INTRODUCTION

In 1989, prostate cancer became the most common cancer diagnosed in American men and the second leading cause of death [1]. Unfortunately, at that time most cases of prostate cancer were either locally advanced or metastatic at diagnosis. The toll of prostate cancer is significant; 17% of men will develop prostate cancer at some time and ~3% will die from the disease [2]. Faced with these grim statistics, three approaches are possible. The first is to develop a cure for advanced prostate cancer, but this has not yet been achieved. The second is to try to prevent the disease. An effective preventive agent was recently identified, finasteride, which reduced the 7-year prevalence of prostate cancer [3]. However, because of the higher prevalence of high-grade tumours in men who received finasteride, this approach to prevention was not embraced, despite this phenomenon possibly having been an artefact [4]. A third approach is to find the disease early, treat it and cure it; this approach is known as screening or early detection.

For a screening programme to be feasible, first the disease must be highly prevalent in the population, and second there must be minimally morbid tests available that are sensitive enough to detect the disease. The screening tests should detect clinically important disease that can be treated with minimal morbidity and mortality. Third, the treatment should result in improved survival.

The first requirement is fulfilled because, as already mentioned, prostate cancer is the most common cancer in American men and the second leading cause of death. The second requirement for effective screening is a reasonably accurate way of making the diagnosis. PSA testing is minimally invasive and has a sensitivity of 70–80% when the threshold is 4 ng/mL [5]. The sensitivity of screening mammography is 67–80%. The positive predictive value (PPV) of PSA testing is estimated to be 31–54% in men whose PSA level is >4 ng/mL [5], a higher value than the PPV of mammography, which is 9–22% [6]. Unfortunately, the specificity of the PSA test is not as good as its sensitivity. Although PSA is not a perfect test, high PSA levels should be viewed as a risk factor, much like cholesterol in cardiovascular disease. There is no specific threshold of cholesterol level at which a risk of cardiovascular disease appears; rather, the relation appears to be linear. The same can be said of PSA; PSA has a higher PPV than a DRE, at 30–42% vs 4–11% [7].

There have been numerous attempts to improve the sensitivity and specificity of PSA testing, such as reviewing the PSA velocity, which measures the annual increase in PSA. A study following PSA trends for 5 years showed that the specificity improved from 42% to 96% during that period [8]. The sensitivity could be improved by using a PSA threshold of ≥2.5 ng/mL [8]. Studies of men who were screened and had a biopsy if their PSA was ≥2.5 ng/mL have shown that this threshold can improve the sensitivity of the PSA test to ≥90% [8]. However, recent reports from the Prostate Cancer Prevention Trial showed that 15.2% of men diagnosed with prostate cancer had a PSA level of <3 ng/mL, and 14.9% had a Gleason score of ≥7 [9].

The discovery and use of PSA to detect prostate cancer led to the development of Prostate Cancer Awareness Week (PCAW) in 1989 [10]. As already noted, the incidence of and death rate from prostate cancer began to increase in 1989, but this increase generated little interest in the USA. PCAW was established to educate the community about prostate cancer and to promote early detection, and it has become an internationally recognized programme that annually screens hundreds of thousands of men. The Prostate Cancer Education Council, which oversees PCAW, surveyed public knowledge, attitudes and health practices about prostate cancer. It was clear from this survey that prostate cancer was an ignored disease of men [10]. Much has been learned from the PCAW data. An early report included more than 116 073 men tested [11]. An abnormal PSA level or DRE (or both) was found in 22 014 men when the PSA threshold was defined as 4.0 ng/mL, and in 17 561 men when the abnormal value was an age-specific reference range (ASRR). The study compared the PPV, sensitivity and specificity of the PSA test, DRE, or PSA test and DRE together. Using a PSA threshold of 4.0 ng/mL, the PPV of an abnormal PSA alone was 27.7%; of an abnormal DRE alone, 17.7%; and of abnormal PSA and DRE, 56.0%. Sensitivities were 34.9%, 27.1% and 38.0%, respectively; specificities were 63.1%, 49.0% and 87.9%, respectively. Using an ASRR as the PSA threshold, the PPV of an abnormal PSA was 31.8%, of an abnormal DRE 20.8% and of an abnormal PSA and DRE, 63.7%. Sensitivities were 27.1%, 41.0% and 31.8%, respectively; specificities were 75.0%, 32.8% and 92.2%, respectively. The PPVs of the PSA test were higher than those of DRE. The PPVs of the combined tests were highest when using a PSA threshold of 4.0 ng/mL and an ASRR (P < 0.001). The PPVs of the PSA test, DRE and combined tests were higher when using an ASRR than when using a 4.0-ng/mL PSA threshold, but these differences were not statistically significant (all P > 0.05). The PSA test had a lower sensitivity when using an ASRR than when using a 4.0-ng/mL threshold.

