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Correlation of Insurance, Race, and Ethnicity with Pathologic Risk in a Controlled Retinoblastoma Cohort:

A Children's Oncology Group Study

Adam L. Green, MD¹, Murali Chintagumpala, MD², Mark Krailo, PhD³, Bryan Langholz, PhD³, Daniel Albert, MD⁴, Ralph Eagle, MD⁵, Myles Cockburn, PhD³, Patricia Chevez-Barrios, MD⁶, and Carlos Rodriguez-Galindo, MD⁷

¹Center for Cancer and Blood Disorders, Department of Pediatrics, University of Colorado School of Medicine and Children's Hospital Colorado, Aurora, Colorado

²Texas Children's Cancer Center, Baylor College of Medicine and Texas Children's Hospital, Houston, Texas

³Keck School of Medicine of the University of Southern California, Los Angeles, California

⁴Department of Ophthalmology and Visual Sciences, University of Wisconsin School of Medicine and Public Health, Madison, Wisconsin

⁵Pathology Department, Wills Eye Hospital, Philadelphia, Pennsylvania

⁶Department of Pathology and Genomic Medicine, Houston Methodist Hospital, Houston, Texas

⁷Dana-Farber/Boston Children's Cancer and Blood Disorders Center, Harvard Medical School, Boston, Massachusetts

Abstract

Purpose—To determine whether insurance status, race, and ethnicity correlate with increased retinoblastoma invasiveness as a marker of both risk and time to diagnosis.

Design—Retrospective case-control study.

Participants—All 203 patients from the United States enrolled in the Children's Oncology Group (COG) trial ARET0332, a study of patients with unilateral retinoblastoma requiring enucleation.

Correspondence: Adam L. Green, MD, Center for Cancer and Blood Disorders, Department of Pediatrics, University of Colorado School of Medicine and Children's Hospital Colorado, Anschutz Medical Campus, 12800 E. 19th Avenue, RC1-N, Mail Stop 8302, Aurora, CO 80045. adam.green@ucdenver.edu.

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Data collection: Green, Chintagumpala, Krailo, Langholz, Albert, Eagle, Cockburn, Chevez-Barrios, Rodriguez-Galindo

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Main Outcome Measures—All surgical specimens underwent pathologic review to determine the presence of well-defined histopathologic features correlating with a higher risk of disease progression. Insurance status, race, and ethnicity were compiled from the study record for each patient.

Results—On institutional pathologic review, nonprivate insurance, nonwhite race, and Hispanic ethnicity all correlated significantly with a greater rate of high-risk pathologic findings. Hispanic ethnicity remained a significant predictor on multivariate analysis. On central pathologic review, these correlations remained but did not reach statistical significance. The differences in results from institutional versus central pathologic reviews appeared to be due to a higher likelihood of patients in minority groups of being misclassified as high risk by institutional pathologists.

Conclusions—In this controlled study population of patients with retinoblastoma who had central pathologic review, our findings suggest a higher rate of more advanced disease associated with nonprivate insurance, nonwhite race, and Hispanic ethnicity; these findings may be due to delays in diagnosis for these groups. Future work should use direct methods to study the impact of other variables, including English-language proficiency and socioeconomic status. Further effort also should focus on where in the diagnostic process potential delays exist, so that interventions can be designed to overcome barriers to care for these groups. In addition, potential systematic differences in pathologic reads based on demographic variables deserve further study.

The potential link between health insurance and cancer diagnosis and outcomes has recently been the subject of increasing research interest. In adults, patients with no insurance or Medicaid are more likely to present with stage III and IV disease in 8 common cancers¹ and to have poorer survival in lung cancer² compared with those with private insurance. In adolescents and young adults, the type of insurance affects the timing of cancer diagnosis,³ stage at diagnosis in Hodgkin lymphoma,⁴ and leukemia survival.⁵ The population-based nature of the majority of the research limits the conclusions that can be drawn. Cancer databases have inconsistent follow-up and are not comprehensive in coverage, introducing potential selection bias. In addition, the inclusion of young adults in the pediatric studies clouds the results because young adults have a higher incidence of cancer than children, are usually treated at adult centers, are generally at high risk for underinsurance or no insurance, and delay seeking care for potential cancer symptoms.⁶

