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Case-control study of birth characteristics and the risk of hepatoblastoma

Julia E. Heck [a,*], Travis J. Meyers [a], Christina Lombardi [a], Andrew S. Park [a], Myles Cockburn [b], Peggy Reynolds [c], Beate Ritz [a]

[a] Department of Epidemiology, School of Public Health, University of California, 650 Charles E. Young Drive, Box 951772, Los Angeles, CA 90095-1772, USA
[b] Department of Preventive Medicine, USC/Keck School of Medicine, 1441 Eastlake Ave, MC 9175, Los Angeles, CA 90089-9175, USA
[c] Cancer Prevention Institute of California, 2001 Center Street, Suite 700, Berkeley, CA 94704, USA

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ABSTRACT

Background: Hepatoblastoma is a malignant embryonal tumor typically diagnosed in children younger than five years of age. Little is known on hepatoblastoma etiology. *Methods*: We matched California Cancer Registry records of hepatoblastomas diagnosed in children younger than age 6 from 1988 to 2007 to birth records using a probabilistic record linkage program, yielding 261 cases. Controls (n = 218,277), frequency matched by birth year to all cancer cases in California for the same time period, were randomly selected from California birth records. We examined demographic and socioeconomic information, birth characteristics, pregnancy history, complications in pregnancy, labor and delivery, and abnormal conditions and clinical procedures relating to the newborn, with study data taken from birth certificates. *Results*: We observed increased risks for hepatoblastoma among children with low [1500–2499 g, Odds Ratio (OR) = 2.02, 95% confidence interval (CI) 1.29–3.15] and very low birthweight (<1500 g, OR = 15.4, 95% CI 10.7–22.3), preterm birth <33 weeks (OR = 7.27, 95% CI 5.00, 10.6), small size for gestational age (OR = 1.75, 95% CI 1.25–2.45), and with multiple birth pregnancies (OR = 2.52, 95% CI 1.54–4.14). We observed a number of pregnancy and labor complications to be related to hepatoblastoma, including preeclampsia, premature labor, fetal distress, and congenital anomalies. *Conclusion*: These findings confirm previously reported associations with low birthweight and preeclampsia. The relation with multiple birth pregnancies has been previously reported and may indicate a relation to infertility treatments.

1. Introduction

Hepatoblastoma is a malignant liver tumor in young children which accounts for >90% of liver cancers in children less than 5 years of age [1,2]. Incidence peaks in infancy and declines rapidly in the following years, with few diagnoses occurring after age 5. Internationally, incidence is observed to be high in Japan, parts of China, and the US, with the highest US rates seen in California [3]. Hepatoblastoma is more common in males than females and there is some evidence of variation by ethnicity, with US rates lowest in African Americans [4]. The incidence of hepatoblastoma has risen in the US over the past 40 years, from 0.8 per million in the 1970's to 1.5 per million in the early 1990's [4], which suggests non-genetic factors are likely to be important in its etiology.

Due to its rarity there are only a small number of published epidemiologic studies of hepatoblastoma, making it difficult to draw conclusions regarding causality. The strongest risk factor observed thus far is low or very low birthweight [5–15]. Hepatoblastoma has been additionally linked to medical treatments, such as neonatal oxygen supplementation and furosemide treatment, which may reflect necessary interventions in low birthweight or preterm infants [14–16]. There are additional associations between hepatoblastoma and congenital abnormalities, notably trisomy 18 and organomegaly (such as Beckwith-Wiedemann syndrome or hemihypertrophy) [1,17–21], however the proportion of patients with a congenital anomaly is estimated to be only 7% [19]. Hepatoblastoma is more common in families with familial adenomatous polyposis, a syndrome caused by germline mutations in the *APC* tumor suppressor gene [22]. Apart from low birthweight and rare genetic syndromes, the only other established risk factor is parental smoking [23]. A small number of studies have reported on other risk factors, in particular parental occupational exposures or pesticides [24,25].

Since most epidemiologic studies have been quite small (<100 cases), we wish to capitalize on the availability of our large California statewide database, linked with birth certificates, to

* Corresponding author. Tel.: +1 310 825 8579; fax: +1 310 206 6039.
E-mail addresses: jeheck@ucla.edu (J.E. Heck), meyerstj87@gmail.com (T.J. Meyers), clombard@ucla.edu (C. Lombardi), apark1986@gmail.com (A.S. Park), myles@ccnt.usc.edu (M. Cockburn), Peggy.Reynolds@cpic.org (P. Reynolds), britz@ucla.edu (B. Ritz).

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investigate the associations between birth characteristics and hepatoblastoma. This study updates an earlier report of California hepatoblastoma cases in relation to gestational characteristics, adding 10 additional years of cases [8].

2. Materials and methods

The present investigation collected incident cases of hepatoblastoma born 1983–2007 and diagnosed 1988–2007 from the California Cancer Registry [26,27]. Based upon first and last names and date of birth, we were able to match 89% of cases to a California birth certificate. Controls were frequency-matched by year of birth to all childhood cancer cases during the study period and randomly selected from California birthrolls. Controls had no record of a cancer diagnosis in California prior to age 6. After exclusion of 3 controls for which no sex was identified on the birth certificate, the final dataset included 261 hepatoblastoma cases and 218,277 controls.

