



## Prostate Cancer

# Contribution of a Single Repeat PSA Test to Prostate Cancer Risk Assessment: Experience from the ProtecT Study

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### Abstract

**Objective:** To examine whether a single repeat prostate-specific antigen (PSA) helps discriminate cancer from non-cancer-related PSA elevation.

**Methods:** Men aged 50–70 yr ( $n = 54,087$ ) in a multicentre randomised controlled trial comparing treatments for localised prostate cancer were tested. A total of 4102 (7.6%) with an initial PSA in the range of 3–19.9 ng/ml had repeat measurement (median interval: 50 d) followed by prostate biopsy. The decision to biopsy was based on the first PSA level. The outcome was the presence of prostate cancer on biopsy.

**Results:** Men with a 20% drop in PSA had a lower risk of cancer (odds ratio [OR] = 0.43; 95% confidence interval [CI], 0.35–0.52;  $p < 0.001$ ) and high-grade cancer (OR = 0.29; 95%CI, 0.19–0.44;  $p < 0.001$ ) compared to the rest of the cohort. The effect of percentage reduction was greater in men aged  $\leq 60$  yr than in those  $> 60$  yr. (OR for any cancer = 1.6; 95%CI, 1.0–2.4;  $p = 0.05$ ; OR for high-grade cancer = 2.9; 95%CI, 1.2–6.7;  $p = 0.014$ ). This equated to a risk reduction of high-grade cancer from 4% to 0.5%, 6% to 2%, and 15% to 2% in men  $\leq 60$  yr with an initial PSA of 3.0–3.99, 4.0–5.99, and  $\geq 6$  ng/ml, respectively. No level of repeat PSA confidently predicted absence of cancer.

**Conclusion:** Following an initial PSA of 3.0–19.99 ng/ml in men aged 50–70 yr, repeat PSA within 7 wk allows more accurate risk prediction that may assist in the decision-making as to whether or not to proceed with prostate biopsy.

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## 1. Introduction

Despite limitations of prostate-specific antigen (PSA) as a screening investigation for prostate cancer, PSA testing worldwide remains common; three fourths of men in the United States have had a PSA test performed [1] and the rate of testing is rising in the United Kingdom [2]. Multicentre studies assessing PSA testing in screening for prostate cancer are underway in many countries.

The Prostate Cancer Prevention Trial (PCPT) found a significant prevalence of prostate cancer in men with a PSA level previously considered to be normal [3]. It is now accepted that PSA provides a risk assessment and biopsy is undertaken on the basis of level of risk. The exact level at which to recommend biopsy is controversial; the original cut-off suggested was 4 ng/ml [4], but Catalona et al subsequently recommended 2.5 ng/ml on the basis of similar incidence and pathologic characteristics of cancer at a PSA level of 2.5–4.0 ng/ml [5]. In the European Randomised Study of Screening for Prostate Cancer (ERSPC), Schröder et al concluded the optimal cut-off level was 3.0 ng/ml [6].

Intraindividual fluctuations of 10–20% in the range 0.1–20 ng/ml are described [7,8]. The causes and clinical significance of such variabilities are unknown. In the present study, the cohort from the Prostate Testing for Cancer and Treatment ( ProtecT) study [9] was used to test the hypothesis that short-term variability in PSA levels may contribute useful information. The clinical implications in the context of prostate cancer screening and risk assessment are discussed.

## 2. Patients and methods

### 2.1. Patients

The ProtecT study [9] is a multicentre UK-based randomised clinical trial evaluating external-beam radiotherapy, active monitoring, and radical prostatectomy for clinically localised prostate cancer (Health Technology Assessment programme of the National Health Service). In line with the ERSPC, a PSA level of 3.0 ng/ml is used as the threshold for prostate biopsy [6]. Following counselling regarding risks and benefits of PSA testing and early detection of prostate cancer, community-dwelling men aged 50–70 yr undergo PSA testing in nine centres. Between 1 January 2002 and 31 October 2006, 54,087 men were tested. Of these, 4102 (7.6%) with an initial PSA level between 3.0 and 19.9 ng/ml underwent biopsy. On attending for biopsy, blood was taken for a repeat PSA immediately prior to any manipulation (Fig. 1). The decision to biopsy was based on the first PSA alone. Transurethral ultrasound-guided biopsy was carried out using a 10-core lateral biopsy template [10]. Pathologic evaluation was carried out by specialist

uropathologists in each centre. Serum for the repeat PSA was treated and analysed similarly to the initial specimen. All laboratories participate in the UK National External Quality Assessment Service (UK NEQAS) programme for PSA testing.

