

## Parental Smoking and Alcohol Consumption and Risk of Neuroblastoma<sup>1</sup>

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### Abstract

**Previous studies and animal evidence have suggested a relationship between parental tobacco or alcohol use and the risk of some childhood cancers, including neuroblastoma. A case-control study was conducted to investigate the relationship between parental tobacco smoking, alcohol consumption, and risk of neuroblastoma. Cases were children diagnosed with neuroblastoma over the period 1992–1994 at Children's Cancer Group and Pediatric Oncology Group institutions throughout the United States and Canada. One matched control was selected using random-digit dialing. Information on parental smoking and drinking history was obtained from 504 case and 504 control parents by telephone interview. Overall, there was no consistent pattern of association with parental smoking and alcohol consumption. For example, both maternal smoking and drinking during the period from 1 month before pregnancy through breastfeeding had adjusted odds ratios (ORs) of 1.1 [95% confidence interval (CI), 0.8–1.4]. There was no association with paternal smoking (OR, 1.2; 95% CI, 0.8–1.6) or paternal drinking 1 month before conception (OR, 1.0; 95% CI, 0.7–1.4). There was no consistent increase in risk by the amount of smoking or drinking during any time period relative to pregnancy. There was no suggestion of an increased risk when only one parent smoked.**

Received 3/22/00; revised 6/6/00; accepted 6/19/00.

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<sup>1</sup> This study was supported in part by Grant CA57004 from the National Cancer Institute and by numerous grants from the Division of Cancer Treatment, National Cancer Institute, NIH Department of Health and Human Services to Children's Cancer Group and Pediatric Oncology Group investigators, listed with their institutions and grant numbers in the Appendices.

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**Smoking or drinking among both parents did not jointly increase the risk of neuroblastoma in their offspring. The child's age at diagnosis, stage, or MYCN oncogene amplification status did not materially alter the OR estimates. It is concluded that the results from this study do not indicate any evidence for a relationship between neuroblastoma and parental tobacco or alcohol use.**

### Introduction

Neuroblastoma is an embryonic tumor of the sympathetic nervous system. It is the third most common neoplasm of children under 15 years of age and the most common tumor in infants (1–2), but little is known about the etiology of neuroblastoma. This early age at diagnosis suggests that prenatal exposures might play an important role. Previous epidemiological studies have reported that an increased risk of neuroblastoma was associated with maternal use of certain medications during pregnancy, parental occupational exposures, and birth characteristics (3).

Tobacco smoke is of interest as a potential risk factor for childhood cancers because it contains a number of mutagenic and carcinogenic compounds that can cross the placenta (4–6). Of particular interest are *N*-nitroso compounds (NNOs), which have been shown to induce nervous system tumors in animals (7–8). Compounds in tobacco smoke, including *N*-nitroso compounds, can also induce male germ cell mutations (9). Alcohol and its metabolites have been shown to be teratogenic, mutagenic, and carcinogenic (10–12). Additionally, there have been case reports of fetal alcohol syndrome and neuroblastoma (13). However, parental smoking and alcohol consumption were not consistently associated with an increased risk in previous epidemiological studies (14, 15). This inconsistency may have resulted from the relatively small study sizes, failure to consider specific time windows of exposure, and limited information on confounding factors. We report the results of a large case-control study that evaluated potential risk factors for neuroblastoma, including parental smoking exposure and alcohol consumption during time periods before conception and pregnancy and after birth.

### Subjects and Methods

**Cases.** Cases were children under age 19 years, newly diagnosed with neuroblastoma during the study period (1992–1994) at member institutions of two North American collaborative clinical trial groups: the Children's Cancer Group (CCG) and the Pediatric Oncology Group (POG). All of the neuroblastoma cases were pathologically confirmed. Case eligibility criteria included: physician consent; the availability of the biological mother for interview; the ability on the part of the parents to speak either English or Spanish; and the

presence of a telephone in the household. Among the 741 potentially eligible cases, a total of 538 (73% of eligible) case mothers were successfully interviewed. A total of 405 case fathers were independently interviewed, and proxy interviews were conducted with case mothers when fathers were unavailable ( $n = 67$ ; 12%). Reasons for nonparticipation of mothers included physician refusal ( $n = 90$ ; 12%), mother's refusal ( $n = 57$ ; 8%), not traceable ( $n = 44$ ; 6%), and other reasons ( $n = 12$ ; 2%).

