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Retinoblastoma and ambient exposure to air toxics in the perinatal period

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Abstract

We examined ambient exposure to specific air toxics in the perinatal period in relation to retinoblastoma development. Cases were ascertained from California Cancer Registry records of children diagnosed 1990–2007 and matched to California birth certificates. Controls were randomly selected from state birth records for the same time period. We chose 27 air toxics for the present study that had been listed as possible, probable, or established human carcinogens by the International Agency for Research on Cancer. Children (103 cases and 30,601 controls) included in the study lived within 5 miles (~8K) of an air pollution monitor. Using logistic regression analyses, we modeled the risk of retinoblastoma due to air toxics exposure, separately for exposures in pregnancy and the first year of life. With a per interquartile range increase in air toxics exposure, retinoblastoma risk was found to be increased with pregnancy exposure to benzene (OR=1.67, 95%CI 1.06, 2.64) and other toxics which primarily arise from gasoline and diesel combustion: toluene, 1,3 butadiene, ethyl benzene, ortho-xylene, and meta/para-xylene; these 6 toxics were highly correlated. Retinoblastoma risk was also increased with pregnancy exposure to chloroform (OR=1.35, 95%CI 1.07, 1.70), chromium (OR=1.29, 95%CI 1.04, 1.60), para-dichlorobenzene (OR=1.24, 95%CI 1.04, 1.49), nickel (OR=1.48, 95%CI 1.08, 2.01), and in the first year of life, acetaldehyde (OR=1.62, 95%CI 1.06, 2.48). Sources of these agents are discussed.

Keywords

Retinoblastoma; Air pollution; Benzene; Chromium; Nickel; Xylenes

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Introduction

Retinoblastoma is a malignant tumor of the retina which occurs most commonly in young children. Approximately two-thirds of cases (63%) are diagnosed before age 2, and 95% before age 5, suggesting that exposures occurring during the perinatal period are likely to be important to retinoblastoma development.[1] Retinoblastoma occurs due to a loss or mutation of both alleles of the *RB1* gene. In hereditary retinoblastoma, a defective allele is inherited from a parent (most often, the father[2]) due to an hereditary or *de novo* mutation in parental germline cells; most of these cases present as bilateral disease. In sporadic (non-hereditary) retinoblastoma, both alleles are inactivated somatically at some point after conception, and these cases present as unilateral disease.

Little is known about retinoblastoma etiology. Recently, we observed associations between exposure to traffic-related air pollution in pregnancy and subsequent development of retinoblastoma.[3,4] There are few other studies on retinoblastoma in relation to air pollution. No relation was observed between retinoblastoma and industrial air pollutant releases in Texas, in an analysis which summed across all emissions releases from certain industries (petroleum refineries and related industries, chemical industries, and plastics production) to assess risk.[5] In studies that examined the distribution of retinoblastoma by urban or rural residence, results have been equivocal.[5–11] However most of these studies did not stratify by laterality or report the distributions of heritable and sporadic tumors, making it difficult to draw conclusions.

The purpose of the present study was to further investigate possible traffic-related and industrial pollution effects by investigating the influence of specific air toxics on retinoblastoma risk.

Subjects and methods

The Air Pollution and Childhood Cancer (APCC) study is a large case-control investigation of air pollution exposure among California children. The study is described in detail elsewhere.[12] Briefly, cases were ascertained from California Cancer Registry records of cancer diagnoses 1990–2007 among children younger than age 6. We included cases with International Classification of Childhood Cancer, Third edition (ICCC-3) code 050. We were able to match 89% of cases to a California birth certificate using first and last names, date of birth, and when available, social security number. Population-based controls were selected at random from California birth records for the same time period and frequency-matched to all childhood cancer cases by birth year. Controls had no cancer diagnosis listed in the California Cancer Registry before age 6. We linked participants to California death records in order to exclude 1 550 controls who had died of other causes in early childhood (< age 6).

