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Rhabdomyosarcoma Incidence and Survival in Whites, Blacks, and Hispanics from 1973-2013: Analysis from the Surveillance, Epidemiology, and End Results Program

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Rhabdomyosarcoma Incidence and Survival in Whites, Blacks, and Hispanics from 1973 to 2013: Analysis from the Surveillance, Epidemiology, and End Results Program

by

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Abstract

Purpose

Our objectives were to 1) determine the difference in Rhabdomyosarcoma (RMS) incidence and survival between different race/ethnicity groups, and 2) evaluate the difference in survival of RMS between children and adults of these race/ethnicity groups, using the Surveillance, Epidemiology, and End Results Program (SEER) database between 1973-2013.

Patients and Methods

We analyzed racial characteristic and incidence data from 4,280 patients diagnosed with RMS, between 1973-2013, that were reported to the SEER database. Survival and hazard analyses were conducted on 4,268 patients with known follow-up data, with end point being death from any cause.

Results

Over the 40-year study period overall RMS incidence rates have experienced a statistically significant decline (APC: -0.78, 95% CI: -1.28 – -0.28). Whites have experienced a significant decline in incidence rates (APC: -1.05, 95% CI: -1.60 – -0.50). Though not statistically significant, incidence rates in Blacks and Hispanics have trended upwards. While adjusted survival was not predicted by race, survival did significantly differ among racial/ethnic groups in children, with Hispanics and “Others” having the lowest 5- and 10-year survival rates (65% and 58% verses 58% and 56%,

respectively). Black race/ethnicity was also shown to be a predictor for mortality for the time period 1990-2013.

Conclusion

Racial/ethnic minorities have worse RMS clinical presentation and incidence rates than Whites. While overall survival is not predicted by race, being an ethnic minority child diagnosed with RMS is predictive of survival. These disparities point towards a genetic component in RMS that has not yet been described.

Introduction

While the annual incidence of Rhabdomyosarcoma (RMS) among those younger than 20 years is 4.6 cases per million people [1,2], RMS is one of the most common childhood and adolescent tumors, representing more than 50% of soft tissue sarcoma cases in this age group [2,3], and nearly 3.4% of cancers overall [4]. Approximately 350 children and adolescents in the United States (US) are diagnosed with RMS per year, with half of these cases occurring in patients under 10 years of age [1,2]. RMS can occur in those older than 20, though it is exceedingly rare [3], accounting for only 3% of soft-tissue sarcomas and less than 1% of cancers overall in this age group [4].

RMS is a rare, highly malignant soft tissue sarcoma that originates from the embryonal mesenchyme [5,6], which imitates normal striated muscle tissue [7]. Although RMS tumors are typically found within striated muscle, they can occur virtually anywhere in the body [6,7], excluding bone [8]. RMS is further classified as embryonal (approximately 70% of cases), alveolar (approximately 30% of cases), pleomorphic, spindle cell, mixed-type, and RMS not otherwise specified (NOS) histologic subtypes [1,5], which makes it difficult to classify patients into homogenous treatment groups [8]. Due to the rarity of RMS, little is known about the etiology and epidemiology of this disease [6].

Collaborative pediatric trials from the Intergroup Rhabdomyosarcoma Study Group (IRSG) have revolutionized the therapeutic methods for this sarcoma [8-10]. Based on the conclusions of these studies multimodality treatment regimens, involving chemotherapy and/or radiation, are decided by tumor staging (based on tumor primary site, tumor size, and the presence or absence of regional lymph node involvement and of distant metastasis), grouping (defined by the amount of residual tumor after initial surgery), and the histologic subtype of the tumor [8-10]. Pediatric patients with nonmetastatic disease have received the most benefit from these studies, with cure rates up to approximately 70% [3,5,11] from 25% in 1970 [5,11]. Prognosis in adults with RMS is very poor, with overall survival rates of 20% to 40% [3,4] verses rates of 60% to 80% for children [4], calling into question whether or not chemotherapy (which is a key feature in pediatric treatment) should be used at all in adults [3]. Unfortunately this question is not easily answered, as large multi-institutional studies focusing on adult RMS have not been conducted, and only small, single institution reports have been published [3].

There are gaps in the literature involving regarding disparities in survival by race or ethnicity for RMS, for both adults and children [3,4,11-17]. This is presumably due to either limitations in the data prior to expansion of certain cancer registry programs, or as a result of underrepresentation of certain populations in clinical trials for cancer [18].

Our objectives were to 1) determine the difference in RMS incidence and survival between race/ethnicity groups, and 2) evaluate the difference in survival of RMS between children and adults within these race/ethnicity groups, using the Surveillance, Epidemiology, and End Results Program (SEER) database between 1973-2013.

Methods

Data Source and Study Population

The November 2015 release of SEER program data [19] were analyzed to evaluate incidence and survival rates of RMS in the United States between 1973 and 2013. The SEER Program collects information from population-based registries on demographics, histology, tumor site, tumor stage at diagnosis, first course of treatment, and vital status [19]. The SEER 18 Program is an expansion on two previous SEER programs. The first, SEER 9, covered the states of Connecticut, Iowa, New Mexico, Utah, and Hawaii; the metropolitan areas of Detroit, Atlanta, San Francisco-Oakland, and Seattle-Puget Sound, starting in 1973 [19]. The next program, SEER 13, added registries in 1992 in Los Angeles, San Jose-Monterey, Alaska Native Registry, and rural Georgia, allowing for analysis on Hispanic populations [19]. The latest program, SEER 18, added Kentucky, Greater California, New Jersey, Louisiana, and Greater Georgia, which increased program coverage to 30% of the US Population [19].

The study population for this analysis is all microscopically confirmed cases of RMS. International Classification of Disease for Oncology, Third Edition (ICD-O-3) morphology codes were analyzed to include the following RMS subtypes: 8900/3 (RMS, NOS), 8901/3 (pleomorphic); 8902/3 (mixed type); 8910/3 (embryonal); 8912/3 (spindle cell); and 8920/3 (aveolar). A total of 4,325 RMS patients were identified from the SEER

data using the IDC-O-3 morphology codes. A total of 45 patients were excluded from the analysis either because they had no microscopic confirmation of diagnosis or diagnosis was confirmed by autopsy/death certificate only. After exclusion, 4,280 patients remained in the analysis. A total of 12 patients were further excluded due to unknown survival time, leaving 4,268 patients in these analyses. A total of 30 patients with localized/regional prostate SEER stage were recoded as regional stage. Patients were further classified by age and diagnostic era. Pediatric patients are defined as being 19 years or younger, and adults as 20 years or older. Diagnosis era was divided into two categories: diagnosis in the period 1973 to 1989, and diagnosis in the period 1990 to 2013. This was done for two reasons: first, because results from two pediatric clinical trials conducted by the IRSG [9,10] were made available, which revolutionized how RMS is treated; and second because the addition of SEER 13 registries in 1992 expanded coverage, allowing for analysis of Hispanics [19]. Although SEER does not directly collect information on Hispanic ethnicity, SEER does code Hispanic origin using the North American Association of Central Cancer Registries (NAACCR) Hispanic Identification Algorithm (NHIA), which uses surname and maiden name to determine Hispanic ethnicity [19]. Race was coded as White, Black, Hispanic, and Other for this analysis. After recoding for Hispanic ethnicity, 44 patients in the 1973 to 1989 diagnostic era were further recoded from Hispanic ethnicity to “Other” because data on Hispanic ethnicity in this era was not specifically collected until SEER 13 program expansion in 1992. Due to the rarity of RMS, and small cell counts, all other ethnicities (eg. American Indian/AK Native, Asian/Pacific Islander, unknown, etc) were recoded as “Other”, in both treatment eras, for the purposes of this analysis.