Therefore, barriers to care in pediatric oncology deserve further controlled study. Retinoblastoma is a cancer mostly affecting infants and toddlers. Its timely diagnosis and treatment depend on access to multiple layers of care. Parents may recognize symptoms and bring their children to primary care attention, or primary care providers may find signs on screening examinations. Subsequently, patients are referred to ophthalmologists for definitive diagnosis, and treatment usually is collaborative among ophthalmologists, pediatric oncologists, and radiation oncologists. Of note, time from first symptoms to diagnosis correlates with degree of tumor invasiveness.⁷ Thus, tumor invasiveness can be used as a proxy for measuring time to diagnosis. Recently, our group published a population-based analysis of retinoblastoma using the Surveillance, Epidemiology, and End Results database showing a greater extent of disease at diagnosis for Hispanic children and those living in socioeconomically disadvantaged areas, as well as poorer survival for black children.⁸

A suitable patient population for a controlled study of the influence of insurance type and other demographic variables on retinoblastoma diagnosis is available from the Children's Oncology Group (COG) protocol ARET0332. In this study, all patients had undergone unilateral enucleation before enrollment. Surgical specimens were first reviewed for high-risk features institutionally and then centrally. Together, these reviews provide the most validated and unbiased measure of disease invasiveness available. The primary objective of the present study was to compare demographic and pathologic data from the patients enrolled in ARET0332 to determine whether patients newly diagnosed with retinoblastoma who are uninsured or have public insurance have a higher rate of high-risk pathologic features than patients with private insurance. Secondary aims included determining whether nonwhite race or Hispanic ethnicity also correlate with more advanced disease at diagnosis.

Methods

Study Population and Pathologic Review

The COG protocol ARET0332, open from 2005 to 2010, studied children with unilateral retinoblastoma who had undergone up-front unilateral enucleation for advanced intraocular disease before enrollment. Surgical specimens were reviewed locally by pathologists at the treating institutions for the presence of the following high-risk features: tumor involvement of the optic nerve posterior to the lamina propria, posterior uveal invasion greater than 3 mm in depth, or any concurrent optic nerve and scleral involvement. Specimens were then sent for central review by 3 pediatric ophthalmologic pathologists, who decided definitively on the presence or absence of these high-risk features. The presence of any of these features qualified as high-risk disease; the absence of all 3 meant the patient was classified as having standard-risk disease. Of note, patients with tumor infiltration at the cut end of the optic nerve were excluded from the study. Enrollment included documentation of demographic data, including the patient's type of health insurance, race, ethnicity, and address (all reported by the patient's family). Patients with high-risk pathology received 6 cycles of adjuvant chemotherapy with vincristine, carboplatin, and etoposide; patients with standard-risk pathology were observed.

Data Collection and Analysis

The study enrolled 324 patients in total from both inside and outside the United States. For this study, we have included only the 203 patients living in the United States at the time of enrollment. Permission from the COG Retinoblastoma and Scientific Committees for this study was sought and obtained, and a depersonalized data set including patients' birth date, date of diagnosis, sex, ZIP code, race, ethnicity, type of insurance, and institutional/central pathologic strata was created. Patients were grouped by insurance status (no insurance or public insurance vs. private insurance), race (nonwhite vs. white), and ethnicity (Hispanic vs. non-Hispanic). Univariate analysis and comparisons between groups incorporating multiple demographic variables were performed using the 2-tailed Fisher exact test. The influence of a number of demographic risk categories was analyzed by the chi-square test, and demographic risk scores were assigned for each patient by assigning 1 point each for nonprivate or no insurance, nonwhite race, and Hispanic ethnicity. Multivariate analysis was

done through backward stepwise exact logistic regression with STATA (StataCorp LP, College Station, TX).

