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Perinatal characteristics and retinoblastoma

Julia E Heck¹, Christina A Lombardi¹, Travis J Meyers¹, Myles Cockburn², Michelle Wilhelm¹, and Beate Ritz¹

¹Department of Epidemiology, Fielding School of Public Health, University of California, Los Angeles, CA, USA

²Department of Preventive Medicine, USC/Keck School of Medicine, Los Angeles, CA, USA

Abstract

Purpose—The etiology of retinoblastoma remains poorly understood. In the present study, we examined associations between perinatal factors and retinoblastoma risk in California children.

Methods—We identified 609 retinoblastoma cases (420 unilateral, 187 bilateral, and 2 with laterality unknown) from California Cancer Registry records of diagnoses 1988–2007 among children <6 years of age. We randomly selected 209,051 controls from California birthrolls. The source of most study data was birth certificates. Multivariable logistic regression was used to examine associations between retinoblastoma and perinatal characteristics.

Results—Bilateral retinoblastoma was associated with greater paternal age [for fathers over 35, crude Odds Ratio (OR)=1.73, 95% Confidence Interval (CI) 1.20, 2.47] and with twin births (OR=1.93, 95% CI 0.99, 3.79). Among unilateral cases, we observed an increased risk among children of US-born Hispanic mothers (OR=1.34, 95% CI 1.01, 1.77) while a decreased risk was observed for infants born to mothers with less than 9 years of education (OR=0.70, 95% CI 0.49–1.00), a group that consisted primarily of mothers born in Mexico. We observed that maternal infection in pregnancy with any STD (OR=3.59, 95% CI 1.58, 8.15) was associated with bilateral retinoblastoma.

Conclusions—This study supports the findings of previous investigations reporting associations between parental age, HPV infection and retinoblastoma.

Keywords

Anemia; Assisted Reproductive Techniques; Human papillomavirus; Mexican Americans; Rhesus blood group system; Risk factors; Social class

Introduction

Retinoblastoma is a malignant tumor of the retina which typically occurs in children younger than 6 years of age. The disease results from loss or mutation of both alleles of the *RB1* tumor suppressor gene. A sizable percentage of retinoblastoma cases (40%) is considered hereditary and most present as bilateral disease. These persons carry a germline mutation in one allele of a retinal progenitor cell (occurring due to *RB1* inheritance from a parent, *de novo* mutation in parental germline cells, or during early embryonic development) and lose the second allele somatically. Hereditary retinoblastoma has high penetrance (90%). In sporadic (nonhereditary) retinoblastoma (60% of cases), both *RB1* alleles are inactivated somatically; these cases present as unilateral disease [1, 2]. Prevalence of

bilateral retinoblastoma varies little worldwide, with age-standardized rates typically estimated at 3–5 per million in most countries. Unilateral retinoblastoma exhibits more geographic variation, with 50–100% greater incidence observed in many developing nations in comparison to much of Europe, suggesting some environmental exposure is contributing to its causation [3, 4].

Few etiologic factors have been associated with retinoblastoma. Increased risk was linked to older parental age [5–9], human papillomavirus (HPV) infection [5, 10–16], sunlight exposure [17, 18], diet [19], X-ray exposure [5], some paternal occupations [20–22], and in vitro fertilization [23–26]. However, the limited number of studies and the contradictory findings makes it difficult to draw conclusions regarding possible causality.

In this large population-based study of California children, we sought to examine the relationship between perinatal factors reported on the birth certificate and retinoblastoma occurrence. Our population includes a large number of Hispanic families, with half of Hispanic mothers born in Mexico.

