Chapter 57
What is prostate cancer? How is it diagnosed? What is its prevalence?

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Prostate cancer is the most common solid malignancy in men, estimated to affect two million American men at present (cdc.gov); moreover, more than 200,000 men are expected to be diagnosed with prostate cancer in the year 2023 (cancer.org). The prostate is centrally important to male reproductive and sexual function and prostate care drives a significant percentage of visits to the urologist annually. Urologists, and especially andrologists, are behooved to have a thorough understanding of both the prostate itself, its function, and its capacity to become cancerous.

The growth and development of the functioning prostate depends on testosterone (T) and its metabolite dihydrotestosterone (DHT). These two hormones enable the growth and proliferation of the glandular component of the prostate through binding and activation of androgen receptor (AR) expressed by prostatic epithelial cells (Chapter 3). Research has established that the activation of this receptor enables both benign prostatic hyperplasia (BPH, Chapter 56) and carcinogenesis within prostatic epithelial cells leading to prostate cancer (PCa). Both diseases are common and burdensome conditions in aging men (Chapter 52). However, the relationship between testosterone and these two conditions is unclear; the simple observation that hypogonadism (low T), BPH, and PCa are all age-related conditions reinforces this confusion.

In this chapter, we review the existing data regarding these relationships. Pharmacologic treatments for prostate cancer depends upon manipulation of these pathways; we will review these treatments, as well as outline future directions for treatment that are being explored.

Androgen Physiology and Prostate Carcinogenesis

The data regarding the relationship between testosterone and prostate cancer are numerous and varied in terms of their implications.

However, one aspect of this complex relationship is well illustrated in the studies examining 5α-reductase (5-ar) inhibitors.

Two large, prospective, randomized, placebo controlled trials were done examining the relationship between chronic 5-ar inhibitor usage and prostate cancer incidence: The REDUCE trial and the Prostate Cancer Prevention Trial (PCPT). Both studies demonstrated an approximate 30% risk reduction in the development of prostate cancer over the ten year window of the study. Some initial concern regarding slight increases in high risk cancers in the treatment arms of both studies was dismissed initially as being most likely due to detection bias (as opposed to treatment effect); the long term follow-up of the PCPT, published in 2013, supported this theory, at least in so far as disease specific mortality in the treatment arm was far less than in the placebo arm (thereby implying no meaningful increase in high risk, clinically significant cancers with 5-ar inhibitor use).

The conclusion reached therefore, is that a) DHT levels can in part drive prostate carcinogenesis and that b) decreasing these levels, in addition to preventing prostate enlargement, can prevent prostate cancer. The corresponding question of whether T levels themselves influence prostate cancer risk remains unanswered. Numerous data exist regarding this specific question; they point to different conclusions. Some studies implicate low T levels as conferring a higher likelihood of high risk prostate cancer, implying that more than one pathway for prostate carcinogenesis might exist. The data regarding management of metastatic prostate cancer through chemical castration further supports the relationship between testosterone levels and prostate cancer progression.

Regardless, given that low T levels should correlate to low DHT levels, one would think that the observations from the above trials would hold and that hypogonadal patients would be less likely to develop any kind of prostate cancer. Instead, the common epidemiological observation that both prostate cancer and low T are diseases of aging men confounds this picture. A man in his 80s is far more likely to have both low testosterone and prostate cancer than he was in his 20s. Whether or not this observation is correlative but not causal remains to be proved. Certainly, given the common and burdensome nature of both problems, further study is warranted.

