Pergamon

European Journal of Cancer Vol. 32A, No. 7, pp. 1097–1099, 1996

Printed in Great Britain
0959-8049/96 $15.00+0.00

PII: S0959-8049(96)00098-6

Editorial

PSA and Prostate Cancer Diagnosis

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PROSTATE CANCER is the second most common malignancy of European men. There is considerable regional variation in the incidence of this tumour which reaches its highest levels in Scandinavia. Currently, in England and Wales, there are nearly 12000 new cases and over 8500 deaths annually [1]. The disease is increasing in incidence, which leads to predictions that prostate cancer will become the commonest cause of cancer deaths in men by the year 2010. In this context, the introduction of effective screening for early disease linked to curative treatment should be considered a priority.

Prostate cancer is the most prevalent cancer in men. Postmortem figures demonstrate that microscopic prostate malignancy is present in 30% of all men aged over 50 years, rising to 50% of men in their eighties [2,3]. Prostate cancer is a slow growing malignancy with an intraprostatic doubling time estimated to be between 4 months and 2 years [4]. As a result, clinically apparent malignancy occurs late in life at a median age of 72 years. It might be thought that the long period of asymptomatic localised disease would give an excellent opportunity for early diagnosis. However, it is contentious whether the natural history of prostate cancer makes it a rational target for screening. Some clinicians are of the view that early stage, small bulk, good histology prostate cancer does not impact significantly on survival and that all other disease stages are thought to be incurable. Screening currently plays a role in a small number of tumour types and there are established programmes for cervical cancer and breast cancer in many countries. Not all observers believe screening to have any significant impact on mortality except in cervical cancer [5].

To leave aside for the moment the issue of the curability of early stage prostate cancer, we will now review the screening methods. It is clear that current screening methodologies for early stage disease are lacking in both sensitivity and specificity. Currently, well man screening for prostatic tumours involves a physical examination and blood testing [6]. Historically, digital rectal examination (DRE) has been the most important method used in screening. However, this method is associated with considerable observer error [7], and rarely diagnoses early stage disease, so that nearly two-thirds of tumours detected are advanced cancers [8]. Transrectal ultrasonography (TRUS) has been reported to double the rate of detection [9], but not all observers are able to achieve these figures, and unacceptably high false-positive rates have been reported [10], suggesting that TRUS is impracticable as a primary screening procedure.

The best screening test currently available is the measurement of the serum concentration of prostate-specific antigen (PSA). PSA is a 33 kDa serine protease produced by both normal and malignant prostatic epithelial cells. Disruption of the normal glandular structure by either benign hypertrophy or malignant tumours results in the elevation of blood levels [11]. Serum PSA levels are closely related to tumour volume and clinical stage, in that, 60–80% of patients with a PSA of <10 μg/l will have early stage localised disease; values of 10–20 μg/l signify local invasion in over 90% of patients; and values above 50 μg/l are almost invariably associated with metastatic disease [12,13]. PSA levels are used extensively to monitor response to systemic hormonal therapy and radiotherapy [14] and as a predictor of relapse following treatment of localised disease by prostatectomy [15] or radiotherapy [16]. Elevations in PSA levels can be observed up to 10 years prior to the clinical diagnosis of prostate cancer [17], but the role of PSA in prospective cancer screening is yet to be fully clarified. Although the normal range for PSA is usually defined as <4 μg/l, it should be noted that PSA elevations are not specific for prostate cancer, with up to 20% of patients with benign prostatic hypertrophy having PSA values in the 4–10 μg/l range [18], which greatly reduces the predictive value of a single PSA reading in this range.

A number of methodologies have been evaluated to increase the predictive value of PSA. The most simple approach has been to compare the PSA value with an age matched normal range; if a non-matched cut-off of 4 μg/l is used, the false-positive rate can rise from 0% at <50 years to 26% in the over 70 years old age group [19]. Another approach has been to assess changes in serial PSA values. Retrospective studies indicate that PSA values giving an increase of greater than 0.75 μg/l per year yield a detection sensitivity of 79% and specificity of 66% in patients with initial PSA values below 4 μg/l [20].

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Received 22 Feb. 1996; accepted 29 Feb. 1996.

