The perils of overdiagnosis

MARGARET McCARTNEY

Overdiagnosis as a consequence of PSA screening for prostate cancer is a major hazard of modern medicine, claims Margaret McCartney. Jon Rees, GP with a special interest in men's health, and urologist Roger Kirby respond with their perspectives on this dilemma.

Go to the *Trends* website (www.trendsinurology.com) and click on 'Trends debate' to have your say about early detection and the risks of overdiagnosis.

Margaret McCartney,
MB ChB, MRCGP, GP, Glasgow

We are going in the wrong direction. I have talked to enough people who were alive before the NHS to know that a lack of effective medical care killed people. Then, it was prohibitively expensive to take a sick child to the doctor. Parents routinely dressed and repaired cuts and injuries – even broken bones – without recourse to A&E.

But 60 years later, the philosophy that more treatment must make for better medicine has resulted in an increasingly vast problem: overdiagnosis. Making an unnecessary diagnosis is one of the biggest modern medical hazards we face.

Testing and imaging have essentially become a modern-day curate's egg. We have computed tomography, magnetic resonance and positron emission tomography scanning, which are capable of discerning our bodily image down to a millimetre or two. The problem is that very often, we do not know what any of this actually means for our health. What is normal? What is abnormal? What is disease, and what is not? New medical tests have taken us into these hinterlands, but without a guidebook.

PSA TESTING AND PROSTATE CANCER

When it comes to prostate-specific antigen (PSA) screening, the problem of overdiagnosis becomes illuminated to the maximum. Many people harbour abnormalities – including genuine cancers – that will not go on to harm them. It goes against most of what we were taught, and is strikingly counterintuitive. Some people have unknown and real cancers, yet live and die without the knowledge that such a serious diagnosis existed. The truth is, some things that we identify as 'cancers' do not behave malignantly.

Prostate cancer remains a serious disease; the fourth most common cause of cancer death in the UK and the second most common cause of cancer death in men. That is more than 10 000 deaths per year; 93 per cent in men aged over 65, and 54 per cent in men aged over 80.[1] The incidence of prostate cancer has been increasing over the past 20 years in European countries, but the mortality rate has been falling in some, particularly higher resource countries.[2] There is no doubt that prostate cancer can and does kill. But it also may not.

The more we look for prostate cancer, the more we find it. As more transurethral prostatectomies have been performed, the more prostate cancer has been detected.[3] We also know from autopsy studies that prostate cancer is found frequently, even when not expected.

Discovery of latent tumours

In 1954, a pathologist, L.M. Franks, working for the then Imperial Cancer Research Fund at Lincoln's Inn Fields, examined the entire prostate glands of 220 men who had sudden or unexpected deaths. He found 69 cancers in this group: 37 per cent of men over 50 had an unsuspected prostate cancer.[4] In a lecture given to the Royal College of Surgeons in 1954, he presented his work, saying that 'I want to discuss today a concept of tumour growth which is by no means new but it is one which many people find difficult to accept completely'. He told his audience that there was a group of cancers which he called 'latent', and which was a 'plateau type. The tumour reaches a certain stage in its development, which then ceases, and the tumour remains latent to this level for a considerable period.'

In fact, by 1954, Franks had identified nine other series of autopsy prostate examinations published after 1935. All found unexpected prostate cancers, in between 14 and 44 per cent of cases. 'There is a strong emotional barrier against believing the unexpected' said Franks 'and like many other pathologists and clinicians I did not choose to accept these figures'. He took the slides to a colleague for a second opinion, fearing that he was wrong. Instead, his diagnoses were confirmed, with him describing 'the lesions in the prostate have the morphological

characters of malignant tumours and their structure and age incidence is identical with that seen in typical metastasising prostatic cancer'.[5] These were cancers, but they were not behaving in the way that the prostate cancers, as known to doctors, behaved. As Franks said, 'they are apparently true cancers but they seem to do no harm'. This was in 1954. We thus have no excuses – we have always known about overdiagnosis. The problem is that we have not utilised this knowledge when we have enthusiastically offered screening tests.