**Controls.** One control was selected for each case using a random-digit dialing method based on the first eight digits of the case's telephone number (16). Each randomly selected control number was contacted up to 6 times. Controls were individually matched to cases on date of birth ( $\pm 6$  months for cases  $\leq 3$  years of age and  $\pm 1$  year for cases  $> 3$  years of age). The response proportion for the random-digit dialing screening phase was 74%. Eligibility criteria for controls were the same as for the cases. Among the 703 eligible controls, 504 (72%) control mothers were successfully interviewed, and 304 control fathers were directly interviewed. Proxy interview for fathers was obtained for 142 (28%) controls. The reasons for mothers' nonparticipation were refusal ( $n = 143$ ; 20%) or not traceable ( $n = 57$ ; 8%).

**Interview.** Trained interviewers administered a structured telephone interview to parents. Parents of cases and controls were asked for information about occupational history, medication use, pregnancy history, pregnancy and birth complications, and other factors. Parental smoking history included smoking status (never, past, and current), timing of smoking (month before the index pregnancy; first, second, and third trimesters separately; after birth; and during breastfeeding), intensity of smoking (number of cigarettes or packs per day), and duration of smoking (years). Ever-smoking was defined as a history of smoking at least one cigarette per day for 6 months or longer. In addition, information on tobacco type (cigarette, cigar, pipe, chewing, snuff) was also requested from fathers. Mothers of cases and controls were asked about alcohol consumption with respect to timing (month before, during pregnancy, and during breastfeeding), types of alcohol (wine, beer, and hard liquor), frequency and quantity of consumption (glass/cans of beer or shots of liquor or glasses of wine per day, week, or month). For paternal alcohol consumption, the timing of exposure was restricted to 2–12 months and 1 month before pregnancy.

**Data Analysis.** We estimated the risk of neuroblastoma associated with parental cigarette smoking and alcohol consumption using conditional logistic regression. Cigarette smoking was analyzed as dichotomous (no, yes) and quantitative (cigarettes per day and pack-years) variables. Paternal smoking was also evaluated according to type of tobacco consumed. The total amount of alcohol consumption was calculated by summing the number of grams of alcohol for all of the three types of alcoholic beverages. It was assumed that a 12-ounce bottle or can of beer contained 12.8 g of alcohol; a 4-ounce glass of wine contained 10.8 g of alcohol; and a 1.5-ounce shot of liquor contained 15.1 g of alcohol (United States Department of Agriculture Nutrient Database for Standard Reference, Release 12, March 1998). Alcohol consumption was examined in different forms: a dichotomous variable (none, yes), a quantitative variable (grams per day), and by type (beer, wine, and liquor). The exposure variables were further evaluated based on the timing of exposure such as before pregnancy; in first, second, and third trimesters; during breastfeeding; and after birth. In the anal-

Table 1 Demographic factors

Factor	Case		Control		OR <sup>a</sup>	95% CI
	n	%	n	%		
Gender						
Male	279	55.4	251	49.8	1.0	
Female	225	44.6	253	50.2	0.8	0.6–1.0
Mother's race						
White	409	81.2	396	78.6	1.0	
Black	36	7.1	39	7.7	0.7	0.4–1.4
Hispanic	41	8.1	54	10.7	0.6	0.4–1.1
Other	18	3.6	15	3.0	1.3	0.6–2.8
Mother's education						
<High school	54	10.7	51	10.1	2.2	0.8–6.3
High school	341	67.7	318	63.1	1.3	0.9–1.8
College	109	21.6	135	26.8	1.0	
Mother's age						
<20 yr	44	8.7	35	6.9	1.3	0.6–2.7
20–24	112	22.2	110	21.8	1.2	0.8–1.8
25–30	200	39.7	206	40.9	1.0	
31–39	138	27.4	146	29.0	0.8	0.6–1.2
40+	10	2.0	7	1.4	3.5	0.7–16.8
Household income in birth year (in thousands)						
<\$10	84	17.7	54	11.1	1.6	0.8–3.3
\$10–20	85	17.9	91	18.7	1.4	0.7–2.7
\$21–30	82	17.3	114	23.5	1.0	
\$31–40	73	15.4	86	17.7	1.8	0.9–3.6
\$41–50	51	10.7	52	10.7	1.0	0.4–2.3
>\$50	100	21.0	89	18.3	1.6	0.7–3.5

