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HIGHLIGHTS

Incidence

- Primary neoplasms of the liver are rare in children, comprising only 1.1% of malignancies for children younger than 20 years of age. In the US, 100-150 children are diagnosed with liver cancer each year.
- Primary liver cancer is subdivided into the following histologic subtypes: hepatoblastoma comprises over two-thirds of the malignant tumors of the liver in children and adolescents (79% <15 years of age; 66% <20 years of age) and hepatocellular carcinoma accounts for most of the remaining cases. Hepatoblastoma occurs primarily in children younger than 5 years of age while hepatocellular carcinoma occurs primarily after 10 years of age (Figure VII.2).
- The rate of hepatoblastoma was highest among infants with rates rapidly declining with increasing age (Figure VII.3). In contrast, the incidence of hepatocellular carcinoma increased as age increased (Figure VII.2).
- For those younger than 20 years of age, there was little change in liver cancer incidence during the 21-year period, with rates between 1.4 and 1.6 per million throughout the time period (Table VII.1).
- The incidence of hepatoblastoma for children younger than 15 years of age increased during the 1975-95 period while the incidence of hepatocellular carcinoma decreased during the same period (Figure VII.4).

Survival

- Five-year survival rates for children with hepatoblastoma improved from 51% to 59% between 1976-84 and 1985-94 (Figure VII.5). Survival rates were substantially lower for children and adolescents with hepatocellular carcinoma, with an improvement in 5-year survival rates from 31% for the years 1976-84 to 42% for the years 1985-94 (Figure VII.5).

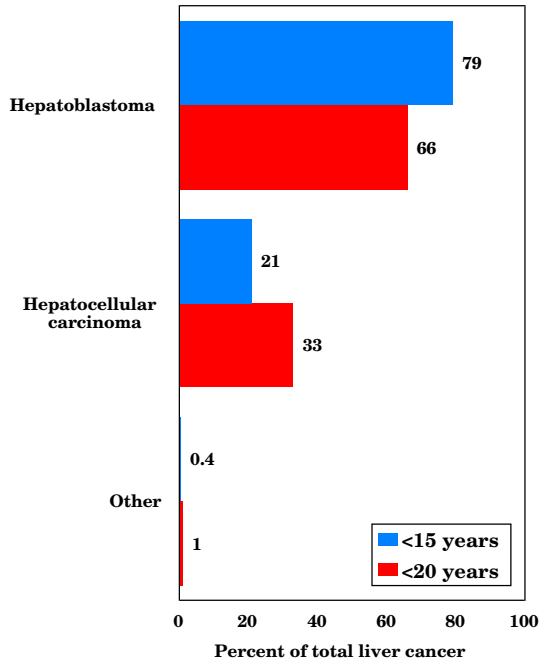
Risk factors

- The etiology of hepatoblastoma is as yet unknown but there are some tantalizing clues (Table VII.2).

INTRODUCTION

Primary neoplasms of the liver are rare in children, comprising only 1.1% of malignancies in SEER areas for children younger than 20 years of age. The ICCC category for liver cancers (VII) is subdivided into the following histologic subtypes: hepatoblastoma (VIIa), hepatic carcinomas (hepatocellular carcinoma) (VIIb), and "unspecified" tumors of the liver (VIIc) [1]. In the US, 100-150 children younger than 20 years of age are diagnosed with hepatic tumors each year. Hepatoblastoma comprises over two-thirds of the malignant tumors of the liver in children (79% younger than 15 years of age; 66% younger than 20 years of age) and hepatocellular carcinoma accounts for most of the remaining cases. Most patients with hepatoblastoma are younger than 4 years of age at diagnosis, while hepatocellular carcinoma occurs primarily after 10 years of age.

Figure VII.1: Distribution of liver cancer by histology and age, all races both sexes, SEER 1975-95



