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Parental tobacco and alcohol use and risk of hepatoblastoma in offspring: A report from the Children's Oncology Group

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Abstract

Background—Hepatoblastoma (HB) is a rare pediatric liver tumor that has significantly increased in incidence over the last several decades. The International Agency for Cancer Research (IARC) recently classified HB as a tobacco-related cancer. Parental alcohol use has shown no association. We examined associations between parental tobacco and alcohol use around the time of pregnancy and HB in a large case-control study.

Methods—Maternal interviews were completed for 383 cases diagnosed in the U.S. during 2000–2008. Controls (n=387) were identified through U.S. birth registries and frequency-matched to cases on birth weight, birth year, and region of residence. We employed unconditional logistic regression to calculate odds ratios (ORs) and 95% confidence intervals (CIs) for associations between parental smoking and maternal drinking and offspring HB.

Results—We found no association between HB and maternal smoking at any time (OR=1.0; 95% CI=0.7–1.4), within the year before pregnancy (OR=1.1; 95% CI=0.8–1.6), early in pregnancy (OR=1.0; 95% CI=0.7–1.6), or throughout pregnancy (OR=0.9; 95% CI=0.5–1.6). We observed marginally positive associations between HB and paternal smoking in the year before pregnancy (OR=1.4; 95% CI=1.0–2.0) and during pregnancy (OR=1.4; 95% CI=0.9–2.0). Maternal alcohol use was not associated with HB.

Conclusion—Our results do not provide evidence for an etiological relationship between maternal smoking or drinking and HB, and only weak evidence for an association for paternal smoking in the year before pregnancy.

Impact—Our study provides limited support for HB as a tobacco-related cancer; however, it remains wise to counsel prospective parents on the merits of smoking cessation.

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Keywords

hepatoblastoma; alcohol; smoking; childhood cancer

INTRODUCTION

Hepatoblastoma (HB) is a rare pediatric liver cancer affecting about 100 children each year in the United States (1). The incidence of HB has increased significantly over the period from 1992–2010 at a rate of approximately 3% per year (2). The increasing incidence of HB is contemporaneous to a rise in the prevalence of low birth weight (<2500 grams), which has been strongly associated with HB (3, 4). The biological mechanism underlying the association between low birth weight and HB is unknown. Known risk factors for HB are limited to the inherited cancer syndromes Familial Adenomatous Polyposis and Beckwith-Wiedemann syndrome (3).

Evidence from case-control studies (the largest consisting of 155 cases) has recently accumulated that parental smoking may be associated with HB. Six studies examined maternal and/or paternal smoking prior to conception and during pregnancy and although the associations differed with respect to the time period and parent conferring risk (5–10), three studies reported significant odds ratios ranging from 2.1–4.7 (6, 8, 9). Based on results from some of these studies, the International Agency for Research on Cancer (IARC) recently classified HB as a tobacco-related cancer (11).

Although alcohol indisputably contributes to liver cancer in adults, little evidence has been generated regarding a potential association between maternal alcohol use and HB. Two small case-control studies and one case report have considered the possibility of an association, but results were not significant (7, 12, 13). Since byproducts and metabolites of alcohol are known or suspected carcinogens (14), and are known to cross the placenta (15, 16), further investigation in a larger study is warranted.

Here we examined parental tobacco and alcohol use prior to and during pregnancy in the largest case-control study of HB to date.

MATERIALS AND METHODS

Study population

Characteristics of the study population and design have been previously reported (17, 18). Cases were identified through the Children's Oncology Group (COG). Controls were identified through 32 U.S. birth registries and frequency-matched to cases on birth weight (<1500g, 1500–2500g, and >2500g), gender, birth year, and region. After informed consent, participating mothers completed a computer-assisted telephone interview that gathered information about events and exposures around the time of pregnancy. Eligibility criteria for cases included having confirmed diagnosis of HB from a United States COG institution between 2000 and 2008, diagnosis before age 6 years, being born in the United States, and having an English- or Spanish-speaking birth mother available for a phone interview. Deceased cases were eligible for inclusion. Controls were eligible if born in the United

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States between 1994 and 2008, and if they had an English- or Spanish-speaking birth mother available for a phone interview.

