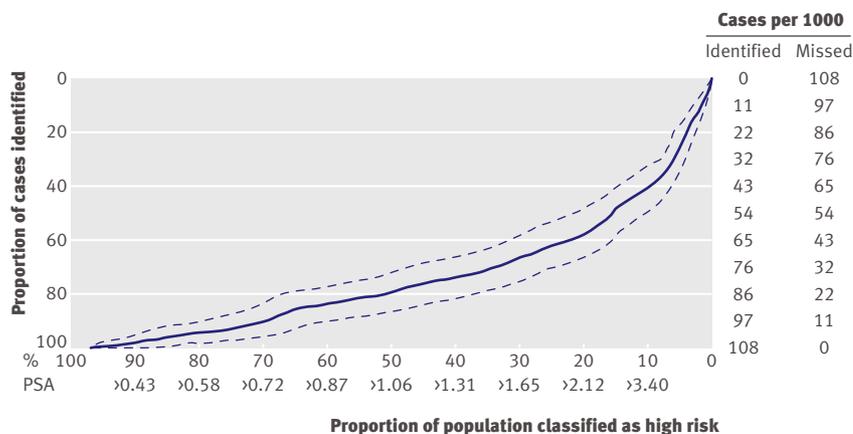


Fig 2 | Lorenz curve for clinically detected prostate cancer: x axis shows percentage of population with prostate specific antigen (PSA) above indicated concentrations, hence percentages run from 100 down to 0; y axis shows number of events that would be included (or missed) if we consider only men with prostate specific antigen above any given concentration

mean over 200 replications used as the final estimate. Centile based confidence intervals for both the risk curve and the Lorenz curve²⁰ were obtained with bootstrap methods.

RESULTS

Table 1 shows characteristics of the entire cohort at 31 December 2006. A total of 126 men were diagnosed with prostate cancer, of whom 43 either had metastatic disease at diagnosis (n=13), subsequently developed metastases (n=18), or died from prostate cancer without clinical documentation of metastases (n=12). Thirty five men died from prostate cancer. We excluded one case (a man who died from prostate cancer) from the analysis because blood samples were insufficient to measure prostate specific antigen. We also excluded 11 controls (two matched for prostate cancer, five matched for metastases, and four matched for death) with insufficient blood samples. Median times to diagnosis, metastasis, and cancer specific death were 15.3, 15.7, and 15.9 years, respectively. The similarity of these estimates is because only a subset of men diagnosed with cancer went on to develop metastases and these tended to be diagnosed earlier. The imputed median prostate specific antigen concentration for the entire cohort was 1.06 ng/ml (interquartile range 0.65-1.92), similar to that reported for US men.²¹

Table 2 gives details of the diagnosis in the 126 affected men. Most commonly, prostate cancer was detected during investigation for urinary symptoms (79%). No man had cancer detected by screening. Curative treatment was rare, with only one man undergoing radical prostatectomy. Bone scans were not routine for much of the period of the study, and many patients are therefore not classified for metastasis at diagnosis.

Prostate specific antigen at age 60 was associated with risk of prostate cancer diagnosed clinically by

Table 2 | Characteristics of 126 (11%) men from study cohort with diagnosis of prostate cancer. Figures are numbers (percentages) unless stated otherwise

	Data
Clinical T stage:	
T1	33 (26)
T2	45 (36)
T3/T4	37 (29)
Unknown	11 (9)
Clinical N stage:	
N0	9 (7)
N1	3 (2)
NX	114 (90)
Clinical M stage:	
M0	57 (45)
M1	13 (10)
MX	56 (44)
Biopsy grade:	
WHO I or Gleason ≤5	29 (23)
WHO II or Gleason 6 or 7	53 (42)
WHO III or Gleason ≥8	20 (16)
Unknown	24 (19)
Median (IQR) PSA at diagnosis (n=86)	17.8 (8.9-38.5)
Age at diagnosis (years):	
61-65	15 (12)
66-70	19 (15)
71-75	33 (26)
76-80	27 (21)
81-86	32 (25)
Reason for investigation leading to diagnosis (n=77)*:	
Lower urinary tract symptoms*	61 (79)
Haematuria	5 (6)
Erectile dysfunction*	3 (4)
Pain	6 (8)
Metastases (lymph node or bone)	2 (3)
Fatigue	1 (1)
Received treatment for prostate cancer (n=115)†:	
Received any treatment	66 (57)
Within six months of diagnosis:	
Radical prostatectomy	1 (1)
Medical therapy	32 (28)
Orchidectomy	14 (12)
Radiation therapy	5 (4)
After six months of diagnosis:	
Medical treatment	18 (16)
Orchidectomy	6 (5)
Radiation therapy	12 (10)

IQR=interquartile range; PSA=prostate specific antigen.