Diagnosis and Treatment of Prostate Cancer

For many years, the diagnostic algorithm for patients suspected of having prostate cancer involved PSA (prostate specific antigen) testing followed by transrectal ultrasound guided prostate biopsy in patients with PSA abnormality. There have been numerous improvements upon this algorithm; first, many of the large studies evaluating prostate size depend upon transrectal ultrasound for measurement of prostate volume. This is a highly variable modality; inexact measurements can be obtained for any number of reasons including operator variability and patient discomfort. Second, prostate cancer incidence in both the REDUCE and PCPT trials was determined using transrectal ultrasound guided prostate needle biopsy. This modality is also inexact. Numerous data show clearly that both prostate volume measurement and prostate cancer detection are improved upon with utilization of multiparametric MRI of the prostate. Follow up studies incorporating MRI as a means of following prostate volume change and development of prostate cancer might help illuminate the true effect of testosterone and DHT within the prostate. Biopsy of the prostate – whether ultrasound or MRI guided – results in a pathologic Gleason score (sum of two numbers 1-5; e.g. Gleason 3+4, with higher numbers characterizing further de-differentiation and increased aggressiveness); more recently Gleason scores have been simplified into Gleason grade groups 1-5 again with a higher number indicating a more aggressive cancer.

Better diagnostic accuracy has enabled more accurate characterization of low, intermediate, and high risk prostate cancers. This has in turn enabled some significant fraction of patients to safely embark on active surveillance of their prostate cancer (observation without definitive treatment, thereby precluding side effects associated with standard treatments). The gold standard treatments of surgery (radical prostatectomy, either open or robotic assisted) or radiation (including external beam radiation, brachytherapy, stereotactic targeted beam, and proton therapy) have been joined by focal treatments designed to treat the cancer and leave the remainder of the prostate unaffected. Modalities enabling focal treatment of prostate cancer include cryotherapy, high intensity focused ultrasound, and steam/vaportherapy. These treatment options are made possible again only by localization of prostate cancer as enabled by MRI of the prostate.

Future Directions

Assays of T and DHT represent a source of variability as well; both measurements are subject to diurnal variability – testosterone levels to a greater degree - and this introduces a further source of inaccuracy to the existing data. "Who is the truly hypogonadal patient?" is a question that first needs to be answered before figuring out whether or not he is at increased or lesser risk of prostate cancer. Assays of AR function at the cellular level including the upregulation of downstream genetic targets of activated AR could represent a future means to more accurately distinguish hypogonadal from eugonadal patients.

Lastly, data from another study published in 2015 by Finkelstein et al neatly illustrated that our understanding of hypogonadism as a disease driven only by T levels is incomplete. Patients enrolled in this study were eugonadal; they were initially treated with a gonadotropin releasing hormone receptor agonist (leuprolide) which subsequently resulted in castrate levels of testosterone. They were then given varying degrees of testosterone replacement; some were replaced to therapeutic levels, some to sub- or supra-therapeutic levels. They were also randomized to treatment with an aromatase inhibitor (anastrozole) or a placebo; blockade of aromatization in the treatment arm resulted in absent levels of estrogen in these patients, this was in spite of normal or near normal testosterone levels. Unexpectedly, some patients in the treatment arm, again with normal testosterone levels and low estrogen levels, complained of symptoms that are normally attributed to low testosterone (central obesity, fatigue, low libido). This effect could only be explained by the inadequate levels of estrogen in these patients. Previously, no data existed that implicated estrogen levels in the male in any of these processes.

The idea that testosterone, DHT, and estrogen are all powerful hormones with effects on male physiology is incompletely understood. The relationship between these three hormones within the prostate and the possibility that different patients respond differently to these hormones at the cellular level (in much the same way that estrogen and progesterone have different cellular effects in some women versus others with regard to breast cancer) warrants further investigation.

Conclusions

The relationship between testosterone and prostate health is centrally important to men's health. Prostate growth, sexual and reproductive function, the risk of prostate cancer, and the likelihood of urinary symptoms related to prostate obstruction; all of these men's health issues are in some fashion related to testosterone. While the existing data is extensive and illuminates this many faceted relationship, our understanding of the pathways by which testosterone and the prostate influence each other is incomplete. Further research is certainly warranted given the central importance of prostate health to the male population.

Suggested reading

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