Analysis of Population Variables

For analysis of English proficiency, socioeconomic status, and educational attainment, we used Census 2000 data on these variables for the population living in the ZIP code of each patient. Because we had access only to patients' ZIP code at diagnosis, and not their address, we determined the census tract closest to the centroid of each patient's ZIP code and used that as the proxy for their residential location at diagnosis. The census tract data were obtained from the 2000 Census. Variables assessing English proficiency included percentage speaking English only, percentage speaking a language other than English at home, percentage speaking English less than very well, and percentage speaking Spanish at home. Variables assessing socioeconomic status included median household income and percentage of persons whose income is below the poverty level. Variables assessing educational attainment included percentage graduating high school or higher and percentage receiving a bachelor's degree or higher. We divided patients' census tract values for each of these variables into quartiles, and 2×4 tables were made on the basis of the presence or absence of high-risk pathology. We determined the correlation of each variable with high-risk pathology rates by chi-square testing.

Results

Demographic Characteristics of the Study Population

A total of 203 US patients were enrolled in the study because they underwent institutional pathologic review and had slides submitted for central review as required; a total of 193 had central review completed. Tables 1 and 2 show demographic characteristics of the study population, with the number and percentage from each group showing high-risk and standard-risk pathologic features.

Univariate Analysis

Results of the univariate analysis are shown in Table 3 and Figure 1. On institutional review (Fig 1A), patients with no insurance or public insurance had a significantly higher rate of high-risk pathologic findings than patients with private insurance (32.4% vs. 19.4%; $P=0.039$). This was also true for patients of nonwhite versus white race (34.2% vs. 21.0%; $P=0.049$) and Hispanic versus non-Hispanic ethnicity (36.9% vs. 21.0%; $P=0.025$). On central review (Fig 1B), patients with no insurance or public insurance showed a trend toward a higher rate of high-risk pathologic findings than patients with private insurance (38.2% vs. 27.5%; $P=0.13$). The same was true for nonwhite versus white patients (35.9% vs. 31.3%; $P=0.54$) and Hispanic versus non-Hispanic patients (38.1% vs. 30.8%; $P=0.33$).

Multivariate Analysis

Multivariate analysis is shown in Table 3 and Figure 2. On institutional review, only Hispanic ethnicity remained a significant risk factor for high-risk pathology in the final multivariate model ($P=0.027$; odds ratio [OR], 2.191; 95% confidence interval [CI], 1.086–4.416). By looking at race and ethnicity together, white, non-Hispanic patients had a

significantly lower high-risk pathology rate than all other patients (OR, 0.44; 95% CI, 0.23–0.84) (Fig 2A). In addition, patients of nonwhite race or Hispanic ethnicity who also had public or no health insurance showed high-risk pathology more frequently than all other patients (OR, 2.58; 95% CI, 1.36–4.92) (Fig 2B). The rate of high-risk pathology on institutional analysis varied significantly with the patient's demographic risk score ($P=0.007$) (Fig 2C).

None of the 3 minority demographic characteristics carried a significantly higher risk of high-risk pathology on central review (Table 2). When race and ethnicity were examined together, white, non-Hispanic patients showed a slight trend toward a lower rate of high-risk pathology versus all other patients (OR, 0.72; 95% CI, 0.39–1.32) (Fig 2D). By looking at all 3 variables, white, non-Hispanic patients with private health insurance showed a trend toward less-frequent high-risk pathology versus all other patients (OR, 1.51; 95% CI, 0.82–2.80) (Fig 2E). The rate of high-risk pathology did not vary significantly with the demographic risk score ($P=0.31$) (Fig 2F), although patients with no minority characteristics showed a trend toward a lower likelihood of high-risk pathology compared with those with at least 1 ($P=0.14$; OR, 0.60; 95% CI, 0.31–1.18) and those with 3 ($P=0.10$; OR, 0.44; 95% CI, 0.18–1.10).