Variables

We focused on interview questions concerning parental use of tobacco and alcohol. Specifically, we examined four questions assessing mothers' tobacco smoking habits (any history of smoking one cigarette or more; smoking within the year prior to pregnancy; smoking early in pregnancy before knowing about pregnancy; smoking during pregnancy, up until giving birth) and four questions assessing their alcohol drinking habits (any history of consuming at least two drinks per month for one year or more; drinking within the year prior to pregnancy; drinking early in pregnancy before knowing about pregnancy; drinking during pregnancy, up until giving birth). We derived new variables to examine dose response for maternal cigarette smoking. For three time periods (within the year prior to pregnancy; early in pregnancy before knowing about the pregnancy; during pregnancy, up until giving birth), we considered the effects of no smoking, smoking fewer than 10 cigarettes per day, smoking between 10 and 14 cigarettes per day, and smoking 15 or more cigarettes per day. We also analyzed fathers' smoking habits that were reported by the study subject's mother (smoking within the year prior to the index pregnancy; smoking during the index pregnancy). We did not collect data on paternal drinking or paternal cigarettes per day. Finally, we derived new variables to consider the combined effect of both parents smoking one year prior to the index pregnancy or during the pregnancy.

Statistical analyses

All statistical analyses were conducted using Statistical Analysis Software version 9.3 (SAS Institute, Cary, NC). Adjusted odds ratios (ORs) and 95% confidence intervals (CIs) were calculated using logistic regression. Associations between HB and parental smoking and alcohol exposures were modeled separately. All models were adjusted for the matching variables (index child's birth weight, year of birth, and sex) as well as maternal race and educational attainment. Subjects with missing data were excluded from analyses. Effect modification on the multiplicative scale was evaluated in logistic regression models by including an interaction term for the exposure and the third variable of interest. Wald-chi square tests were used to evaluate the statistical significance of main effects and interaction terms. Associations were considered statistically significant at a p-value < 0.05.

RESULTS

Of the 408 consenting cases identified from COG institutions, 383 completed a telephone interview. Of the 5813 control mothers identified from birth registries, we were able to reach 754 of 1718 control mothers where contact was attempted. Of the 754 control mothers that were reached, 387 completed the telephone interview.

Cases and controls were frequency matched on sex and birth weight resulting in a similar percentage of female cases and controls; however the frequency matching worked less well for low birth weight resulting in a greater percentage of cases that had low birth weight (especially ranging from 1500–2499 grams) than controls. Case mothers reported less

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education (29% of cases attaining high school or less vs. 22% in controls) and lower incomes (31% of cases earning <$30,000 vs. 23% in controls) than control mothers. A lower percentage of case than control mothers were White (69% vs. 75%), and a higher percentage of case mothers were Hispanic (19% vs. 9%) (Table 1).

We found no associations between maternal smoking and HB in the offspring for any history of maternal smoking (OR=1.0, 95% CI 0.7–1.4), smoking within the year prior to pregnancy (OR=1.1, 95% CI 0.8–1.6), smoking early in pregnancy (OR=1.0, 95% CI 0.7–1.6), or smoking up until giving birth (OR=0.9, 95% CI 0.5–1.6). We found no evidence of a dose-response relationship for maternal smoking and HB. There was no statistically significant association between the number of cigarettes smoked and HB, whether the smoking occurred in the year prior to pregnancy, early in the pregnancy, or throughout the pregnancy (data not shown). We also observed no positive associations between HB and maternal drinking for any of these time periods with non-significant ORs ranging from 0.8–1.0 (Table 2).

Paternal smoking within the year prior to the pregnancy was positively associated with HB in the offspring (OR = 1.4; 95% CI 1.0–2.0, p=0.06). Similarly, mothers reported that case fathers were more likely to be smokers during the pregnancy than control fathers (OR=1.4; 95% CI 0.9–2.0); however, neither of these associations reached statistical significance. Both parents smoking, one year prior to pregnancy and during the pregnancy, showed weakly positive non-significant associations with HB (Table 2).

Finally, we evaluated whether there was any evidence for effect modification by race between parental smoking and drinking during the peri-gestational period (Table 2). The results were stronger for most parental smoking associations in Non-Hispanic whites, most notably for both parents smoking within the year prior to pregnancy; however the interaction term was not significant (p=0.17).

