Male Reproductive Cancers
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Editors

Male Reproductive Cancers

Epidemiology, Pathology and Genetics
Contents

Part A Epidemiology

1 The Epidemiology of Prostate Cancer .................................................... 3
Graham Giles

2 The Epidemiology of Testicular Cancer .................................................. 51
Katherine A. McGlynn and Michael B. Cook

Part B Pathology

3 Prostate Cancer: A Pathological Perspective ......................................... 87
Louis R. Bégin and Tarek A. Bismar

4 Testicular Tumor Pathology ..................................................................... 121
Kirk J. Wojno and Louis R. Bégin

Part C Molecular Genetics

5 Somatic Molecular Genetics of Prostate Cancer .................................... 143
Laure Humbert and Mario Chevrette

6 Molecular Genetics of Testicular Germ Cell Tumor .............................. 181
Katherine L. Nathanson

Part D Inherited Susceptibility

7 Identification of Genetic Risk Factors for Prostate Cancer:
Analytic Approaches Using Hereditary Prostate Cancer Families
......................................................................................................................... 203
Ethan M. Lange
8  The Identification of Rare and Common Variants Which Predispose to Prostate Cancer .................................................. 229
Rosalind A. Eeles, Zsofia Kote-Jarai, Michelle Guy, and Douglas Easton

9  Prostate Cancer in Special Populations ........................................... 249
Introduction by William D. Foulkes. With contributions from
William D. Foulkes, Julius Gudmundsson, Kári Stefánsson,
Cezary Cybulski, Jan Lubinski, Sabrina Notte,
Agnes B. Baffoe-Bonnie and Isaac J. Powell

10 Inherited Susceptibility of Aggressive Prostate Cancer .................. 289
Audrey H. Schnell and John S. Witte

11 Susceptibility Alleles for Testicular Germ Cell Tumor ..................... 317
Elizabeth A. Rapley

Summary and Future Directions ....................................................... 337

Index .................................................................................................. 339
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Introduction

The aim of this book is to present a thoughtful, comprehensive, and up-to-date overview of the etiology of two of the most important sites of cancer in the male reproductive tract, namely the prostate gland and the testes. Whereas the clinical presentations and treatment of these two cancers are very different, both cancers have been the focus of a tremendous amount of research over the past several decades. Here, we present reviews that summarize much of this research taking place in the three most important etiological disciplines – epidemiology, pathology, and genetics.

Testicular cancer is relatively uncommon with approximately 8,000 new cases expected in the USA in 2009. The disease is most commonly diagnosed in young men between the ages of 15 and 40 years and typically presents as a mass or enlargement of the testicle. Testicular cancer is more common in men of European descent and less common in African and Asian populations. Clinically, the most striking feature of testicular cancer is the ability to cure men with wide-spread metastatic disease using standard chemotherapy regimens which include cisplatinum and also radiation therapy in some cases.

In contrast, prostate cancer is a disease of advancing age which often presents with changes in urinary function as well as signs and symptoms related to metastatic disease including bone pain, weight loss, and fatigue. In the early 1990s, it was proposed that serum testing for prostate specific antigen or PSA could be utilized in combination with digital rectal examination to detect early asymptomatic cases of prostate cancer. This has led to many studies conducted throughout the world to determine whether early detection and treatment of this common cancer results in improved survival. While these studies are ongoing, many groups have developed varying recommendations with regard to use of strategies for early detection of prostate cancer. Populations that support testing asymptomatic men for prostate cancer generally have more early onset cases, as well as higher rates of localized disease at presentation. Whether or not death rates are concomitantly reduced at population levels will await the results of large randomized trials being conducted currently in the USA and Europe. Like testicular cancer, there are marked geographic and racial differences in prostate cancer incidence throughout the world. African Americans have the highest incidence of prostate cancer in the world while Asian populations generally have a reduced incidence.
Although prostate cancer and testicular cancer have very different clinical presentations and epidemiology, family history is a recognized risk factor for both diseases. This has led to the collection of families with multiple cases of prostate or testicular cancer for use in genetic studies. While the search for definitive high penetrance genes that may serve as susceptibility loci is ongoing, such genes are unlikely to account for more than a very small fraction of all prostate or testicular cancer. Perhaps due to the paucity of highly penetrant alleles, new leads have come from genome-wide association studies. There has also been an explosion of laboratory and bioinformatics approaches that have been applied to tumor tissues resulting in novel observations such as the identification of common gene fusion transcripts in prostate cancer tissue. These innovative strategies can be used to complement ongoing genetic linkage studies to shed additional light onto the molecular basis of cancers of the male reproductive system.

