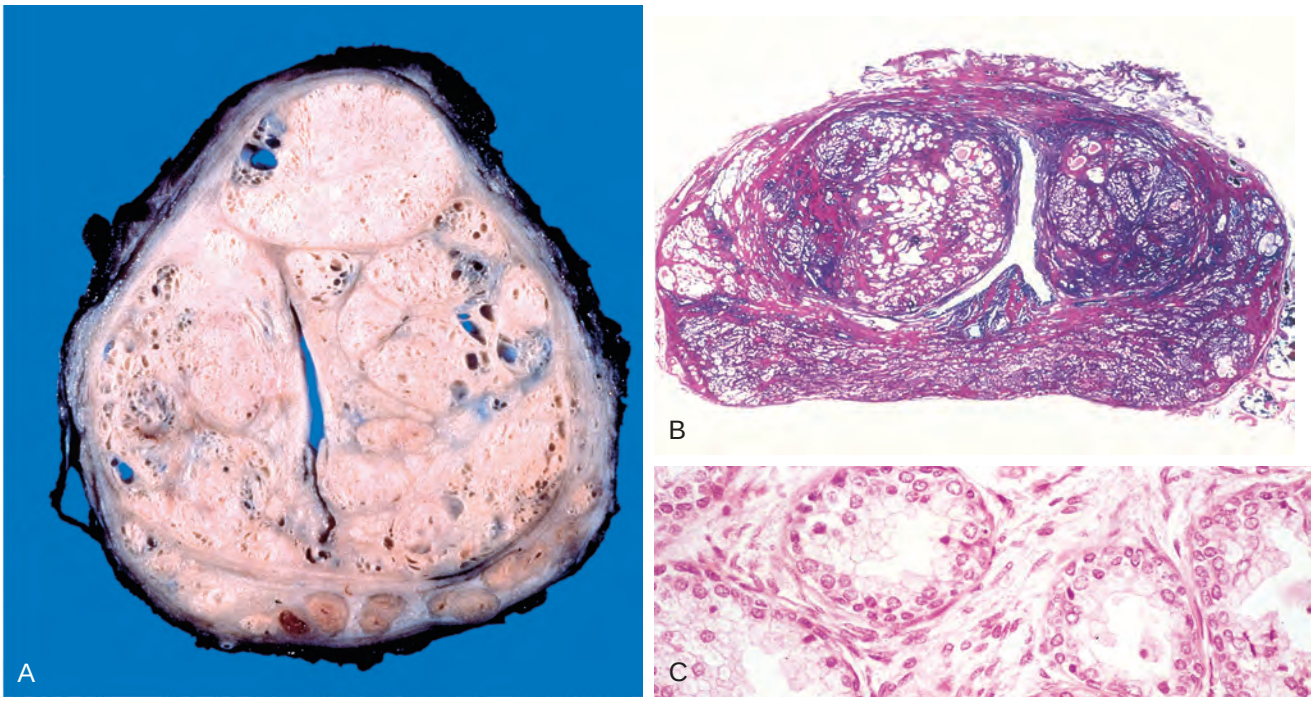

Figure 21-33 Nodular prostatic hyperplasia. **A,** Well-defined nodules of benign prostatic hypertrophy compress the urethra into a slitlike lumen. **B,** A microscopic view of a whole mount of the prostate shows nodules of hyperplastic glands on both sides of the urethra. **C,** Under high power the characteristic dual cell population: the inner columnar and outer flattened basal cell can be seen.

behaviors, from very aggressive lethal cancers to incidentally discovered clinically insignificant cancers.

Incidence. Cancer of the prostate is typically a disease of men older than age 50 years, in whom it is quite common. Based on autopsy studies, its incidence increases from 20% in men in their 50s to approximately 70% in men between the ages of 70 and 80 years. There are some remarkable and puzzling national and racial differences in the incidence of the disease. Prostatic cancer is uncommon in Asians and occurs most frequently among blacks. In addition to hereditary factors, environment plays a role, as evidenced by the rise in the incidence of the disease in Japanese immigrants to the United States, though not nearly to the level of that of native-born Americans. Also, as the diet in Asia becomes more westernized, the incidence of clinically significant prostate cancer in this region of the world seems to be increasing. Whether this is due to dietary factors or other lifestyle changes is not clear.

Etiology and Pathogenesis. Our knowledge of the causes of prostate cancer is far from complete. Several factors, including age, race, family history, hormone levels, and environmental influences are suspected to play a role. The increased incidence of this disease upon migration from a low-incidence region to one with a high incidence is consistent with a role for environmental influences. There are many candidate environmental factors, but none has been proven to be causative. For example, increased consumption of fats or carcinogens present in charred red meats has been implicated. Other dietary products suspected of preventing or delaying prostate cancer development include lycopenes (found in tomatoes), soy products, and vitamin D.

Androgens play an important role in prostate cancer. Like their normal counterparts, the growth and survival of prostate cancer cells depends on androgens, which bind to the androgen receptor (AR) and induce the expression of pro-growth and pro-survival genes. Of interest with respect to differences in prostate cancer risk among races, the X-linked AR gene contains a polymorphic sequence composed of repeats of the codon CAG (which codes for glutamine). Very large expansions of this stretch of CAGs cause a rare neurodegenerative disorder, Kennedy disease, characterized by muscle cramping and weakness. However, even in normal individuals, there is sufficient variation in the length of the CAG repeats to affect AR function. ARs with the shortest stretches of polyglutamine have the highest sensitivity to androgens. The shortest polyglutamine repeats on average are found in African Americans, while Caucasians have an intermediate length and Asians have the longest, paralleling the incidence and mortality of prostate cancer in these groups. More directly, the length of the repeats is inversely related to rate at which prostate cancer develops in mouse models.

The importance of androgens in maintaining the growth and survival of prostate cancer cells can be seen in the therapeutic effect of castration or treatment with antiandrogens, which usually induce disease regression. Unfortunately, most tumors eventually become resistant to androgen blockade. Tumors escape through a variety of mechanisms, including acquisition of hypersensitivity to low levels of androgen (e.g., through AR gene amplification); ligand-independent AR activation (e.g., via splice variants that lack the ligand binding domain); mutations in AR that allow it to be activated by non-androgen ligands; and other mutations or epigenetic changes that activate alternative signaling pathways, which may bypass the