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Trends in Incidence and Survival of Pediatric and Adolescent Germ Cell Tumors in the United States, 1975-2006

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Abstract

Background—Pediatric germ cell tumors (GCTs) are rare and heterogeneous tumors with uncertain etiology. We used data from the National Cancer Institute's Surveillance, Epidemiology and End Results (SEER) Program to evaluate trends in incidence and survival of GCTs in boys and girls ≤ 19 years of age. Few studies have evaluated trends in pediatric GCTs. Results from these analyses may provide clues to the etiology of GCTs.

Methods—Frequencies, incidence rates and five-year relative survival rates stratified by sex were evaluated overall and for demographic subgroups based on age (0-9 and 10-19 years), race (white, black, and other), and ethnicity (non-Hispanic and Hispanic) as sample size permitted.

Results—In whites, the incidence of GCTs was lower for females than males in the 10-19 year age group (RR=0.47, 95% CI 0.42—0.53) while the rates were similar in the 0-9 year age group. In contrast, incidence rates were higher in black females than in black males in both age groups (RR=2.01, 95%CI 1.08—3.84 in 0-9 year olds; RR=3.30, 95% CI 2.13—5.28 in 10-19 year olds). The incidence of ovarian GCT was significantly higher in Hispanic than non-Hispanic girls in the 10—19 year age group. Incidence rates increased during the study period in boys ages 10-19 (APC 1.2, 95% CI 0.4—2.1) and girls ages 0-9 (APC 1.9, 95% CI 0.3-2.5).

Conclusions—The incidence of pediatric GCTs in the United States is increasing only in certain subgroups, suggesting that the etiology is not completely overlapping in all age groups. Differences in incidence patterns by race and ethnicity merit further investigation.

Keywords

pediatric cancer; germ cell tumors; SEER; incidence

Introduction

Pediatric GCTs are rare and heterogeneous tumors hypothesized to occur as a result of events *in utero*[1, 2], although the etiology is largely unknown. GCTs are grouped together due to their presumed common cell of origin, the primordial germ cell (PGC). During normal fetal development, PGCs originate in the embryonic yolk sac and then migrate to the gonads[3]. GCTs typically occur in the testes or ovaries; however, extragonadal GCTs can

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occur and have been hypothesized to result from abnormal germ cell migration during development[4]. GCTs are grouped into two broad classes including seminomas, comprised of the seminomas of the testes and dysgerminomas of the ovaries, and nonseminomas, comprised of yolk sac tumors, teratomas, embryonal carcinomas, and choriocarcinomas[5]. Teratomas are composed of tissues from all three germ layers (ectoderm, mesoderm and endoderm) and are the most common GCT in the ovary and extragonadal locations. Yolk sac tumors (endodermal sinus tumors) are the most common malignant GCT in the testes of infants and young boys[5].

The increasing incidence of testicular cancer in adults has been well documented[6-12]. This increase is thought to be the result of a birth cohort effect, which supports a role for prenatal exposures in the etiology of this malignancy[6, 10, 11]. In contrast, no clear trend in incidence has been observed in studies of pediatric testicular GCT, with several studies suggesting an increase in incidence[9, 12, 13] while others have observed no significant change in incidence[14-16]. Survival is favorable for boys with GCTs[17], which can be attributed to the effectiveness of platinum based chemotherapy in these tumors[18-20].

Trends in incidence of GCTs in girls have not been studied extensively. Several recent analyses using data from the NCI's Surveillance, Epidemiology and End Results (SEER) Program[21] have evaluated ovarian GCTs in both the pediatric and adult populations[22-25]. These data suggest that the incidence of ovarian GCTs has not changed significantly[22]. Similar to testicular GCTs, the survival rate is very high for ovarian GCTs[22-24].

In recent publications from our group[17, 26], we reported on incidence (1992-2004) and five year survival trends (1975-1999) for pediatric cancers, including GCTs overall, using data from the SEER Program[21]. In this analysis, we have evaluated GCTs in considerably more detail in a larger dataset with longer follow-up (1975-2006). Specifically, we have evaluated frequencies, incidence and survival by *tumor location* and *histology*, which may provide clues to the etiology of these tumors.