Population Variable Analysis

Comparison of census data on language proficiency, income, and education between the populations living in the ZIP codes of patients with high-risk versus standard-risk pathologic findings revealed no clear differences between these groups (Supplemental Table S1, available at www.aaojournal.org). These variables were ones to which we did not have direct access through patient questioning. Although there are significant overall differences in the rate of high-risk pathology between median household income quartiles, there is no clear “dose effect” of decreasing income, and a comparison between the bottom and top half of the census tract shows almost no difference in high-risk pathology rates ($P=0.85$; OR, 0.94; 95% CI, 0.51–1.73) (Supplemental Fig S1, available at www.aaojournal.org).

Analysis of Institutional versus Central Pathology Discrepancies

A total of 10 patients' surgical specimens did not undergo central pathologic review because the timing of the review made them ineligible to receive chemotherapy. Of the 193 patients centrally reviewed, 34 had their risk category from institutional review changed. A total of 11 specimens were changed from high risk to standard risk, and 23 specimens were changed from standard risk to high risk (Fig 3). Patients with a change from high risk to standard risk pathology had a significantly higher mean demographic risk score (1.82) versus patients with an unchanged risk category on central review (1.23; $P=0.044$) and versus those with a change from standard risk to high risk (1.17; $P=0.042$).

Discussion

In patients newly diagnosed with retinoblastoma who had undergone unilateral enucleation for advanced intraocular disease, those with Medicaid or no health insurance, and those of nonwhite race or Hispanic ethnicity had significantly higher rates of more invasive disease

on institutional pathologic review than those outside of these demographic groups; non-Hispanic ethnicity remained a risk factor even when the analysis was adjusted for confounding between groups. On the basis of central pathologic review, these demographic risk groups showed trends toward higher rates of high-risk pathologic findings, but the differences were not statistically significant. Overall, given that disease invasiveness in retinoblastoma can serve as a proxy for timing of diagnosis, we believe these findings raise the concerning possibility of delays in diagnosis for these demographic risk groups.

We included analyses using both institutional and central pathologic reviews for several reasons. First, although the institutional review obviously is flawed for the purposes of this study because different pathologists read each specimen, the central review also is problematic because 10 study patients did not undergo central review, even though this was mandated in the study guidelines. Second, both are presented for completeness because this cohort presents a unique opportunity to study our questions and is unlikely to be replicated in the future, making full use of the current data crucial.

The third reason to present both is the questions raised by comparison of the 2 pathologic analyses. Patients with a change from high risk to standard risk after central review had significantly higher demographic risk scores than those whose institutional review was deemed accurate and those with a change from standard risk to high risk. This explains the discrepancy in the magnitude of differences between high-risk pathology rates for demographic groups found on institutional versus central review. It also raises the question of whether pathologists at the institutions where patients from minority groups received care were too conservative in their interpretations, that is, overcalled the presence of high-risk features. This would put these patients at risk of receiving unnecessary chemotherapy if trial results are implemented prospectively and institutional review becomes deterministic of true risk category.

The most significant factor in predicting high-risk pathologic features on institutional review was Hispanic ethnicity. Because there is no known difference in biology or incidence⁹ between retinoblastoma in Hispanic versus non-Hispanic children, one plausible reason for this increased effect over and above that of race and insurance status is limited English proficiency of approximately half of Hispanic families in the United States, according to 2000 Census data, and its effect on access to care. Research on the effect of language barriers on access to care in cancer is limited, and there were no data on English proficiency collected on ARET0332 registration. Therefore, we attempted to study the effects of English proficiency, as well as other potential socioeconomic determinants of access to care, indirectly on a population level using census data for each patient's ZIP code. There were no clear differences found in this analysis. One possible explanation is that the issues discussed with the institutional pathologic review mean that Hispanic ethnicity is not truly more predictive than other factors, especially given our central review results, although our recently published population analysis of risk factors in retinoblastoma did show a correlation of Hispanic ethnicity with greater extent of disease at diagnosis.⁸ It is also possible that differences based on English proficiency do exist, but our method of determining patient characteristics led to our results being biased toward the null. Using ZIP code centroid as a proxy for residential location provides data that we could not otherwise

collect but fails to accurately assess the substantial heterogeneity in any on these measures within ZIP codes.

