Increased Risk of Hepatoblastoma among Immature Children with a Lower Birth Weight

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ABSTRACT

Hepatoblastomas among children with very low birth weights have significantly increased recently, according to the data from the Japan Children’s Cancer Registry for the years 1985–1993. We then analyzed more Registry data for 1969–1994 to clarify the possible relationship between low birth weight and hepatoblastoma.

The percentage of low birth weights was compared between 543 hepatoblastoma children in the Registry and all live births in Japan in four successive periods during the 26 years from 1969 to 1994, in relation to the given birth year. The percentage of children with birth weights of 1500–1999 g among hepatoblastomas was higher, at 2.94–1.60%, than that among all live births in each of the four periods (0.79–0.92%), and the percentage of children with birth weights of 2000–2499 g was slightly higher. The percentage of children with birth weights of <1500 g and, especially, <1000 g, has increased rapidly among children born after 1988 (1.60 and 6.40%, respectively), when most very low birth weight infants began to survive. Compared with children with birth weight of 2500 g or more, the relative risks of hepatoblastoma among children with birth weights of <1000, 1000–1499, 1500–1999, and 2000–2499 g were 15.64 ($P < 0.001$), 2.53 ($P = 0.129$), 2.71 ($P = 0.001$), and 1.21 ($P = 0.381$), respectively, suggesting the lower the birth weight, the higher the risk of hepatoblastoma. There was no association between hepatoblastomas with a low birth weight and either age at diagnosis or congenital malformations or light-for-date weight.

The risk of hepatoblastoma for low birth weight children may be inherently high, especially for lower birth weights, and the recent rapid increase may be a result of an increase in the number of more immature infants with a more sensitive liver and also more frequent exposure to risk factors related to perinatal treatment.

INTRODUCTION

Hepatoblastoma is the most common malignant hepatic tumor in childhood and is considered to be an embryonal tumor caused by developmental disturbances during organogenesis. Using the database of the Japan Children’s Cancer Registry (1985–1993), we found that the percentage of very low birth weights (<1500 g) among patients with hepatoblastoma had significantly increased from 1990 to 1993 (1). Ross (2) called for these observations to be confirmed in different countries.

Because perinatal medicine has rapidly progressed and its services have become standard, the survival of children with low birth weights has increased recently in Japan. Are hepatoblastomas that developed in fetal life being detected now because of improved survival of low birth weight infants? Or does hepatoblastoma tend to occur in children with a very low birth weight? To clarify these points, we analyzed the possible relationship between hepatoblastoma and birth weight in relation to a given birth year, based on the data in the Registry for 26 years, from 1969 to 1994.

MATERIALS AND METHODS

The Japan Children’s Cancer Registry was established in 1969. Its annual nationwide survey includes all malignant neoplasms and related conditions diagnosed in patients under 15 years of age at pediatrics, pediatric surgery, and other departments of major hospitals in Japan (3).

Because the Registry is estimated to account for ~50–60% of all childhood cancers in Japan and fluctuates slightly each year, it is not suitable to compare the annual incidence rate of patients. Hence, the rate of low birth weights was compared between hepatoblastoma patients and the general population of Japan. There were 543 children with hepatoblastoma born from 1969 to 1994, including 52 cases with a low birth weight (9 cases weighing <1000 g, 4 weighing 1000–1499 g, 12 weighing 1500–1999 g, and 27 weighing 2000–2499 g) and 21,780 patients with other childhood cancers, including 1,246 cases with a low birth weight.

Data used on the general Japanese population were the frequency of live births by birth weight and year from the Vital Statistics of Japan (4). To determine light-for-date weight, the standard values of mean and SD of birth weight in Japan, by sex, parity, and gestational week (5), were used. In the “Discussion,” the numbers of malignant tumors among stillbirths and neonatal deaths were obtained from tables on the number of malignant tumors by age and tissue type in the Annual Report of the Pathological Autopsy Cases in Japan (1982–1994; Ref. 6).

The difference in the percentage of low birth weights between patients with hepatoblastoma and the general population was examined by χ² test. The risk of hepatoblastoma among low birth weight children was presented as a relative risk compared with non-low birth weight children (≥2500 g) and assessed by χ² test. The comparison of age at diagnosis of hepatoblastoma between low and non-low birth weight children was analyzed by the Mann-Whitney U test.

