VOLUME 29 · NUMBER 1 · JANUARY 1 2011

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Racial and Ethnic Disparities in Risk and Survival in Children With Neuroblastoma: A Children's Oncology Group Study

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Submitted March 30, 2010; accepted September 1, 2010; published online ahead of print at www.jco.org on November 22, 2010.

Supported by the Children's Oncology Group Statistics and Data Center Grants No. U10CA29139, CA25408, CA98543, and CA30969; the Neuroblastoma Children's Cancer Society; the Children's Neuroblastoma Cancer Foundation, Little Heroes Children's Cancer Research Fund; and the Elise Anderson Neuroblastoma Research Fund.

Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

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0732-183X/11/2901-76/$20.00

DOI: 10.1200/JCO.2010.29.6103

ABSTRACT

Purpose
Although health disparities are well-described for many cancers, little is known about racial and ethnic disparities in neuroblastoma. To evaluate differences in disease presentation and survival by race and ethnicity, data from the Children's Oncology Group (COG) were analyzed.

Patients and Methods
The racial/ethnic differences in clinical and biologic risk factors, and outcome of patients with neuroblastoma enrolled on COG ANBL00B1 between 2001 and 2009 were investigated.

Results
A total of 3,539 patients (white, 72%; black, 12%; Hispanic, 12%; Asian, 4%; and Native American, < 1%) with neuroblastoma were included. The 5-year event-free survival (EFS) rates were 67% for whites (95% CI, 65% to 69%), 69% for Hispanics (95% CI, 63% to 74%), 62% for Asians (95% CI, 51% to 71%), 56% for blacks (95% CI, 50% to 62%), and 37% for Native American (95% CI, 17% to 58%). Blacks ($P < .001$) and Native Americans ($P = .04$) had a higher prevalence of high-risk disease than whites, and significantly worse EFS ($P = .01$ and $P = .002$, respectively). Adjustment for risk group abrogated these differences. However, closer examination of the EFS among high-risk patients who remained event free for 2 years or longer, revealed a higher prevalence of late-occurring events among blacks compared with whites (hazard ratio, 1.5; 95% CI, 1.0 to 2.3; $P = .04$).

Conclusion
Black and Native American patients with neuroblastoma have a higher prevalence of high-risk disease, accounting for their worse EFS when compared with whites. The higher prevalence of late-occurring events among blacks with high-risk disease suggests that this population may be more resistant to chemotherapy. Studies focused on delineating the genetic basis for the racial disparities observed in this study are planned.

J Clin Oncol 29:76-82. © 2010 by American Society of Clinical Oncology

INTRODUCTION

Neuroblastoma is a common extracranial childhood cancer that has remarkable clinical heterogeneity and widely varying rates of cure depending on a range of clinical features at diagnosis and biologic characteristics of the tumor.[1] Risk groups have been defined based on combinations of these prognostic clinical and biologic markers,[1,2] and modern treatment strategies, tailored according to risk, have led to improved survival.[3-5] However, little is known about associations between race/ethnicity and survival in children with neuroblastoma. To investigate the relationship between race/ethnicity, tumor biology, and survival in neuroblastoma, we analyzed data collected from 3,539 children enrolled on the Children's Oncology Group (COG) neuroblastoma biology protocol ANBL00B1 between 2001 and 2009

PATIENTS AND METHODS

Patient Cohort

Children diagnosed with neuroblastoma, ganglioneuroblastoma, or ganglioneuroma (maturing type) and enrolled on the COG biology protocol ANBL00B1 between 2001 and 2009 with available outcome data formed the analytic cohort. The diagnosis was confirmed by either central pathologic review of tumor tissue or by the presence of unequivocal tumor cells in the bone marrow and increased urine catecholamines or metabolites, as described by the International Neuroblastoma Staging

System criteria.[6] Eligibility requirements also include enrollment within 21 days of diagnosis, and a good faith effort to submit a tissue sample of sufficient quality for *MYCN* analysis to the COG Neuroblastoma Resource Laboratory. The median time from diagnosis to enrollment was 7 days. Subjects with unknown risk profile, age, and/or race/ethnicity were excluded from the analysis. The study was conducted with parental/patient informed consent for research participation. Institutional review board guidelines were followed for procurement of tumor samples for prognostic factors including *MYCN* status, tumor cell ploidy, and histology. Tumor staging was based on the International Neuroblastoma Staging System criteria,[6] and patients were stratified into risk groups defined by COG according to the age, stage, histology, *MYCN* status, and tumor cell ploidy (Appendix Table A1, online only).[1] Outcome data were frozen on April 8, 2009. The racial groups were categorized as: American Indian/Alaskan Native, Hawaiian/Pacific Islander (hereafter referred to as Native American); Asian; black or African American (hereafter referred to as black); and white. Ethnicity was categorized as: Hispanic and non-Hispanic. A combined race/ethnicity variable was created taking into consideration both the racial and ethnic backgrounds and coded as follows: non-Hispanic white, non-Hispanic black, Native American, Asian, and Hispanic.

