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ORIGINAL ARTICLE

Repeating an abnormal prostate-specific antigen (PSA) level: how relevant is a decrease in PSA?

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To examine the practice of repeating an abnormal prostate-specific antigen (PSA) level before proceeding to prostate biopsy, we assessed the pattern of PSA change following an initially raised ($\geqslant 4.0\,ng\,ml^{-1}$) PSA, and the relationship of this to prostate cancer diagnosis. In 7052 men, 71.2% with initially raised PSA had a reduction in PSA, with values $<4.0\,ng\,ml^{-1}$ in 37.8%. A total of 43.0% of men with prostate cancer showed a PSA decrease below their baseline level. Short-term decreases in PSA may occur in men with prostate cancer, including high-grade cancer, and so should not influence the decision to proceed to prostate biopsy.
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Introduction

As prostate-specific antigen (PSA) increases at a faster rate in men with prostate cancer compared to men with benign disease,[1] the change in PSA over time (PSA kinetics) may enable better selection of men for further investigation.[1–3] However, changes in PSA over short time periods may be due to the inherent variability of PSA as opposed to a true change in PSA level.[4,5] Due to this variability, some studies recommended repeating an abnormal PSA prior to proceeding to prostate biopsy,[4–6] with a PSA which returns to 'normal' ($<4.0\,ng\,ml^{-1}$) interpreted as representing a low risk of prostate cancer, and biopsy being deferred. To assess the risk of prostate cancer when PSA decreased from an abnormal ($\geqslant 4.0\,ng\,ml^{-1}$) value, we studied the pattern of PSA change following an initially raised PSA, and the relationship of this with progression to invasive investigation and prostate cancer diagnosis.

Methods

Study population

The Northern Ireland Cancer Registry PSA database has previously been described.[7,8] Briefly, data on all men undergoing PSA testing in Northern Ireland (NI) are maintained on a central electronic database. Using unique identifiers (name, date of birth and address), PSA results are matched to identify repeat tests for each individual. These data are routinely linked to hospital discharge and histopathology data to identify men who have been diagnosed with prostate cancer or histologically confirmed benign disease.

All men with a raised initial PSA ($4.0–9.99\,ng\,ml^{-1}$), performed between 1 January 1994 and 31 December 2003, and at least three PSA tests within the same time period were included. Men were followed for a diagnosis of prostate cancer or benign disease (histologically confirmed cases only) until 31 December 2003. Those without a diagnosis of cancer or benign disease were considered to have no prostate-related diagnosis. Serial PSA levels before 31 December 2003 or prior to a diagnosis of prostate cancer or benign disease were categorized into four groups based on the pattern of PSA change (Figure 1).

(1) Pattern 1—a steadily increasing PSA.
(2) Pattern 2—a generally increasing trend however the PSA may decrease occasionally without falling below the baseline level.
(3) Pattern 3—PSA decreases to below the baseline level but not to $<4.0\,ng\,ml^{-1}$.
(4) Pattern 4—PSA decreases to $<4.0\,ng\,ml^{-1}$ at some time point

All patient identifiable information was removed prior to the research team accessing the data used in this study and no patient contact was made during the study. Therefore, ethical approval was not sought.

