Prostate cancer: a serious disease suitable for prevention

John M. Fitzpatrick, Claude Schulman*, Alexandre R. Zlotta† and Fritz H. Schröder‡

Mater Misericordiae Hospital and University College Dublin, Dublin, Ireland, *Department of Urology, Erasme Hospital, University Clinics of Brussels, Brussels, Belgium, †Division of Urology, Murray Koffler Urologic Wellness Centre, Mount Sinai Hospital, University of Toronto, Toronto, Ontario, Canada, and ‡Department of Urology, Erasmus MC, University Medical Centre Rotterdam, the Netherlands

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Prostate cancer is among the most common causes of death from cancer in men, and accounts for 10% of all new male cancers worldwide. The diagnosis and treatment of prostate cancer place a substantial physical and emotional burden on patients and their families, and have considerable financial implications for healthcare providers and society. Given that the risk of prostate cancer continues to increase with age, the burden of the disease is likely to increase in line with population life-expectancy. Reducing the risk of prostate cancer has gained increasing coverage in recent years, with proof of principle shown in the Prostate Cancer Prevention Trial with the type 2 5α-reductase (5AR) inhibitor, finasteride. The long latency period, high disease prevalence, and significant associated morbidity and mortality make prostate cancer a suitable target for a risk-reduction approach. Several agents are under investigation for reducing the risk of prostate cancer, including selenium/vitamin E and selective oestrogen receptors modulators (e.g. toremifene). In addition, the Reduction by Dutasteride of Prostate Cancer Events trial, involving >8000 men, is evaluating the effect of the dual 5AR inhibitor, dutasteride, on the risk of developing prostate cancer. A successful risk-reduction strategy might decrease the incidence of the disease, as well as the anxiety, cost and morbidity associated with its diagnosis and treatment.

KEYWORDS
prostate cancer, prevention, 5α-reductase inhibitors

INTRODUCTION

Although prostate cancer is commonly regarded as a disease of ageing that more men will die with than die from, it is one of the most common causes of cancer death among men [1]. In its early stages when the disease is curable, prostate cancer tends to cause few or no clinical symptoms; however, by the time it becomes large enough to cause symptoms prostate cancer is commonly incurable [2]. Despite PSA-induced stage migration at diagnosis, a high cure rate for localized disease and improved understanding of prostate cancer biology, most men who develop metastases will die as a result of the disease [3]. Even with early detection, clinicians have lacked the tools to differentiate with certainty between prostate tumours that will progress and those that will remain quiescent; recent progress has been made in this area with the development of a nomogram for predicting indolent prostate cancer among screen-detected populations [4]. Although effective treatments are available for localized prostate cancer, doubt remains as to whether early intervention improves long-term outcomes [5,6]. The prospect of preventing or reducing the risk of prostate cancer has gained increasing coverage in published literature over recent years. The objective of this review is to examine the significant burden imposed by prostate cancer, the characteristics of prostate cancer that make it suitable for a risk-reduction approach, and potential drug candidates for reducing the risk of prostate cancer.

INCIDENCE, PREVALENCE AND DISEASE-RELATED MORTALITY

European national registry data indicate that prostate cancer is now the most common cancer in men (excluding nonmelanoma skin cancers) [7,8]. Worldwide, >650 000 men are diagnosed with prostate cancer every year, accounting for 10% of all new male cancers [1]. Furthermore, substantial increases in prostate cancer incidence have been reported for many countries around the world [9]; the highest prostate cancer incidence rates are in the developed world and the lowest rates in Africa and Asia (Fig. 1). The extremely high rate of prostate cancer in the USA (125 per 100 000), more than twice the reported rate in the UK (52 per 100 000), is likely to be due to the particularly high rates of PSA testing in the USA. Furthermore, African-American men have higher rates than white Americans [10]. Prostate cancer is the third leading cause of cancer death among men [8]. Mortality rates can vary considerably depending on tumour Gleason score; men with low-grade prostate cancers (Gleason score 2–4) have a minimal risk of dying from prostate cancer during 20 years of follow-up (six deaths per 1000 person-years; 95% CI, 2–11), while men with high-grade prostate cancers (Gleason score 8–10) have a high probability of dying from prostate cancer within 10 years of diagnosis (121 deaths per 1000 person-years; 95% CI, 90–156) [5].