For all children born 1998 or later, air pollution exposure assessment was based upon the home address as listed on the birth certificate. For children born prior to 1998, home addresses were not available on electronic birth certificate records, therefore participants were assigned exposures based on the population-weighted centroid of their zip code of

residence. Home (and zip code centroid) locations of all participants were mapped using our open source geocoder with manual resolution process for unmatched addresses.[13]

The California Air Resources Board (CARB)'s Air Toxics Program has maintained an air toxics monitoring network since 1985 (with data available from 1990), which measures ambient concentrations of air toxics, collecting 24-hour integrated samples every 12 days from each monitor. Different CARB monitors collect information on different toxics, with some toxics collected over the entire study period, and others collected for shorter periods of time and/or only at specific monitors. The number of toxics collected has varied over time, ranging from ~60–189. Although monitors are situated across the state, they are most frequently located in heavily trafficked urban areas, industrial neighborhoods, or agriculturally-intense rural regions (for map, see [14]). Using latitude/longitude locations provided by CARB, we determined the distance from each monitor to each family's home, and participants were assigned pollutant values based upon the measurements of the nearest monitor. We additionally explored assigning values based upon estimates using kriging, but did not observe meaningful differences (unpublished data). Time-specific exposure averages were generated based on the gestational age and date of birth reported on the birth certificate for each child. Children who were missing information on gestational age (20 cases, 9219 controls) were excluded from analyses. Average measurements over each time period of interest (3 months preconception, each trimester, the entire pregnancy period, and the first year of life) were determined. For each pollutant, we only included children in the analysis who had at least 1 reading for each full month within the time period of interest, as well as one reading within the last 30 days of pregnancy. Analyses for the present study were limited to families residing within 5 miles of a monitor. Sensitivity analyses were conducted to determine whether the use of smaller radii (5K and 3K) changed effect estimates. For most pollutants, we observed similar point estimates across radii, and therefore report 5 mile estimates only. We additionally compared the population in the present study to the children who were not living within 5 miles of a monitor.

Of the air toxics collected by CARB, we selected 42 air toxics for the present study because they were listed as established, possible, or probable carcinogens by the International Agency for Research on Cancer (IARC).[15] Of these, 16 were not usable due to insufficient data (<40 cases within a 5 mile radius of a monitor), generally because these were only collected for a few years of the study period.

Because many air toxics arise from the same sources they can be highly correlated. We checked for correlations across the air toxics and report Pearson correlation coefficients as well as the mean, standard deviation (s.d.), and the interquartile range for the entire pregnancy period (IQR) of each pollutant. To address the issue of correlated pollutants, we applied factor analysis using principal components extraction with varimax rotation. For each factor, we included pollutants with loadings >0.80. Because the polycyclic aromatic hydrocarbons (PAH) were highly correlated, we additionally created a new variable, total PAHs, which consisted of the sum of all PAH values [benzo(b)fluoranthene, benzo(k)fluoranthene, indeno(1,2,3-cd)pyrene, dibenz(a,h)anthracene, benzo(g,h,i)perylene, and benzo(a)pyrene].

For each time period of interest, we examined the risk of disease associated with each interquartile range increase (units for each pollutant listed in Table 2) in pollutant exposure allowing us to compare effect sizes across pollutants. Effect estimates for exposures in the first year of life only included patients diagnosed after age 1; because bilateral retinoblastoma is largely diagnosed in infancy, these results primarily reflected risk for unilateral disease (82% of cases in first year analyses were unilateral). We additionally examined pollutant correlations across time periods.

Logistic regression analyses were conducted for each pollutant separately, with adjustment for potential confounding variables. Choice of potential confounders was guided by our prior work on retinoblastoma,[16] with all confounding factor information taken from birth certificates. We adjusted for maternal race/ethnicity and nativity (White non-Hispanic, Hispanic and US-born, Hispanic and foreign-born, other race/not specified), paternal age (<29, 30–34, 35+), and year of birth. We additionally adjusted for a socioeconomic status indicator, the method of payment for prenatal care (private health insurance vs. Medi-Cal/other government-sponsored health insurance/self-pay), which we have observed to be a reasonable proxy for family income.[17] Race, Latino ethnicity, and socioeconomic status are related to air pollution exposures in California.[18] We conducted sensitivity analyses to examine associations across regions of California. We additionally examined whether effect estimates differed by time periods (1990–1997 vs. 1998–2007) to examine potential differential effect estimates when we used zip code centroid vs. home address to assign exposure estimates.

