Published in final edited form as:

Cancer Epidemiol. 2013 August ; 37(4): 390–395. doi:10.1016/j.canep.2013.03.004.

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

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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 1988–2007 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.

Conclusions—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.

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Conflict of interest statement
None.

Keywords

hepatoblastoma; birth weight; preterm labor; fetal distress; gestational age; pre-eclampsia; multiple birth offspring; risk factors; epidemiology; etiology

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 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].

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 hours 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.

We calculated odds ratios (ORs) and 95% confidence intervals using unconditional logistic regression with SAS 9.1 (SAS, Cary, NC). We report unadjusted and adjusted results, with adjusted regressions controlling for year of birth, maternal age and maternal race/ethnicity. Although other papers on this topic have additionally adjusted for birthweight, we felt it may introduce bias to adjust for a likely intermediate in the cancer pathway [32], thus we only adjusted for birthweight for factors which occurred after birth, e.g. NICU admission, newborn transferred to another facility within 24 hours of delivery, and any clinical procedure on the newborn. We also compared our findings to the earlier study in California by Reynolds [8]. Because it has been speculated that hepatoblastoma may be caused by a procedure that the child undergoes in a neonatal intensive care unit (NICU)[33], we compared the ages at diagnosis of cases admitted to a NICU vs. cases not admitted.

Results

Of the 261 hepatoblastoma cases, 113 (43.3%) had localized disease, 76 (29.1%) regional, 58 (22.2%) distant, and 14 (5.4%) unknown. The proportions of children with localized, regional, and distant disease stayed consistent over the 20 year period (2-sided $p=0.7$).

Hepatoblastoma was more common among male children (Table 1). In comparison to mothers in their 20's, hepatoblastoma occurred more frequently among children whose mothers were both younger (<20 years) and older (35+ years). The risk remained increased for mothers over 35 after adjustment for presumptive fertility treatment or multiple births (data not shown). Disease risk was lower among children of Black mothers compared to non-Hispanic White mothers. None of the paternal characteristics that we examined were associated with disease. We also observed little association between socioeconomic characteristics and hepatoblastoma, with no associations observed with either maternal or paternal years of education. Families whose prenatal care was paid by government sources or self-pay did not differ in hepatoblastoma risk (OR=0.87, 95% CI 0.67, 1.12), nor was there evidence for differential risk by neighborhood socioeconomic index. No evidence of a trend was seen with any SES measure (data not shown).

Gestational characteristics are shown in table 2. There was a higher risk for hepatoblastoma among children with low (1500–2499 g) and very low (<1500 g) birthweight. When examining singleton pregnancies only, the increased risk of hepatoblastoma was still evident among children with low (OR=1.83, 95% CI 1.10–3.06) and very low birthweight (OR=14.6, 95% CI 9.72–22.0). Children who were born very preterm (<33 weeks gestation) also had a higher risk of hepatoblastoma, as were children who were small for gestational age. Hepatoblastoma cases were more likely to have been delivered by Cesarean section and to have been a twin or higher order multiple birth.

A number of pregnancy and labor complications were associated with hepatoblastoma (Table 3). Preeclampsia, fetal distress, premature labor, and breech presentation all increased risk for hepatoblastoma. Cases had a higher risk of any congenital anomaly. Cases who had been admitted to a NICU after birth had a similar age at diagnosis (mean=14.8 months) to cases who had not been admitted to a NICU (mean=13.9 months, 2-sided $p=0.9$).

Of the complications associated with increased risk in other studies, we observed an increased risk with presumptive fertility treatment, although this was based upon only 3 cases (adjusted OR=7.45, 95% CI 2.35–23.6). We did not observe associations between polyhydramnios/oligohydramnios and hepatoblastoma (1 case mother and 965 control mothers exposed). Maternal smoking began to be reported on California birth certificates in 2007. Of the 6 cases born that year, all mothers were listed as nonsmokers.