Analysis of MYCN *Status, Ploidy, and Histology*

MYCN amplification was determined by fluorescence in situ hybridization (FISH) using standard procedures[7] in the COG Neuroblastoma Resource Laboratory. DNA index was determined in the COG laboratory by flow cytometry and was reported as ≤ 1.0 versus higher than 1.0.[8] Histology was classified as favorable or unfavorable after central review according to criteria described by Shimada et al.[9]

Statistical Considerations

Annual follow-up data are collected for all patients enrolled on ANBL00B1, and institutions are required to report events including relapse, progressive disease, second malignancy, and death. For patients concurrently enrolled on a COG clinical trial, follow-up data are collected according to schedule outlined in the clinical trial. χ^2 tests were used to test for association of demographic and clinical characteristics with racial/ethnic groups; non-Hispanic whites served as the reference group. In the χ^2 tests, a Bonferroni correction was made for the significance level; P values lower than .0014 (.05/35 χ^2 tests) were considered statistically significant. Event-free survival (EFS) time was calculated from the time of biology study enrollment, which coincides closely with the date of diagnosis (defined as the date of the surgical biopsy or other definitive diagnostic procedure) until the time of first occurrence of relapse, progression, secondary malignancy, or death, or until the time of last contact if no event occurred. Overall survival time was calculated until the time of death or until time of last contact if the patient was alive. The product-limit method was used to estimate EFS and overall survival (OS), and expressed as the estimate with or without the SE, with SEs calculated using Greenwood's method. Kaplan-Meier curves were generated for each racial/ethnic group. Log-rank tests were used to compare survival curves across racial/ethnic groups. Cox proportional hazards regression was use to examine the ability of demographic and clinical factors to predict OS and EFS; and reported as hazard ratio (HR) with 95% CIs. Only statistically significant factors were retained in the Cox model. EFS, was also calculated among the subgroup of patients with 2 or more years of event-free time. For this subgroup, EFS time was recalculated starting from 2 years after study enrollment. In the survival analyses, P values lower than .05 are considered statistically significant. SAS version 9.2 (SAS Institute, Cary, NC) was used for data analysis.

RESULTS

Patient Characteristics

Of the 4,439 children and young adults enrolled on ANBL00B1 between 2001 and 2009, 3,922 had a confirmed diagnosis of neuroblastoma, ganglioneuroblastoma, or ganglioneuroma (maturing subtype) and known outcome (Fig 1). Subjects with unknown risk profile (n = 120), age (n = 2), and/or race/ethnicity (n = 261) were excluded from the analysis, and the remaining 3,539 patients formed the analytic cohort. Among the 261 patients who were excluded because of unknown race/ethnicity, 81 (31%) were classified as low-risk, 71 (27%) as intermediate, and 105 (41%) as high risk, and four had unknown risk. Of the patients with known race/ethnicity, the proportions were 33%, 20%, and 46% for low-, intermediate-, and high-risk groups, respectively. Of the 3,539 patients enrolled on ANBL00B1, 1,909 (49%) were also enrolled on at least one COG therapeutic trial.

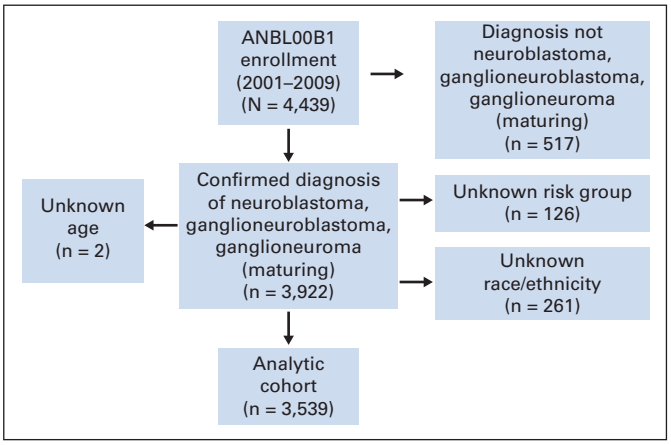

Fig 1. Formation of the analytic cohort.

Whites (n = 2,541) constituted 72% of the cohort; 12% were Hispanic (n = 418), 12% were black (n = 415), 4% were Asian (n = 137), and fewer than 1% were Native American (n = 28). The clinical and biologic characteristics of this cohort are summarized in Table 1. Within the overall cohort, 50% were diagnosed at age 18 months or older, 46% had stage 4 disease, and 54% were male. Using the COG criteria to define risk (Appendix Table A1),[1] 34% of the patients were classified as low risk, 20% were intermediate risk, and 46% met the criteria for high-risk disease. *MYCN* status was evaluated in tumors from 3,303 patients and amplification of this oncogene was detected in 19% of the patients. Of the 3,217 tumors evaluated for ploidy, 30% were diploid. Histology was known in 3,127 patients, and 41% had unfavorable histology.

