women at high-risk for ovarian carcinoma (*BRCA* mutation carriers and women with a strong family history of breast/ovarian cancer), as these women now undergo salpingo-oophorectomy, instead of simple oophorectomy.

Regardless of their origin, studies have shown that low- and high-grade serous carcinomas have distinct mutational profiles, as follows:

- Low-grade tumors arising in serous borderline tumors have mutations in the *KRAS*, *BRAF*, or *ERBB2* oncogenes, and usually have wild type *TP53* genes.
- High-grade tumors have a high frequency of *TP53* mutations and lack mutations in either *KRAS* or *BRAF*. Genomic imbalances are very common and include amplifications of a number of oncogenes (e.g., *PIK3CA*, the gene encoding the catalytic subunit of PI3K) and deletions of tumor suppressor genes (e.g., *RB*). Almost all ovarian carcinomas arising in women with *BRCA1* or *BRCA2* mutations are high-grade serous carcinomas with *TP53* mutations. Interestingly, *BRCA1/2* mutations are rare in sporadic high-grade serous carcinoma.

MORPHOLOGY

Serous tumors may present as either a multicystic lesion in which papillary epithelium is contained within a few fibrous walled cysts (intracystic) (Fig. 22-32*A*) or as a mass projecting from the ovarian surface. Benign tumors typically have a smooth glistening cyst wall with no epithelial thickening or with small papillary projections. Borderline tumors contain an increased number of papillary projections (Fig. 22-32*A* and *C*). Larger areas of solid or papillary tumor mass, tumor irregularity, and fixation or nodularity of the capsule are features associated with malignancy (Fig. 22-32*B*). Bilaterality is common, occurring in 20% of benign serous cystadenomas, 30% of serous borderline tumors, and approximately 66% of serous carcinomas. A significant proportion of both serous borderline tumors and malignant serous tumors involve the surface of the ovary (Fig. 22-32*C*).

Microscopically, the cysts are lined by columnar epithelium, which has abundant cilia in benign tumors (Fig. 22-33*A*). Microscopic papillae may be found. **Serous borderline tumors** exhibit increased complexity of the stromal papillae, stratification of the epithelium and mild nuclear atypia, but invasion of the stroma is not seen (Fig. 22-33*B*). This epithelial proliferation often grows in a delicate, papillary pattern referred to as "micropapillary carcinoma," which is thought to be the precursor to **low-grade serous carcinoma** (Fig. 22-33*C*). **High-grade serous carcinomas** are distinguished from low-grade tumors by having more complex growth patterns and widespread infiltration or frank effacement of the underlying stroma (Fig. 22-33*D*). The individual tumor cells display marked nuclear atypia, including pleomorphism, atypical mitotic figures, and multinucleation. The serous tubal intraepithelial carcinomas consist of cells morphologically identical to high-grade serous carcinomas but are distinguished by the lack of invasion. The cells of invasive high-grade serous carcinoma can even become so undifferentiated that serous features are no longer recognizable. Concentric calcifications (psammoma bodies) characterize serous tumors, but are not specific for neoplasia. Ovarian serous tumors, both low- and high-grade, have a propensity to spread to the peritoneal surfaces and omentum and are commonly associated with the presence of ascites. As with other tumors, the extent of the spread outside the ovary determines the stage of the disease.

The biologic behavior of serous tumors depends on the degree of differentiation and the distribution and characteristics of the disease in the peritoneum, if present. Importantly, serous tumors may occur on the surface of the ovaries and, rarely, as primary tumors of the peritoneal surface, which are referred to as primary peritoneal serous carcinoma. As discussed, at least some of these carcinomas may originate from the fallopian tube. Predictably, unencapsulated serous tumors of the ovarian surface are more likely to spread to the peritoneal surfaces, and prognosis is closely related to the histologic appearance of the tumor and its growth pattern on the peritoneum. Borderline serous tumors may arise from or extend to the peritoneal surfaces as noninvasive implants, remaining localized and causing no symptoms, or slowly spread, producing intestinal obstruction or other complications after many years. As discussed earlier, low-grade serous carcinomas can arise in borderline serous tumors and may be associated with spread to the peritoneal surfaces. However, low-grade carcinomas, even after spread outside the ovary, often progress slowly, and patients may survive for relatively long periods before dying of disease. In contrast, high-grade tumors are often widely metastatic throughout the abdomen at the time of presentation, a picture

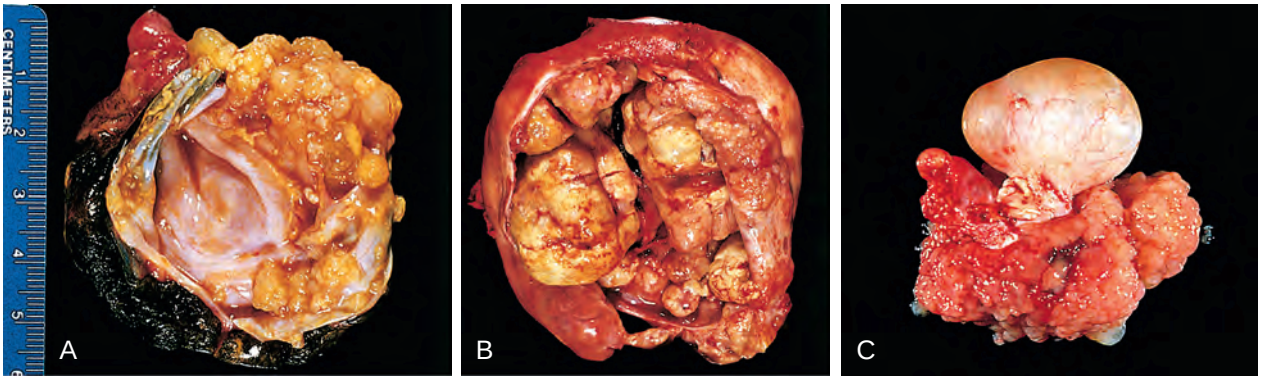

Figure 22-32 Gross appearances of serous tumors of the ovary. **A,** Serous borderline tumor opened to display a cyst cavity lined by delicate papillary tumor growths. **B,** Carcinoma. The cyst is opened to reveal a large, bulky tumor mass. **C,** Another borderline tumor growing on the ovarian surface *(lower)*.