Due to sample size constraints, and also because our prior work found associations between traffic-related pollution and both bilateral and unilateral retinoblastoma,[3,4] we grouped together unilateral and bilateral disease in main models. We report results stratified by laterality only for pollutants associated with disease in the combined analyses. We examined trimester-specific effect estimates, but observed little to no differences in point estimates across trimesters; thus, we report results for the entire pregnancy period only. Due to the greater likelihood of inheriting de novo *RB1* mutations from the father,[2] we limited analyses of exposures in the 3-month preconception period to bilateral cases, however results were not informative due to small sample sizes. Results stratified by laterality are presented in supplemental tables.

Results

In our study, 30704 children (103 cases, 30601 controls) were included in analyses because they were living within 5 miles of a monitor and had sufficient values recorded for at least one pollutant. The 131,314 additional children who were excluded from the present study because they were not living within 5 miles of any monitor were much more likely to be residing in a rural county (21% vs. 6%). Mothers of the excluded children were more likely to be White non-Hispanic (36% vs. 25%), and born in the US (56% vs. 47%).

Characteristics of the cases and controls that we included are shown in Table 1. Of the 103 cases, 75 were unilateral and 28 were bilateral. The mean distance between participants' homes and their nearest monitor was 4.9K (s.d. 2.0).

In the factor analysis, only two factors had eigenvalues>1 (the 1st factor included 9 pollutants and the 2nd factor included 7) and the remainder of pollutants did not load on a factor. Ortho-xylene, toluene, ethyl benzene, 1,3-butadiene, benzene, styrene, perchloroethylene, lead, and meta/para-xylene loaded to factor 1. The 2nd factor included total PAHs as well as each PAH separately. Mean pollutant values and interquartile ranges are shown in table 2.

Odds ratios and 95% confidence intervals for associations between pollutants and retinoblastoma are shown in table 3. Increased risk was observed with pregnancy exposure to many of the pollutants listed in factor 1. Ortho-xylene, toluene, ethyl benzene, 1,3 butadiene, benzene, and meta/para-xylene all increased risk for retinoblastoma. Although the sample size was reduced for analyses of first year exposures, effect estimates were similar for pregnancy and first year exposures. Average pregnancy exposure values were moderately to highly correlated with values for first year exposures (r~0.34–0.94). No associations were observed between PAHs and retinoblastoma at any time period. Of the other pollutants, we observed increased risk with pregnancy and first year exposure to chloroform, para-dichlorobenzene, nickel, and total chromium. Associations were also seen with first year exposure to acetaldehyde and formaldehyde. It should be noted that formaldehyde and chloroform were moderately correlated (r=0.56).

When we stratified results by California region, higher point estimates were observed in urban areas (the Bay Area and the South Coast Air Basin) in comparison to the San Joaquin Valley or more rural areas, however sample sizes were small for most regions. When we examined findings by the time period, effect estimates were similar at the different time points for most air toxics, with wide confidence intervals. We examined odds ratios across the buffer distances (3K, 5K, and 5 miles) and found that point estimates were relatively stable for BTEX toxics. There was more variability across the buffer distances when we examined the estimates for chromium, chloroform, and in particular, for formaldehyde. However, sample sizes were quite small at the 3K distance, and confidence intervals overlapped.

Examining trimester-specific exposures, effect estimates tended to be highest for second and third trimester exposures; however confidence intervals overlapped, making it difficult to discern a specific time window most relevant to risk. Our measures of traffic-related pollutants were strongly correlated in the 2nd and 3rd trimesters (r~0.41–0.70), while the 1st and 3rd trimesters were more weakly correlated (r~0.11–0.63). When we stratified by laterality, no pattern emerged that suggested effect estimates differed for bilateral or unilateral disease.

Discussion

Due to the rarity of retinoblastoma, it has been the subject of few epidemiologic investigations and consequently, little is known about its causes. This is the first study to link ambient exposure to air toxics in the perinatal period to retinoblastoma development. Our results showed that several air toxics were related to the disease, including benzene, 1,3 butadiene, toluene, ethyl benzene, and xylenes. This group of air toxics is sometimes

referred to as “BTEX,” and the largest primary source of these toxics is road traffic. In California, 47% of benzene emissions arise from on-road traffic, and another 40% from other mobile combustion sources (e.g. boats, lawn equipment).[19] Benzene and 1,3-butadiene are established carcinogens and there is strong evidence of their genotoxicity.[20] However there are thousands of measured and unmeasured chemical agents in traffic exhaust. Other constituents of gasoline combustion such as carbon monoxide are known to damage the human retina,[21] making it difficult to discern from our data which agents may be most relevant for retinoblastoma carcinogenesis or whether it is the mixture of exhaust chemicals that may be responsible. Further, the correlations between BTEX and other agents must be considered when interpreting the results of our study.

