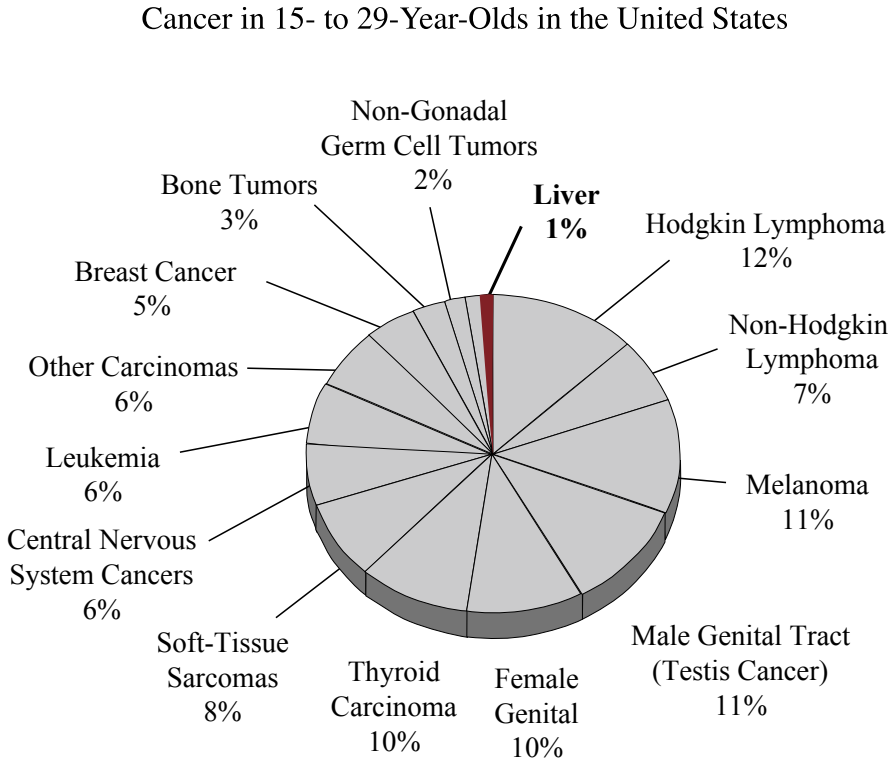
Chapter 11

Liver and Intrahepatic Bile Duct Cancers



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HIGHLIGHTS

Incidence

- Primary neoplasms of the liver are rare in adolescents and young adults. They accounted for 1% of all neoplasms in this age group between 1975 and 2000. Hepatocellular carcinoma was the prominent histologic type.
- The estimated incidence of liver cancer increased with age, from 1.1 per million per year in individuals 15 to 19 years of age to 2.7 per million per year for those 25 to 29 years of age.
- The incidence of liver tumors in males and females younger than 30 years of age was relatively equal. In persons older than age 30, the incidence of liver cancer increased much more rapidly in males than in females.

Mortality & Survival

- Mortality for liver cancer increased with age, especially for males.
- Mortality decreased significantly over time (1975 to 2000) for patients younger than 45 years of age. This progress was most apparent for patients younger than 29 years of age.
- The 5-year survival rate of patients diagnosed with cancer of the liver before age 15 was nearly 60%. For those 15 to 29 years of age it was approximately 16%, and decreased progressively with advancing age.
- These differences in survival rates appear to be due primarily to the fact that hepatoblastoma was the primary cell type in patients younger than 15 years of age whereas hepatocellular carcinoma and other bile duct tumors were most common in older patients.
- Although survival was not different for males younger than 15 years of age compared to females, females had a much better survival rate than males in the 15- to 29-year age group.

Risk Factors

- Known risk factors for hepatoblastoma are familial adenomatous polyposis, Gardner syndrome, Beckwith-Wiedemann syndrome, hemihypertrophy, and low birth weight.
- Hepatocellular carcinomas appear to be a consequence of previous hepatic damage due to metabolic or inflammatory disorders.
- Hepatocellular carcinoma is associated with congenital diseases such as hereditary tyrosinemia, biliary cirrhosis, glycogen storage disease and alpha 1-antitrypsin deficiency.
- Prolonged exposure to anabolic steroids, toxin-contaminated foods (aflatoxin), and potential hepatic carcinogens (pesticides, vinyl chloride, Thorotrast®) have also been associated with the development of hepatocellular carcinoma.

