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Trends in Childhood Rhabdomyosarcoma Incidence and Survival in the United States (1975–2005)

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Abstract

Background—Rhabdomyosarcoma (RMS) is the most common soft tissue sarcoma in children and adolescents aged <20 years; its etiology remains largely unknown. Embryonal (ERMS) and alveolar rhabdomyosarcoma (ARMS), the most common subtypes, are thought to arise through distinct biological mechanisms. We evaluated incidence and survival trends by RMS demographic subgroups to inform future etiologic hypotheses.

Methods—Incidence and survival trends in RMS among children and adolescents aged <20 years were analyzed using data from the Surveillance, Epidemiology and End Results Program. Frequencies, age-adjusted incidence and survival rates, and jointpoint regression results, including annual percent change (APC) and 95% confidence intervals (CI), were calculated.

Results—Between 1975 and 2005, the incidence of ERMS was stable, while a significant increase in the incidence of ARMS was observed (APC=4.20%, 95%CI=2.60%–5.82%). This trend may be partially attributable to shifts in diagnosis, as a significant negative trend in RMS, not otherwise specified was observed concurrently. A bimodal age peak for ERMS was observed, with the second, smaller peak in adolescence noted for males only; ARMS incidence did not vary by age or sex. Five-year survival rates for RMS and ERMS increased from the period 1976–1980 (52.7% and 60.9%, respectively) to 1996–2000 (61.8% and 73.4%, respectively), while there was little improvement for ARMS (40.1% and 47.8%, respectively).

Conclusions—Observed differences in incidence and survival for two major RMS subtypes across gender and age subgroups further support unique underlying etiologies for these tumors. Exploration of these differences presents an opportunity to increase our knowledge of RMS.

Keywords

pediatric rhabdomyosarcoma; incidence; survival; trends

INTRODUCTION

Soft tissue sarcomas (STS) comprise about 7% of all malignancies in children and adolescents under the age of 20 years and rhabdomyosarcoma (RMS) accounts for about 40% of pediatric STS(1). The incidence of RMS is 4.5 cases/million children/adolescents per year and in more than 50% of cases, RMS occurs during the first decade of life(2).

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RMS originates from tissue that imitates normal striated muscle(3). Due to its origin in embryonal mesenchyme, RMS can arise virtually anywhere in the body, often in sites where striated muscle is not ordinarily found. Very little is known about the etiology of RMS, primarily due to its rarity and diagnostic diversity.

Several environmental exposures have been associated with increased RMS risk, including paternal cigarette smoking(4), advanced maternal age and x-ray exposure in utero(5), maternal(4) and child's(6) antibiotic use, stillbirths(7) and maternal recreational drug use(8). The largest case-control study of childhood RMS thus far was conducted in the US in the mid-1980s and included 249 RMS cases(9). The majority of associations between environmental exposures and risk for RMS found in the literature result from this study (4,5,8). Other associations between environmental exposures and risk of RMS were reported in very small epidemiological studies (<100 cases).

In addition to environmental exposures, genetic changes may play an important role in RMS development. Although the majority of RMS cases appear to be sporadic, familial syndromes associated with inherited gene defects, such as neurofibromatosis and Li-Fraumeni syndrome, have been associated with RMS(10). Within Li-Fraumeni families carrying germ-line mutations in *TP53*, RMS is the most frequently observed childhood cancer(11). Similarly, *NF1* gene mutations associated with neurofibromatosis lead to 20-fold increased risk of RMS compared to the general population(12). In addition, several Beckwith-Wiedeman syndrome cases(13) and as many as 10% of Costello syndrome patients subsequently developed RMS(14). Cancer is more often observed in the families of children affected by STS than in families with healthy children; mothers of children with STS develop breast cancer more frequently (11,15), while their siblings have an increased incidence of brain tumors and adrenocortical carcinoma(16). An analysis of 338 childhood RMS cases showed that 21% of them had a family history of cancer(17). Moreover, congenital malformations are more frequently (32%) observed in children and adolescents with RMS(18) compared to the general population, where the frequency of such malformations is approximately 3%(19). Taken together, the greater incidence of cancer in the families of RMS children, the higher frequency of malformations in these children, as well as the clear link between the above genetic syndromes and RMS, collectively suggest that genetic predisposition may also play an important role in RMS development.

RMS are classified based on the histological and biological features of the tumor. The two largest subgroups are embryonal (ERMS) and alveolar (ARMS). ERMS has an earlier age of onset (the majority of cases occur before 10 years of age) and is associated with better prognosis. In contrast, ARMS is more evenly distributed throughout childhood and adolescence (half of the cases occur after the age of 10 years) and has different primary sites than ERMS(1). Translocations t(2;13) and t(1;13) are often observed in ARMS, while allelic loss on chromosome 11 is frequent in ERMS. Due to these clinical and pathological differences between ERMS and ARMS, it has been hypothesized that these two subtypes occur as a result of different biological mechanisms of tumorigenesis(20).