Our results differ from those in a British study of paternal occupational exposure to exhaust fumes, which found no relation with retinoblastoma.[22] However, our research focuses on maternal exposures in pregnancy, and biologic effects might occur via a different mechanism. Retinal abnormalities are seen in newborns whose mothers smoked in pregnancy,[23] which supports that inhaled pollutants cross the placenta and cause retinal damage.

Air toxics vary with regards to stability in ambient air with toluene, xylenes, and 1,3 butadiene reactively decaying faster than either benzene or ethyl benzene, suggesting that risk estimates based on residences within 5 miles of a monitor might be more accurate for the latter two agents.[24,25] Chloroform, nickel, and dichlorobenzenes are quite stable in the atmosphere, while chromium has moderate stability and formaldehyde is quite reactive.[24]

Chromium emissions in California arise in part from gasoline combustion (52% of chromium VI emissions), which may explain the moderate correlations seen with BTEX (r~0.40–0.56), and it is possible these correlations may be driving the elevated risks we observed. Other important sources of ambient chromium include chrome plating, metal finishing, and emissions from the firebrick lining of glass furnaces.[19] Hexavalent chromium exposure has been related to lung and sinonasal cancers[26] and is a developmental toxicant in animal studies.[27]

Nickel causes chromosomal aberrations and excesses of lung and nasal cancers among exposed workers. In experimental studies, nickel injection caused retinoblastoma in rats[28] and transplacental exposures are associated with renal and pituitary tumors in offspring.[29] Parental employment in metal industries has been associated with retinoblastoma and been attributed to either nickel or hexavalent chromium.[22,30,31]

Chloroform is included in some pesticide formulations, used as a solvent in manufacturing, and emitted into the atmosphere as a byproduct from bleaching of paper pulp and in water chlorination. Chloroform is an established carcinogen in animals, but data are limited on its carcinogenicity in humans.[32] It is a developmental toxicant associated with fetal death, growth retardation, and sperm abnormalities in animals.[33] Gestational exposure to trihalomethanes has been related to eye malformations in rats.[34] However, since this is the first study to link this chemical to retinoblastoma the correlations with BTEX pollutants (r~0.27–0.64) should be noted.

Important emissions sources of para-dichlorobenzene in California are consumer products such as non-aerosol insect repellants and solid/gel air fresheners.[19] Para-dichlorobenzene is classified by IARC as a possible carcinogen and causes chromosomal aberrations, DNA strand breaks, and sister chromatid exchanges in animal studies, however research in humans is quite limited.[32]

Other than BTEX, the pollutants which loaded to factor 1 were perchloroethylene, styrene, and lead. Although lead was removed from US automobile and general aviation fuel several decades ago, it has remained in gasoline used by smaller piston-engine aircraft. According to the EPA, 45% of lead emissions in the United States arise from this source.[35] Lead was also deposited in soil decades ago from traffic and may be blown via dust into communities abutting heavily trafficked roads.[36] Perchloroethylene (also called tetrachloroethylene) is a solvent used in dry cleaning operations, metal degreasing, and chlorofluorocarbon production, while styrene is emitted from engine exhaust, office machines, building materials, and during the manufacture of plastics, rubber, and resins. Correlations between these toxics and traffic-related pollution have been reported elsewhere and likely reflect emissions common to urban areas.[37,38]