<sup>a</sup>Unadjusted matched OR.

yses of the fathers' data, results from the entire dataset (direct and proxy interview combined) were compared with the analysis of data from direct paternal interview.

Maternal education, household income in the birth year, child's gender, and mother's race were included as potential confounders in the logistic regression analysis. The joint effects (interaction) of maternal and paternal smoking as well as parental drinking were also evaluated. Child's age at diagnosis was investigated as a potential effect modifier. Because stage and tumor *MYCN* oncogene amplification status may represent a clinically and genetically distinct subgroup of neuroblastoma cases (17), additional analyses were conducted among the subgroups defined by these factors. The International Neuroblastoma Staging System was used. *MYCN* copy number was determined by Southern blot (18) or fluorescence *in situ* hybridization (19).

## Results

In total, 504 matched pairs were used for the analysis of maternal smoking and alcohol consumption. Of the 409 cases with staging data, 16% were stage 1, 6% stage 2a, 6% stage 2b, 18% stage 3, 46% stage 4, and 7% stage 4S. A total of 381 cases had *MYCN* data, with 67 case tumors having detectable amplification. Complete information about paternal exposure was available for 390 matched pairs. Table 1 presents the distribution of cases and controls according to selected sociodemographic factors. Slight case-control differences were found for gender and maternal race. More case mothers than control mothers had less than a high school

Table 2 Maternal smoking

Maternal smoking <sup>a</sup>	Case		Control		OR <sup>b</sup>	95% CI
	n	%	n	%		
Lifetime						
Never	299	59.7	311	61.8	1.0	
Ever	202	40.3	192	38.2	1.0	0.7–1.3
Around pregnancy <sup>c</sup>						
Never	351	70.1	371	73.8	1.0	
Ever	150	29.9	132	26.2	1.1	0.8–1.4
1 mo before conception						
Never	354	70.7	371	73.8	1.0	
Ever	147	29.3	132	26.2	1.1	0.8–1.4
1st trimester						
Never	390	77.8	401	79.7	1.0	
Ever	111	22.2	102	20.3	1.0	0.7–1.3
2nd trimester						
Never	414	82.6	421	83.7	1.0	
Ever	87	17.4	82	16.3	0.9	0.7–1.3
3rd trimester						
Never	410	81.2	421	83.7	1.0	
Ever	91	18.2	82	16.3	1.0	0.7–1.4
Breastfeeding						
Never	364	92.2	377	90.8	1.0	
Ever	31	7.9	38	9.2	0.9	0.5–1.5
Cigarettes/day during 1st trimester						
Nonsmoker	390	78.0	401	79.9	1.0	
≤5	22	4.4	25	5.0	0.8	0.5–1.5
5–10	39	7.8	34	6.8	1.0	0.6–1.6
10–15	12	2.4	9	1.8	1.2	0.5–3.0
>15	37	7.4	33	6.6	0.9	0.6–1.6
Cigarettes/day during 2nd trimester						
Nonsmoker	414	82.8	421	84.0	1.0	
≤5	17	3.4	16	3.2	1.0	0.5–2.0
5–10	34	6.8	30	6.0	1.0	0.6–1.6
10–15	11	2.2	7	1.4	1.3	0.5–3.5
>15	24	4.8	27	5.4	0.8	0.4–1.4

<sup>a</sup> A total of three cases and one control had missing smoking-history information.

<sup>b</sup> Adjusted for child's gender, mother's race and education, and household income in the birth year.