International Classification of Disease for Oncology, Third Edition (ICD-O-3) topography codes was used to define tumor primary site and tumor prognostic site. Prognostic site was classified as favorable for tumors of the nonparameningeal head and neck, the genitourinary system (excluding the kidney, bladder, and prostate), and the biliary tract, and as unfavorable for all other sites. Tumor stage was classified using the SEER staging system. Localized stage refers to an invasive tumor that is completely confined to its organ of origin; regional stage refers to a tumor that has expanded beyond its organ of origin, into surrounding tissues, and/or has spread to the regional lymph nodes; distant stage refers to a tumor that has spread to distant organs and tissue in remote parts of the body, and/or to distant lymph nodes [19].

This study was determined to be exempt from human research regulations by the University of South Florida Institutional Review Board (IRB).

Statistical Analysis

Statistical Analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC). Frequency distributions, total and stratified by race, were calculated for categorical variables, and means and standard deviations were calculated for continuous variables. Associations between categorical variables were tested using Chi-Squared tests, with an association deemed statistically significant if χ^2 p-value<0.05. The effects of demographic, pathologic, clinical, and treatment variables on survival were tested using the univariate log-rank method for categorical variables. Multivariate analyses to test significant prognostic factors (overall, by diagnostic era, by age, and by race) were

conducted using the Cox proportional hazards regression. Cox modeling was further performed to analyze racial survival rates, while adjusting for age category, sex, diagnostic era, geographic region, histology, SEER stage of disease, primary tumor site prognosis, and treatment. Kaplan-Meier survival estimates were used to construct racial survival curves that were stratified by age category. Log-rank method was employed to compare the survival curves.

SEER*Stat software (v. 8.3.2) was utilized to analyze incidence rates, trends, and annual percentage change (APC). The SEER 9 population data was analyzed from 1973 to 2013 for Whites, Blacks, and Overall (all races), while the SEER 13 population data was used to analyze the time period was 1992 to 2013 for Hispanics. All incidence data were age-adjusted using the 2000 US Standard population and calculated per 100,000 person-years of follow-up. To determine the APC, the weighted least squares method was used. P-values<0.05 were deemed statistically significant. Incidence rates and APC were not analyzed for the race category Others due to limitations with the SEER*Stat program.

Results

Patient Characteristics

Of the 4,268 RMS patients included in this study, 2,427 (56.9%) were classified as children (≤19 years) and 1,841 (43.1%) as adults. The median age of the entire sample was 16 years (± 26.5 years, range: birth to 98 years). While Whites, Blacks, and Others shared a similar median age to that of the overall, Hispanics had a lower median age of 12 years (± 21.0 years). Males comprise majority of the sample, at 2,410 patients (56.5%) verses females with 1,858 patients (43.5%). Significantly more patients were diagnosed in the latter diagnostic period of 1990-2013 (3,371, 79.0%). More than half of the RMS patients were diagnosed in the Western region (52.7%); however among Blacks more than a third (37.2%) were diagnosed in the Southern region (Table 1).

Overall, Embryonal was the most common RMS histologic type with 1,698 (39.8%) patients, followed by RMS NOS (1,044, 24.5%), Alveolar (974, 22.8%), Pleomorphic (395, 9.3%), Spindle Cell (85, 2.0%), and Mixed-type (72, 1.7%). Among all races: Blacks were more likely to develop Embryonal RMS; Hispanics more likely to develop Alveolar; and Whites more likely to develop RMS NOS. Regional metastasis was found to be the most common SEER stage in the sample, with 1,271 patients (29.8%), followed closely by localized (1,264, 29.6%), and distant disease (1,234, 28.9%). Although localized disease was the most frequent among Whites, compared to

all races Blacks were more likely to develop localized disease. Distant disease was found to be most common among each Blacks and Hispanics, with Hispanics being the most likely to develop either regional or distant disease when compared to all races (Table 1).

The most frequent tumor site for the entire sample was the head and neck, excluding the orbit, with 1,073 patients (25.1%). Although the trunk was the most common tumor site for Whites (767, 29.5%), Whites were more likely than any other race to develop extremity tumors. Among Blacks, the most frequent tumor site was also the trunk (173, 27.6%), and they were most likely race to develop genitourinary tumors. Head and neck tumors were the most common tumor site among Hispanics (196, 29.5%), and were more likely to develop in Hispanics compared to all other races. In this sample, majority of patients had an unfavorable primary tumor site (2,712, 63.5%).

For treatment, most patients received both radiation and surgery (1,300, 30.5%). Hispanics and Others were more likely than Whites to receive no treatment or radiation only. Whites were more likely than Blacks or Hispanics to receive surgery only, or both radiation and surgery (Table 1).

Incidence and Annual Percentage Change

Across the entire study period, Whites had similar incidence rates to the overall rate, Blacks had higher rates for majority of the study period, and Hispanics experienced inconsistent rates (Figure 1). The overall APC for 1973 to 2013 is a statistically significant decline of -0.78 (95% CI: -1.28 to -0.28). Whites also experienced a statistically significant decline from 1973 to 2013, with an APC of -1.05 (95% CI: -1.60 to -0.50). Blacks had an increased 1973 to 2013 APC of 0.39 (95% CI: -0.74 to 1.53),

though this increase was not statistically significant. Hispanics also experienced an increased APC of 1.29 (95% CI: -1.33 to 3.97), from 1992-2013, that was not statistically significant.

Survival Analysis

Survival for all races significantly dropped in the first 5 years, and then began to level off (Figure 2). The log-rank p-value is 0.23, meaning that the survival curves do not significantly differ and race is not a predictor of survival after adjustment for all other variables in the model. Overall 5-year survival rate was 56%, the 15-year rate was 52%, and the 30-year rate was 49%. For Whites the 5-, 15-, and 30-year survival rates were 57%, 53%, and 51%, respectively; for Blacks the rates were 53%, 49%, and 46%; for Hispanics the rates were 56%, 52%, and 49%; and for Others the rates were 54%, 49%, and 47%.