*1 patient presented with both lower urinary tract symptoms and erectile dysfunction.

†4 patients received both medical therapy and orchidectomy; 1 patient had both radiation therapy and orchidectomy; 1 patient had radiation, medical therapy and orchidectomy.

age 85 (area under the curve 0.76, 95% confidence interval 0.71 to 0.81; $P<0.001$). This association remained for cancers detected more than 20 years after the blood sample (33 cases, 0.69, $P=0.005$). Prostate specific antigen was also associated with prostate cancer metastases (0.86, 0.79 to 0.92; $P<0.001$), and

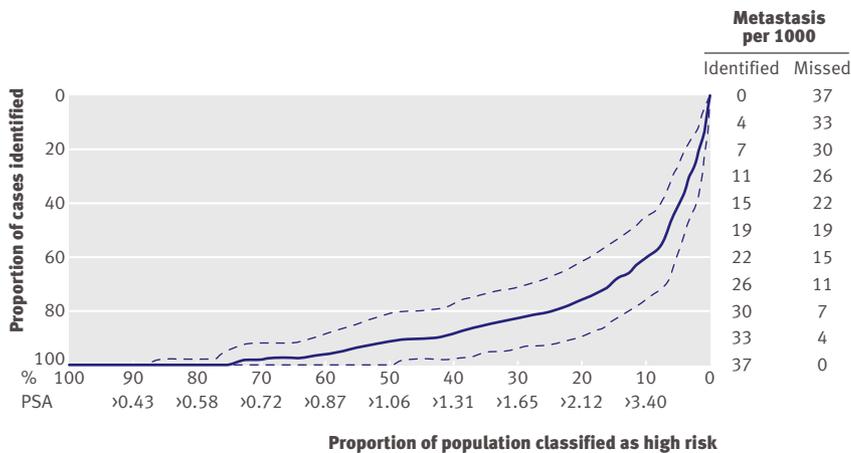


Fig 3 | Lorenz curve for prostate cancer metastasis: x axis shows percentage of population with prostate specific antigen (PSA) above indicated concentrations, hence percentages run from 100 down to 0; y axis shows number of events that would be included (or missed) if we consider only men with prostate specific antigen above any given concentration

death from prostate cancer (0.90, 0.84 to 0.96; $P < 0.001$). Again, these associations remained for events occurring after 20 years (0.83, $P = 0.046$, in 12 patients with metastasis; 0.84, $P = 0.051$, in 10 patients who died).

Table 3 gives an initial descriptive analysis of the association between prostate specific antigen and subsequent prostate cancer events after we categorised the data by population quarters of prostate specific antigen concentration. As an example, men with a prostate specific antigen concentration ≥ 2 ng/ml at age 60, have, on average, 26 times the odds of dying from prostate cancer than men with a concentration < 2 ng/ml. Table 4 gives predicted risks of a diagnosis of prostate cancer, metastasis, and death by age 85 for population centiles of prostate specific antigen; the association is shown graphically in figure 1, showing strong trends with increasing concentration. If adjustment is made for overdiagnosis,¹⁰ the relation between prostate specific antigen and subsequent clinically detected cancer is comparable with that reported between prostate specific antigen and biopsy detectable cancer in the US population,⁴ indicating broad applicability of our findings. The risk of a clinically detected prostate cancer rises smoothly with increasing concentration of prostate specific antigen; in contrast, metastases and death from prostate cancer were rare in men with a concentration less than 1 ng/ml at age 60, but then rose rapidly as the concentrations increased. As a result, prostate specific antigen concentration at age 60 can predict the probability that a man will die from prostate cancer after a subsequent diagnosis. For example, of 25 men with baseline concentrations of 1-2 ng/ml who were later diagnosed with prostate cancer, only two (8%) died from prostate cancer by the end of the study. In comparison, of 18 men with baseline concentrations of 5-10 ng/ml who were later diagnosed with prostate cancer, six (33%) died from prostate cancer.