This book is comprised of four distinct parts: Epidemiology, Pathology, Molecular Genetics, and Inherited Susceptibility. Within each section, the chapters are divided by disease. Part A of this book reviews the epidemiology of prostate cancer followed by testicular cancer with an emphasis on clinical and environmental factors associated with these diseases. Part B begins with a describing the various pathological features of prostate cancer that may explain some of the clinical heterogeneity of the disease. This is followed by a complete description of the wide variety of testicular cancers from seminoma to lymphoma as well as a brief section on the use of tumor markers for monitoring disease. Part C focuses on somatic genetic changes in prostate and testicular cancers using new technologies such as comparative genomic hybridization and gene expression profiling. The last section of the book Part D concentrates on the progress made toward understanding inherited susceptibility to prostate cancer and to testicular cancer. The chapters on prostate cancer begin with a comprehensive review of genetic linkage and association studies and their use in identifying susceptibility loci for common diseases such as cancer. This is followed by a review of the special issues relating to studying prostate cancer in specific, unique populations including Icelandic, Polish, Ashkenazi Jewish, and African American men. The chapters on prostate cancer are concluded with a review of approaches used to identify genetic loci that predispose to aggressive forms of prostate cancer. The final chapter focuses on linkage and association studies used to identify testicular cancer susceptibility genes.

Despite the many successes in genetic research over the past several decades, the molecular basis for many common cancers remains elusive. Although it is clear that family history is an important risk factor for both prostate and testicular cancer, it has been difficult to use family based studies to identify susceptibility loci. It is important to consider that what we call “prostate cancer” or “testicular cancer” is likely a group of diseases that may be characterized by a unique set of genetic changes. For example, it has been demonstrated that there are multiple types of breast cancer characterized by unique “intrinsic” patterns of gene expression, categorizing breast cancers into basal, luminal, HER2 positive tumors. Teams of clinicians, pathologists, and researchers must work closely together to unravel the complex nature of prostate and testicular cancer using advanced technologies and
bioinformatics approaches. The resulting potential gain in the understanding of cancer phenotypes as well as the genetic factors that predispose to these cancers has many positive outcomes. Ideally, the most penetrant genes could be used individually to create laboratory tests to characterize cancer risk, and combinations of less penetrant genes could perhaps be pooled to perform a similar function. More importantly, characterization of the key molecular changes in cancer can lead to specific therapies which may target these changes (e.g., the development of the monoclonal antibody trastuzumab for use in treating breast cancers that are express HER2). In addition to a highly collaborative environment, this type of research will necessitate large tissue repositories and clinical registries so that laboratory findings can be quickly translated into clinical practice. International studies will also be required since the epidemiology of both prostate and testicular cancer demonstrates geographical and ethnic differences in incidence and mortality. The future of cancer research will be bright if we continue to support and reward scientists and clinicians for developing successful, large-scale collaborations to unravel the molecular basis for male reproductive cancers.

In this book, we have provided a view of the current state of knowledge regarding testicular cancer and prostate cancer. By broadly covering the epidemiology, pathology, and genetic aspects of these male reproductive cancers, we hope that the reader will be able to begin to consider how information in these three distinct disciplines will coalesce and improve our understanding of these potentially lethal cancers.

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Part A
Epidemiology
1.1 Introduction

Prostate cancer presents several enduring challenges that continue to defy solution despite extensive research. It has long been known that prostate tumours become increasingly prevalent with age, so much so that their occurrence could be viewed as part of the normal ageing process, as the vast majority of men will develop them if they live long enough (Giles 2003). Importantly, the preponderance of prostate tumours is of low metastatic potential and of slow growth so, although the majority of older men zealously investigated will be found to have microscopically detectable tumours, most men will die with a prostate tumour rather than from one (Bostwick et al. 2004).