RMS survival by age, for each race is illustrated in Figure 3. The log-rank p-value for the survival curves is <.0001, meaning there is a significant difference in survival between children and adults. Child race categories Other and Hispanic had a statistically significant lower survival rate than Whites and Blacks (p-value: 0.03). The 5-, 15-, and 30-year survival rates were: for children overall 65%, 62%, and 59%, respectively; for White children 66%, 63%, and 61%, respectively; for Black children 62% represents all three survival rates; for Hispanic children 65%, 58%, and a 39% 22-year survival rate; for Other children 58%, 56%, and 56%, respectively. Adult race categories Black, Other, and Hispanic had lower survival rates than Whites, although this was not statistically significant (p-value: 0.21). The 5-, 15-, and 30-year survival rates are: for adults overall 39%, 36%, and 33%, respectively; for White adults 42%,

40%, and 35%; for Black adults 35%, 31%, and 31%, respectively; for Hispanic adults 30%, 26%, and 26% 18-year survival rate; and for Other adults 35%, 30%, and 30%, respectively.

Univariate and Multivariate Analysis

Cox proportional hazard regression was performed for both the univariate and multivariate analyses. In the univariate analysis (data not shown), adjusted for only age at diagnosis and year of diagnosis, Black, Hispanic, and Other race served as significant predictors for mortality. After inclusion of all variables in the multivariate model, for the entire study period, race is no longer a predictor for mortality (Table 2). Black race does trend towards significance with a hazard ratio (HR) of 1.14, and a p-value of 0.06. Age at diagnosis, histologic type, SEER stage, and prognostic site all serve as predictors for mortality when adjusted for all other variables in the model. Year of diagnosis and treatment method served as protective factors in the model. When stratified by year of diagnosis (Table 3), black race does become a significant predictor of mortality (HR: 1.18, 95% CI: 1.01-1.38) in the model for diagnosis from 1990 to 2013. Stratifying the model by age of diagnosis (Table 4), Other race becomes predictive in children (HR: 1.31, 95% CI: 1.03-1.66). When stratified by race (Table 5), Black adults have a higher HR of 2.86 (95% CI: 2.16-3.79) than adults of the other races. Blacks also have higher HR's in regional, distant, and unknown metastasis. Male sex is protective in Hispanics (HR: 0.71, 95% CI: 0.55-0.91) in the stratified model. The race category "Others" has higher HR's in all of the histologic subtypes, except for pleomorphic, where Whites have the highest HR.

Discussion

This study of 4,268 patients diagnosed with RMS, ages ranging from birth to 98 years, revealed that race may play an important role in RMS incidence and survival. We found that ethnic minorities were more likely than Whites to have mixed-type, spindle cell, or alveolar histologies, regional or distant metastasis, unfavorable prognostic tumor site, and no treatment. Ethnic minorities were also less likely than Whites to receive multimodal treatment of radiation and surgery. The disparity in treatment methods in our study could be due to underrepresentation of these populations in RMS clinical trials, and therefore hesitance from physicians to administer these therapies in ethnic minorities [8,9,10]. Current literature is inconclusive with some reporting statistically significant differences in these characteristics by race [7,11,17], and others reporting no differences by race [5].

Blacks were found to have higher RMS incidence rates over the study period than Whites. APC in Blacks trended towards an increase, but was not statistically significant. Overall RMS APC and APC in Whites did have a statistically significant trend downwards, meaning that RMS incidence overall and for Whites is declining. Previous studies have found that while males and Black children have higher incidence rates of RMS [7,12], there were no differences in survival by gender or race, for both children and adults [3,5,11,17]. Although adjusted overall survival was not predicted by race in our study, stratification by age group did uncover significant racial survival

disparities, particularly among children diagnosed with RMS. One study did report that Hispanic children seemed to have lower 5-year survival rates than white children for certain histologic subtypes [7], though these results were based on a relatively small number of children in each category, so caution must be taken in interpreting these results.

In our study Blacks were found to have a 14% increase in risk for mortality that trended towards significance (p-value: 0.06) in the full adjusted model. When the analysis was stratified by diagnostic era, the risk for mortality increased to 18% (p-value: 0.04) in the 1990-2013 diagnostic period. This difference could be the result of an increase in sample size, due to the expansion of the SEER registries over the second diagnostic period [19].

Some possible explanations for our findings could be differences in racial/ethnic immunization schedule compliance, or differences in genetic predisposition. It has been found that children diagnosed with RMS are five-times more likely to have incomplete immunization schedules when compared to controls [2]; however, this study did not analyze race as a predictor for immunization schedule compliance. Non-white race has been found to be a significant predictor of non-compliance to immunization schedules in other studies [20]. This could also aid in explaining why a greater proportion of ethnic minority children were diagnosed with RMS than white children our study.

Studies have estimated that ~5% of RMS cases are associated with genetic predisposition to several different conditions, such as TP53 mutations (Li-Fraumeni syndrome), Costello syndrome, neurofibromatosis, and Beckwith-Wiedeman syndrome [1,6,7]. One study in endometrial cancer has found that the incidence in p53

overexpression, as a result of TP53 mutations, was higher in Black cases than White cases in both early and advanced disease, and that survival was worse in Blacks than Whites with similar disease stage and p53 expression [22]. These results may help to explain racial disparities in cancers associated with TP53 mutations. TP53 mutations have been analyzed in childhood cases of RMS [22], and results have shown that patients that carry the TP53 mutation are predisposed to developing RMS at a younger age. In this study, a greater percentage of ethnic minority cases were children, compared to White cases, with Hispanics containing the highest percentage of children (68%). The association between RMS, TP53 mutations, and race has not yet been described, but future studies on the topic may aid in explaining why ethnic minorities have several significant differences in clinical presentation of RMS than Whites [17].

A primary strength of using the SEER dataset is that it provides a large sample size of RMS cases, over a large period of time, which creates adequate statistical power for analysis of this rare malignancy. Data gathered from SEER also provide important information on clinical characteristics and treatment methods. Another strength of this study is the inclusion of Hispanics and other minority races.

This study is not without limitations. Survival estimates and incidence rates for Whites and Blacks from the SEER 9 database may contain Hispanic data for cases diagnosed prior to the SEER 13 expansion in 1992. Analyses on the effect of treatment are also limited by the fact that SEER does not collect information on chemotherapy, which is a mainstay of RMS management [3,4,8-10,19]; therefore we were unable to account for the treatment effect of chemotherapy in the current study. Information on diagnoses reported to SEER is rendered by a multitude of oncologists and pathologists

with variable equipment and expertise, and there is no central pathological review of this information. However, in 1995 the International Classification of RMS (ICR) was established, improving the reproducibility of RMS classification, as well as outcome prediction [7]. Follow-up for cases in the SEER database is passive, and incomplete data is often a problem [5]; this analysis excluded 12 patients (0.3%) due to incomplete follow-up data, but it is unlikely this affected the results. Our analysis spans a 40-year time period, and within this time period great progress has been made in areas of diagnosis and treatment of RMS. It is possible that some RMS NOS and pleomorphic cases diagnosed prior to the establishment of the IRC were misdiagnosed, and are actually not RMS [3]. The spindle cell variant of RMS was not described until efforts in 1992 [23] and 1993 [24] made the distinction of this subtype from the more common embryonal RMS. Therefore, it is possible that diagnoses of embryonal RMS made prior to these two studies may actually be cases of spindle cell RMS [15]. Spindle cell RMS is exceedingly rare and most cases of this subtype occur in the favorable prognostic site of the paratesticular region [15,23,24], so any affect on the results of this study is likely to be small to negligible.