Figures 2-4 show Lorenz curves for each event, with cumulative probabilities by population centile shown in

table 5. These results can be used to evaluate risk stratification strategies for screening and early detection. It can be seen, for example, that 90% of metastases and 95% of deaths occur in men with prostate specific antigen concentrations above the median at age 60, equivalent to a concentration of about 1 ng/ml. Men with concentrations ≤ 1 ng/ml had a 0.5% probability of metastasis by age 85 and a 0.2% probability of death from prostate cancer. Two men in our cohort had concentrations close to or less than 1 ng/ml at age 60 and subsequently died from prostate cancer. These deaths occurred at age 84 (1.04 ng/ml at baseline) and 85 (0.86 ng/ml at baseline).

Six men in our dataset had prostate specific antigen concentrations of 20 ng/ml or more, and four of these men died of prostate cancer. These men might have had incurable disease at the time of the blood sample and therefore prostate specific antigen based screening at this age would possibly have made little difference to their survival. In a sensitivity analysis, we excluded these six cases but saw no important influence on our findings: the proportion of deaths from cancer in men in the top quarter of prostate specific antigen remained at 90%. The proportion of deaths occurring in the top quarter was also unaffected if we excluded men dying of prostate cancer within five (91%) or 10 (89%) years.

Baseline free prostate specific antigen, free:total prostate specific antigen ratio, and hK2 predicted all three end points. Total prostate specific antigen, however, was the best single marker, and its predictive accuracy was enhanced only by the other kallikrein markers for men with concentrations above the median (table 6).

DISCUSSION

Overview of findings

Concentrations of prostate specific antigen at age 60 predict the risk that a man will die from prostate cancer by the age of 85. The association between prostate spe-

Table 3 | Conditional logistic regression based on prostate specific antigen (PSA) concentrations at age 60. Categories of PSA are close to quarters of distribution

PSA (ng/ml)	No (%) of cases	No (%) of controls	Odds ratio (95% CI)
Clinically diagnosed prostate cancer			
<0.65	9 (7)	101 (27)	Reference
0.65-0.99	15 (12)	79 (21)	2.3 (0.89 to 5.7)
1.00-1.99	24 (19)	118 (32)	2.5 (1.1 to 5.9)
≥ 2.00	77 (62)	75 (20)	13 (5.7 to 29)
Prostate cancer metastases			
<0.65	0 (0)	34 (28)	
0.65-0.99	3 (7)	19 (16)	Reference
1.00-1.99	5 (12)	36 (30)	
≥ 2.00	34 (81)	32 (26)	17 (5.2 to 57)
Death from prostate cancer			
<0.65	0 (0)	25 (26)	
0.65-0.99	1 (3)	15 (15)	Reference
1.00-1.99	2 (6)	32 (33)	
≥ 2.00	31 (91)	26 (27)	26 (6.2 to 113)

Table 4 | Risk of clinically diagnosed prostate cancer and death from prostate cancer before age 85 by prostate specific antigen (PSA) concentration at age 60. Figures are predicted risk (95% confidence interval)

Centile	PSA (ng/ml)*	Clinically diagnosed prostate cancer	Prostate cancer metastases	Death from prostate cancer
99	14.8	60 (46 to 73)	32 (21 to 44)	30 (19 to 42)
95	5.17	39 (31 to 47)	19 (12 to 25)	17 (11 to 23)
90	3.40	28 (22 to 33)	12 (8.3 to 16)	11 (7.1 to 15)
80	2.12	17 (14 to 20)	6.6 (4.6 to 8.8)	5.7 (3.8 to 7.7)
75	1.92	15 (13 to 19)	5.8 (4.0 to 7.7)	4.8 (3.2 to 6.6)
67	1.50	11 (8.9 to 14)	3.5 (2.2 to 4.9)	2.7 (1.6 to 3.9)
50	1.06	7.2 (5.4 to 9.1)	1.6 (0.75 to 2.5)	0.9 (0.30 to 1.7)
25	0.65	4.3 (2.4 to 6.4)	0.53 (0.17 to 0.97)	0.28 (0.08 to 0.53)
10	0.43	2.6 (0.91 to 4.9)	0.22 (0.1 to 0.38)	0.14 (0.06 to 0.22)

*Imputed to whole population from case-control data.

cific antigen and death from prostate cancer is stronger than the association between prostate specific antigen and cancer detectable at biopsy,⁴ suggesting that prostate specific antigen concentrations are more useful in detecting tumours of greater malignant potential.