PROSTATE CANCER DETECTION AND SCREENING: EPIDEMIOLOGICAL IMPACT

The 5-year survival rate for localized prostate cancer is 100% compared with only 34% for
metastatic disease [11]. In the absence of an organized screening programme, by the time of diagnosis only 55% of tumours are clinically localized [12]. Moreover, studies indicate that 30–45% of patients with clinically localized disease are found to have extracapsular extension at pathological staging [13,14]. Earlier diagnosis and treatment would therefore be expected to improve outcomes. However, population-based screening is not yet advocated by European guidelines, on the basis that it is still unclear whether outcomes are improved [15]. Two large trials are underway, the Prostate, Lung, Colorectal and Ovarian screening study in the USA and the European Randomized Screening for Prostate Cancer (ERSPC) in Europe, to evaluate the efficacy of prostate cancer screening [16,17]; the first of these to report will be the ERSPC, with data analysis expected in 2010.

Measurement of PSA levels for the early detection of prostate cancer has been a contentious issue for more than a decade. While PSA is an imperfect predictor of prostate cancer, it remains a useful tool that is widely used in clinical practice. In the USA and elsewhere, widespread PSA testing of asymptomatic men has resulted in a dramatic increase in the incidence of prostate cancer and a stage migration at diagnosis, with a decrease in the number of patients presenting initially with evidence of metastatic disease [1,18–20]. In general, prostate biopsy has only been recommended when PSA levels exceed a threshold value of 4 ng/mL; however, applying this threshold would result in nearly 80% of all prostate malignancies going undetected [21]. Lowering the threshold to 1.1 ng/mL would detect 83.4% of tumours but result in 61.1% of men without cancer receiving a needless prostate biopsy [21]. Although lowering the PSA threshold for biopsy would increase the detection of prostate cancer, it would also heighten the risk of detecting clinically insignificant tumours, thereby resulting in overtreatment and unnecessary anxiety for the patient. Indeed, about five prostate cancers are detected for every one that proves to be lethal [22] and it might not be possible for clinicians to differentiate with absolute certainty between tumours that will progress and those that will remain quiescent. This results in difficult decision-making processes between patients and their clinicians. Ultimately, other established risk factors for prostate cancer, such as family history and race, are important in treatment decisions for individual patients. This uncertainty in how to screen for and treat the disease is one of the factors that make a risk-reduction approach desirable.

THE BURDEN OF PROSTATE CANCER DIAGNOSIS AND TREATMENT: PHYSICAL, EMOTIONAL AND FINANCIAL CONSIDERATIONS

IMPACT OF THE DIAGNOSIS

Newly diagnosed patients can endure significant anxiety and uncertainty relating to both diagnosis and prognosis and, in the PSA era, it is possible for a perfectly healthy young man to be diagnosed with cancer, have a diagnostic evaluation, endure the adverse effects of therapy, and have a biochemical relapse without ever having had a disease-related symptom [23,24]. A prostate cancer diagnosis can also affect the entire family unit. For example, Mellon and Northouse [25] reported a 63% decline in the family’s overall quality of life after the diagnosis. Issues of stress, fatigue, pain, anxiety, hopelessness, financial concerns, loss of a job or time away from work, and grief, all affect the family during the time of diagnosis, treatment, cure, or possible death from the illness.

Men with localized prostate cancer report more urinary and sexual problems than men of similar age without the disease [26–28]. Men with progressive disease have significantly more bodily pain, less vitality/energy and poorer social and emotional well-being than those in remission [29]. With prostate cancer of any stage, patients experience a steady decline in health-related quality of life within the last year of life, regardless of whether they die with or because of the disease [30].

There are three recommended treatment options for early (localized) prostate cancer in the USA and in Europe: active surveillance, radical radiotherapy and radical prostatectomy. All aggressive treatments can result in urinary, sexual and bowel dysfunction that can affect quality of life; these changes in quality of life also influence satisfaction with treatment outcomes among patients and their partners [31]. Men who are diagnosed with localized prostate cancer can suffer for many years with the sequelae of the treatments they receive [32–34]. Although surgical expertise has decreased the rate of complications and improved cancer cure, radical prostatectomy still carries surgical risks, as well as the risk of incontinence and erectile dysfunction (ED). Rates of postoperative ED in published series range from 29% to >80% of patients [32,35,36]. The degree of postoperative incontinence varies in published studies from mild to severe, with overall incontinence rates ranging from zero to >30% of patients [32,36]. Radiotherapy can also be associated with ED and bowel or bladder symptoms. Chronic irritative voiding symptoms develop in up to 5% of patients [37,38], rectal irritation in up to 10%, and decreased erectile function in up to 50% [36–38]. These same complications have been associated with brachytherapy [39].

