prostate is composed of branching tubuloalveolar glands arranged in lobules surrounded by fibromuscular stroma. The acinar unit includes an epithelial compartment made up of epithelial, basal, and neuroendocrine cells and separated by a basement membrane, and a stromal compartment that includes fibroblasts and smooth-muscle cells. Prostate-specific antigen (PSA) and prostatic acid phosphatase (PAP) are produced in the epithelial cells. Both prostate epithelial cells and stromal cells express androgen receptors (ARs) and depend on androgens for growth. Testosterone, the major circulating androgen, is converted by the enzyme 5α-reductase to dihydrotestosterone in the gland.

The periurethral portion of the gland increases in size during puberty and after the age of 55 years due to the growth of nonmalignant cells in the transition zone of the prostate that surrounds the urethra. Most cancers develop in the peripheral zone, and cancers in this location may be palpated during a digital rectal examination (DRE).

PROSTATE CANCER

In 2013, approximately 238,590 prostate cancer cases were diagnosed, and 29,720 men died from prostate cancer in the United States. The absolute number of prostate cancer deaths has decreased in the past 5 years, which has been attributed by some to the widespread use of PSA-based detection strategies. However, the benefit of screening on survival is unclear. The paradox of management is that although 1 in 6 men will eventually be diagnosed with the disease, and the disease remains the second leading cause of cancer deaths in men, only 1 man in 30 with prostate cancer will die of his disease.

EPIDEMIOLOGY

Epidemiologic studies show that the risk of being diagnosed with prostate cancer increases by a factor of two if one first-degree relative is affected and by four if two or more are affected. Current estimates are that 40% of early-onset and 5–10% of all prostate cancers are hereditary. Prostate cancer affects ethnic groups differently. Matched for age, African-American males have both a higher incidence of prostate cancer and larger tumors and more worrisome histologic features than white males. Polymorphic variants of the AR, the cytochrome P450 C17, and the steroid 5α-reductase type II (SRD5A2) genes have been implicated in the variations in incidence.

The prevalence of autopsy-detected cancers is similar around the world, while the incidence of clinical disease varies. Thus, environmental and dietary factors may play a role in prostate cancer growth and progression. High consumption of dietary fats, such as α-linoleic acid or the polycyclic aromatic hydrocarbons that form when red meats are cooked, is believed to increase risk. Similar to breast cancer in Asian women, the risk of prostate cancer in Asian men increases when they move to Western environments. Protective factors include consumption of the isoflavonoid genistein (which inhibits 5α-reductase) found in many legumes, cruciferous vegetables that contain the isothiocyanate sulforaphane, retinoids such as lycopene found in tomatoes, and inhibitors of cholesterol biosynthesis (e.g., statin drugs). The development of prostate cancer is a multistep process. One early change is hypermethylation of the *GSTP1* gene promoter, which leads to loss of function of a gene that detoxifies carcinogens. The finding that many prostate cancers develop adjacent to a lesion termed proliferative inflammatory atrophy (PIA) suggests a role for inflammation.

PREVENTION

Currently no drugs or dietary supplements are approved by the U.S. Food and Drug Administration (FDA) for prevention of prostate cancer, nor are any recommended by the major clinical guidelines. Although statins may have some protective effect, the potential risks outweigh the benefits given the small number of men who die of prostate cancer. The results from several large, double-blind, randomized chemoprevention trials established 5α-reductase inhibitors (5ARI) as the most likely therapy to reduce the future risk of a prostate cancer diagnosis. The Prostate Cancer Prevention Trial (PCPT), in which men older than age 55 years received placebo or the 5ARI finasteride, which inhibits the type 1 isoform, showed a 25% (95% confidence interval 19–31%) reduction in the period prevalence of prostate cancer across all age groups in favor of finasteride (18.4%) over placebo (24.4%). In the Reduction by Dutasteride of Prostate Cancer Events (REDUCE) trial, a similar 23% reduction in the 4-year period prevalence was observed in favor of dutasteride ($p = .001$). Dutasteride inhibits both the type 1 and type 2 5ARI isoforms. While both studies met their endpoint, there was concern that most of the cancers that were prevented were low risk and that there was a slightly higher rate of clinically significant cancers (those with higher Gleason score) in the treatment arm. Neither drug was FDA-approved for prostate cancer prevention. In comparison, the Selenium and Vitamin E Cancer Prevention Trial (SELECT), which enrolled African-American men age ≥50 years and others age ≥55 years, showed no difference in cancer incidence in patients receiving vitamin E (4.6%) or selenium (4.9%) alone or in combination (4.6%) relative to placebo (4.4%). A similar lack of benefit for vitamin E, vitamin C, and selenium was seen in the Physicians Health Study II.

THE CLINICAL STATES MODEL

The prostate cancer continuum—from the appearance of a preneoplastic and invasive lesion localized to the prostate, to a metastatic lesion that results in symptoms and, ultimately, mortality—can span decades. To facilitate disease management, competing risks are considered in the context of a series of clinical states **(Fig. 115-1)**. The states are defined operationally on the basis of whether or not a cancer diagnosis has been established and, for those with a diagnosis, whether or not metastases are detectable on imaging studies and the measured level of testosterone in the blood. With this approach, an individual resides in only one state and remains in that state until he has progressed. At each assessment, the decision to offer treatment and the specific form of treatment are based on the risk posed by the cancer relative to competing causes of mortality that may be present in that individual. It follows that the more advanced the disease, the greater is the need for treatment.

For those without a cancer diagnosis, the decision to undergo testing to detect a cancer is based on the individual's estimated life expectancy and, separately, the probability that a clinically significant cancer may be present. For those with a prostate cancer diagnosis, the clinical states model considers the probability of developing symptoms or dying from prostate cancer. Thus, a patient with localized prostate cancer who has had all cancer removed surgically remains in the state of localized disease as long as the PSA remains undetectable. The time within a state becomes a measure of the efficacy of an intervention, although the effect may not be assessable for years. Because many men with active cancer are not at risk for metastases, symptoms, or death, the clinical states model allows a distinction between *cure*—the elimination of all cancer cells, the primary therapeutic objective when treating most cancers—and *cancer control*, in which the tempo of the illness is altered and symptoms are controlled until the patient dies of other causes. These can be equivalent therapeutically from a patient standpoint if the patient has not experienced symptoms of the disease or the treatment needed to control it. Even when a recurrence is documented, immediate therapy is not always necessary. Rather, as at the time of diagnosis, the need for intervention is based on the tempo of the illness as it unfolds in the individual, relative to the risk-to-benefit ratio of the therapy being considered.

SCREENING AND DIAGNOSIS

Physical Examination The need to pursue a diagnosis of prostate cancer is based on symptoms, an abnormal DRE, or, more typically, a change in or an elevated serum PSA. The urologic history should focus on symptoms of outlet obstruction, continence, potency, or change in ejaculatory pattern.

The DRE focuses on prostate size and consistency and abnormalities within or beyond the gland. Many cancers occur in the peripheral zone and may be palpated on DRE. Carcinomas are characteristically hard, nodular, and irregular, while induration may also be due to benign prostatic hypertrophy (BPH) or calculi. Overall, 20–25% of men with an abnormal DRE have cancer.