In comparing our findings to the earlier report by Reynolds [8] which used California cases diagnosed 1988–1997, we observed similar associations across most demographic and gestational risk factors. Due to the larger sample size, we observed higher risks of hepatoblastoma among older mothers as well as more sharply decreased risks among children of Black mothers. Reynolds observed a later age at diagnosis among lower birthweight infants; while we observed differing average ages at diagnosis according to birthweight, there was no evidence of a trend ($p=0.2$). Children of very low birthweight had an age at diagnosis (mean=21.1 months) close to that of children of average birthweight (mean=18.3 months), while children with low (mean=13.6 months) or high birthweight (mean=13.8 months) were diagnosed earlier.

Discussion

In this large population-based study of California children, we found several demographic and gestational characteristics to be associated with hepatoblastoma. We observed strong increased risk with low birthweight, as noted in other studies [6–15], and also when examining singleton births only. Similarly, hepatoblastoma was associated with being small for gestational age, and with preterm birth. Hepatoblastoma was further associated with a spectrum of neonatal complications associated with preterm birth and low birthweight. Non-vertex presentation, precipitous labor, and caesarian section are all more common in prematurity [34,35]. Preeclamptic pregnancies are more likely to be delivered prematurely because of concerns for maternal and child safety. Overall our findings suggest that some insult in pregnancy that is related to both birth weight and prematurity can also result in hepatoblastoma as well as a number of perinatal conditions and interventions.

The positive association seen with young maternal age (<20 years) has been reported elsewhere [7,36]. We also observed increased risk with older maternal age (>35 years), even after additional adjustment for presumptive fertility treatment or for multiple births. We were not able to confirm earlier reports of associations between hepatoblastoma and high birthweight [12] or large size for gestational age [5]. However, our record-linkage approach allowed only for the measurement of fetal growth with size for gestational age, and there are several other metrics which may be used to assess accelerated growth.

We did not observe an increase in risk among children of Asian mothers, as was reported in a small study in Minnesota; in that study, authors did not report the specific country of origin of Asian mothers, but stated that most were of Southeast Asian descent [17]. The varying findings may in part reflect the differing Asian immigrant populations in California and Minnesota. Of our Asian cases, the largest proportions identified their country of origin as China, the Philippines, or Vietnam, with small numbers from several other countries. Asian nations have reported a wide variance in hepatoblastoma rates, with the highest rates seen in China (Tianjin) and Japan, and lower rates observed in India, Singapore, and Vietnam [3]. Rates in smaller countries, however, may fluctuate greatly given the small number of cases diagnosed in any given time period.

The lower risk of hepatoblastoma that we observed among children of Black mothers is consonant with rates reported by SEER [3]. Paradoxically, Black mothers in the US are twice as likely to deliver preterm babies as non-Hispanic White mothers [37], which suggests that the causes of preterm delivery generally are different from the causes of hepatoblastoma.

We observed associations with a number of labor complications and medical procedures, some of which have been reported elsewhere. One study reported a sharply increased risk for hepatoblastoma (OR=52.5) among children of severely preeclamptic pregnancies [14], and a case series also reported one case of hepatoblastoma that occurred after a preeclamptic pregnancy [15]. A large study in Denmark reported that children of mothers who had preeclampsia had elevated risks for any cancer in childhood or young adulthood (OR=1.3, 95% CI 1.0–1.6); that study did not report which cancer types were associated with increased risk [38]. Although the mechanisms for such a relation are not known, studies have shown that estrogen levels are reduced and testosterone levels increased in preeclamptic pregnancies, likely due to poor placental aromatization of the precursor androgens, dehydroepiandrosterone and androstenedione, to estrogen. Preeclampsia is also characterized by varying levels of other hormones: elevated progesterone, human chorionic gonadotropin (hCG), and Cortisol, and lowered insulin-like growth factor-1 (IGF-1).

Alterations in these hormones have been described among hepatoblastoma cases and in liver cancers in adults [39–42].

We observed an increased risk of hepatoblastoma among children of multiple birth pregnancies, and with presumptive fertility treatment. The findings for presumptive fertility treatment were based upon 3 cases of hepatoblastoma among children who were part of triplet pregnancies. Some previous epidemiologic studies have linked hepatoblastoma to fertility treatment [7,14]. There have also been case reports and record-linkage studies which reported cases of hepatoblastoma in children whose parents underwent treatment for infertility [13,43–46]. Parental treatment for infertility has been previously hypothesized to be a cause of childhood cancers. Studies of multiples prior to 1980, when the use of fertility treatments became more widespread, observed no association or a decreased risk for childhood cancers in multiples compared to singletons [47,48]. A more recent study, which includes some of the same cases from our study, reported an increased risk of hepatoblastoma among twins in crude analyses (OR=2.6); after adjustment for birthweight no relation remained (OR=0.9) [49].

