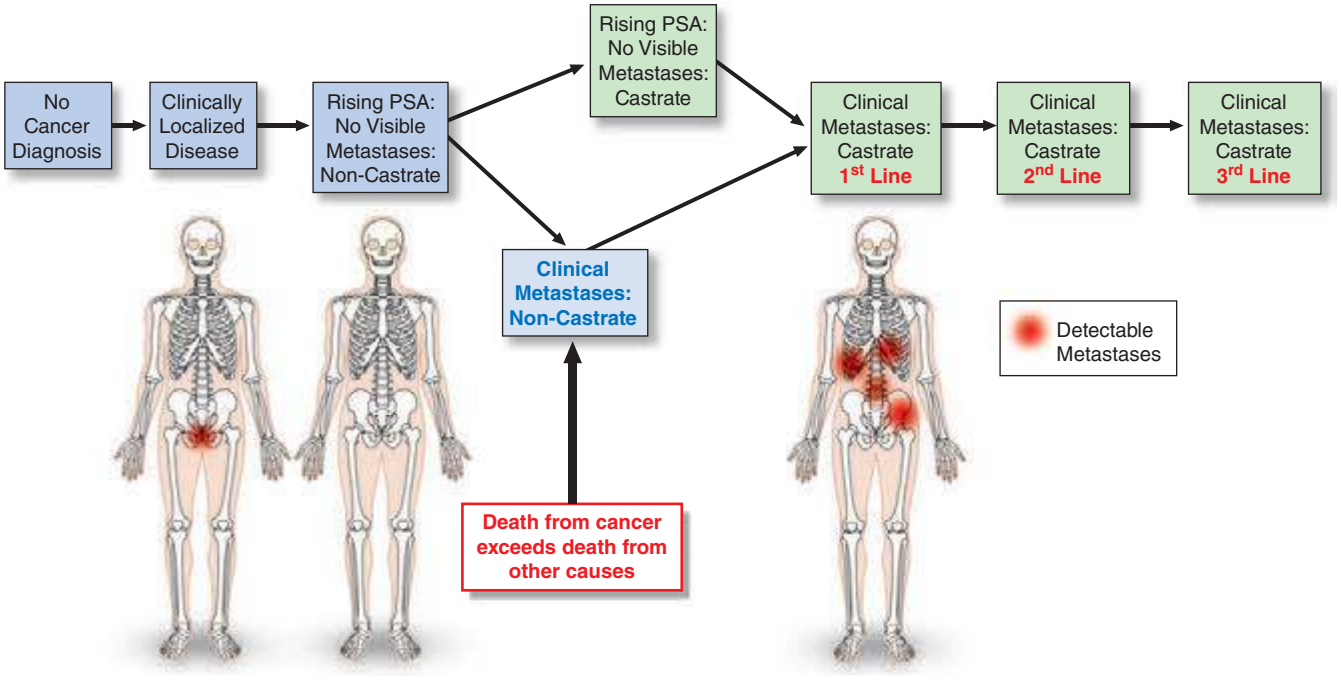

FIGURE 115-1 **Clinical states of prostate cancer.** PSA, prostate-specific antigen.

Prostate-Specific Antigen PSA (kallikrein-related peptidase 3; *KLK3*) is a kallikrein-related serine protease that causes liquefaction of seminal coagulum. It is produced by both nonmalignant and malignant epithelial cells and, as such, is prostate-specific, not prostate cancer–specific. Serum levels may also increase from prostatitis and BPH. Serum levels are not significantly affected by DRE, but the performance of a prostate biopsy can increase PSA levels up to tenfold for 8–10 weeks. PSA circulating in the blood is inactive and mainly occurs as a complex with the protease inhibitor α_1-antichymotrypsin and as free (unbound) PSA forms. The formation of complexes between PSA, α_2-macroglobulin, or other protease inhibitors is less significant. Free PSA is rapidly eliminated from the blood by glomerular filtration with an estimated half-life of 12–18 h. Elimination of PSA bound to α_1-antichymotrypsin is slow (estimated half-life of 1–2 weeks) because it too is largely cleared by the kidneys. Levels should be undetectable after about 6 weeks if the prostate has been removed. Immunohistochemical staining for PSA can be used to establish a prostate cancer diagnosis.