### 2.2. Analysis

The primary end point was the presence or absence of cancer on biopsy. High-grade cancer was defined by a Gleason score of  $\geq 7$ . Thresholds for the initial PSA result alone, for the repeat PSA test result, and combinations of information from both PSA results (mean of the two results and percentage change in PSA level from the initial to the repeat test in conjunction with the initial PSA) were investigated for their discriminatory ability using the area under their receiver operating characteristic (ROC) curves [11]. Different thresholds were considered to illustrate sensitivity, specificity, likelihood ratio, number of biopsies avoided, and number of cancers missed.

Multivariable logistic regression (Stata version 9, StataCorp 2005) was carried out investigating risk prediction using the initial PSA result in conjunction with repeat PSA, mean PSA, percentage difference between the two PSA levels, and age. Percentage change in PSA was taken as the difference between the logarithms of initial and repeat PSA and age as a continuous covariate. All models were adjusted for study centre by the inclusion of eight dummy variables distinguishing men at the nine centres.

Interaction terms were added to examine changes in risk prediction with repeat PSA and percentage change in PSA with either age or initial PSA, with *p* values for interaction calculated using the likelihood ratio test.

## 3. Results

### 3.1. Cohort characteristics

Median age was 62.2 yr. Of 4102 men undergoing biopsy, 1318 (32%) were found to have cancer, of whom 366 (27.8%) had high-grade disease. The correlation coefficient between the two PSA results was 0.74 (Spearman rho,  $p < 0.001$ ). Age and initial and repeat PSA levels differed between those men without cancer, with cancer, and with high-grade cancer on biopsy (Table 1). Men with high-grade disease showed a median increase on repeat PSA testing of 5% compared with a reduction of 4% in men without prostate cancer ( $p < 0.001$ ).

### 3.2. PSA performance

ROC curves (Fig. 2A) showed improvement in the area under the curve (AUC) from 0.624 for initial PSA alone to 0.648 for repeat PSA level ( $p < 0.001$ ) and 0.647 for percentage change in PSA level ( $p < 0.001$ ). AUC for high-grade disease (Fig. 2B) showed similar improvement from 0.708 for initial PSA level alone to 0.740 and 0.739 for repeat PSA level and percentage