Exposure misclassification is likely to have occurred in our study due to families moving during pregnancy. A recent review of residential mobility reported that 9–32% of US families move during pregnancy, with most moves occurring in the 2nd trimester; however, most people move locally,[39] which would lessen the error from exposure misclassification in our study. Our study would also not be able to include any participants born in California but who moved out of state in early childhood, and any of those children who developed cancers would likely have been diagnosed elsewhere; however, we do not expect this misclassification to be differential. We also were not able to identify cancers in any children who changed their names prior to cancer diagnosis. We were not able to adjust for any confounding by maternal smoking, because California birth certificates only began reporting maternal smoking status in 2007; but previous studies have found inconsistent results as to whether maternal smoking is a cause of retinoblastoma.[40–43] A further limitation of our study was the lack of information on whether *RB1* mutations were inherited or *de novo*, as the ability to stratify by germline or somatic mutations would provide a clearer picture of the true risks incurred across different groups. Our study was also limited by the multiple comparisons, and certain findings may have been due to chance or driven by collinearity with other pollutants. The study covered a long time period, during which changes in gasoline formulations, among other factors, changed ambient concentrations of a number of pollutants.[19] We attempted to account for this by adjusting for birth year in regressions. Retinoblastoma incidence in the US has remained relatively stable across the past 3 decades.[44]

This was the first study to link ambient exposure to air toxics in pregnancy to retinoblastoma. Strengths of our study include the large sample size and the many years of air sampling conducted by CARB. The findings on traffic-related pollutants and retinoblastoma were previously observed by our group, in analyses within different populations (all of California and LA county only) which used well-validated models of traffic-related pollution.[3,4] Diesel exhaust is classified by IARC as a Group 1 (established)

carcinogen, while gasoline exhaust is a Group 3 (possible) carcinogen.[45] However, our California studies are the first to link these agents to retinoblastoma, and replication in other populations is recommended.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Characteristics of retinoblastoma cases and controls

	Cases (N = 103) (%)	Controls (N = 30601) (%)
Mother's race/ethnicity and birthplace		
White non-Hispanic	23 (22.3)	7734 (25.3)
Hispanic, US born	12 (11.7)	5079 (16.6)
Hispanic, foreign born	37 (35.9)	11100 (36.3)
Other/not specified	31 (30.1)	6688 (21.9)
Father's age		
<29	50 (52.1)	14016 (49.7)
30–34	22 (22.9)	7106 (25.2)
35+	24 (25.0)	7065 (25.1)
Source of payment for prenatal care		
Private insurance, HMO	46 (44.7)	13687 (45.1)
Medi-Cal/other government/self-pay	57 (55.3)	16639 (54.9)
Child's Sex		
Male	59 (57.3)	15517 (50.7)
Female	44 (42.7)	15084 (49.3)

Table 2

Descriptive statistics of air toxics

Air toxic	Mean (SD) [a]	IQR
Ortho-xylene (ppbV)	0.50 (0.33)	0.39
Toluene (ppbV)	2.89 (1.77)	2.20
Ethyl Benzene (ppbV)	0.38 (0.19)	0.18
1,3-Butadiene (ppbV)	0.30 (0.18)	0.26
Benzene (ppbV)	1.30 (0.86)	1.22
Styrene (ppbV)	0.16 (0.12)	0.14
Perchloroethylene (ppbV)	0.20 (0.20)	0.23
Lead (ng/m3)	22.99 (18.63)	19.93
Meta/para-xylene (ppbV)	1.05 (0.59)	0.67
Total PAHs (ng/m3)	1.44 (1.06)	1.05
Benzo(b)fluoranthene (ng/m3)	0.25 (0.22)	0.19
Benzo(k)fluoranthene (ng/m3)	0.10 (0.09)	0.08
Indeno(1,2,3-cd)pyrene (ng/m3)	0.31 (0.24)	0.23
Benzo(a)pyrene (ng/m3)	0.20 (0.21)	0.16
Dibenz(a,h)anthracene (ng/m3)	0.03 (0.03)	0.01
Benzo(g,h,i)perylene (ng/m3)	0.56 (0.35)	0.45
Carbon Tetrachloride (ppbV)	0.10 (0.02)	0.03
Trichloroethylene (ppbV)	0.08 (0.12)	0.05
Ortho-Dichlorobenzene (ppbV)	0.11 (0.04)	0.08
Chloroform (ppbV)	0.04 (0.01)	0.02
Para-Dichlorobenzene (ppbV)	0.15 (0.04)	0.04
Formaldehyde (ppbV)	2.87 (1.20)	1.33
Selenium (ng/m3)	1.56 (0.70)	0.73
Chromium (total; ng/m3)	5.31 (2.75)	3.22
Hexavalent chromium (ng/m3)	0.19 (0.11)	0.13
Acetaldehyde (ppbV)	1.42 (0.69)	0.90
Nickel (ng/m3)	5.08 (2.27)	3.18

[a] Mean values shown are among controls only.