Methods

Using data from the NCI's SEER Program[21], we analyzed incidence and survival of pediatric and adolescent GCTs in boys and girls, overall and by tumor location and histologic subtype as previously described[17, 26]. We used data from the SEER 9 registries, which actively collects information on demographics, tumor site and morphology, stage at diagnosis, and vital status from nine cancer registries in five states (Connecticut, Hawaii, Iowa, New Mexico, and Utah) and four metropolitan areas (Atlanta, Detroit, San Francisco-Oakland, and Seattle-Puget Sound)[27]. The SEER 9 registries represent ~9% of the U.S. population[27] with an estimated case ascertainment rate of 98%[28]. We included first malignancies diagnosed from 1975—2006 among individuals ≤ 19 years of age. Moreover, data from the SEER 13 registries (SEER 9 registries plus Los Angeles, San Jose-Monterey, Rural Georgia and the Alaskan Native Tumor Registry) were used to evaluate incidence and survival by ethnicity (non-Hispanic vs. Hispanic).

International Classification of Disease for Oncology, 3rd edition (ICD-O-3)[29] histology and topology codes included in the International Classification of Childhood Cancer (ICCC), 3rd Edition[30] categories Xb. (malignant extracranial and extragonadal GCTs) and Xc. (malignant gonadal GCTs) were used to classify GCTs. In this analysis, we included only GCTs coded as malignant in the SEER database. For analyses by tumor location, we stratified the tumors into gonadal (topography codes C56.9, C62.0-C62.9) and extragonadal (C00.0-C55.9, C57.0-C61.9, C63.0-C69.9, C73.9-C75.0, C75.4-C76.8, C80.9). The following histology categories were evaluated: germinoma (ICCC 9060-9065), malignant

teratoma (9080-9084), embryonal carcinoma (9070-9072), yolk sac tumor (9071), choriocarcinoma (9100, 9103, 9104), and mixed GCT (9085, 9101, 9102, 9105).

This analysis used existing data with no personal identifiers; therefore, the study was exempt from review by the University of Minnesota Institutional Review Board.

Statistical Analysis

Frequencies and age-adjusted incidence rates were calculated using SEER*STAT software[31]; incidence rates are reported as the number of cases per 1,000,000 person-years of follow-up. The U.S. 2000 standard population was used in direct age standardization. Rate ratios (RR) were used to compare incidence rates in demographic subgroups. Trends in incidence rates were evaluated using the weighted least-squares regression in Joinpoint[32, 33]. The average annual percentage changes (APC) and corresponding 95% confidence intervals (CIs) were calculated using calendar year as the independent variable and the natural logarithm of the age-adjusted incidence rate as the dependent variable. Joinpoints, which are points in time where a trend changes, were not permitted. The APC was considered significant if the confidence interval did not include 0.

The life tables method in SEER*Stat [31, 34] was used to calculate five-year relative survival rates and corresponding standard errors for five 5-year diagnostic cohorts (1976-1980, 1981-1985, 1986-1990, 1991-1995, 1996-2000). SEER follow-up rates into 2006 were high for both males and females aged 0-19 years (94% and 93%, respectively)[27]. Relative survival rates are ratios of observed-to-expected survival and are reported as percentages. The expected rates were based on data from the National Center for Health Statistics and take into account differences in distributions of age, sex, race, and year of diagnosis. Relative rates were adjusted if they exceeded 100%, increased over time, or involved heterogeneity in withdrawal (exact method). We used Z tests to compare relative survival rates across cohorts[35].

All analyses were stratified by sex. Incidence and survival were evaluated for the entire cohort and for demographic subgroups based on age (0-9 and 10-19 years), race (white, black, and other [includes American Indian/Alaskan Native, Asian/Pacific Islander]), and ethnicity (non-Hispanic and Hispanic) as sample size permitted.

Results

Incidence

Malignant GCTs were recorded in the SEER registry in 1,140 boys and 970 girls from 1975—2006. Incidence peaks were observed before age 1 year and from age 15—19 years in both boys and girls (Figure 1). Gonadal and extragonadal tumors were equally represented in boys diagnosed prior to age 4 years while the majority of tumors diagnosed after age 10 years were located in the testes (Figure 1A). In girls, the tumors diagnosed before age 4 years were comprised almost exclusively of extragonadal tumors while the majority of tumors diagnosed after age 10 years were mainly located in the ovaries (Figure 1B).

