Few causes of hepatoblastoma have been conclusively identified, mainly due to the extreme rarity of the disease. Inherited conditions including Familial Adenomatous Polyposis and Beckwith–Wiedemann Syndrome dramatically raise risk of hepatoblastoma but account for few cases overall. A small number of case–control studies investigating risk factors for sporadic hepatoblastoma have been conducted to date. Although most of these studies feature fewer than 200 cases, several clues have emerged. Most notably there is a roughly 20-fold increased risk of hepatoblastoma among children with very low birth weight (<1,500 g) and a doubling of risk among those with moderately low birth weight (1,500–2,500 g). A modicum of evidence points to a possible role of parental tobacco use prior to or during pregnancy in the causation of hepatoblastoma as well.

**INTRODUCTION**

The etiology of hepatoblastoma, like that of most childhood cancers, is mostly obscure. The main impediment to identifying its causes is its extreme rarity. Incidence rates are difficult to calculate precisely, hampering the ability to make comparisons across populations. Meanwhile only a handful of case–control studies, with fairly small sample sizes, have been conducted to date. Despite these limitations several clues have emerged, most notably the prominent association of hepatoblastoma with small size at birth, which suggest that determining etiology may be possible for at least a fraction of patients.

**DESCRIPTIVE EPIDEMIOLOGY**

During 2002–2008 the rate of HB in the United States Surveillance, Epidemiology, and End Results (SEER) program data were 10.5 and 5.2 cases per million children <1 and 1–4 years, respectively, and was too infrequent thereafter to calculate incidence (Fig. 1) [1]. An estimate of SEER data in 1999 suggested that about 100 cases of HB are diagnosed each year in the United States [2]. However, as incidence of HB has risen roughly 4% per year between 1992 and 2004, faster than for any other childhood cancer, the current number of cases per year likely is higher [3]. Five-year survival for HB was 74% in the most recent period, which is relatively low for a childhood cancer [1].

Incidence of hepatoblastoma appears to vary little between nations, although true differences are difficult to detect given the instability of rates calculated in the single digits per million. Parkin et al. [4], in the International Incidence of Childhood Cancer, provided the most comprehensive compilation of rates across the globe. Most estimates of rates among children 0–14 years of age ranged between 0.5 and 2, with no discernible pattern of difference between continents. These data from the 1980s and early 1990s may not, however, be reflective of recent experience given the documented rise in incidence in several countries. However, there is no convenient single contemporary source of incidence data worldwide. The rising incidence noted in the United States was not apparent in Europe during 1978–1997. While there was a nominal 1% rise in hepatoblastoma incidence in the ACCIS system, including data from 19 European countries, it was not significant [5]. Hepatoblastoma is slightly more frequent in males but shows no noticeable difference in incidence by ancestry in the United States [2].

**ETIOLOGIC RESEARCH**

The assumption is that hepatoblastoma originates in utero, for a number of reasons. Given that incidence of hepatoblastoma is highest at birth the necessity for a latent period strongly suggests initiation during gestation, as does the histologic resemblance of HB cells to embryonal liver cells. Case reports of antenatal diagnosis also provide proof-of-principle [6]. Hence, many investigations of hepatoblastoma focus on exposures or events occurring around gestation.

**Inherited Syndromes**

HB is a rare outcome in Familial Adenomatous Polyposis (FAP), which results from inactivating mutations of the APC gene. Incidence of HB among children 0–4 years of age in the Johns Hopkins Polyposis registry was 847 (95% CI: 230–2,168) times the incidence in the SEER population [7]. Two studies have estimated the proportion of HB cases with germ line APC mutations with disparate results; Harvey et al. [8] detected no APC mutations out of 29 cases examined while Hirschman et al. [9] detected 8 out of 93 cases (9%). Descriptions of the methods were not clear enough to determine if differences in mutation detection might be attributable to technology.

Beckwith–Wiedemann syndrome (BWS) is an overgrowth syndrome, characterized by gigantism, macroglossia, omphalocele, hemihyper trophy, and neonatal hypoglycemia. Most cases are attributed to defective imprinting of the IGF2-H19 locus on chromosome 11p15, with uniparental disomy (UPD) underlying many of the remainder [10]. The rate of HB among children ages 0–4 years in a BWS registry was 2,280 (95% CI: 928–11,656) times that of the US population of the same age [11].