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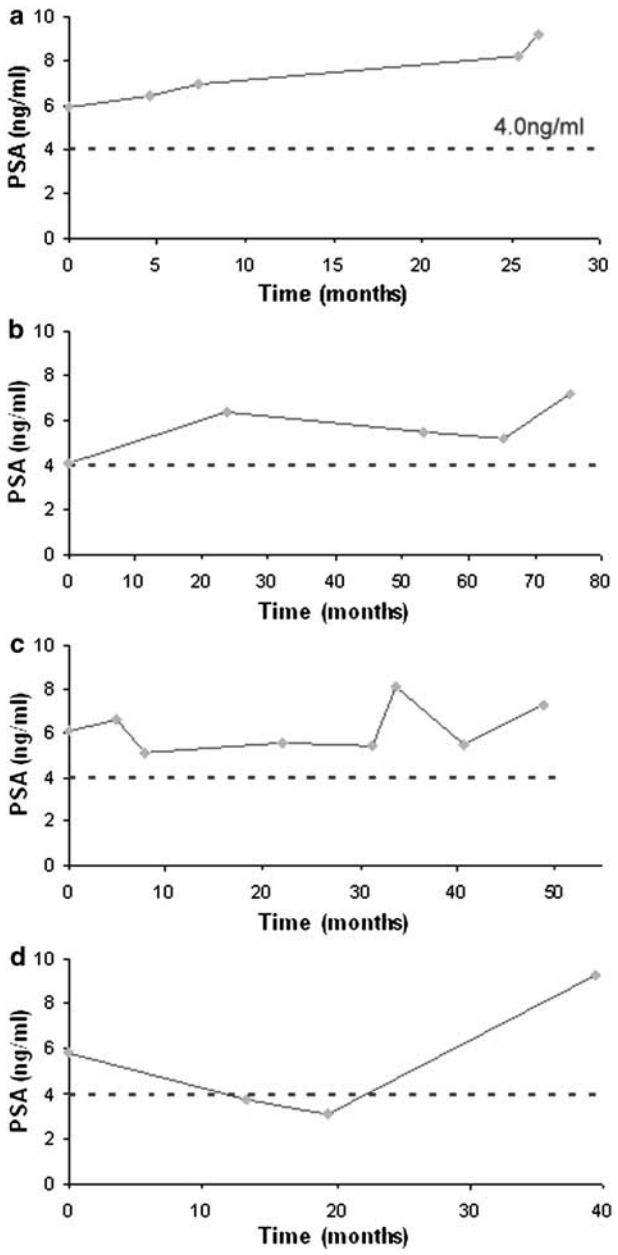

Figure 1 Patterns of prostate-specific antigen (PSA) change prior to diagnosis: examples in four men with prostate cancer. (**a**) Pattern 1; (**b**) pattern 2; (**c**) pattern 3; (**d**) pattern 4.

Statistical analysis

Men were categorized according to their diagnostic status: prostate cancer, histologically confirmed benign disease and no prostate-related diagnosis, respectively. Cohort characteristics were compared across diagnostic categories using analysis of variance (ANOVA) and Kruskal–Wallis tests for trend in the mean and median of continuous variables, respectively. χ^2-test was used to compare the number of PSA tests across diagnostic categories. The proportion of men with any diagnosis (cancer or benign) was compared to the proportion of men with no diagnosis across patterns using the χ^2-statistic. Similarly, the proportion of men diagnosed with prostate cancer was compared to the proportion of men with benign disease using χ^2-test. Prostate specific antigen velocity (PSAV) was calculated for all men by linear regression analysis using all PSA values. A tumour was considered aggressive if the Gleason score was $\geqslant 7$ or, when Gleason scoring was not available, the tumour had any poorly differentiated component. All statistics were performed using Stata (Intercooled Stata 8.0; Stata Corporation, College Station, TX, USA).

Results

A total of 7052 men were included, with 617 (8.7%) having prostate cancer and 1099 (15.6%) histologically confirmed benign disease. Mean (s.d.) follow-up was 5.9 (2.4) years. Group characteristics are presented in Table 1. Mean age was higher in men with prostate cancer compared to benign disease ($P<0.05$), but lower than those with no prostate-related diagnosis ($P<0.001$). Initial PSA was higher in men with prostate cancer compared to benign disease and no diagnosis groups ($P<0.05$), although the magnitude of this difference was small. The last PSA prior to diagnosis was clearly elevated in men with cancer ($P<0.001$). The mean and median PSA velocity were substantially higher in men with cancer compared to benign disease and no diagnosis, respectively ($P<0.001$; Table 1).