Birth certificates are a data source with varying validity depending on the factor under study. In other US states, validation studies of several demographic variables reported on birth certificates (maternal age, race, education, parity) suggested a validity of >90%. In general, factors associated with the pregnancy, labor and delivery of the infant tend to have reasonably good validity. Sensitivity is lower for factors such as previous pregnancy history and pregnancy complications [50–52]. The possibility for differential reporting of complications on the birth certificate between cases and controls exists, as there may be increased provider vigilance of reporting of pregnancy complications among children born preterm.

The literature to date examining risk factors for hepatoblastoma has been very limited due to its rarity, making epidemiologic research challenging. Apart from sample size, a strength of our study was the objective nature of exposure data reported on birth certificates, with misclassification expected to be non-differential. The study design is likely to be free of selection bias, as all children cancer-free at age 6 and born in California had equal likelihood of being selected into the control sample. Our findings necessitate confirmation in other populations, ideally with linkage to medical records.

Acknowledgments

The study was supported by grants from the US National Institute of Environmental Health Sciences (R21ES018960, R21ES019986, P30ES007048).

References

1. Cancer incidence and survival among children and adolescents. Bethesda, MD: NCI; 1999.
2. Stiller CA, Pritchard J, Steliarova-Foucher E. Liver cancer in European children: incidence and survival, 1978–1997. Report from the Automated Childhood Cancer Information System project. *Eur J Cancer*. 2006; 42:2115–2123. [PubMed: 16919775]
3. Parkin, DM. International incidence of childhood cancer. Vol. vol. II. Lyon: International Agency for Research on Cancer; 1998. International Agency for Research on Cancer.
4. Bulterys, M.; Goodman, MT.; Smith, MA.; Buckley, JD. Hepatic tumors. In: Ries, LAG.; Smith, MA.; Gurney, JG., et al., editors. *Cancer incidence and survival among children and adolescents: United States SEER Program 1975–1995*. Bethesda, MD: National Cancer Institute, SEER Program; 1999.
5. de Fine Licht S, Schmidt LS, Rod NH, Schmiegelow K, Lahteenmaki PM, Kogner P, et al. Hepatoblastoma in the Nordic countries. *Int J Cancer*. 2011; 131:E555–E561. [PubMed: 22095187]