PSA-BASED SCREENING AND EARLY DETECTION PSA testing was approved by the U.S. FDA in 1994 for early detection of prostate cancer, and the widespread use of the test has played a significant role in the proportion of men diagnosed with early-stage cancers: more than 70–80% of newly diagnosed cancers are clinically organ-confined. The level of PSA in blood is strongly associated with the risk and outcome of prostate cancer. A single PSA measured at age 60 is associated (area under the curve [AUC] of 0.90) with lifetime risk of death from prostate cancer. Most prostate cancer deaths (90%) occur among men with PSA levels in the top quartile (>2 ng/mL), although only a minority of men with PSA >2 ng/mL will develop lethal prostate cancer. Despite this and mortality rate reductions reported from large randomized prostate cancer screening trials, routine use of the test remains controversial.

The U.S. Preventive Services Task Force (USPSTF) reviewed the evidence for screening for prostate cancer and made a clear recommendation against screening. By giving a grade of "D" in the recommendation statement that was based on this review, the USPSTF concluded that "there is moderate or high certainty that this service has no net benefit or that the harms outweigh the benefits." Whether the harms of screening, overdiagnosis, and overtreatment are justified by the benefits in terms of reduced prostate cancer mortality is open to reasonable doubt. In response to the USPSTF, the American Urological Association (AUA) updated their consensus statement regarding prostate cancer screening. They concluded that the quality of evidence for the benefits of screening was moderate, and evidence for harm was high for men age 55–69 years. For men outside this age range, evidence was lacking for benefit, but the harms of screening, including overdiagnosis and overtreatment, remained. The AUA recommends shared decision making considering PSA-based screening for men age 55–69, a target age group for whom benefits may outweigh harms. Outside this age range, PSA-based screening as a routine test was not recommended based on the available evidence. The entire guideline is available at *www.AUAnet.org/education/guidelines/prostate-cancer-detection.cfm*.

The PSA criteria used to recommend a diagnostic prostate biopsy have evolved over time. However, based on the commonly used cut point for prostate biopsy (a total PSA ≥4 ng/mL), most men with a PSA elevation do not have histologic evidence of prostate cancer at biopsy. In addition, many men with PSA levels below this cut point harbor cancer cells in their prostate. Information from the PCPT demonstrates that there is no PSA below which the risk of prostate cancer is zero. Thus, the PSA level establishes the likelihood that a man will harbor cancer if he undergoes a prostate biopsy. The goal is to increase the sensitivity of the test for younger men more likely to die of the disease and to reduce the frequency of detecting cancers of low malignant potential in elderly men more likely to die of other causes. Patients with symptomatic prostatitis should have a course of antibiotics before biopsy. However, the routine use of antibiotics in an asymptomatic man with an elevated PSA level is strongly discouraged.

Prostate Biopsy A diagnosis of cancer is established by an image-guided needle biopsy. Direct visualization by transrectal ultrasound (TRUS) or magnetic resonance imaging (MRI) assures that all areas of the gland are sampled. Contemporary schemas advise an extended-pattern 12-core biopsy that includes sampling from the peripheral zone as well as a lesion-directed palpable nodule or suspicious image-guided sampling. Men with an abnormal PSA and negative biopsy are advised to undergo a repeat biopsy.

BIOPSY PATHOLOGY Each core of the biopsy is examined for the presence of cancer, and the amount of cancer is quantified based on the length of the cancer within the core and the percentage of the core involved. Of the cancers identified, >95% are adenocarcinomas; the rest are squamous or transitional cell tumors or, rarely, carcinosarcomas. Metastases to the prostate are rare, but in some cases colon cancers or transitional cell tumors of the bladder invade the gland by direct extension.