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Birth Characteristics and Risk of Early-Onset Synovial Sarcoma

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Abstract

Background: Synovial sarcoma is a rare cancer with peak incidence in the young adult period. Despite poor outcomes of this aggressive cancer, there is little epidemiologic research addressing its etiology.

Methods: We collected birth characteristic data on synovial sarcoma cases born during 1978–2015 and diagnosed during 1988–2015 in California (n = 244), and 12,200 controls frequency

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Disclosure of Potential Conflicts of Interest

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matched on year of birth. We also constructed a dataset of cancer cases in siblings of sarcoma subjects to assess familial risk.

Results: In multivariable logistic regression analyses, synovial sarcoma was more frequent in Hispanics compared with non-Hispanic whites [OR, 1.48; 95% confidence interval (CI), 1.06–2.08]. Higher birth weight was a risk factor in Hispanics; each 500 g increase in birth weight was associated with a 22% increase in disease risk (OR, 1.22; 95% CI, 1.00–1.48). Also, a strong role for birth order was suggested, with highest risk for the first born (second child compared with first: OR, 0.61; 95% CI, 0.44–0.84; third or later compared with first: OR, 0.53; 95% CI, 0.36–0.77). Siblings of patients with synovial sarcoma did not display elevated cancer incidence, suggesting the low likelihood that strong familial predisposition alleles play a significant role in this disease.

Conclusions: The associations with birth weight and birth order suggest that nutritional, developmental, and environmental factors may play a role in the etiology of synovial sarcoma.

Impact: Further epidemiologic research on synovial sarcoma should evaluate epigenetic and developmental mechanisms and the formation of the archetypical t(X;18) translocation that defines this disease.

Introduction

Synovial sarcoma, the second most common soft tissue sarcoma in children and young adults, is typically an invasive and metastatic tumor with poor prognosis. It does not display synovial features despite commonly arising from positions proximal to developing joints; instead, the tumors have epithelial histology with spindle or biphasic morphology (1). A primary characterizing feature of synovial sarcoma is the t(X;18; p11;q11) translocation resulting in a fusion between the entire coding region of the *SS18* gene and a portion of an *SSX* gene (*SSX1, SSX2*, or *SSX4*; ref. 2). The singular association of this fusion gene with synovial sarcoma suggests that the causes of its formation may be the key to understanding the genesis of this disease. The fusion oncogene participates in chromatin remodeling complexes, underscoring the possibility that epigenetic alterations may represent a major component of the transformation process (2). Epidemiologic data on etiology specific to synovial sarcoma are scant, which is likely attributable to its rarity. More common sarcomas have been included in prior studies, and such research has noted associations with parental age (3), gestational age (4, 5), birth weight (5–8), and birth order (9). We examined the potential etiologic role of such birth characteristics here in a large, population-based case–control study of synovial sarcoma in California, as well as any indication for familial cancer clustering (reflective of genetic predisposition) using high quality data from the California Cancer Registry (CCR) and statewide birth records.

Materials and Methods

We constructed two separate datasets by merging data from the CCR and California birth records to examine birth characteristics and familial cancer clustering, respectively. The study protocol was approved by the Institutional Review Boards at the California Health and Human Services Agency, University of Southern California (Los Angeles, CA), University of California at Berkeley (Berkeley, CA), and Yale University (New Haven, CT).

Birth characteristics

We identified a total of 244 synovial sarcoma cases who were born in California during 1978–2015, diagnosed with synovial sarcoma [International Classification of Diseases (ICD) for Oncology, 3rd edition, ICD-O-3 codes: 9040–9043] at the age of 0–35 years during 1988–2015, and reported to the CCR. Statewide birth records maintained by the California Department of Public Health were used to randomly select 50 times as many control subjects ($n = 12{,}200$) who were frequency matched to the cases by year of birth; none of the controls had been diagnosed with any type of cancer up to the age of 35 years based on CCR records.