Of the cancers detected, 90% were localized, a finding that reaffirmed the efficacy of screening to detect early-stage disease. Indeed, the number of men who have advanced disease at the time of diagnosis has markedly decreased over the years, and it is rare for a man who has annual screening to present with advanced disease [11]. During PCAW, several issues on PSA testing were examined, including the influence of DRE on the PSA level, in >2700 men. There was no effect of DRE on serum PSA levels [12]. There was also no correlation between vasectomy and the presence of prostate cancer. Another study examined the effect of ejaculation on PSA level, and in 750 men ejaculation did not significantly increase the PSA level [13].

Despite the data from PCAW and other screening programmes worldwide, the value of early detection remains controversial, with
the controversy focusing on ‘lead-time’ bias (which suggests that the natural history of the disease is not truly affected by screening) and ‘length-time’ bias (which suggests that annual screening is more likely to detect slow-growing, non-lethal tumours than fast-growing, lethal ones). Several important trials are ongoing to determine the value of screening, including the Prostate, Lung, Colorectal, and Ovarian Cancer trial, which began in 1992 [14]. More than 154 000 men and women aged 55–74 years have enrolled in this trial. Hopefully, data will soon emerge that confirm the value of screening.

Numerous medical organizations around the world support screening, but numerous others discourage it. This dichotomy leads to confusion for our colleagues and our patients. At least five separate concerns are voiced by critics of prostate screening.

- Many men die with prostate cancer rather than from it. This concern reflects the data of Sakr et al. [15], who reported a very high incidence of prostate cancer beginning in the fourth decade of life (Fig. 1). Alarmingly, >25% of those in their fourth decade had microscopic prostate cancer.
- Most men with prostate cancer are not helped by screening; most die with the disease, and in others the disease onset is so rapid that screening fails to detect it at a curable stage (Fig. 2) [16].
- Screening is costly; Optenberg and Thompson [17] estimated that, in the USA, it would cost US$25 billion during the first year alone, and they added that some countries do not encourage screening, because they fear that it will ‘break the bank’ in healthcare costs.
- Another concern with screening involves the anxiety [18], the side-effects of biopsy [18], the risk of treatment morbidity and mortality, and the risk of recurrence.
- There is no proof that screening really prevents deaths or that we are dealing with lead-time and length-time biases.

To address the first of these concerns that most of the cancers we find are insignificant, Dugan et al. [19] analysed 337 men undergoing radical prostatectomy and found that, in the worst-case scenario, only one in seven of the cancers was insignificant. Regarding the cost of screening, when assessing both the best- and the worst-case scenarios, the cost of a quality-adjusted life-year gained as a result of prostate cancer screening is well below those for liver transplantation and coronary artery bypass. Screening for prostate cancer is therefore cost-effective [20]. In addition, the incidences of erectile dysfunction, incontinence and death resulting from treatment have markedly decreased during recent years. The last concern is that screening does not affect survival. Screening began in earnest between 1986 and 1988, shortly after which there was a marked increase in the number of patients diagnosed with prostate cancer; screening found previously undetected cancer. It is to be hoped that we will next see a reduction in metastatic prostate cancer; indeed, at the 1999 AUA meeting, Thompson presented data from the US Department of Defense showing that the prostate cancer mortality rate is falling. Other studies have also supported a reduction in prostate cancer mortality rate [21]. In countries where screening is not used the mortality rate has risen.

Although there are many concerns about screening, the ‘bottom line’ is that it appears...
to be doing what it is supposed to do, finding tumours early, that can be cured, and that need to be cured. The natural experiment appears to be saving lives. In the future, improvements in diagnostic techniques and molecular markers will help to determine more readily who is in need of treatment.

CONFLICTS OF INTERESTS

The authors have declared no conflicts of interests.

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Abbreviations: ASRR, age-specific reference range; PCAW, Prostate Cancer Awareness Week; PPV, positive predictive value.