Our study has several strengths. Participants were followed to an advanced age, when most had died. The use of archival anticoagulated plasma has been shown to reflect prostate specific antigen concentrations had they been measured contemporaneously.¹⁵ Few, if any, men in the cohort would have undergone prostate specific antigen screening; we therefore avoided verification bias²² and were able to provide estimates for the risk of clinically diagnosed cancer, rather than biopsy detectable cancer,⁴ which might never affect a man before he dies from another cause. All men in the study were the same age—one typical for those currently undergoing screening—ensuring the direct applicability of our findings. The cohort was highly representative of the population, and the large cohort size led to narrow confidence intervals around most of the risk estimates.

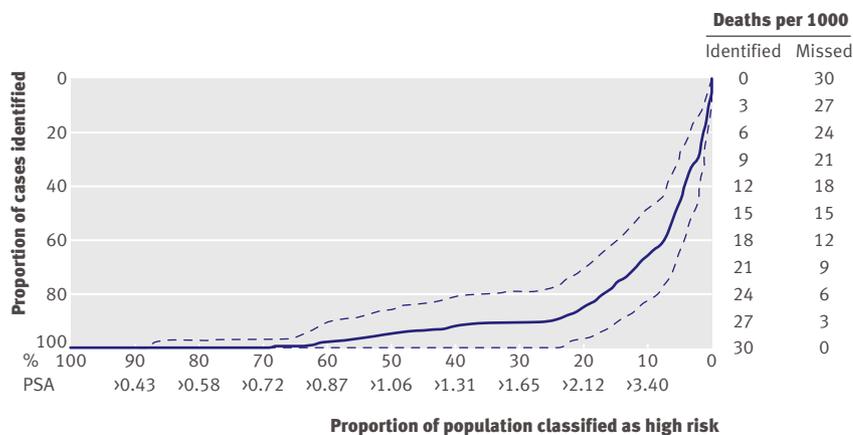


Fig 4 | Lorenz curve for death from prostate cancer: x axis shows percentage of population with prostate specific antigen (PSA) above indicated concentrations, hence percentages run from 100 down to 0; y axis shows number of events that would be included (or missed) if we consider only men with prostate specific antigen above any given concentration

The reason why prostate specific antigen concentrations predict events occurring 25 years subsequently is not entirely clear. There are data suggesting that a significant proportion of men with concentrations above the median, but below conventional biopsy thresholds, have prostate cancer detectable either by biopsy⁷ or pathological analysis of the prostate at autopsy.⁸ Alternatively, such increases in prostate specific antigen might be associated with pre-malignant conditions. Either way, however, the implications are not obvious. Even if our findings are driven by detectable prostate cancers, biopsy would be indicated only if it could be shown that waiting for the prostate specific antigen concentration to rise further would result in a substantial risk of the cancer becoming incurable. It is also unclear whether chemoprevention would be effective only for pre-malignant states, or whether it might also have a cytostatic effect on established cancers.²³

Comparison with other studies

Several studies have reported findings that support those presented here. Stenman and coworkers identified 44 cases of prostate cancer in a cohort of over 20 000 Finnish men and reported associations between baseline prostate specific antigen and the risk of clinically detected cancer within six to 10 years.²⁴ Concentrations were also found to be raised five to six years before diagnosis among the 366 participants in the US Physicians' Health Study who were identified with palpable prostate cancer.²⁵ More recently, Holmström and colleagues reported on 540 cases of prostate cancer in a Swedish cohort, with a comparable finding to ours that prostate specific antigen less than 1 ng/ml "virtually ruled out prostate cancer" during a mean follow-up of seven years.²⁶ We have previously reported data from the Malmö cohort showing a strong association between a prostate specific antigen concentration measured at age 44-50 and prostate cancer diagnosed clinically up to 25 years subsequently¹¹; the association was strengthened for cancers that were advanced at diagnosis.²⁷ Our current data, however, are unique in examining the relation of prostate specific antigen concentrations at the age appropriate for screening with lifetime risk of metastases or death from prostate cancer.