We have recently analyzed trends in childhood cancer incidence and found no evidence of an *overall* increase in RMS incidence during the last decade (1992–2004) in data obtained from thirteen registries of the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) Program(21). However, a more detailed and larger analysis is required to include a sufficient number of RMS cases to allow analyses by subtype. We therefore examined SEER Program data, including nine registries with a longer follow up (1975–2005), in order to examine incidence and survival trends by RMS subtype. Differences in incidence and survival trends of these subtypes may provide further clues into the etiology of these tumors.

METHODS

SEER Program data(22) were analyzed to evaluate incidence and survival rates of pediatric and adolescent RMS in the United States between 1975 and 2005. The SEER program actively collected information on demographics, tumor site and morphology, stage at diagnosis, treatment, and vital status during this period from nine registries encompassing five states (Connecticut, Hawaii, Iowa, New Mexico, and Utah) and four metropolitan areas (Detroit, San Francisco-Oakland, Seattle-Puget Sound, and Atlanta).

These SEER 9 registries represent approximately 9% of the total U.S. population(2) and have an estimated case ascertainment rate of 98%.(23) The SEER Program added four registries by 1992 (Los Angeles, San Jose-Monterey, rural Georgia, and the Alaskan Native Tumor Registry);(22) the expanded SEER 13 dataset allowed for the analysis of incidence and survival rates among Hispanic children.

All primary cases of RMS among the pediatric and adolescent population (aged 0–19 years) were included. International Classification of Disease for Oncology, Third Edition (ICD-O-3)(24) morphology codes included in the International Classification of Childhood Cancer, Third Edition (ICCC-3)(25) category IXa – RMS were analyzed overall and separately and include: 8900/3 (RMS, not otherwise specified (NOS)); 8901/3 (pleomorphic); 8902/3 (mixed type); 8910/3 (ERMS); 8912/3 (spindle cell RMS); 8920/3 (ARMS); and 8991/3 (embryonal sarcoma). All morphologies were included in data presented as RMS overall. ERMS and ARMS were also presented separately, while small sample sizes precluded this for other RMS morphologies. Nearly all RMS diagnoses were confirmed by histology (99.4%).

Statistical Analysis

SEER*STAT software(26) was used to evaluate frequencies and incidence rates in RMS incidence rates during the period 1975–2005, while for Hispanics, the evaluation period was 1992–2005. Incidence rates were calculated per 1,000,000 person-years of follow-up and were age-adjusted to the 2000 U.S. Standard Population. Annual population estimates used to calculate incidence rates were obtained from the U.S. Census Bureau by the SEER Program. Incidence trends were evaluated by weighted least squares regression via Joinpoint software,(27) where the independent variable was calendar year and the dependent variable was the natural logarithm of the age-adjusted incidence rate, resulting in average annual percent changes (APC) in incidence rates and corresponding 95% confidence intervals (CIs); joinpoints were not permitted. Trend calculations that included one or more years with <10 cases are noted and should be interpreted with caution. Five-year relative survival rates and corresponding standard errors among five 5-year (1976–1980, 1981–1985, 1986–1990, 1991–1995, 1996–2000) diagnostic cohorts were computed via the life tables method in SEER*STAT.(26,28) The cohorts included all individuals diagnosed with a first malignancy during the given time period who were actively followed though 2005. Relative survival rates are ratios of observed-to-expected survival and are reported as percentages. The use of expected rates, derived from mortality data of the National Center for Health Statistics, takes into account the population distribution of age, sex, race, and calendar year. Relative rates were adjusted if they exceeded 100%, increased over time, or involved heterogeneity in withdrawal (exact method) within a survival function. The 95% CIs were calculated from standard errors to display the amount of variability in the rates and Z-tests compared the relative 10 survival functions across the 1976–1980, 1986–1990, and 1996–2000 cohorts. (29) Relative 5-year survival rates and corresponding 95% CIs were also evaluated for Hispanic children diagnosed in 1996–2000; the survival functions were compared to those among non-Hispanic white and black children (data not shown) via Z-tests.(29)

Incidence and survival rates were examined overall and with respect to the following demographic groups: sex (males and females), age group (0–4, 5–9, 10–14, and 15–years), and race (white, black, and American Indian/Alaskan Native and Asian/Pacific Islander combined). Cases with an unspecified or unknown race were excluded from subgroup analyses due to small sample sizes.

RESULTS

Incidence

A total of 987 children aged 0–19 years were newly diagnosed with RMS between 1975 and 2005 in the SEER 9 registries. These included: 564 (57%) ERMS, 227 (23%) ARMS, 22 (2%) embryonal sarcoma, 15 (1.5%) pleomorphic, 14 (1.4%) mixed type, 6 (0.6%) spindle cell, and 139 (14%) RMS, NOS. The corresponding incidence rates for RMS overall, ERMS, and ARMS are shown in Table 1.