For all cases and controls, data on the following variables were retrieved from their birth records: sex, race/ethnicity (white, black, Hispanic/Latino, Asian/Pacific Islander, and other), birth weight, gestational age, birth plurality, birth order, mode of delivery (vaginal or cesarean section), year of birth, maternal and paternal age, maternal education, mother's place of birth (United States/foreign), history of miscarriage/stillbirth (yes/no), complication during pregnancy (yes/no), and maternal history of cesarean section (yes/no). A multivariable unconditional logistic regression analysis was performed with case status as the outcome and all birth characteristics described above as independent variables. In addition, stratified analyses were performed for larger racial/ethnic groups (Hispanic and non-Hispanic whites), age at diagnosis, and histology subtype.

Familial cancer clustering

To assess potential familial aggregation that may reflect genetic predisposition to cancer, we captured the siblings of all young patients with synovial sarcoma (ages 0–19, 127 cases) from the statewide birth records and examined whether any of them had been diagnosed with any type of cancer per CCR record. We calculated standardized incidence ratios (SIR) for siblings' RR by dividing the observed number of cancer cases by the expected number of cases among siblings based on age-specific cancer incidence rates derived from the Surveillance Epidemiology and End Results (SEER) program (10). Similar analyses were performed for comparison on additional sarcomas including Ewing sarcoma (ICD-O-3 code 9260; 353 cases), osteosarcoma (ICD-O-3 codes: 9180–83, 9185–87, and 9192–95; 576 cases), and rhabdomyosarcoma (ICD-O-3 codes: 8900–02, 8910, 8912, 8920, and 8991; 719 cases).

All tests were two-sided with an alpha of 0.05 and were conducted using SAS version 9.4 (SAS Inc.).

Results

Of the 244 cases with synovial sarcoma, 94 were recorded with ICD-O-3 code 9040 (synovial, not otherwise specified), 92 with ICD-O-3 code 9041 (spindle cell), one with ICD-O-3 code 9042 (epithelioid), and 57 with ICD-O-3 code 9043 (biphasic). A comparison with the number of California statewide cases reported to the SEER program during 2000–2015 suggested that we captured 77% of cases diagnosed under the age of 15 years and 56% of cases diagnosed at the age of 15–35 years; the noncaptured cases were presumably born

outside of California. Of the 244 cases, 228 (93%) had their sarcoma located in connective tissue; among the 228 cases, the most commonly observed locations were the lower limb or hip (53%) and upper limb/shoulder (23%). Cases were 56.6% male which was not significantly higher than controls, and the largest group of cases and controls were Hispanic (Table 1). While both younger and older mothers and fathers were in excess among cases, parental ages were not significantly associated with case/control status. The only factor that appeared to significantly predict risk was "birth order," where synovial sarcoma cases were more likely to be first born compared with controls in the bivariate χ^2 analysis ($P < 0.01$; Table 1).

Hispanics appeared to have a higher risk of synovial sarcoma than non-Hispanic whites [OR, 1.48; 95% confidence interval (CI), 1.06– 2.08; Table 2), especially for synovial sarcoma diagnosed in young adults (age 19–35 years; OR, 1.94; 95% CI, 1.12–3.35; Supplementary Table S1) and spindle cell sarcoma (OR, 2.30; 95% CI, 1.27–4.17; Supplementary Table S1). Higher birth weight was a risk factor for synovial sarcoma in Hispanics, each 500 g increase in birth weight was associated with a 22% increase in disease risk (OR, 1.22; 95% CI, 1.00–1.48; Table 2). No relationship with birth weight was demonstrated among non-Hispanic whites. A similar association was observed between higher birth weight and the risk of pediatric synovial sarcoma (age 0–19 years; OR, 1.21; 95% CI, 1.03–1.42 for each 500 g increase in birth weight; Supplementary Table S1), with no association noted for those patients with synovial sarcoma diagnosed over 19 years.

