As can be surmised from this discussion, breast cancer is not one disease, but many, each with its own clinical characteristics and optimal prevention and treatment strategies. This recognition has led to the introduction of new molecular classification systems, which are discussed later.

KEY CONCEPTS

Breast Cancer Incidence, Epidemiology, and Etiology

- Breast cancer is the most common non-skin malignancy in women and the second most common cause of cancer deaths.
- The most important risk factors are estrogenic stimulation and age.
- All cancers arise by the accumulation of DNA alterations and epigenetic changes.
- Tumorigenesis also requires changes in the normal supporting cells—alteration of the normal crosstalk and function of stromal cells may be an important determinant of stromal invasion.
- The hormonal milieu of the breast plays an important role in expanding populations of potential precursor cells, altering stroma during pregnancy, and driving the proliferation of cancers.

Types of Breast Carcinoma

Almost all (>95%) of breast malignancies are adenocarcinomas that first arise in the duct/lobular system as carcinoma in situ; at the time of clinical detection the majority (at least 70%) will have breached the basement membrane and invaded the stroma. Carcinoma in situ refers to a neoplastic proliferation of epithelial cells that is confined to ducts and lobules by the basement membrane. Invasive carcinoma (synonymous with "infiltrating" carcinoma) has penetrated through the basement membrane and grows within stroma. Here, the cells have the potential to invade into the vasculature and thereby reach regional lymph nodes and distant sites.

The terms *ductal* and *lobular* are still used to describe subsets of both in situ and invasive carcinomas, but most evidence suggests all breast carcinomas actually arise from cells in the terminal duct lobular unit. Carcinoma in situ was originally classified as DCIS or lobular carcinoma in situ (LCIS) based on the resemblance of the involved spaces to normal ducts or lobules. It is now recognized that these growth patterns are not related to the cell of origin, but rather reflect differences in tumor cell genetics and biology. By current convention, "lobular" refers to invasive carcinomas that are biologically related to LCIS, and "ductal" is used more generally for adenocarcinomas that cannot be classified as a special histologic type.

Carcinoma in Situ

Ductal Carcinoma in Situ (DCIS)

DCIS is a malignant clonal proliferation of epithelial cells limited to ducts and lobules by the basement membrane. The term "ductal" was used to describe this lesion because when it involves lobules, the expanded acini take on an appearance resembling small ducts. Myoepithelial cells are preserved in involved ducts/lobules, although they may be diminished in number. DCIS can spread throughout the ductal system and produce extensive lesions involving an entire sector of a breast.

DCIS is almost always detected by mammography. Without screening, fewer than 5% of all carcinomas are detected when in situ, but DCIS comprises 15% to 30% of carcinomas in screened populations (Fig. 23-14). Most are identified as a result of calcifications associated with secretory material or necrosis; less commonly, periductal fibrosis surrounding DCIS forms a mammographic density or a vaguely palpable mass. Rarely, DCIS (often of micropapillary or papillary types) produces a nipple discharge or is detected as an incidental finding upon biopsy for another lesion.

MORPHOLOGY

DCIS can be divided into two major architectural subtypes, comedo and noncomedo (Fig. 23-17). Some cases of DCIS have a single growth pattern, but most are comprised of a mixture of patterns. Nuclear grade and necrosis are better predictors of local recurrence and progression to invasion than architectural type.

Comedo DCIS may occasionally produce vague nodularity, but more often it is detected on mammography as clustered or linear and branching areas of calcification (Fig. 23-17*A*). It is defined by two features: (1) tumor cells with pleomorphic, high-grade nuclei and (2) areas of central necrosis (Fig. 23-17*B*).

Noncomedo DCIS lacks either high-grade nuclei or central necrosis. Several patterns may be seen. Cribriform DCIS may have rounded (cookie cutter–like) spaces (Fig. 23-17*C*) within the ducts, or a solid DCIS pattern. Micropapillary DCIS produces bulbous protrusions without a fibrovascular core, often arranged in complex intraductal patterns (Fig. 23-17*D*). In other cases, DCIS produces true papillae with fibrovascular cores that lack a myoepithelial cell layer. Calcifications may also be seen in noncomedo forms of DCIS in association with focal necrosis or intraluminal secretions.

Paget disease of the nipple is a rare manifestation of breast cancer (1% to 4% of cases) that presents as a unilateral erythematous eruption with a scale crust. Pruritus is common, and the lesion may be mistaken for eczema. Malignant cells (Paget cells) extend from DCIS within the ductal system via the lactiferous sinuses into nipple skin without crossing the basement membrane (Fig. 23-18). The tumor cells disrupt the normal epithelial barrier, allowing extracellular fluid to seep out onto the nipple surface. The Paget cells are readily detected by nipple biopsy or cytologic preparations of the exudate.

A palpable mass is present in 50% to 60% of women with Paget disease, and almost all of these women have an underlying invasive carcinoma. The carcinomas are usually poorly differentiated, ER-negative, and overexpress HER2. In contrast, the majority of women without a palpable mass have only DCIS. Prognosis of Paget disease depends on the features of the underlying carcinoma and is not affected by the presence or absence of DCIS involving the skin when matched for other prognostic factors.