Males had a higher incidence of RMS than females (5.2/1,000,000 vs. 3.8/1,000,000, respectively), with a rate ratio of 1.37 (95% CI: 1.21–1.56). This male predominance in RMS was comprised almost solely of ERMS, with a male/female rate ratio of 1.51 (95% CI: 1.27–1.80). ERMS was most common in the youngest children aged 0–4 years (42%), whereas ARMS was found nearly equally distributed amongst all 4 age groups examined (Table 1). Notably, a bimodal age distribution was observed for RMS and ERMS, including a larger peak between ages 0–5 years and a smaller peak in adolescence (Figure 1). Upon further examination, this second peak was only observed in males (data not shown).

When the incidence rates were analyzed by race/ethnicity, black children had slightly higher rates of ARMS than white children (1.3/1,000,000 vs. 1.0/1,000,000, respectively). The American Indian/Alaskan Native/Asian/Pacific Islander group had somewhat lower RMS incidence rates (2.9/1,000,000) than white or black children; however, this combined group represented only 6.5% of all children. The data available for Hispanic children covered a shorter reference period; rates for these children were lower than for non-Hispanic white and black children.

Incidence trends

While the annual percent change (APC) in incidence of overall RMS and ERMS did not change significantly, we observed a statistically significant increase in ARMS incidence (APC=4.20, 95% CI=2.60%–5.82%) (Table 1). Further, a significant negative trend was observed for RMS, NOS (APC= −3.05, 95% CI: −4.73% - −1.34%) (data not shown). However, caution in interpretation is warranted, as both ARMS and RMS, NOS included fewer than 10 cases in several years.

Survival rates

ARMS relative 5-year survival rates have not increased significantly over the past 25 years; rates increased from 40.1% (95% CI: 22.5%–57.7%) in 1976–1980 to 47.8% (95% CI: 33.9%–61.7%) in the 1996–2000 period (Table 2). ERMS relative 5-year survival rates improved from 60.9% (95% CI: 50.2%–71.5%) to 73.4% (95% CI: 64.2%–82.6%) over this period, although this increase was not statistically significant (data not shown). Five-year survival rates for five diagnostic time periods between 1976 and 2000 are shown in Figure 2. By visual inspection, the largest improvements in survival were achieved between the 1976–1980 and 1981–1985 cohorts. Thereafter, survival rates for ERMS tended to stabilize around 70%, while ARMS survival rates showed a small but continuous rise until the most recent period (1996–2000), when rates stabilized or possibly decreased.

Table 2 shows 5-year survival rates for the diagnostic period 1996–2000 by gender, age and race/ethnicity. Children aged 15–19 years had the poorest overall survival rates (1996–2000: 46.6%, 95% CI=28.0%–65.1%) compared to the 0–4 year age group (70.5%, 95% CI=59.3%–81.8%). Male children had better five year survival rates compared to female children, which was primarily reflected in higher survival rates amongst the ARMS group (1996–2000: 55.6% vs. 37.9%, respectively). Exploration of race/ethnicity differences showed that black children may have better 5-year survival rates compared to whites, particularly for the ARMS subtype (1996–2000: 50.1% vs. 39.4%, respectively). Hispanic children had lower relative 5-year survival rates compared with non-Hispanic white and black children; the difference achieved statistical significance for ERMS compared with non-Hispanic whites. Of note, observed differences by race and ethnicity were based on a small number of children in each category and should therefore be interpreted with caution.

DISCUSSION

We have analyzed incidence and survival rates, as well as trends, for two major RMS subtypes in children and adolescents diagnosed at younger than age 20 years from 13 1975 to 2005 using SEER Program data. We are not aware of any prior SEER reports specifically addressing trends in incidence and survival of pediatric and adolescent RMS subtypes. We found a 4.20% (95% CI=2.60%–5.82%) annual increase in the incidence of ARMS. Further, and unexpectedly, we found that five year survival rates for ARMS have not improved significantly over the last 30 years, rising only 7.7% during this entire period. For ERMS, incidence rates have not changed significantly, while 5-year survival rates have largely improved (from 60.9% during the 1976–1980 period to 73.4% during 1996–2000).

Many changes in classification and diagnosis of RMS were introduced over the last three decades(30–32). In 1995 a consensus classification of RMS, the International Classification of RMS (ICR) was established(33), thus improving the reproducibility of classification as well as prediction of outcome(34). Review of 800 cases of different RMS subtypes showed high concordance between the review using the new ICR criteria and initial diagnosis established at individual institutions for the ERMS subtype.

However, there was a “disturbing level” of disconcordant diagnosis (37%) reported for the ARMS subtype, which was thought to reflect poor recognition of some of ARMS histologies (34). For example, a solid form of ARMS morphologically resembles ERMS and is associated with a misdiagnosis rate of about 20%(35). As we examined the incidence of RMS during the period of 1975–2005, the vast majority of diagnoses were based on histology. Only within the last decade has the biology of tumors been taken into consideration during diagnosis relying on advances in immunologic and molecular methods. While immunologic studies are not necessary to establish the histologic diagnosis in the majority of cases, approximately one fifth of cases require such analyses in order to establish or confirm diagnosis.(34) In addition, the application of molecular methods to detect translocations t(1, 13) and t(2, 13) characteristic for ARMS(36) is useful in confirming diagnosis. These changes in classification and application of novel methods over the last decade may have partly contributed to the rise in incidence rates of ARMS and the decrease in RMS, NOS and to a lesser extent the decrease in ERMS we have observed. However, given the relatively smaller number of RMS, NOS cases in any given time period, this change in classification would attenuate, but likely not eliminate, the annual increase in ARMS we observed.