Development of the PSA test

The PSA test was developed in the 1980s, firstly for monitoring the response to treatment for prostate cancer. In 1987, Thomas Stamey and colleagues published in the *New England Journal of Medicine*, showing that PSA was elevated in the vast majority of patients with newly diagnosed prostate cancer.[6] In the same journal, in 1991, another study of 1653 men claimed that PSA testing 'provides a better method of detecting prostate cancer than rectal examination alone'. The men had their PSA measured, and those with a result of over 4µg/l had a rectal examination and ultrasound of the prostate with biopsies taken. These men were compared with 300 men referred because of prostatic abnormalities palpated on rectal examination. Of the men in the first group with raised PSA, 22 per cent had prostate cancer on biopsy.[7]

In 1993, a prospective non-randomised trial of 10 251 men was published in the *Journal of the American Medical Association*.[8] The men had presented to a PSA screening programme and were divided into three groups: a comparison group, who had been referred because of prostate abnormalities on rectal examination, and two other groups, who had either PSA screening initially or serially. They found a lower proportion of advanced cancers in the screened groups and a higher proportion compared with rectal examination alone.[8] By 1994, the Food and Drugs Administration in the USA had approved PSA for use as a screening test.

Is PSA a useful test?

Yet the fundamental issue of whether the PSA test helped men to avoid death, or whether it simply picked up some of these 'latent' cancers had gone unanswered. What did this test mean in the context of finding prostate tumours? Did it detect cancers usefully? Or was it responsible for overdiagnosing cancers, 'cancers' that were never going to maim or kill?

The initial trials, which did not include mortality as an end point, did not detract from the popularity of PSA as a screening test. In the USA, it was made available on Medicare. Various charity campaigns in the UK and USA urged men to have a PSA screening test, with some urging women to take their partner to the doctor to request a prostate 'check-up'. Yet the issue of overdiagnosis remained partially or completely hidden from the people to whom it was being advertised.

In 2008, modelling studies indicated that lead time bias and overdiagnosis rates in PSA screening were substantive; the implications for the validity of many of the studies previously published on screening were large. They estimated that between 23 and 42 per cent of prostate cancers detected by screening were overdiagnosed.[9] The following year, the *New England Journal of Medicine* published two randomised controlled trials of PSA screening, one from Europe, the other from North America. The European study found that PSA screening could reduce deaths from prostate cancer, with 1410 men needing to be screened and 48 men treated to prevent one death over nine years.[10] The US study found no prostate cancer mortality difference.[11]

Richard Albin, one of the researchers who discovered PSA, wrote in the *New York Times* in 2010 that 'I never dreamed that my discovery four decades ago would lead to such a profit-driven public health disaster'. By disaster, he meant all the men who were overdiagnosed with a prostate 'cancer' that was never going to kill them, and instead suffered the effects of 'treatments' (for example, impotence and incontinence) that could only harm them.

Importance of acknowledging overdiagnosis

Overdiagnosis is real, and we ignore it at our peril. First, understanding why some people have genuine cancers that behave indolently may hold crucial information that could be applied to people who die because of them. Understanding the natural history of disease is one of Wilson and Junger's key descriptors of good screening,[12] yet one that has been virtually ignored when it came to PSA screening. Without this, we cannot know whether we offer useful tests to discover a disorder.

When we do not acknowledge overdiagnosis, we fail to protect our patients. We also open the door to the popularity paradox, namely, that the worse a test is, the more false positives it generates, and the more people believe (wrongly) that they have been saved by the test. This kind of knowledge would help us to understand what is happening when alternative therapists claim – wrongly – that their 'treatments' have cured cancers. Instead, the knowledge about overdiagnosis and overtreatment should be mainline medicine.

But most troubling is the problem that the PSA screening debate has meant for symptomatic men diagnosed with prostate cancer. One doctor has recently written of the reaction from other doctors on hearing of his illness. Some told him that it was not serious, another advised him that he should not worry, for more men die with, than from prostate cancer. This is true, but it is true at least partially because the prevalence for screen-detected disease, which is overdiagnosed disease, has risen.[13]

Prostate cancer still kills. But screening increases the number of diagnoses of prostate cancer in men who will never die of it. Does screening for prostate cancer thus generate further unhelpful changes in the perceptions of prostate cancer? I doubt if this unintended harm was even considered as a potential harm of PSA screening, way back in the 80s. Screening is a recent invention. It is doing us harm. We need to rethink, and put it carefully back in its box.

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Making sense of PSA testing

JON REES

Jon Rees, *MB ChB, MD, MRCS, MRCGP, DRCOG, GP, Bristol*

Overdiagnosis and subsequent overtreatment of prostate cancer are clearly issues worthy of debate. However, for many GPs and most patients it is becoming increasingly difficult to come up with a pragmatic and realistic approach to PSA testing in primary care. Screening advocates (whether urologists, patient groups or men's health charities) will cite the statistics from trials such as the European Randomised Study of Screening for Prostate Cancer (ERSPC) and argue for the introduction of a national screening programme, but a screening programme that has been estimated by the UK National Screening Committee[1] to cost £0.8 billion per year (based on four-yearly testing between ages 50 and 74) is not going to happen anytime soon, given the uncertain evidence and current financial situation.

