Prospective observational study to assess value of prostate specific antigen as screening test for prostate cancer

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Abstract

***Objective*—To evaluate measurement of serum prostate specific antigen as a potential screening test for future clinical prostate cancer among healthy men.**

***Design*—Nested case-control study with stored serum samples collected from 49 261 men with follow up using national death and cancer registration systems.**

***Subjects*—265 asymptomatic men who subsequently developed clinical prostate cancer and 1055 controls matched for age, study centre, and duration of storage of samples.**

***Main outcome measures*—Distribution of concentrations of the antigen in men who developed prostate cancer and in controls.**

***Results*—Prostate specific antigen concentrations were significantly higher in men who subsequently developed prostate cancer than in controls. In the first three years after blood collection the median concentration was 23 times greater in cases than in controls of the same age at the same centre (that is, 23 multiples of the median). A smaller difference persisted thereafter; 4·0 multiples of the median 3-6 years after blood collection, 3·6 6-10 years, and 1·8 after 10 years. In the first three years the proportion of men who developed prostate cancer and had raised levels of the antigen ($\geq$12 multiples of the median) (detection rate or sensitivity) was 81% (95% confidence interval 54% to 96%). The proportion of men who did not develop prostate cancer but had levels this high (false positive rate) was only 0·5%.**

***Conclusion*—Prostate specific antigen measurement is a highly discriminatory screening test for prostate cancer among healthy men. In the general population, 60-74 year old men who had $\geq$12 times the normal median level would have about a 50% chance of developing clinical prostate cancer in the next three years. Measurement of this antigen is a good enough screening test to justify a randomised controlled trial to determine any reduction in mortality from prostate cancer.**

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Introduction

In 1993 there were 9530 deaths from prostate cancer in the United Kingdom—the second commonest cause of death from cancer in men. Over 90% of deaths occur in men aged over 65 years. Prostate specific antigen is a glycoprotein produced only by the prostate gland; its function is to liquefy semen, and low concentrations are normally found in serum. As a tumour marker in the diagnosis and management of prostate cancer, concentrations of prostate specific antigen have been shown to increase with increasing stage of the cancer[1] and increasing volume of the tumour,[2] but there are insufficient data to evaluate adequately its performance as a screening test for preclinical prostate cancer among healthy men. Studies of men with symptoms would be expected to produce greater false positive rates. In studies of asymptomatic men in which prostate biopsies were performed only in those with positive results of tests for the antigen, the detection rate (sensitivity) of the test cannot be estimated because cancers were not sought in men who screened negative. The results could also be distorted by including prostate cancers that may never have presented clinically. We therefore designed a collaborative study to avoid these problems by using stored serum samples collected from four prospective epidemiological studies.

Methods

The project was based on four cohorts totalling 49 261 healthy men: the BUPA study[3] (London), the CLUE study[4] (United States), the North Karelia project[5] and the Social Insurance Institution mobile clinic health survey[6] (both in Finland). Serum taken from the men on recruitment was frozen and stored. Of men from whom a serum sample was available, 265 (cases) subsequently developed clinical prostate cancer or died of prostate cancer. Of the cases of prostate cancer, 120 were ascertained from national death records and 145 from cancer registries. A nested case-control study design was used. Controls were men from the same study who had not developed prostate cancer at the end of follow up. Five controls were selected per case, except in the CLUE study (two controls selected per case), making a total of 1055. Controls were matched with each case for age at the time of serum collection (within one year), duration of storage of the sample (collected within the same year), and the number of freeze-thaw cycles. They were otherwise selected at random. The median age at entry was 57 years (5th-95th centile 45-68 years). Cases were followed up for a median of 17·5 years and controls for 17·4 years (range 10-20 years).

Samples from each subject were retrieved from storage and assayed without knowledge of which were from cases or controls by using Tandem R-Prostate specific antigen radioimmunoassay kits (Hybritech)[7] at the Wolfson Institute of Preventive Medicine, London. Measurement of serum prostate specific antigen is not materially affected by freezing and thawing.[8]

In the controls there was no significant change in the concentration of the antigen with duration of storage or number of freeze-thaw cycles, but there were unexplained differences in concentrations between centres. For example, at 50 years of age the median concentrations in the controls were 0·75, 0·75, 0·60, and 0·47 ng/ml in the four centres. The median concentrations in the controls increased with age by 3·7% per year. In the BUPA study the medians at age 50, 60, and 70 years were 0·75, 1·08, and 1·55 ng/ml, respectively. In the analysis the matching was broken, and to allow for variation with centre and age each prostate specific antigen concentration was expressed as a multiple of the median for a given centre and age and referred to as the "level." The "normal" medians were derived from the controls by using a weighted linear regression of median concentration on age (in five year age groups) for each centre.