Many of our findings affirm previous incidence reports of RMS, including early age of onset (more than half of RMS cases are diagnosed before the age of 10 years) and a strong male predominance. We showed that this male predominance was driven by ERMS, while there

were no sex differences in ARMS incidence. Further, we found slightly higher incidence rates of RMS and ARMS for black children compared to white children.

We also observed a bimodal distribution of ERMS incidence rates with a larger peak during the first 5 years of life and a smaller peak between the ages of 12 and 17 years. Importantly this second peak was only observed in males. It is not clear why males would experience an increased incidence of ERMS in adolescence compared to females. Anecdotally, a recent study showed that pre-pubertal girls and boys have similar muscle size, while androgens have a strong impact on muscle enlargement resulting in larger muscle gain in males during puberty(37). It is therefore plausible that the smaller peak of ERMS incidence rates observed during adolescence in males only may be related to these sex-specific hormonal differences; this would be of interest to investigate further.

Our analyses of race/ethnic differences in RMS incidence and survival were exploratory, as many of the categories compared were comprised of relatively small numbers. In a previous analysis of childhood STS in the SEER 9 registries during the period 1975–1995(2), only white and black race were considered. While black children had higher incidence rates of all STS, the authors found no differences by histological subgroups, acknowledging that this may be due to small numbers.

Strengths of our analysis include evaluation of an additional 10 years of data, inclusion of both RMS subtypes, and exploration of additional races/ethnicities. Compared to whites, black children and American Indian/Alaskan Native/Asian/Pacific Islander children had better 5-year survival rates, most strikingly for ARMS; there were notably few cases among these subgroups, however. The only exception was Hispanic children, who tended to fare more poorly than non-Hispanic white and black children, most notably for the ERMS subtype (1996–2000: 57.3% survival, compared to 79.2% in non-Hispanic whites and 82.5% in non-Hispanic blacks).

The observed differences in 5-year survival rates among black and white children are notable. Ries et al(2) found that white children had slightly better 5-year survival rates for STS compared to black children. These authors analyzed all STS together for the time period (1985–1994), while we focused on 1996–2000, and explored the histological subtypes of RMS, which may account for differences in findings.

The considerable variation in incidence patterns observed here for the two major subtypes of RMS strengthens the notion that these tumors are etiologically diverse. Molecular evidence comparing ERMS and ARMS gene expression further indicates that these tumors have distinct gene signatures(38,39). ERMS frequently shows loss of the chromosome 11p15 locus resulting in loss of heterozygosity (LOH) in the region that contains a number of imprinted genes implicated in oncogenesis, including *H19* and insulin-like growth factor-2 (*IGF-2*)(40). In contrast, translocations are a hallmark of ARMS, present in 80% of all cases(41) and most commonly involving the PAX3-FKHR or PAX7-FKHR fusion(42). Such translocations can arise in somatic muscle cells independently throughout adulthood; notably we observed no significant variation in ARMS incidence by age. Several studies have implicated DNA repair pathways in neoplastic transformation involving translocations(43,44), but this has not been explored in ARMS.

There are a few limitations to this study. Our review of children with RMS and its two main subtypes reported to a population-based registry does not suffer from ascertainment biases reflecting referral patterns to regional centers that may be present in other epidemiologic studies. However, cancer registry data are limited by the information they are provided. These reports are based upon diagnoses rendered by multiple pathologists and oncologists with variable expertise and equipment(45) over an extended period of time; this may be

especially pertinent for RMS in which molecular classification has changed over the past several decades. However, as diagnostic techniques have improved for RMS, there is higher confidence in the most recent decade regarding accurate diagnosis. New cases registered using ICD-O-3 (begun on January 1, 2001) include more information on RMS subtypes. These data hold promise for future explorations of the relationship between RMS subtypes, race/ethnicity, incidence and survival.

In summary, the observed gender, age, and racial/ethnic differences in incidence and survival of two major RMS subtypes further support the view that these tumors have a distinct underlying etiology. Exploration of these differences presents the opportunity to increase our knowledge of RMS. As improvements in cure rates of RMS, especially ARMS, are slowing, progress will, at least in part, depend on improved understanding of tumor and host biology.(41)