In infants and young children, teratomas and yolk sac tumors were the most common tumor type in both boys and girls (data not shown). Tumors with non-seminoma histology (teratoma, embryonal carcinoma and mixed GCTs) were the most common histologic subtypes in boys diagnosed after the age of 10 years. Germinomas and teratomas were the most common tumor types in adolescent girls.

There were no statistically significant differences in incidence of GCTs overall in boys or girls diagnosed before age 10 years by race; however, differences were observed by tumor

location (Table 1). The incidence of gonadal tumors was higher in boys in the other race category than in white boys ages 0-9 years (RR=2.16, 95% CI 1.31—3.44). In adolescent boys, the incidence was highest for whites and lowest for blacks, overall and for gonadal GCTs (Table 1). This difference was noted for most histologic subtypes as well. In contrast, for adolescent girls, the incidence was significantly higher in blacks than in whites for GCTs overall. The incidence of gonadal GCTs was significantly higher in girls in the other race category than in whites (RR=1.48, 95% CI 1.10—1.95), and the incidence of extragonadal GCTs was significantly higher in blacks than in whites (RR=2.44, 95% CI 1.41—4.08). The incidence of teratomas was significantly higher in both blacks and the other race category than whites for girls in this age category (RR=1.57, 95% CI 1.03—2.44 and RR=1.68, 95% CI 1.03—2.68, respectively).

Differences were also observed in the ratio of incidence in males and females in different racial groups. In whites, the incidence of GCTs was lower for females than males in the 10-19 year age group (RR=0.47, 95% CI 0.42—0.53) while incidence was similar in the 0-9 year age group (RR=1.01, 95% CI 0.80—1.29). In contrast, incidence rates were higher in black females than in black males in both age groups (RR=2.01, 95%CI 1.08—3.84 in 0-9 year olds; RR=3.30, 95% CI 2.13—5.28 in 10-19 year olds). In the “other” race category, no significant differences in incidence were observed by sex in either age group (RR=0.56, 95% CI 0.28—1.08 for 0-9 year olds; RR=1.11, 95% CI 0.76—1.61 for 10-19 year olds).

There were no significant differences in incidence of GCTs overall, by tumor location, or by tumor histology in non-Hispanic vs. Hispanic boys and girls ages 0—9 years. Similarly, no significant differences in incidence were observed by ethnicity in 10-19 year old boys, overall or by tumor location (Table 1). We did observe a higher incidence of mixed GCTs in Hispanic boys than in non-Hispanic boys in this age group (RR=1.39, 95% CI 1.09—1.76). The incidence of GCTs overall was higher in 10—19 year old girls with Hispanic ethnicity, and this difference was due to the increased incidence of gonadal GCTs in this subgroup (RR=1.39, 95% CI 1.10—1.75).

Incidence Trends

Trends in incidence of GCTs during the period 1975-2006 are shown in Figure 2. There was no evidence for an increase in incidence of GCTs in boys ages 0-9 years (APC −0.3, 95%CI −1.9-1.5). In contrast, we observed a statistically significant increase in incidence during the study period in boys ages 10-19 years (APC 1.2, 95% CI 0.4—2.1). In girls, the data suggest that incidence of GCTs increased in ages 0-9 years (APC 1.9, 95% CI 0.3-2.5) while no increase was seen in ages 10-19 years (APC −0.1, 95% CI −0.8-0.7). These findings should be interpreted with caution because all subgroups included <10 cases in several years. The small sample size did not permit evaluation of incidence trends by tumor location, tumor histology or race/ethnicity.