Compared with the whites, black patients were diagnosed at an older age ($P < .001$), had a higher prevalence of stage 4 disease ($P = .001$) and unfavorable histology tumors ($P < .001$; Table 1). Blacks were also more likely to present with high-risk disease than white children (57% *v* 44%; $P < .001$). However, no difference in the frequency of *MYCN* amplification ($P = .27$) or ploidy ($P = .46$) was detected between blacks and whites. Compared with whites, Asians had more diploid tumors ($P < .01$). The prevalence of high-risk disease among the Asians was higher compared to the whites, but did not reach statistical significance (50% *v* 43%; $P = .18$). Although the cohort of Native Americans was small (n = 28), a significantly higher prevalence of high-risk disease was seen in this population as compared to whites (68% *v* 43%; $P = .04$). The prevalence of high-risk disease among Hispanics (43%; $P = .76$) did not differ from whites.

Survival Probabilities

The 5-year OS and EFS for the entire cohort of patients were 69% (95% CI, 67% to 70%) and 65% (95% CI, 63% to 67%), respectively (Fig 2). Univariate analysis revealed older age at diagnosis (≥ 18

Table 1. Demographic and Clinical Characteristics of Patients With Neuroblastoma (N = 3,539)

Clinical Characteristic	Entire Cohort		Race/Ethnicity										
			White		Black		Asian		Native American		Hispanic		
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	*P*
Overall No.	3,539		2,541		415		137		28		418		
Age, months													**< .001**
< 18	1,758	50	1,301	51	157	38	65	47	12	43	223	53	
≥ 18	1,781	50	1,240	49	258	62	72	53	16	57	195	47	
Stage													**.002**
1, 2, 3, 4s	1,895	54	1,392	55	192	46	64	47	11	39	236	56	
4	1,644	46	1,149	45	223	54	73	53	17	61	182	44	
Sex													.662
Female	1,618	46	1,167	46	181	44	59	43	11	39	200	48	
Male	1,921	54	1,374	54	234	56	78	57	17	61	218	52	
MYCN status													.535
Not amplified	2,645	75	1,913	75	293	71	101	74	19	68	319	76	
Amplified	658	19	467	19	83	20	26	19	8	29	74	18	
Unknown	236	6	161	6	39	9	10	7	1	3	25	6	
Ploidy													.038
Hyperdiploid	2,166	61	1,564	62	255	62	68	50	16	57	263	63	
Diploid	1,051	30	758	30	113	27	56	41	8	29	116	28	
Unknown	322	9	219	8	47	11	13	9	4	14	39	9	
Histology													**< .001**
Favorable histology	1,661	47	1,233	49	150	36	57	42	11	39	210	50	
Unfavorable histology	1,466	41	1,026	40	206	50	61	44	15	54	158	38	
Unknown	412	12	282	11	59	14	19	14	2	7	50	12	
Risk group													**< .001**
Low	1,185	34	880	35	120	29	37	27	5	18	143	34	
Intermediate	718	20	531	21	58	14	31	23	4	14	94	22	
High	1,636	46	1,130	44	237	57	69	50	19	68	181	43	

NOTE. *P* indicates value for overall comparison among all racial/ethnic categories.

months), stage 4 disease, *MYCN* amplification, diploidy, and unfavorable histology to be associated with significantly worse OS and EFS (Table 2). As expected, patients with high-risk disease had statistically significantly worse OS ($P < .001$) and EFS ($P < .001$) when compared with those with low-risk tumors. Furthermore, intermediate-risk patients had worse OS when compared with low-risk patients ($P = .004$).

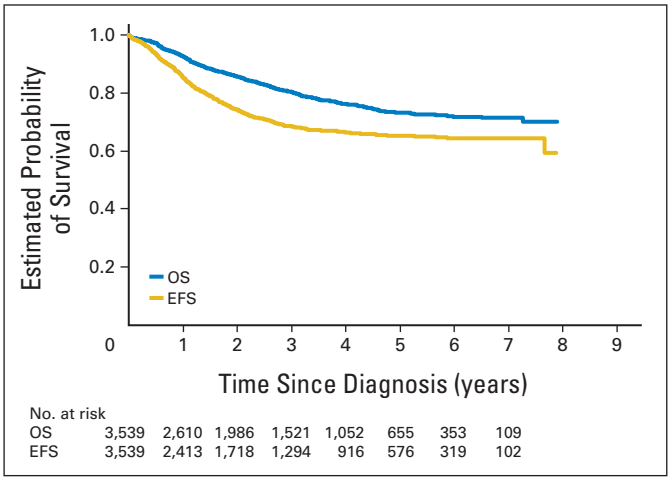

Fig 2. Overall survival (OS) and event-free survival (EFS) curves for the entire cohort of patients (n = 3,539) with numbers of patients at risk over time.

No sex difference in either OS or EFS was detected, thus sex was not adjusted in the multivariable analysis.