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REFERENCES

1. Gurney, JG.; Young, JL.; Roffers, SD.; Smith, MA.; Bunin, GR. SEER Pediatric Monograph. National Cancer Institute; 2005. Soft Tissue Sarcomas.
2. Ries, LAG.; Smith, MA.; Gurney, JG.; Linet, M.; Tamra, T.; Young, JL.; Bunin, GR., editors. Cancer incidence and survival among children and adolescents: United States SEER Program 1975–1995. Bethesda: National Cancer Institute; 1999.
3. Stout AP. Rhabdomyosarcoma of the Skeletal Muscles. Ann Surg. 1946; 123:447–472. [PubMed: 17858752]
4. Grufferman S, Wang HH, DeLong ER, Kimm SY, Delzell ES, Falletta JM. Environmental factors in the etiology of rhabdomyosarcoma in childhood. J Natl Cancer Inst. 1982; 68:107–113. [PubMed: 6948120]
5. Grufferman S, Gula MJ, Olshan AF, Falletta JM, Pendergrass TW, Buckley J, Maurer HM. In utero x-ray exposure and risk of childhood rhabdomyosarcoma. Paediatr Perinat Epidemiol. 1991; 5:A6.
6. Hartley AL, Birch JM, McKinney PA, Teare MD, Blair V, Carrette J, Mann JR, Draper GJ, Stiller CA, Johnston HE, et al. The Inter-Regional Epidemiological Study of Childhood Cancer (IRESCC): case control study of children with bone and soft tissue sarcomas. Br J Cancer. 1988; 58:838–842. [PubMed: 3224086]
7. Ghali MH, Yoo KY, Flannery JT, Dubrow R. Association between childhood rhabdomyosarcoma and maternal history of stillbirths. Int J Cancer. 1992; 50:365–368. [PubMed: 1735603]
8. Grufferman S, Schwartz AG, Ruymann FB, Maurer HM. Parents' use of cocaine and marijuana and increased risk of rhabdomyosarcoma in their children. Cancer Causes Control. 1993; 4:217–224. [PubMed: 8318638]
9. Yang P, Grufferman S, Khoury MJ, Schwartz AG, Kowalski J, Ruymann FB, Maurer HM. Association of childhood rhabdomyosarcoma with neurofibromatosis type I and birth defects. Genet Epidemiol. 1995; 12:467–474. [PubMed: 8557179]
10. Dagher R, Helman L. Rhabdomyosarcoma: an overview. Oncologist. 1999; 4:34–44. [PubMed: 10337369]
11. Malkin D, Li FP, Strong LC, Fraumeni JF Jr, Nelson CE, Kim DH, Kassel J, Gryka MA, Bischoff FZ, Tainsky MA, et al. Germ line p53 mutations in a familial syndrome of breast cancer, sarcomas, and other neoplasms. Science. 1990; 250:1233–1238. [PubMed: 1978757]
12. Sung L, Anderson JR, Arndt C, Raney RB, Meyer WH, Pappo AS. Neurofibromatosis in children with Rhabdomyosarcoma: a report from the Intergroup Rhabdomyosarcoma study IV. J Pediatr. 2004; 144:666–668. [PubMed: 15127010]