6. Tanimura M, Matsui I, Abe J, Ikeda H, Kobayashi N, Ohira M, et al. Increased risk of hepatoblastoma among immature children with a lower birth weight. *Cancer Res.* 1998; 58:3032–3035. [PubMed: 9679968]
7. McLaughlin CC, Baptiste MS, Schymura MJ, Nasca PC, Zdeb MS. Maternal and infant birth characteristics and hepatoblastoma. *Am J Epidemiol.* 2006; 163:818–828. [PubMed: 16510543]
8. Reynolds P, Urayama KY, Von Behren J, Feusner J. Birth characteristics and hepatoblastoma risk in young children. *Cancer.* 2004; 100:1070–1076. [PubMed: 14983504]
9. Ikeda H, Matsuyama S, Tanimura M. Association between hepatoblastoma and very low birth weight: a trend or a chance? *J Pediatr.* 1997; 130:557–560. [PubMed: 9108853]
10. Spector LG, Puumala SE, Carozza SE, Chow EJ, Fox EE, Horel S, et al. Cancer risk among children with very low birth weights. *Pediatrics.* 2009; 124:96–104. [PubMed: 19564288]
11. Smith A, Lightfoot T, Simpson J, Roman E. Birth weight, sex and childhood cancer: A report from the United Kingdom Childhood Cancer Study. *Cancer Epidemiol.* 2009; 33:363–367. [PubMed: 19932649]
12. Lee J, Chia KS, Cheung KH, Chia SE, Lee HP. Birthweight and the risk of early childhood cancer among Chinese in Singapore. *Int J Cancer.* 2004; 110:465–467. [PubMed: 15095317]
13. Maruyama K, Ikeda H, Koizumi T, Tsuchida Y. Prenatal and postnatal histories of very low birthweight infants who developed hepatoblastoma. *Pediatr Int.* 1999; 41:82–89. [PubMed: 10200142]
14. Ansell P, Mitchell CD, Roman E, Simpson J, Birch JM, Eden TO. Relationships between perinatal and maternal characteristics and hepatoblastoma: a report from the UKCCS. *Eur J Cancer.* 2005; 41:741–748. [PubMed: 15763651]
15. Maruyama K, Ikeda H, Koizumi T, Tsuchida Y, Tanimura M, Nishida H, et al. Case-control study of perinatal factors and hepatoblastoma in children with an extremely low birthweight. *Pediatr Int.* 2000; 42:492–498. [PubMed: 11059537]
16. Oue T, Kubota A, Okuyama H, Kawahara H, Nara K, Kawa K, et al. Hepatoblastoma in children of extremely low birth weight: a report from a single perinatal center. *J Pediatr Surg.* 2003; 38:134–137. discussion –7. [PubMed: 12592636]
17. Spector LG, Johnson KJ, Soler JT, Puumala SE. Perinatal risk factors for hepatoblastoma. *Br J Cancer.* 2008; 98:1570–1573. [PubMed: 18392049]
18. Maruyama K, Ikeda H, Koizumi T. Hepatoblastoma associated with trisomy 18 syndrome: a case report and a review of the literature. *Pediatr Int.* 2001; 43:302–305. [PubMed: 11380930]
19. Narod SA, Hawkins MM, Robertson CM, Stiller CA. Congenital anomalies and childhood cancer in Great Britain. *Am J Hum Genet.* 1997; 60:474–485. [PubMed: 9042906]
20. DeBaun MR, Tucker MA. Risk of cancer during the first four years of life in children from The Beckwith-Wiedemann Syndrome Registry. *J Pediatr.* 1998; 132:398–400. [PubMed: 9544889]
21. Fraumeni JF Jr, Miller RW, Hill JA. Primary carcinoma of the liver in childhood: an epidemiologic study. *J Natl Cancer Inst.* 1968; 40:1087–1099. [PubMed: 5648134]
22. Hughes LJ, Michels W. Risk of hepatoblastoma in familial adenomatous polyposis. *Am J Med Genet.* 1992; 43:1023–1025. [PubMed: 1329510]
23. IARC Monographs Program. A review of human carcinogens--Part E. *Lancet Oncol.* 2009; 10:1033–1034. [PubMed: 19891056]
24. Carozza SE, Li B, Elgethun K, Whitworth R. Risk of childhood cancers associated with residence in agriculturally intense areas in the United States. *Environ Health Perspect.* 2008; 116:559–565. [PubMed: 18414643]
25. Buckley JD, Sather H, Ruccione K, Rogers PC, Haas JE, Henderson BE, et al. A case-control study of risk factors for hepatoblastoma. A report from the Childrens Cancer Study Group. *Cancer.* 1989; 64:1169–1176. [PubMed: 2547509]
26. Heck JE, Lombardi CA, Meyers TJ, Cockburn M, Wilhelm M, Ritz B. Perinatal characteristics and retinoblastoma. *Cancer Causes Contr.* 2012; 23:1567–1575.
27. Heck JE, Lombardi CA, Cockburn M, Meyers TJ, Wilhelm M, Ritz B. Epidemiology of rhabdoid tumors of early childhood. *Pediatr Blood Cancer.* 2013; 60:77–81. [PubMed: 22434719]