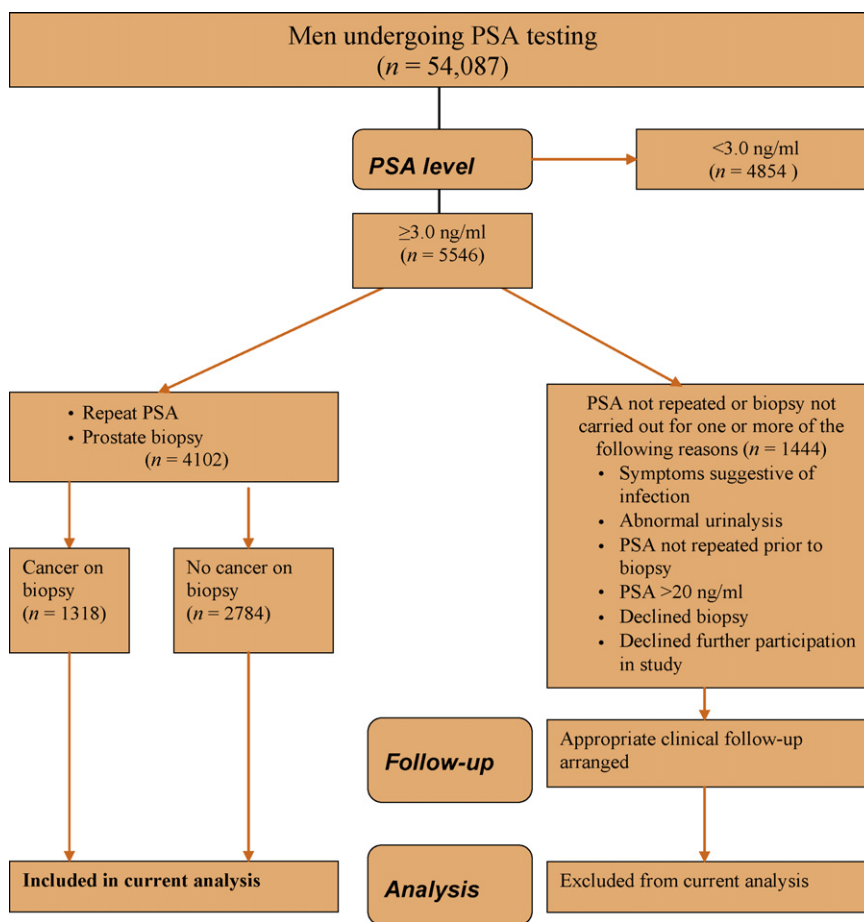


Fig. 1 – Consort diagram for cohort studied. PSA = prostate-specific antigen.

change PSA, respectively ( $p < 0.001$ ). Table 2 illustrates the outcomes using the data from this cohort to investigate different thresholds for initial PSA, repeat PSA, and percent change in PSA levels. It can be seen that raising the threshold of initial PSA from 3.0 to 3.5 would have resulted in 980 (24%) fewer biopsies being performed but at the expense of missing 220 (17%) of the cancers diagnosed. Thus, the

ratio of men biopsied to cancers diagnosed remains exactly the same at 3.1:1. If one examines the effect of applying a threshold to the repeat PSA level, limiting a biopsy to men with a repeat PSA in excess of 3.0 ng/ml results in 683 fewer biopsies, missing 114 cancers and reducing the biopsy-to-cancer ratio to 2.8:1. Similar data are shown for percentage reduction PSA where a reduction of 20% between the first and second PSA

Table 1 – Age at first PSA test and each PSA measure for men with and without a diagnosis of cancer at biopsy and with high-grade cancer\* at biopsy

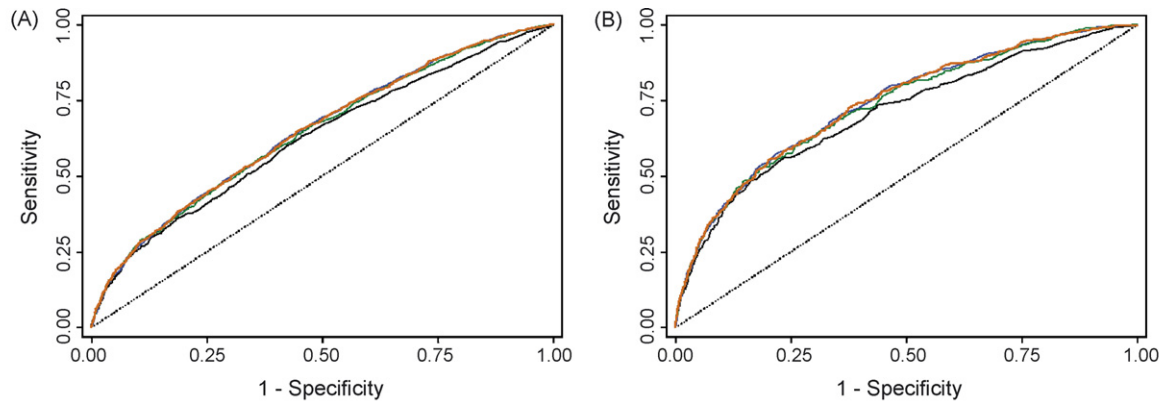
	No cancer (n = 2784)	All cancer (n = 1318)	High-grade cancer* (n = 366)
	Median (interquartile range)	Median (interquartile range)	Median (interquartile range)
Age, yr	62 (58, 66)	63 (59, 67) <sup>†</sup>	64 (60, 67) <sup>‡</sup>
Initial PSA, ng/ml	4.1 (3.4, 5.5)	4.9 (3.7, 7.6) <sup>†</sup>	6.5 (4.2, 10) <sup>‡</sup>
Repeat PSA, ng/ml	4.0 (3.1, 5.4)	5.0 (3.7, 7.8) <sup>†</sup>	6.7 (4.5, 10.4) <sup>‡</sup>
% change between initial and repeat PSA	-4 (-21, +10)	0 (-11, +14) <sup>†</sup>	+5 (-7, +15) <sup>‡</sup>
Interval, d	50 (33, 69)	50 (34, 69)	50 (33, 70)

PSA = prostate-specific antigen.