Trisomy 18 (Edwards Syndrome) occurs in 1 in 3,000 to 1 in 7,000 births and survival beyond the first year is rare [12]. It is

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**Key words:** case–control studies; hepatoblastoma; prematurity

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associated with multiple congenital anomalies including heart defects, cranio-facial anomalies, skeletal abnormalities, intrauterine growth retardation and short stature, microcephaly and mental retardation. At least seven cases of HB in children with trisomy 18 have been published [13]. This suggests an etiologic association rather than chance given the rarity of the two conditions. However, the incidence of HB among children with trisomy 18 is unknown and, given the high mortality during infancy, will be difficult to estimate.

In addition, HB in children with a variety of other inherited syndromes has been the subject of case reports. These include Simpson–Golabi–Behmel syndrome, Prader–Willi syndrome, Sotos syndrome, Kabuki syndrome, Neurofibromatosis type 1, Fanconi Anemia, Tyrosinemia type 1, Noonan syndrome, DiGeorge syndrome, and a FGFR3 mutation [14]. However, as these syndromes have been reported in only one or two patients they are presumed not to be important causes of HB.

**Congenital Anomalies**

Hepatoblastoma has been associated with congenital anomalies in a few studies [15–17] and case reports [18–20]. In the largest study, the prevalence of congenital anomalies among 165 hepatoblastoma cases was examined in the British National Registry of Childhood Tumors; 6.4% of cases displayed anomalies, of various types, which was a significantly greater proportion than among reference populations [15]. Other studies have yielded estimates as high as 14% [16] and 41% [17]. These markedly different results highlight the difficulty of consistent assessment and classification of congenital anomalies. Especially among studies collecting data by self-report the prevalence of anomalies may be sensitive to questionnaire design. The extent to which these associations are independent from known risk factors is unclear. For example, BWS often presents with anomalies such as omphaloceles while major anomalies are over represented among children with very low birth weight [21].

**Gestational Risk Factors**

As we have mentioned, very low birth weight (VLBW; variably defined, but generally <1,500 g) is strongly associated with HB (Table I) [16,17,22–27]. Reports supporting this association come from diverse nations, including the United States [16,22,24,25], the United Kingdom [17], the four Nordic countries [27], Japan [26], and China [23] (Table I), indicating that whatever phenomenon underlies these observations is widespread.

Moderately low birth weight (1,500–2,500 g) demonstrated smaller but still elevated OR’s of around 2–3 as well in the two larger studies [25,26]. Gestational age was not independently associated with hepatoblastoma in one study that controlled for it simultaneously with birth weight [25], although it was in another [27]; virtually all VLBW newborns are born prematurely to some degree. For convenience’ sake we will use the term VLBW rather than preterm, premature, or intrauterine growth restricted, while acknowledging that the relationship of hepatoblastoma to birth weight and gestational age is likely more complex than reported to date.

The association of hepatoblastoma with VLBW appears to have emerged in the mid-to-late 1980s and was first noted in the mid-1990s [28]. In Japan, the proportion of hepatoblastoma cases with birth weight <1,000 g and 1,000–1,499 g rose

**TABLE I. Association Between HB and Low-Birth Weight in Five Regions**

<table>
<thead>
<tr>
<th>Location</th>
<th>N cases</th>
<th>Lowest reported birth weight category (g)</th>
<th>Odds ratio (95% CI)</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>Japan</td>
<td>543</td>
<td>&lt;1,000</td>
<td>15.6 (7.6–31.1)</td>
<td>[26]</td>
</tr>
<tr>
<td>United Kingdom</td>
<td>18</td>
<td>&lt;1,500</td>
<td>69.0 (12.0–397.2)</td>
<td>[17]</td>
</tr>
<tr>
<td>United States</td>
<td>273</td>
<td>&lt;1,500</td>
<td>17.2 (7.5–39.5)</td>
<td>[25]</td>
</tr>
<tr>
<td>China</td>
<td>87</td>
<td>&lt;2,500</td>
<td>26.0 (14.0–65.7)</td>
<td>[23]</td>
</tr>
<tr>
<td>Nordic countries</td>
<td>155</td>
<td>&lt;1,500</td>
<td>9.5 (2.3–38.2)</td>
<td>[27]</td>
</tr>
</tbody>
</table>
dramatically in 1988–1994 compared to the previous 5 years [26]. In the United States, it has been noted that the increase in hepatoblastoma incidence parallels the increasing proportion of infants born VLBW [29]. These observations are consistent with two explanations.