INCIDENCE

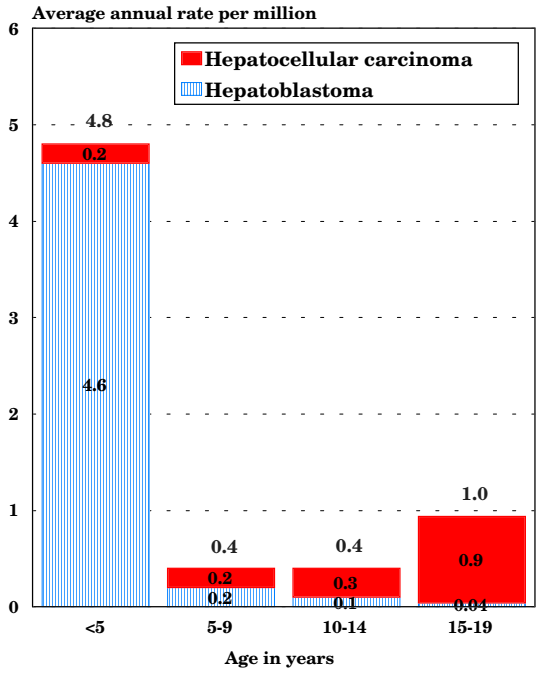
During the 21-year period from 1975 through 1995, there were 316 children younger than 20 years of age in SEER areas who were diagnosed with a primary liver cancer, with 262 (83%) of these children being younger than 15 years of age at the time of diagnosis. Figure VII.1 shows that the majority of these cancers were hepatoblastomas, with the remainder being almost exclusively hepatocellular carcinomas. For the entire 21-year period, hepatoblastoma represented 79% of the liver cancers for the younger than 15 year age group, although for the most recent 6-year period (1990-95) hepatoblastoma accounted for an even higher proportion (90%) of childhood liver cancers.

Age-specific incidence

The incidence rates for hepatoblastoma and hepatocellular carcinomas were very age-dependent. Among children younger than 5 years of age, over 95% of liver cancers were hepatoblastoma, whereas hepatoblastoma was distinctly uncommon for older age groups (Figure VII.2). Within the younger than 5-year age group, the rate of hepatoblastoma was highest among infants with rates rapidly declining with increasing age (Figure VII.3).[1] During the most recent period (1986-94), the incidence rate during infancy was approximately 11.2 per million. In contrast to the age-incidence relationship for hepatoblastoma, the incidence of hepatocellular carcinoma increased with each successive 5-year age group, with rates for 15-19 year olds (0.9 per million) being substantially higher than for any of the younger age groups (Figure VII.2).

[1] Enumeration of the population at risk by single years of age was available only for the census years 1980 and 1990. The US Bureau of the Census provides intercensal population estimates by 5-year age groups, but not by single years of age. Therefore, the population estimates for 1980 were used in rate calculations for cases diagnosed from 1976-84 and the 1990 estimates were used for cases diagnosed from 1986-94.

Figure VII.2: Liver cancer age-specific incidence rates by histology and age all races, both sexes, SEER, 1986-95



Sex and race-specific incidence

For children younger than 15 years of age, the incidence of liver cancers was slightly higher in males than females (male:female ratio = 1.2) and somewhat lower in black children compared with white children (1.3 per million versus 1.6 per million). For children younger than 20 years of age, incidence rates were similar for blacks and whites (1.4 per million versus 1.5 per million) and were slightly higher for males than females (male:female = 1.2). The incidence of hepatoblastoma was slightly higher in males than females (male:female = 1.2), while the incidence of hepatocellular carcinoma was similar in both sexes (male:female = 1).

TRENDS

The incidence for total liver cancers in children younger than 15 years of age increased slightly from 1975 to 1995. The rate was 1.4 per million for 1975-79 and increased to 1.7 per million for 1990-95 (Table VII.1). For children younger than 20 years of age, there was little change in liver cancer incidence during the 21-year period, with rates between 1.4 and 1.6 per million throughout the time period (Table VII.1).

The incidence of hepatoblastoma increased markedly during the 1975-95

Figure VII.3: Hepatoblastoma and hepatocellular carcinoma age-specific incidence rates all races, both sexes SEER, 1976-84, 1986-94