<sup>c</sup> Included 1 month before and during the pregnancy and during breastfeeding.

education (OR,<sup>3</sup> 2.2; 95% CI, 0.8–6.3). There was also some indication of cases being more likely than controls to have lived in a household with an income either <\$10,000 or >\$50,000 in the year of the birth. There was some indication of an increased risk of advanced maternal age (≥40 years), although the estimate was imprecise. The pattern of case-control difference was similar for paternal demographic characteristics (data not shown).

Overall, 40% of women in the case group and 38% of women in the control group had ever smoked (OR, 1.0; CI, 0.7–1.3). No association with smoking around pregnancy (1 month before pregnancy through breastfeeding; OR, 1.1; CI, 0.8–1.4) was found (Table 2). Smoking before pregnancy, during pregnancy (three trimesters), or during breastfeeding did not show any increased risk. Further evaluation of the average number of cigarettes smoked per day during the first and second trimesters did not show any pattern of association, although the estimates were imprecise. Similar

Table 3 Maternal alcohol consumption

Maternal drinking <sup>a</sup>	Case		Control		OR <sup>b</sup>	95% CI
	n	%	n	%		
Lifetime						
Never	247	49.4	244	48.5	1.0	
Ever	253	50.6	259	51.5	0.9	0.7–1.1
Around pregnancy <sup>c</sup>						
Never	264	52.9	281	56.1	1.0	
Ever	235	47.1	220	43.9	1.1	0.8–1.4
1 mo before conception						
Never	294	58.9	312	62.3	1.0	
Ever	205	41.1	189	37.7	1.1	0.8–1.4
1st trimester						
Never	403	80.8	423	84.4	1.0	
Ever	96	19.2	78	15.6	1.2	0.9–1.7
2nd trimester						
Never	439	88.0	461	92.0	1.0	
Ever	60	12.0	40	8.0	1.6	1.0–2.4
3rd trimester						
Never	441	88.4	458	91.4	1.0	
Ever	58	11.6	43	8.6	1.4	0.9–2.1
Breastfeeding						
Never	266	83.1	284	85.5	1.0	
Ever	54	16.9	48	14.5	1.0	0.5–2.0
1st trimester (g/day)						
Nondrinker	429	86.0	450	89.8	1.0	
≤1.5	26	5.2	22	4.4	1.1	0.6–1.9
1.5–5	24	4.8	13	2.6	1.9	0.9–3.9
>5	20	4.0	16	3.2	1.0	0.5–2.1
2nd trimester (g/day)						
Nondrinker	458	91.8	471	94.0	1.0	
≤1.5	23	4.6	19	3.8	1.2	0.6–2.2
1.5–5	15	3.0	7	1.4	2.1	0.8–5.3
>5	3	0.6	4	0.8	0.9	0.2–4.0

<sup>a</sup> A total of four cases and one control had missing information on alcohol use history.

<sup>b</sup> Adjusted for child's gender, mother's race and education, and household income in the birth year.

<sup>c</sup> Included 1 month before and during the pregnancy and during breastfeeding.

results were found for the amount of smoking during other time periods and the duration of smoking during pregnancy (data not shown).

Overall, there was no association observed for women who ever drank alcohol around pregnancy (OR, 1.1; CI, 0.8–1.4; Table 3). There were moderate associations with drinking during the first, second, and third trimesters, with the strongest effect in the second trimester (OR = 1.6; CI = 1.0–2.4). However, when the amount of alcohol consumption during those specific periods was evaluated, a strong dose-response gradient was not found, although the category 1.5–5 g/day showed elevated but imprecise ORs in the first (OR, 1.9; CI, 0.9–3.9) and second (OR, 2.1; CI, 0.8–5.3) trimesters. No association was found with the type of alcohol (wine, beer, or liquor) that women consumed.

With respect to paternal smoking, 46.4% of case fathers and 45.5% of control fathers ever smoked, on average, at least one cigarette per day for at least 6 months during their lifetime (OR, 1.0; CI, 0.7–1.3; Table 4). No elevated ORs were observed for smoking around pregnancy (OR, 1.0; CI, 0.7–1.4) and during each trimester (Table 4). Dose-response relationships were not found for average number cigarette per day, pack-years, or duration of smoking. However, a weak association was found for smoking more than 20 cigarettes per day during the month before pregnancy (OR, 1.5; CI, 0.8–2.7).