Conclusion

Racial disparities in RMS are not yet completely understood, but it is thought to be a result of both environmental and socioeconomic factors [11,14]. Our study highlights the racial disparities in RMS presentation, incidence, and survival in ethnic minorities. Ethnic minorities are at an increased risk for developing RMS, and children of ethnic minorities have lower survival rates than White children within this study. While RMS incidence is significantly declining overall, and in Whites, it is trending upwards for ethnic minorities. Differences in incidence rates and clinical characteristics in ethnic minority populations in this study may point towards a genetic component in RMS. Future studies should aim at describing immunization compliance in ethnic minority children with RMS, compared to White children with RMS, as well as describing the link between TP53 mutations and RMS by race.

Table 1. Characteristics of RMS Patients During Period of 1973-2013 Stratified by Race

	Total N=4,268 N (%)	NHW N=2,601 N (%)	NHB N=626 N (%)	Hispanic N=664 N (%)	Other* N=377 N (%)	P-value
Age at diagnosis						<.0001
Child (0-19 years)	2427 (56.9)	1395 (53.6)	357 (57.0)	452 (68.0)	223 (59.2)	
Adult (>19 years)	1841 (43.1)	1206 (46.4)	269 (43.0)	212 (32.0)	154 (40.8)	
Median ± SD	16 ± 26.5	17 ± 28.2	16 ± 23.9	12 ± 21.0	16 ± 24.2	
Sex						0.29
Female	1858 (43.5)	1110 (42.7)	288 (46.0)	302 (45.5)	158 (41.9)	
Male	2410 (56.5)	1491 (57.3)	338 (54.0)	362 (54.5)	219 (58.1)	
Diagnostic period†						<.0001
1973-1989	897 (21.0)	719 (27.6)	87 (13.9)	0 (0.0)	91 (24.1)	
1990-2013	3371 (79.0)	1882 (72.4)	539 (86.1)	664 (100)	286 (75.9)	
Geographic region						<.0001
Northeast	659 (15.4)	479 (18.4)	79 (12.6)	65 (9.8)	36 (9.5)	
Midwest	675 (15.8)	548 (21.1)	104 (16.6)	10 (1.5)	13 (3.5)	
South	686 (16.1)	394 (15.2)	233 (37.2)	40 (6.0)	18 (4.8)	
West	2249 (52.7)	1180 (45.4)	210 (33.6)	549 (82.7)	310 (82.3)	
Histologic type						<.0001
Pleomorphic	395 (9.3)	271 (10.4)	48 (7.7)	41 (6.2)	35 (9.3)	
Mixed-Type	72 (1.7)	40 (1.5)	14 (2.2)	15 (2.3)	3 (0.80)	
Embryonic	1698 (39.8)	1036 (39.8)	259 (41.4)	261 (39.3)	142 (37.7)	
Spindle Cell	85 (2.0)	41 (1.6)	16 (2.6)	23 (3.5)	5 (1.3)	
Alveolar	974 (22.8)	523 (20.1)	158 (25.2)	198 (29.8)	95 (25.2)	
RMS (NOS)	1044 (24.5)	690 (26.5)	131 (20.9)	126 (19.0)	97(25.7)	
Tumor behavior						<.0001
Localized	1264 (29.6)	788 (30.3)	195 (31.2)	166 (25.0)	115 (30.5)	
Regional metastasis	1271 (29.8)	750 (28.8)	183 (29.2)	217 (32.7)	121 (32.1)	
Distant metastasis	1234 (28.9)	695 (26.7)	201 (32.1)	230 (34.6)	108 (28.7)	
Un-staged	499 (11.7)	368 (14.2)	47 (7.5)	51 (7.7)	33 (8.8)	
Anatomical site						0.0001
Head and neck‡	1073 (25.1)	641 (24.6)	141 (22.5)	196 (29.5)	95 (25.2)	
Trunk	1247 (29.2)	767 (29.5)	173 (27.6)	187 (28.2)	120 (31.8)	
Genitourinaryᵀ	662 (15.5)	368 (14.2)	145 (23.2)	101 (15.2)	48 (12.7)	
Orbital	199 (4.7)	127 (4.9)	26 (4.2)	24 (3.6)	22 (5.8)	
Extremity	789 (18.5)	501 (19.3)	110 (17.6)	110 (16.6)	68 (18.0)	
Kidney	16 (0.4)	13 (0.5)	1 (0.2)	1 (0.2)	1 (0.3)	
Prostate	94 (2.2)	63 (2.4)	7 (1.1)	15 (2.3)	9 (2.4)	
Bladder	112 (2.6)	69 (2.7)	16 (2.6)	18 (2.7)	9 (2.4)	
Biliary tract	28 (0.7)	15 (0.6)	2 (0.3)	9 (1.4)	2 (0.5)	
Other/Unknown	48 (1.1)	37 (1.4)	5 (0.8)	3 (0.5)	3 (0.8)	
Prognostic site						0.05
Favorable	1508 (35.3)	891 (34.3)	250 (39.9)	236 (35.5)	131 (34.8)	
Unfavorable	2712 (63.5)	1673 (64.3)	371 (59.3)	425 (64.0)	243 (64.5)	
Unknown	48 (1.1)	37 (1.4)	5 (0.8)	3 (0.5)	3 (0.80)	
Treatment						0.01
No treatment	637 (14.9)	370 (14.2)	92 (14.7)	113 (17.0)	62 (16.5)	
Radiation only	973 (22.8)	553 (21.3)	153 (24.4)	180 (27.1)	87 (23.1)	
Surgery only	1215 (28.5)	766 (29.5)	182 (29.1)	172 (25.9)	95 (25.2)	
Radiation & Surgery	1300 (30.5)	817 (31.4)	175 (28.0)	184 (27.7)	124 (32.9)	
Either or both treatments unknown	143 (3.4)	95 (3.7)	24 (3.8)	15 (2.3)	9 (2.4)	0.15
Vital status						
Alive	2519 (59.0)	1547 (59.5)	359 (57.4)	407 (61.3)	206 (54.5)	
Dead	1749 (41.0)	1054 (40.5)	267 (42.6)	257 (38.7)	172 (45.5)	

Abbreviations: SD, standard deviation; HR, hazard ratio; RMS, rhabdomyosarcoma; NOS, not otherwise specified; NHW, non-hispanic white; NHB, non-hispanic black; SEER, Surveillance, Epidemiology, and End Results

*Includes American Indian/Alaskan Native, Asian/Pacific Islander, unspecified and unknown.

†The SEER program has expanded since its establishment to cover 9.5% (SEER 9), 13.8% (SEER 13) and 30% (SEER 18) of the total United States population; therefore, more patients were registered in 1990-2013 period. The latter time period also represents a longer time in years.