INTRODUCTION

Primary neoplasms of the liver are rare in adolescents and young adults aged 15 to 29 years; they accounted for 1% of all neoplasms in this age group, similar to the proportion in individuals 0 to 14 years of age. However, while hepatoblastomas comprised over two-thirds of the malignant liver tumors in children, most of the tumors seen in adolescents and young adults were hepatocellular carcinomas (HCC).The estimated incidence of liver and intrahepatic bile duct tumors in the U.S. in the year 2000 increased with age, from 1.1 per million in individuals 15 to 19 years of age to 2.7 per million for those 25 to 29 years of age. According to Surveillance, Epidemiology, and End Results (SEER) data, 101 adolescents and young adults in the United States were diagnosed with these tumors in the year 2000 (Table 11.1).

METHODS, CLASSIFICATION SYSTEM, AND BIOLOGICAL IMPLICATIONS

In the International Classification of Childhood Cancer (ICCC), hepatic tumors and intrahepatic bile duct cancers are found in category VII. In the ICCC, hepatoblastoma is category VII (a), hepatic carcinoma in the liver or intrahepatic bile duct system is VII(b) and unspecified malignant hepatic and intrahepatic bile duct tumors are VII(c).[1] In the International Classification of Diseases for Oncology (ICD-O), histologies for cholangiocarcinoma, bile duct cystadenocarcinoma, hepatocellular carcinoma, and combinations are listed in categories 8160 to 8180, as follows: hepatocellular carcinoma NOS (8170), fibrolamellar hepatocellular carcinoma (8171), cholangiocarcinoma (8160), bile duct cystadenocarcinoma (8161), Klatskin tumor (8162), and combined hepatocellular carcinoma and cholangiocarcinoma (8180). New hepatocellular histologies in ICD-O-3 are included with hepatocellular carcinoma NOS (8170): scirrhous (8172), hepatocellular carcinoma, spindle cell variant (8173), hepatocellular carcinoma, clear cell type (8174), and hepatocellular carcinoma, pleomorphic type (8175). Hepatoblastoma, ICCC VII(a), corresponds to ICD-O 8970.

In attempting to apply the ICCC and ICD-O systems to hepatic and bile duct tumors in 15- to 29-year-olds, there is evidence that hepatic parenchymal cancers in 15- to 29-year-olds differs from tumors of the same name in younger and older persons. Most of the hepatocellular carcinomas in this age group are not related to pre-existing chronic viral hepatitis and histologically may be "transitional" in nature, with over-expression of beta-catenin.[2] The missing variants of hepatocellular carcinoma described above may also compromise the analysis of 15- to 29-year-old patients who may be at risk of these subtypes.

INCIDENCE

Between 1975 and 2000, the incidence of liver and intrahepatic bile duct tumors in 15- to 29-year-olds in the U.S. SEER sites averaged 1.59 new cases per year per million. The data on liver tumors in adolescents and young adults 15 to 29 years of age were obtained from SEER data collected between 1975 and 2000. Approximately 10,000 individuals in this age group were diagnosed with liver tumors during this period, corresponding to an incidence of 7.4 per million/per year. Although these data include both liver and intrahepatic bile duct tumors, the occurrence of intrahepatic bile duct cancers in individuals younger than 29 years of age was extremely rare, as shown in Figure 11.1.

Age-Specific Incidence

The incidence of liver tumors was relatively constant between 5 and 35 years of age, but increased progressively thereafter (Figure 11.1). The incidence of liver tumors in children under 5 years of age was at least 3 times that observed for individuals 15 to 29 years of age.