\* High-grade refers to Gleason sum score of  $\geq 7$  on biopsy.

<sup>†</sup> Compared to the 2784 men without prostate cancer, Wilcoxon rank-sum test gives  $p < 0.001$ .

<sup>‡</sup> Compared to the 3736 men without high-grade prostate cancer, Wilcoxon rank-sum test gives  $p < 0.001$ .



	Any cancer versus no cancer (A)			High-grade cancer versus other men (B)		
	Area under ROC curve	95%CI	<i>p</i> (comparison with initial PSA level)	Area under ROC curve	95%CI	<i>p</i> (comparison with initial PSA level)
Initial PSA level —	0.624	0.606–0.643		0.708	0.679–0.738	
Repeat PSA level —	0.648	0.630–0.666	<i>p</i> < 0.001	0.740	0.713–0.767	<i>p</i> < 0.001
Mean PSA —	0.643	0.625–0.661	<i>p</i> < 0.001	0.734	0.706–0.761	<i>p</i> < 0.001
% change in PSA* —	0.647	0.629–0.665	<i>p</i> < 0.001	0.739	0.712–0.766	<i>p</i> < 0.001

\*Percent change is always considered in conjunction with initial PSA because it is ineffective when considered in isolation.

**Fig. 2 – Comparison of the four prostate-specific antigen (PSA) measures using area under the receiver operating characteristic curve for all cancers (A) and high-grade cancer (B). ROC = receiver operating characteristic; CI = confidence interval.**

estimation is associated with optimal performance (Table 2).

### 3.3. Individual risk prediction

Increasing age was associated with an increased incidence of high-grade prostate cancer (odds ratio

[OR] = 1.18; 95% confidence interval [CI], 1.05–1.33; *p* < 0.005) at any given level of initial PSA, but not the presence of any cancer on biopsy (OR = 1.06; 95%CI, 0.99–1.44; *p* = 0.07). An association was found between initial PSA level and a fall in repeat PSA to below threshold (3.0 ng/ml); fewer men returned to below threshold in the highest initial risk group

**Table 2 – Performance of initial PSA, repeat PSA, and percent reduction PSA at different thresholds for each variable**

Variable & threshold	Biopsies avoided (%)	Biopsy-to-cancer ratio	Likelihood ratio (for presence of cancer)	All cancers (n = 1318)			High-grade cancers (n = 366)		
				Cancers missed (%)	Sensitivity	Specificity	Cancers missed (%)	Sensitivity	Specificity
Initial PSA, ng/ml									
3.0	0 (0)	3.1	1.0	0 (0)	1.00	0	0 (0)	1.00	0
3.5	980 (24)	3.1	1.14	220 (17)	0.83	0.27	33 (9)	0.91	0.25
4.0	1699 (41)	2.6	1.30	404 (31)	0.69	0.47	76 (21)	0.79	0.43
Repeat PSA, ng/ml									
2.0	187 (5)	3.0	1.04	24 (2)	0.98	0.06	2 (1)	0.99	0.05
2.5	345 (8)	2.9	1.09	44 (3)	0.97	0.11	3 (1)	0.99	0.09
3.0	683 (17)	2.8	1.14	114 (9)	0.91	0.20	15 (4)	0.96	0.18
3.5	1250 (30)	2.7	1.27	257 (19)	0.81	0.36	35 (10)	0.90	0.33
4.0	1789 (44)	2.5	1.38	402 (31)	0.69	0.50	61 (17)	0.83	0.46
% reduction PSA									
30%	467 (11)	2.9	1.09	78 (6)	0.94	0.14	10 (3)	0.97	0.12
20%	784 (19)	2.8	1.16	149 (11)	0.89	0.23	24 (7)	0.93	0.20
10%	1405 (34)	2.7	1.23	326 (25)	0.75	0.39	61 (17)	0.83	0.36

PSA = prostate-specific antigen.