The number of cancer, benign and no prostate-related diagnosis cases by PSA pattern, as well as the proportion of men with a prostate-related diagnosis, proportion diagnosed with cancer and the numbers of aggressive cancers by pattern are presented in Table 2. The majority of men had a PSA level which decreased or returned to low levels ($<4.0\,\mathrm{ng\,ml^{-1}}$) at some time point (33.4% of all men had pattern 3 and 37.8% had pattern 4). In men with prostate cancer, 57.1% had PSA pattern 1 or 2 compared to 34.6% of men with benign disease and 24.4% of those with no diagnosis ($P<0.001$).

The proportion of men with a diagnosis (prostate cancer or histologically confirmed benign disease) decreased across PSA pattern ($P<0.001$), with only 12% of men who had a PSA which returned to $<4.0\,\mathrm{ng\,ml^{-1}}$ proceeding to invasive investigation (Table 2). In those with a prostate-related diagnosis, the proportion of cancer was markedly different in each PSA pattern ($P<0.001$), with over half of those in pattern 1 being diagnosed with prostate cancer. However, 23.1% of men with PSA pattern 4 were also subsequently diagnosed with cancer. Tumour aggressiveness was available in 501 (81.2%) cases. There was no relationship observed between Gleason score or overall tumour aggressiveness and pattern of PSA change (P for trend $=0.19$ and 0.42, respectively). There was also no association between PSA pattern and age.

Discussion

Men who had PSA values which increased (patterns 1 and 2) were more likely to have prostate cancer compared to those in whom PSA decreased or returned to $<4.0\,\mathrm{ng\,ml^{-1}}$ at some point (patterns 3 and 4, respectively). However, due to the inherent variability of PSA, 71.2% of men with an initially raised PSA ($4.0–9.99\,\mathrm{ng\,ml^{-1}}$) had a subsequent decrease in their

Table 1 Group characteristics

	Prostate cancer	*Benign histology*	*No prostate diagnosis*
Age (years)			
<50 (%)	14 (10.4)[a]	12 (9.0)[a]	108 (80.6)[a]
50–59 (%)	111 (11.6)	250 (26.1)	598 (62.4)
60–69 (%)	261 (10.6)	458 (18.7)	1736 (70.7)
⩾70 (%)	231 (6.9)	379 (11.2)	2760 (81.9)
Total number of men	617	1099	5202[b]
Mean (s.d.)*	67.4 (8.7)	66.5 (8.4)	70.0 (9.4)
Initial PSA (ng ml^{-1})			
Mean (s.d.)*	6.9 (1.7)	6.5 (1.7)	6.2 (1.6)
Median (IQR)†	6.8 (2.8)	6.2 (2.7)	5.9 (2.5)
Last PSA (ng ml^{-1})			
Mean (s.d.)*	37.5 (126.0)	8.7 (7.4)	8.1 (42.9)
Median (IQR)[b]	11.7 (12.5)	7.2 (1.9)	5.6 (4.7)
Number of PSA tests			
Mean (s.d.) ±	5.5 (3.2)	4.7 (2.2)	4.9 (2.4)
Median (IQR)	4.0 (4.0)	4.0 (3.0)	4.0 (3.0)
PSA velocity (ng ml per year)			
Mean (s.d.)*	10.4 (43.6)	0.7 (16.1)	0.6 (17.0)
Median (IQR)[b]	1.8 (4.0)	0.4 (2.0)	0.0 (1.3)

Abbreviations: IQR, interquartile range; PSA, prostate-specific antigen.
*$P<0.001$, ANOVA; †$P<0.001$, Kruskal–Wallis; ±$P<0.001$, χ^2.
[a]Numbers in brackets relate to percentage of men within each diagnostic group by age category.
[b]Age not available for 136 men.

PSA, which returned to 'normal' (<4.0 ng ml^{-1}) levels in 37.8%. Of these men in whom the PSA level decreased to <4.0 ng ml^{-1} and who were subsequently investigated, 23.1% were diagnosed with prostate cancer.