Methods

The present investigation relied on all subjects enrolled in the Air Pollution and Childhood Cancers (APCC) study, which collected incident cases of histologically confirmed childhood cancers diagnosed 1988–2007 from the California Cancer Registry [27]. All children were ages 5 and younger at diagnosis. We matched each case born in California with his or her birth certificate by first and last names and dates of birth; in this manner, we were able to match 89% of cases to their birth certificate. Controls (N=209,700), frequency-matched by year of birth, were randomly selected from California birthrolls for the same time period, only including children for whom there was no record of a cancer diagnosis in California before age 6. After exclusion of likely non-viable births (gestational age < 20 weeks and/or birthweight < 500g), and 1577 controls who died in childhood of other causes (<6 years of age), the final dataset included 609 retinoblastoma cases (including 187 bilateral, 420 unilateral, and 2 with laterality unknown) and 209,051 controls.

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

The sources of study data were birth certificates, California Cancer Registry records, and year 2000 census data. California birth certificates record information on parental demographics, gestational information and maternal medical history. They further collect data on complications in pregnancy and in labor and delivery, concurrent illnesses of the mother, clinical procedures done in the perinatal period, and abnormal conditions of the child. Not all variables were collected throughout the period under study.

Socioeconomic status (SES) was measured as maternal education (years), paternal education (years), and the source of payment for prenatal care. This was defined as private insurance (including Health Maintenance Organizations, Blue Cross-Blue Shield, and any other private insurance) vs. other payment methods (including self-pay and government aid programs, such as Medicare, Medi-Cal, worker's compensation, Title V, and CHAMPUS/TRICARE). We have previously shown that the source of payment for prenatal care measure to be a reasonable proxy for family income [28]. To further examine any potential association between retinoblastoma and socioeconomic status, we also used a multifactorial socioeconomic index developed by Yost et al.[29] which uses principal components analysis to develop a single, 5-level SES measure from seven census-level indicators of SES

(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). Gestational age was estimated from the date of last menses; when the length of time was improbably long (>45 weeks) it was listed as missing. 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 between 1988 and 2006 using the method described by Alexander et al [30].

With regards to pregnancy and labor complications and clinical procedures, we reported upon those variables seen among at least 5 cases and on those found to be associated with retinoblastoma in other studies. We examined whether any medical procedure was done to the child after birth, which included admission to a neonatal intensive-care unit (NICU), surfactant replacement therapy, antibiotics administered for suspected neonatal sepsis, or newborn transferred to another facility within 24 hours of delivery. On California birth certificates, infection with an STD in pregnancy was recorded as follows: from 1986–1988, genital herpes infection was collected; from 1989–2006, genital herpes infection and “other sexually transmitted diseases” were collected; and starting in 2007, herpes, syphilis, chlamydia, and gonorrhea were collected. Due to the low prevalence of specific infections, we pooled results to examine infection with any STD. STD screening became a routine part of prenatal care after the September 1989 publication of screening recommendations by CDC [31]. Given the likelihood of misclassification prior to routine screening and in years when only genital herpes was ascertained on the birth certificate, we limited analyses of this variable to the cohort of children born 1990 and after.

We examined associations between demographics, socioeconomic factors, and retinoblastoma using chi-square and unadjusted logistic regression. We examined associations between labor and pregnancy complications and retinoblastoma using logistic regression. Confounding variables included in multivariate models were year of birth, paternal age, urban or rural county of residence, maternal race and maternal place of birth.

Finally, we examined the reported use of assisted reproduction technologies (which was reported on birth certificates starting in 2006) and maternal anemia in pregnancy, because these factors have been associated with retinoblastoma in previous studies [5, 23].

Results

Bilateral retinoblastoma was more common among male children (Table 1). Among unilateral cases, maternal birthplace in Mexico was less common (crude OR=0.76, 95% CI 0.59, 0.97), while children of US-born Hispanic mothers had a higher risk of disease (crude OR=1.34, 95% CI 1.01, 1.77). When examining this finding by year of birth, no clear pattern of a changing trend was evident. Risk was increased for bilateral disease when fathers were ages 30–34 (crude OR=1.44, 95% CI 0.99, 2.10) or 35 and older (crude OR=1.73, 95% CI 1.20, 2.47). The average age of fathers at the child's birth was 30.2 [standard deviation (s.d.) 7.0] for controls, in comparison to 29.9 (s.d. 6.7) for unilateral cases and 31.9 (s.d. 8.1) for bilateral cases ($p=0.001$). Bilateral cases were more common in urban areas. After adjustment for confounding variables, no association was observed between urban county of residence and bilateral retinoblastoma (OR=1.26, 95% CI 0.82, 1.94).