**Table 3 – Risk ( $\pm 95\%$  confidence intervals) of any cancer and high-grade cancer based on age, initial PSA, and whether or not  $\geq 20\%$  reduction in repeat PSA**

Age	Initial PSA, ng/ml	n	'a priori' risk of cancer on biopsy		Proportion with 20% reduction in PSA on repeat testing	Revised risk of cancer on biopsy if $\geq 20\%$ reduction in PSA		Revised risk of cancer on biopsy if no significant reduction in PSA	
			Any cancer	High-grade cancer		Any cancer	High-grade cancer	Any cancer	High-grade cancer
$\leq 60$ yr	3.0–3.99	691	0.23 $\pm$ 0.03	0.04 $\pm$ 0.02	0.26 $\pm$ 0.03	0.11 $\pm$ 0.02	0.005 $\pm$ 0.005	0.27 $\pm$ 0.03	0.05 $\pm$ 0.02
	4.0–5.99	516	0.32 $\pm$ 0.04	0.06 $\pm$ 0.02	0.26 $\pm$ 0.03	0.21 $\pm$ 0.04	0.02 $\pm$ 0.01	0.35 $\pm$ 0.04	0.07 $\pm$ 0.02
	6.0–19.99	285	0.42 $\pm$ 0.06	0.15 $\pm$ 0.04	0.19 $\pm$ 0.05	0.11 $\pm$ 0.04**	0.02 $\pm$ 0.02	0.49 $\pm$ 0.06	0.18 $\pm$ 0.04
$> 60$ yr	3.0–3.99	1008	0.24 $\pm$ 0.03	0.05 $\pm$ 0.01	0.16 $\pm$ 0.02	0.13 $\pm$ 0.02	0.03 $\pm$ 0.01	0.26 $\pm$ 0.03	0.05 $\pm$ 0.01
	4.0–5.99	854	0.31 $\pm$ 0.03	0.07 $\pm$ 0.02	0.19 $\pm$ 0.03	0.23 $\pm$ 0.03	0.03 $\pm$ 0.01	0.33 $\pm$ 0.03	0.08 $\pm$ 0.02
	6.0–19.99	748	0.49 $\pm$ 0.04	0.21 $\pm$ 0.04	0.16 $\pm$ 0.03	0.32 $\pm$ 0.03	0.08 $\pm$ 0.02	0.52 $\pm$ 0.04	0.24 $\pm$ 0.03

(6.0–19.99 ng/ml) than the lowest (3.0–3.99 ng/ml; 4% vs. 30%;  $p = 0.01$ ). There was no evidence of interaction between initial PSA and percentage reduction in PSA (17% vs. 20%,  $p = 0.07$ ). Men with a  $\geq 20\%$  reduction in PSA had a lower risk of cancer (OR = 0.43; 95%CI, 0.35–0.52;  $p < 0.001$ ) and high-grade cancer (OR = 0.29; 95%CI, 0.19–0.44,  $p < 0.001$ ) compared to those without. There was greater effect of percentage reduction in repeat PSA for the presence of any cancer (OR = 1.6; 95%CI, 1.0–2.4;  $p = 0.05$ ) and particularly for the presence of high-grade cancer (OR = 2.9; 95%CI, 1.2–6.7;  $p = 0.014$ ) in men aged  $\leq 60$  than those  $> 60$  yr. Table 3 illustrates these findings. On repeat testing, between 16% and 26% of men had a reduction of  $\geq 20\%$  in PSA level, depending on age and initial PSA level. This allowed definition of low- and high-risk groups depending on the repeat PSA level. For example, a man aged 55 with an initial PSA of 3.5 ng/ml would have an *a priori* risk of finding prostate cancer on biopsy of 23%  $\pm$  3% with a 4%  $\pm$  2% risk of finding high-grade cancer. If his subsequent PSA level is  $\leq 2.8$  ng/ml, he falls into the lower risk category with a revised risk of prostate cancer of 1%  $\pm$  2% and of high-grade cancer of  $< 1\%$ . Conversely, if his PSA level on repeat is  $> 2.8$  ng/ml, his revised risk of prostate cancer is 27%  $\pm$  3% and his risk of harbouring high-grade disease is significantly higher at 5%  $\pm$  2%. This appears to hold true for all levels of PSA (3.0–19.99 ng/ml) in all men, although it seems of most clinical relevance to men aged  $\leq 60$  yr (Table 3).