Impact of Race and Ethnicity on Survival

Entire cohort. As shown in Figure 3A, the 5-year OS was 75% for whites (95% CI, 72% to 77%), 75% for Hispanics (95% CI, 69% to 80%), 67% for black (95% CI, 60%% to 73%), 63% for Asians (95% CI, 50% to 73%), and 39% for Native Americans (95% CI, 13% to 64%). The 5-year EFS was 67% for whites (95% CI, 65% to 69%), 69% for Hispanics (95% CI, 63% to 74%), 56% for blacks (95% CI, 50% to 62%), 62% for Asians (95% CI, 51% to 71%), and 37% for Native American (95% CI, 17% to 58%; Fig 3B). Univariate analysis revealed that in comparison to whites, OS was significantly worse for blacks (HR, 1.37; $P = .01$), Asians (HR, 1.62; $P = .01$), and Native Americans (HR, 3.00; $P < .001$; Table 2); and the EFS was significantly worse for blacks (HR, 1.30; $P = .01$) and Native Americans (HR, 2.37; $P = .002$; Table 2).

Multivariable analysis. Adjustment for risk group abrogated the inferior EFS observed among blacks and Native Americans when compared with whites. After adjustment for risk group, inferior OS was identified for the Native Americans (HR, 2.05; $P = .02$) and Asians (HR, 1.46; $P = .05$; Table 3).

Low-risk group. Among patients with low-risk disease, the 5-year OS was 97% (95% CI, 95% to 98%) and the 5-year EFS was

Table 2. Univariate Analyses of Overall and Event-Free Survival in Patients With Neuroblastoma

Characteristic	No.	Overall Survival			Event-Free Survival		
		Hazard Ratio	95% CI	*P*	Hazard Ratio	95% CI	*P*
Race/ethnicity							
White	2,541	1.00			1.00		
Hispanic	418	1.01	0.79 to 1.31	.92	0.90	0.72 to 1.12	.33
Black	**415**	**1.37**	**1.09 to 1.72**	**.01**	**1.30**	**1.07 to 1.57**	**.01**
Asian	**137**	**1.62**	**1.11 to 2.36**	**.01**	1.29	0.92 to 1.80	.14
Native American	**28**	**3.00**	**1.65 to 5.45**	**.0003**	**2.37**	**1.37 to 4.10**	**.002**
Age, months							
< 18	1,758	1.00			1.00		
≥ 18	**1,781**	**3.99**	**3.29 to 4.83**	**< .001**	**3.02**	**2.61** to **3.51**	**< .001**
Stage							
1, 2, 3, 4s	1,895	1.00			1.00		
4	**1,644**	**8.89**	**7.08 to 11.15**	**< .001**	**5.08**	**4.34 to 5.95**	**< .001**
Sex							
Female	1,618	1.00					
Male	1,921	1.15	0.98 to 1.34	.09	1.11	0.97 to 1.26	.13
MYCN status							
Not amplified	2,645	1.00			1.00		
Amplified	**658**	**5.22**	**4.41 to 6.17**	**< .001**	**3.44**	**2.99 to 3.97**	**< .001**
Ploidy							
Hyperdiploid	2,166	1.00			1.00		
Diploid	**1,051**	**2.45**	**2.07 to 2.91**	**< .001**	**2.02**	**1.75 to 2.32**	**< .001**
Histology							
Favorable	1,661	1.00			1.00		
Unfavorable	**1,466**	**11.60**	**8.65 to 15.56**	**< .001**	**4.93**	**4.12 to 5.90**	**< .001**
Risk group							
Low	1,185	1.00			1.00		
Intermediate	**718**	**2.22**	**1.29 to 3.83**	**.004**	1.31	0.97 to 1.78	.08
High	**1,636**	**23.28**	**15.47 to 35.04**	**< .001**	**6.99**	**5.67 to 8.61**	**< .001**

NOTE. Bold font denotes groups at statistically significantly higher risk of death and/or event.

89% (95% CI, 87% to 91%). No differences in OS or EFS by race/ethnicity were identified.

Intermediate-risk group. Among patients with intermediate-risk disease, the 5-year OS was 95% (95% CI, 92% to 96%) and 5-year EFS was 87% (95% CI, 84% to 90%). Again, no differences in OS or EFS were identified by race/ethnicity.

High-risk group. Overall, the 5-year OS was 48% (95% CI, 44% to 51%); and the 5-year EFS was 39% (95% CI, 36% to 42%). The 5-year OS was 49% for whites (95% CI, 45% to 53%), 46% for Hispanics (95% CI, 36% to 56%), 46% for blacks (95% CI, 38% to 55%), 37% for Asians (95% CI, 22% to 52%), and 17% for Native Americans (95% CI, 1% to 48%; $P = .02$). The 5-year EFS was 41% for whites (95% CI, 37% to 44%), 39% for Hispanics (95% CI, 29% to 48%), 34% for blacks (95% CI, 26% to 42%), 39% for Asians (95% CI, 25% to 52%), and 21% for Native Americans (95% CI, 5% to 44%; $P = .24$).