‡Head and neck, excluding orbital tumors

ᵀGenitourinary, excluding kidney, prostate, and bladder tumors

Table 2: Multivariate Cox Proportional Hazard Analysis of RMS During Period of 1973-2013

		Period of 1973-2013 N = 4,268	
	n	**HR (95% CI)**	**P**
Age at diagnosis			
Children	2427	Ref.	
Adults	1841	**2.19 (1.97-2.44)**	**<.0001**
Sex			
Female	1858	Ref.	
Male	2410	0.97 (0.88-1.07)	0.57
Race/ethnicity			
NHW	2601	Ref.	
NHB	626	1.14 (0.99-1.31)	0.06
Hispanic	664	1.05 (0.91-1.22)	0.52
Other	377	1.13 (0.96-1.34)	0.15
Diagnostic period			
1973-1989	897	Ref.	
1990-2013	3371	**0.63 (0.56-0.71)**	**<.0001**
Geographic region			
Northeast	659	Ref.	
Midwest	675	**1.35 (1.13-1.61)**	**0.0009**
South	685	1.14 (0.95-1.37)	0.10
West	2249	**1.22 (1.04-1.41)**	**0.01**
Histologic type			
Embryonic	1698	Ref.	
Pleomorphic	395	**1.59 (1.32-1.92)**	**<.0001**
Mixed-type	72	**1.80 (1.26-2.57)**	**0.001**
Spindle cell	85	0.94 (0.59-1.52)	0.81
Alveolar	974	**1.37 (1.21-1.57)**	**<.0001**
RMS (NOS)	1044	**1.51 (1.33-1.73)**	**<.0001**
Tumor behavior			
Localized	1264	Ref.	
Regional	1271	**1.96 (1.68-2.28)**	**<.0001**
Distant	1234	**4.56 (3.92-5.30)**	**<.0001**
Un-staged	499	**2.31 (1.91-2.79)**	**<.0001**
Prognostic site			
Favorable site	1508	Ref.	
Unfavorable site	2712	**1.38 (1.23-1.55)**	**<.0001**
Unknown	48	**2.19 (1.48-3.23)**	**<.0001**
Treatment			
No treatment	637	Ref.	
Radiation only	973	**0.64 (0.56-0.74)**	**<.0001**
Surgery only	1215	**0.57 (0.49-0.67)**	**<.0001**
Radiation & surgery	1300	**0.48 (0.41-0.55)**	**<.0001**
Either or both treatments unknown	143	**0.71 (0.55-0.92)**	**0.001**

Abbreviations: CI, confidence interval; HR, hazard ratio; N, Total number; n, cell number; P, P-value; RMS, rhabdomyosarcoma; NOS, not otherwise specified; NHW, non-hispanic white; NHB, non-hispanic black

Table 3: Multivariate Cox Proportional Hazard Analysis of RMS Stratified Analysis by Diagnostic Period

	Period of 1973-1989 N = 897			Period of 1990-2013 N = 3,371		
	n	**HR (95% CI)**	**P**	**n**	**HR (95% CI)**	**P**
Age at diagnosis						
Children	480	Ref.		1947	Ref.	
Adults	417	**2.56 (2.06-3.18)**	**<.0001**	1424	**2.11 (1.85-2.39)**	**<.0001**
Sex						
Female	372	Ref.		1486	Ref.	
Male	525	1.11 (0.92-1.34)	0.26	1885	0.93 (0.83-1.04)	0.18
Race/ethnicity						
NHW	719	Ref.		1882	Ref.	
NHB	87	1.17 (0.86-1.61)	0.32	539	**1.18 (1.01-1.38)**	**0.04**
Hispanic	0	NA	----	664	1.07 (0.91-1.24)	0.42
Other	91	1.09 (0.80-1.50)	0.58	286	1.15 (0.95-1.41)	0.16
Diagnostic period						
1973-1989		----	----		----	----
1990-2013		----	----		----	----
Geographic region						
Northeast	153	Ref.		506	Ref.	
Midwest	318	1.36 (0.98-1.90)	0.07	357	**1.26 (1.00-1.59)**	**0.05**
South	53	0.94 (0.56-1.56)	0.80	632	1.17 (0.96-1.44)	0.13
West	373	1.24 (0.89-1.73)	0.10	1876	**1.20 (1.00-1.43)**	**0.05**
Histologic type						
Embryonic	391	Ref.		1307	Ref.	
Pleomorphic	60	0.96 (0.63-1.46)	0.83	335	**1.97 (1.58-2.45)**	**<.0001**
Mixed-type	10	1.79 (0.79-4.10)	0.17	62	**1.83 (1.23-2.72)**	**0.003**
Spindle cell	0	N/A		85	1.00 (0.62-1.61)	1
Alveolar	115	1.00 (0.75-1.34)	0.99	859	**1.56 (1.34-1.82)**	**<.0001**
RMS (NOS)	321	**1.30 (1.03-1.64)**	**0.03**	723	**1.63 (1.38-1.93)**	**<.0001**
Tumor behavior						
Localized	327	Ref.		937	Ref.	
Regional	194	**1.75 (1.32-2.33)**	**0.0001**	1077	**1.98 (1.65-2.39)**	**<.0001**
Distant	213	**4.33 (3.31-5.68)**	**<.0001**	1021	**4.65 (3.86-5.59)**	**<.0001**
Un-staged	163	**2.13 (1.57-2.90)**	**<.0001**	336	**2.30 (1.80-2.95)**	**<.0001**
Prognostic site						
Favorable site	283	Ref.		1225	Ref.	
Unfavorable site	593	**1.61 (1.28-2.03)**	**<.0001**	2119	**1.29 (1.13-1.48)**	**0.0003**
Unknown	21	**2.46 (1.33-4.53)**	**0.004**	27	**2.54 (1.51-4.30)**	**0.0005**
Treatment						
No treatment	116	Ref.		521	Ref.	
Radiation only	160	0.94 (0.69-1.23)	0.70	813	**0.57 (0.49-0.67)**	**<.0001**
Surgery only	289	**0.56 (0.41-0.78)**	**0.0004**	926	**0.59 (0.50-0.71)**	**<.0001**
Radiation & surgery	270	**0.59 (0.43-0.80)**	**0.0007**	1030	**0.44 (0.37-0.52)**	**<.0001**
Either or both treatments unknown	62	1.05 (0.66-1.66)	0.84	81	**0.56 (0.39-0.80)**	**0.001**

Abbreviations: CI, confidence interval; HR, hazard ratio; N, Total number; n, cell number; P, P-value; RMS, rhabdomyosarcoma; NOS, not otherwise specified; NHW, non-hispanic white; NHB, non-hispanic black

Table 4. Multivariate Cox Proportional Hazards Analysis of RMS During Period of 1973-2013, Stratified by Age