The main strengths of this study were that it is population based and included a large number of participants. Many men had numerous PSA tests (mean 4.9) and follow-up was a mean of 5.9 years. Further, patterns were assigned based on PSA levels only. The presence of cancer did not determine which pattern was assigned, as had previously been described by Ito *et al*.[9] There are a number of limitations of note. First, the PSA patterns described were assigned arbitrarily and retrospectively. Although it is not known if the pattern of PSA change influenced the decision to proceed to biopsy, this is likely to have occurred as many more men with increasing PSA levels proceeded to invasive investigation. Second, the time between tests was not taken into account when determining PSA pattern. Carter *et al*.[10] have shown that changes in PSA over short-time intervals may be due to PSA variability alone, and many of the observed changes in PSA in this study may have occurred over short time periods. However, given recent recommendations to repeat an abnormal PSA prior to proceeding with prostate biopsy,[4–6] and with increasing patient expectations, decisions on further investigation may often be based on short-term changes in PSA, and so our findings may more accurately represent clinical practice. Third, different PSA assays were used during the study period which, given their inherent variability, may not provide results that are directly comparable; there is potential for some of the PSA changes to be observed due to analytical variation. Fourth, only 24.3% of men in the study had a prostate-related diagnosis made and undoubtedly there are cases of prostate cancer, which have not yet been diagnosed. Many men with PSA levels ⩾4.0 ng ml^{-1} did not proceed to prostate biopsy; this is in keeping with the practice relating to PSA testing in Northern Ireland in the 1990s, where men tended to be investigated only if their PSA increased to ⩾10.0 ng ml^{-1}.[8] The PSA changes and cancer diagnosis rate observed may have differed if all men had undergone prostate biopsy. Further, the decision to proceed to prostate biopsy and the biopsy technique used were not standardized and were at the discretion of each individual's clinician. These may have been affected by clinical data not available to the research team such as family history or prostate gland size. Men in whom PSA decreased or returned to <4.0 ng ml^{-1} are likely to have had a subsequent rise in PSA or other clinical findings such as an abnormal digital rectal examination which led to them undergoing further investigation; there is therefore a selection bias towards these individuals. Finally, the lack of clinical details on men, some of which may have an effect on PSA or path of investigation, such as presenting symptoms, digital rectal examination findings, use of 5α-reductase inhibitors, the presence of prostatitis or variation in prostate biopsy techniques prevents inferences being made about how these factors may have affected the PSA changes or cancer diagnosis rates observed.

In this study, over 70% of men with an initially raised PSA (4.0–9.99 ng ml^{-1}) had a level which decreased or returned to <4.0 ng ml^{-1} at some time. Marked variability in PSA also occurred in men with prostate cancer; 28.8% of men with a decrease in their PSA (pattern 3) and 23.1% of those in which PSA returned to <4.0 ng ml^{-1} (pattern 4) were subsequently diagnosed with prostate cancer (Table 2). These variations in PSA, even in men with prostate cancer, highlight the difficulty of interpreting short-term changes in PSA. The natural variability of PSA levels has previously been recognized. In prospective studies, the mean coefficient of variation (CV) tended to be 10–15%.[11,12] A recent systematic review on

Table 2 Number of cancer, benign and no diagnosis cases, proportion of men with a prostate-related diagnosis, proportion diagnosed with cancer and number of aggressive cancers by PSA pattern

PSA pattern	*Cancer (%)*	*Benign (%)*	*No diagnosis (%)*	*Proportion with diagnosis vs no diagnosis (%)**	*Proportion diagnosed with cancer vs benign disease (%)**	*Number of aggressive cancers (%)*
1	169 (27.4)	138 (12.6)	494 (9.3)	38.3	55.1	65 (45.5)
2	183 (29.7)	242 (22.0)	806 (15.1)	34.5	43.1	41 (27.7)
3	191 (31.0)	472 (43.0)	1693 (31.7)	28.1	28.8	58 (36.0)
4	74 (12.0)	247 (22.5)	2343 (43.9)	12.0	23.1	21 (42.0)
Total	617	1099	5336	24.3	36.0	185 (36.9)

Abbreviation: PSA, prostate-specific antigen.
*$P<0.001$, χ^2-test.