28. Secretan B, Straif K, Baan R, Grosse Y, El Ghissassi F, Bouvard V, et al. A review of human carcinogens--Part E: tobacco, areca nut, alcohol, coal smoke, and salted fish. *Lancet Oncol.* 2009; 10:1033–1034. [PubMed: 19891056]
29. Ritz B, Wilhelm M, Hoggatt KJ, Ghosh JK. Ambient air pollution and preterm birth in the environment and pregnancy outcomes study at the University of California, Los Angeles. *Am J Epidemiol.* 2007; 166:1045–1052. [PubMed: 17675655]
30. Yost K, Perkins C, Cohen R, Morris C, Wright W. Socioeconomic status and breast cancer incidence in California for different race/ethnic groups. *Cancer Causes Contr.* 2001; 12:703–711.
31. Alexander GR, Himes JH, Kaufman RB, Mor J, Kogan M. A United States national reference for fetal growth. *Obstet Gynecol.* 1996; 87:163–168. [PubMed: 8559516]
32. VanderWeele TJ, Mumford SL, Schisterman EF. Conditioning on intermediates in perinatal epidemiology. *Epidemiology.* 2012; 23:1–9. [PubMed: 22157298]
33. Spector LG, Birch J. The epidemiology of hepatoblastoma. *Pediatr Blood Cancer.* 2012; 59:776–779. [PubMed: 22692949]
34. Gouyon JB, Vintejoux A, Sagot P, Burguet A, Quantin C, Ferdynus C. Neonatal outcome associated with singleton birth at 34–41 weeks of gestation. *Int J Epidemiol.* 2010; 39:769–776. [PubMed: 20304783]
35. Bottoms S. Delivery of the premature infant. *Clin Obstet Gynecol.* 1995; 38:780–789. [PubMed: 8616975]
36. Johnson KJ, Carozza SE, Chow EJ, Fox EE, Horel S, McLaughlin CC, et al. Parental age and risk of childhood cancer: a pooled analysis. *Epidemiology.* 2009; 20:475–483. [PubMed: 19373093]
37. Goldenberg RL, Culhane JF, Iams JD, Romero R. Epidemiology and causes of preterm birth. *Lancet.* 2008; 371:75–84. [PubMed: 18177778]
38. Wu CS, Nohr EA, Bech BH, Vestergaard M, Catov JM, Olsen J. Health of children born to mothers who had preeclampsia: a population-based cohort study. *Am J Obstet Gynecol.* 2009; 201:269. e1–e10. [PubMed: 19733276]
39. Galifer RB, Sultan C, Marguerite G, Barneon G. Testosterone-producing hepatoblastoma in a 3-year-old boy with precocious puberty. *J Pediatr Surg.* 1985; 20:713–714. [PubMed: 3003322]
40. Braunstein GD, Bridson WE, Glass A, Hull EW, McIntire KR. In vivo and in vitro production of human chorionic gonadotropin and alpha-fetoprotein by a virilizing hepatoblastoma. *J Clin Endocrinol Metab.* 1972; 35:857–862. [PubMed: 4343937]
41. Stuver SO, Kuper H, Tzonou A, Lagiou P, Spanos E, Hsieh CC, et al. Insulin-like growth factor 1 in hepatocellular carcinoma and metastatic liver cancer in men. *Int J Cancer.* 2000; 87:118–121. [PubMed: 10861461]
42. Demanes DJ, Friedman MA, McKerrow JH, Hoffman PG. Hormone receptors in hepatoblastoma: a demonstration of both estrogen and progesterone receptors. *Cancer.* 1982; 50:1828–1832. [PubMed: 6288226]
43. Pinborg A, Loft A, Nyboe Andersen A. Neonatal outcome in a Danish national cohort of 8602 children born after in vitro fertilization or intracytoplasmic sperm injection: the role of twin pregnancy. *Acta Obstet Gynecol Scand.* 2004; 83:1071–1078. [PubMed: 15488125]
44. Toren A, Sharon N, Mandel M, Neumann Y, Kenet G, Kaplinsky C, et al. Two embryonal cancers after in vitro fertilization. *Cancer.* 1995; 76:2372–2374. [PubMed: 8635045]
45. Melamed I, Bujanover Y, Hammer J, Spier Z. Hepatoblastoma in an infant born to a mother after hormonal treatment for sterility. *N Engl J Med.* 1982; 307:820. [PubMed: 6287262]
46. Kallen B, Finnstrom O, Nygren KG, Olausson PO. In vitro fertilization in Sweden: child morbidity including cancer risk. *Fertil Steril.* 2005; 84:605–610. [PubMed: 16169392]
47. Inskip PD, Harvey EB, Boice JD Jr. Stone BJ, Matanoski G, Flannery JT, et al. Incidence of childhood cancer in twins. *Cancer Causes Control.* 1991; 2:315–324. [PubMed: 1932544]
48. Rodvall Y, Hrubec Z, Pershagen G, Ahlbom A, Bjurman A, Boice JD Jr. Childhood cancer among Swedish twins. *Cancer Causes Control.* 1992; 3:527–532. [PubMed: 1420855]
49. Puumala SE, Carozza SE, Chow EJ, Fox EE, Horel S, Johnson KJ, et al. Childhood cancer among twins and higher order multiples. *Cancer Epidemiol Biomarkers Prev.* 2009; 18:162–168. [PubMed: 19124494]

