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Diagnostic and Therapeutic Strategies for Prostate Cancer

Mary Nguyen-Nielsen, MD,[*,†] and Michael Borre, MD, PhD, DMSc[*]

Prostate cancer (PC) is a major disease that affects men's health worldwide. It is the second most common form of cancer in men, surpassed only by nonmelanoma skin cancers such as basal and squamous cell carcinomas. Diagnostic strategies with population screening for prostate cancer using prostate-specific antigen (PSA) has been surrounded with controversy and debated intensively ever since the PSA protein was first purified in 1979 by Wang et al. At the same time, advances in diagnostic imaging, surgery, radiation, and chemotherapy have increased the opportunity to effectively diagnose, treat, and manage PC. Given the sheer burden of PC disease in Denmark and worldwide, new and innovative strategies for cancer diagnosis and care are needed. This article is a short review of current diagnostic and therapeutic strategies for the care and management of prostate cancer in Denmark.
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Introduction

Prostate cancer (PC) is a major disease that affects men's health worldwide. It is the second most common form of cancer in men, surpassed only by nonmelanoma skin cancers such as basal and squamous cell carcinomas.

The age-standardized incidence (European, year 2012) of PC in Denmark was 138 per 100,000, which is comparable to other Europe Union countries (106 per 100,000) and USA (129 per 100,000).[1,2] Globally, PC accounts for approximately 15% of all new cancers diagnosed among men (year 2012).[3] However, as the elderly population in Denmark and elsewhere expands, the prevalence and sheer burden of PC disease expects to increase dramatically in the coming decades. Although the 5-year relative survival for PC has been steadily improving in Denmark from 54% during the period from 1999 to 2001 to 86% in the period 2011 to 2013,[4] the number of deaths due to PC remains paradoxically constant at approximately 1250 deaths per year in Denmark in the most recent years.[5]

PC is a complex and heterogeneous cancer that can be classified as aggressive and nonaggressive PC, high-grade and low-grade PC, or early-onset PC (ie, occurring before age 55 years) and indolent PC. Although evidence in the literature suggests that exogenous factors (ie, diet, physical activity, sexual behavior, and occupation) affect PC disease progression, there are currently only 3 well-established risk factors for prostate cancer: age (ie, increased PC risk with increasing age), ethnicity (ie, increased risk among African Americans), and heredity (ie, first-line relatives or relatives with early-onset PC).[6-8]

Moreover, diagnostic strategies with population screening for prostate cancer using prostate-specific antigen (PSA) has been surrounded with controversy and debated intensively ever since the protein was first purified in 1979 by Wang et al.[9] At the same time, advances in diagnostic imaging, surgery, radiation, and chemotherapy have increased the opportunity to effectively diagnose, treat, and manage PC.

Given the sheer burden of PC disease in Denmark and worldwide, new and innovative strategies for cancer diagnosis and care are needed. In this article, we will review current diagnostic and therapeutic strategies for the care and management of prostate cancer in Denmark.

Diagnostic Strategies for Prostate Cancer

Opportunistic Screening (Early Detection) in Denmark

Population screening for PC (ie, systematic screening of asymptomatic men at risk) has not been practiced in Denmark.

*Department of Urology, Aarhus University Hospital, Aarhus, Denmark.
†Diet, Genes and Environment, Danish Cancer Society Research Center, Copenhagen, Denmark.
Address reprint requests to Mary Nguyen-Nielsen, MD, Department of Urology, Aarhus University Hospital, Palle Juul-Jensens Boulevard 99, 8200 Aarhus, Denmark. E-mail: maryniel@rm.dk

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Table 1 Age-Stratified Cutoff Levels for PSA

Age (y)	PSA Cutoff Level (ng/mL)
Under 60	>3.0
60-70	>4.0
>70	>5.0

Rather, Denmark has had a tradition for opportunistic screening or early detection, which are individual-based screenings initiated by the patient or doctor for case-specific reasons.[10]

PSA, which is a glycoprotein, is a unique multipurpose biomarker used in screening, diagnosis, and staging, as well as monitoring of disease progression and treatment efficacy. Several variations of PSA are currently used in the clinical setting including PSA density (related to prostate volume), PSA kinetics (PSA levels as a function over time), and the ratio of free PSA over total PSA.