The combination of PSA measurement with DRE increases the predictive value of screening; generally the predictive value of an abnormal DRE is in the order of 30% and that of PSA in the range of 4–10 μg/l is 20%. However, the predictive value rises to 38–50% when an abnormal DRE and a PSA level of 4–10 μg/l is combined [12,21].

Screening using PSA has its limitations in an asymptomatic population, but its role in the assessment of patients with urological symptoms is even more difficult to clarify due to the increased proportion of patients who will have PSA elevations due to BPH. In this issue (pages 1125–1128), Filella and colleagues report the results of screening patients with urological symptoms using PSA and DRE [22]. 2054 patients, of whom 73% had urological symptoms, were screened. 1412 (68.7%) had a PSA value ≤3 μg/l (the cut-off value), whilst 1830 (89.1%) had an unremarkable DRE. Patients with both a normal PSA and DRE had no further investigation. 587 of the 680 patients with abnormal PSAs or DREs proceeded to a prostatic biopsy. A total of 131 cases of prostate cancer were identified on biopsy to give an overall detection rate of 6.28%. Analysis of the screening methods show that an abnormal DRE had a positive predictive value of 44% and would yield 90 cases, including 6 with PSA screening below 3 μg/l. Used alone, a PSA value above a cut-off of 3 μg/l had a positive predictive value of 23% and would yield 125 cases, whilst above a cut-off of 4 μg/l, the positive predictive value would be 24% and yield 121 cases. Raising the PSA cut-off to 10 μg/l would improve the positive predictive value to 46%, but the number of cases detected would be reduced to 96.

In combination with an abnormal DRE, the positive predictive value of PSA elevations of >4 μg/l and >10 μg/l increases to 52% and 70%, respectively. These figures are in overall agreement with a similar study by Cooner and colleagues who recorded predictive values of 35.9% for DRE alone, 20% for a PSA of 4–10 μg/l and 42.6% for the combination in a similar group of urology outpatients [23].

Filella and colleagues conclude that for patients with urological symptoms, elevations in PSA below 10 μg/l are not as important as in an asymptomatic screening population. The authors recommend that, with a normal DRE, a PSA of >10 μg/l should be chosen as the level to initiate further investigation. By following this policy of investigating only if the DRE is abnormal or the PSA > 10 μg/l, 118 (90.1%) of the total of 131 cases would have been diagnosed. The small loss in sensitivity resulting in raising the investigation cut-off from >4 μg/l to >10 μg/l in this population contrasts with the reduction in sensitivity from 60% to 30% that would occur with this change in an asymptomatic population [24].

It is, of course, important to limit unnecessary investigations. However, the 10% of cases that would be missed by raising the cut-off to >10 μg/l are more likely to have localised disease and this is the group of patients that some urologists feel would benefit from early diagnosis. However, due to the current lack of proven efficacy from treatment for early stage disease, the identification of the correct cut-off for PSA values in screening is generally regarded as being of mainly academic concern.

The results from this study confirm two long standing views regarding PSA and screening. Firstly that standard single PSA measurements producing values between 4–10 μg/l are of limited value in discriminating prostatic cancer from benign prostatic hypertrophy. Secondly, that screening detection rates are at best only one-fifth of the documented incidence of microscopic prostatic cancer.

Whilst it appears likely that the value of standard PSA assays in screening for early stage disease will be limited, assays that examine the level of serum PSA binding to α1-anti-chymotrypsin may be more successful. The bulk of immunoreactive serum PSA is complexed to the protease inhibitor α-antichymotrypsin with only 10–20% non-complexed. Differential immunoassays demonstrate that the ratio of free to total immunoreactive PSA is significantly reduced in patients with prostatic cancer compared to those with benign hypertrophy. In the PSA range 4–20 μg/l associated with early stage disease, a free/total PSA ratio cut off of 0.18 leads to diagnosis with a specificity of 95% and a sensitivity of 71% [25]. These figures are obviously superior to conventional PSA screening results, and it will be interesting to prospectively assess the value of this method in conjunction with DRE in screening both normal and symptomatic populations. Hopefully, by the time the results are available from the clinical trials currently in progress in the U.S.A. and Europe, we will have more information on how best to manage patients with early stage asymptomatic prostate cancer.

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