EDITORIAL

The vagaries of prostate cancer screening

Prostate specific antigen (PSA) is associated with prostate cancer mortality,[1,2] so measuring it in healthy men may bring forward diagnosis and reduce mortality. Review articles take care to point out, however, that we do not know whether such screening is worthwhile.[3–5] Diagnosis is not necessarily sufficiently brought forward for earlier treatment to reduce mortality. We must await the results of ongoing randomised controlled trials. Furthermore, false-positives are common and such men will receive invasive investigations, prolonged follow-up (which may cause anxiety) and treatment that is both of unproven efficacy and toxic[4,5] (about two thirds of men receiving treatment for prostate cancer without extra capsular spread may develop incontinence, impotence or other serious complications).[3,6] PSA testing could do more harm than good.

Such wisdom has fallen on deaf ears in many quarters. In the US and Italy, for example, PSA screening is widespread: a third of healthy men aged over 50 have had PSA measured in the last two years.[7] PSA testing is becoming an industry, and recommendations against it may be met with hostility.

It is not difficult to see why. Screening appears a one-way bet: earlier diagnosis must be better, and the only question is 'by how much?'[8] Prostate cancer is the second most common cause of cancer death; why deny men an intervention that may prolong their life? Public figures (for example Norman Schwarzkopf and Arnold Palmer) have had prostate cancer diagnosed after screening and have done well. Set against the death sentence that many people perceive cancer to be, this observation alone seems proof of efficacy. In the face of such optimism, the toxicity of the treatment seems a price worth paying. Even the American Cancer Society, apparently undaunted by lack of evidence, recommends PSA testing and digital rectal examination yearly for men aged 50 and older.[4]

This issue of the *Journal* contains a report of the inevitable next step when scientific evidence and public perception are at odds. Interviews with 405 men indicated that two thirds of them would ascribe fault to a general practitioner who had advised a man against screening if the man subsequently developed prostate cancer. On the other hand only one sixth of them would ascribe responsibility to a general practitioner who recommended screening that subsequently led to the diagnosis of prostate cancer with treatment that had serious complications, even though the cancer appeared indolent and there was no indication that the treatment had served any useful purpose.[9]

To assess the problem, we need to examine the validity of the one-way bet argument from published data. First, a cancer discovered on biopsy of an organ in an asymptomatic person may be indolent.[5] Histologically invasive cancer is found in about 40% of prostates removed at autopsy from men over 50 years dying of non-prostatic causes,[10] while only 4% of men over 50 die of prostate cancer. Cancers that prove innocent or lethal can be distinguished histologically at the time of screening only to a limited extent.

Published data from cohort studies provide valuable information on the association between PSA and prostate cancer.[1,2] In these studies, blood was taken from healthy men and the serum was stored. PSA was measured on this serum sample in those men who subsequently presented clinically with prostate cancer after one or two decades of follow-up and in controls who did not (nested case-control design). The results of such a study,[1] based on an amalgamation of data from four cohorts, are summarised in Table 1 according to the time interval between the blood collection and diagnosis of prostate cancer.

The results show that PSA testing is highly effective at detecting prostate cancers that would have presented clinically in the short term (the first three years). Using a cut-off of eight multiples of the age-specific median (MoM), 94% of cancers are detected at a false-positive rate as low as 1%. Cancers associated with so high a PSA, however, may have extra-prostatic spread which would make curative treatment unrealistic.[11] A fast rate of increase in PSA denotes poor prognosis.[12] In the randomised trials of mammographic screening for breast cancer by analogy no reduction in mortality was seen until several years after the first screen. If we allow a longer time period, the cohort study data corresponding to the period 6–9.9 years after the PSA measurement indicate that about 43% of the men who present with prostate cancer would be detected at a false-positive rate of 5% using a PSA cut-off of 4 MoM (see Table 1). If the earlier detection allowed effective treatment in half of these, for example, PSA testing would reduce prostate cancer mortality by about 20%, a modest but probably worthwhile effect. Screening at a lower PSA cut-off (a false-positive rate above 5%) seems unlikely to be worthwhile because raising the false-positive rate from 5 to 10% would detect only an estimated additional 11% of cases (detection rate increasing from 43 to 54%). Raising it from 10 to 50% would mean investigating an additional 40% of all screened

Table 1 Result of a cohort study of serum PSA and prostate cancer:[1] detection rate according to serum PSA concentration and time interval between blood collection and diagnosis

			Detection rate according to time interval between blood collection and diagnosis of prostate cancer			
Serum PSA concentration: centile	MoM	False positive rate	<3 years (16 cases)	3–5.9 years (29 cases)	6–9.9 years (56 cases)	10–20 years (164 cases)
≥99	≥8	1%	94%	24%	13%	5%
≥95	≥4	5%	100%	45%	43%	17%
≥90	≥3	10%	100%	59%	54%	27%
≥50	≥1	50%	100%	100%	91%	79%

MoM – multiple of age-specific median value. PSA – prostate serum antigen.

men as screen-positive while detecting less than 40% more cases. From these data, PSA testing could produce a modest but not a substantial reduction in prostate cancer mortality.