As this was a record-based study, we did not seek informed consent from individual subjects. The study received approvals from the human subject protection boards of the University of California Los Angeles and the California Health and Human Services Agency.

Our source of data were birth certificates, which report demographic and socioeconomic information, birth characteristics, pregnancy history, complications in pregnancy and labor and delivery, and abnormal conditions and clinical procedures relating to the newborn. Not all variables were collected on birth certificates over the entire period under study: maternal and paternal education, the source of payment for prenatal care, meconium staining of the amniotic fluid, NICU admission, any abnormal condition and any procedure conducted at birth was reported 1989–2007; fetal distress was reported 1983–2005; dysfunctional labor, method of delivery, transfer to another facility within 24 h of delivery, breech presentation, and any congenital anomaly was reported 1983–2007. With regards to general birth certificate variables, pregnancy and labor complications, and clinical procedures, we report on those variables reported for at least 5 cases and on those factors previously reported as potential risk factors for hepatoblastoma in other studies: polyhydramnios [14], maternal tobacco use [28], and fertility treatment [7]. As the use of assisted reproductive technologies began to be reported on California birth certificates in 2006, we examined presumptive fertility treatment, as defined by McLaughlin et al. as any reported fertility treatment or a triplet or higher-order plural birth [7]. Parity was defined as the number of viable previous pregnancies.

As the child's race/ethnicity was not collected on birth certificates for the entire time period under study, we report maternal and paternal race/ethnicity only. Socioeconomic status was measured using maternal and paternal educational attainment as well as the method of payment for prenatal care (private insurance vs. Medi-Cal, other government-funded care or self-pay), which we have previously found to be a good predictor of family income [29]. To further assess socioeconomic status, we used a multifactorial socioeconomic index which used principal components analysis to develop a single, 5-level measure from seven census tract-level indicators of socioeconomic status (census-tract average education, median household income, percent living 200% below poverty, percent blue-collar workers, percent older than 16 years without employment, median rent, and median house value) [30].

Size for gestational age was defined as small if birth weight was less than the 10th percentile and defined as large if greater than the 90th percentile of the birthweight standards for a given gestational age. The 10th and 90th percentile values were obtained for each gestational week (20–45 weeks) by maternal race/ethnicity (non-Hispanic white, Hispanic of any race, black, Asian/Pacific Islander, and other) and child's sex based on the total singleton live births in California using the method described by Alexander [31]. California birth certificates report estimates for gestational age based on the first day of the last normal menses. When this length of time was implausibly long (>45 weeks) we considered it as missing.

Table 1
Demographic characteristics in relation to hepatoblastoma among California children.

Characteristic	Case *n*(%) *n* = 261	Control *n*(%) *n* = 218,277	Crude OR (95% CI)
Child's sex			
Male	154 (59.0)	111,450 (51.1)	1.38 (1.08, 1.77)
Female	107 (41.0)	106,827 (48.9)	1 (ref)
Mother's age (years)			
<20	39 (14.9)	23,842 (10.9)	1.77 (1.23, 2.56)
20–29	106 (40.6)	114,946 (52.7)	1 (ref)
30–34	61 (23.4)	50,157 (23.0)	1.32 (0.96, 1.81)
35+	55 (21.1)	29,290 (13.4)	2.04 (1.47, 2.82)
Mother's race/ethnicity			
White non-Hispanic	97 (37.2)	80,503 (36.9)	1 (ref)
Hispanic (of any race)	129 (49.4)	96,913 (44.4)	1.10 (0.85, 1.44)
Black	9 (3.4)	15,378 (7.0)	0.49 (0.25, 0.96)
Asian/Pacific Islander	24 (9.2)	21,022 (9.6)	0.95 (0.61, 1.48)
Other/not specified	2 (0.8)	4461 (2.0)	0.37 (0.09, 1.51)
Mother's birthplace			
US	142 (54.4)	124,289 (57.0)	1 (ref)
Mexico	79 (30.3)	54,732 (25.1)	1.26 (0.96, 1.66)
Other foreign	40 (15.3)	38,997 (17.9)	0.90 (0.63, 1.28)
Father's age (years)			
<20	8 (3.2)	8431 (4.1)	0.84 (0.41, 1.73)
20–29	104 (41.6)	92,409 (45.2)	1 (ref)
30–34	67 (26.8)	52,440 (25.7)	1.14 (0.83, 1.54)
35+	71 (28.4)	50,997 (25.0)	1.24 (0.91, 1.67)
Father's race/ethnicity			
White non-Hispanic	96 (36.8)	76,621 (35.1)	1 (ref)
Hispanic (of any race)	125 (47.9)	92,850 (42.5)	1.07 (0.82, 1.40)
Black	12 (4.6)	16,876 (7.7)	0.57 (0.31, 1.03)
Asian/Pacific Islander	18 (6.9)	18,307 (8.4)	0.78 (0.47, 1.30)
Other/not specified	10 (3.8)	13,623 (6.2)	0.59 (0.31, 1.12)