Gender-Specific Incidence

The male-to-female incidence ratio for liver tumors was close to 1.1 for individuals 15 to 29 years of age. This is similar to the ratio seen in children younger than 5 years of age. However this ratio increased progressively after the age of 30, as the rate of liver tumors among males increased much more rapidly than among females (Figure 11.2).

Racial/Ethnic Differences in Incidence

Based on the SEER data collected between 1990 and 2000, the incidence of liver and intrahepatic bile duct tumors in adolescents and young adults younger than 25 years of age was too low to determine in all racial/ethnic groups

Table 11.1: *Incidence of Liver and Intrahepatic Bile Duct Cancers in Persons Younger Than 30 Years of Age, U.S., 1975-2000*

AGE AT DIAGNOSIS (YEARS)	<5	5-9	10-14	15-19	20-24	25-29
U.S. population, year 2000 census (in millions)	19.176	20.550	20.528	20.220	18.964	19.381
Average incidence per million, 1975-2000, SEER	4.9	0.7	0.8	1.1	1.5	2.3
Average annual % change in incidence, 1975-2000, SEER	^	^	^	^	1.8	2.6
Estimated incidence per million, year 2000, U.S.	4.9	0.7	0.8	1.1	1.8	2.7
Estimated number of persons diagnosed, year 2000, U.S.	94	15	17	21	33	47

^ Too few for a reliable estimate

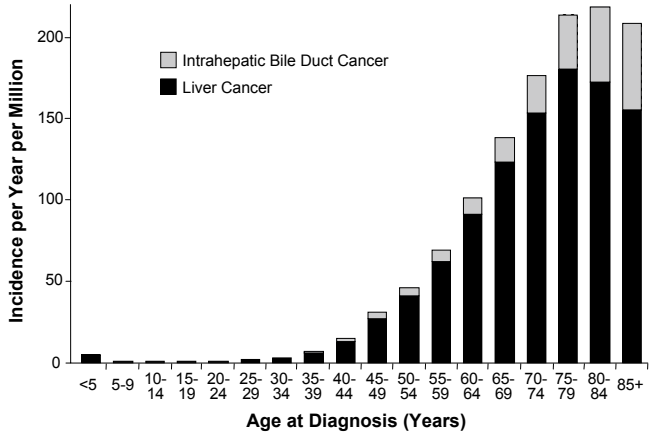

Figure 11.1: Incidence of Liver versus Intrahepatic Bile Duct Cancer, SEER 1975-2000

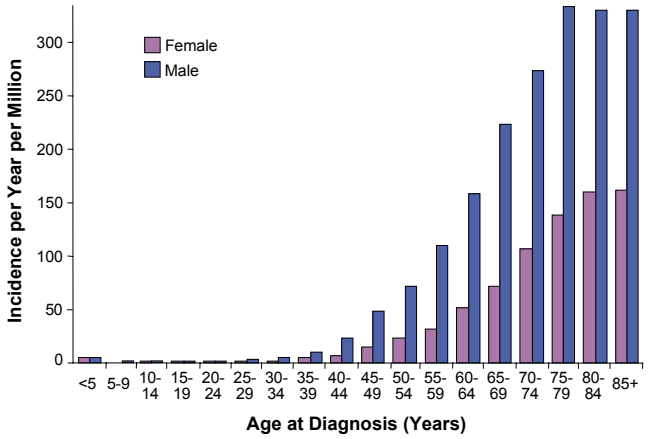

Figure 11.2: Incidence of Liver & Intrahepatic Bile Duct Cancer by Gender, SEER 1975-2000

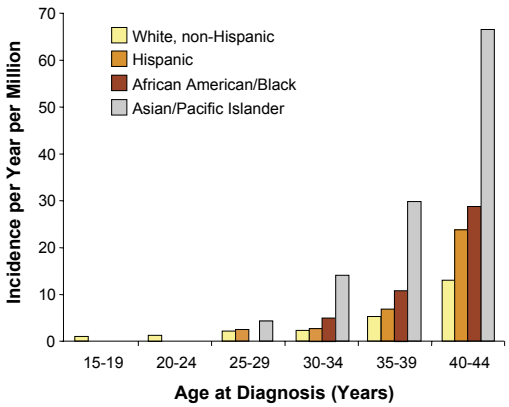

Figure 11.3: Liver & Intrahepatic Bile Duct Cancer Incidence Rate by Race/Ethnicity, U.S., 1990-2000

except white non-Hispanics (Figure 11.3). From age 25 to 45, Asians/Pacific Islanders had a higher incidence than any other racial/ethnic group, likely due to the high incidence of hepatitis B infection in this population.