The percentage of light-for-date weight among low birth weight patients was compared between hepatoblastoma and other childhood cancer using χ² test or Fisher’s exact test.

RESULTS

Relationship between Low Birth Weight and Hepatoblastoma.

Fig. 1 shows the percentages of children with a low birth weight in three groups: patients with hepatoblastoma entered in the Japan Children’s Cancer Registry, patients with the other childhood cancers in the Registry, and children in the general Japanese population (all live births in Japan: Ref. 4), born in four successive periods, 1969–1975, 1976–1981, 1982–1987, and 1988–1994. In the general population, the respective percentages of children with birth weights of <1000, 1000–1499, and 2000–2499 g tended to increase slightly with time. Among childhood malignancies other than hepatoblastoma, the percentages of low birth weights (<2000 g) were similar to those in the general population, but those with weights of 2000–2499 g were slightly higher throughout the four periods mentioned.

On the other hand, among children with hepatoblastoma, the percentage of birth weights of <1000 g was low, at 0–0.79% in the first to the third periods, similar to that in the general population, but rapidly increased to 6.40% in the fourth period, which was significa-
cantly higher than the 0.19% in the general population ($P < 0.001$). The percentage of birth weights of 1000–1499 g was also low in the first to the fourth periods (0.36%, 0.74%, respectively), as well as in the general population, and increased to 1.60% in the fourth period. The risk was low in the first to the third periods for children with birth weights of <1500 g because of the very low survival rate of these children in those periods (see “Discussion” for details). Over 26 years, the relative risks among children with birth weights of 2000–2499, 1500–1999, 1000–1499, and <1000 g were 1.21, 2.71, 2.53, and 16.64, respectively ($P = 0.381, 0.001, 0.129, \text{and} P < 0.001$). In the fourth period, the relative risk clearly increased from 1.61, 2.02, and 5.10 to 37.57, with the decrease of birth weight. This would suggest that the lower the infant birth weight, the higher the incidence of hepatoblastoma.

**Low Birth Weight and Age at Diagnosis of Hepatoblastoma.** The distribution of age at diagnosis of hepatoblastoma was compared between low birth weights and non-low birth weights ($\geq 2500$ g; Table 2). Because hepatoblastoma patients with a very low birth weight increased in the past several years and many of them have not reached later childhood, the patients compared were limited to children under 5 years of age. Among patients born until 1989 and diagnosed under 5 years of age, there was no significant difference of the diagnosed age in patients with birth weights of <1500 g (median, 17 months; Mann-Whitney $U$ test, $P = 0.236$) and patients weighing 1500–2499 g (median, 7 months; $P = 0.220$), compared to non-low birth weight patients (median, 13 months). Also, for patients born up to 1991 whose hepatoblastomas were diagnosed at under 3 years of age, no significant difference was observed. The minimum age at which hepatoblastoma was diagnosed tended to be later among patients with birth weights of <1500 g than among those with a birth weight of $\geq 2500$ g.

**Relationship with Congenital Malformations and Light-for-Gestation Weight.** Among 52 hepatoblastoma patients with low birth weights, there were only 1 Prader-Willi syndrome and 1 18-trisomy

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**Table 1 Relative risk of hepatoblastoma for low birth weight children**

<table>
<thead>
<tr>
<th>Birth weight (g)</th>
<th>All live births (A)</th>
<th>Hepatoblastoma registered (B)</th>
<th>$(R/B)^a$ per $10^3$ live births</th>
<th>RRb</th>
<th>RR by birth yearc</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>41,248,682</td>
<td>543</td>
<td>1.32</td>
<td>2.91&lt;sup&gt;d&lt;/sup&gt;</td>
<td>2.84</td>
</tr>
<tr>
<td>&lt;2000 g</td>
<td>522,696</td>
<td>25</td>
<td>4.78</td>
<td>3.79&lt;sup&gt;e&lt;/sup&gt;</td>
<td>2.02</td>
</tr>
<tr>
<td>&lt;1000 g</td>
<td>45,655</td>
<td>9</td>
<td>19.71</td>
<td>15.64&lt;sup&gt;e&lt;/sup&gt;</td>
<td>1.00</td>
</tr>
<tr>
<td>1000–1499 g</td>
<td>125,555</td>
<td>4</td>
<td>3.19</td>
<td>2.53</td>
<td>2.51</td>
</tr>
<tr>
<td>1500–1999 g</td>
<td>351,486</td>
<td>12</td>
<td>3.41</td>
<td>2.71&lt;sup&gt;e&lt;/sup&gt;</td>
<td>3.22&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>2000–2499 g</td>
<td>1,764,193</td>
<td>27</td>
<td>1.53</td>
<td>1.21</td>
<td>1.21</td>
</tr>
<tr>
<td>$\geq 2500$ g</td>
<td>38,961,793</td>
<td>491</td>
<td>1.26</td>
<td>1.00</td>
<td>1.00</td>
</tr>
</tbody>
</table>

