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

A Children's Oncology Group Study

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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.

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. *Ophthalmology 2016;■:1–7 © 2016 by the American Academy of Ophthalmology.*

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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 cancers[1] and to have poorer survival in lung cancer[2] 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

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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