First, hepatoblastoma may be initiated, or a nascent tumor promoted, by iatrogenic hazards encountered in Neonatal Intensive Care Units (NICUs) [30] in combination with the lessened xenobiotic [31] and antioxidant [32] defense mechanisms of preterm infants. While NICUs entail exposure to multiple interventions [33], a few stand out for their potential carcinogenicity. For instance, infants in NICUs receive frequent diagnostic irradiation, although one large dosimetry study estimated a median cumulative liver dose of 414 μSV [34], although this is far lower than 10 mSV limit below which the risk of fetal irradiation is unclear [35]. A large proportion of infants weighing <1,500 g receive high-fraction oxygen for extended periods of time, leading to a constellation of diseases sometimes termed “oxygen radical disease of neonatology” [36]. Lastly, total parenteral nutrition (TPN) may also be a source of oxygen radicals [37]. A further concern with TPN is that the plasticizer di-(2-ethylhexyl)phthalate, which is a rodent hepatocarcinogen, leaches from tubing and its metabolites can be detected in infants [38].

Two small studies from Japan (n = 12 [39] and n = 15 [40] cases) have compared exposures in the NICU between VLBW hepatoblastoma cases and controls. Each suggested that cases had more days on oxygen therapy and more use of the diuretic furosemide, however, these are very tentative conclusions given the sample sizes. Another study from Japan compared a biomarker of oxidative DNA damage, 8-hydroxy-2'-deoxyguanosine (8-OHdG), in the livers of 9 cases and 14 controls [41]. While there were higher levels of 8-OHdG among cases the relatively few cases limits the strength of any conclusions to be drawn from this study. A larger case–control study by the United States Children’s Oncology Group designed to address the issue of NICU exposures and hepatoblastoma will be reporting results in the near future [42].

Alternatively, rather than hepatoblastoma being caused or promoted by exposures in the NICU, it may be that hepatoblastoma and VLBW share a common etiology and the increasing survival of small infants that began in the 1980s brought the association to light. VLBW has numerous environmental and genetic causes, making this hypothesis more difficult to test.

Hepatoblastoma has also been associated with pre-eclampsia [17], poly- or oligohydramnios [17,22,23], high maternal pre-pregnancy weight [22,23], and treatment for infertility [22]. In the latter study in vitro fertilization, use of fertility drugs, and triplet birth as recorded on birth certificates and combined into a composite variable were far more prevalent among cases than controls (OR = 9.2; 95% CI: 2.1–31.5). Of note, in vitro fertilization has also been associated with BWS [43], but was not accounted for in the latter study. Hepatoblastoma has not been associated with maternal or paternal age [44].

### Parental Tobacco Use

Several studies have suggested that maternal and paternal tobacco smoking are associated with hepatoblastoma, although the literature differs with regards to whether maternal or paternal use and the timing of exposure (pre- or post-conception) influence risk (Table II) [22,23,45–47]. The United Kingdom Childhood Cancer Study (UKCCS) was the first to note a link, having noted the significant association of maternal preconception smoking with hepatoblastoma, alone among all childhood cancers, despite having only 28 cases [46]. Examining the data in further detail, there was a suggestive trend in the OR with rising maternal preconception cigarette consumption that fell just short of significance. Paternal preconception cigarette consumption approached significance (OR = 2.2; 95% CI: 0.9–5.1) but maternal consumption during pregnancy was not associated with disease. Notably the OR was markedly elevated if both the mother and father smoked prior to conception (OR = 4.7; 95% CI: 1.6–13.35). These observations remained after adjustment for birth weight.

Data on 43 hepatoblastoma cases from an earlier UK study, the Oxford Survey of Childhood Cancer, were next examined [47]. The magnitude and significance of associations was sensitive to the choice of model, but in at least one analysis the OR of 2.69 (95% CI: 1.18–6.13) for both maternal and paternal smoking approached that seen in the UKCCS. However, the period of exposure was not clearly distinguished in these data.