<sup>a</sup> $R/B$, incidence rate of hepatoblastoma $\times$ registry rate (per 100,000 live births).

<sup>b</sup> RR, relative risk of hepatoblastoma for low birth weight children, compared with children with birth weights of $\geq 2500$ g.

<sup>c</sup> $P < 0.001$, $X^2$ test.

<sup>d</sup> $P < 0.05$, $X^2$ test.

<sup>e</sup> $P < 0.001$, $X^2$ test.
syndrome, which are acknowledged to often be accompanied by hepatoblastoma, 2 congenital heart diseases, and 1 dolichocephaly with undescended testis. There was no specific association with other congenital malformations.

Light-for-date weight was determined according to the Japanese standard birth weight (5). Because the percentage of light-for-date weight was not independent of birth weight logically, it was compared between low birth weight patients with hepatoblastoma and those with other childhood cancers. Regarding all patients as a single parity, the percentage of light-for-date weights (<2 SD) among patients with birth weights of <1500 g was 10.0% (1 of 10) in the hepatoblastoma group and did not significantly differ from the 18.4% (7 of 38) in the group with other childhood malignancies (P = 0.874). Also, for patients with birth weights of 1500–2499 g, there was no significant difference between the two groups, at 30.4 (7 of 23) and 24.4% (185 of 759), respectively.

**DISCUSSION**

The results indicate that the rate of low birth weights was high among hepatoblastoma infants for the 26 years studied, and the rate of very low birth weights, especially those <1000 g, rapidly increased among patients born after ~1988. It was also suggested that the risk of hepatoblastoma was higher for children with lower birth weights. Although the Registry data covers 50–60% of all childhood cancers in Japan, one may not presume that the percentage of low birth weight infants is different between registered and unregistered cases. Moreover, the rate of low birth weights among children with cancers other than hepatoblastoma was almost equal to that among all live births in Japan (Fig. 1). Thus, the observed association of hepatoblastoma with low birth weight seems not to be caused by any Registry sampling bias but rather reflects fact. Because all live births were used as a control population and infant death was not considered, the results of the significance test might be underestimated.

The increase in the rate of low birth weight infants reflects the recent progress and spread of perinatal care in Japan. Following the enactment of the Maternal and Children Health Promotion Law in 1965, many children’s hospitals have been established nationwide, and perinatal medical care has certainly been in place. Judging from the change in the number of early neonatal survivals per 1000 births (<1 week; Ref. 4), for children with birth weights of 2000–2499 g and 1500–1999 g, it was already 977 and 858 in 1969 and then gradually improved even further. This suggests that neonatal care for these children was already standard and then improved even further. Our observation that the relative risk of hepatoblastoma among these children has been high since 1969 but tended to decrease may reflect the improvement of neonatal care for these children with birth weights of ≥1500 g. On the other hand, for children with birth weights of 1000–1499 g, the number of early neonatal survivals per 1000 births rose rapidly from 568 to 882 from 1969 to 1988 and then has increased gradually. The number of children with birth weights of <1000 g was also only 142 in 1972 and increased rapidly to 779 in 1990 and has since been increasing. The neonatal care for such children with a very low birth weight has not yet been established.

Concerning the cause of the association of hepatoblastoma with low birth weight and the recent increase, there are two possible explanations. The first is that hepatoblastoma in a fetus had not been noticed before because of abortion or stillbirth, whereas an immature child now survives due to the recent progress of perinatal care, thus allowing the hepatoblastoma to be detected. As for the reason, there must also be: (a) some cases in which the hepatoblastoma develops in the fetal stages; (b) a fetus with a hepatoblastoma tends to be born earlier; and, conceivably, (c) some chromosomal aberration or genetic mutation may result in both immaturity and hepatoblastoma in early life. The second explanation is that the risk of hepatoblastoma is higher among children with a low birth weight.