50. Reichman NE, Hade EM. Validation of birth certificate data. A study of women in New Jersey's HealthStart program. *Ann Epidemiol.* 2001; 11:186–193. [PubMed: 11248582]
51. Baumeister L, Marchi K, Pearl M, Williams R, Braveman P. The validity of information on “race” and “Hispanic ethnicity” in California birth certificate data. *Health Serv Res.* 2000; 35:869–883. [PubMed: 11055453]
52. Northam S, Knapp TR. The reliability and validity of birth certificates. *J Obstet Gynecol Neonatal Nurs.* 2006; 35:3–12.

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)	111450 (51.1)	1.38 (1.08, 1.77)
Female	107 (41.0)	106827 (48.9)	1 (ref)
Mother's age (years)			
<20	39 (14.9)	23842 (10.9)	1.77 (1.23, 2.56)
20–29	106 (40.6)	114946 (52.7)	1 (ref)
30–34	61 (23.4)	50157 (23.0)	1.32 (0.96, 1.81)
35+	55 (21.1)	29290 (13.4)	2.04 (1.47, 2.82)
Mother's race/ethnicity			
White non-Hispanic	97 (37.2)	80503 (36.9)	1 (ref)
Hispanic (of any race)	129 (49.4)	96913 (44.4)	1.10 (0.85, 1.44)
Black	9 (3.4)	15378 (7.0)	0.49 (0.25, 0.96)
Asian/Pacific Islander	24 (9.2)	21022 (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)	124289 (57.0)	1 (ref)
Mexico	79 (30.3)	54732 (25.1)	1.26 (0.96, 1.66)
Other Foreign	40 (15.3)	38997 (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)	92409 (45.2)	1 (ref)
30–34	67 (26.8)	52440 (25.7)	1.14 (0.83, 1.54)
35+	71 (28.4)	50997 (25.0)	1.24 (0.91, 1.67)
Father's race/ethnicity			
White non-Hispanic	96 (36.8)	76621 (35.1)	1 (ref)
Hispanic (of any race)	125 (47.9)	92850 (42.5)	1.07 (0.82, 1.40)
Black	12 (4.6)	16876 (7.7)	0.57 (0.31, 1.03)
Asian/Pacific Islander	18 (6.9)	18307 (8.4)	0.78 (0.47, 1.30)
Other/not specified	10 (3.8)	13623 (6.2)	0.59 (0.31, 1.12)

Table 2

Gestational characteristics and maternal medical history in relation to hepatoblastoma