Compared with first borns, those whose birth order was second or higher had a significantly lower risk of synovial sarcoma (second: OR, 0.61; 95% CI, 0.44–0.84; third or higher: OR, 0.53; 95% CI, 0.36–0.77; Table 2). This association was consistently observed across major racial/ethnic groups (Hispanics and non-Hispanic whites), both the pediatric and young adult populations, as well as histopathology and tumor site (Supplementary Table S1). Another familial characteristic, parental age, also demonstrated some marginal, but potentially notable associations. Both maternal and paternal age was divided into five groups, using the central group as the reference. In unadjusted bivariate analyses, both younger and older parental ages appeared to carry some risk, particularly for paternal age (Table 2). When adjusting for each other (and other birth characteristics), some of these relationships sustained, suggesting that increased or decreased maternal and paternal ages independently influence risk of synovial sarcoma. For instance, paternal age over 40 years was associated with an OR of 1.90 (95% CI, 1.07–3.35; Table 2) when adjusting for maternal age and other covariates for synovial sarcoma overall. The other factors assessed here, including gestational age, birth plurality, mode of delivery, maternal history of fetal loss, and pregnancy complications, were not significantly associated with synovial sarcoma risk.

Our family-based analysis included a total of 127 families with a case of pediatric synovial sarcoma (diagnosed at the age of 0–19 years). Of all siblings identified ($n = 153$), none had been diagnosed with any types of cancer per CCR record, rendering an inability to estimate SIR. For other sarcomas of childhood, we identified cancer diagnoses among siblings of patients with pediatric Ewing sarcoma (SIR, 1.79; 95% CI, 0.47–6.85), osteosarcoma (SIR, 3.83; 95% CI, 1.44–10.20), and rhabdomyosarcoma (SIR, 6.47; 95% CI, 3.01–13.95). On comparing father's birthdates, we found that 14% of siblings in this analysis with a shared

mother had a nonshared father. These siblings will only share the genetic complement from their mothers and therefore our familial clustering analysis will be slightly biased toward the null.

Discussion

Synovial sarcoma is the second most common soft tissue sarcoma across all ages (after rhabdomyosarcoma), and typically presents as a high-grade disease with local invasion and a high propensity to metastasize. While a variety of single institution and multicenter survival and prognostic studies on synovial sarcoma populate the literature, we believe this is the first study examining the role of birth characteristics in the etiology of synovial sarcoma.

Our analysis highlights several unknown or underappreciated aspects of the epidemiology of synovial sarcoma. First, Hispanics appear to have an increased risk of the disease, particularly the spindle cell form. Higher birth weight was a risk factor for synovial sarcoma in Hispanics but not the other racial/ethnic groups. Hispanics are known to exhibit faster growth rates than non-Hispanic whites in mid-gestation (11). When stratifying by age, the birth weight association was only observed for those who were diagnosed at younger ages (0–19 years) and null for young adults (>19 years). It should be reiterated that the association of synovial sarcoma with Hispanic ethnicity was independent of birth weight, and therefore the birth weight association here exclusively among Hispanics suggests that cultural or nutritional differences among Hispanics may drive the association possibly interacting with ethnic-specific genetic factors. Embryogenesis and adolescence are two points in life where the fastest growth rates occur for the human organism, which may implicate hormonal or nutritional influences on synovial sarcoma growth or genetic propensity for growth. These periods of rapid growth correspond to periods of sensitivity to environmental agents, which could impact synovial sarcoma risk, underscoring the need for further investigation particularly among Hispanics.

Our most intriguing finding is the strong association between birth order and synovial sarcoma risk, which is consistently observed across different racial/ethnic groups and different ages of diagnosis. Birth order is known to impact risk of childhood cancer overall (OR for subsequent births compared with the first = 0.87; 95% CI, 0.81–0.93 in a multistate analysis including California; ref. 9). While it is not necessarily a causal factor in itself, birth order is associated with a variety of developmental and environmental factors. First, later-born children are presumably exposed to more infectious agents earlier in life than their first-born siblings, potentially affecting immune system development. Having a higher birth order is thought to reduce risk of diseases such as atopy (12), leukemia (13–15), and type-1 diabetes (16) and increase risk of non-Hodgkin lymphoma (17), to name a few. Second, first-born children experience differential nutrition during pregnancy compared with their later-born siblings; specifically, placentation is less efficient during first pregnancies, resulting in a degree of nutrient restriction *in utero* compared with later borns (18). The first born tends to be taller, thinner, have greater IGF-1 concentrations at birth, and exhibit a reduction in insulin sensitivity (19). Third, estrogens are higher in first births compared with later births (20, 21). Birth order has not been consistently linked to the risk of breast cancer but has been suggested to play a role in the etiology of testicular cancer and adult glioma (22, 23). Fourth

and finally, birth order is related to fetal microchimerism, in which circulating cells from a former pregnancy may be passed through the mother to subsequent pregnancies. This phenomenon has implications for immunologic diseases such as scleroderma (24) with uncertain effects on cancer. Given the association with birth weight seen here, it is likely that nutritional and growth-related attributes related to first-born birth status may influence synovial sarcoma incidence, but the other mechanisms listed above cannot be ruled out.