PSA variability,[5] including 12 studies with 1324 patients, showed a mean CV of 20% with a 95% confidence interval of approximately 33%.

The clinical significance of this degree of variability is debated, with some authors considering a single PSA value to be reliable,[13–15] whereas others suggest that a single PSA has limited use and recommend repeating the PSA value before proceeding with prostate biopsy.[4–6] Eastham *et al*.[4] examined changes in PSA levels in 972 men who had sera stored on five occasions, 1 year apart. A total of 37% had at least one abnormal PSA (based on numerous criteria including total PSA $\geqslant 2.5\,ng\,ml^{-1}$ and PSAV $\geqslant 0.75$ ng ml per year) during the study period. Of these, 26–37% had a 'normal' PSA in the following sample, with this increasing to 40–55% at any time following the initially abnormal value. Eastham *et al*.[4] recommended repeating the PSA four to 6 weeks following an initially abnormal test to confirm that it was raised, although a major limitation of this study was that there were no diagnostic data available on men with raised PSA levels. Singh *et al*.[6] assessed the utility of repeating an initially abnormal PSA (above age-specific reference range) in a referred population, and deferring biopsy in those in whom the PSA returned to normal and who had a normal rectal examination. In 35% of men, the PSA returned to the normal range, with 82% of these remaining normal after 2 years follow-up. In those with an abnormal repeat PSA and not subsequently diagnosed with prostate cancer, the PSA value also returned to normal in 50% of cases after 2 years. The main limitations of the study by Singh *et al*.[6] were that only 47% of men with an initially raised PSA proceeded to biopsy and follow-up was short at 2 years, meaning there may be cancer cases in the non-cancer group which were not identified within the follow-up period. These limitations were addressed by Boddy *et al*.[13] who, using similar inclusion criteria, repeated an initially abnormal PSA test but proceeded to prostate biopsy in all cases. In 13% of men the PSA returned to normal levels however, 23.8% of these had prostate cancer on biopsy, with high-grade prostatic intraepithelial neoplasia (PIN) diagnosed in a further 14.3%. A similar investigation in 861 men biopsied as a part of the ProTect study,[14] found that in 22.4% of men diagnosed with prostate cancer, the repeat PSA value prior to biopsy had fallen below $4.0\,ng\,ml^{-1}$. A total of 11.1% of cancers in this study would have been missed had prostate biopsy been deferred in PSA-normalized men. Our findings confirm those of the above studies[13–14] that PSA can decrease and normalize in men with prostate cancer, and that these may be clinically significant cancers.

These results are not surprising when PSA variability is considered with data from the Prostate Cancer Prevention Trial.[15] When all men were biopsied, the risk of cancer was 23.9% when PSA was 2.0–3.0 ng ml^{-1} and 26.9% when PSA was 3.0–4.0 ng ml^{-1}. In the absence of infection, when an elevated PSA value is repeated, even though it may fall to $<4.0\,ng\,ml^{-1}$, the risk of prostate cancer if biopsy is performed is unlikely to decrease markedly. If the decision to proceed to prostate biopsy is based on the risk of prostate cancer being diagnosed as opposed to whether the PSA value is above or below an arbitrary cutoff, repeating the PSA is unlikely to change this risk. Therefore, a repeat PSA test after a short time period should not affect clinical decision-making, even if the PSA level were to decrease from the initial value.

Conclusion

Men who have PSA values which increase (patterns 1 and 2) are more likely to have prostate cancer compared to those in whom PSA decreases or returns to $<4.0\,ng\,ml^{-1}$ (patterns 3 and 4, respectively). However, many men with an initially raised PSA (4.0–9.99 ng ml^{-1}) will have a subsequent decrease in their PSA, which may even return to 'normal' ($<4.0\,ng\,ml^{-1}$) levels. This decrease in PSA may occur in men with prostate cancer, including clinically significant and aggressive prostate cancers, and so should not influence the decision to proceed to prostate biopsy.

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Conflict of interest

There is no conflict of interest for any author.

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