Role of screening in urological malignancies

ALASDAIR SCOTT

Urological malignancies, in particular prostate and bladder cancers, are significant causes of morbidity and mortality. Alasdair Scott discusses whether these conditions are suitable for population-based screening programmes, which must balance mortality reductions with the harm done by investigation, overdiagnosis and overtreatment.

Urological malignancies – cancers of the prostate, bladder, kidney, testis and penis – are the most common group of non-cutaneous cancers in the UK. In 2008, there were more than 58,000 new diagnoses of urological cancers compared with 48,000 new cases of breast cancer, the next commonest (Figure 1a). Urological malignancies also have one of the highest mortality rates of any cancer; they accounted for nearly 20,000 deaths in 2009, second only to lung cancer with 35,000 deaths (Figure 1b). These figures highlight the significant disease burden imposed by urological cancers and provide impetus to the medical profession to confront the problem.

Population-based screening programmes have proven efficacy in reducing cancer mortality. A Lancet study estimated that the UK cervical screening programme prevents up to 80 per cent of cervical cancer-related deaths (5000 deaths per year).

Figure 1. The (a) incidence and (b) mortality of urological cancers in the UK in 2008 and 2009 respectively. Data for lung and breast cancers are provided for comparison.

*Urological cancers consist of the sum of prostate, bladder, kidney, testicular and penile cancers

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while a large meta-analysis found that screening mammography reduces the mortality from breast cancer by 26 per cent in women aged 50–74 years. Given these successes, there is considerable interest in screening for urological cancers.

The principles of an effective screening programme were detailed by the World Health Organization in 1968 and still comprise the tenets that any proposed screening programme must fulfil:

- the condition should be an important health problem
- the screening test must be of sufficient sensitivity and specificity with acceptable morbidity
- the test must detect the disease at an early stage, when intervention is of more benefit than treatment initiated later
- the programme should be cost-effective.

Discussion of the role of screening in urological malignancy will necessarily be centred on the above axioms. To provide a comprehensive yet succinct review, scope will be limited to prostate and bladder cancer – the two commonest urological malignancies and the two for which there has been most interest in population screening.

**PROSTATE CANCER**

Prostate cancer is the commonest cancer among UK men; one in nine men will be diagnosed with prostate cancer during their lifetime, most (80 per cent) when they are aged 70 years or older. Although prostate cancer is the second most frequent cause of male cancer death in the UK, only 1 in 25 men (3.8 per cent) will actually die from the disease – men are more likely to die with prostate cancer than from it. This has important implications when considering screening.

**The prostate-specific antigen test**

Prostate cancer remains asymptomatic in most patients until it reaches a late and often incurable stage. Prostate-specific antigen (PSA) is a glycoprotein secreted by prostatic epithelial cells; studies in the 1990s demonstrated that serum PSA levels could be used to detect early prostate cancer.

PSA is not prostate cancer-specific and elevated levels are seen in numerous benign conditions. A PSA level >4ng/ml has traditionally been considered an indication for prostatic biopsy, from which a definitive diagnosis of carcinoma can then be made. The PSA threshold is a subject of considerable debate and evidence suggests that more than 25 per cent of cancers will be detected in men with a PSA <4ng/ml. Even PSA >4ng/ml has a sensitivity of only 21 per cent and a specificity of 94 per cent.

There has been more controversy over the use of PSA to screen for prostate cancer than for any other screening programme. The debate can be reduced to two fundamental questions:

- does PSA screening reduce the risk of dying from prostate cancer?
- if there is a mortality reduction, does it justify the harm done by overdiagnosis?

**PSA testing reduces prostate cancer mortality**

In the USA, the mortality from prostate cancer has declined by 35 per cent since the widespread use of the PSA test. Although this reduction cannot be causally attributed to screening because of the presence of confounding factors, population modelling has suggested that 45–70 per cent of the decline can be ascribed to screening.

Prospective randomised control trials (RCTs) are the gold standard to determine the effect of screening on mortality. A 2006 Cochrane meta-analysis combined the results of two early RCTs by Labrie et al. in 1999 and Sandblom and colleagues in 2004. Analysis of these studies with an intention-to-screen methodology demonstrated no difference in mortality from prostate cancer in screened men compared with unscreened controls. However, both of these studies had methodological flaws (discussed by Lin et al.) that limit their utility.

In 2009 the results of two large multicentre RCTs were published: the American Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial (PLCO) and the European Randomized Study of Screening for Prostate Cancer (ERSPC). Table 1 summarises the key findings of these studies and shows that PLCO found no difference in prostate cancer mortality between screened and unscreened men. In contrast, ERSPC demonstrated a 20 per cent mortality reduction, although the 95 per cent confidence intervals were consistent with as little as 2 per cent.

<table>
<thead>
<tr>
<th>Trial</th>
<th>No. of participants</th>
<th>Cancer incidence (%)</th>
<th>Mortality per 10000 person-years</th>
<th>Relative risk of prostate cancer mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Screened</td>
<td>Controls</td>
<td>Screened</td>
<td>Controls</td>
</tr>
<tr>
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<td>ERSPC15</td>
<td>72,952</td>
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<td>4.8</td>
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</tbody>
</table>

**Table 1. Summary of the findings from the PLCO and ERSPC trials comparing prostate cancer incidence and mortality in PSA-screened men versus unscreened controls**

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reduction. The reasons underlying the discrepancy between the two results are multifactorial, but a major contributor is contamination of the PLCO control group, over 50 per cent of which underwent PSA testing.