Survival Rates

Five-year relative survival rates for GCTs overall were high in all age groups. For example, in the diagnostic period 1996-2000, 5-year relative survival was 94.1 (95% CI 75.8-98.7) in boys ages 0-9 years, 94.5 (95% CI 89.0-97.2) in boys ages 10-19 years, 89.3 (95% CI 69.2-96.6) in girls ages 0-9 years, and 97.7 (95% CI 90.5-99.5) in girls ages 10-19 years. Five-year relative survival rates differed by tumor location with more favorable survival for gonadal tumors than for extragonadal tumors (Figure 3). Significant improvements in survival from gonadal GCTs were observed in all diagnostic periods compared with the 1976—1980 diagnostic period in boys ages 10-19 years, and survival was higher for extragonadal tumors in this age group for 1996—2000 compared with 1976—1980 and 1986—1990. For females, survival improved significantly for the 1996—2000 period

compared with 1976—1980. The difference in survival between gonadal and extragonadal tumors was more pronounced in boys than girls and decreased in more recent diagnostic periods. Survival was significantly higher for extragonadal tumors during the 1996—2000 diagnostic period compared with the 1976—1980 and the 1981—1985 periods in 0-9 year old boys ($p < 0.05$). Survival was especially poor for extragonadal tumors during the 1976—1980 diagnostic period in adolescent boys and girls, with marked improvement over time. The small sample size precludes analysis of survival by tumor histology and race/ethnicity.

Discussion

We have evaluated incidence and survival of pediatric and adolescent GCTs during the period of 1975-2006 using data from the SEER Program. This relatively large dataset has allowed us to evaluate incidence overall in boys and girls, and also for subgroups based on tumor location and histology. No significant differences in incidence rates by race or ethnicity were observed in children diagnosed between ages 0-9 years; however, statistically significant differences were observed in the older age group. Moreover, incidence rates increased significantly during the study period for boys in the 10-19 year age group and girls in the 0-9 year age group.

The distribution of tumors by location differed in the pediatric and adolescent age groups, with extragonadal tumors comprising a larger percentage of tumors diagnosed in children before the age of 4 years than children diagnosed after age 10 years. Previous reports have estimated that 40-55% of pediatric GCTs are found in extragonadal locations[36-40] while only 5-10% of GCTs in adults are found in extragonadal locations[3, 41]. This difference is hypothesized to be due to differences in the maturity of the germ cells that give rise to the tumors in these age groups[4]. Pediatric GCTs likely originate from a PGC that underwent immediate reprogramming to become a pluripotent embryonic germ cell, while GCTs in adolescents and young adults most likely originate from more mature PGCs[42], which may be unable to survive outside of the normal niches of the ovary and testis or specialized sites such as the thymus, in the case of mediastinal GCTs.

The incidence of GCTs was similar in boys and girls in the 0-9 year age group while the incidence was much higher in boys in the 10-19 year age group. This is thought to be due to the more limited number of germ cells in females in the mature ovaries[43, 44]. Incidence patterns differed by tumor location in boys and girls. Several factors may contribute to these differences. The higher rate of gonadal GCTs in young boys may reflect a more permissive environment in the immature testis than in the immature ovary. Another factor may be physiologic differences between the sexes: in females, germ cells undergo a prenatal meiotic arrest that persists until puberty, whereas in males, mitotic proliferation of germ cells resumes shortly after birth and continues throughout childhood[45]. Yet another factor may be the lower number of germ cells in young girls, owing to apoptosis of germ cells during development. In this context, it is particularly interesting that when germ cell apoptosis is inhibited in a mouse model, a population of ectopic germ cells with delayed maturation can be identified in the sacral/tail region specifically in female mice[46]. If a similar phenomenon occurs in humans, it may be that germ cells escaping developmental apoptosis go on to form sacrococcygeal tumors, particularly in girls.

The increase in incidence of testicular GCTs in young adults during the past half century has been well documented in the literature[6-12]. These data from the SEER Program support other reports that GCTs are increasing in adolescent males; however, there is no corresponding increase in incidence in the younger pediatric male age group. In contrast, we observed increasing incidence of GCTs in girls in the pediatric age group (0-9 years) but no

corresponding increase in adolescent girls (10-19 years). These data suggest that differing etiologic factors are involved in GCTs in different age groups and by sex.