DISCUSSION

Three of six prior studies have suggested that parental smoking increases risk of HB in offspring, although associations were not consistent with respect to parent or time period (Table 3). Significant increased risks for HB in the offspring were reported for mothers and for both parents who smoked prior to pregnancy in one childhood cancer study out of the United Kingdom (U.K.) (6). In contrast, a case-control study of 75 cases and 75 controls in the U.S. and Canada found no association between maternal or paternal preconception smoking and HB (7). Parental smoking of the mother (5–7) or father (7) during pregnancy was also not associated with HB in these studies. Significant positive associations were reported between HB and maternal smoking during an unspecified time period in three studies (8–10), and for paternal smoking and both parents smoking in one study (8). Our large study that comprehensively evaluated maternal, paternal, and both parents smoking at several different developmental time periods provides no evidence of a role of maternal smoking in HB, and only weak evidence for a role of paternal preconception smoking.

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It is interesting to note from the small body of literature on this topic described in table 3 some differences in results depending on study location and data source. In studies that collected exposure data by parental interview (UKCSS, OCSS, and CCSG), only the U.K. studies (UKCSS and OCSS) reported positive associations. Varying results between the U.K. studies and the North American CCSG study could stem from differential reporting by participants from North America vs. the U.K. due to cultural differences in the acceptability of smoking during the peri-gestational period between the two geographic locations. With respect to data source, the results are inconsistent. Assessment of maternal prenatal smoking by birth certificate prior to knowledge of disease in the U.S. NYSCR study would presumably eliminate the concern that the reported positive association was an artifact due to differential reporting between case and control mothers. However, the larger Nordic study that also collected data on maternal smoking by birth certificate prior to disease did not show an association (5, 19).

Biological plausibility for a causal role of paternal preconception smoking in HB stems from known DNA mutagens contained in cigarette smoke (20) that could cause heritable genetic aberrations in sperm. Cigarette smoking has been associated with oxidative sperm DNA damage in some (21–23) but not all studies (24) and evidence from animal models has demonstrated that mice exposed to mainstream tobacco smoke can develop mutations at the Ms6-hm tandem repeat locus that can be passed on to their offspring (25, 26). However, a declining U.S. population prevalence of smoking over the last couple of decades contemporaneous to an increasing HB incidence argues against a major role for paternal smoking in HB etiology (27).

We found no evidence for an association between maternal drinking and HB. Two small studies (<100 cases each) also did not find any significant associations between parental alcohol consumption and HB (7, 12). In the CCSG study of 75 case-control pairs from the U.S. and Canada, a positive association was reported between maternal alcohol use at the time of pregnancy and HB (OR=1.9) (7), but no association with paternal alcohol use at the time of pregnancy (OR=1.0). A brief case report described a 27-month old child diagnosed with HB whose mother drank heavily during pregnancy, but other substances were also ingested and the child had numerous concurrent birth defects and health complications (13). Taken together, there is no support for a major role for parental alcohol consumption in HB etiology.

Major strengths of our study include its large size, high participation rate by cases, and pathologically confirmed cases. In addition, data collection was uniform between cases and controls, minimizing the possibility of interviewer bias.

Methodological limitations of case-control studies include the potential for selection, information, and overmatching biases. Selection bias was not evident in our study compared to U.S. population-based data on the prevalence of smoking and drinking around the time of pregnancy. The CDC's Pregnancy Risk Assessment Monitoring System estimated that between 2000–2008, 23% of women nationwide smoked during the 3 months prior to pregnancy (28), similar to the 22.1% prevalence of smoking among controls within the year prior to pregnancy in our study. Data from the Behavioral Risk Factor Surveillance System

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in 2010 found that 7.6% of pregnant women reported alcohol use in the past 30 days (29), which is also similar to the control mothers in our study where 7.9% reported drinking during pregnancy. However, we note that evidence for selection bias was detected in a sensitivity analysis of birth certificate demographic data from non-participating eligible control mothers; participants were significantly older, more White, and had higher education levels than non-participants (data not shown). Although we did not obtain information on smoking status on non-participants, the prevalence of smoking has been reported to be lower among older and more educated moms (30). This would not be a likely explanation for our failure to find evidence for a positive association between maternal smoking on HB in the offspring, since the effect of higher participation by non-smoking mothers would be to bias the ORs away from the null.

Case-control studies are also prone to information biases including reporting bias, particularly nondisclosure and recall bias. Nondisclosure of smoking among pregnant women has been reported to be high in the U.S. (31). The effect of non-differential nondisclosure of smoking during the peri-gestational period by both cases and controls would tend to bias results toward the null. This could explain why the U.K studies found positive associations between parental smoking and HB, while ours and the other North American study that collected data by interview did not. In addition recall bias could have influenced our results if case mothers reported very trivial amounts of smoking and drinking during the pregnancy with the index child compared to control mothers. While either source of reporting bias may be present in our results, it is not possible to detect this type of bias with our study design.

