

# PSA – targeting the men at highest risk

JONATHAN REES, WILLIAM CROSS, GEMMA BORWICK, ALI COOPER AND SARAH CANT

**A move towards targeted screening of men at higher risk of prostate cancer offers the potential to improve outcomes. In this article, members of the Prostate Cancer UK Education Advisory Group outline ways in which primary care physicians can ensure that PSA testing is targeted at those who are most likely to benefit.**

The use of PSA testing as a screening tool for prostate cancer remains as controversial as ever. The results of the long-term screening study, the European Randomised Study of Screening for Prostate Cancer (ERSPC), have clearly demonstrated a decrease in prostate-cancer-specific mortality and metastatic disease in men aged 50–69 years undergoing regular PSA testing, with numbers needed to screen and numbers needed to diagnose comparing favourably with established screening programmes such as for breast cancer.<sup>1,2</sup>

However, the observed relative reduction in prostate cancer mortality came along with a considerable risk of overdiagnosis and overtreatment. For this reason, major reviews of the evidence for PSA screening have concluded that it cannot be recommended. The influential US Preventive Services Task Force

## Box 1. Factors to help identify men at highest risk of prostate cancer

- Increasing age
  - prostate cancer mainly affects men over the age of 50 and the risk increases with age. The average age for men to be diagnosed with prostate cancer is between 70 and 74 years
- Family history of prostate cancer
  - risk increases with number of relatives affected and closeness of relation
- Genetic factors
  - risk is particularly increased in men with *BRCA1* gene mutations
  - take note of family history of breast and ovarian cancer
- Ethnicity
  - black men are more likely to get prostate cancer than men of other ethnic backgrounds
- Baseline PSA
  - risk of clinically significant prostate cancer is increased in men with PSA reading above median level when tested at a young age
- For more information visit: <http://prostatecanceruk.org/information/who-is-at-risk>

recommended that physicians discourage men from partaking in PSA screening due to 'moderate or high certainty that the service has no net benefit or that the harms outweigh the benefits',<sup>3</sup> and a review in the *British Medical Journal* concluded that 'the most effective way to reduce prostate cancer incidence is to reduce PSA testing or raise thresholds that define abnormality' and 'physicians should recommend against PSA screening for prostate cancer'.<sup>4</sup>

## BLOG

What do you think? Is this a sensible approach, or still not worthwhile? Are there any other factors that should be taken into account when targeting men for testing?

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*Jonathan Rees, MB ChB, MD, MRCS, MRCGP, DRCOG, GP with a special interest in urology and men's health, Backwell and Nailsea Medical Group, North Somerset; Chair of Education Advisory Group, Prostate Cancer UK; William Cross, BMedSci, BM BS, FRCS(Urol), PhD, Consultant Urological Surgeon, Leeds Teaching Hospitals NHS Trust; Gemma Borwick, Education Manager, Prostate Cancer UK; Ali Cooper, Senior Research Analyst, Prostate Cancer UK; Sarah Cant, Director of Policy and Strategy, Prostate Cancer UK; on behalf of the Prostate Cancer UK Education Advisory Group*

### WHAT IS CURRENT PRACTICE FOR PSA TESTING IN THE UK?

There is no national screening programme for prostate cancer detection in asymptomatic men. The main guidance to GPs is given by the Prostate Cancer Risk Management Programme (PCRMP; [www.cancerscreening.nhs.uk/prostate](http://www.cancerscreening.nhs.uk/prostate)), which recommends a policy of 'informed choice' by 'providing high quality information to enable men to decide whether or not to have the PSA test based on the available evidence about risks and benefits'. UK national policy is therefore that 'after consideration of this information and in discussion with their GP, men over 50 who choose to have the test may do so free of charge, on the NHS'. However, awareness of the existence of the PCRMP is low in primary care, with a survey of 500 GPs in 2011 showing that 64% had not heard of the PCRMP.<sup>5</sup>