	Child N = 2,427			Adult N = 1,841		
	n	**HR (95% CI)**	**P**	**n**	**HR (95% CI)**	**P**
Sex						
Female	998	Ref.		860	Ref.	
Male	1429	1.06 (0.92-1.22)	0.42	981	0.93 (0.81-1.06)	0.27
Race/ethnicity						
NHW	1395	Ref.		1206	Ref.	
NHB	357	1.05 (0.86-1.29)	0.63	269	1.20 (0.99-1.45)	0.07
Hispanic	452	1.05 (0.86-1.29)	0.65	212	1.07 (0.86-1.33)	0.55
Other	223	**1.31 (1.03-1.66)**	**0.03**	154	0.98 (0.77-1.24)	0.85
Diagnostic period						
1973-1989	480	Ref.		417	Ref.	
1990-2013	1947	**0.62 (0.52-0.74)**	**<.0001**	1424	**0.63 (0.54-0.75)**	**<.0001**
Geographic region						
Northeast	347	Ref.		312	Ref.	
Midwest	382	1.29 (0.98-1.69)	0.07	293	**1.40 (1.10-1.77)**	**0.006**
South	396	1.22 (0.92-1.61)	0.17	289	1.10 (0.86-1.41)	0.46
West	1302	**1.27 (1.00-1.60)**	**0.05**	947	1.17 (0.96-1.43)	0.11
Histologic type						
Embryonic	1348	Ref.		350	Ref.	
Pleomorphic	18	**2.14 (1.10-4.19)**	**0.03**	377	**1.34 (1.07-1.67)**	**0.01**
Mixed-type	36	**1.73 (1.03-2.92)**	**0.04**	36	**1.63 (1.00-2.67)**	**0.05**
Spindle cell	45	0.98 (0.48-1.99)	0.95	40	0.83 (0.44-1.58)	0.57
Alveolar	682	**1.67 (1.42-1.99)**	**<.0001**	293	0.99 (0.79-1.23)	0.91
RMS (NOS)	299	**1.58 (1.28-1.95)**	**<.0001**	745	**1.27 (1.05-1.53)**	**0.01**
Tumor behavior						
Localized	728	Ref.		536	Ref.	
Regional metastasis	773	**2.06 (1.63-2.62)**	**<.0001**	498	**1.86 (1.51-2.28)**	**<.0001**
Distant metastasis	667	**5.07 (4.02-6.38)**	**<.0001**	567	**3.95 (3.22-4.84)**	**<.0001**
Un-staged	259	**2.66 (1.99-3.57)**	**<.0001**	240	**2.00 (1.55-2.58)**	**<.0001**
Prognostic site						
Favorable site	985	Ref.		523	Ref.	
Unfavorable site	1428	**1.53 (1.30-1.81)**	**<.0001**	1284	**1.26 (1.07-1.49)**	**0.006**
Unknown	14	**3.00 (1.46-6.16)**	**0.003**	34	**1.96 (1.22-3.16)**	**0.006**
Treatment						
No treatment	262	Ref.		375	Ref.	
Radiation only	708	**0.69 (0.56-0.84)**	**0.0003**	265	**0.63 (0.51-0.77)**	**<.0001**
Surgery only	564	**0.62 (0.48-0.79)**	**0.0001**	651	**0.52 (0.43-0.64)**	**<.0001**
Radiation & surgery	820	**0.53 (0.43-0.66)**	**<.0001**	480	**0.44 (0.36-0.54)**	**<.0001**
Either or both treatments unknown	73	0.95 (0.65-1.38)	0.78	70	**0.60 (0.43-0.85)**	**0.004**

Abbreviations: CI, confidence interval; HR, hazard ratio; N, Total number; n, cell number; P, P-value; RMS, rhabdomyosarcoma; NOS, not otherwise specified; NHW, non-hispanic white; NHB, non-hispanic black

Table 5. Multivariate Cox Proportional Hazards Analysis of RMS During Period of 1973-2013, Stratified by Race/Ethnicity

		NHW N = 2,601			NHB N = 626			Hispanic N = 664			Other N = 377	
	n	HR (95% CI)	P	n	HR (95% CI)	P	n	HR (95% CI)	P	n	HR (95% CI)	P
Age												
Children	1395	Ref.		357	Ref.		452	Ref.		223	Ref.	
Adults	1206	**2.26 (1.96-2.61)**	**<.0001**	269	**2.86 (2.16-3.79)**	**<.0001**	212	**2.25 (1.71-2.97)**	**<.0001**	154	**1.48 (1.04-2.12)**	**0.03**
Sex												
Female	1110	Ref.		288	Ref.		302	Ref.		158	Ref.	
Male	1491	1.05 (0.93-1.19)	0.43	338	1.09 (0.85-1.41)	0.49	362	**0.71 (0.55-0.91)**	**0.008**	219	0.86 (0.62-1.18)	0.34
Diagnostic Period												
1973-1989	719	Ref.		87	Ref.		0	Ref.		91	Ref.	
1990-2013	1882	**0.63 (0.54-0.72)**	**<.0001**	539	**0.57 (0.40-0.80)**	**0.001**	664	NE	----	286	**0.67 (0.46-0.98)**	**0.04**
Geographic region												
Northeast	479	Ref.		79	Ref.		65	Ref.		36	Ref.	
Midwest	548	**1.42 (1.16-1.74)**	**0.0008**	104	1.24 (0.75-2.05)	0.40	10	1.43 (0.53-3.89)	0.48	13	2.00 (0.68-5.89)	0.21
South	394	1.18 (0.94-1.49)	0.15	233	1.24 (0.80-1.90)	0.33	40	0.68 (0.34-1.39)	0.29	18	1.07 (0.37-3.11)	0.90
West	1180	**1.26 (1.05-1.52)**	**0.01**	210	1.21 (0.78-1.88)	0.41	549	0.96 (0.62-1.49)	0.86	310	1.49 (0.74-3.00)	0.27
Histologic type												
Embryonic	1036	Ref.		259	Ref.		261	Ref.		142	Ref.	
Pleomorphic	271	**1.45 (1.14-1.84)**	**0.003**	48	**1.76 (1.03-3.02)**	**0.04**	41	**1.87 (1.08-3.22)**	**0.02**	35	**2.83 (1.51-5.30)**	**0.001**
Mixed-type	40	**2.07 (1.28-3.34)**	**0.003**	14	1.53 (0.70-3.36)	0.29	15	1.46 (0.65-3.29)	0.36	3	3.37 (0.45-25.25)	0.24
Spindle cell	41	0.69 (0.31-1.56)	0.37	16	0.91 (0.33-2.52)	0.85	23	1.20 (0.54-2.65)	0.65	5	1.29 (0.16-10.15)	0.81
Alveolar	523	**1.33 (1.12-1.57)**	**0.001**	158	**1.56 (1.11-2.19)**	**0.01**	198	1.20 (0.85-1.67)	0.30	95	**2.07 (1.33-3.23)**	**0.001**
RMS (NOS)	690	**1.44 (1.21-1.71)**	**<.0001**	131	**1.44 (1.02-2.04)**	**0.04**	126	**1.78 (1.24-2.56)**	**0.002**	97	**2.19 (1.38-3.48)**	**0.002**
Tumor behavior												
Localized	788	Ref.		195	Ref.		166	Ref.		115	Ref.	
Regional metastasis	750	**1.91 (1.57-2.32)**	**<.0001**	183	**2.71 (1.80-4.07)**	**<.0001**	217	**1.97 (1.28-3.01)**	**0.002**	121	**1.69 (1.05-2.72)**	**0.03**
Distant metastasis	695	**4.58 (3.77-5.55)**	**<.0001**	201	**5.69 (3.81-8.48)**	**<.0001**	230	**4.62 (3.02-7.06)**	**<.0001**	108	**3.68 (2.27-5.97)**	**<.0001**
Un-staged	368	**2.14 (1.70-2.70)**	**<.0001**	47	**4.05 (2.33-7.03)**	**<.0001**	51	**2.25 (1.26-4.02)**	**0.006**	33	**3.02 (1.54-5.92)**	**0.001**
Prognostic site												
Favorable site	891	Ref.		250	Ref.		236	Ref.		131	Ref.	
Unfavorable site	1673	**1.48 (1.27-1.72)**	**<.0001**	371	**1.37 (1.02-1.84)**	**0.04**	425	1.31 (0.97-1.78)	0.08	243	1.13 (0.77-1.65)	0.53
Unknown	37	**2.55 (1.62-3.99)**	**<.0001**	5	0.51 (0.13-2.01)	0.34	3	**8.89(1.95-40.57)**	**0.005**	3	1.02 (0.21-4.95)	0.99
Treatment												
No treatment	370	Ref.		92	Ref.		113	Ref.		62	Ref.	
Radiation only	553	**0.65 (0.53-0.78)**	**<.0001**	153	**0.67 (0.47-0.95)**	**0.03**	180	**0.59 (0.41-0.85)**	**0.005**	87	**0.54 (0.34-0.85)**	**0.008**
Surgery only	766	**0.52 (0.42-0.63)**	**<.0001**	182	0.82 (0.55-1.22)	0.32	172	0.68 (0.45-1.04)	0.07	95	**0.39 (0.24-0.65)**	**0.0002**
Radiation & surgery	817	**0.46 (0.38-0.56)**	**<.0001**	175	**0.53 (0.36-0.79)**	**0.002**	184	**0.57 (0.39-0.84)**	**0.004**	124	**0.29 (0.18-0.47)**	**<.0001**
Either or both treatments unknown	95	0.83 (0.60-1.14)	0.24	24	**0.50 (0.26-0.99)**	**0.05**	15	0.70 (0.32-1.51)	0.36	9	**0.32 (0.11-0.94)**	**0.04**