Other data are discouraging. Comparisons between similar populations with high and low rates of PSA testing tend not to show a difference in prostate cancer.[13] A US study[11] is also illustrative: 1653 men aged 50–89 (mean age 63) had PSA testing and 137 (8%) of them were positive (PSA ≥4.0 μg/L). On investigation 37 of these 137 men had prostate cancer, whereas from age-specific US death rates at the time of the study only 11 of the 1653 men would have been expected to die from prostate cancer in the subsequent 10 years. The problem of over-diagnosis is confirmed. Of the 37 men with cancer, 18 had very high PSA levels (≥10 μg/L – above the 98th centile) and all but one of these were found on surgical staging to have extra-prostatic spread. It seems unlikely therefore that the 11 cancers that would have caused death are detected as localised cancers that could be excised on simple prostatectomy. Of the remaining 19 of the 37 men with cancer (PSA 4.0–9.9 μg/L) the cancer was confined to the prostate in most patients (10 of the 17 who underwent surgical staging), but this group is likely to include cancers that would not have presented clinically and cancers that would have presented but not caused death. The results suggest that some men would indeed have had unnecessary treatment (which may commonly have serious consequences), while providing little grounds for optimism that the 11 cancers likely to cause death in these men are detected at an early stage.

Will not the ongoing randomised trials of PSA testing[14] provide an answer in due course? They may, but in two respects they are not testing an efficient method of screening. First, age is not used as a screening test: 84% of prostate cancer deaths are in men aged 70 and over, yet almost all the men in the trials are under 70, some as young as 45. While screening should commence a few years earlier than the age group in which it is anticipated that deaths may be prevented, there seems little point in screening men in their fifties; 60 years might be a reasonable starting point. Second, insufficient consideration has been given to the cut-off point used to define a high PSA: it has been set at 4 μg/L irrespective of age based simply on the normal range set by manufacturers of the kits used to measure PSA. This generates a positive rate as high as 20% in men in their 70s who get most of the cancers (albeit lower in younger men); as discussed above, high positive rates are unlikely to be worthwhile. If the trials show a reduction in prostate cancer mortality it will be at the cost of a high positive rate, and it would be useful to be able to determine whether screening was also effective at a lower positive rate (for example it clearly would be if cancers presenting in the first three years could be effectively treated – see Table 1). If blood had been taken from the unscreened groups in the trials and serum stored, PSA could be measured at the end of the trial in the control men who died of prostate cancer and compared with PSA values at screening in the smaller number of screened men who died of prostate cancer. In this way the PSA range within which most of the deaths were prevented would be apparent. Taking blood from the control men at the outset of these trials may have added to the cost, but in the longer term this would have been repaid by enabling the examination of the effect of screening at a lower false positive rate. As things stand, however, many men must be screened to detect one who would die of prostate cancer because of the young age, and many false positives must be investigated and treated because of the high false positive rate. PSA testing in these trials will be more intrusive and harmful, as well as less cost-effective, than it need have been.

To the extent that screening is a one-way bet, therefore, the bet is against screening. Yet in many populations the public want it and may hold their doctors blameworthy if they do not offer it. The doctors cannot win.

What is to be done? A common view is that men should be given information and decide for themselves, but the only honest information is uncertainty. When a new drug is developed experimental data must be presented before it is licensed for use, and until it is licensed patients cannot obtain it: letting them decide for themselves is unthinkable. This should also apply to screening.

Doctors are professionals and should not perform unproven screening tests (except in research situations) any more than they should use unproven drugs, resisting patient pressure if necessary. In addition, health authorities and health maintenance organisations should not expend their limited resources on PSA screening (with the associated costs of the investigation and treatment of false positives) until its value is determined. PSA testing should be limited to symptomatic men, to monitoring prostate cancer treatment and for use in randomised trials to assess its value. It is unethical and bad medicine to provide a service that is costly and hazardous when its value is so uncertain.

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