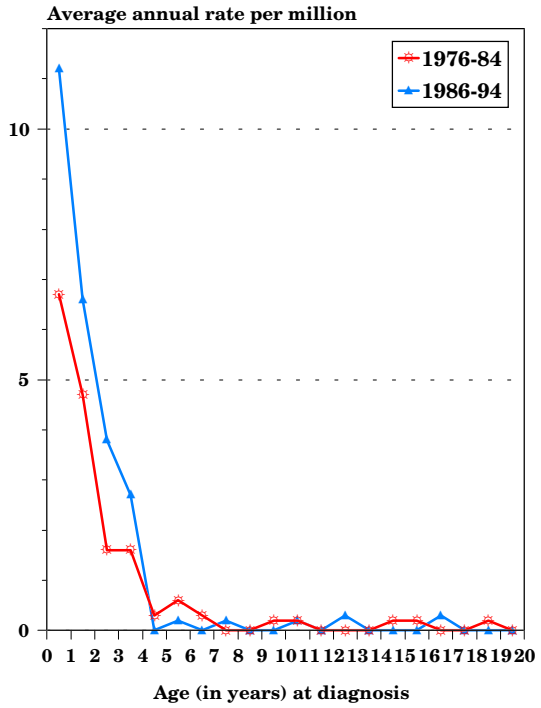


Table VII.1: Age-adjusted* incidence rates per million of liver cancers by age group, type, and time period, all races, both sexes, SEER, 1975-95

<15 Years

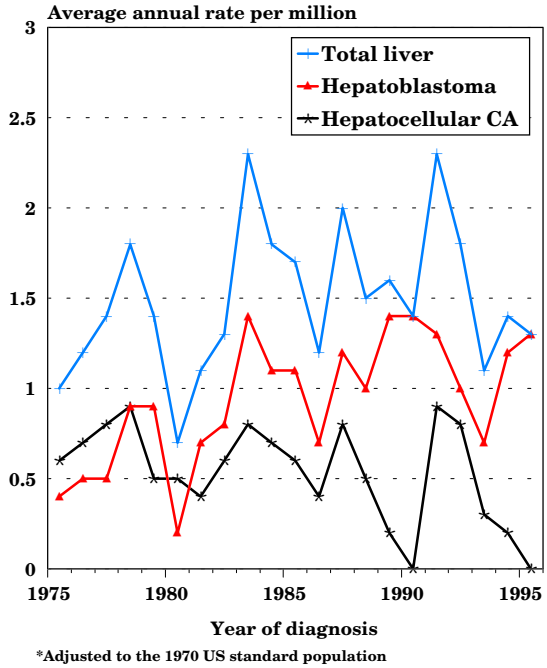
Diagnosis	ICCC Category	1975-79	1980-84	1985-89	1990-95	1975-95
Hepatic tumors (total)	VII(total)	1.4	1.6	1.7	1.7	1.6
Hepatoblastoma	VIIa	0.8	1.1	1.4	1.5	1.3
Hepatocellular carcinoma	VIIb	0.6	0.5	0.3	0.2	0.4

<20 Years

Diagnosis	ICCC Category	1975-79	1980-84	1985-89	1990-95	1975-95
Hepatic tumors (total)	VII(total)	1.4	1.4	1.6	1.5	1.5
Hepatoblastoma	VIIa	0.6	0.9	1.1	1.1	1.0
Hepatocellular carcinoma	VIIb	0.7	0.6	0.5	0.4	0.5

*Adjusted to the 1970 US standard population

Figure VII.4: Trends in liver cancer age-adjusted* incidence rates by histology, age <20 all races, both sexes, SEER, 1975-95



*Adjusted to the 1970 US standard population

period (Figure VII.4). The incidence rate for children younger than 15 years of age from 1975-79 was 0.8 per million and increased to 1.5 per million for 1990-95 (Table VII.1). The incidence of hepatocellular carcinoma decreased during the period 1975-95, in contrast to the increase observed for hepatoblastoma (Figure VII.4). For children younger than 15 years of age, the rate decreased from 0.6 per million in 1975-79 to 0.2 per million for 1990-95 (Table VII.1). Possible changes over time in the assignment by histologic category could only account for a small portion of the observed opposite trends in incidence for hepatoblastoma and hepatocellular carcinoma.

SURVIVAL

Five-year survival rates for children with hepatoblastoma improved from 51% to 59% between 1975-84 and 1985-94 (Figure VII.5). Survival rates were substantially lower for children and adolescents with hepatocellular carcinoma, with an improvement in 5-year survival rates from 31% for the years 1975-84 to 42% for the years 1985-94 (Figure VII.5).

