

Katherine Turner

"This house believes that the UK government should introduce a screening programme for prostate cancer".

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Abstract

In this essay I will argue the UK government should not introduce a screening programme for prostate cancer. There is currently no prostate cancer screening programme in the UK based on the criteria originally proposed by Wilson and Junger over 40 years ago. The candidate screening test, the Prostate Specific Antigen is not particularly sensitive or specific, the natural history of the disease is not fully understood and screening has been shown to result in a level of over-diagnosis and over-treatment above what is acceptable. Recent identification of potential markers of aggressive disease and targets for therapy could mean that screening becomes a more feasible option in future. In the meantime, testing should be offered to symptomatic men and those considered to be at high risk.

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The current situation in the UK

Over 40 years ago Wilson and Junger proposed the now 'classic' screening criteria (Wilson and Junger, 1968). Although they have been adapted somewhat they are still used to assess screening programmes and it is on the basis of these criteria that there is currently no national prostate cancer screening programme in the UK. Instead, the Prostate Cancer Risk Management Programme aims to provide concerned men with advice about the benefits and potential drawbacks of the Prostate Specific Antigen (PSA) test and available treatment for prostate cancer (Programme, 2013).

Screening debate in USA.

The screening debate is not limited to the UK. In the United States there is disagreement between organisations about screening protocols (Andriole et al., 2009). The American Urological Association and American Cancer Society recommend annual PSA testing and digital rectal examination is offered from age 50 to men with normal risk of prostate cancer and from an earlier age if they are at increased risk (2000, Society, 2013). However, the National Comprehensive Cancer Network recommends risk-based screening and the US Preventative Services Task Force does not recommend screening because of insufficient evidence of benefit in men under 75 (2008).

Serious Health Problem

There is no question that prostate cancer is an important health problem. Prostate cancer is the commonest cancer in males in the UK: 40,975 new cases were diagnosed in 2010, of which 75% were in men over 65 (UK, 2013). The UK incidence has increased since the 1970s, reflecting the introduction and subsequent uptake of PSA testing. Worldwide, prostate cancer is the second commonest cancer in males and the fourth commonest cancer overall, so why is there no screening programme in the UK (Cancer, 2014)?

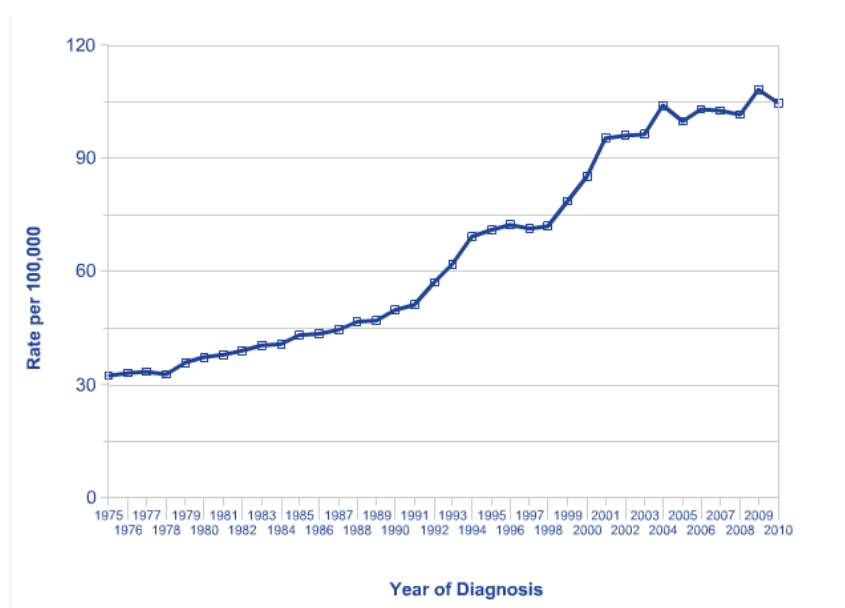


Figure 1: European Age-Standardised Incidence Rates, Males, Great Britain, 1975-2010 (Cancer, 2014).