13. Smith AC, Squire JA, Thorner P, Zielenska M, Shuman C, Grant R, Chitayat D, Nishikawa JL, Weksberg R. Association of alveolar rhabdomyosarcoma with the Beckwith-Wiedemann syndrome. Pediatr Dev Pathol. 2001; 4:550–558. [PubMed: 11826361]
14. Hennekam RC. Costello syndrome: an overview. Am J Med Genet C Semin Med Genet. 2003; 117C:42–48. [PubMed: 12561057]
15. Olivier M, Goldgar DE, Sodha N, Ohgaki H, Kleihues P, Hainaut P, Eeles RA. Li-Fraumeni and related syndromes: correlation between tumor type, family structure, and TP53 genotype. Cancer Res. 2003; 63:6643–6650. [PubMed: 14583457]
16. Moutou C, Le Bihan C, Chompret A, Poisson N, Brugieres L, Bressac B, Feunteun J, Lemerle J, Bonaiti-Pellie C. Genetic transmission of susceptibility to cancer in families of children with soft tissue sarcomas. Cancer. 1996; 78:1483–1491. [PubMed: 8839555]
17. Maurer HM. Rhabdomyosarcoma in childhood and adolescence. Curr Probl Cancer. 1978; 2:1–36. [PubMed: 109248]
18. Ruymann FB, Maddux HR, Ragab A, Soule EH, Palmer N, Beltangady M, Gehan EA, Newton WA Jr. Congenital anomalies associated with rhabdomyosarcoma: an autopsy study of 115 cases. A report from the Intergroup Rhabdomyosarcoma Study Committee (representing the Children's Cancer Study Group, the Pediatric Oncology Group, the United Kingdom Children's Cancer Study Group, and the Pediatric Intergroup Statistical Center). Med Pediatr Oncol. 1988; 16:33–39. [PubMed: 3277029]
19. Center for Disease Control and Prevention (CDC). Birth Defects: Frequently asked questions. Atlanta: 2006.
20. Pappo, A., editor. Pediatric Bone and Soft Tissue Sarcomas. Heidelberg: Springer; 2006.
21. Linabery AM, Ross JA. Trends in childhood cancer incidence in the U.S. (1992–2004). Cancer. 2008; 112:416–432. [PubMed: 18074355]
22. Surveillance, Epidemiology, and End Results (SEER) Program (www.seer.cancer.gov) Limited-use Data (1975–2005). National Cancer Institute, DCCPS, Surveillance Research Program, Cancer Statistics Branch, released April 2008, based on the November 2007 submission.
23. Zippin C, Lum D, Hankey BF. Completeness of hospital cancer case reporting from the SEER Program of the National Cancer Institute. Cancer. 1995; 76:2343–2350. [PubMed: 8635041]
24. Fritz, AG. World Health Organization. International classification of diseases for oncology : ICD-O. Geneva: World Health Organization; 2000.
25. Steliarova-Foucher E, Stiller C, Lacour B, Kaatsch P. International Classification of Childhood Cancer, third edition. Cancer. 2005; 103:1457–1467. [PubMed: 15712273]
26. SEER*Stat software Version 6.3.6. Bethesda, MD: Surveillance Research Program, National Cancer Institute; (www.seer.cancer.gov/seerstat)
27. Joinpoint Regression Program, Version 3.0. Bethesda, MD: Statistical Research and Applications Branch, National Cancer Institute; 2005 April. (http://srab.cancer.org/joinpoint).
28. Ederer F, Axtell LM, Cutler SJ. The relative survival rate: a statistical methodology. Natl Cancer Inst Monogr. 1961; 6:101–121. [PubMed: 13889176]
29. Brown CC. The statistical comparison of relative survival rates. Biometrics. 1983; 39:941–948. [PubMed: 6671129]
30. International Classification of Diseases for Oncology. Geneva: World Health Organization; 2000.
31. International Classification of Disease for Oncology. Geneva: World Health Organization; 1992.
32. International Classification of Diseases for Oncology (ICD-O). Geneva: World Health Organization; 1976.
33. Newton WA Jr, Gehan EA, Webber BL, Marsden HB, van Unnik AJ, Hamoudi AB, Tsokos MG, Shimada H, Harms D, Schmidt D, et al. Classification of rhabdomyosarcomas and related sarcomas. Pathologic aspects and proposal for a new classification--an Intergroup Rhabdomyosarcoma Study. Cancer. 1995; 76:1073–1085. [PubMed: 8625211]
34. Qualman SJ, Coffin CM, Newton WA, Hojo H, Triche TJ, Parham DM, Crist WM. Intergroup Rhabdomyosarcoma Study: update for pathologists. Pediatr Dev Pathol. 1998; 1:550–561. [PubMed: 9724344]

35. Triche, TJ.; Hicks, J.; Sorensen, PHB. Diagnostic Pathologies of Pediatric Malignancies. In: Pizzo, PA.; Poplack, DG., editors. Principles and Practice of Pediatric Oncology. Philadelphia: Lippincott Williams & Wilkins; 2006.

36. Edwards RH, Chatten J, Xiong QB, Barr FG. Detection of gene fusions in rhabdomyosarcoma by reverse transcriptase-polymerase chain reaction assay of archival samples. Diagn Mol Pathol. 1997; 6:91–97. [PubMed: 9098647]

37. Hogler W, Blimkie CJ, Cowell CT, Inglis D, Rauch F, Kemp AF, Wiebe P, Duncan CS, Farpour-Lambert N, Woodhead HJ. Sex-specific developmental changes in muscle size and bone geometry at the femoral shaft. Bone. 2008; 42:982–989. [PubMed: 18337201]

38. Lae M, Ahn EH, Mercado GE, Chuai S, Edgar M, Pawel BR, Olshen A, Barr FG, Ladanyi M. Global gene expression profiling of PAX-FKHR fusionpositive alveolar and PAX-FKHR fusion-negative embryonal rhabdomyosarcomas. J Pathol. 2007; 212:143–151. [PubMed: 17471488]

39. Davicioni E, Finckenstein FG, Shahbazian V, Buckley JD, Triche TJ, Anderson MJ. Identification of a PAX-FKHR gene expression signature that defines molecular classes and determines the prognosis of alveolar rhabdomyosarcomas. Cancer Res. 2006; 66:6936–6946. [PubMed: 16849537]

40. Feinberg AP. Imprinting of a genomic domain of 11p15 and loss of imprinting in cancer: an introduction. Cancer Res. 1999; 59:1743s–1746s. [PubMed: 10197590]

41. Barr, FG.; Meyer, WH. Rhabdomyosarcoma: An overview of biology, clinical features and the currentChildren's Oncology Group studies. ASCO Educational Book. Alexandria, Virginia: American Society for Clinical Oncology; 2008.

