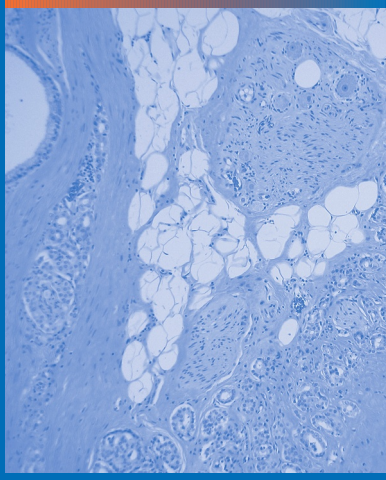
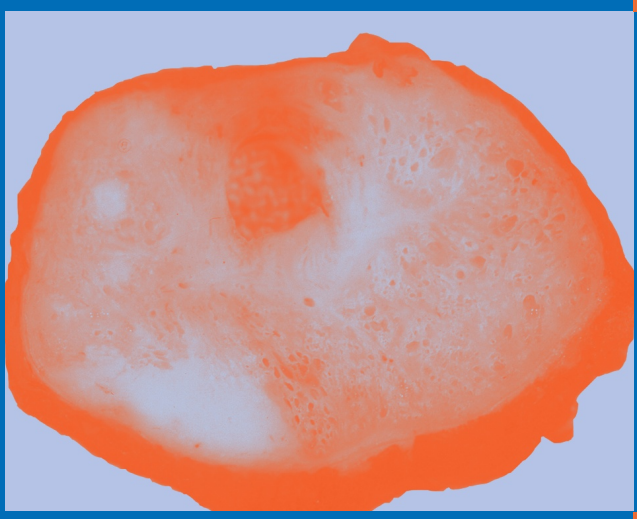
Cancer Genetics



William D. Foulkes
Kathleen A. Cooney
Editors

Male Reproductive Cancers

Epidemiology, Pathology and Genetics



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Male Reproductive Cancers

Cancer Genetics

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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 the 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.

Kathleen A. Cooney, MD
William D. Foulkes, MB, PhD

Part A
Epidemiology

Chapter 1
The Epidemiology of Prostate Cancer

Graham Giles

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).

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