Lobular carcinoma is the subtype with the clearest association of phenotype and genotype. Most cases show biallelic loss of expression of *CDH1*, the gene that encodes E-cadherin. Due to loss of E-cadherin, lobular carcinomas are discohesive and often fail to incite a desmoplastic response. They also have characteristic patterns of metastatic spread, often involving the peritoneum and retroperitoneum, the leptomeninges (carcinomatous meningitis), the gastrointestinal tract, and the ovaries and uterus. Males and females with heterozygous germline mutations in *CDH1* also have a greatly increased risk of gastric signet ring cell carcinoma.

Medullary carcinoma is of great interest due to the finding that many tumors of this type have features that are characteristic of *BRCA1*-associated carcinomas. Among cancers arising in *BRCA1* carriers, 13% are of medullary type, and up to 60% have a subset of medullary features (Table 23-3). Although the majority of medullary carcinomas are not associated with germline *BRCA1* mutations, hypermethylation of the *BRCA1* promoter leading to downregulation of *BRCA1* expression is observed in 67% of these tumors. The basis for the relatively good prognosis of this subtype compared to other poorly differentiated carcinomas is not known, but it has been noted that the presence of lymphocytic infiltrates within the tumors is associated with higher survival rates and a greater response to chemotherapy, suggesting that improved outcomes may be related to a host immune response to tumor antigens.

Micropapillary carcinoma shows a characteristic pattern of anchorage-independent growth. Although the cells are adherent to each other and express E-cadherin, they lack adhesion to the stroma.

Many of the other special histologic types of breast cancer (too numerous to list) also have unique biologic, genetic and clinical features. There is much that remains to be learned about the biology and pathogenesis of these tumors, some of which are described below.

MORPHOLOGY

Some special histologic types of cancer are almost always ER-positive and have gene expression profiles that resemble luminal cancers. These include lobular carcinoma, mucinous carcinoma, tubular carcinoma, and papillary carcinoma.

Lobular carcinoma most commonly forms hard irregular masses similar to other breast cancers, but (as already mentioned) may also have a diffuse infiltrative pattern with minimal desmoplasia. Such cancers can be difficult to palpate or detect by imaging. This is the most common type of breast carcinoma to present as an occult primary. The histologic hallmark is the presence of discohesive infiltrating tumor cells, often including signet-ring cells containing intracytoplasmic mucin droplets (Fig. 23-24*A*). Tubule formation is absent. Alveolar and solid variants consist of circumscribed clusters of tumor cells.

Mucinous (colloid) carcinoma is soft or rubbery and has the consistency and appearance of pale gray-blue gelatin. The borders are pushing or circumscribed. The tumor cells are arranged in clusters and small islands of cells within large lakes of mucin (Fig. 23-24*B*).

Tubular carcinoma consists exclusively of well-formed tubules and is sometimes mistaken for a benign sclerosing lesion (Fig. 23-24*C*). A cribriform pattern may also be present. Apocrine snouts are typical, and calcifications may be present within the lumens. Tubular carcinomas are frequently associated with flat epithelial atypia, atypical lobular hyperplasia, LCIS, or low-grade DCIS.

Papillary carcinoma, as the name implies, produces true papillae, fronds of fibrovascular tissue lined by tumor cells (Fig. 23-24*D*).

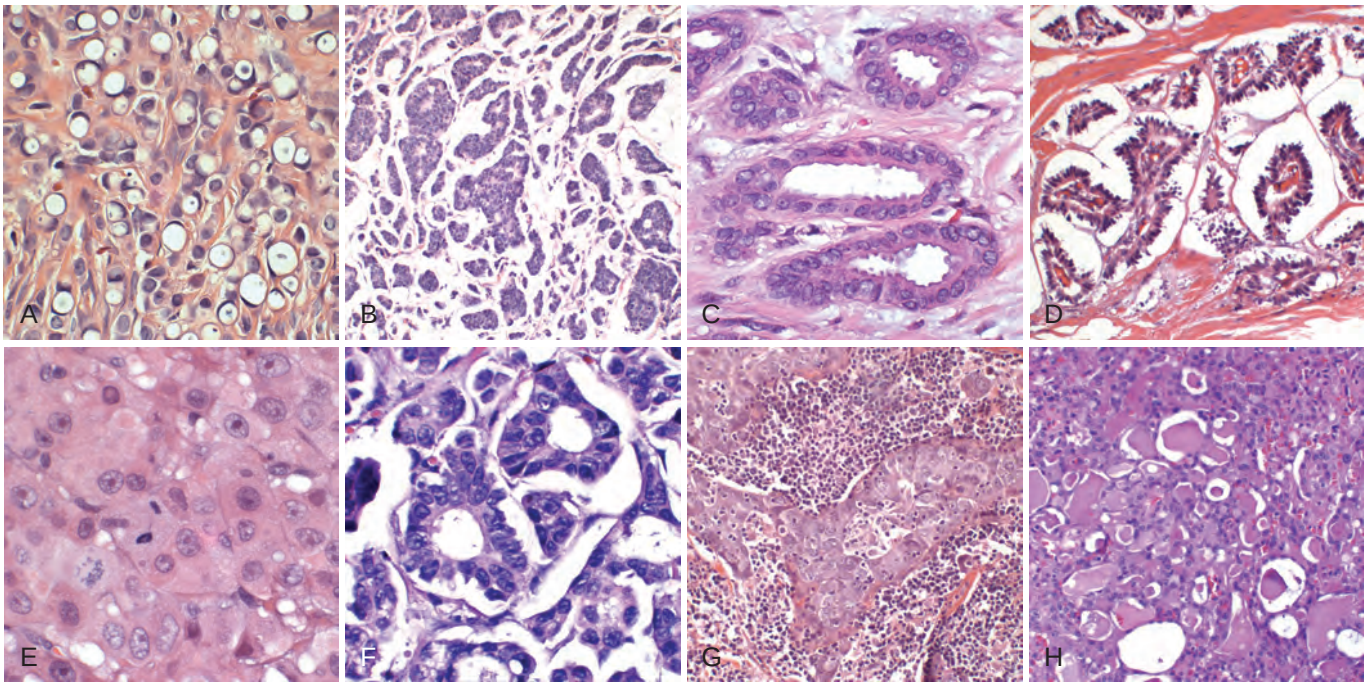

Figure 23-24 Special histologic types of invasive carcinoma. **A,** Lobular carcinoma. **B,** Mucinous carcinoma. **C,** Tubular carcinoma. **D,** Papillary carcinoma. **E,** Apocrine carcinoma. **F,** Micropapillary carcinoma. **G,** Medullary carcinoma. **H,** Secretory carcinoma. See text for morphologic descriptions.