Characteristic	Case n (%) n=261	Control n (%) n=218,277	Unadjusted OR (95% CI)	Adjusted OR (95% CI) ^a
Child's birth weight (g)				
<1500 g	35 (13.4)	2366 (1.1)	15.1 (10.5, 21.7)	15.4 (10.7, 22.3)
1500–2499	22 (8.4)	11133 (5.1)	2.01 (1.29, 3.13)	2.02 (1.29, 3.15)
2500–3999	178 (68.2)	181134 (83.1)	1 (ref)	1 (ref)
4000 g +	26 (10.0)	23427 (10.7)	1.13 (0.75, 1.70)	1.12 (0.74, 1.69)
Gestational age (weeks)				
Very preterm (<33)	33 (13.3)	4507 (2.2)	7.04 (4.86, 10.22)	7.27 (5.00, 10.6)
Preterm (33–36)	26 (10.5)	17242 (8.4)	1.45 (0.96, 2.19)	1.44 (0.95, 2.17)
Term (37–42)	183 (73.8)	176064 (85.3)	1 (ref)	1 (ref)
Postterm (43+)	6 (2.4)	8651 (4.2)	0.67 (0.30, 1.51)	0.73 (0.32, 1.64)
Size for gestational age				
Small	42 (17.0)	21922 (10.6)	1.77 (1.26, 2.47)	1.75 (1.25, 2.45)
Normal	177 (71.7)	163193 (79.2)	1 (ref)	1 (ref)
Large	28 (11.3)	20863 (10.1)	1.24 (0.83, 1.84)	1.24 (0.83, 1.85)
Method of delivery ^b				
Vaginal	172 (66.4)	159785 (76.2)	1 (ref)	1 (ref)
Cesarean	87 (33.6)	49782 (23.8)	1.62 (1.25, 2.10)	1.55 (1.19, 2.01)
Multiple birth				
Singleton	244 (93.5)	212769 (97.5)	1 (ref)	1 (ref)
Twin or more	17 (6.5)	5507 (2.5)	2.69 (1.65, 4.40)	2.52 (1.54, 4.14)
Start of prenatal care				
During 1st trimester	210 (80.8)	171948 (79.8)	1 (ref)	1 (ref)
No care or after 1st trimester	50 (19.2)	43416 (20.2)	0.94 (0.69, 1.28)	1.01 (0.73, 1.38)
Parity				
0	110 (42.1)	86505 (39.7)	1 (ref)	1 (ref)
1	75 (28.7)	68785 (31.5)	0.86 (0.64, 1.15)	0.87 (0.64, 1.18)
2 or more	76 (29.1)	62798 (28.8)	0.95 (0.71, 1.28)	0.90 (0.65, 1.24)

^aModels adjust for maternal age, race, and birth year.

Table 3

Complications of pregnancy and labor, concurrent illnesses of the mother, and procedures conducted in the perinatal period, compares hepatoblastoma cases to controls.

	Case n(%) n=261	Control n(%) n=218,277	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
<i>Complications and procedures of pregnancy and concurrent illnesses of the mother^a</i>				
Chronic diabetes	5 (1.9)	3906 (1.8)	1.07 (0.44, 2.60)	0.93 (0.38, 2.27)
Preeclampsia	13 (5.6)	3943 (2.1)	2.70 (1.54, 4.73)	2.62 (1.49, 4.58)
<i>Complications or procedures of labor and delivery^a</i>				
Dysfunctional labor	14 (6.0)	6633 (3.6)	1.71 (1.00, 2.94)	1.70 (0.99, 2.92)
Premature labor ^b	18 (8.4)	4439 (2.5)	3.54 (2.18, 5.74)	3.52 (2.17, 5.71)
Breech presentation	17 (6.5)	6555 (3.0)	2.25 (1.38, 3.68)	2.27 (1.39, 3.72)
Moderate/ heavy meconium in amniotic fluid ^b	12 (5.2)	7671 (4.2)	1.25 (0.70, 2.23)	1.27 (0.71, 2.27)
Fetal distress ^b	15 (6.2)	6696 (3.2)	2.00 (1.19, 3.38)	2.08 (1.23, 3.51)
<i>Abnormal conditions and clinical procedures relating to the newborn^b</i>				
NICU admission ^c	27 (11.6)	5493 (3.0)	4.26 (2.85, 6.37)	1.40 (0.86, 2.30)
Newborn transferred to another facility within 24 hours of delivery ^c	7 (3.0)	1029 (0.6)	5.51 (2.59, 11.72)	1.54 (0.69, 3.44)
Any clinical procedure on the newborn ^c	30 (12.9)	7065 (3.8)	3.70 (2.52, 5.44)	1.27 (0.79, 2.05)
Any congenital anomaly ^a	6 (2.3)	1408 (0.7)	3.51 (1.56, 7.90)	3.59 (1.59, 8.08)

^aModels control for maternal age, race, and birth year.

^bVariable was not collected on birth certificates in all years of the study.

^cModels control for maternal age, race, birth year, and birth weight.