frequency of *TP53* mutations of all histologic types of lung carcinoma. p53 protein overexpression (as seen by immunohistochemical staining), a marker of *TP53* mutations, is also an early event, being reported in 10% to 50% of squamous dysplasias and 60% to 90% of squamous cell carcinoma in situ. Loss of expression of the retinoblastoma (RB) tumor suppressor is identified by immunohistochemistry in 15% of squamous cell carcinomas. The cyclin-dependent kinase inhibitor gene *CDKN2A* is inactivated and its protein product, p16, is lost in 65% of tumors. It has recently been recognized that many squamous cell carcinomas have amplification of *FGFR1*, a gene encoding the fibroblast growth factor receptor tyrosine kinase.

- *Small cell carcinoma* shows the strongest association with smoking and despite its divergent histologic features shares many molecular features with squamous cell carcinoma. This includes frequent loss-of-function aberrations involving *TP53* (75% to 90% of tumors), *RB* (close to 100% of tumors), and chromosome 3p deletions. Also common is amplification of genes of the *MYC* family.
- *Adenocarcinoma* is marked by oncogenic gain-of-function mutations involving components of growth factor receptor signaling pathways. All are found in a minority of tumors, but together they make up a substantial fraction of tumors as a whole. These include gain-of-function mutations in multiple genes encoding receptor tyrosine kinases, including *EGFR, ALK, ROS, MET,* and *RET*, which are all also mutated in other forms of cancer. Tumors without tyrosine kinase gene mutations often have mutations in the *KRAS* gene, which you will remember lies downstream of receptor tyrosine kinases in growth factor signaling pathways.

Lung Cancer in Never Smokers. The WHO estimates that 25% of lung cancer worldwide occurs in never smokers. This percentage is probably closer to 10% to 15% in Western countries. These cancers occur more commonly in women and most are adenocarcinomas. Cancers in nonsmokers are more likely to have *EGFR* mutations, and almost never have *KRAS* mutations; *TP53* mutations are not uncommon, but occur less frequently than in smoking-related cancers.

Table 15-9 Histologic Classification of Malignant Epithelial Lung Tumors

Tumor Classification
Squamous cell carcinoma
Papillary, clear cell, small cell, basaloid
Small-cell carcinoma
Combined small-cell carcinoma
Adenocarcinoma
Minimally invasive adenocarcinoma (nonmucinous, mucinous)
Lepidic, acinar; papillary, solid (according to predominant pattern)
Mucinous adenocarcinoma
Large-cell carcinoma
Large-cell neuroendocrine carcinoma
Adenosquamous carcinoma
Carcinomas with pleomorphic, sarcomatoid, or sarcomatous elements
Carcinoid tumor
Typical, atypical
Carcinomas of salivary gland type

Precursor (Preinvasive) Lesions. Four types of morphologic precursor epithelial lesions are recognized: (1) squamous dysplasia and carcinoma in situ, (2) atypical adenomatous hyperplasia, (3) adenocarcinoma in situ, and (4) diffuse idiopathic pulmonary neuroendocrine cell hyperplasia. It should be remembered that the term *precursor* does not imply that progression to cancer is inevitable. Currently it is not possible to distinguish between precursor lesions that progress and those that remain localized or regress.

Classification. Tumor classification is important for consistency in patient treatment and because it provides a basis for epidemiologic and biologic studies. The most recent classification is given in Table 15-9. Several histologic variants of each type of lung cancer are described; however, their clinical significance is still undetermined, except as mentioned herein. The relative proportions of the major categories are:

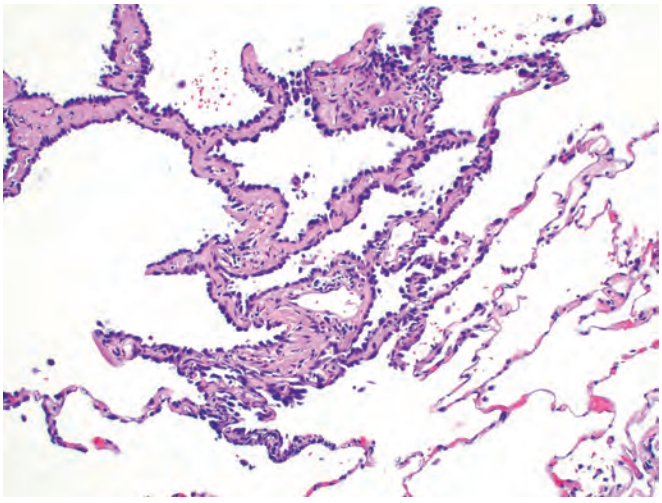

Figure 15-41 Atypical adenomatous hyperplasia. The epithelium is cuboidal and there is mild interstitial fibrosis.

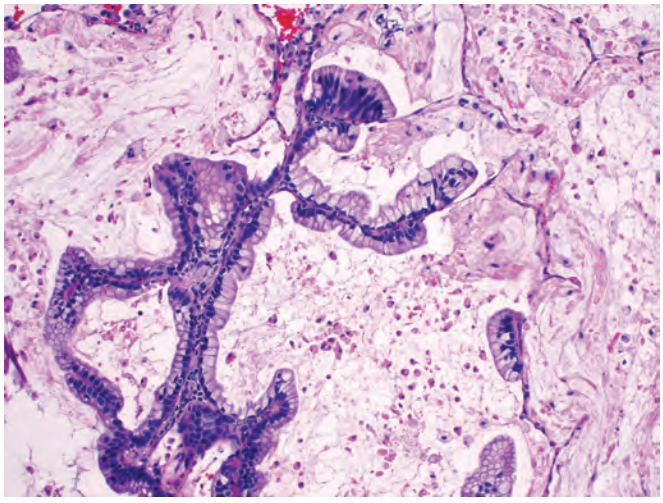

Figure 15-42 Adenocarcinoma in situ, mucinous subtype. Characteristic growth along pre-existing alveolar septa is evident, without invasion.