Associations between retinoblastoma and socioeconomic variables are shown in Table 2. When univariate odds ratios were computed, we observed a reduced risk for unilateral retinoblastoma among mothers (OR=0.70, 95% CI 0.49, 1.00) and fathers (OR=0.68, 95% CI 0.48, 0.97) with 8 or fewer years of formal education. After adjustment for maternal race and birthplace, no associations remained.

There were few gestational risk factors associated with retinoblastoma (Table 3). While no retinoblastoma cases arose from births of triplets or more, there was a trend towards bilateral cases being more likely to be twin births (OR=1.93, 95% CI 0.99, 3.79).

There were few pregnancy or labor complications associated with retinoblastoma (Table 4). The mothers of bilateral cases were more likely to have been concurrently infected in pregnancy with an STD (OR=3.59, 95% CI 1.58, 8.15). When we stratified by type of STD, there was a trend towards genital herpes being associated with increased risk of bilateral retinoblastoma (OR=3.06, 95% CI 0.97, 9.67) while “other STDs” were more strongly associated (OR=4.04, 95% CI 1.28, 12.74). There was an increased risk of bilateral disease among children with maternal-child Rhesus (Rh) incompatibility, although this was based upon only 4 cases. There was also an increased risk of disease among children who had undergone any medical procedure at birth (OR=1.46, 95% CI 1.00, 2.14). Age at diagnosis was earlier for those who had undergone procedures at birth (mean=12.3 months, s.d. 12.7) than among children who hadn’t undergone any procedure (mean=17.3 months, s.d. 13.8, $p=0.05$). In particular, children who had undergone assisted ventilation had an increase in bilateral retinoblastoma, although of the 4 bilateral cases with assisted ventilation, 2 were diagnosed at birth. We did not observe associations between retinoblastoma and the reported use of fertility-enhancing drugs (n cases=0) nor of maternal anemia (1 bilateral case).

Discussion

In this large population-based study, we observed several risk factors to be predictive of retinoblastoma. Male children had higher risk of disease, as has been reported elsewhere [32, 33]. The association that we observed with older paternal age was also reported in studies in the Netherlands, Japan, and India [7, 9, 34, 35]. This association, which occurred mostly in bilateral disease, may be explained by a higher occurrence of new germline mutations with increasing age. This finding is consonant with the observation that new germline mutations predisposing to retinoblastoma are inherited most often from fathers [36, 37].

Of the few studies which have reported on retinoblastoma in relation to socioeconomic status, only smaller, hospital-based designs have observed an association; notably, another large population-based investigation did not find SES to be predictive of retinoblastoma [5, 19, 38, 39]. Similarly, our large population-based study observed little association with social class measures, with the exception of decreased risk of unilateral disease among children of parents with less than 8 years of education. This association may be explained in part by the relation between years of education and parental age. In addition, women with less than 8 years of education in our population were overwhelmingly Hispanic (90.3%) and foreign-born (94.4%), with the majority of these mothers having been born in Mexico (82.2%). In comparison to US-born women, Mexican-born mothers frequently have better pregnancy outcomes [40, 41], despite higher levels of poverty and lower education (the “Hispanic paradox” [42]). The lower disease risk in this group may reflect healthier behaviors which lessen exposure to some unknown risk factor; alternatively, the possibility exists that parents whose children exhibit retinoblastoma symptoms choose to take their child home to their country of origin for diagnosis and treatment.

In contrast, we observed increased risk of unilateral disease among US-born women of Mexican descent. US-born Mexican women are known to have poorer health behaviors and perinatal outcomes compared to Mexican immigrants. US-born Mexican women are more likely to have used tobacco, drugs, and alcohol in pregnancy and to have generally poorer diets, in comparison with Mexican immigrant women [43, 44]. In the perinatal period, US-born Mexican women have higher risks of low birth weight, preterm birth, infant mortality, maternal morbidity and also have lower rates of breastfeeding [41, 45–48]. A number of these factors have been associated with pediatric cancers in other studies [49–52]. Further study of retinoblastoma risk among children of these women may improve understanding of retinoblastoma etiology.

