the anus is identical when corrected for tumor size and the presence or absence of nodal spread.

The development of anal cancer is associated with infection by human papillomavirus, the same organism etiologically linked to cervical cancer. The virus is sexually transmitted. The infection may lead to anal warts (condyloma acuminata), which may progress to anal intraepithelial neoplasia and on to squamous cell carcinoma. The risk for anal cancer is increased among homosexual males, presumably related to anal intercourse. Anal cancer risk is increased in both men and women with AIDS, possibly because their immunosuppressed state permits more severe papillomavirus infection. Vaccination against human papilloma viruses may reduce the eventual risk for anal cancer. Anal cancers occur most commonly in middle-aged persons and are more frequent in women than men. At diagnosis, patients may experience bleeding, pain, sensation of a perianal mass, and pruritus.

Radical surgery (abdominal-perineal resection with lymph node sampling and a permanent colostomy) was once the treatment of choice for this tumor type. The 5-year survival rate after such a procedure was 55–70% in the absence of spread to regional lymph nodes and <20% if nodal involvement was present. An alternative therapeutic approach combining external beam radiation therapy with concomitant chemotherapy (5-FU and mitomycin C) has resulted in biopsy-proven disappearance of all tumor in >80% of patients whose initial lesion was <3 cm in size. Tumor recurrences develop in <10% of these patients, meaning that ~70% of patients with anal cancers can be cured with nonoperative treatment and without the need for a colostomy. Surgery should be reserved for the minority of individuals who are found to have residual tumor after being managed initially with radiation therapy combined with chemotherapy.

111 Tumors of the Liver and Biliary Tree

Brian I. Carr

HEPATOCELLULAR CARCINOMA

INCIDENCE

Hepatocellular carcinoma (HCC) is one of the most common malignancies worldwide. The annual global incidence is approximately 1 million cases, with a male-to-female ratio of approximately 4:1 (1:1 without cirrhosis to 9:1 in many high-incidence countries). The incidence rate equals the death rate. In the United States, approximately 22,000 new cases are diagnosed annually, with 18,000 deaths. The death rates in males in low-incidence countries such as the United States are 1.9 per 100,000 per year; in intermediate areas such as Austria and South Africa, they range from 5.1–20; and in high-incidence areas such as in the Orient (China and Korea), they are as high as 23.1–150 per 100,000 per year (Table 111-1). The incidence of HCC in the United States is approximately 3 per 100,000 persons, with significant gender, ethnic, and geographic variations. These numbers are rapidly increasing and may be an underestimate. Approximately 4 million chronic hepatitis C virus (HCV) carriers are in the United States alone. Approximately 10% of them, or 400,000, are likely to develop cirrhosis. Approximately 5%, or 20,000, of these patients may develop HCC annually. Add to this the two other common predisposing factors—hepatitis B virus (HBV) and chronic alcohol consumption—and 60,000 new HCC cases annually seem possible. Future advances in HCC survival will likely depend in part on immunization strategies for HBV (and HCV) and earlier diagnosis by screening of patients at risk of HCC development.

Current Directions With the U.S. HCV epidemic, HCC is increasing in most states, and obesity-associated liver disease (nonalcoholic steatohepatitis [NASH]) is increasingly recognized as a cause.

TABLE 111-1 AGE-ADJUSTED INCIDENCE RATES FOR HEPATOCELLULAR CARCINOMA

	Persons per 100,000 per Year	
Country	Male	Female
Argentina	6.0	2.5
Brazil, Recife	9.2	8.3
Brazil, Sao Paulo	3.8	2.6
Mozambique	112.9	30.8
South Africa, Cape: Black	26.3	8.4
South Africa, Cape: White	1.2	0.6
Senegal	25.6	9.0
Nigeria	15.4	3.2
Gambia	33.1	12.6
Burma	25.5	8.8
Japan	7.2	2.2
Korea	13.8	3.2
China, Shanghai	34.4	11.6
India, Bombay	4.9	2.5
India, Madras	2.1	0.7
Great Britain	1.6	0.8
France	6.9	1.2
Italy, Varese	7.1	2.7
Norway	1.8	1.1
Spain, Navarra	7.9	4.7

EPIDEMIOLOGY

There are two general types of epidemiologic studies of HCC—those of country-based incidence rates (Table 111-1) and those of migrants. Endemic hot spots occur in areas of China and sub-Saharan Africa, which are associated both with high endemic hepatitis B carrier rates as well as mycotoxin contamination of foodstuffs (aflatoxin B_1), stored grains, drinking water, and soil. Environmental factors are important, for example, Japanese in Japan have a higher incidence than Japanese living in Hawaii, who in turn have a higher incidence than those living in California.

ETIOLOGIC FACTORS

Chemical Carcinogens Causative agents for HCC have been studied along two general lines. First are agents identified as carcinogenic in experimental animals (particularly rodents) that are thought to be present in the human environment (Table 111-2). Second is the association of HCC with various other clinical conditions. Probably the best-studied and most potent ubiquitous natural chemical carcinogen is a product of the *Aspergillus* fungus, called aflatoxin B_1. This mold and aflatoxin product can be found in a variety of stored grains in hot, humid places, where peanuts and rice are stored in unrefrigerated conditions. Aflatoxin contamination of foodstuffs correlates well with incidence rates in Africa and to some extent in China. In endemic areas of China, even farm animals such as ducks have HCC. The most potent carcinogens appear to be natural products of plants, fungi, and bacteria, such as bush trees containing pyrrolizidine alkaloids as well as tannic acid and safrole. Pollutants such as pesticides and insecticides are known rodent carcinogens.

Hepatitis Both case-control and cohort studies have shown a strong association between chronic hepatitis B carrier rates and increased incidence of HCC. In Taiwanese male postal carriers who were hepatitis B surface antigen (HBsAg)-positive, a 98-fold greater risk for HCC was found compared to HBsAg-negative individuals. The incidence of HCC in Alaskan natives is markedly increased related to a high prevalence of HBV infection. HBV-based HCC may involve rounds of hepatic destruction with subsequent proliferation and not necessarily frank cirrhosis. The increase in Japanese