Evidence suggests that at least some risk factors, such as cryptorchidism[47, 48], overlap for pediatric and adult testicular GCTs; however, the distinct clinical[3, 19, 49, 50] and genetic profiles[51-53] of pediatric and adult GCTs provide support for distinct etiologies. Several mechanisms have been hypothesized for the increase in testicular GCTs in males, with much attention focused on exposure to estrogens and environmental hormone disruptors[54]; however, the exact mechanism is not clear. Epidemiologic studies have evaluated the role of *in utero* hormone exposure in both adult TGCT[1, 2, 55, 56] and in pediatric GCTs[40, 57, 58], with conflicting results. Endocrine disrupting agents, including persistent organochlorine pesticides (POP)[59-61] and polychlorinated biphenyls[59, 62] have also been investigated in epidemiologic studies of adult TGCT, with evidence suggesting that POPs[60] may be associated with increased risk. Data from *in vitro* and *in vivo* studies provides evidence that exposure to estrogens and endocrine disruptors may influence germ cell apoptosis[63-66] and stimulate cell proliferation[67, 68]. Exposure to these chemicals has increased over time and could be responsible for the observed increase in incidence. Further investigation will be required to draw definitive conclusions on the role of these agents in risk of GCTs, especially in girls.

We observed different patterns of GCT incidence by race and ethnicity in males and females. In the adolescent age group, the incidence was significantly higher in white males than in males in the other race groups. This higher incidence of testicular GCT in adult white males has been well-documented in the literature[10, 69, 70]. In contrast, incidence rates were significantly lower in white females in the adolescent age category compared with females in the other race categories. In addition, higher incidence of gonadal GCTs was observed in Hispanic females in the 10-19 year age group. Previous studies have also reported differences in GCT incidence by race and ethnicity. A recent study of Southeast Asian Children in California reported a higher incidence of GCTs in Asians compared with non-Hispanic whites[71]. Previous reports have reported a higher incidence of GCTs in Hispanic children in the United States[72-74], and one of these studies found that the increased incidence was confined mainly to gonadal GCTs and reached statistical significance only in females[74]. Any explanations for these differing incidence patterns would be purely speculative; however, it is possible that genetic factors or differences in hormone levels may play a role.

Five-year relative survival rates are very high for pediatric GCTs, mainly due to the effectiveness of platinum-based chemotherapy[18-20]. While survival rates were high overall, differences were observed in survival rates by tumor location, with more favorable survival in tumors located in the gonads than in extragonadal locations. This finding is supported by numerous publications showing lower survival rates in pediatric GCTs in extragonadal locations[38, 75, 76]. Differing survival rates based on extragonadal location have also been reported[38, 77], unfortunately the number of cases in this analysis was not sufficient to stratify by extragonadal location. The higher survival rate in gonadal than extragonadal tumors has been hypothesized to be due to more complete tumor excision in tumors located in the gonads[19]. Other potential explanations for the higher survival rate for gonadal GCTs include differences in sensitivity to chemotherapy and induction of apoptosis.

The SEER dataset has many strengths, including a high rate of case ascertainment and high quality data. However; several limitations must also be considered. The SEER 9 registries provide population-based ascertainment of cancer cases for approximately 9% of the US population. Differences in demographic characteristics[78] and cancer incidence rates[79] may exist in the 91% of the population not covered by the SEER 9 registries. Teratomas in

children are frequently considered benign, and misreporting of these tumors is a possibility. Clinical and diagnostic practices have changed during the long time period of case ascertainment for this analysis (1975—2006), which may have influenced our results. Improved imaging and diagnosis would most likely lead to an increasing incidence over time. Since we observed increasing incidence rates in some subgroups, this is unlikely to completely explain the increases observed here. The large number of tests we have conducted leads to the possibility that some findings may be due to chance. The small numbers in some analyses, particularly for analyses of tumor histology, is also a limitation of this analysis as unstable estimates caused by small cells could lead to spurious findings.

In summary, this analysis of the SEER data suggests that the incidence of GCTs may be increasing in young girls (0-9 years) in addition to the well-documented increase in adolescent males (10-19 years). This analysis also highlights differences in incidence patterns in racial and ethnic subgroups. These findings should be explored further as they may shed light on the etiology of this poorly understood group of tumors.