PSA testing is therefore available to all men over 50 in the UK, meaning that current screening practice is based on an *ad hoc* system of patient demand, largely secondary to personal experience of prostate cancer (*ie* when diagnosed in a friend or work colleague) or as a result of media coverage. This has meant that PSA testing is targeted not at those who most stand to benefit, but at those who ask to be tested, regardless of underlying risk or need. This has led to significant skew of PSA testing in UK primary care, with tests concentrated in an elderly population (highest testing rates are in the 75- to 79-year age bracket, with 11.3% undergoing testing in 1 year, compared to an average of 6.2% for all men aged 45–89) and in areas of lower social deprivation (for every 20 points increase in the index of multiple deprivation score, the proportion of men undergoing PSA testing falls by 1.7%).<sup>6</sup>

For men presenting in primary care with lower urinary tract symptoms (LUTS), it is again controversial as to whether to offer PSA testing routinely. NICE LUTS guidance concludes that men should be offered

'information, advice and time to decide if they wish to have a PSA test if their LUTS are suggestive of bladder outflow obstruction due to benign prostatic enlargement, if their prostate feels abnormal on digital rectal examination or if they are concerned about prostate cancer'.<sup>7</sup> There is evidence to suggest that men with LUTS, their partners and their GPs are usually concerned about the risk of prostate cancer as a cause for symptoms,<sup>8,9</sup> and therefore, it would appear that consideration of PSA testing and discussion of pros and cons of PSA testing should be a routine component of the assessment of the man with LUTS. NICE referral guidelines for suspected cancer state that 'patients presenting with symptoms suggesting prostate cancer should have a digital rectal examination and PSA test after counselling. Symptoms will be related to the lower urinary tract and may be inflammatory or obstructive'.<sup>10</sup>

### WHOM SHOULD WE BE TESTING?

The aims of PSA screening are primarily to reduce both all-cause and prostate-cancer-specific mortality in the long term. However, while the ERSPC has suggested this may be possible, survival advantages come at a significant cost in terms of a high 'number needed to screen', large numbers of men having unnecessary biopsies with associated morbidity, and significant overdiagnosis and, more importantly, overtreatment of low-risk disease. Therefore, if we are to impact on prostate cancer survival, we need to improve our PSA testing practice, moving away from those who simply ask for testing, and towards those who are at increased risk of developing clinically significant prostate cancer (Box 1).

### WHO IS AT INCREASED RISK?

#### Family history

There is a large body of evidence showing that men with a family history of the disease have a higher risk of prostate cancer, compared to those with no affected relatives.<sup>11</sup> On average in the UK, 12.5%

(one in eight) of men will be diagnosed with prostate cancer in their lifetime.<sup>12</sup> A man with no family history of prostate cancer is estimated to have an 8% (one in 13) lifetime risk of clinical prostate cancer, increasing to approximately 40% (one in three) for a man with three or more diagnosed male relatives.<sup>13</sup> Degree of relatedness has a significant impact on risk, with a relative risk (RR) of 2.22 for those with a diagnosed first-degree relative compared with 1.88 for a diagnosed second-degree relative. Further, risk is significantly higher for men with a brother with prostate cancer (RR 2.87) than for those with a father with prostate cancer (RR 2.12).

#### BRCA1 and BRCA2 genes

Mutations in the DNA repair genes, breast cancer 1 and 2, better known as *BRCA1* and *BRCA2*, are widely recognised as risk factors for the development of female breast and ovarian cancer. Less well recognised, however, is their impact on men. The presence of *BRCA1* gene mutations causes an eight-fold increase in the risk of prostate cancer, commonly with early onset and an aggressive clinical course.<sup>14,15</sup> *BRCA2* mutations have a lesser impact on prostate cancer risk. While mutations in *BRCA1* are uncommon in the general population (they are thought to account for only 1% of cases of prostate cancer diagnosed under the age of 65), it would appear sensible to include a strong family history of breast and/or ovarian cancer when assessing a man's risk of developing prostate cancer. Trials of targeted screening of men with the *BRCA1/2* gene mutations are underway and preliminary results from the IMPACT study<sup>16</sup> suggest that these mutations may be indicative of an increased likelihood of aggressive disease.