Finally, it is also possible that overmatching bias may have impacted our findings on maternal smoking during pregnancy and HB, since we matched cases and controls on birth weight and both maternal smoking and HB have established associations with low birth weight (3, 32). The effect of this type of bias on the risk estimates for associations between maternal smoking and HB would be toward the null.

In conclusion, in the largest case-control study to date of HB, we found little evidence for an association between maternal smoking and HB in the offspring, and weak evidence for an association with paternal smoking. We also found no association with maternal alcohol use during pregnancy. While our study does not support or entirely rule out IARC's conclusion that HB is a tobacco-related cancer, it remains wise to counsel prospective parents on the merits of smoking cessation.

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Table 1

Characteristics of cases and controls.

Infant Characteristics	Controls	Cases
Gender		
Male	225 (58.1)	228 (59.5)
Female	162 (41.9)	155 (40.5)
Birth weight (grams)		
<1500	61 (16.0)	57 (14.9)
1500–2499	76 (19.9)	23 (6.0)
2500+	245 (64.1)	302 (79.1)
Maternal Characteristics		
Age		
<20	15 (3.9)	27 (7.0)
20–24	66 (17.2)	59 (15.4)
25–29	122 (31.8)	101 (26.4)
30–34	113 (29.4)	127 (33.2)
35+	68 (17.7)	69 (18.0)
Educational attainment		
HS or less	85 (22.2)	110 (29.0)
Some college	107 (27.9)	106 (27.9)
College or more	191 (49.9)	164 (43.1)
Income		
<$30,000	88 (23.0)	117 (31.1)
$30,000–$75,000	166 (43.5)	143 (38.0)
>$75,000	128 (33.5)	116 (30.9)
Maternal race/ethnicity[a]		
Non-Hispanic White	284 (74.5)	261 (68.9)
Non-Hispanic Black	33 (8.7)	18 (4.7)
Hispanic	34 (8.9)	72 (19.0)
Other[b]	30 (7.9)	28 (7.4)

[a] 10 subjects had missing data on race; White ref

[b] Other includes Native American Indian or Alaskan Native, Asian, Asian-American, Pacific Islander, or Other reported race

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Table 2

Associations between HB and parental smoking and drinking.

	All subjects				Non-Hispanic Whites			
	Controls N (%)	Cases N (%)	OR[a]	95% CI	Controls N (%)	Cases N (%)	OR[a]	95% CI
Maternal Smoking								
Any history (1 cigarette or more)								
Yes	251 (66.4)	247 (65.3)	1.0	0.7–1.4	199 (70.6)	195 (75.0)	1.3	0.9–2.0
No	127 (33.6)	131 (34.7)	1.0	ref.	82 (29.4)	65 (25.0)	1.0	ref.
Within the year prior to pregnancy								
Yes	83 (22.0)	92 (24.3)	1.1	0.8–1.6	66 (23.4)	80 (30.8)	1.4	0.9–2.2
No	295 (78.0)	286 (75.7)	1.0	ref.	216 (76.6)	180 (69.2)	1.0	ref.
Early in pregnancy before knowing about pregnancy								
Yes	67 (17.7)	70 (18.5)	1.0	0.7–1.6	55 (19.5)	61 (23.5)	1.2	0.7–1.9
No	311 (82.3)	308 (81.5)	1.0	ref.	227 (80.5)	199 (76.5)	1.0	ref.
During pregnancy, up until giving birth								
Yes	34 (9.0)	34 (9.0)	0.9	0.5–1.6	28 (9.9)	31 (11.9)	1.1	0.6–2.0
No	344 (91.0)	344 (91.0)	1.0	ref.	254 (90.1)	229 (88.1)	1.0	ref.
Maternal alcohol								
Any history (at least 2 drinks per month, for 1 year or more)								
Yes	185 (48.9)	176 (46.6)	1.0	0.7–1.3	155 (55.0)	137 (52.7)	1.1	0.7–1.6
No	193 (51.1)	202 (53.4)	1.0	ref.	127 (45.0)	123 (47.3)	1.0	ref.
Within the year prior to getting pregnant								
Yes	228 (60.3)	214 (56.6)	1.0	0.7–1.3	184 (65.3)	171 (65.8)	1.0	0.7–1.5
No	150 (39.7)	164 (43.4)	1.0	ref.	98 (34.8)	89 (34.2)	1.0	ref.
Early in pregnancy, before knowing about pregnancy								
Yes	117 (31.0)	102 (27.0)	0.8	0.6–1.2	96 (34.0)	79 (30.4)	0.8	0.6–1.2
No	261 (69.1)	276 (73.0)	1.0	ref.	186 (66.0)	181 (69.6)	1.0	ref.
During pregnancy, up until giving birth								
Yes	30 (7.9)	31 (8.2)	0.9	0.5–1.7	29 (10.3)	25 (9.6)	0.8	0.5–1.5