Clinical implications

Our results have a clear application to early detection and chemoprevention of prostate cancer. Two randomised trials have recently reported the effects of prostate specific antigen screening on death from prostate cancer. The Prostate, Lung, Colorectal, and Ovarian Screening trial (PLCO) in the US did not find an advantage to screening at a median follow-up of seven years,¹ although important concerns have been raised as to the widespread use of prostate specific antigen testing in the control arm of this trial.²⁸ The European Randomised Trial of Screening for Prostate Cancer (ERSPC) reported a 20% reduction in death from prostate cancer with screening,² though it was estimated that 1410 men needed to be screened to prevent one death. We found that a high proportion of deaths from prostate cancer occur in men with the highest prostate

Table 5 | Cumulative proportion (%) of cases (95% confidence intervals) above centiles of prostate specific antigen (PSA) concentration

Centile	PSA (ng/ml)*	Prostate cancers	Prostate cancer metastases	Prostate cancer deaths
90	3.40	41 (33 to 50)	61 (46 to 77)	66 (49 to 83)
80	2.12	58 (50 to 66)	76 (61 to 89)	85 (71 to 97)
75	1.92	62 (54 to 70)	80 (68 to 93)	90 (78 to >99)
67	1.50	70 (61 to 78)	84 (72 to 95)	91 (79 to >99)
50	1.06	80 (72 to 87)	91 (81 to >99)	95 (86 to >99)
25	0.65	93 (88 to 97)	99 (94 to >99)	>99 (97 to >99)
10	0.43	99 (95 to >99)	>99 (—)	>99 (—)

*Imputed to whole population from case-control data.

specific antigen concentrations: 66% in the top 10% (>3.4 ng/ml) and 95% in men above the median (>1 ng/ml). For men over 60, focusing screening on those at increased risk—that is, men with concentrations greater than the median at age 60—is likely to shift the ratio of harms to benefits for screening. In response to advocates of screening who might criticise a risk stratification approach as mere cost cutting, we argue that risk stratification would probably lead to increased acceptance for screening among patients. Despite several recommendations in favour of prostate cancer screening,^{29,30} currently only half of age appropriate US men undergo regular tests.³ Compliance would probably increase among those at high risk if they were informed of their risk status.

Similar considerations apply to chemoprevention. Targeting treatment to men with increased prostate specific antigen concentrations will reduce the medical

harms and financial costs associated with chemoprevention. As for screening, we argue that risk stratification would also increase the benefits of chemoprevention: despite recommendations,³¹ few men currently undergo chemoprevention for prostate cancer.³² This could change if a subgroup of men were told that they were at high risk of clinically relevant prostate cancer.

With regard to counselling of individual patients, it has been suggested that the prostate specific antigen test is insufficiently sensitive for prostate cancer on the grounds that a substantial proportion of men with low concentrations have prostate cancer on biopsy.^{4,7} In contrast, our findings suggest that 60 year old men with low concentrations can be reassured that even if they do harbour cancer, it is unlikely to become apparent during their lifetime and even less likely to become life threatening.

None the less, a raised prostate specific antigen is far from being an inevitable harbinger of advanced prostate cancer. For instance, only one in six men at the 95th centile of prostate specific antigen at age 60 (5.2 ng/ml) will die of prostate cancer by age 85. Hence, while a concentration below the median (≤ 1 ng/ml) can probably “rule out” subsequent death or metastasis from prostate cancer, higher concentrations indicate only that careful monitoring might be warranted.

Limitations

Our findings are subject to several important caveats. Firstly, our data are based on a single blood test in 60 year old men without screening. This means that, for men undergoing screening in their 50s, we probably overestimate the risk of a clinical diagnosis of prostate cancer after the age of 60. This is because some men would have been diagnosed early with cancer detected at screening and thus be removed from the risk set. That said, a small decrease in risk has little effect for most men because most are at low risk, and there are no practical implications to misclassifications between different levels of reduced risk. Moreover, it is prudent to be conservative with respect to risk. We might have also overestimated the risk of clinically detected prostate cancer because overdiagnosis can occur even in the absence of screening. For example, a man presenting to a urologist with prostate symptoms might have a cancer detected during the clinical investigation that would never have become apparent had the patient not developed concurrent benign disease.