#### 4. Discussion

A repeat PSA test improves individual risk prediction for the presence of prostate cancer. The strengths of the current study are the large numbers involved with elimination of verification bias in that all men underwent biopsy, regardless of the level of repeat

PSA. The data from the ROC curves indicate a modest effect of combining the results of a repeat PSA with the initial PSA in discriminating cancer from non-cancer. However, from the perspective of risk prediction, it is evident from Table 3 that the risk profile for an individual can be better calculated using the results of the two PSA tests rather than just the one. The improved precision of risk estimation may prove to be beneficial, particularly if the estimate of risk falls below that which would normally lead to biopsy. The limitations of applying the 'c' statistic (area under the ROC curve) to risk assessment have been highlighted in the field of cardiovascular risk assessment [12] and seem to be borne out by the current data in prostate cancer risk prediction. In this context, it must be restated that there is no specific level of initial or repeat PSA at which the risk of prostate cancer is zero [3]. A significant limitation of the current study is that none of the men with an initial PSA level  $< 3.0$  ng/ml underwent biopsy.

Because PSA is used to guide decision-making regarding prostate biopsy, for the change in risk to be clinically meaningful, it is imperative that the altered risk profile would result in a meaningful change in advice, that is, delay/defer biopsy. In this cohort of men with an initial PSA between 3.0 and 19.99 ng/ml, a clinically meaningful risk reduction becomes evident; the lowest generally acceptable cut-off level for PSA is 2.5 ng/ml with an estimated risk of prostate cancer of 23.9% at that level [13]. We can see from Table 3 that if we set a risk of prostate cancer of  $\geq 23\%$  at which we would recommend biopsy, the risk of cancer is reduced to below this level in all men aged  $\leq 60$  yr with an initial PSA of 3.0–19.99 ng/ml and a  $\geq 20\%$  reduction in PSA level on repeat testing within 2 mo and in men aged  $> 60$  yr with an initial PSA level of  $< 4.0$  ng/ml. This would result in repeating a PSA test in 2500 men (61%) and a meaningful reduction of cancer risk in

529 (13%), thereby avoiding one biopsy for every five repeat PSA tests performed. PSA surveillance would be applicable to these men with referral for biopsy should the PSA be further elevated during follow-up. Reduction in PSA to below threshold (3.0 ng/ml) predicted a similar reduction in risk (table available from authors on request).

Eastham et al found the PSA level in 30% of 972 men [14] returned to <4.0 ng/ml and in 26% to <2.5 ng/ml 12 mo later. These percentages increased to 44% and 40%, respectively, if all men whose PSA level returned to within the normal range at any point during their 4-yr follow-up were included. On this basis, a repeat PSA test was recommended rather than proceeding directly to biopsy. However, no corroborating biopsy evidence was presented to demonstrate a lower risk of prostate cancer with the reduction in PSA. Singh et al [15] followed 101 men referred with an elevated PSA level and a normal digital rectal examination for 2 yr. Normalisation of PSA level was associated with an extremely low risk of prostate cancer. They concluded that it was safe to avoid biopsy in such men. Conversely, Boddy and associates [16] found a 24% risk of prostate cancer in 160 men with a return of PSA to within an age-specific range and concluded that biopsy should be carried out regardless of any subsequent reduction in PSA level. The latter studies reported on a small number of men making extrapolation to a wider population difficult.

The reason for the variability observed in PSA in this cohort is not immediately clear. It seems unlikely that it can be attributed to benign prostatic hyperplasia because the incidence of this increases with age [17]; hence one would expect greater variability in the older patient, which is not the case in this cohort. Within the younger age group the revised cancer risk is more marked at either extreme of the PSA range in question. It is likely that there are separate factors responsible for this; at the lower levels of the range, physiologic oscillations in PSA level may be more easily detected in men with benign disease than with cancer. At the higher limit, it is likely that in a significant proportion young men with a very high PSA, a self-resolving pathologic event has occurred; in this cohort, of 60 men aged  $\leq 60$  yr with an initial PSA level  $> 10$  ng/ml, 10 had a reduction of  $> 20\%$  on repeat testing with only one of these having cancer compared with 34 of 50 with cancer in those with a static or increasing PSA.

Analytic differences between PSA assays have been described [18]. Although different assays were used in several centres in this multicentre study, the difference in variability between men with cancer

and those without was consistent across centres and therefore across assays.