How do we screen for prostate cancer?

PSA is a protein produced by the prostate gland; high levels may indicate prostate cancer (UK., 2014). Although PSA testing is currently the best available method for prostate cancer screening its sensitivity is only 21% and 32% using cut-offs of 4.0ng/ml and 3.0ng/ml respectively (UpToDate, 2014), so two thirds with raised a PSA without cancer will subsequently have further, unnecessary tests (Oncology, 2014). Conversely, although PSA may be raised secondary to conditions including prostatitis, benign prostatic enlargement and lower urinary tract infections, PSA levels may be normal in as many as 15% with

prostate cancer, 2% of whom have high grade cancer (Burford et al., 2010.). There is no accepted cut-off value for PSA testing; some argue 4.0ng/ml is too high as diagnoses of prostate cancer have been made in men with a PSA of 4.0ng/ml and normal PR examination findings (UpToDate, 2014). A lower PSA threshold would improve sensitivity at a cost of specificity. Whilst there are recognised age-related cut-offs for PSA (Table 1) (UK., 2014), it has been shown that rather than being categorical values, they are on a continuum (Thompson et al., 2005). According to Wilson and Junger “there should be a suitable test or examination” (Wilson and Junger, 1968), I would argue the difficulties I have described with the PSA test mean it is not a suitable test for the screening programme.

| PSA Cut-off Values | |
|---------------------------|--------------------|
| Age (years) | PSA (ng/ml) |
| 50-59 | >/3.0 |
| 60-69 | >/4.0 |
| >70 | >/5.0 |

Table 1:PSA age specific cut-off values (UK, 2014).

Why is prostate cancer different?

Breast, bowel and cervical cancers are currently screened for in the UK; so what makes prostate cancer different? For breast cancer, despite some debate (Adams, 2012, Collins, 2013, Hope, 2013), it has been shown that lives saved by screening outweigh the harm done by over-diagnosis (Paci, 2012); this cannot be said of prostate cancer screening. Unlike the cancers that are screened for, management of prostate cancer is somewhat uncertain which contributes to the controversy about screening (Burford et al., 2010.). National Institute for Health and Care Excellence guidelines published earlier this year aimed to clarify some of this uncertainty. They recommend that all newly diagnosed prostate cancers should be assigned a risk stratification to help guide treatment (Excellence., 2014) but the uncertainty

about the best treatment option is reflected in the fact they leave some treatment decisions to the patient. A further complication is the difficulty distinguishing between indolent and aggressive forms of disease, consequently men with less aggressive forms may unnecessarily be put through active treatment with significant side effects including impotence.

Natural History of the Disease

“The natural history of the condition...should be adequately understood”; this cannot be said of prostate cancer (Burford et al., 2010.). Whilst some will men die *of* prostate cancer, many will die *with* prostate cancer of other causes. The disease’s unpredictability poses one of the biggest challenges for screening and treatment, although recent developments could change this. Four groups have identified different genes they suggest could be used as markers of prostate cancer, its severity and aggressiveness. The Prolaris test determines the aggressiveness of the cancer based on 31 genes (Choices, 2013., Berney et al., 2013), a second study identified levels of a protein NAALADL2 as a marker of high risk prostate cancer (Choices, 2013, Whitaker et al., 2013). A third group identified a protein, EN2, produced apparently uniquely by cancerous tissue; the fourth identified the gene GATA2 as a prostate-metastasis driving gene and potential target for future therapy. Additionally, thirteen mutations have been identified in eight genes involved in DNA damage and repair in fourteen men with familial prostate cancer. These men were diagnosed at a similar age, with similar PSA levels, grading and staging, and were more likely to have advanced disease (OR 15.09, 95% CI: 2.95–95.81, P=0.00164) (2014, Choices., 2014.). In future, this may enable the identification of men most likely to develop life-threatening prostate cancer.