Neither of these considerations would have an important effect on our estimates of death from prostate cancer. Such estimates might, however, be affected by improvements in treatment, such as the use of higher dose radiotherapy. Even so, under the assumption of an approximately constant relative reduction from improved treatment, changes in treatment are unlikely to have an important effect on estimates of cumulative proportions, such as that 90% of prostate cancer deaths occur in men in the top quarter of prostate specific antigen concentrations at age 60.

Table 6 | Association between prostate cancer outcomes and total prostate specific antigen (PSA), free PSA, % free PSA, and kallikrein related peptidase 2 (hK2) at age 60, overall and for men with total PSA above median. Figures are areas under curve (95% CI); the greater the value the better the test

	Clinically diagnosed prostate cancer	Prostate cancer metastases	Death from prostate cancer
All men aged 60			
No of cases/controls	125/373	42/121	34/98
Model:			
Total PSA	0.76 (0.71 to 0.81)	0.86 (0.79 to 0.93)	0.90 (0.84 to 0.96)
Free PSA	0.74 (0.69 to 0.80)	0.83 (0.77 to 0.91)	0.88 (0.81 to 0.95)
% free PSA	0.70 (0.65 to 0.75)	0.78 (0.70 to 0.86)	0.80 (0.71 to 0.88)
hK2	0.69 (0.64 to 0.75)	0.77 (0.64 to 0.86)	0.81 (0.72 to 0.90)
Combination*	0.76 (0.71 to 0.81)	0.87 (0.81 to 0.93)	0.91 (0.86 to 0.97)
Men aged 60 with PSA ≥ 1.0 ng/ml (median)			
No of cases/controls	101/193	39/68	33/58
Model:			
Total PSA	0.75 (0.69 to 0.81)	0.82 (0.73 to 0.91)	0.85 (0.77 to 0.94)
Free PSA	0.73 (0.67 to 0.79)	0.79 (0.70 to 0.88)	0.83 (0.74 to 0.92)
% free PSA	0.65 (0.58 to 0.71)	0.73 (0.63 to 0.83)	0.76 (0.65 to 0.86)
hK2	0.68 (0.62 to 0.75)	0.75 (0.64 to 0.85)	0.77 (0.66 to 0.88)
Combination*	0.74 (0.68 to 0.81)	0.85 (0.76 to 0.92)	0.89 (0.83 to 0.96)

*Total PSA, free PSA, % free PSA, and hK2.

WHAT IS KNOWN ON THIS TOPIC

Prostate specific antigen screening is widely used for the early detection of prostate cancer

Screening is associated with considerable overdiagnosis, and many men need to be screened to save one life

WHAT THIS STUDY ADDS

A single measure of prostate specific antigen at age 60 is associated with a man's lifetime risk of death from prostate cancer

Most (90%) of deaths from prostate cancer occur in men in the top quarter of prostate specific antigen concentrations (>2 ng/ml), though only a minority of such men will develop fatal prostate cancer

Men aged 60 with concentrations ≤ 1 ng/ml can be told that though they might have cancer, it is unlikely to become life threatening

At least half of men at age 60 can be exempted from further screening and chemoprevention

Further research

Several questions remain for future research. One is whether these results can be replicated in an independent group. Secondly, it is unclear how well our risk estimates apply to men of other races. Both incidence of and mortality from prostate cancer are higher in African-Americans and lower in Asians than in white people.³³ Whether there are also racial differences in the relation between prostate specific antigen at age 60 and future risks of prostate cancer metastases and death is a question that can be answered only by further research.

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Ethical approval: The study was approved by the ethics committee at Lund University. Consent was not obtained from study participants, but the presented data are anonymised and risk of identification is minimal.

Data sharing: A full dataset along with the statistical code used for analysis are available from the authors on request, and from the Swedish national data archive (<http://www.ssd.gu.se/en>). These data can be used only for replication of the analyses published in this paper or for private study. Express written permission must be sought from the authors for any other data use.

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