Late-occurring events. A close examination of the patients who remained event-free for 2 years or longer revealed statistically significantly more late-occurring events among blacks, when compared to white patients (HR, 1.50; $P = .04$; Table 3). In a multivariable analysis confined to high-risk patients who remained event-free for 2 years or longer, blacks had significantly worse EFS (HR, 1.51; $P = .04$) when compared to white patients (Table 4). The number of events among the low- and intermediate-risk cohort was too few to examine EFS among patients with 2 years or longer of event-free time.

DISCUSSION

Risk-stratified treatment strategies have led to improvements in the outcome of children with neuroblastoma, and efforts to further refine risk classification using molecular signatures and global genomic patterns are ongoing.[10,11] However, despite more than four decades of research investigating classifiers for neuroblastoma, little is known about the prognostic significance of race and ethnicity, factors that contribute to health disparities in many diseases including cancer.[12] Here, we examined survival based on race and ethnicity in more than 3,500 patients with neuroblastoma. To our knowledge, this is the largest neuroblastoma cohort ever analyzed for outcome disparities, and the first to show that black, Asian, and Native American children have a significantly worse outcome than white children.

Interestingly, a significantly higher proportion of patients with high-risk disease was seen in the black and Native American populations compared with the white population. In contrast, the prevalence of high-risk disease among Hispanics and Asians did not differ significantly from whites. In concordance with the higher prevalence of high-risk disease, black and Native American children had significantly worse OS and EFS. Asian children were also found to have significantly poorer OS than white children, but no statistically significant difference in EFS was seen. No significant differences in OS or EFS were seen in the Hispanic children compared to white children.

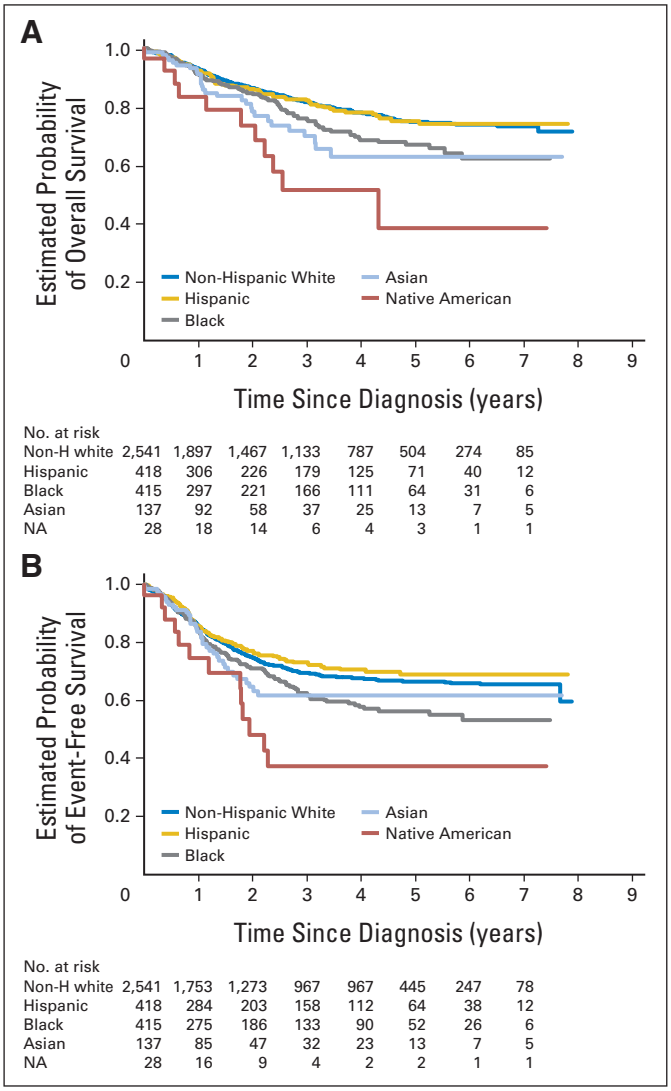

Fig 3. (A) Overall and (B) event-free survival by race and ethnicity with numbers of patients at risk over time. Non-H, non-Hispanic; NA, Native American.

When the EFS data were analyzed controlling for risk group, the outcome disparities were abrogated. However, examination of the EFS of the subgroup of patients who remained event-free for 2 years or longer revealed that blacks had significantly more late-occurring events than white children. This was confirmed in a multivariable analysis restricted to high-risk patients who remained event-free 2 years or longer from diagnosis, where blacks had significantly worse EFS compared to white children. Taken together, these observations suggest that black children are more likely than white children to have chemotherapy-resistant residual disease that progresses or relapses 2 or more years from diagnosis.

