aflatoxin for hepatocarcinogenesis. Aflatoxin also synergizes with HBV (perhaps also with HCV) to increase risk further. Alcohol is another toxin which probably, by itself, is a risk factor for HCC, but it also synergizes with HBV and HCV, and even, possibly, cigarette smoking.

Metabolic diseases such as hereditary hemochromatosis and α_1AT deficiency markedly increase the risk of HCC. Wilson disease probably does so with much less frequency. Of probably greater import is the metabolic syndrome associated with obesity, diabetes mellitus, and nonalcoholic fatty liver disease, all of which increase the risk of HCC.

No single, universal sequence of molecular or genetic alterations leads to emergence of HCC. *Activation of β-catenin and inactivation of p53 are the two most common early mutational events.* Activating β-catenin mutations are identified in up to 40% of persons with HCC. These tumors are more likely to be unrelated to HBV and to demonstrate genetic instability. Inactivation of p53 is present in up to 60% of HCC cases. These tumors are strongly associated with aflatoxin. Neither of these alterations, however, is found in premalignant lesions.

Recent evidence has provided some novel insights into the role of HBV, HCV, alcoholic liver disease and other states of chronic inflammation in the pathogenesis of HCC. Traditional thinking has been that cycles of cell death and regeneration in chronic inflammatory states increases the risk of mutations in regenerating hepatocytes. But the precise molecular mechanisms of such changes have remained obscure. More recent studies implicate a role for signaling through the IL-6/JAK/STAT pathway in the causation of HCC. IL-6 is an inflammatory cytokine that is overproduced in many chronic hepatitides. Based on some preliminary experiments, it has been proposed that IL-6 can suppress hepatocyte differentiation and promote their proliferation by regulating the function of the transcription factor HNF4-α. In keeping with this, hepatic carcinogenesis can be suppressed by uncoupling HNF4-α from the control of IL-6, in experimental animals. More studies are needed to determine the significance of IL-6/HNF4-α signaling axis in human HCC.

Precursor Lesions of HCC

Several cellular and nodular precursor lesions to HCC have been identified (Table 18-12). Hepatocellular adenoma has already been discussed, in particular those with β-catenin activating mutations. In chronic liver disease there are cellular dysplasias, called *large cell change* and *small cell change* (Fig. 18-57)**.** These may be found at any stage of chronic liver disease, before or after development of cirrhosis, and serve as markers in biopsy specimens to indicate which patients need more aggressive cancer surveillance. *Small cell change is thought to be directly premalignant. Large cell change is at least a marker of increased risk of HCC in the liver as a whole, but in hepatitis B they may also be directly premalignant.*

Dysplastic nodules are usually detected in cirrhosis, either radiologically or in resected specimens (including explants). These are nodules that have a different appearance from the surrounding cirrhotic nodules (Fig. 18-58). The differences are in size or vascular supply (increasingly arterial with increasingly high grade, a defining feature in contrast radiologic studies) or other aspects of appearance (color, texture). *Low-grade dysplastic nodules*, may or may not

Table 18-12 Precursor Lesions of Hepatocellular Carcinoma and Cholangiocarcinoma

	Hepatocellular Carcinoma					Cholangiocarcinoma		
	Hepatocellular Adenoma	Small Cell Change	Large Cell Change	Low Grade Dysplastic Nodule	High Grade Dysplastic Nodule	BilIN-3	Mucinous Cystic Neoplasm	Intraductal Papillary Biliary Neoplasia
Focality in liver	Single or multiple (adenomatosis)	Diffuse	Diffuse	Single or multiple	Single or multiple	Diffuse or multifocal	Single	Focal or diffuse
Premalignant	Yes	Yes	In some HBV*	Uncertain*	Yes	Yes	Yes	Yes
Association with cirrhosis	Rare	Common	Common	Usual	Usual	Sometimes	No	No
Commonly associated diseases	NAFLD, Sex hormone exposures Glycogen storage diseases	HBV, HCV, Alcohol, NAFLD, A1AT, HH, PBC	HBV, HCV, Alcohol, NAFLD, A1AT, HH PBC	HBV, HCV, Alcohol, NAFLD, A1AT, HH PBC	HBV, HCV, Alcohol, NAFLD, A1AT, HH PBC	PSC, Hepatolithiasis, Liver flukes	None	None
Occurrence without identified predisposing condition	Occasional	No	No	No	No	Yes	Yes	Yes
Need for surveillance cancer screening	± depending on presence of predisposing condition	Yes	Yes	Yes	Yes	Yes	No	Yes

*While these are not certain to be directly premalignant, they are always at least an indication of increased risk for malignancy in the liver as a whole.
BilIN-3, Biliary intraepithelial neoplasia, high grade; NAFLD, nonalcoholic fatty liver disease; HBV, hepatitis B virus; HCV, hepatitis C virus; A1AT, α_1-antitrypsin deficiency; HH, hereditary hemochromatosis; PBC, primary biliary cirrhosis; PSC, primary sclerosing cholangitis.