Over-diagnosis

Over-diagnosis: the detection and diagnosis of cancer in men who would not have died of prostate cancer (Schröder et al., 2009) has been estimated to be as high as 50% (Draisma et al., 2003). Over-diagnosis and over-treatment are considered by some to be the most

adverse effects of prostate cancer screening and are reported to be commoner in prostate cancer screening than in programmes for breast, colorectal and cervical cancer (Hakama and Auvinen, 2008). Over-diagnosis can have life-long consequences including affecting a person's ability to obtain life insurance (Welch and Black, 2010). The best management of men with persistently raised PSA but negative biopsy is unclear and consequently these men face periods of prolonged follow-up which can cause significant anxiety (Burford et al., 2010.). The problem of over-diagnosis is another reason I would argue against the introduction of prostate-cancer screening in the UK.

Findings of the Studies

Recently studies support the argument against prostate cancer screening. The Prostate, Colorectal, Lung and Ovarian Screening Trial on prostate mortality failed to show a reduction in mortality in an already over-screened population; after 7-10 years of follow up the mortality rate from prostate cancer was very low in both the screening and control group (Andriole et al., 2009). Two further studies demonstrated a reduction in death by between 20% and 50% at the cost of a high risk of over-diagnosis (Schröder et al., 2009, Hugosson et al., 2010). Schröder et al. found that to prevent one death from prostate cancer 1410 men would have to be screened and an additional 48 men would have to be treated. In comparison, for breast cancer one life is saved for every 113 people screened (Duffy et al., 2010).

The Role of Celebrity

It is interesting to consider the role of celebrity in a screening programme. In 2009 reality TV star Jade Goody died from cervical cancer, which is screened for in the UK. During the surrounding the coverage, over 400,000 extra women were screened, most of whom presented late (Lancucki et al., 2012). Whilst the increase is likely to have resulted in saved lives, the phenomena and the media interest was largely limited to the time Jade was suffering, in keeping with similar episodes (Chapman, Howe et al., 2002). Figure 2 (Centre, 2013a) demonstrates the overall trend in cervical cancer is actually downwards (Centre,

2013b). Recently, Bill Bailey has become the face of Prostate Cancer UK's campaign "Men United Vs Prostate Cancer" (UK, 2014), arguably significantly raising the public profile of the condition. Whilst promoting conditions such as these raises their profile their effect is only beneficial if sustained.

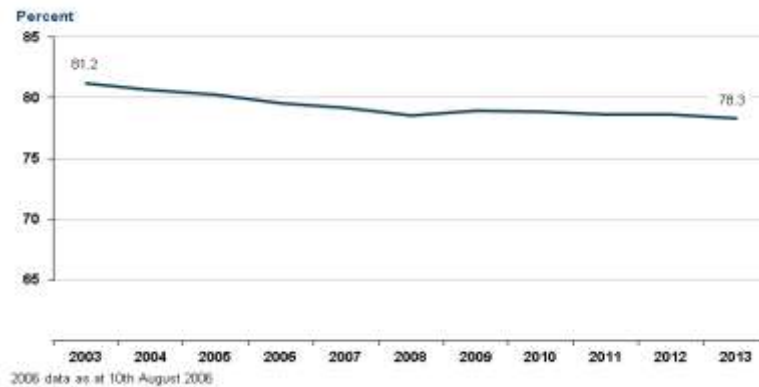


Figure 2: Cervical screening – Five year coverage of the target age group (25-64). England at 31st March, 2003 to 2013 (Centre, 2013a).

Conclusion

I do not believe the UK government should introduce a screening programme for prostate cancer at present because of problems associated with the test sensitivity and specificity and current difficulties differentiating between aggressive and indolent forms of the disease. However, I recognise that prostate cancer is a serious health problem; it is important that there is an understanding among the general public of the PSA test as a entity as well as symptoms and signs of prostate cancer. In time, I hope the novel tests described above will become part of prostate cancer management and enable implementations of a more acceptable screening programme. In the mean time, testing should be offered to symptomatic men and those considered at high risk of prostate cancer who have a family history of brother, relative < 60, or several relatives having prostate cancer.

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