Our results contrast those recently reported by Linabery and Ross using Surveillance, Epidemiology and End Results (SEER) data collected between 1975 to 1999.[12] In the SEER cohort of 757 patients, no difference in survival of non-Hispanic white versus non-Hispanic black and Hispanic patients was observed. In the most recent SEER cohort, diagnosed between 1995 and 1999, the 5-year survival rate for non-Hispanic whites was 67.0% (95% CI, 60.7% to 73.2%) compared to 68.1% (95% CI, 53.5% to 82.8%) for non-Hispanic blacks and 69% (95% CI, 58.3% to 79.6%) for Hispanics. The children analyzed in our study were diagnosed between 2001 and 2009, and treatment strategies have been significantly modified in the past decade.[13,14] The disparities in outcome observed in our cohort suggest that modern treatment strategies may be more effective in the non-Hispanic whites and Hispanic children than in the black cohort. Linabery and Ross[12] did find that black children and adolescents with other cancers had worse outcome than whites. Using SEER data, others have reported that blacks, Native Americans, and Hispanic children with acute lymphocytic leukemia have worse survival than white and Asian children.[15] Similarly, a COG acute lymphocytic leukemia study demonstrated worse survival among black and Hispanic children compared to white children, whereas outcome was better for Asian children.[16] Studies of acute myelogenic leukemia outcomes have also shown that black patients have poorer outcomes than white counterparts.[17,18]

Multiple factors contribute to the racial and ethnic differences in survival observed in pediatric and adult cancers. Outcome disparities have been shown in some cases to reflect differences in access to health care.[19] This may result in delayed detection of illness or differences in treatment adherence. In our cohort of children with neuroblastoma, a higher prevalence of high-risk disease was observed in the blacks compared to whites, and a number of studies have indicated that it is unusual for favorable biology tumors to progress to high-risk tumors over time. A watch and wait approach has been followed in a subset of infants detected by mass screening, and none of the patients with tumor growth necessitating surgical removal were found to have unfavorable tumor biology.[20] Other studies have shown that *MYCN* status and ploidy do not change over time.[21-23] Taken together, these studies indicate that a delay in diagnosis is not likely to account for the higher percentage high-risk disease observed in the black cohort. Nonadherence is also a less common problem in neuroblastoma, since patients with high-risk disease receive almost all of their therapy in the hospital.

Genetic factors have also been shown to contribute to outcome disparities. Specific polymorphisms have been shown to play a critical role in the racial and ethnic diversity in drug effectiveness and/or toxicity.[24-26] In addition, genomewide association studies conducted in white children with neuroblastoma have shown that variability of genes located at common 6p22 single nucleotide polymorphism alleles and less-common single nucleotide polymorphisms at 2p35 within *BARD1* contribute to the etiology of clinically aggressive disease.[27,28] Studies are planned to determine if these or other at-risk alleles are contributing to the higher prevalence of high-risk disease and poor outcome we observed in our cohort of black children with neuroblastoma.

Despite the large size of this modern cohort of neuroblastoma patients, there are some notable limitations to this study. It is possible that patients for whom complete biologic information was not available may have introduced bias if the reasons for not having these assays performed were associated with prognosis and race/ethnicity. However, a good-faith effort to submit tumor tissue for *MYCN* analysis was a requirement for enrollment on ANLB00B1. Although we excluded 261 patients with unknown race/ethnicity in our analysis, these patients were found to have a similar distribution of risk to that of the entire cohort. Thus, elimination of this cohort most likely did not impact our study results. In addition, patients missing from the

Table 3. Multivariable Analysis of Overall and Event-Free Survival in Patients With Neuroblastoma

Characteristic	Overall Survival					Event-Free Survival				Event-Free Survival Among Patients Who Were Event Free for ≥ 2 Years				
	No. of Patients	No. of Deaths	Hazard Ratio	95% CI	*P*	No. of Events	Hazard Ratio	95% CI	*P*	No. of Patients	No. of Events	Hazard Ratio	95% CI	*P*
Race/ethnicity														
White	2,541	429	1.00			635	1.00			1,273	123	1.00		
Hispanic	418	69	1.13	0.88 to 1.46	.35	93	0.98	0.79 to 1.22	.86	203	17	1.01	0.61 to 1.68	.97
Black	415	90	1.09	0.87 to 1.37	.47	127	1.10	0.90 to 1.33	.35	**186**	**33**	**1.50**	**1.02 to 2.20**	**.04**
Asian	**137**	**29**	**1.46**	**1.00 to 2.12**	**.05**	36	1.18	0.84 to 1.65	.34	47	2	0.39	0.10 to 1.59	.19
Native American	**28**	**11**	**2.05**	**1.13 to 3.73**	**.02**	13	1.63	0.94 to 2.83	.08	9	2	2.10	0.52 to 8.51	.30
Risk group														
Low	1,185	24	1.00			101	1.00			729	14	1.00		
Intermediate	**718**	**28**	**2.22**	**1.29 to 3.83**	**.004**	72	1.32	0.97 to 1.78	.08	380	5	0.76	0.27 to 2.11	.60
High	**1636**	**576**	**23.09**	**15.34 to 34.76**	**< .001**	**731**	**6.92**	**5.61 to 8.53**	**< .001**	**609**	**158**	**16.26**	**9.39 to 28.14**	**< .001**

NOTE. Bold font denotes groups at statistically significantly higher risk of death and/or event; only statistically significant factors were retained in the analysis.