Abbreviations: CI, confidence interval; HR, hazard ratio; N, Total number; n, cell number; P, P-value; RMS, rhabdomyosarcoma; NOS, not otherwise specified; NHW, non-hispanic white; NHB, non-hispanic black; NE, not estimable

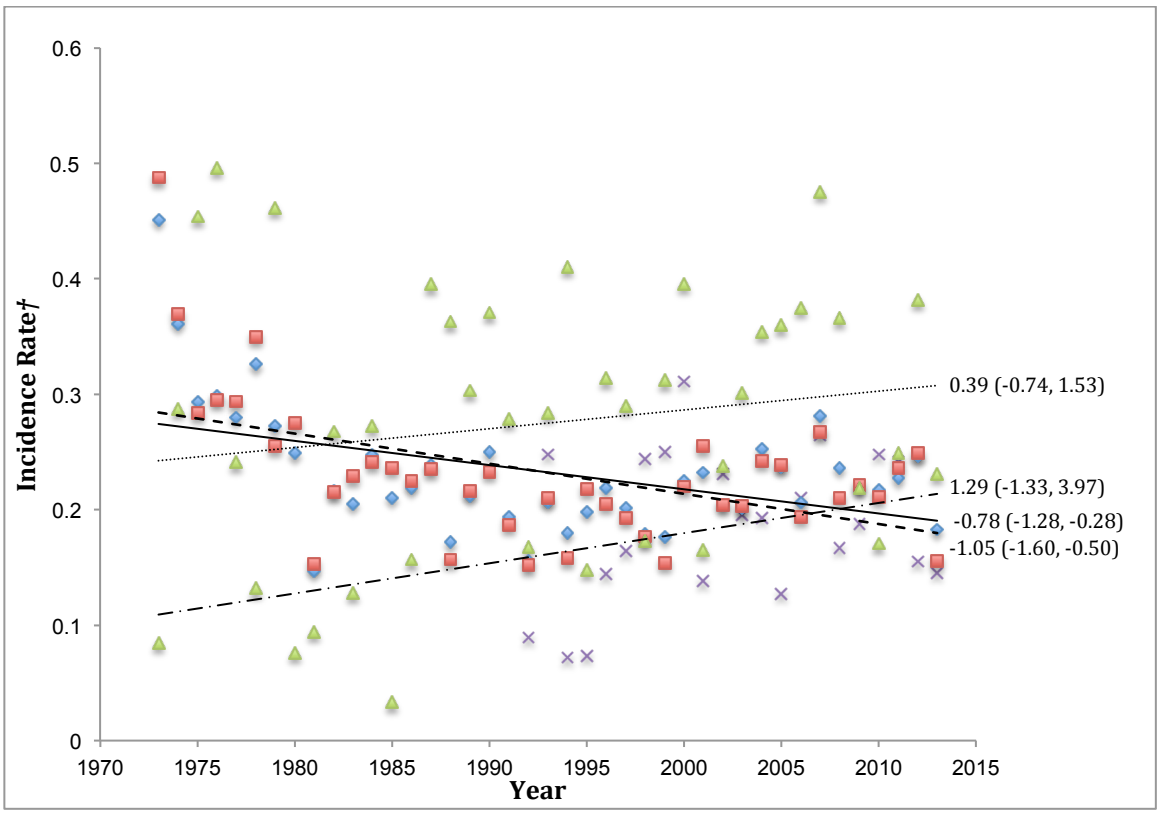

Figure 1. RMS Incidence Rates from 1973-2013*

*Overall, White, and Black rates from SEER 9 incidence data; Hispanic rates from SEER 13 data.
ŦRace/Ethnicity groups are represented by the following symbols: Overall – blue diamonds and a solid line; Whites – red squares and a dashed line; Blacks – green triangles and a dotted line; Hispanics – purple crosses and dotted/dashed line.
◊Data are shown as: Annual Percentage Change (95% Confidence Interval).
†Rates are per 100,000 and age-adjusted to the 2000 US Std Population standard.
‡Percentage changes were calculated using 1 year for each end point; Annual Percentage Changes were calculated using weighted least squares method.