42. Barr FG. Gene fusions involving PAX and FOX family members in alveolar rhabdomyosarcoma. Oncogene. 2001; 20:5736–5746. [PubMed: 11607823]

43. Papaefthymiou MA, Giaginis CT, Theocharis SE. DNA repair alterations in common pediatric malignancies. Med Sci Monit. 2008; 14:RA8–RA15. [PubMed: 18160950]

44. Mosor M, Ziolkowska I, Januszkiewicz-Lewandowska D, Nowak J. Polymorphisms and haplotypes of the NBS1 gene in childhood acute leukaemia. Eur J Cancer. 2008

45. McNeil DE, Cote TR, Clegg L, Mauer A. SEER update of incidence and trends in pediatric malignancies: acute lymphoblastic leukemia. Med Pediatr Oncol. 2002; 39:554–557. discussion 552-3. [PubMed: 12376977]

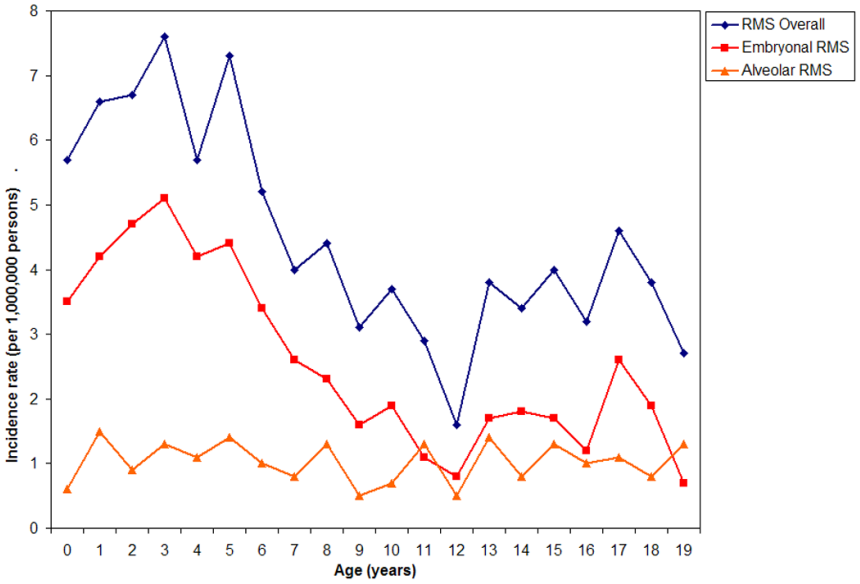

Figure 1.

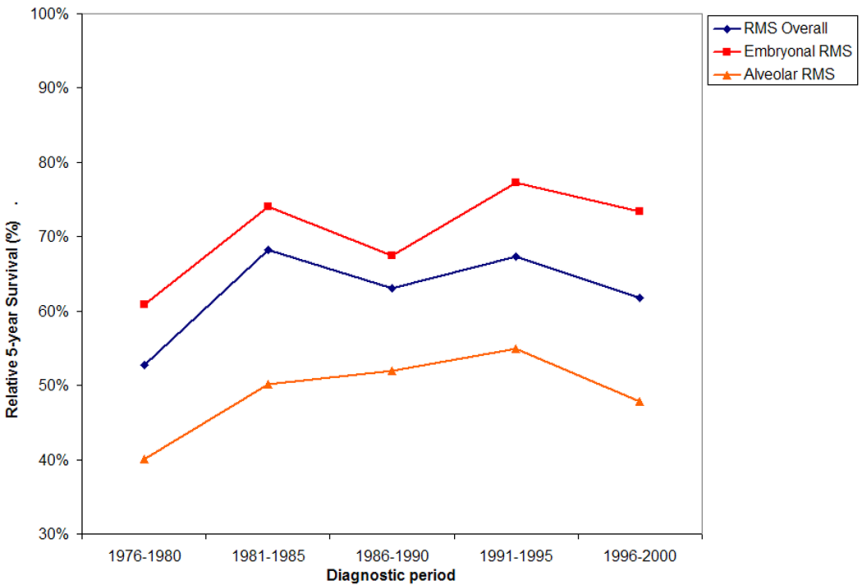

Figure 2.

Table 1

Frequencies and incidence rates of RMS in SEER registries.

	Reference period: 1975–2005; SEER 9 registries					
	RMS Overall		**Embryonal RMS**		**Alveolar RMS**	
	No. (%)	**Incidence Rate***	**No. (%)**	**Incidence Rate***	**No. (%)**	**Incidence Rate***
Total	987 (100.0%)	4.5	564 (100.0%)	2.6	227 (100.0%)	1.0
APC† (95% CI‡)	0.52 (−0.25 – 1.31)		−0.41 (−1.52 — 0.71)		4.20 (2.60 – 5.82)	
Sex						
Male	581 (58.9%)	5.2	345 (61.2%)	3.1	118 (52.0%)	1.1
Female	406 (41.1%)	3.8§	219 (38.8%)	2.0§	109 (48.0%)	1.0
Age						
0–4 years	352 (35.7%)	6.5	236 (41.8%)	4.3	59 (26.0%)	1.1
5–9 years	259 (26.2%)	4.8	155 (27.5%)	2.9	55 (24.2%)	1.0
10–14 years	171 (17.3%)	3.1	81 (14.4%)	1.5	51 (22.5%)	0.9
15–19 years	205 (20.8%)	3.7	92 (16.3%)	1.6	62 (27.3%)	1.1
Race						
White	775 (78.5%)	4.6	453 (80.3%)	2.7	171 (75.3%)	1.0
Black	146 (14.8%)	4.9	82 (14.5%)	2.7	39 (17.2%)	1.3
American Indian/Alaskan Native, Asian/Pacific Islander	64 (6.5%)	2.9	29 (5.1%)	1.3	16 (7.0%)	0.7
	Reference period: 1992–2005; SEER 13 registries					
	RMS Overall		**Embryonal RMS**		**Alveolar RMS**	
	No. (%)	**Incidence Rate***	**No. (%)**	**Incidence Rate***	**No. (%)**	**Incidence Rate***
Ethnicity						
Hispanic	148 (100.0%)	3.6	81 (54.7%)	1.9	39 (26.4%)	1.0
APC† (95% CI‡)	1.54 (−1.73 – 4.92)‖		¶		¶	