Trends in Incidence

Figure 11.4 demonstrates the progressive increase in incidence of liver and intrahepatic bile duct tumors between 1975 and 2000. However this increase was more pronounced in patients older than 45 years of age. This increase was seen for all tumor stages, i.e., localized, regional or metastatic (Figure 11.5).

OUTCOME

Mortality

Mortality for liver tumors increased with age, especially for males (Figure 11.6). Mortality decreased significantly over time (1975 to 2000) for patients younger than 30 years of age (Figure 11.7). Above age 30, liver cancer mortality significantly increased (Figure 11.7), consistent with the increase in incidence in this age group (Figure 11.4). In the more recent era, a reduction in mortality was not as apparent for those 15 to 29 years of age. In contrast to the decline in mortality seen previously in this age group, mortality increased during the period 1992 to 2000 (11.7; right panel).

Survival

With the introduction of a multidisciplinary therapeutic approach to liver tumors in the early 1980s, a significant improvement in the survival rates has been noted for individuals younger than 15 years of age. However, progress has been much slower for older individuals, as shown in Figure 11.8. Survival of patients younger than 15 years of age was close to 60%, while for those 15 to 29 years of age it was approximately 16%, and decreased progressively with the advancement of age. This is likely due to the fact that younger patients were diagnosed predominantly with hepatoblastomas, which are more responsive to treatment overall than hepatocellular carcinomas and other bile duct tumors. Although survival was not different for males compared to females younger than 15 years of age, females had much better survival in the 15- to 29-year age group (Figure 11.9).

RISK FACTORS

Hepatoblastoma is rarely seen in adolescents and young adults; it is much more common in younger children. Known risk factors for the development of hepatoblastoma are familial adenomatous polyposis, Gardner syndrome, Beckwith-Wiedemann syndrome, hemihypertrophy, and low birth weight.[3-6] Suggestive but not conclusive factors that may pose a risk for the development of hepatoblastoma are treatment for prematurity; parental exposure to metal, petroleum products, and paint; parental smoking; and genetic susceptibility.[7-13] Single case reports provide limited evidence but have suggested an association between childhood hepatoblastoma and fetal alcohol syndrome, maternal oral contraceptive use during pregnancy, and maternal fertility treatment.[14-16]

Hepatocellular carcinoma is the most prevalent liver tumor in adolescents and young adults (15 to 29 years of age). Hepatocellular carcinomas appear to be a consequence of previous hepatic damage due to metabolic or inflammatory disorders. Infection with hepatitis B or C virus is associated with the development of HCC,[17,18] and chronic infection with hepatitis B virus is the leading cause of HCC in children, adolescents, and young adults in Asian and African countries. However, in Western countries, a cause such as hepatitis or other inflammatory liver disease has been identified in fewer than a third of the adolescent or young adult patients diagnosed with HCC.[19,20] This is in marked contrast to older adults, in whom almost 90% of the cases have been related to cirrhosis secondary to viral infection or alcohol consumption.[21,22] The prevention of a carrier state in children by a universal program of hepatitis B immunization has shown a dramatic decrease in the chronic hepatitis B virus prevalence and a decline in the rates of HCC in Taiwan among children younger than 15 years of age.[23,24]

Less frequently, HCC is associated with congenital diseases such as hereditary tyrosinemia, biliary cirrhosis, glycogen storage disease, α-1 antitrypsin deficiency, and hemochromatosis.[25-29] Prolonged exposure to anabolic steroids, toxin-contaminated foods (aflatoxin), and potential hepatic carcinogens (pesticides, vinyl chloride, Thorotrast®) has also been associated with the development of HCC.[30-32] Polymorphic variation in