In a minority of cases prostate tumours become invasive and potentially lethal. The conundrum here, elegantly articulated by Boccon-Gibod (1996), is how to distinguish “tigers” from “pussycats”; i.e. how to identify at a curable stage the minority of lethal cancers from the majority of non-aggressive tumours. Answers to this question remain elusive. Schnell and Witte (this volume) focus on inherited aspects of susceptibility to aggressive prostate cancer.

Since the late 1980s in many countries the increasingly widespread use of the prostate-specific antigen (PSA) test to screen asymptomatic men for prostate cancer has profoundly altered the definition, diagnosis and treatment of what we know as prostate cancer (Giles 2003). Our inability on the one hand to accurately identify the potentially lethal prostate tumour phenotype(s), and our increasing ability on the other hand to detect what were historically termed “latent” tumours (Yatani et al. 1982), has considerable implications not only for the diagnosis and treatment of prostate cancer but also for research at every level from molecular biology and genetics through to epidemiology and public health (Platz et al. 2004a).
1.1.1 Prostate Structure and Function

To better understand some of the problems confronting research on prostate cancer requires some understanding of the prostate’s development, structure, and function. The gland is located at the base of the pelvis beneath the urinary bladder and surrounds the urethra. It is said to resemble a walnut and is contained within a fibrous inelastic capsule. The embryonic prostate remains quiescent from birth until puberty during which time it grows under the influence of testosterone to reach its adult weight of 20 g at around 20 years of age (Aumuller 1991). At maturity the prostate has between 30 and 50 branched ducts that are lined with glandular epithelium and which open into the prostatic urethra.

The prostate contributes up to 30% of the volume of semen with its slightly alkaline secretions that contain a number of molecules including prostaglandins, proteolytic enzymes, acid phosphatase, zinc, and citric acid. During sexual arousal, the prostatic secretions are mixed with those (including sperm) from the seminal vesicles to form seminal fluid. The role of the prostatic secretions is to assist in maintaining sperm viability after ejaculation and during transit through the relatively hostile environment of the female reproductive tract (Isaacs 1983).

It was not until the 1980s that McNeal first described the prostate’s zonal anatomy (McNeal 1981) and showed the gland to have four distinct anatomical zones. The dorsal aspect, which is accessible via digital rectal examination, is called the peripheral zone and contains about 70% of total volume and 60 to 70% of tumours. The central zone, which includes the ejaculatory ducts, contains 25% of the gland’s total volume and is where inflammatory processes such as prostatitis occur. The transitional zone contains only 5% of the gland’s volume and 25% of tumours. The anterior zone is fibromuscular and assists in ejaculation.

Full details of the anatomy and pathology of the prostate gland are provided by Bégin and Bismar in their chapter in this volume.

Throughout life the health of the prostate is a balance between cellular proliferation and differentiation and apoptosis. The prostate’s development and continued maintenance is strongly influenced by endogenous hormones, particularly androgens but also oestrogens. The action of androgens on the prostate is mediated by the androgen receptor which has a far greater affinity for dihydrotestosterone than for testosterone. Testosterone is converted to dihydrotestosterone by 5 alpha reductase, particularly by the type 2 isoenzyme, and men born with a congenital deficiency of 5 alpha reductase do not develop a normal prostate and are, thus, at low risk of prostate cancer (Randall 1994). Paradoxically, prostate cancer incidence increases contemporaneously with the fall in men’s circulating testosterone levels with age. Androgens alone, however, do not explain the full complexity of control mechanisms in the prostate. The proliferative action of androgens (testosterone and dihydrotestosterone) is balanced by other molecules including adrenal androgens (Bosland 2006), oestrogens (Bosland 2005), insulin-like growth factors (IGFs) (Wu et al. 2006a, b; Kambhampati et al. 2005), insulin (Schiell et al. 2006), leptin (Ribeiro et al. 2006) and vitamin D (Weigel 2007). These agents and their complex
interactions, especially with the androgen receptor, are not fully understood and continue to attract considerable research interest.