We did observe an association with parental age, particularly for paternal age, which appeared to be independent of maternal age. Paternal age is associated with epigenetic changes, DNA mutations, and aneuploidy, which are all characteristics of cancer cells and as such may contribute to risk should such features be contributed to the germline.

Our familial clustering analysis did not provide evidence for any increased risk of cancer among siblings of patients with pediatric synovial sarcoma, suggesting that strong cancer inherited predisposition alleles are not likely to play a major role in the incidence of this disease, at least in pediatric (0–19 years) synovial sarcoma examined here. In a prior study in the Utah Population Database, a 2-fold excess of *BCL2*-related malignancies (exclusively hematopoietic) were found in first- and second-degree relatives (25). This study presumably tracked adults which we did not consider here. In contrast to synovial sarcoma in our study, significant familial risks were demonstrated for pediatric osteosarcoma and rhabdomyosarcoma, which is expected given prior evidence for these cancers to be associated with cancer predisposition syndromes such as Li Fraumeni (26). We cannot exclude a significant role for low and intermediate penetrance susceptibility alleles for early-onset synovial sarcoma based on our data because our sample size was small.

This analysis, essentially a nested case–control study within the California birth cohort, has several strengths. First, cases were ascertained from the population-based CCR, and controls were randomly selected from the statewide birth records. None of the cases and controls had to be contacted for inclusion in this study, minimizing selection bias. Second, all data on birth characteristics were abstracted from preexisting birth records, reducing information bias in general and recall bias in particular. In addition, the diversity of the California population allowed us to include a large number of Hispanic subjects in this study. While the number of synovial sarcoma cases was relatively small due to the rarity of this disease, we included 50 times as many controls to help improve statistical power. To be included, cases must have been born and diagnosed in California, and controls only were required to have been born in the state. It is possible that some controls might have moved out of California, developed synovial sarcoma elsewhere, and therefore were not captured by CCR. However, we expect this to have very small, if any impact on our analysis, given the rarity of synovial sarcoma. In an extremely unlikely scenario where all of the 122,000 controls in our study moved out of California, we would only expect 1.98 cases, given SEER-based age-specific incidence rates of synovial sarcoma (10).

In summary, our findings regarding birth order and birth weight provide support that developmental and nutritional factors may contribute to the risk of synovial sarcoma. We found no evidence for strong familial genetic predisposition, apart from a disparity of risk by Hispanic status, which may be attributable to ethnic differences in genetic profiles or

cultural differences related to diet or environmental exposures. Further studies into the etiology of synovial sarcoma will likely benefit from the evaluation of nutritional, environmental, and epigenetic factors, along with the mechanisms of formation of the archetypical t(X;18) translocations that define the disease.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1.

Characteristics of subjects with synovial sarcoma and controls, California, 1978–2015.

	Synovial sarcoma *n* = 244		Control group *n* = 12,200		
	Number of participants	**%**	**Number of participants**	**%**	***P*[a]**
Overall	244		12,200		
Sex					
Female	106	43.4	5,940	48.7	0.10
Male	138	56.6	6,260	51.3	
Race/ethnicity					
White	93	38.1	4,834	39.6	0.45
Black	17	7.0	1,097	9.0	
Hispanic	112	45.9	4,965	40.7	
Asian	20	8.2	1,139	9.3	
Other	2	0.8	165	1.4	
Birth weight (grams)					
250–2,499	15	6.1	721	5.9	0.76
2,500–2,999	32	13.1	1,928	15.8	
3,000–3,499	95	38.9	4,480	36.7	
3,500–3,999	71	29.1	3,674	30.1	
4,000+	31	12.7	1,397	11.5	
Gestational age (weeks)					
37–41	19	7.8	1,118	9.2	0.56
22–36	183	75.0	8,820	72.3	
42–44	20	8.2	1,268	10.4	
Unknown	22	9.0	994	8.1	
Birth plurality					
Singleton	239	98.0	11,927	97.8	0.84
Multiple	5	2.0	273	2.2	
Birth order					
1st	128	52.5	4,873	39.9	<0.01