Much more research has been conducted into the treatment of advanced prostate cancer than localized disease, and androgen deprivation (surgical or medical castration) remains the standard treatment. Androgen-deprivation therapy is associated with vasomotor flushing, loss of libido, ED, gynaecomastia, weight gain, osteoporosis and loss of muscle mass [40]. Patients receiving hormonal therapy can also experience bothersome fatigue and sleep disturbances.
More recently, evidence has emerged that androgen-deprivation therapy might be associated with an increased risk of diabetes and cardiovascular disease [41,42].

The Prostate Cancer Outcomes Study showed that impairments in urinary, bowel and sexual function after curative therapy for clinically localized prostate cancer can persist for 5 years after diagnosis [43]. Furthermore, data from the National Health Interview Survey, conducted in the USA in 2003, showed that prostate cancer survivors have poorer health outcomes than similar individuals without cancer across several measures of burden (Table 1) [44,45]. The physical burden of prostate cancer is therefore considerable and affects quality of life in men with localized or metastatic disease. The impact on quality of life stems as much from treatment for prostate cancer as from the disease itself, and the effect can continue for many years after diagnosis.

FINANCIAL CONSIDERATIONS

Data from numerous countries show the considerable financial expenditure associated with prostate cancer. In a retrospective matched-cohort control analysis ion the USA, Chang et al. [46] reported that the total direct medical costs of prostate cancer were $2187 (quoted as £1215) per month compared with $329 (£187) for those without cancer. In a UK analysis, treatment and 5-year follow-up was estimated at £92.74 million; hormonal therapy was estimated to account for over two-thirds of this cost [47]. In Sweden, the average lifetime cost of prostate cancer was SEK 79 000 (US $12 400), with half of the total treatment cost incurred during the year before death [48]. In the mid-1990s, Canada and the Netherlands spent 4–6% of their national cancer expenditure on prostate cancer [49,50], while more recent data estimate this to be 6–10% in Australia and Germany [51,52].

PROSTATE CANCER: THE DISEASE PROCESS

Genetic and epigenetic changes intermediate between normal prostatic epithelium and prostate cancer have been described in several histological lesions, such as atypical small acinar proliferation, proliferative inflammatory atrophy, and prostatic intraepithelial neoplasia (PIN) [53]. PIN develops over ≈20 years; progression from PIN to high-grade PIN (HGPIN) and early latent cancer can take ≥10 years, and clinically significant carcinoma might not occur for another 3–15 years [54]. This provides ample time for preventive measures.

The relatively high rates of recurrence and mortality associated with high-grade tumours compared with low-grade tumours are well documented [55,56]. More recently, data from a large population-based cohort study showed that the probability of progression from localized and indolent to metastatic mortal disease increases markedly after long-term follow-up [6]. These data also suggest that metastases might arise as a consequence of late mutations rather than being predetermined by the early mechanisms of malignant transformation. Overall, the long latency, high prevalence and significant mortality and morbidity associated with prostate cancer make it a suitable target for primary prevention with drug therapy, the goal of which is to decrease the incidence of the disease and thereby reduce both treatment-related adverse events and mortality. Reducing the risk of prostate cancer could also have a considerable impact on the financial and emotional burden associated with the disease.

WHAT IS THE FUTURE FOR PROSTATE CANCER RISK REDUCTION?

Several different agents are currently being investigated for their potential in reducing the risk of prostate cancer [57]. Studies are underway to determine if vitamin D, which has pro-apoptotic and antiproliferative effects in human prostate cancer cell lines, can prevent prostate cancer [57]. Pilot studies are also being conducted to assess the effectiveness of soy for prostate cancer prevention. Soy is rich in isoflavones and vitamin E, and selectively inhibits the α-oestrogen receptor; a soy-based dietary supplement has been shown to delay PSA progression in a small-scale (49 men), prospective, randomized study of men with increasing PSA levels after potentially curative treatment [58]. In addition, large-scale studies are evaluating the dual 5α-reductase (5AR) inhibitor dutasteride, selenium/vitamin E, and toremifene, a selective oestrogen receptor modulator (SERM).