Detection rate (sensitivity) was defined as the proportion of cases in the study with a level of prostate specific antigen above a specified cut off level. The

false positive rate (1−specificity) was defined as the proportion of controls with a value above the same level.

Results

Table I shows the number of cases from each centre according to the interval between blood collection and diagnosis of prostate cancer. Table II shows the median levels of prostate specific antigen and the 10th and 90th centiles for the cases for all centres combined expressed in multiples of the median. Median levels declined as the interval between blood collection and date of diagnosis increased. With an interval of less than three years the median level in cases was 23 multiples of the median. Thereafter it declined rapidly but was still raised after 10 years (1·8 multiples of the median, $P<0·001$, t test). Figure 1 shows the individual results of the 265 cases.

Table III shows the proportions with levels of prostate specific antigen greater than or equal to specified values for cancers diagnosed within three, six, and 10 years and for controls. By using a cut off level of 12 multiples of the median the detection rates for the three observation times were, respectively, 81%, 40%, and 22% with a false positive rate of only 0·5%. Detection was greater in patients who died (89% (8/9), 65% (13/20), and 33% (17/52) respectively). The results were similar if only cases diagnosed between one and three years after blood collection were included (that is, excluding the first year). As the median age of cases was similar for those presenting less than 3 years, 3-5, 6-9, and 10 or more years after collection (61, 60, 60, and 57 years, respectively) the early cases were not concentrated in the older men.

The distribution of serum prostate specific antigen expressed in multiples of the median in cases and controls fitted a log Gaussian distribution well (values were higher than expected only above the 95th centile in cases and the 99·5th centile in controls). Figure 2 shows the Gaussian distributions in cases who developed prostate cancer within three years and in controls; the small overlap between the two curves illustrates the potential value of the test in screening.

To see if there were any cases of no clinical consequence diagnosed incidentally at necropsy we examined the records of the 41 cases notified only at necropsy. In 36 prostate cancer was the certified cause of death, not an incidental finding. The five remaining cases occurred over 10 years after blood collection and did not therefore affect the results up to 10 years.

TABLE I—*Number of men who developed prostate cancer from each centre according to observation time between blood collection and diagnosis of prostate cancer*

Observation time (years)	Centre: BUPA, London	Washington County, Maryland, United States	North Karelia, Finland	Social Insurance Institution, Finland	All
<3	4	8	0	4	16
3-<6	12	8	1	8	29
6-<10	24	10	4	18	56
≥10	35	64	31	34	164
All	75	90	36	64	265

TABLE II—*Level of serum prostate specific antigen according to observation time between blood collection and diagnosis of prostate cancer*

Observation time (years)	Prostate specific antigen (multiples of median*): 10th Centile	Median†	90th Centile
<3	8·6	23	58
3-<6	1·8	4·0	25
6-<9	1·0	3·6	9·4
≥10	0·5	1·8	6·0
All	0·7	2·6	10

*Multiple of median of controls of same age and from same centre.
†In men who subsequently died of prostate cancer medians were 40, 6·3, 3·6, and 2·1 multiples of median.

TABLE III—*Percentage of cases and controls with levels of prostate specific antigen above or equal to specified values of multiples of median according to observation time between blood collection and diagnosis of clinical prostate cancer (95% confidence interval)*

Prostate specific antigen (multiples of median*)	Percentage of controls (false positive rate)	Percentage of cases (detection rate): Less than 3 years† (n=16)	Less than 6 years (n=45)	Less than 10 years (n=101)
≥4	5·4	100 (79 to 100)	67 (51 to 80)	54 (45 to 64)
≥6	1·9	100 (79 to 100)	58 (42 to 72)	38 (28 to 47)
≥8	1·3	94 (70 to 100)	49 (34 to 64)	31 (22 to 40)
≥12	0·5	81 (54 to 96)	40 (26 to 56)	22 (14 to 30)
≥16	0·2	75 (48 to 93)	36 (22 to 51)	17 (10 to 24)

*Multiple of median of controls of same age and from same centre.
†When cases diagnosed within one year of sample collection are removed (four cases) detection rates are 100%, 100%, 92%, 83%, 75% in the groups.
n=Number of men who developed clinical prostate cancer.