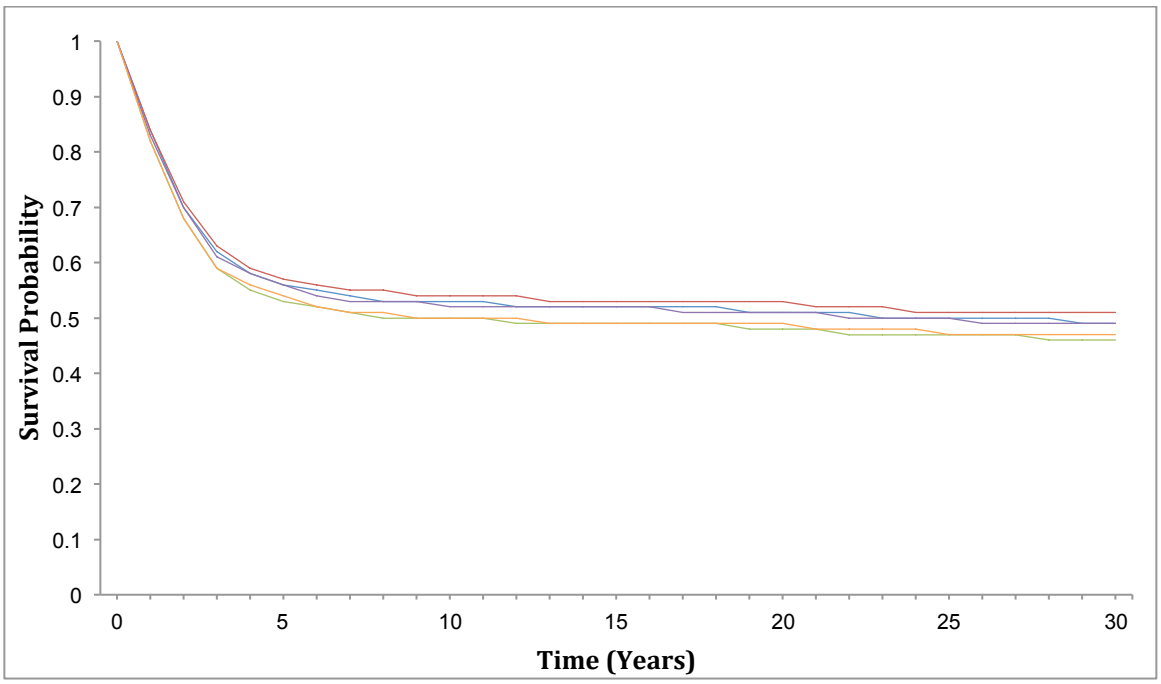

Figure 2. Adjusted RMS Survival, by Race*

*Race/Ethnicity groups are represented by the following symbols: Overall – blue line; Whites – red line; Blacks – green line; Hispanics – purple line; Others – orange line.

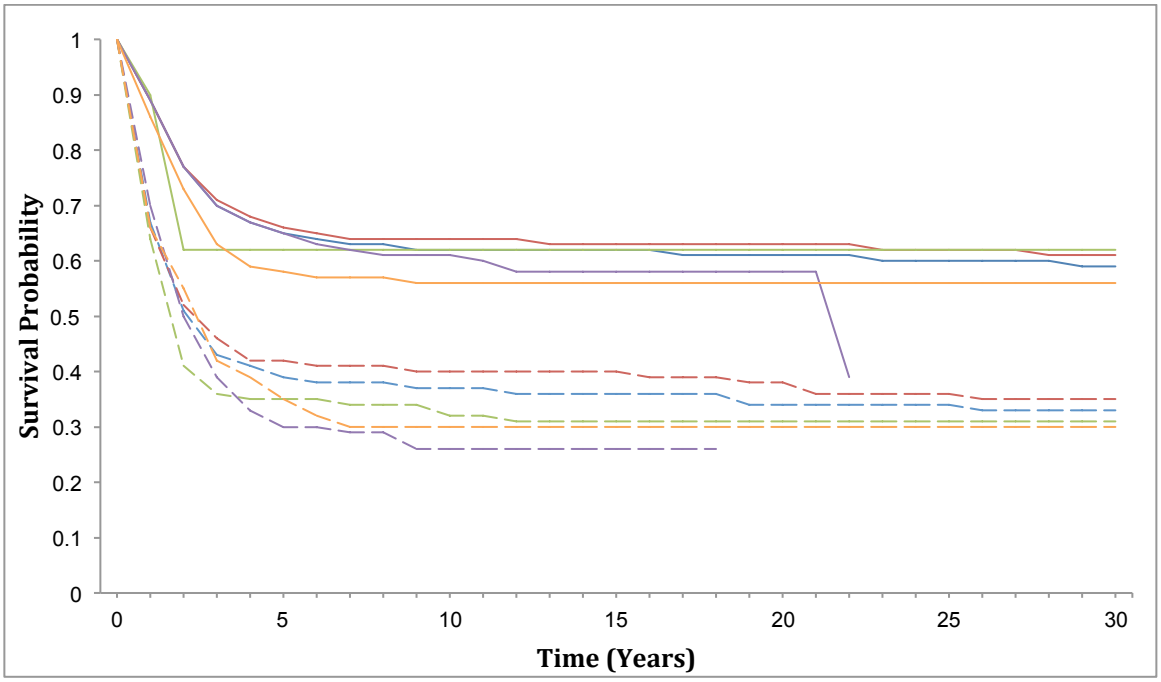

Figure 3. RMS Survival in Children and Adults, by Race*

*Race/Ethnicity groups are represented by the following symbols: Overall Children – solid blue line; Overall Adults – dashed blue line; White Children – solid red line; White Adults – dashed red line; Black Children – solid green line; Black Adults – dashed green line; Hispanic Children – solid purple line; Hispanic Adults – dashed purple line; Other Children – solid orange line; Other Adults – dashed orange line.

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Appendix

USF
UNIVERSITY OF
SOUTH FLORIDA

RESEARCH INTEGRITY AND COMPLIANCE
Institutional Review Boards, FWA No. 00001669
12901 Bruce B. Downs Blvd., MDC035 • Tampa, FL 33612-4799
(813) 974-5638 • FAX(813)974-7091

11/1/2016

Heather Tinsley
Epidemiology and Biostatistics
Tampa, FL 33612

RE: **Not Human Subjects Research Determination**
IRB#: Pro00028332
Title: Rhabdomyosarcoma Incidence and Survival in Whites, Blacks, and Hispanics from 1973-2013: Analysis from the Surveillance, Epidemiology and End Results Program

Dear Ms. Tinsley:

The Institutional Review Board (IRB) has reviewed your application and determined the activities do not meet the definition of human subjects research. Therefore, this project is not under the purview of the USF IRB and approval is not required. If the scope of your project changes in the future, please contact the IRB for further guidance.

All research activities, regardless of the level of IRB oversight, must be conducted in a manner that is consistent with the ethical principles of your profession. Please note that there may be requirements under the HIPAA Privacy Rule that apply to the information/data you will utilize. For further information, please contact a HIPAA Program administrator at 813-974-5638.

We appreciate your dedication to the ethical conduct of research at the University of South Florida. If you have any questions regarding this matter, please call 813-974-5638.

Sincerely,

V Jorgensen MD

E. Verena Jorgensen, M.D., Chairperson
USF Institutional Review Board