<sup>3</sup> The abbreviations used are: OR, odds ratio; CI, confidence interval.

Table 4 Paternal smoking

Paternal smoking <sup>a</sup>	Case		Control		OR <sup>b</sup>	95% CI
	n	%	n	%		
Lifetime						
Never	209	53.6	212	54.5	1.0	
Ever	181	46.4	177	45.5	1.0	0.7–1.3
Around pregnancy <sup>c</sup>						
Never	248	63.6	253	65.5	1.0	
Ever	142	36.4	133	34.5	1.0	0.7–1.4
1 mo before conception						
Never	253	64.9	267	68.6	1.0	
Ever	137	35.1	122	31.4	1.2	0.8–1.6
1st trimester						
Never	260	66.7	269	69.2	1.0	
Ever	130	33.3	120	30.9	1.1	0.8–1.5
Cigs <sup>d</sup> /day 1 mo before conception						
0	253	65.5	267	69.2	1.0	
≤5	15	3.9	13	3.4	1.3	0.6–2.8
5–10	24	6.2	24	6.2	1.0	0.5–1.9
10–20	60	15.5	58	15.0	1.1	0.7–1.7
>20	34	8.8	24	6.2	1.5	0.8–2.7
Cigs/day during 1st trimester						
0	260	67.4	269	70.1		
≤5	14	3.6	12	3.1	1.3	0.5–3.0
5–10	20	5.2	22	5.7	0.9	0.5–1.8
10–20	61	15.8	57	14.8	1.1	0.7–1.7
>20	31	8.0	24	6.3	1.3	0.7–2.3
Smokeless tobacco 1 mo before conception						
Never	348	93.1	365	94.1		
Ever	26	7.0	23	5.9	1.3	0.7–2.6

<sup>a</sup> A total of one control had missing information on tobacco use history. Includes direct and proxy data.

<sup>b</sup> Adjusted for child's gender, mother's race, father's education, and household income in birth year.

<sup>c</sup> Included 1 month before and during the pregnancy.

<sup>d</sup> Cigs, cigarettes.

There was no association with smokeless tobacco use. Cigar and pipe smoking could not be evaluated because of the small number of users. Additional analyses of paternal smoking among offspring of nonsmoking mothers did not reveal any important elevations in risk. No differences were found using only paternal self-reported data.

No associations were found for lifetime paternal drinking (OR, 0.8; CI, 0.5–1.1), drinking 2–12 months before pregnancy (OR, 1.1; CI, 0.8–1.6), or one month before pregnancy (OR, 1.0; CI, 0.7–1.4; Table 5). There was no suggestion of a dose-response relationship for amount of alcohol consumption per day or variation in risk according to type of alcohol consumed. Analysis of smoking and alcohol consumption history using only the direct self-reported information gave similar results (data not shown). No substantial changes were shown from the analysis controlling for maternal smoking and drinking status.

The joint effects of maternal smoking and paternal smoking as well as maternal drinking and paternal drinking were also examined (data not shown). Using nonsmokers (or nondrinkers) as the reference category, we found no increased risk for any separate or joint effect. For example, with a history of both parents having smoked around pregnancy the OR was 1.3 (CI, 0.9–2.0) and for both parents having reported drinking around pregnancy the OR was 1.2 (CI, 0.8–1.8). The results did not

Table 5 Paternal alcohol consumption

Paternal drinking <sup>a</sup>	Case		Control		OR <sup>b</sup>	95% CI
	n	%	n	%		
Lifetime						
Never	94	24.4	81	20.9	1.0	
Ever	291	75.6	307	79.1	0.8	0.5–1.1
During 1 y before pregnancy						
Never	77	19.9	81	21.0	1.0	
Ever	310	80.1	305	79.0	1.2	0.8–1.7
2–12 mo before pregnancy						
Never	79	20.4	81	21.0	1.0	
Ever	308	79.6	305	79.0	1.1	0.8–1.6
1 mo before pregnancy						
Never	118	30.5	115	29.8	1.0	
Ever	269	69.5	271	70.2	1.0	0.7–1.4
1 mo before pregnancy (g/day)						
0	122	31.6	117	31.0	1.0	
≤1.5	25	6.5	22	5.8	1.2	0.6–2.2
1.5–5	46	11.9	56	14.8	0.9	0.5–1.4
5–15	88	22.8	97	25.7	0.9	0.6–1.4
15–25	34	8.8	26	6.9	1.4	0.8–2.6
>25	71	18.4	60	15.9	1.3	0.8–2.1

<sup>a</sup> A total of four cases and two controls had missing information on alcohol use history. Includes direct and proxy data.

