need for AR altogether. Among the latter are changes that lead to increased activation of the PI3K/AKT signaling pathway (such loss of the *PTEN* tumor suppressor gene), which is observed most often in tumors that have become resistant to antiandrogen therapy.

There is much interest in the role of other inherited polymorphisms in the development of prostate cancer. Compared with men with no family history, men with one first-degree relative with prostate cancer have twice the risk and those with two first-degree relatives have five times the risk of developing prostate cancer. Men with a strong family history of prostate cancer also tend to develop the disease at an earlier age. Men with germline mutations of the tumor suppressor *BRCA*2 have a 20-fold increased risk of prostate cancer, and a germline mutation in *HOXB13*, a homeobox gene encoding a transcription factor that regulates prostatic development, also confers substantially increased risk in the small percentage of families that carry it. However, the vast majority of familial prostate cancers are due to variation in other loci that confer a small increase in cancer risk. Family and genome-wide association studies have identified more than 40 risk-associated loci, which explain approximately 25% of the familial risk. Of possible interest, a number of the candidate genes in these regions are involved in innate immunity, leading to speculation that inflammation, an emerging hallmark of cancer (Chapter 7) may set the stage for the development of prostate carcinoma.

Other work is focused on the role of tumor-specific acquired mutations and epigenetic changes. **One very common structural genetic change in prostate cancer is chromosomal rearrangements that juxtapose the coding sequence of an ETS family transcription factor gene (most commonly *ERG* or *ETV1*) next to the androgen-regulated *TMPRSS2* promoter.** These rearrangements, which occur in approximately half of prostate cancer cases in Caucasian cohorts, place the involved ETS gene under the control of the *TMPRSS2* promoter and lead to its overexpression in an androgen-dependent fashion. Overexpression of ETS transcription factors does not directly transform prostate epithelial cells, but it does make normal prostate epithelial cells more invasive, possibly through the upregulation of matrix metalloproteases. The clinical significance of these gene rearrangements remains unclear, as most studies show that in surgically treated cohorts, the presence of ETS gene rearrangement alone does not portend a worse prognosis.

In contrast to breast and colon cancer, recent whole genome sequencing efforts have demonstrated that genomic deletions and amplifications are more common in prostate cancer than point mutations involving oncogenes. Common genetic alterations in prostate cancer include amplification of the 8q24 locus containing the *MYC* oncogene, and deletions involving the *PTEN* tumor suppressor. In late stage disease, loss of *TP53* (by deletion or mutation), and deletions involving *RB* are common, as are amplifications of the androgen receptor gene locus.

The most common epigenetic alteration in prostate cancer is hypermethylation of the glutathione *S*-transferase (*GSTP1*) gene, which down-regulates *GSTP1* expression. The *GSTP1* gene is located on chromosome 11q13 and is an important part of the pathway that prevents damage from a wide range of carcinogens. Other genes silenced by epigenetic modifications in a subset of prostate cancers include a number of tumor suppressor genes, including genes involved in cell cycle regulation (*RB*, *CDKN2A*, maintenance of genomic stability (*MLH1*, *MSH2*), and suppression of Wnt pathway signaling (*APC*).

As can be surmised from the multiplicity of abnormalities, prostate carcinoma (like other cancers) is the product of some critical combination of acquired genomic structural changes, somatic mutations and epigenetic changes. A putative precursor lesion, prostatic intraepithelial neoplasia (PIN), has been described. There are several lines of evidence relating PIN to invasive cancer. First, both PIN and cancer typically predominate in the peripheral zone and are relatively uncommon in other zones. Prostates containing cancer have a higher frequency and a greater extent of PIN, which is also often seen in proximity to cancer. Studies have revealed that many of the molecular changes seen in invasive cancers are present in PIN (for example, rearrangements involving *ETS* genes are found in a subset), strongly supporting the argument that PIN is a precursor of invasive cancer. Despite all this evidence, we do not know the natural history of PIN, and in particular how often it progresses to cancer. Thus, unlike in cancer of the cervix, the term "carcinoma in situ" is not used for PIN.

MORPHOLOGY

When the terms **"prostate cancer"** or **"prostate adenocarcinoma"** are used without qualifications it refers to the common or acinar variant of prostate cancer. In approximately 70% of cases, carcinoma of the prostate arises in the peripheral zone of the gland, classically in a posterior location, where it may be palpable on rectal examination (Fig. 21-34). Characteristically, on cross-section of the prostate **the neoplastic tissue is gritty and firm, but when embedded within the prostatic substance it may be extremely difficult to visualize and be more readily apparent on palpation**. Local extension most commonly involves periprostatic tissue, seminal vesicles, and the base of the urinary bladder, which in advanced disease may produce ureteral obstruction. Metastases spread via lymphatics to the obturator nodes and eventually to the para-aortic

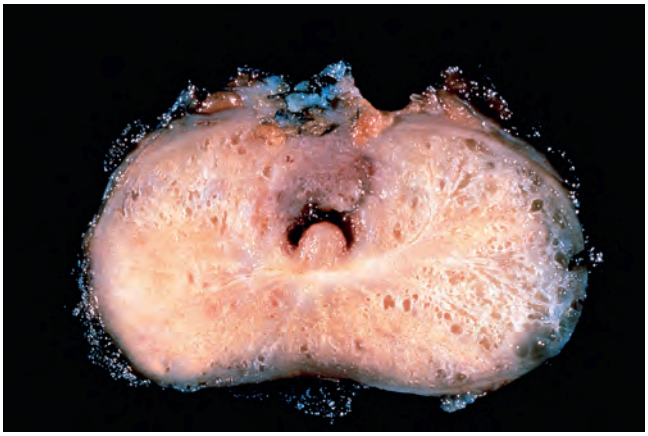

Figure 21-34 Adenocarcinoma of the prostate. Carcinomatous tissue is seen on the posterior aspect *(lower left)*. Note solid whiter tissue of cancer in contrast to spongy appearance of benign peripheral zone in the contralateral side.