#### Ethnicity

In the UK, black men are approximately three times more likely to be diagnosed with prostate cancer than white men of the same age, and are more likely to

### Box 2. What can a GP do now?

- Take a look at the Prostate Cancer Risk Management Programme (PCRMP; [www.cancerscreening.nhs.uk/prostate](http://www.cancerscreening.nhs.uk/prostate)) and signpost patients towards patient information leaflets such as those provided by the PCRMP and Prostate Cancer UK
- Be more proactive in discussing risk factors and tests available with men at higher risk of prostate cancer
- Ask men newly diagnosed with prostate cancer if they have any brothers or sons who may wish to discuss PSA testing with their own GP
- Take a look at the help for health professionals provided by Prostate Cancer UK – sign up for the newsletter, follow on Twitter (@ProstateUKProfs), or sign up to attend a free masterclass, which includes a balanced debate on the complexities of PSA testing (<http://prostatecanceruk.org/health-professionals/education/primary-care-masterclasses>)
- Provide information in your waiting room on PSA testing and prostate cancer – Prostate Cancer UK provides free resources for primary care (<http://prostatecanceruk.org/health-professionals/patient-support>)

present with prostate cancer at a younger age.<sup>17,18</sup> In the UK, one in four black men will be diagnosed with prostate cancer in their lifetime<sup>19</sup> – double the overall one in eight risk faced by all men in the UK.<sup>12</sup> The UK age-adjusted incidence for prostate cancer is 174 per 100 000 in black men compared to 77 per 100 000 in white men (2010 data on request from Public Health England, 2014), with no significant difference seen between the minor ethnic groups Black African or Black Caribbean. The mortality rate from prostate cancer is higher in black men than their white counterparts,<sup>20</sup> but despite this, there is poor awareness, both within the black community<sup>21</sup> and also to some degree in primary care, of black ethnicity as a significant risk factor for prostate cancer.

#### Baseline PSA

There is an increasing body of evidence to support the concept that taking a baseline PSA reading at a relatively young age (eg men in their 40s) can allow men to be stratified into low- and high-risk groups, not only for the subsequent development of prostate cancer over the following 20–25 years, but more importantly to identify those men most at risk of clinically significant disease in the future.<sup>22–24</sup>

Thresholds are not yet established, but it is proposed that men in their 40s with a PSA value <1.0ng/ml can be stratified as 'low risk' and may be able to avoid a further PSA test for a considerable interval – perhaps up to 8 years.<sup>25,26</sup> However, men with a PSA >1.0ng/ml would fall into the 'high-risk' category and should be monitored more closely, perhaps every 2–4 years.<sup>27</sup> This concept is based on retrospective data, but recruitment for the first prospective study, PROBASE, has commenced in Germany.<sup>28</sup>

#### CONCLUSION

We already have a good understanding of which men are at highest risk of developing prostate cancer, and this understanding is likely to improve significantly in the near future, with developments in the field of clinical genetics allowing further identification and stratification of risk.

In the absence of a national screening programme using PSA to detect prostate cancer, a move towards targeted screening of higher-risk groups offers a potential to improve prostate cancer outcomes. Primary care physicians armed with an understanding of these risk factors for prostate cancer can

at least begin to ensure that men at higher risk are not denied PSA testing through lack of awareness of the test or their personal risk (Box 2).

Risk-based screening is the future. This needs to be coupled with risk calculators, designed for use in primary care, which feed information such as prostate size, urinary symptoms, family history, ethnicity, etc. into a computer algorithm to predict risk of both a positive biopsy and clinically significant disease, helping the primary care physician with referral decisions. Risk calculators are already in existence, such as those derived from the ERSPC ([www.prostatecancer-riskcalculator.com](http://www.prostatecancer-riskcalculator.com)) and the Prostate Cancer Prevention Trial (<http://deb.uthscsa.edu/URORiskCalc/Pages/uroriskcalc.jsp>), but are more suited to use in a secondary care setting.

Prostate Cancer UK, with part funding from the Movember Foundation, recently launched a targeted research call to specifically address the need for the development of a more effective tool, aimed at primary care, that combines a range of known risk factors to give a more useful indication of a man's risk of prostate cancer than that obtained through a PSA test alone (<http://prostatecanceruk.org/research/information-for-researchers/pilot-awards-and-project-grants>). Their vision is that this will be ready for widescale clinical implementation through NHS primary care within 5 years.

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#### PROSTATE CANCER UK

Prostate Cancer UK offers support to GPs and other health professionals in the form of online courses, study days and educational bursaries. Our series of masterclasses travel the country and tackle the topics addressed in this paper. To find out more, please visit: [www.prostatecanceruk.org/education](http://www.prostatecanceruk.org/education)

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