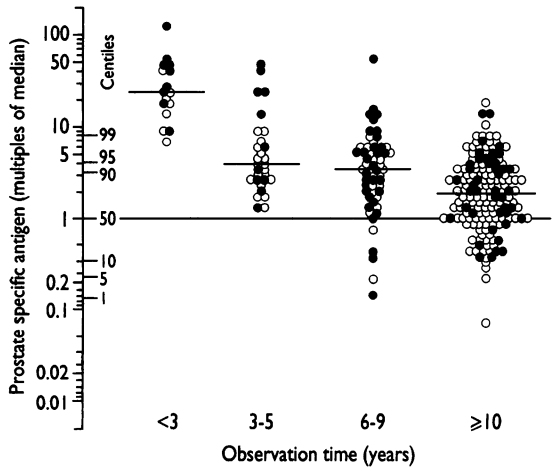

FIG 1—*Concentration of serum prostate specific antigen in men who developed clinical prostate cancer according to interval between blood collection and date of diagnosis (observation time). Median of the cases is shown (——). Concentrations are expressed in multiples of median for controls of same age from same centre. Nine cases and four controls from Washington County study[12] and one case from the Social Insurance Institution study[13] were previously published. Results are shown separately for men who died of prostate cancer (solid dots) and for those who presented clinically with prostate cancer and were still alive or had died from other causes at end of follow up (open dots). Numbers to the right of the vertical axis are centiles in controls.*

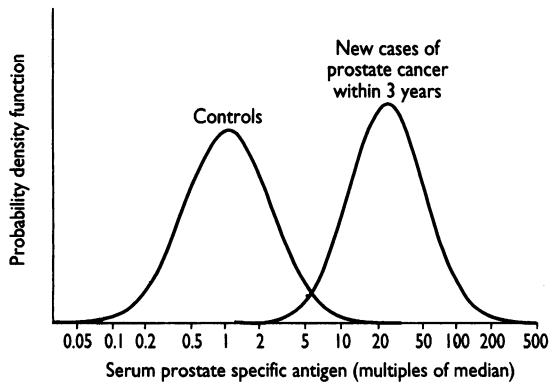

FIG 2—*Relative frequency distribution of serum prostate specific antigen in men who developed clinical prostate cancer within three years of sample collection (16) and in controls (1055). Concentrations of prostate specific antigen are expressed in multiples of median in controls of same age from same centre*

Discussion

Our results show that a single measurement of the concentration of prostate specific antigen in healthy men effectively distinguished between men who did and did not develop clinical prostate cancer. By using a cut off level of 12 multiples of the median the detection rate over a three year period was 81% and the false positive rate was 0·5%. Though this estimate of detection was based on only 16 cases, the lower limit of the 95% confidence interval was 54%, which represents a reasonable screening performance with a 0·5% false positive rate.

Our study design, testing asymptomatic men and following up all until death or clinical presentation with cancer, provides an unbiased evaluation of measurement of prostate specific antigen as a screening test. It avoided bias from linking levels of prostate specific antigen with incidental prostate cancer, which is common in elderly men (about one third of prostates

Key messages

- Until now few data have been available to evaluate the performance of prostate specific antigen as a potential screening test for prostate cancer among healthy men
- In a study of 49 261 healthy men the measurement of this antigen identified four out of every five men who developed clinical prostate cancer over the next three years with a false positive rate of only 0·5%
- Concentrations were raised for over 10 years before prostate cancer presented clinically
- Men aged 60-74 years with a serum prostate concentration greater than or equal to 12 times the normal median have about a 50% chance of developing clinical prostate cancer over the next three years
- Measurement of prostate specific antigen is a good enough screening test to justify a randomised controlled trial to determine whether screening can lead to a reduction in mortality from prostate cancer and if so to what extent

examined at routine necropsy have been found to have cancer[9-11]) or from linking levels with prostate cancer in men with prostatic symptoms.