It should be noted that the percentage of uninsured patients in this study was well below the national average. It is likely that some patients who were uninsured at presentation acquired Medicaid before enrollment and were counted as having Medicaid in this study. This could lead to an overstatement of barriers to care for Medicaid patients, when they actually exist for uninsured patients.

Correlations of minority race and ethnicity with later cancer diagnosis and poorer outcomes have been found in other recent studies.¹⁰ The current study expands the evidence of potential barriers to cancer care for these groups, now through a controlled study population. It also focuses on a group of patients with similar disease at presentation: all had unilateral disease severe enough to warrant primary enucleation but no extraocular, bilateral, or metastatic disease. The relatively subtle differences in disease invasiveness make the differences found between demographic groups more substantial. One potential source of bias is patients who might have opted out of this study in favor of treatments designed for eye salvage, but this study took place before most of these strategies, including intra-arterial chemotherapy, were commonly recommended. Going forward, however, it will be important to assess for any demographic differences between those who receive intra-arterial treatment and those who do not.

Study Strengths and Limitations

Strengths of this study include the use of a controlled patient group versus most studies looking at similar issues through cancer databases. The use of a group enrolled in a clinical trial maximizes accuracy of information collected and completeness of follow-up. It also minimizes differences in patient disease and allows for unbiased central pathologic review.

However, the restricted patient population is also a study weakness. Most differences between demographic groups on central pathologic review failed to reach statistical significance. Because the trends suggesting greater high-risk pathology rates for minority groups were consistent, this is most likely an issue of inadequate power due to a small study population compared with database studies. Also, as a result of small population size, this study was not powered to examine patient outcomes. The fact that the high-risk pathology group received chemotherapy also clouds the outcome question, but this group's need for chemotherapy is an important outcome itself, given the associated potential morbidity. Previous population-based studies of retinoblastoma did find that African-American race is a risk factor for mortality,^{8,11} demonstrating how population-based studies can amplify the power of findings for diseases in which death is a rare outcome. Another weakness of our study is an inability to exclude biologic differences in tumors between groups as an alternate explanation for the differences in disease invasiveness. The difference in high-risk pathology rates between patients of similar race/ethnicity with private versus nonprivate insurance argues against an entirely biologic explanation, because these different rates seem to be due to insurance type alone.

There are many opportunities for early diagnosis in retinoblastoma, but these depend on the presence of a primary care home providing consistent eye examinations at well-child checks.¹² Although the lack of these advantages for the minority demographic groups in this study may be the most likely explanation for our findings, we cannot yet pinpoint where in the diagnostic process delays are occurring. Because no data were collected on the date of first symptoms or presentation, it is unclear whether the barriers lie in parent symptom recognition, primary care access, timing or quality of primary screening, or access to an ophthalmologist. Efforts at improving the timing of retinoblastoma diagnosis have been effective in other countries.¹³ The effectiveness of any intervention, however, from expanding insurance coverage to increasing public awareness to improving screening, depends on knowing where delays occur, so this must be the center of future study.

In conclusion, this study suggests that barriers to care exist for patients lacking private insurance, and for racial and ethnic minorities, in retinoblastoma. Late diagnosis, even if vision is preserved, has a major impact on patients and families through all the difficulties associated with the disease and its treatment.¹⁴ Especially given the population-based studies discussed, it seems likely that these barriers extend well beyond retinoblastoma. Approximately 80% of children with cancer are now cured of their disease. A significant portion of the remaining 20% present with highly advanced disease. Curing this group is likely to be difficult and highly morbid even with advances in treatments. A complementary strategy is to diagnose these patients at an earlier stage. Increasing quality cancer care access is a key area of emphasis for oncologists in the United States,¹⁵ and insurance coverage is increasing as a result of the Affordable Care Act,¹⁶ so this seems to be a strategy whose time has come. Thus, there is an immediate need to pinpoint barriers to diagnosis in our system and address them.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations and Acronyms

CI	confidence interval
COG	Children's Oncology Group
OR	odds ratio

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Figure 1.

Differences in the percentage of patients with high-risk pathologic features by univariate analysis on (A) institutional review and (B) central review.

Figure 2.