*Incidence rate per 1,000,000 person-years, age-adjusted to the 2000 U.S. Standard population.

†APC: Annual percent change calculated via weighted least squares regression

‡95% CI: 95% confidence interval

§The rate among females is significantly different than the rate among males ($p<0.0001$).

//Trend calculation involves one or more years with <10 cases and should be interpreted with caution.

¶The statistic could not be calculated.

Table 2

Relative 5-year survival rates of rhabdomyosarcomas in SEER registries for the diagnostic period 1996–2000.

	SEER 9 registries								
	RMS Overall			Embryonal RMS			Alveolar RMS		
	No. (%)	5-year Survival Rate (%)[*¶]	95% CI[†]	No. (%)	5-year Survival Rate (%)[*¶]	95% CI[†]	No. (%)	5-year Survival Rate (%)[*¶]	95% CI[†]
Total	166 (100.0%)	61.8[§//]	(54.3 – 69.2)	91 (100.0%)	73.4	(64.2 – 82.6)	50 (100.0%)	47.8	(33.9 – 61.7)
Sex									
Male	96 (57.8%)	64.4[§//]	(54.8 – 74.1)	53 (58.2%)	73.3[§]	(61.2 – 85.4)	27 (54.0%)	55.6	(36.8 – 74.4)
Female	70 (42.2%)	58.0	(46.3 – 69.7)	38 (41.8%)	73.4	(59.1 – 87.6)	23 (46.0%)	37.9	(17.6 – 58.2)
Age									
0–4 years	65 (39.2%)	70.5	(59.3 – 81.8)	42 (46.2%)	76.0	(62.9 – 89.1)	16 (32.0%)	68.1	(44.8 – 91.5)
5–9 years	46 (27.7%)	60.2	(45.8 – 74.5)	24 (26.4%)	78.5[§//]	(61.8 – 95.3)	16 (32.0%)	37.5	(13.8 – 61.3)
10–14 years	27 (16.3%)	59.3	(40.8 – 77.9)	11 (12.1%)	72.8	(46.4 – 99.2)	10 (20.0%)	40.0	(9.6 – 70.5)
15–19 years	28 (16.9%)	46.6	(28.0 – 65.1)	14 (15.4%)	57.3	(31.3 – 83.3)	8 (16.0%)	37.6[§//]	(3.9 – 71.2)
Race									
White	121 (72.9%)	59.0[//]	(50.1 – 67.8)	68 (74.7%)	73.0[§]	(62.3 – 83.8)	35 (70.0%)	39.4	(23.0 – 55.8)
Black	30 (18.1%)	66.8	(49.9 – 83.8)	14 (15.4%)	78.7	(57.1 – 100[‡])	10 (20.0%)	50.1	(19.0 – 81.2)
American Indian/ Alaskan Native, Asian/Pacific Islander	14 (8.4%)	71.5	(47.8 – 95.2)	9 (9.9%)	66.7	(35.9 – 97.6)	4 (8.0%)	100.0	(100.0 – 100.0)
	SEER 13 registries								
	RMS Overall			**Embryonal RMS**			**Alveolar RMS**		
	No. (%)	**5-year Survival Rate (%)[*]**	**95% CI[†]**	**No. (%)**	**5-year Survival Rate (%)[*]**	**95% CI[†]**	**No. (%)**	**5-year Survival Rate (%)[*]**	**95% CI[†]**
Ethnicity									
Hispanic	48 (100.0%)	50.2	(35.7 – 64.6)	28 (58.3%)	57.3[**]	(38.9 – 75.7)	13 (27.1%)	33.4	(6.7 – 60.1)

[*] 5-year relative survival rate calculated via actuarial method.

[†] 95% CI: 95% confidence interval

[‡] Upper confidence level truncated at 100%.

[§] Survival curve is significantly different from 1976–1980 curve ($p<0.05$).

[//] 1986–1990 survival curve is significantly different from 1976–1980 curve ($p<0.05$).

[¶] None of the 1996–2000 survival curves is significantly different from 1986–1990 curve.

[**] Survival curve is statistically significantly different than the curve among non-Hispanic white children ($p<0.02$).