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	All subjects				Non-Hispanic Whites			
	Controls N (%)	**Cases N (%)**	**OR[a]**	**95% CI**	**Controls N (%)**	**Cases N (%)**	**OR[a]**	**95% CI**
No	348 (92.1)	347 (91.8)	1.0	ref.	253 (89.7)	235 (90.4)	1.0	ref.
69								
Paternal smoking								
Within the year prior to pregnancy								
Yes	84 (22.3)	115 (30.5)	1.4	1.0–2.0	61 (21.7)	79 (30.5)	1.5	1.0–2.3
No	293 (77.7)	262 (69.5)	1.0	ref.	220 (78.3)	180 (69.5)	1.0	ref.
During pregnancy	69 (1							
Yes	69 (18.4)	95 (25.2)	1.4	0.9–2.0	52 (18.9)	64 (24.7)	1.4	0.9–2.1
No	307 (81.7)	282 (74.8)	1.0	ref.	228 (81.4)	195 (75.3)	1.0	ref.
Both parents smoking								
Within year prior to pregnancy								
Both parents	41 (10.9)	56 (14.9)	1.4	0.9–2.3	34 (12.1)	51 (19.7)	1.8	1.0–3.0
One parent	85 (22.6)	95 (25.2)	1.2	0.8–1.8	59 (21.0)	57 (22.0)	1.2	0.8–1.9
Neither parent	251 (66.6)	226 (60.0)	1.0	ref.	188 (66.9)	151 (58.3)	1.0	ref.
During pregnancy								
Both parents	20 (5.3)	24 (6.4)	1.1	0.6–2.2	16 (5.7)	22 (8.5)	1.3	0.6–2.8
One parent	63 (16.8)	81 (21.4)	1.3	0.9–2.0	48 (17.1)	51 (19.6)	1.3	0.8–2.1
Neither parent	293 (77.9)	273 (72.2)	1.0	ref.	216 (77.1)	187 (71.9)	1.0	ref.

[a] Adjusted for birth weight (<1500g, 1500–2500g, and >2500g), year of birth, sex, maternal education, maternal race (Non-Hispanic White, Non-Hispanic Black, Hispanic, Other)

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Table 3

Associations between HB and parental smoking in previous studies.

Parent	Study (citation no.)[a]	Diagnosis years	No. of cases	Pre-conception RR (95% CI)	During pregnancy RR (95% CI)	Timing unspecified RR (95% CI)
Mother	UKCSS(6)	1991–1996	28	2.7 (1.2–6.2)	1.1 (0.4–2.7)	ND
	CCSG(7)	1980–1983	75	1.0 (NR)	0.7 (NR)	ND
	OSCC (8)	1953–1984	43	ND	ND	1.7 (0.9–3.2)
	NYSCR(9)	1985–2001	58	ND	ND	2.1 (1.0–4.2)
	Pu et. al(10)[b]	NR	NR	NR	NR	2.9 (1.1–4.2)
	Nordic (5)	1985–2006	155	ND	1.0 (0.6–0.8)	ND
Father	UKCSS(6)	1991–1996	27	2.2 (0.9–5.1)	ND	ND
	CCSG(7)	1980–1983	75	0.9 (NR)	1.2 (NR)	ND
	OSCC (8)	1953–1984	40	ND	ND	2.1 (1.0–4.3)
Both parents	UKCCS(6)	1991–1996	10	4.7 (1.7–13.4)	ND	ND
	OSCC (8)	1953–1984	43	ND	ND	2.7 (1.2–6.1)

NR=not reported

ND=not determined

[a] All studies used a case-control study design except for Pu et al. that reported using a case-cohort design. Parental smoking data was collected by parental interview (UKCSS, OSCC, CCSG), birth certificates (NYSCR, Nordic), and medical records (Pu et al.).

[b] Source of information was from the abstract only