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	Synovial sarcoma *n* = 244		Control group *n* = 12,200		
	Number of participants	**%**	**Number of participants**	**%**	***P*[a]**
2nd	66	27.0	3,932	32.2	
3rd and higher	50	20.5	3,395	27.8	
Mode of delivery					
Vaginal	193	79.1	9,630	78.9	0.95
Cesarean section	51	20.9	2,570	21.1	
Year of birth					
1978–1982	47	19.3	2,350	19.3	1.00
1983–1987	66	27.0	3,300	27.0	
1988–1992	66	27.0	3,300	27.0	
1993–2013	65	26.6	3,250	26.6	
Maternal education					
Up to 8 years	10	4.1	981	8.0	0.20
9–11 years	23	9.4	1,171	9.6	
12 years	47	19.3	2,079	17.0	
13–15 years	31	12.7	1,365	11.2	
16 or more years	24	9.8	1,114	9.1	
Unknown	109	44.7	5,490	45.0	
Mother’s place of birth					
United States	157	64.3	7,668	62.9	0.63
Foreign	87	35.7	4,532	37.1	
Miscarriage/stillbirth					
Never	205	84.0	10,114	82.9	0.60
Ever	38	15.6	2,060	16.9	
Unknown	1	0.4	26	0.2	
Maternal complication during pregnancy					
Never	196	80.3	9,872	80.9	0.79
Ever	37	15.2	1,775	14.5	
Unknown	11	4.5	553	4.5	
Previous cesarean section					

	Synovial sarcoma *n* = 244		Control group *n* = 12,200		P^a
	Number of participants	%	Number of participants	%	
Never	221	90.6	10,735	88.0	0.23
Ever	15	6.1	1,004	8.2	
Unknown	8	3.3	461	3.8	
Maternal age (years)					
<20	30	12.3	1,484	12.2	0.44
20–24	76	31.1	3,373	27.6	
25–29	60	24.6	3,591	29.4	
30–34	56	23.0	2,532	20.8	
≥35	22	9.0	1,220	10.0	
Paternal age (years)					
<25	66	27.0	2,938	24.1	0.11
25–29	78	32.0	3,421	28.0	
30–34	42	17.2	2,901	23.8	
35–39	31	12.7	1,484	12.2	
≥40	22	9.0	865	7.1	
Unknown	5	2.0	591	4.8	

[a] *P* values were derived from χ^2 tests.

Table 2.

ORs for the risk for synovial sarcoma according to race/ethnicity, birth weight and birth order, and parental age, California 1978–2015.