Few population-based data are available on retinoblastoma rates in Mexico. However, researchers have stated that retinoblastoma is the second most common solid tumor among Mexican children and rates are believed to be higher there in comparison to the US and elsewhere.[53]

We observed associations between maternal history of STDs in pregnancy and bilateral retinoblastoma. As HPV often co-occurs with other STDs (particularly *Chlamydia trachomatis* in persistent HPV infection) [54, 55], we hypothesize that these STDs may be surrogate markers for HPV infection. Although our results were based upon a small number of reported cases, this finding supports the results of an earlier study which observed the use of barrier contraception to be associated with a reduced risk of retinoblastoma [5]. Laboratory and clinical evidence suggests a role for maternal HPV infection in the pathogenesis of sporadic retinoblastoma in children. The HPV E6 and E7 oncoproteins bind to and inactivate p53 and retinoblastoma (pRb) tumor-suppressor proteins, respectively [13, 52]. In addition, seven studies have tested for HPV DNA in retinoblastoma samples, most often among unilateral cases, and reported prevalences ranging from 5% (7 of 153 cases) to 82% (42 of 51 cases). Varying HPV types, not all considered high risk (HPV 16 or 18), were detected [10–16]. In contrast, a US study of retinoblastoma tumor samples (mostly unilateral) found all samples to be negative for 37 HPV types [56]. However, HPV DNA (and in particular high-risk HPV) is also not consistently found in cervical tumor tissue nor in cancers from other HPV-related sites [57, 58]. Researchers have hypothesized that shared risk factors for HPV infection and retinoblastoma, such as social class or lower maternal education, could explain these associations [13]. However, a link between socioeconomic status and retinoblastoma has not been demonstrated, and was not observed in our study [5, 19, 38, 39].

We did not observe any association with reported fertility treatment, as another study reported,[23] however assisted reproductive technologies (ART) began to be reported on California birth certificates only in 2006, limiting our sample size to address this question. However, we did observe a higher risk of bilateral disease among twin births, which may support an association with fertility treatment. In our data, the mean age of mothers who had twin births (mean=29.5) was higher than that of mothers of singleton births (mean=27.2, $p<0.0001$), suggesting twin births may be related to fertility treatment. Assisted reproductive technologies are estimated to be used in 5% of births nationally, while one study of California births which surveyed rural mothers observed a prevalence of <1% [59, 60]. Among controls in our sample, ART was reported in 0.6% of births.

This study is limited by its use of birth certificates as the primary data source. Birth certificate validity is known to vary by data item, with factors such as race, age and parity having strong validity (>90%) [61–63], while factors associated with pregnancy, labor and delivery tend to have reasonably good validity [64–66]. The use of assisted reproduction technologies is also likely underreported on birth certificates [67]. A potential source of bias

in this study would be if the retinoblastoma cases were diagnosed in utero, which might increase medical surveillance and provider vigilance in reporting any pregnancy and labor complications on the birth certificate.

In conclusion, we observed risk of retinoblastoma to be related to several risk factors. Bilateral disease risk was higher among children of older fathers, and among children of multiple birth pregnancies. We observed a higher risk of unilateral disease among children of US-born Hispanic women. Further research should be done to confirm this finding and to examine the unique risks experienced in this population.