ANBL00B1 cohort we analyzed may have introduced bias. For example, our study cohort did not capture rare infants with stage 4S disease who were too sick to biopsy and small numbers of infants with localized neuroblastomas in which a watch and wait strategy was taken because they were not eligible for enrollment on ANBL00B1. Furthermore, children diagnosed at institutions that do not participate in COG neuroblastoma studies were not enrolled. Nevertheless, since the inception of ANBL00B1, approximately 75% (average yearly enrollment; n = 486) of the 650 children diagnosed in the United States with neuroblastoma each year[29] were enrolled. The significantly older age at diagnosis of the black children in our cohort is consistent with SEER data that show that white infants have a higher incidence of neuroblastoma than black infants, whereas little difference by race was observed among older children.[30] We also found that the proportion of blacks and Hispanics in our cohort is consistent with 2000 US census data,[31] further indicating that our cohort is representative.

We did not have access to patient treatment data, and as such could not control for the different chemotherapeutic agents and doses patients received. It is also important to note that race/ethnicity is not a mutually exclusive variable, and some patients may have mixed racial and ethnic ancestry. Reflecting the general population in North America, the vast majority of patients in our cohort were white, with significantly fewer numbers of black and Hispanic patients, and very small numbers of Native American and Asian patients. Because of the small numbers of Native American and Asian patients in the cohort, the survival results for these populations must be interpreted with caution.

In conclusion, we show for the first time that blacks and Native American neuroblastoma patients are statistically significantly more likely to present with high-risk disease than whites, and that, overall, this likely accounts for the inferior EFS observed in these populations. However, we report a higher prevalence of late-occurring events among blacks compared to white patients after controlling for clinical and biologic features of disease, suggesting that blacks may be more resistant to chemotherapy. Future research must focus on understanding the reasons for these disparities, including racial and ethnic differences in drug metabolism and bioavailability of commonly used agents, and genetic differences that may contribute to the etiology of clinically aggressive disease. A better understanding of the genetic basis of the outcome disparities observed in children with neuroblastoma will further refine risk classification, and may also direct us to more effective, individualized treatment strategies.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

Table 4. Multivariable Analysis of OS and EFS in Patients With High-Risk Neuroblastoma

Race/Ethnicity	OS Model (n = 1,636)				EFS Model (n = 1,636)				EFS Model Among Patients Event Free for ≥2 Years (n = 609)			
	No. of Events	HR	95% CI	*P*	No. of Events	HR	95% CI	*P*	No. of Events	HR	95% CI	*P*
White	389	1.0			501	1.0			110	1.0		
Hispanic	63	1.17	0.89 to 1.52	.26	76	1.07	0.84 to 1.37	.57	14	0.96	0.55 to 1.68	.87
Black	85	1.09	0.87 to 1.38	.46	111	1.13	0.92 to 1.38	.26	**31**	**1.51**	**1.01 to 2.25**	**.04**
Asian	**28**	**1.54**	**1.05 to 2.26**	**.03**	31	1.25	0.87 to 1.81	.22	1	0.19	0.03 to 1.43	.11
Native American	**11**	**2.16**	**1.18 to 3.93**	**.01**	12	1.69	0.95 to 2.99	.07	2	2.23	0.55 to 9.03	.26

NOTE. Bold font denotes groups at statistically significantly higher risk of death and/or event.
Abbreviations: OS, overall survival; EFS, event-free survival; HR, hazard ratio.

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REFERENCES

1. Maris JM, Hogarty MD, Bagatell R, et al: Neuroblastoma. Lancet 369:2106-2120, 2007

2. Cohn SL, Pearson AD, London WB, et al: The International Neuroblastoma Risk Group (INRG) classification system: An INRG Task Force report. J Clin Oncol 27:289-297, 2009

3. Schmidt ML, Lukens JN, Seeger RC, et al: Biologic factors determine prognosis in infants with stage IV neuroblastoma: A prospective Children's Cancer Group Study. J Clin Oncol 18:1260-1268, 2000

4. Bagatell R, Rumcheva P, London WB, et al: Outcomes of children with intermediate-risk neuroblastoma after treatment stratified by MYCN status and tumor cell ploidy. J Clin Oncol 23:8819-8827, 2005

5. De Bernardi B, Gerrard M, Boni L, et al: Excellent outcome with reduced treatment for infants with disseminated neuroblastoma without MYCN gene amplification. J Clin Oncol 27:1034-1040, 2009

6. Brodeur GM, Pritchard J, Berthold F, et al: Revisions of the international criteria for neuroblastoma diagnosis, staging, and response to treatment. J Clin Oncol 11:1466-1477, 1993

7. Shapiro DN, Valentine MB, Rowe ST, et al: Detection of N-*myc* gene amplification by fluorescence in situ hybridization: Diagnostic utility for neuroblastoma. Am J Pathol 142:1339-1346, 1993