Differences in the percentage of patients with high-risk pathologic features by race and ethnicity on (A) institutional review and (D) central review; differences between the percentage of patients with high-risk pathologic features by race/ethnicity (with white indicating white and non-Hispanic and minority indicating nonwhite or Hispanic) and insurance on (B) institutional review and (E) central review; influence of patient demographic risk score on the rate of high-risk pathologic findings by (C) institutional review and (F) central review.

Figure 3.

Differences in mean patient demographic risk score among groups determined by discrepancy between institutional and central pathologic review.

Table 1

Number and Percentage of Patients with High-Risk and Standard-Risk Pathologic Features on Institutional and Central Review by Single Demographic Categorization

	High-Risk (%)	Standard-Risk (%)	Total
Institutional review			
Insurance			
Private	19 (19.4)	79 (80.6)	98
Nonprivate	34 (32.4)	71 (67.6)	105
Race			
White	26 (21.0)	98 (79.0)	124
Nonwhite	27 (34.2)	52 (65.8)	79
Ethnicity			
Non-Hispanic	29 (21.0)	109 (79.0)	138
Hispanic	24 (36.9)	41 (63.1)	65
Central review			
Insurance			
Private	25 (27.5)	66 (72.5)	91
Nonprivate	39 (38.2)	63 (61.8)	102
Race			
White	36 (31.3)	79 (68.7)	115
Nonwhite	28 (35.9)	50 (64.1)	78
Ethnicity			
Non-Hispanic	40 (30.8)	90 (69.2)	130
Hispanic	24 (38.1)	39 (61.9)	63

Table 2

Number and Percentage of Patients with High-Risk and Standard-Risk Pathologic Features on Institutional and Central Review by Multiple Demographic Categorization

Insurance	Race	Ethnicity	High-Risk	Standard-Risk	Total
Institutional review					
Private	White	Non-Hispanic	12 (17.6)	56 (82.4)	68
		Hispanic	3 (42.9)	4 (57.1)	7
	Nonwhite	Non-Hispanic	3 (27.3)	8 (72.7)	11
		Hispanic	1 (8.3)	11 (91.7)	12
Nonprivate	White	Non-Hispanic	7 (20.0)	28 (80.0)	35
		Hispanic	4 (28.6)	10 (71.4)	14
	Nonwhite	Non-Hispanic	7 (29.2)	17 (70.8)	24
		Hispanic	16 (50.0)	16 (50.0)	32
Central review					
Private	White	Non-Hispanic	16 (25.8)	46 (74.2)	62
		Hispanic	3 (42.9)	4 (57.1)	7
	Nonwhite	Non-Hispanic	4 (36.4)	7 (63.6)	11
		Hispanic	2 (18.2)	9 (81.8)	11
Nonprivate	White	Non-Hispanic	12 (36.4)	21 (63.6)	33
		Hispanic	5 (38.5)	8 (61.5)	13
	Nonwhite	Non-Hispanic	8 (33.3)	16 (66.7)	24
		Hispanic	14 (43.8)	18 (56.3)	32

Table 3

Significance of Correlations between Demographic Groups and Rate of High-Risk Pathology on Institutional and Central Review

Analysis	Characteristic	P	OR	95% CI
Institutional review				
Univariate				
	Insurance	0.039	1.99	1.04–3.80
	Race	0.049	1.96	1.04–3.69
	Ethnicity	0.025	2.2	1.15–4.21
Multivariate				
	Insurance	0.25	1.585	0.76–3.35
	Race	0.46	1.386	0.64–2.99
	Ethnicity	0.20	1.693	0.78–3.67
Final Model				
	Ethnicity	0.027	2.191	1.09–4.42
Central review				
Univariate				
	Insurance	0.13	1.63	0.89–3.01
	Race	0.54	1.23	0.67–2.26
	Ethnicity	0.33	1.38	0.74–2.60
Multivariate				
	Insurance	0.33	1.453	0.73–2.93
	Race	1	1.307	0.49–2.16
	Ethnicity	0.61	1.274	0.60–2.70

CI = confidence interval; OR = odds ratio.