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Table 1

Demographic characteristics in relation to retinoblastoma among California children ^a

Characteristic	Controls (n=209051)			All cases (n=609)			Unilateral cases (n=420)			Bilateral cases (n=187)		
	N (%)	Case n (%)	p-value	Case n (%)	p-value	Case n (%)	p-value	Case n (%)	p-value			
Child's sex			0.03				0.3				0.03	
Male	102757 (51.0)	333 (55.4)				221 (53.6)		110 (58.8)				
Female	98673 (49.0)	268 (44.6)				191 (46.4)		77 (41.2)				
Mother's age (years)			0.7				0.3				0.7	
<20	21919 (10.9)	66 (11.0)				43 (10.4)		23 (12.3)				
20–29	104831 (52.1)	323 (53.7)				232 (56.3)		90 (48.1)				
30–34	46816 (23.2)	127 (21.1)				82 (19.9)		44 (23.5)				
35+	27827 (13.8)	85 (14.1)				55 (13.3)		30 (16.0)				
Mother's race/ethnicity			0.3				0.4				0.9	
White non-Hispanic	72397 (35.9)	202 (33.6)				138 (33.5)		64 (34.2)				
Hispanic of any race	91356 (45.4)	275 (45.8)				187 (45.4)		87 (46.5)				
Other/not specified	37677 (18.7)	124 (20.6)				87 (21.1)		36 (19.3)				
Mother's birthplace			0.5				0.08				0.4	
US	112932 (56.1)	345 (57.4)				248 (60.2)		97 (51.9)				
Mexico	51818 (25.8)	142 (23.6)				86 (20.9)		55 (29.4)				
Other Foreign	36455 (18.1)	114 (19.0)				78 (18.9)		35 (18.7)				
Mother's race and birthplace			0.2				0.06				0.9	
White non-Hispanic	72397 (35.9)	202 (33.6)				138 (33.5)		64 (34.2)				
Hispanic, US born	30152 (15.0)	103 (17.1)				77 (18.7)		26 (13.9)				
Hispanic, foreign born	61162 (30.4)	172 (28.6)				110 (26.7)		61 (32.6)				
Other/not specified	37719 (18.7)	124 (20.6)				87 (21.1)		36 (19.3)				
Father's age (years)			0.5				0.8				0.02	
<20	7795 (4.1)	22 (3.8)				13 (3.3)		9 (5.1)				
20–29	83906 (44.6)	242 (42.2)				182 (46.2)		60 (33.7)				
30–34	48573 (25.8)	151 (26.3)				100 (25.4)		50 (28.1)				
35+	47828 (25.4)	159 (27.7)				99 (25.1)		59 (33.1)				
Father's race/ethnicity			0.9				0.9				0.8	
White non-Hispanic	68941 (34.2)	205 (34.1)				138 (33.5)		67 (35.8)				

Characteristic	Controls (n=209051)		All cases (n=609)		Unilateral cases (n=420)		Bilateral cases (n=187)	
	N (%)		Case n (%)	p-value	Case n (%)	p-value	Case n (%)	p-value
Hispanic of any race	87342 (43.4)		261 (43.4)		179 (43.4)		81 (43.3)	
Other/not specified	45147 (22.4)		135 (22.5)		95 (23.1)		39 (20.9)	
Urban or rural county				0.7		0.5		0.09
Urban	160790 (80.1)		483 (80.6)		323 (78.8)		159 (85.0)	
Rural	40050 (19.9)		116 (19.4)		87 (21.2)		28 (15.0)	

^aP-values compare each case group to controls; values computed by chi-square.