8. Look AT, Hayes FA, Shuster JJ, et al: Clinical relevance of tumor cell ploidy and N-*myc* gene amplification in childhood neuroblastoma: A Pediatric Oncology Group study. J Clin Oncol 9:581-591, 1991

9. Shimada H, Chatten J, Newton WA Jr, et al: Histopathologic prognostic factors in neuroblastic tumors: Definition of subtypes of ganglioneuroblastoma and an age-linked classification of neuroblastomas. J Natl Cancer Inst 73:405-416, 1984

10. Janoueix-Lerosey I, Schleiermacher G, Michels E, et al: Overall genomic pattern is a predictor of outcome in neuroblastoma. J Clin Oncol 27:1026-1033, 2009

11. Vermeulen J, De Preter K, Naranjo A, et al: Predicting outcomes for children with neuroblastoma using a multigene-expression signature: A retrospective SIOPEN/COG/GPOH study. Lancet Oncol 10:663-671, 2009

12. Linabery AM, Ross JA: Childhood and adolescent cancer survival in the US by race and ethnicity for the diagnostic period 1975-1999. Cancer 113:2575-2596, 2008

13. Matthay KK, Reynolds CP, Seeger RC, et al: Long-term results for children with high-risk neuroblastoma treated on a randomized trial of myeloablative therapy followed by 13-cis-retinoic acid: A children's oncology group study. J Clin Oncol 27:1007-1013, 2009

14. Yu AL, Gilman AL, Ozkaynak MF, et al: Anti-GD2 antibody with GM-CSF, IL-2 and isotretinoin for neuroblastoma. N Engl J Med 363:1324-1334, 2010

15. Kadan-Lottick NS, Ness KK, Bhatia S, et al: Survival variability by race and ethnicity in childhood acute lymphoblastic leukemia. JAMA 290:2008-2014, 2003

16. Bhatia S, Sather HN, Heerema NA, et al: Racial and ethnic differences in survival of children with acute lymphoblastic leukemia. Blood 100:1957-1964, 2002

17. Rubnitz JE, Lensing S, Razzouk BI, et al: Effect of race on outcome of white and black children with acute myeloid leukemia: The St. Jude experience. Pediatr Blood Cancer 48:10-15, 2007

18. Aplenc R, Alonzo TA, Gerbing RB, et al: Ethnicity and survival in childhood acute myeloid leukemia: A report from the Children's Oncology Group. Blood 108:74-80, 2006

19. Clegg LX, Reichman ME, Miller BA, et al: Impact of socioeconomic status on cancer incidence and stage at diagnosis: Selected findings from the surveillance, epidemiology, and end results: National Longitudinal Mortality Study. Cancer Causes Control 20:417-435, 2009

20. Tanaka M, Kigasawa H, Kato K, et al: A prospective study of a long-term follow-up of an observation program for neuroblastoma detected by mass screening. Pediatr Blood Cancer 54:573-578, 2010

21. Berthold F, Hero B, Breu H, et al: The recurrence patterns of stages I, II and III neuroblastoma: Experience with 77 relapsing patients. Ann Oncol 7:183-187, 1996

22. Brodeur GM, Hayes FA, Green AA, et al: Consistent N-*myc* copy number in simultaneous or consecutive neuroblastoma samples from sixty individual patients. Cancer Res 47:4248-4253, 1987

23. Taylor SR, Blatt J, Costantino JP, et al: Flow cytometric DNA analysis of neuroblastoma and ganglioneuroma: A 10-year retrospective study. Cancer 62:749-754, 1988

24. Spitz MR, Wu X, Mills G: Integrative epidemiology: From risk assessment to outcome prediction. J Clin Oncol 23:267-275, 2005

25. Huang RS, Duan S, Kistner EO, et al: Genetic variants associated with carboplatin-induced cytotoxicity in cell lines derived from Africans. Mol Cancer Ther 7:3038-3046, 2008

26. Collie-Duguid ES, Pritchard SC, Powrie RH, et al: The frequency and distribution of thiopurine methyltransferase alleles in Caucasian and Asian populations. Pharmacogenetics 9:37-42, 1999

27. Maris JM, Mosse YP, Bradfield JP, et al: Chromosome 6p22 locus associated with clinically aggressive neuroblastoma. N Engl J Med 358:2585-2593, 2008

28. Capasso M, Devoto M, Hou C, et al: Common variations in BARD1 influence susceptibility to high-risk neuroblastoma. Nat Genet 41:718-723, 2009

29. Ries LAG, Smith MA, Gurney JG, et al: Cancer Incidence and Survival among Children and Adolescents; United States SEER Program 1975-1995, National Cancer Institute, SEER Program. Bethesda, MD, National Institutes Health, Pub. No. 99-4649, 1999

30. Goodman MT, Gurney JG, Smith MA, et al: Sympathetic Nervous System Tumors: SEER Pediatric Monograph, 2008. http://www.seer.cancer.gov/publications/childhood/sympathetic.pdf

31. United States Census 1980-2000: Race and ethnicity selections. http://www.censusscope.org