5AR INHIBITORS

Androgens play a vital role in both the normal and abnormal growth of the human prostate [59]. The two main androgens involved are testosterone and dihydrotestosterone (DHT); testosterone is converted to DHT by the action of 5AR isoenzymes (type 1 and type 2). Available evidence indicates that 5AR1 expression is greater in prostate cancer than in benign tissue, whereas 5AR2 expression and activity are decreased [60].

DHT, which has a five-fold greater affinity for the AR than has testosterone [61], is generally regarded as the major androgen driving prostate growth. Suppression of intraprostatic DHT with 5AR inhibitors is associated with a reciprocal rise in intraprostatic testosterone levels [62,63]; nevertheless, the increase in testosterone after treatment with a 5AR inhibitor appears to be smaller than the rise in DHT levels in untreated men, indicating that 5AR inhibitors lower the overall androgen level in the prostate [62].

The role of DHT in prostate growth makes it a logical target for prostate cancer risk reduction via inhibition of 5AR isoenzymes. The Prostate Cancer Prevention Trial (PCPT) showed that the type 2 5AR inhibitor, finasteride, reduced the risk of prostate cancer by 24.8% relative to placebo over
a 7-year period [95% CI, 18.6–30.6%; \( P < 0.001 \)]. However, tumours of Gleason grade 7–10 were more common in the finasteride group than in the placebo group [37% vs 22.2%, respectively; \( P < 0.001 \) for the comparison between groups] [64]. This unexpected finding led to the suggestion that low levels of DHT are associated with more aggressive prostate cancer. Other studies have reported a link between reduced androgenic activity and aggressive prostate cancer in the form of the risk of PSA failure and metastases at the time of diagnosis [65,66]. In addition, an association was reported between aggressive prostate cancer and a low-activity variant of the gene for 5AR type 2 [67]. In another study, the change in DHT levels was assessed in relation to prostate cancer grade (Gleason score) in 26 men with clinically localized disease receiving androgen-deprivation therapy [68]. The authors concluded that low levels of intraprostatic DHT are probably sufficient to propagate growth of aggressive prostate cancers.

Alternative explanations have been provided by further analyses of data from the PCPT, which strongly suggest a detection bias as a result of prostate volume reduction and enhanced utility of the PSA test for detecting cancer in finasteride-treated patients [69–71]. A more recent study provides further evidence that effects on prostate volume, rather than on tumour morphology, contributed to the increase in high-grade tumours with finasteride [72]. This study also suggests that selective inhibition of low-grade cancer was a contributory factor to the observed increase in high-grade tumours, and that high-grade cancer was detected earlier and was less extensive in the finasteride group than in the placebo group. Another issue to emerge from the PCPT is whether the prostate cancers that were prevented with finasteride, which were predominantly low-grade tumours, are of clinical significance. If 5AR inhibitors only prevent low-grade disease this would represent an improvement over current management; these prostate cancers are often over-detected and over-treated, and preventing them by using a pill would remove the associated anxiety, treatment-related adverse effects and costs.

A recent Cochrane review concluded that 5AR inhibitors have potential as agents to prevent prostate cancer, but highlighted the need for further studies to clarify the role of 5AR inhibitors in prostate cancer risk reduction [73]. Unlike finasteride, dutasteride is a dual inhibitor of both type 1 and type 2 5AR isoenzymes [74,75]. Studies show that dutasteride suppresses serum DHT by >90%, compared with 70% seen with finasteride [76]. A large-scale (>8000 men) randomized, placebo-controlled study, the Reduction by Dutasteride of Prostate Cancer Events (REDUCE) trial, is in progress to fully evaluate whether dutasteride has an effect on prostate cancer risk reduction [77]. The primary endpoint in REDUCE is biopsy-detectable prostate cancer; effects of dutasteride on Gleason score at diagnosis, occurrence and volume of HGPIN at biopsy, percentage of cores with prostate cancer at diagnosis, number of cancer-positive cores, treatment alteration score and the incidence of intervention (surgical and nonsurgical) for the treatment of prostate cancer will be assessed as secondary endpoints. There are important differences between the REDUCE study population and that of the PCPT; REDUCE is specifically recruiting men at increased risk of prostate cancer because they have an elevated PSA level at baseline (2.5–10 ng/mL, vs <3 ng/mL in the PCPT), and eligible patients must have a negative prostate biopsy within 6 months of enrolment, to ensure recruitment of men without prostate cancer or those with clinically undetectable disease.