The findings of the current study show that in men with prostate cancer, particularly high-grade prostate cancer, PSA levels are more likely to remain stable when repeated at a median of 50 d than in men without prostate cancer. Our results may reflect early differences in PSA dynamics in men with and without prostate cancer. It is feasible that this pattern can be identified at much lower ranges of PSA (within what are currently accepted to be normal ranges). Carter et al have shown that PSA velocity in the decade preceding cancer diagnosis predicts outcome of prostate cancer [19]. As currently used, PSA measurements at the lower range of PSA lack specificity for the detection of prostate cancer. Patterns of fluctuations identified in PSA level on a single repeat are likely to be similar even if a cut-off level of 2.5 ng/ml or even lower were to be applied, although this assumption has not been tested in the current study. Repeated PSA levels in this range may help identify those men at risk of aggressive prostate cancer where early treatment would be beneficial and avoid over-treatment of clinically insignificant disease. The data quantify the pattern of fluctuation as well as the risk of cancer; in men with high-grade prostate cancer, there is an increase in PSA detectable at a median interval of only 7 wk, whereas in those without prostate cancer there is a reduction in PSA level. Such differences can only be quantified in a cohort of this size. Several repeats over longer periods may further help the specificity of PSA testing, but the improved performance may be offset by the drawback of increasing anxiety whilst carrying out repeats.

The association of PSA variability and age with detection of high-grade disease is particularly noteworthy—advancing age was associated with an increase in the prevalence of high-grade cancer at any level of PSA, thus bringing into question the validity of age-adjusted reference values in the age group 50–70 yr. Similarly, high-grade disease was associated with reduced variability in PSA level compared with all cancers or absence of cancer. It must be stated that although a high Gleason grade is a predictor of a more aggressive cancer phenotype, we cannot currently distinguish clinically significant from nonsignificant disease with certainty. Despite a strong association between stability of PSA measurement and the presence of prostate cancer, there was no level of repeat PSA that could confidently predict the absence of prostate cancer. Furthermore, high-grade disease may exist in the resected specimen at surgery even if it has not been detected on biopsy.

Other approaches have been advocated to improve the specificity of PSA in diagnosing prostate cancer. The use of age-specific PSA ranges has been recommended to improve the sensitivity of the test in younger men and improve specificity in older men [20], particularly in avoiding the detection of clinically insignificant disease in the older population. Based on the results of this large cohort it would seem that there is no valid basis for an age-specific range in the age range studied; PSA performs at least as well at a cut-off of 3.0 ng/ml in the population older than 60 yr as in the younger population, particularly with regards to detection of high-grade disease. It is worth noting that the cohort is restricted to men aged 50–70 yr and the results may not apply outside this age range.

Nomograms using a number of known risk factors have been developed [3,21,22] for the diagnosis of prostate cancer. A potential drawback of these is their relative complexity, making them more appropriate to specialist urologic practice rather than easily accessible to the general medical practitioner. The potential benefit of the current approach is its simplicity; only two variables are required for a risk calculation that is, the age of the man and the PSA level, and both are easily available, making the algorithm accessible to general medical and urologic practice.

## 5. Conclusions

1. A repeat PSA level in a man with a PSA level between 3.0 and 19.99 ng/ml allows more accurate risk estimation as to whether or not biopsy will reveal prostate cancer. This is particularly predictive for the presence of high-grade prostate cancer.
2. For individual risk assessment, men aged  $\leq 60$  yr would benefit most from this approach.
3. There is no justification for a discriminatory age-specific PSA cut-off for men  $>60$  or  $<60$  yr of age within the 50–70 age range.

## Conflicts of interest

The authors have nothing to disclose.