### 1.1.2 Aspects of Prostate Pathology Relevant to Cancer Epidemiology

As the male’s hormonal milieu changes from middle age onwards, the prostate commonly tends to grow in volume, a condition termed benign prostatic hyperplasia (BPH) (Hafez and Hafez 2004). BPH was once considered a risk factor for prostate cancer but this view is no longer held; both BPH and tumours commonly occur in ageing prostates. Due to the inelasticity of the prostate’s fibrous outer capsule, in the presence of BPH increasing pressure is placed on the prostatic urethra, producing a range of lower urinary tract symptoms including reduced stream, increased frequency especially at night, increased urgency, incomplete voiding and increased risk of urinary tract infections. Depending on severity and inconvenience, lower urinary tract symptoms bring men to medical attention, and it is in this context that cancer is often incidentally diagnosed (McVary 2006). Transurethral resection of the prostate has commonly been performed to relieve obstructive symptoms of BPH, and a small proportion of prostate tumours are found incidentally on pathological examination of tissue fragments removed during this procedure leading to a degree of over-diagnosis (Bostwick and Chang 1999). As the management of BPH has increasingly become a pharmaceutical rather than a primarily surgical intervention and with the increased use of PSA for cancer early detection, this mode of prostate tumour diagnosis is diminishing.

Prostatic tumours are virtually all adenocarcinomas that arise from the glandular epithelium which lines the prostatic ducts. As described earlier, prostate tumours commonly occur in the peripheral zone of the gland and also tend to be multi-focal with different foci within the same gland often differing in size and morphology. Much research has been spent on identifying tumour markers that would separate the lethal from the indolent tumour phenotypes, but this is still beyond our ability (van Leenders 2007). Currently, a tumour’s potential lethality is assessed on the circulating level of PSA in the blood, evidence of spread beyond the capsule and histopathological assessment of needle biopsy cores to estimate tumour volume and grade (Presti 2007).

Prostate tumour aggressiveness is commonly assessed according to the method proposed by Dr. Donald Gleason (Gleason 1992). Using this method, the two largest tumour foci (primary and secondary patterns) are each graded from 1 to 5 according to the histological patterns described by Gleason. The Gleason grades for the two foci, that are rarely more than one grade apart, are added to give a Gleason sum (or score) from 2 to 10. Tumours with Gleason sums below 5 are not considered aggressive. Historically, those tumours with Gleason sums 5 to 7 were considered to be of moderate grade, but in the most recent edition of the TNM Classification of Malignant Tumours (UICC 2002) Gleason sum 7 was added to the poorly
differentiated and undifferentiated grade category, formerly Gleason sum 8 to 10. The significance of Gleason sum 7 tumours remains controversial, especially with respect to decisions about treatment. About 30% of cases with a Gleason score sum of 7 have a primary pattern of grade 4 and are considered to be more aggressive than cases having a primary pattern of grade 3. Some consider that any focus of Gleason grade 4 warrants increased clinical suspicion, and this thinking has extended to include any tertiary pattern of grade 5 (Patel et al. 2007). Whatever the clinical importance of these changes, their adoption in epidemiological studies to classify tumours as aggressive/advanced inflates the proportion of cases, so described, and can perturb a study’s capacity to detect associations (Platz et al. 2004a). For further information, see additional discussion about the Gleason Grading System in the chapter by Bégin and Bismar.

1.1.3 Prostate Cancer Diagnosis, Screening and Treatment

Prostate cancer has no specific symptoms. In the past, it most commonly presented as was as advanced disease. The diagnosis of prostate cancer is often made during an assessment of symptoms caused by BPH. During diagnostic work up, the prostate’s size and the presence of any nodules are assessed by digital rectal examination and ultrasound. The diagnosis of cancer is aided by measuring serum levels of PSA, a protease enzyme produced by the glandular epithelium, some of which permeates into the bloodstream. PSA was originally used clinically to monitor cancer progression after treatment (Kuriyama et al. 1981) but is now commonly used for early detection (Stamey et al. 1987). High serum PSA levels typically indicate the presence of malignancy, but investigations prompted at lower PSA levels lead to the over-diagnosis of many tumours that would probably never have progressed to clinically significant disease during life (Albertsen 2005).