	Entire population (*n* = 244 cases and 12,200 controls)				non-Hispanic White only (*n* = 93 cases 1,939 controls)	Hispanic only (*n* = 112 cases 2,345 controls)
	Case *n* (%)	Control *n* (%)	Unadjusted OR (95% CI)	Adjusted[a] OR (95% CI)	Adjusted[a] OR (95% CI)	Adjusted[a] OR (95% CI)
Sex						
Female	106(43.3)	5,940 (48.7)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Male	138 (56.6)	6,260 (51.3)	1.24 (0.96–1.60)	1.21 (0.94–1.57)	1.44 (0.93–2.24)	0.96 (0.65–1.43)
Race/ethnicity						
White	93 (38.1)	4,834 (39.6)	1.00 (Reference)	1.00 (Reference)		
Black	17 (7.0)	1,097 (9.0)	0.81 (0.48–1.36)	0.90 (0.53–1.54)		
Hispanic	112 (45.9)	4,965 (40.7)	1.17 (0.89–1.55)	1.48 (1.06–2.08)		
Asian	20 (8.2)	1,139 (9.3)	0.91 (0.56–1.49)	1.03 (0.60–1.78)		
Other	2 (0.8)	165 (1.4)	0.63 (0.15–2.58)	0.67 (0.16–2.78)		
Birth weight (grams)						
250–2,499	15 (6.1)	721 (5.9)	0.98 (0.57–1.70)	1.06 (0.57–1.98)	0.94 (0.29–3.12)	0.78 (0.27–2.23)
2,500–2,999	32 (13.1)	1,928 (15.8)	0.78 (0.52–1.17)	0.78 (0.52–1.18)	0.71 (0.34–1.48)	0.80 (0.43–1.52)
3,000–3,499	95 (38.9)	4,480 (36.7)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
3,500–3,999	71 (29.1)	3,674 (30.1)	0.91 (0.67–1.24)	0.90 (0.66–1.23)	0.70 (0.42–1.19)	1.15 (0.72–1.82)
4,000+	31 (12.7)	1,397 (11.5)	1.05 (0.69–1.58)	1.09 (0.72–1.66)	1.00 (0.52–1.90)	1.26 (0.65–2.47)
Every 500 g				1.08 (0.95–1.23)	1.07 (0.87–1.33)	1.22 (1.00–1.48)
Birth order						
1st	128 (52.5)	4,873 (39.9)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
2nd	66 (27.0)	3,932 (32.2)	0.64 (0.47–0.86)	0.61 (0.44–0.84)	0.58 (0.35–0.98)	0.54 (0.32–0.89)
3rd and higher	50 (20.5)	3,395 (27.8)	0.56 (0.40–0.78)	0.53 (0.36–0.77)	0.46 (0.23–0.90)	0.53 (0.30–0.95)
Maternal age (years)						
<20	30 (12.3)	1,484 (12.2)	1.21 (0.78–1.88)	0.92 (0.53–1.59)	0.79 (0.24–2.63)	0.97 (0.46–2.07)
20–24	76 (31.1)	3,373 (27.6)	1.35 (0.96–1.90)	1.13 (0.78–1.66)	1.16 (0.59–2.30)	1.23 (0.70–2.16)
25–29	60 (24.6)	3,591 (29.4)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
30–34	56 (23.0)	2,532 (20.8)	1.32 (0.92–1.91)	1.49 (1.00–2.23)	2.61 (1.39–4.88)	0.68 (0.31–1.50)
≥35	22 (9.0)	1,220 (10.0)	1.08 (0.66–1.77)	1.06 (0.59–1.91)	1.08 (0.41–2.88)	1.81 (0.77–4.30)
Paternal age (years)						

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	Entire population (*n* = 244 cases and 12,200 controls)				non-Hispanic White only (*n* = 93 cases 1,939 controls)	Hispanic only (*n* = 112 cases 2,345 controls)
	Case *n* (%)	**Control *n* (%)**	**Unadjusted OR (95% CI)**	**Adjusted[a] OR (95% CI)**	**Adjusted[a] OR (95% CI)**	**Adjusted[a] OR (95% CI)**
<25	66 (27.0)	2,938 (24.1)	1.55 (1.05–2.29)	1.41 (0.86–2.32)	1.35 (0.56–3.25)	1.72 (0.82–3.62)
25–29	78 (32.0)	3,421 (28.0)	1.57 (1.08–2.30)	1.60 (1.06–2.41)	1.87 (0.97–3.60)	1.59 (0.80–3.16)
30–34	42 (17.2)	2,901 (23.8)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
35–39	31 (12.7)	1,484 (12.2)	1.44 (0.90–2.30)	1.49 (0.92–2.41)	1.60 (0.80–3.20)	2.07 (0.87–4.90)
≥40	22 (9.0)	865 (7.1)	1.76 (1.04–2.96)	1.90 (1.07–3.35)	2.39 (1.05–5.44)	1.32 (0.45–3.90)
Unknown	5 (2.0)	591 (4.8)	0.58 (0.23–1.48)	0.63 (0.24–1.64)		0.54 (0.12–2.50)

[a]The adjusted ORs were derived from multivariable logistic regression models in which all the variables listed in the table were included simultaneously. Three separate models were fit for the overall study population, Hispanics, and non-Hispanic Whites, respectively.