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## References

- [1] Thompson IM, Ankerst DP, Chi C, et al. Operating characteristics of prostate-specific antigen in men with an initial PSA level of 3.0 ng/ml or lower [see comment]. *JAMA* 2005;294:66–70.
- [2] McLernon DJ, Donnan PT, Gray M, Weller D, Sullivan F. Receiver operating characteristics of the prostate specific antigen test in an unselected population. *J Med Screen* 2006;13:102–7.
- [3] Thompson IM, Ankerst DP, Chi C, et al. Assessing prostate cancer risk: results from the Prostate Cancer Prevention Trial. *J Natl Cancer Inst* 2006;98:529–34.
- [4] Catalona WJ, Smith DS, Ratliff TL, et al. Measurement of prostate-specific antigen in serum as a screening test for prostate cancer. *N Engl J Med* 1991;324:1156–61.
- [5] Catalona WJ, Smith DS, Ornstein DK. Prostate cancer detection in men with serum PSA concentrations of 2.6 to 4.0 ng/mL and benign prostate examination. Enhancement of specificity with free PSA measurements [see comment]. *JAMA* 1997;277:1452–5.
- [6] Schroder FH, Roobol-Bouts M, Vis AN, van der KT, Kranse R. Prostate-specific antigen-based early detection of prostate cancer—validation of screening without rectal examination. *Urology* 2001;57:83–90.
- [7] Bruun L, Becker C, Hugosson J, Lilja H, Christensson A. Assessment of intra-individual variation in prostate-specific antigen levels in a biennial randomized prostate cancer screening program in Sweden. *Prostate* 2005;65:216–21.
- [8] Soletormos G, Semjonow A, Sibley PE, et al. Biological variation of total prostate-specific antigen: a survey of published estimates and consequences for clinical practice [review] [71 refs]. *Clin Chem* 2005;51:1342–51.
- [9] Donovan JL, Mills N, Smith M, et al. Improving design and conduct of randomised trials by embedding them in qualitative research: ProtecT (prostate testing for cancer and treatment) study. *BMJ* 2002;325:766–70.
- [10] Eskicorapci SY, Baydar DE, Akbal C, et al. An extended 10-core transrectal ultrasonography guided prostate biopsy protocol improves the detection of prostate cancer. *Eur Urol* 2004;45:444–9.
- [11] Hanley JA, McNeil BJ. A method of comparing the areas under receiver operating characteristic curves derived from the same cases. *Radiology* 1983;148:839–43.
- [12] Cook NR. Use and misuse of the receiver operating characteristic curve in risk prediction. *Circulation* 2007;115:928–35.
- [13] Thompson IM, Pauler DK, Goodman PJ, et al. Prevalence of prostate cancer among men with a prostate-specific

- antigen level  $< \text{or} = 4.0$  ng per millilitre. *N Engl J Med* 2004;350:2239-46.
- [14] Eastham JA, Riedel E, Scardino PT, et al., Polyp Prevention Trial Study Group. Variation of serum prostate-specific antigen levels: an evaluation of year-to-year fluctuations. *JAMA* 2003;289:2695-700.
- [15] Singh R, Cahill D, Popert R, O'Brien TS. Repeating the measurement of prostate-specific antigen in symptomatic men can avoid unnecessary prostatic biopsy [see comment]. *BJU Intl* 2003;92:932-5.
- [16] Boddy JL, Pike DJ, Al-Hayek S, Shaida N, Malone PR. An elevated PSA, which normalizes, does not exclude the presence of prostate cancer. *Prostate Cancer Prostatic Dis* 2005;8:349-52.
- [17] Berry SJ, Coffey DS, Walsh PC, Ewing LL. The development of human benign prostatic hyperplasia with age. *J Urol* 1984;132:474-9.
- [18] Roddam AW, Rimmer J, Nickerson C, Ward AM. NHS Prostate Cancer Risk Management Program. Prostate-specific antigen: bias and molarity of commercial assays for PSA in use in England. *Ann Clin Biochem* 2006;43:1-48.
- [19] Carter HB, Ferrucci L, Kettermann A, et al. Detection of life-threatening prostate cancer with prostate-specific antigen velocity during a window of curability. *J Natl Cancer Inst* 2006;98:1521-7.
- [20] Oesterling JE, Jacobsen SJ, Cooner WH. The use of age-specific reference ranges for serum prostate specific antigen in men 60 years old or older. *J Urol* 1995;153:1160-3.
- [21] Steyerberg EW, Roobol MJ, Kattan MW, van der Kwast TH, De Koning HJ, Schroder FH. Prediction of indolent prostate cancer: validation and updating of a prognostic nomogram. *J Urol* 2007;177:107-12.
- [22] Nam RK, Toi A, Klotz LH, et al. Assessing individual risk for prostate cancer. *J Clin Oncol* 2007;25:3582-8.