If the first explanation is correct, many hepatoblastomas in infants with a low birth weight would be diagnosed at 0 years old; and hepatoblastoma would be frequently detected in stillbirths and neonatal deaths. However, there was no association between birth weight and age at diagnosis of hepatoblastoma (Table 2). Moreover, according to the Annual Report of the Pathological Autopsy Cases in Japan (6), from 1982 to 1994, there were no hepatoblastomas among 52 stillbirths with malignancies and only one hepatoblastoma (0.97%) among 103 neonatal deaths with malignancy in that period. The rate of hepatoblastoma in stillbirths or neonatal deaths does not seem to be high.

If chromosomal aberrations, congenital malformations, or genetic mutations have a role in both low birth weight and hepatoblastoma in early life, the rate of congenital malformations or light-for-date weight would be high among hepatoblastoma children with a low birth weight. In our results, however, no accumulation of specific congenital malformations was observed. The percentage of light-for-date weight among low birth weight infants was not different between hepatoblastoma patients and patients suffering from other childhood cancers. Consequently, the recent increase in hepatoblastomas in connection with low birth weight should not be considered due to the recent increase in survival among children with congenital malformations. (It is undisputable that the possible increase in factors associated with both a very low birth weight and hepatoblastoma may develop in later childhood.)

Thus, the recent marked increase in hepatoblastoma children with a very low birth weight should not be tied to the improved survival of these children who developed hepatoblastoma in the fetal stage but to their inherently high risk of hepatoblastoma and that, due to the improved survival rate, there are more children with a very low birth weight. The higher risk of hepatoblastoma among lower birth weight

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**Table 2** Age at diagnosis of hepatoblastoma by birth weight

<table>
<thead>
<tr>
<th>Comparison 1: cases born between 1969 and 1989 and diagnosed at &lt;5 years of age</th>
<th>Birth weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>&lt;1500 g</td>
</tr>
<tr>
<td>Median</td>
<td>5</td>
</tr>
<tr>
<td>Range</td>
<td>17 M&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>p&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.236</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Comparison 2: cases born between 1969 and 1991 and diagnosed at &lt;3 years of age</th>
<th>Birth weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>&lt;1500 g</td>
</tr>
<tr>
<td>Median</td>
<td>9</td>
</tr>
<tr>
<td>Range</td>
<td>13 M</td>
</tr>
<tr>
<td>p&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.276</td>
</tr>
</tbody>
</table>

<sup>a</sup> M, months of age.

<sup>b</sup> Compared with hepatoblastoma cases with birth weights of ≥2500 g, by Mann-Whitney U test.
INCREASED RISK OF HEPATOBLASTOMA AMONG LOW BIRTHWEIGHT CHILDREN

Increased risk of hepatoblastoma among low birth weight children is very suggestive. Moreover, a surgical and pathological study suggested that hepatoblastoma with unfavorable biological behavior developed in extremely premature children born at 23–25 gestational weeks (7). Lu et al. (8) treated pregnant Erythromus patas monkeys with benzo(a)pyrene by gastric intubation and observed that the DNA adducts level was highest in fetal liver of midgestation (8). In humans also, there have been some reports of the possible effect on hepatoblastoma of alcohol and occupational exposure to metal and petroleum during pregnancy (9, 10). From these results, we suspect that some factors at work during the development and maturation of the fetal organs are responsible for the increased risk of hepatoblastoma in low birth weight infants. Possible factors may include the direct effect of perinatal intensive medical care because of long-term medical treatment and the high sensitivity of the immature liver. As shown in Fig. 1, hepatoblastomas among infants with birth weights of 1500–2000 g has gradually decreased recently. If the same factor has a role in hepatoblastomas among children both weighing <1500 and 1500–2000 g, that factor may well be the perinatal treatment that was generally used for low birth weight infants, at least during the past 26 years, and has recently used for very low birth weight children.

In summary, the risk of hepatoblastoma among low birth weights may have always been high, and the recent rapid increase may be the result of an increase in the number of more immature infants with a more sensitive liver and, also, more frequent exposure to risk factors related to perinatal treatment.

ACKNOWLEDGMENTS

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