Five other studies like ours have been recently reported.[12-16] Because the studies use different periods of observation, cut off levels of antigen, ages of men, and assays, direct comparison is complicated. Three of the published reports[12-14] permit a comparison with our results if cut off levels yielding a 12% false positive rate are used with an observation time of five years to diagnosis. The corresponding detection rates would be 95%[13] (19 cases), 84% (32 cases, our study), 66%[14] (113 cases), and 56%[12] (25 cases). The pooled estimate is 78% (189 cases combined by weighting by inverse of the variance). Our results are consistent with the others.

It is important to adjust for age in interpreting prostate specific antigen values. By using a cut off of 4 ng/ml (which has been widely cited in the literature) the false positive rate increased from 0% for men aged under 50 to 26% for men aged 70 years of over (see table IV). Table IV shows how such a cut off fails to allow for age and yields too high a false postive rate for use in screening. The effect of age was allowed for by expressing concentration of prostate specific antigen as a multiple of the normal median for controls of the same age.

Our age specific false positive rates are consistent with those reported in other studies.[17,18] For a cut off concentration of 4 ng/ml Catalona and his colleagues reported a false positive rate of 2·1% in the age group 50-59 and 6·7% in the age group 60-69,[18] close to our results of 3·5% and 8·5%.

Levels of prostate specific antigen were raised many years before prostate cancer presented clinically. Even more than 10 years (median 14) before clinical presentation the median level was 1·8 multiples of the median.

Our data, like those of others,[13] suggested that a test for prostate specific antigen was more discriminatory for future prostate cancer in younger than in older men. As age increases the false positive rate rises and the detection rate falls (see table IV). This effect is best demonstrated by holding the false positive rate constant. Within three years the age effect was not discernible, but for cancer developing within six years the detection rate (corresponding to a 5% false positive rate) for men under 58 years was 77% (10/13) compared with 53% (17/32) in older men. At a false positive rate of 0·5% the detection rates were 54% (7/13) and 34% (11/32), respectively.

The odds that men with a raised level of prostate specific antigen will present clinically with prostate cancer depend on the cut off level and the prevalence of clinical prostate cancer in the age group. The prevalence of prostate cancer in men aged 60-74 years is about 0·8% (estimated from the weighted average product of the incidence[19] and the median survival[20]). Those with concentrations ≥ 12 multiples of the median will have an approximately even (about 50%) chance of presenting with prostate cancer in the next three years (derived by comparing the incidence over three years[19] multiplied by the detection rate with the false positive rate from table III). This estimate will not be materially affected by the fact that the age group 60-74 years is somewhat older than the men in our study. Restriction of measurement of the antigen to men aged 60 or more would not miss many cases in the population because prostate cancer is a disease of older men; 98% of deaths in England and Wales occur in men aged 60 or more.[21]

In a screening programme men with positive results would be referred for a diagnostic punch biopsy at various sites of the prostate under ultrasound guidance. Pathological diagnosis of cancer would be followed by prostatectomy, radiotherapy, or hormonal treatment. The value of different treatments is uncertain. It has even been suggested that early prostate cancer should be conservatively managed with active treatment only if there is evidence of spread.[22,23] The most appropriate treatment and the associated adverse effects, such as incontinence, are unknown and should be evaluated.

Our study shows that measurements of serum prostate specific antigen in men aged 60 years or more effectively predict future clinical prostate cancer. Whether this can lead to treatment that could reduce mortality and morbidity from the disease is unknown and can be assessed only in a randomised trial of men invited for screening and in controls not invited for screening. A randomised trial of treatment among those allocated to the screened group may also be needed. With evidence on efficacy and an estimate of the size of any benefit a judgment could be made on whether screening for prostate cancer is worth while. Even a 30% reduction in deaths from prostate cancer among men aged 60-74 would save about 900 lives each year in England and Wales. This possibility is reason to perform a randomised trial; it is not a reason to introduce screening routinely.