On the other side, the PSA sceptics argue equally forcefully that PSA is too unreliable and we should dissuade patients from undergoing testing. However, it is difficult to see how PSA testing can be conveniently placed back in the box from which it came – there is too much public concern around prostate cancer and demand for testing for us to be allowed to take such a nihilistic attitude to what is, after all, a major killer of men.

There are three main areas that need to be tightened up to help make some sense of the current chaotic system of *ad hoc* testing largely based on patient request.

WHO TO TEST?

In the UK, PSA testing is currently skewed towards elder men and those in less deprived areas – the 'worried well'.[2] If we are to test men with PSA, we should at the very least try to target our tests at those men most likely to benefit. This should include men with a positive family history or from Afro-Caribbean backgrounds. The use of baseline PSA testing[3,4] is also promising – this is based on the evidence that a single PSA test at a relatively young age, *eg* 50, can stratify men into not only those most likely to develop prostate cancer subsequently, but also more

importantly those most likely to die from it. Use of this approach allows a large number of men with low baseline PSA to be reassured that they are low risk and at the very least need have a PSA test only very infrequently – moving away from the vast numbers of men having annual tests with low and stable PSAs. Those at higher risk could be recommended a PSA test at a regular interval, possibly two-yearly.

WHO TO REFER AND WHO TO BIOPSY?

Use of simple age-specific PSA reference ranges leads to many men being referred to secondary care who have borderline PSA readings because of the background noise of benign prostatic enlargement. We need more sophisticated tools to help GPs interpret PSA results.[5] Risk calculators are already in existence (*eg* the Sunnybrook risk calculator[6]), which add other factors, such as prostate size, family history, ethnicity and presence of urinary symptoms, to give not only a percentage risk of cancer being found on biopsy but also a risk of aggressive cancer. Trials are needed to assess the practicality of primary care-based risk calculators to improve pick-up rates of clinically significant prostate cancer.

WHO TO TREAT?

This is a key element of preventing harm to patients – concentrating treatment on those with more aggressive disease, and increasing the use of active surveillance for low-risk disease will reduce the number needed to treat to save a life from prostate cancer. It has even been proposed[7] that low-grade (Gleason 6) prostate cancer should be considered a non-lethal or even benign condition that should be observed and not treated – but this relies on the accuracy of biopsy techniques to ensure that higher-grade cancer has not been missed.

If PSA tests were targeted at higher-risk patients, biopsies were carried out on a more sophisticated risk-based model, and treatment was reliably reserved for those with high-risk disease, we have the potential for impacting on prostate cancer mortality with a lowered risk of harming patients through overtreatment.

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Circumventing the perils of overdiagnosis

ROGER KIRBY

Roger Kirby, *MA, MD, FRCS(Urol), FEBU, Director, The Prostate Centre, London*

Let me try to reassure Dr McCartney about PSA testing. First and foremost, 'overdiagnosis' is a problem only if it leads to 'overtreatment'. If you, the reader, had a focus of (probably) low-risk, low-grade prostate cancer present, would you not rather know about it so it could be monitored in an active surveillance programme?[1] You might consider some preventative strategies. If there were to be eventual evidence of progression, would you not opt for treatment that has been shown to reduce the risks of metastasis and death from the disease, even at the risk of some side-effects?[2,3]

PSA testing is certainly controversial, especially when used in the context of screening, but it has been shown in the ERSPC study to reduce prostate cancer mortality by 22 per cent.[4] Provided that it is used intelligently, it is an essential part of the urologist's armamentarium. For example, recent evidence suggests that a single PSA test at the age of 50 can provide an estimate of subsequent prostate cancer risk.[5] Moreover, genetic testing has identified more than 30 prostate cancer susceptibility genes that hold the promise of us focusing PSA surveillance on those most at risk of developing the life-threatening form of the disease.[6]

While I understand Dr McCartney's concerns, I would argue that if we worry unduly about 'overdiagnosis', we risk the reverse, namely 'underdiagnosis'. Like Odysseus, we need to find a way, between Scylla and Charybdis. The 10 000 men destined to die in 2013 from prostate cancer will not thank us for throwing the baby away with the bath water. They, and those of us who care for them, are aware that all those men with advanced cancer will have passed

through a phase when their disease was potentially curable.

Current research, funded at least in part by the Movember movement, looks likely to provide us with better tools for diagnosis, and kinder, more effective therapies for this most prevalent cancer of men. We are certainly not there yet, but the future does look more promising than ever before for the many sufferers of prostate disorders. We need to move forwards, not backwards, to conquer this disease.

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