<sup>b</sup> Adjusted for child's gender, mother's race, father's education, and household income in birth year.

differ for other time periods or using only paternal self-report data.

The evaluation of parental smoking and alcohol consumption did not show heterogeneity based on age at diagnosis (data not shown). We also analyzed case subgroups based on case *MYCN* amplification status or stage and did not find a consistent pattern of association. For example, maternal smoking around pregnancy was associated with an imprecise risk estimate among cases with a tumor that had *MYCN* amplification (maternal smoking and *MYCN*+ OR, 0.7; CI, 0.3–1.9; maternal smoking and *MYCN*– OR, 1.0; CI, 0.7–1.5).

## Discussion

Our study was the first to comprehensively evaluate the effect of parental smoking and alcohol consumption on the risk of neuroblastoma, including the evaluation of timing of exposure, type of tobacco and alcohol used, and joint effects of both parents' smoking and alcohol consumption. Overall, we did not find any consistent pattern of association with parental smoking or alcohol consumption during specific periods before, during, or after pregnancy.

Two studies have investigated parental smoking and alcohol consumption as potential risk factors for neuroblastoma, but the results were inconsistent. A study of 104 neuroblastoma cases identified by the Greater Delaware Valley Registry (14) reported an elevated OR for maternal alcohol consumption of one or more drinks per day during pregnancy (OR, 9.0; CI, 2.16–37.56) and for maternal binge alcohol consumption of three or more drinks per day during pregnancy (OR, 6.0; CI, 1.26–28.54). No association with maternal cigarette smoking before or during pregnancy was found (OR, 1.3; CI, 0.8–2.1). Another study (15) based on 101 cases and children with other cancers as controls found an elevated risk with maternal smoking during the year before the child's birth (OR, 1.9; CI, 1.1–3.2), but it did not

find an association with maternal alcohol consumption (OR, 0.7; CI, 0.4–1.1). Random error, the time period when the studies were conducted, and variation in control groups may explain some of the differences among study findings. The relatively small sample size is the major limitation of those studies. In addition, they did not obtain detailed information on the amount of tobacco and alcohol used during different time periods before, during, and after pregnancy. Our relatively large study size allowed us to evaluate changes in consumption levels before and during pregnancy.

The response proportions in both case and control groups were below 75%, which may indicate potential selection bias. We do not have direct information to characterize nonresponders. However, the age at diagnosis in our case group is similar to the distribution in Surveillance, Epidemiology, and End Results data (1).

Misclassification of parental smoking and drinking behaviors is also a concern. Studies with cotinine measurements have shown that pregnant women accurately report whether they had smoked (20, 21); however, they do not accurately report the actual number of cigarettes smoked. In general, good agreement between self-reported alcohol consumption and detailed

records for both women and men has been found (22). One study examined potential misclassification of alcohol and cigarette use during pregnancy in relation to several adverse outcomes, including congenital malformations, and reported little differential reporting bias (23).

In our case group, we had fewer fathers with proxy data (12%) compared with control fathers (28%). To evaluate the effect of this potential problem, we repeated the analyses using only paternal self-reported information and no substantial differences were observed. Although we examined the risk of paternal smoking among children of nonsmoking mothers and the risk of maternal smoking with nonsmoking fathers, we did not directly measure passive smoking exposure from relatives or others in the household. In conclusion, the results of our large comprehensive study indicate that parental smoking or alcohol consumption does not increase the risk of neuroblastoma.

### Acknowledgments

We thank Joanna Smith for programming help and David Savitz for comments on an earlier draft.

## Appendices

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