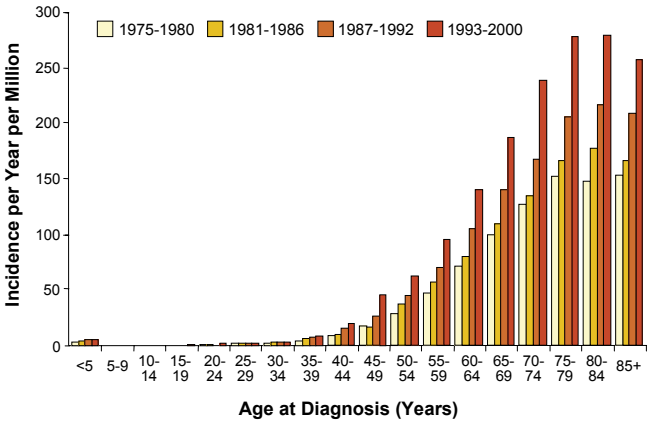

Figure 11.4: Change in Incidence of Liver & Intrahepatic Bile Duct Cancer by Era, SEER 1975-2000

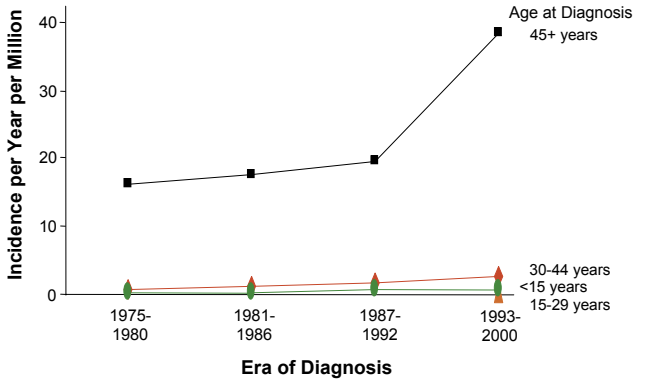

Figure 11.5: Incidence of Liver & Intrahepatic Bile Duct Cancer, Localized Disease, by Era, SEER 1975-2000

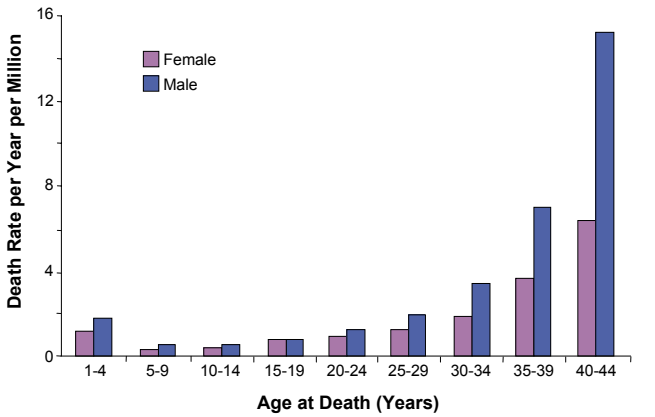

Figure 11.6: Liver & Intrahepatic Bile Duct Cancer, National Mortality by Gender, SEER 1975-2000

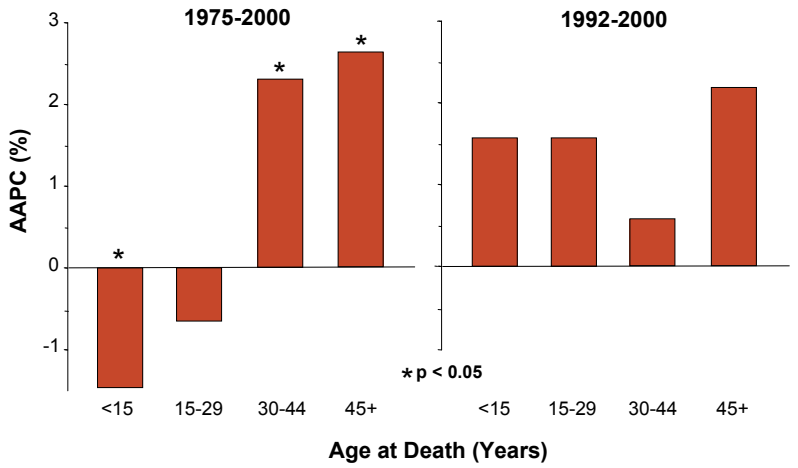

Figure 11.7: Liver & Intrahepatic Bile Duct Cancer, Average Annual Percent Change (AAPC) in National Cancer Mortality