TABLE IV—*Serum prostate specific antigen and subsequent clinical prostate cancer: detection and false positive rates with cut off for prostate specific antigen of 4 ng/ml ($\geq$4 ng/ml) according to age at blood collection and time to diagnosis of cancer*

Age (years)	Detection rate			No (%) of false positive results
	No (%) at <3 years	No (%) at <6 years	No (%) at <10 years	
<50	2/2 (100)	3/3 (100)	4/7 (57)	0/130 (0)
50-59	5/5 (100)	12/16 (75)	19/40 (48)	18/520 (3·5)
60-69	7/7 (100)	13/20 (65)	28/45 (62)	31/366 (8·5)
≥70	2/2 (100)	4/6 (67)	6/9 (67)	10/39 (26)
All	16/16 (100)	32/45 (71)	57/101 (56)	59/1055 (5·6)

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Increased mortality among Dutch development workers

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Early this century Africa was known as the "white man's grave." Little is known about health risks of expatriates in developing countries today. We compared the mortality of development workers who were sent out by Dutch development organisations with that of the general population in the Netherlands, adjusted for age and sex.

Subjects, methods, and results

Records of three large Dutch development organisations were reviewed. From 1984 to 1994 over 6500 development workers and spouses spent a total of 15 144 years abroad. About 75% of them lived in sub-Saharan Africa. Causes of death were classified according to the International Classification of Diseases: mortality caused by traffic accidents (ICD 800-848), other injuries (ICD 880-959 and 980-989), homicide (ICD 960-969), and all other causes (ICD 001-799, 849-879, and 930-959).[1] Age and sex specific mortality rates in the Dutch population were used to calculate the "expected" number of deaths in the study population. The observed number of deaths was divided by the expected number to obtain the standardised mortality ratio (SMR).

The table shows that mortality of development workers was 1·9 times that of the Dutch population, corresponding to an increase from an expected mortality of 1·1 to an observed mortality of 2·1 per 1000. The standardised mortality ratio in women was significantly higher than that in men (ratio of standardised mortality ratios 2·4; 95% confidence interval 1·1 to 5·1). A high standardised mortality ratio was found for traffic accidents, particularly in women. The observed increased risk for other injuries and homicide was not significant. Mortality in development workers from other causes was similar to that in the Dutch population. Mortality from AIDS, however, accounted for 3 (9%) out of 32 deaths.

Those with higher levels of education have a lower mortality.[2] Mortality is reduced by 10% for men and 5% for women for each year of educational attainment in the age group 20-44 years (Anton Kunst, personal communication 1995). On average development workers and their spouses had 3·5 more years of education than the Dutch population. This difference would reduce the expected mortality by 31% for men and 16% for women. After correction for education the standardised mortality ratio would be 2·6 (95% confidence interval 1·8 to 3·7) for the total population of development workers and spouses, 2·0 for men (95% confidence interval 1·2 to 3·2), and 4·0 for women (2·2 to 6·6).

Comment

Dutch development workers had a mortality almost double that of the general Dutch population. The true increase in mortality was probably higher because of a healthy cohort effect (medical selection) and mortality after the end of a contract attributable to infections acquired abroad, but leading to death later, such as hepatitis, malaria, or HIV infection.

In a study among Dutch expatriates returning from sub-Saharan Africa 4 out of 1122 men and 1 out of 846 women were found to have HIV infection, which had probably been acquired abroad, giving an estimated incidence rate of 0·7/1000 person-years.[3] As the observed mortality was 2·1 per 1000 during the

Standardised mortality rates (SMR) in Dutch development workers from 1984 to 1994 by cause of death

Cause of death	Expected No deaths	Observed No deaths	SMR (95% confidence interval)
	Men		
Traffic accidents	0·89	4	4·5 (1·2 to 11·5)
Other injuries	2·04	4	2·0 (0·5 to 5·0)
Homicide	0·18	1	5·6 (0·1 to 31·0)
Other causes	9·22	8	0·9 (0·4 to 1·7)
All causes	12·33	17	1·4 (0·8 to 2·2)
	Women		
Traffic accidents	0·20	7	35·0 (14·1 to 72·1)
Other injuries	0·60	1	1·7 (0·0 to 9·3)
Homicide	0·08	1	12·5 (0·3 to 69·7)
Other causes	3·63	6	1·7 (0·6 to 3·6)
All causes	4·51	15	3·3 (1·9 to 5·5)
	Total		
Traffic accidents	1·09	11	10·1 (5·0 to 18·1)
Other injuries	2·64	5	1·9 (0·6 to 4·4)
Homicide	0·26	2	7·7 (0·9 to 28·8)
Other causes	12·85	14	1·1 (0·6 to 1·8)
All causes	16·84	32	1·9 (1·3 to 2·7)