Current Danish guidelines recommend PSA testing for early detection in men presenting with symptoms and in men with risk of hereditary PC, but are against systematic population screening and PSA testing in asymptomatic men.[11] Current age-stratified cutoff levels for PSA values tested in Denmark are summarized in Table 1 and pros and cons of PSA testing are summarized in Table 2.[11]

Clinical Diagnosis

In Denmark, the diagnostic strategy for PC can be categorized into three phases: the prehospital phase, the National Cancer Pathway ("kræftpakkeforløb") and the hospital phase, with each phase reflecting differing levels of diagnostic intensity.[12] The ideal diagnostic strategy aims to provide personalized care that matches the individual patient's needs and preferences.

The current clinical tools and modalities for diagnosis of PC include digital rectal examination (DRE), PSA measurement, imaging in the form of transrectal ultrasound-guided scan (TRUS) with a minimum of 10 prostate biopsies and multiparametric magnetic resonance imaging scan (mpMRI). PC is clinically suspected following a positive DRE and elevated PSA levels after opportunistic screening. The definitive diagnosis is made after biopsy and histologic verification, although a few postmortem PC diagnoses in Denmark are based on disease history alone (ie, without histologic verification).

(1) *DRE*: Abnormal DRE findings are a string indication for PC biopsy. DRE has a positive predictive value ranging between 5% and 30% and an abnormal DRE is associated with positive diagnosis of PC in 18% and risk of higher Gleason score.[13,14]

(2) *PSA*: PSA screening debate aside, the use of PSA as a biomarker has "revolutionized" PC diagnosis. Methods for measuring PSA and PSA cutoff levels vary around the world, but PSA's universal feature is that higher levels of PSA indicate presence of PC disease activity. This feature makes PSA useful in both diagnosis as well as monitoring for disease progression and response to treatment. Although there are no natural standard or cutoff level for PSA, several nomograms combining PSA and other clinical characteristics have been developed to risk stratify PC patients. Also, several types of PSA measurements can be used including, serum PSA, PSA density, PSA kinetics (ie, PSA velocity and doubling time), free or total PSA ratio, Prostate Health Index test, and the PCA3 marker.

(3) *Prostate biopsy*: Ultrasound-guided biopsy is the standard method for PC biopsies in Denmark. Most PC tumors lies in the peripheral zone and are biopsied using a transrectal, ultrasound-guided approach with a minimum of 10 core biopsies. In the event of continued suspected PC, despite benign biopsies (eg, atypical small acinar proliferation), re-biopsy is indicated and preferably preceded with an mpMRI scan. Appropriate antibiotic coverage (ie, quinolones) is important to prevent postbiopsy infection and low dose anticoagulation (ie, aspirin) is not a contraindication for biopsy because of the risk of bleeding. The main complications from biopsies are summarized in Table 3 (adapted from the European Association of Urology [EAU] guidelines).[15]

Table 3 Complications Associated with PC Biopsy[15]

Complications	Percentage of Patients (%)
Haematospermia	37
Hematuria	15
Rectal bleeding	2
Prostatitis	1.0
Fever	0.8
Epididymitis	0.7
Rectal bleeding	0.7
Urinary retention	0.2
Other complications requiring hospitalization	0.3

Table 2 Pros and Cons of PSA Testing

Pros	Cons
Reassures patient, if PSA level is normal.	False positive/false negative results.
Potential to diagnose PC at early stage, with the possibility of curative treatment.	PSA testing is unable to differentiate between aggressive PC and nonaggressive PC.
Prevention of symptoms and cancer-specific death given timely treatment and cancer care.	TRUS biopsy is unpleasant for the patient and is associated with risk of infection and bleeding.
	Risk of overtreatment, unnecessary side effects, and pathologization.