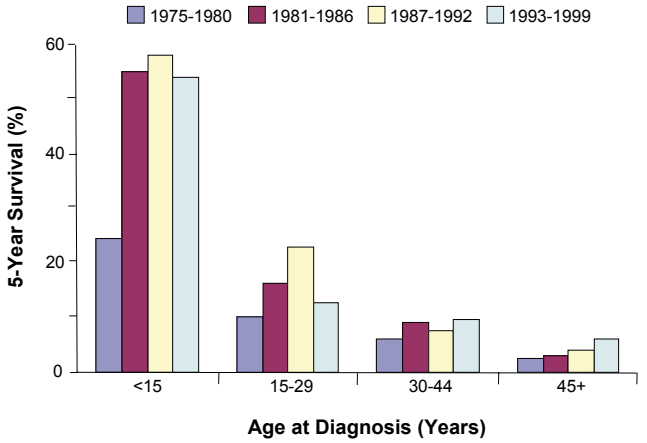

Figure 11.8: Liver & Intrahepatic Bile Duct Cancer 5-Year Survival Rate by Era, SEER 1975-1999

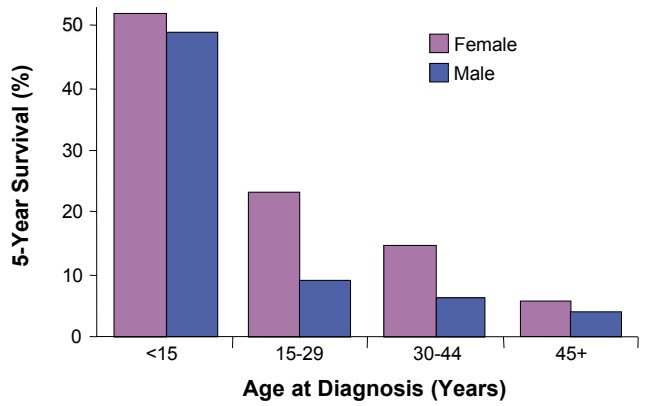

Figure 11.9: Liver & Intrahepatic Bile Duct Cancer, 5-Year Survival Rate by Gender, SEER 1975-1999

xenobiotic metabolism, DNA repair, and immune system genes are all under extensive investigation and have been found to modify the risk of HCC in some studies.[33-35]

SUMMARY

Primary neoplasms of the liver accounted for 1% of all neoplasms in those 15 to 29 years of age, with HCC the most common tumor. The estimated incidence of liver *and* intrahepatic bile duct tumors increased with age, from 2.0 per million in individuals 15 to 19 years of age to 14.6 per million for those 25 to 29 years of age. The incidence of liver tumors was relatively constant between 5 and 35 years of age, but then increased progressively with increasing age. Although there was no gender predilection in the adolescent and young adult age group, male incidence increased more than female incidence with advancing age. Liver tumors were more prevalent in Asians/Pacific Islanders, followed by African Americans/blacks, in comparison to white non-Hispanics and Hispanics. Mortality decreased significantly over time (1975 to 2000) for patients younger than 45 years of age. Survival improved significantly for individuals younger than 15 years of age, but progress has been much slower for older individuals. Chronic infection with hepatitis B virus has been the leading cause of HCC in children, adolescents, and young adults in Asian and African countries. However, the introduction of a universal program of hepatitis B immunization to prevent the carrier state in children has shown a dramatic decrease in chronic hepatitis B virus prevalence and a decline in the rates of HCC.

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