Suspiciously elevated PSA levels are followed up with transrectal-ultrasound-guided, needle biopsies to establish a histopathological diagnosis. Prostate tumours are commonly small and multi-focal, and there is an element of chance in whether the presence of tumour(s) can be adequately sampled by needle biopsy. To reduce the possibility of missing a tumour, the number of needle biopsies taken has increased over time (Shinohara 2006) and the PSA level used as a threshold for biopsy has fallen, especially in the USA (Catalona et al. 2006).

Recognising that PSA testing lacks both specificity and sensitivity, many modifications have been considered to lead to a better cancer test. For example, the PSA molecule is often bound to other serum proteins including protease inhibitors and can be measured in a free or a complexed form. Investigators have noted that there is a lower free/total PSA measurement in men with prostate cancer, and free/total PSA testing has been advocated in the clinical setting in which the total PSA is in the 2.0 to 10 ng/mL range (Hoffman et al. 2000). Others have investigated using age-specific reference ranges and PSA density (PSA/gland volume) and PSA velocity. To date, none of these modifications are in widespread clinical use.
PSA testing for early prostate cancer is performed on a widespread ad hoc basis in many countries. Randomised clinical trials conducted currently are designed to test the efficacy of PSA testing in reducing prostate cancer mortality (Schroder 1994; Gohagan et al. 1994). Because many controls in these trials receive PSA tests as part of their community care, the statistical power of the trials to provide definitive evidence of efficacy has been reduced and this may lengthen them by some years (Beemsterboer et al. 2000).

The WHO has adopted several criteria by which to judge the suitability of a screening program (Wilson and Jungner 1968): the condition considered for screening should be important one, there should be an acceptable treatment for patients with the disease, facilities for diagnosis and treatment should be available, there should be a recognised latent or early symptomatic stage, there should be a suitable test or examination which has few false positives (high specificity) and few false negatives (high sensitivity), the test or examination should be acceptable to the population, the cost, including diagnosis and subsequent treatment, should be economically balanced in relation to expenditure on medical care as a whole. Importantly, the outcome should be measured in terms of mortality reduction rather than improved survival. Prostate cancer screening by PSA testing currently fails to satisfy all these criteria (Denis 1995; Albertsen 1996).

Given the uncertainties that surround its biological heterogeneity and limited evidence of treatment benefits, prostate cancer management is complex (Ali and Hamdy 2007). Men with low-grade, localised cancer and low PSA may opt for watchful waiting with regular repeat PSA tests to monitor the rate of change, PSA velocity. Once PSA velocity reaches a certain rate, decisions may be made with respect to treatment (Lee and D’Amico 2005). Treatments for localised disease include surgery (radical prostatectomy usually with pelvic lymphadenectomy) or external beam radiation therapy. There is also some early success using radioactive seeds implantation to deliver localised radiation (brachytherapy) for men with small and lower-grade tumours (Heysek 2007). Advanced disease is treated by androgen deprivation/blockade which can involve surgical or medical castration. Hormonal therapy is non-curative, and castrate-resistant prostate cancer is typically treated with chemotherapy. External beam radiation may also be used to treat symptomatic bony metastases in the setting of advanced disease.

The principal concern with contemporary approaches to the detection of prostate cancer is over-diagnosis and the considerable effects on quality of life for a substantial proportion of men who are treated unnecessarily (Albertsen 1996; Albertsen et al. 2005). The costs include treatment-related side effects such as impotence, incontinence, and damage to the rectum and bladder neck, and these detriments have to be weighed against the limited evidence of benefit. There are a number of clinical trials that are ongoing in which men with newly diagnosed prostate cancer are randomised to observation or treatment with one of several modalities (e.g. radical prostatectomy or external beam radiation.) These studies are being conducted in different countries with different methods of cancer detection (PSA vs. clinical symptoms) and should begin to provide data to support evidenced-based approaches for detecting and treating prostate cancer (Bill-Axelson et al. 2008; Wilt 2008).