Table 2

Relationship between socioeconomic measures and retinoblastoma ^a

Characteristic	Controls (n=209051)		All cases (n=609)		Unilateral cases (n=420)		Bilateral cases (n=187)	
	Control n (%)	Case n (%)	Case n (%)	p-value	Case n (%)	p-value	Case n (%)	p-value
Mother's education (years) ^a				0.3		0.2		0.4
8 or fewer	24472 (13.6)	59 (10.6)			40 (10.6)		19 (11.0)	
9–<12	33098 (18.4)	107 (19.3)			67 (17.7)		39 (22.5)	
12	52387 (29.1)	167 (30.1)			122 (32.2)		45 (26.0)	
13–15	35573 (19.8)	118 (21.3)			85 (22.4)		32 (18.5)	
16+	34505 (19.2)	103 (18.6)			65 (17.2)		38 (22.0)	
Father's education (years) ^a				0.6		0.3		0.5
8 or fewer	24668 (14.6)	68 (12.9)			41 (11.4)		26 (15.8)	
9–<12	25129 (14.9)	77 (14.6)			53 (14.7)		24 (14.5)	
12	52084 (30.9)	170 (32.3)			127 (35.3)		43 (26.1)	
13–15	29777 (17.7)	87 (16.5)			58 (16.1)		28 (17.0)	
16+	36958 (21.9)	125 (23.7)			81 (22.5)		44 (26.7)	
Source of payment for prenatal care ^b				0.2		0.2		0.6
Private insurance	91615 (50.8)	299 (53.6)			206 (54.4)		93 (52.5)	
Medi-Cal/other gov't/self-pay ^c	88865 (49.2)	259 (46.4)			173 (45.6)		84 (47.5)	
Socioeconomic index [29]				0.9		0.4		0.4
1 (low)	48222 (24.0)	152 (25.4)			105 (25.6)		45 (24.1)	
2	46884 (23.3)	132 (22.0)			80 (19.5)		52 (27.8)	
3	45071 (22.4)	137 (22.9)			101 (24.6)		36 (19.3)	
4	32705 (16.3)	94 (15.7)			69 (16.8)		25 (13.4)	
5 (high)	27921 (13.9)	84 (14.0)			55 (13.4)		29 (15.5)	

^aP-values compare each case group to controls; values computed by chi-square.

^bData collected 1989–2007.

^cIncludes self-pay and government-funded insurance programs, including Medicare, Medi-Cal, and CHAMPUS/TRICARE.

Table 3

Gestational factors and maternal medical history in relation to retinoblastoma

Characteristic	Controls (n=209051)		All cases (n=609)		Unilateral cases (n=420)		Bilateral cases (n=187)	
	Control n (%)	Case n (%)	Adjusted OR (95% CI) ^a	Case n (%)	Adjusted OR (95% CI) ^a	Case n (%)	Adjusted OR (95% CI) ^a	Case n (%)
Child's birthweight (g)								
<2499	5.9	7.0	1.27 (0.92, 1.75)	6.8	1.28 (0.87, 1.88)	7.5	1.27 (0.72, 2.23)	
2500–3999	83.4	81.9	Referent	81.1	Referent	84	Referent	
4000 g +	10.7	11.1	1.04 (0.80, 1.35)	12.1	1.12 (0.82, 1.53)	8.6	0.82 (0.49, 1.37)	
Gestational age (weeks)								
Preterm (<37)	10.2	10.0	1.02 (0.77, 1.34)	8.8	0.89 (0.63, 1.27)	12.8	1.31 (0.84, 2.06)	
Term (37–42)	85.7	86.0	Referent	86.9	Referent	83.9	Referent	
Postterm (43+)	4.1	4.0	1.07 (0.70, 1.63)	4.3	1.12 (0.68, 1.82)	3.3	0.97 (0.43, 2.19)	
Size for gestational age								
Small	10.3	10.8	1.07 (0.83, 1.39)	11	1.07 (0.79, 1.47)	10.4	1.02 (0.64, 1.63)	
Normal	78.3	77.2	Referent	76.7	Referent	78.6	Referent	
Large	11.4	12.0	1.09 (0.83, 1.43)	12.3	1.08 (0.78, 1.50)	11	1.10 (0.68, 1.78)	
Method of delivery								
Vaginal	76.3	76.4	Referent	78.6	Referent	71.1	Referent	
Cesarean	23.7	23.6	0.94 (0.78, 1.15)	21.4	0.84 (0.66, 1.07)	28.9	1.21 (0.87, 1.68)	
Multiple birth								
Singleton	97.5	96.7	Referent	97.3	Referent	95.2	Referent	
Twin or higher ^b	2.5	3.3	1.37 (0.88, 2.15)	2.7	1.12 (0.61, 2.04)	4.8	1.93 (0.99, 3.79)	
Start of prenatal care								
During 1st trimester	80.2	82.9	Referent	82.4	Referent	83.9	Referent	
No care or after 1st trimester	19.8	17.1	0.92 (0.73, 1.15)	17.6	0.92 (0.71, 1.21)	16.1	0.91 (0.60, 1.37)	
Parity								
0	39.3	38.8	Referent	37.4	Referent	42.2	Referent	
1	31.3	29.1	0.93 (0.76, 1.14)	28.4	0.95 (0.74, 1.22)	30.5	0.87 (0.61, 1.25)	
2 or more	29.4	32.1	1.07 (0.87, 1.31)	34.2	1.23 (0.96, 1.58)	27.3	0.75 (0.51, 1.11)	
History of pregnancy terminations								
No	82.8	80.9	Referent	80.3	Referent	81.8	Referent	