Table 3

Odds ratios and 95% confidence intervals for the relation between one interquartile range increase in air toxic exposure and retinoblastoma

	Average pregnancy exposure		Average exposure in the child's first year	
	N cases/controls	OR (95% CI)	N cases/controls	OR (95% CI)
1st factor (traffic-related and other correlated toxics)				
Ortho-xylene	81/22247	1.44 (1.06, 1.96)	42/20720	1.64 (1.03, 2.61)
Toluene	82/22358	1.47 (1.06, 2.06)	42/20862	1.79 (1.10, 2.92)
Ethyl Benzene	79/21544	1.40 (1.08, 1.80)	40/20056	1.41 (0.92, 2.17)
1,3-Butadiene	88/25134	1.59 (1.08, 2.35)	48/23747	1.64 (0.89, 3.01)
Benzene	88/25144	1.67 (1.06, 2.64)	48/23757	1.55 (0.76, 3.17)
Styrene	69/18517	1.28 (0.96, 1.69)	31/15880	1.64 (1.12, 2.39)
Perchloroethylene	83/23171	1.17 (0.89, 1.54)	42/20930	1.23 (0.80, 1.91)
Lead	62/18234	1.09 (0.78, 1.51)	32/15356	0.82 (0.47, 1.44)
Meta/para-xylene	56/15718	1.37 (1.02, 1.83)	29/14342	1.27 (0.77, 2.08)
2nd Factor (PAHs)				
Total PAHs	72/20745	0.95 (0.71, 1.27)	39/16517	1.09 (0.65, 1.83)
Benzo(b)fluoranthene	72/20745	0.86 (0.63, 1.16)	40/17410	1.00 (0.62, 1.59)
Benzo(k)fluoranthene	70/19786	0.87 (0.66, 1.15)	40/17410	1.00 (0.65, 1.53)
Indeno(1,2,3-cd)pyrene	72/20745	0.95 (0.71, 1.27)	39/16517	1.05 (0.61, 1.82)
Benzo(a)pyrene	70/19786	0.90 (0.70, 1.15)	40/17410	1.04 (0.72, 1.51)
Dibenz(a,h)anthracene	70/19786	0.99 (0.88, 1.11)	39/16517	1.00 (0.70, 1.42)
Benzo(g,h,i)perylene	51/14433	1.10 (0.76, 1.60)	39/16517	1.27 (0.63, 2.56)
Pollutants that did not load on a factor				
Carbon Tetrachloride	73/19480	0.83 (0.40, 1.71)	17/7583	1.76 (0.42, 7.38)
Trichloroethylene	86/23605	0.97 (0.86, 1.08)	43/21575	0.93 (0.76, 1.14)
Ortho-Dichlorobenzene	73/19551	1.46 (0.90, 2.37)	35/16706	2.36 (0.92, 6.06)
Chloroform	86/23442	1.35 (1.07, 1.70)	44/21993	1.53 (1.10, 2.12)
Para-Dichlorobenzene	61/17540	1.24 (1.04, 1.49)	35/16762	1.38 (0.98, 1.94)
Formaldehyde	62/18331	1.14 (0.91, 1.43)	48/21783	1.42 (1.08, 1.88)
Selenium	54/15616	0.90 (0.67, 1.23)	31/14603	0.81 (0.49, 1.34)
Chromium (total)	86/23442	1.29 (1.04, 1.60)	32/15379	1.34 (1.01, 1.77)
Hexavalent chromium	62/18351	1.22 (0.97, 1.54)	29/12946	1.23 (0.88, 1.72)
Acetaldehyde	86/23449	1.00 (0.73, 1.39)	48/21783	1.62 (1.06, 2.48)
Nickel	62/18357	1.48 (1.08, 2.01)	32/15379	1.42 (0.90, 2.20)

Odds ratios adjust for paternal age, maternal race and birthplace, birth year, and method of payment for prenatal care. First year analyses only include cases diagnosed after age 1.