SELENIUM/VITAMIN E

Epidemiological, molecular and clinical evidence suggests that selenium and vitamin E might reduce the risk of prostate cancer. However, in the VITamins And Lifestyle cohort study [78], long-term supplemental intake of vitamin E and selenium were not associated with an overall reduced prostate cancer risk. However, the risk of advanced prostate cancer (regionally invasive or distant metastatic) was significantly reduced with greater intake of supplemental vitamin E (hazard ratio 0.43, 95% CI, 0.19–1.0 for a 10-year average intake of ≥400 IU/day vs no use; \( P = 0.03 \)) [78]. The combination of selenium and vitamin E is being further investigated in the prospective, randomized, double-blind Selenium and vitamin E Cancer prevention Trial (SELECT), in which the primary endpoint is the clinical incidence of prostate cancer [79]. Prostate biopsies will be taken at the discretion of study physicians according to local community standards based on abnormalities in the DRE or elevations in serum PSA level [79].

SERMs

The potential of SERMs for preventing prostate cancer stems from an apparent role of oestrogens in the promotion of prostate growth [80]. SERMs might also decrease testosterone levels by suppressing the hypothalamic-pituitary axis [81]. Furthermore, age-related prostatic disease rates parallel increases in serum oestrogen levels, and there is a low incidence of prostate cancer in cultures with diets rich in phytoestrogens [82]. In a multicentre, double-blind study, 514 men with HGPIN and no cancer (determined by biopsies before study) were randomized to once-daily placebo or toremifene 20, 40 or 60 mg given orally, although this design was subsequently changed to a two-arm trial with toremifene 20 mg as the active treatment [83]. Patients were re-biopsied at 6 and 12 months. During the study, 24.4% of patients receiving the 20 mg dose of toremifene were diagnosed with prostate cancer, vs 31.2% of those taking placebo (\( P < 0.05 \)). Among the patients who completed 12 months of treatment, there was a 21.8% reduction in the cumulative risk of prostate cancer in those receiving toremifene 20 mg compared with those in the placebo group [83]. A large phase III study is underway to fully examine the potential for toremifene in reducing the progression of PIN to prostate cancer.

DISCUSSION AND CONCLUSIONS

Prostate cancer is recognized as one of the principal medical problems facing the male population, and the number of cases will rise as the population ages. This, combined with the uncertainty surrounding appropriate treatment and the associated cost and quality-of-life implications, indicates that the future burden of the disease might be substantial. As there are many more prostate cancers in men aged >50 years than ever become clinically apparent or significant, men face serious dilemmas regarding early detection, diagnosis and treatment for this disease. If prostatic carcinoma goes undetected, a given patient could eventually face a debilitating and frequently lethal disease. On the other hand, if his tumour is one that will remain quiescent or ‘clinically insignificant’ throughout his natural life span, detection could lead to the adverse consequences of over-treatment.
Preventing prostate tumours of any grade has the advantage of avoiding the 'burden of cure' (the anxiety, cost and morbidity associated with treatment). The high prevalence, long latency, and significant mortality and morbidity associated with prostate cancer make it a suitable target for primary prevention with drug therapy; the goal of this approach is to decrease the incidence of the disease and simultaneously reduce both treatment-related adverse events and mortality. Although the PCPT has raised interest in the potential for primary prevention with a SAR inhibitor, future prospective, randomized, controlled trials such as REDUCE and SELECT will provide additional insights into this important subject. Further work is also required to fully characterize those patients who would benefit most from a risk reduction approach.

In conclusion, epidemiological and behavioural evidence supports further study of the chemoprevention of prostate cancer. Large-scale clinical trials such as REDUCE and SELECT will be important in defining an evidence-based strategy for prostate cancer risk reduction.

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CONFLICT OF INTEREST

Alexandre R. Zlotta is on the GSK advisory board and speaker.

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Correspondence: Professor John Fitzpatrick, Mater Misericordiae Hospital and University College Dublin, 47 Eccles Street, Dublin 7, Ireland.
e-mail: jfitzpatrick@mater.ie

Abbreviations: DHT, dihydrotestosterone; ERSPC, European Randomized Screening for Prostate Cancer; ED, erectile dysfunction; (HG)PIN, (high-grade) prostatic intraepithelial neoplasia; 5αR, 5α-reductase; SERM, selective oestrogen receptor modulator; PCPT, Prostate Cancer Prevention Trial; REDUCE, Reduction by Dutasteride of Prostate Cancer Events; SELECT, Selenium and Vitamin E Cancer Prevention Trial.