**PSA testing results in significant overdiagnosis**

The incidence of indolent prostate cancer in autopsy studies has been reported to be up to 80 per cent, yet the population mortality is only about 4 per cent, suggesting that most cancers remain clinically covert until the patient dies of other causes. The principal criticism levelled at prostate cancer screening is that it will result in the detection of these indolent tumours – termed overdiagnosis. In the ERSPC, 48 patients needed to be diagnosed with prostate cancer to prevent one death (ie number needed to treat [NNT] = 48) and extrapolation from the dataset estimated overdiagnosis at 42–66 per cent.

We have no way to be certain that a patient will outlive his prostate cancer and many men are uncomfortable with not pursuing active treatment. Thus, overdiagnosis inevitably results in overtreatment. Radical therapy for prostate cancer involves complete surgical resection or radiotherapy and is associated with significant complications, including urinary, bowel, sexual and psychological dysfunction and estimations are drawn from Postma et al. Radical therapy mortality is estimated at 0.5 per cent of patients undergoing radical prostatectomy and the incidences of erectile dysfunction and regular urinary leak following prostatectomy and radiotherapy have been reported by Korfage and colleagues.

**The bottom line**

In spite of the publication of ERSPC and PLCO, the controversies surrounding PSA screening for prostate cancer remain. The current consensus is that the levels of overdiagnosis remain unacceptably high for population-based screening of asymptomatic men. The PSA level should represent a spectrum of risk that must be considered on an individual basis with other risk factors such as age, family history and ethnicity. These risk factors can be integrated into “risk calculators” to estimate a man’s risk of prostate cancer per se and the likelihood of aggressive disease.

Using these tools is more informative than PSA testing alone and allows physicians and their patients to make shared decisions regarding prostate biopsy based on objective measures. Decision aids have been found to improve patient knowledge, promote greater involvement in decision making and reduce the use of radical therapies in patients diagnosed with prostate cancer. In recognition of the vital role that patient education plays in making well-informed decisions regarding prostate cancer screening and management, the NHS has developed the Prostate Cancer Risk Management Programme (www.cancerscreening.nhs.uk/prostate/). This programme aims to present patients and their families with clear and balanced information, while also providing healthcare practitioners with resources to assist in patient counselling.

**BLADDER CANCER**

Bladder cancer is the sixth commonest non-cutaneous malignancy in the UK and the eighth commonest cause of cancer-related death, claiming approximately 5000 lives per year. Bladder cancer occurs two to three times more frequently in men than women and 98 per cent of cases occur in people aged over 50 years.

These cancers have a variable natural history. About 70 per cent are low-grade tumours that are generally not considered
Haematuria screening

The rationale for screening for bladder cancer is the detection of high-grade tumours at a preinvasive, potentially curable stage. The five-year survival rates for preinvasive cancers are 80–90 per cent, significantly higher than for invasive (25–50 per cent) or metastatic (10–15 per cent) disease. Cytoscopy is the gold standard for the diagnosis of bladder cancer, but its invasive nature makes it unsuitable for screening. Testing for haematuria has received most interest as a potential screening tool, as 85 per cent of patients with bladder cancer have painless haematuria (microscopic or gross) and it is an inexpensive test associated with no morbidity. However, haematuria in bladder cancer tends to be intermittent, necessitating repetitive testing. This is reflected in the results of a large retrospective study, which found no difference in the incidence of bladder cancer between asymptomatic patients with and without haematuria on one-time dipstick testing.

Repetitive testing has proved more fruitful. Messing et al. compared repeated urine self-testing in 1575 men aged over 50 with 511 patients newly diagnosed with bladder cancer on a register. Screening proved highly sensitive as, within one year of final testing, all patients who developed bladder cancer had been detected by the presence of haematuria. Overall, the incidence of newly diagnosed bladder cancer was similar between the screened population and a population of men that elected not to undergo screening. In contrast, the proportion of invasive disease was significantly lower among screened men than among patients on the cancer register (5 versus 25 per cent), as was the risk of bladder cancer-related death (0 versus 20 per cent). However, this study did not have a cohort of unscreened controls, was of small size and had sparse data.

Cytology and molecular marker screening

Bladder cancer is a relatively uncommon cause of microscopic haematuria. The study by Messing et al. detected haematuria in 16 per cent of men but bladder cancer in only 1.3 per cent, yielding a positive predictive value of 8.1 per cent for asymptomatic men aged over 50. Further investigation of haematuria typically involves more invasive procedures, which incur significant morbidity and expense. There is great interest in using secondary tests to differentiate between patients who require further investigation and those who need only continued monitoring.

In patients with haematuria or dysuria, urine cytology has a specificity approaching 100 per cent but a low sensitivity (34 per cent) for the detection of bladder carcinoma. Various urine-based molecular tumour markers have also been assessed. Urinary nuclear matrix protein-22 (NMP22) is available as a point-of-care test and has received particular attention. In a meta-analysis, urinary NMP22 was found to have a sensitivity of 73 per cent and a specificity of 80 per cent.

The bottom line

Population screening for bladder cancer is unlikely to be cost-effective with current tests because of its low incidence.
decisions about screening, investigation, overdiagnosis and overtreatment. To achieve this, we should target our preventative strategies at high-risk populations, develop more specific markers to differentiate between indolent and aggressive tumours and scale back our treatment of low-risk disease. Perhaps most importantly, we must develop strategies and risk-assessment tools to aid clinicians and patients in making informed decisions about screening, investigation and treatment.

Declaration of interests: none declared.

REFERENCES