Characteristic	Controls (n=209051)		All cases (n=609)		Unilateral cases (n=420)		Bilateral cases (n=187)	
	Control n (%)	Case n (%)	Adjusted OR (95% CI) ^a	Case n (%)	Adjusted OR (95% CI) ^a	Case n (%)	Adjusted OR (95% CI) ^a	Case n (%)
Yes	17.2	19.1	1.10 (0.89, 1.36)	19.7	1.19 (0.93, 1.53)	18.2	0.93 (0.63, 1.38)	

^aOdds ratios adjusted for year of birth, father's age, urban or rural county of residence, mother's race and birthplace.

^bThere were no retinoblastoma cases among births of triplets or more.

Table 4
Retinoblastoma in relation to pregnancy and labor complications, and clinical procedures relating to the newborn ^a

	All cases (n=609)		Unilateral cases (n=420)		Bilateral cases (n=187)	
	Control N (%)	Case n (%)	Adjusted OR (95% CI)	Case n (%)	Adjusted OR (95% CI)	Case n (%)
Complications and procedures of pregnancy and concurrent illnesses of the mother						
Chronic diabetes	3755 (1.9)	10 (1.7)	0.86 (0.46, 1.62)	9 (2.2)	1.18 (0.61, 2.29)	1 (0.5)
Previous preterm birth	2013 (1.1)	5 (0.9)	0.49 (0.16, 1.53)	3 (0.8)	0.48 (0.12, 1.94)	2 (1.1)
Any STD	1993 (1.2)	10 (1.9)	1.80 (0.96, 3.38)	4 (1.1)	1.03 (0.39, 2.78)	6 (3.5)
Rh sensitive	598 (0.3)	5 (0.8)	2.43 (0.91, 6.54)	1 (0.2)	----	4 (2.1)
Complications or procedures of labor and delivery						
Breech presentation	5734 (3.0)	12 (2.1)	0.75 (0.42, 1.33)	6 (1.5)	0.53 (0.24, 1.20)	6 (3.5)
Prolonged labor (>20 hrs)	1380 (0.8)	5 (0.9)	1.26 (0.52, 3.03)	2 (0.5)	0.74 (0.18, 2.95)	3 (1.7)
Moderate/heavy meconium staining of amniotic fluid	7631 (4.2)	20 (3.6)	0.86 (0.55, 1.37)	12 (3.1)	0.74 (0.41, 1.35)	8 (4.5)
Fetal distress	6071 (3.1)	17 (3.0)	0.91 (0.54, 1.52)	10 (2.6)	0.78 (0.40, 1.51)	7 (4.1)
Abnormal conditions and clinical procedures relating to the newborn						
Any assisted ventilation after birth	1607 (1.0)	8 (1.6)	1.82 (0.90, 3.67)	4 (1.2)	1.33 (0.50, 3.59)	4 (2.4)
Any medical procedure at birth	6788 (4.2)	30 (6.0)	1.46 (1.00, 2.14)	20 (6.0)	1.49 (0.94, 2.38)	10 (6.0)
						1.42 (0.73, 2.79)

^aData from 1990–2007. Odds ratios adjusted for year of birth, father's age, urban or rural county of residence, mother's race and birthplace.