RISK FACTORS

Table VII.2 briefly summarizes current knowledge on causes of hepatoblastoma. The etiology of hepatoblastoma is as yet unknown but there are some tantalizing clues. One case-control study reported elevated odds ratios with specific parental occupational exposures, including maternal exposures to metals, petroleum products, and paints, and paternal exposures to metals [2]. There have also been isolated case reports of hepatoblastoma occurring in association with fetal alcohol syndrome [3], oral contraceptive use during pregnancy [4], hormonal treatment for sterility [5], and liver transplantation in the mother combined with immunosuppressive treatment throughout pregnancy [6]. Investiga-

Figure VII.5: Hepatoblastoma and hepatocellular carcinoma 5-year relative survival rates age <20, all races, both sexes SEER (9 areas), 1975-84 and 1985-94

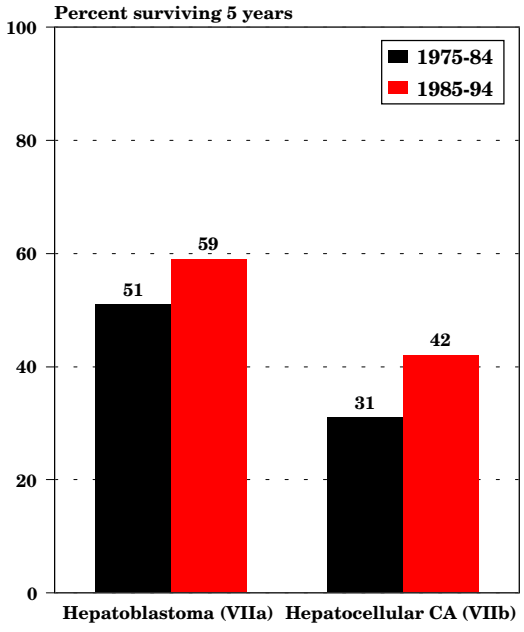


Table VII.2: Current knowledge on causes of hepatoblastoma

Exposure or Characteristic	Comments	References
Known risk factors		
Beckwith-Wiedemann syndrome, hemihypertrophy	Hepatoblastoma, Wilms' tumor and adrenocortical carcinoma are associated with these syndromes that involve organomegaly.	11,20,21
Family history of familial adenomatous polyposis and Gardner's syndrome	Both these syndromes involve multiple colonic polyps, have an autosomal dominant inheritance, and are caused by mutations in the APC gene.	10,22-24
Factors for which evidence is inconsistent or limited		
Parental occupational exposures	Associations with metals, petroleum products, paints and pigments were reported from the only case-control study done to date.	2

tors in Japan recently noted that hepatoblastoma accounted for more than 50% of early malignancies among Japanese children who were of extremely low birth weight (<1000gm) [7,8]. This finding raises the possibility that factors associated with prematurity and its treatment may play a role in the occurrence of hepatoblastoma. As a result, the marked improvement in survival in recent years of extremely low birth weight infants could in part be responsible for a notable increase in hepatoblastoma rates in the United States [9].

Hepatoblastoma has been associated with familial adenomatous polyposis as well as with syndromes involving organomegaly (e.g., Beckwith-Wiedemann syndrome and isolated hemihypertrophy) [10,11]. Genes that are altered in the tumor cells from some cases of hepatoblastoma and that likely play an important role in the pathogenesis of hepatoblastoma include the APC gene (which is responsible for familial adenomatous polyposis) and the b-catenin gene [12]. Another molecular abnormality observed in some cases of hepatoblastoma is loss of heterozygosity in the region of chromosome 11 that is associated with Beckwith-Wiedemann syndrome [13].

Hepatocellular carcinoma in children is most common in regions of the world where adult hepatocellular carcinoma is also highly prevalent, for instance in sub-Saharan Africa and Eastern Asia [1] and among Alaskan Natives [14]. Chronic infection with hepatitis B virus has been implicated as the leading cause of hepatocellular carcinoma in children and young adults. Universal hepatitis B immunization will prevent the carrier state in children and will lead to a dramatic reduction in hepatocellular carcinoma, as demonstrated during the past decade in Taiwan [15]. Chronic infection with hepatitis C virus (e.g., among hemophiliac males) is an emerging risk factor for hepatocellular carcinoma during adolescence [16]. Genes that are altered in the tumor cells from some cases of hepatocellular carcinoma and that may play a role in its pathogenesis include the β-catenin gene [17,18] and the MET protooncogene [19].

SUMMARY

Liver cancers are uncommon in children and represented only 1.1% of malignancies in SEER areas for children younger than 20 years of age, with an annual incidence rate of 1.5 per million (1975-95). Hepatoblastoma was the most common malignancy of the liver in children and its incidence was highest during the first year of life and decreased rapidly with increasing age. Hepatocellular carcinoma was the second most common malignancy of the liver and occurred primarily among adolescents. While the incidence of hepatoblastoma increased from 1975-95, the incidence of hepatocellular carcinoma decreased.

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