Two subsequent studies in New York and China examined maternal smoking during pregnancy without regard to the amount or timing, finding similar ORs [22][23]. Notably, the New York study analyzed data collected prospectively and not subject to differential recall between cases and controls. However, the most recent study, also based on prospectively collected data in the collective registries of the four Nordic countries found no association of maternal smoking with hepatoblastoma [27].

On the basis of four studies [22,45–47], the International Agency for Research on Cancer determined in 2009 that the evidence was sufficient to declare parental tobacco smoking a carcinogen to the fetal liver [48].

### TABLE II. Association Between Hepatoblastoma and Parental Smoking

<table>
<thead>
<tr>
<th>Ref.</th>
<th>N cases/controls</th>
<th>Data source</th>
<th>Association with parental smoking</th>
</tr>
</thead>
<tbody>
<tr>
<td>Buckley et al.</td>
<td>75/75</td>
<td>Interview</td>
<td>No association with maternal or paternal smoking</td>
</tr>
<tr>
<td>Pang et al.</td>
<td>27/6,987</td>
<td>Interview</td>
<td>OR maternal preconception smoking 2.7 (95% CI: 1.2–6.2)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>OR for both parents smoking pre-conception 4.7 (95% CI: 1.7–13.4)</td>
</tr>
<tr>
<td>Sorahan and Lancashire</td>
<td>43/5,777</td>
<td>Interview</td>
<td>OR for both parents smoking pre-conception or during pregnancy 2.7 (95% CI: 1.2–6.1)</td>
</tr>
<tr>
<td>McLaughlin et al.</td>
<td>58/6,056</td>
<td>Birth records</td>
<td>OR for maternal smoking during pregnancy 2.1 (95% CI: 1.0–4.2)</td>
</tr>
<tr>
<td>Pu et al.</td>
<td>97/92</td>
<td>Interview</td>
<td>OR for maternal smoking during pregnancy 2.7 (95% CI: 1.2–6.1)</td>
</tr>
<tr>
<td>de Fine Licht et al.</td>
<td>155/775</td>
<td>Medical registers</td>
<td>No association with maternal smoking; paternal smoking not examined.</td>
</tr>
</tbody>
</table>
Other Risk Factors

The rarity of hepatoblastoma and the paucity of initial clues to its etiology led to investigations of a wide range of potential risk factors. Buckley et al. [45] conducted the broadest survey, which noted no associations with maternal alcohol or estrogen use but found significant associations with maternal and paternal occupational exposure to metals. No subsequent reports addressing parental exposure appear in the literature.

Due to its prominent role in causing hepatocellular carcinoma, hepatitis B virus infection has also been investigated in hepatoblastoma. There was no such association either in a United States case-control study [45] or a compilation of data from case series [49]. Moreover, incidence is not notably higher in areas with endemic hepatitis B virus [4]. We may reasonably conclude that hepatoblastoma is unrelated to this pathogen.

Two reports have addressed single-nucleotide polymorphisms (SNPs) and hepatoblastoma. A functional SNP in the promoter region of the myeloperoxidase gene significantly reduced risk of hepatoblastoma [50] while a splice-site variant in the gene encoding Cyclin D1 was associated with age of onset of disease [51]. However, no further studies of these genes has been reported and in fact replication would be surprising given the poor track record of candidate gene studies. Application of genome-wide arrays, though not necessarily genome-wide association studies due to its etiology led to investigations of a wide range of potential risk factors. Buckley et al. [45] conducted the broadest survey, which noted no associations with maternal alcohol or estrogen use but found significant associations with maternal and paternal occupational exposure to metals. No subsequent reports addressing parental exposure appear in the literature.

CONCLUSION

Several intriguing associations with hepatoblastoma have emerged despite a small epidemiologic literature consisting of less than a dozen studies. Most notably, the very strong association with VLBW calls for explanation, while that with smoking requires further replication. Although progress in determining the etiology of this very rare tumor has been slow recent interest suggests that it will soon accelerate.

REFERENCES

11. Buckley RR, Fawaz R, Tomlinson GE. Other Risk Factors requires further replication. Although progress in determining the etiology of this very rare tumor has been slow recent interest suggests that it will soon accelerate.