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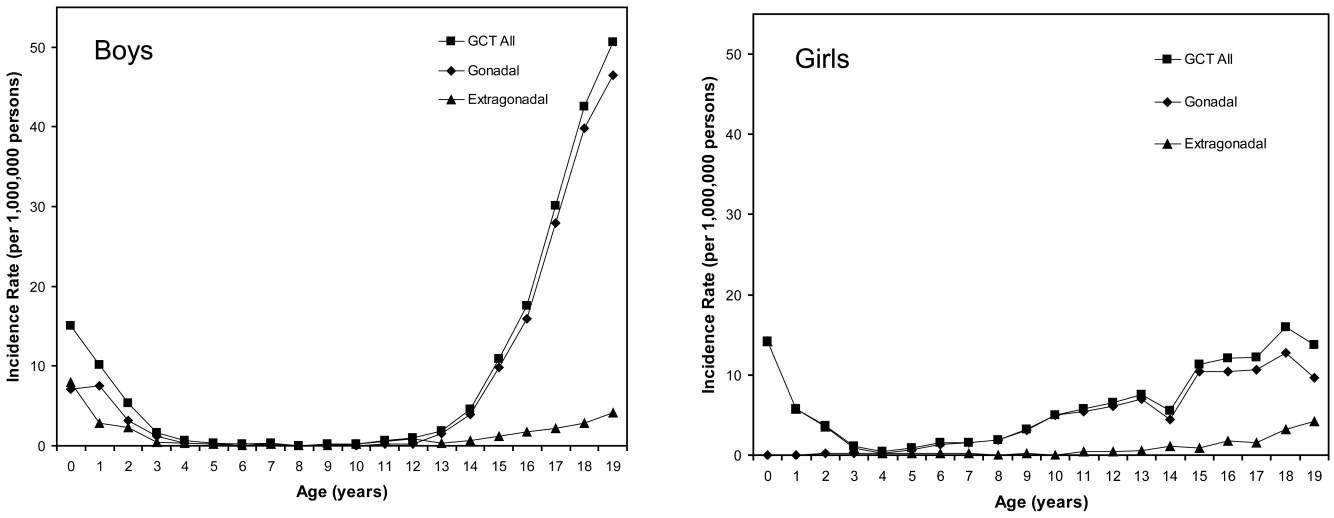

Figure 1.
Incidence of pediatric GCT by tumor location in boys and girls in the SEER registry, 1975—2006.

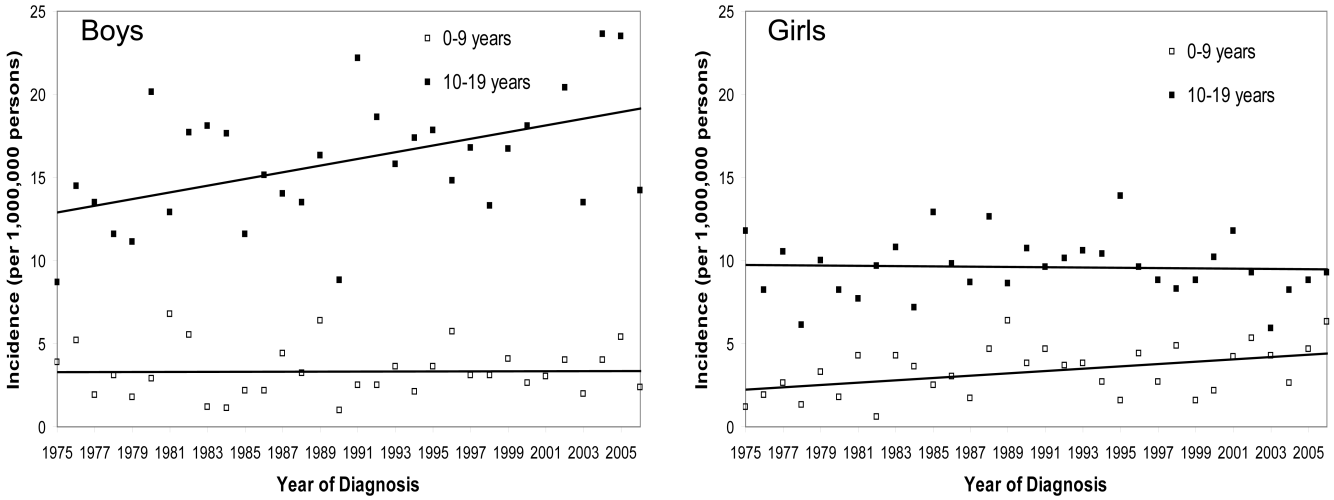

Figure 2.
Incidence trends in pediatric GCTs in boys and girls by age group (1975—2006).

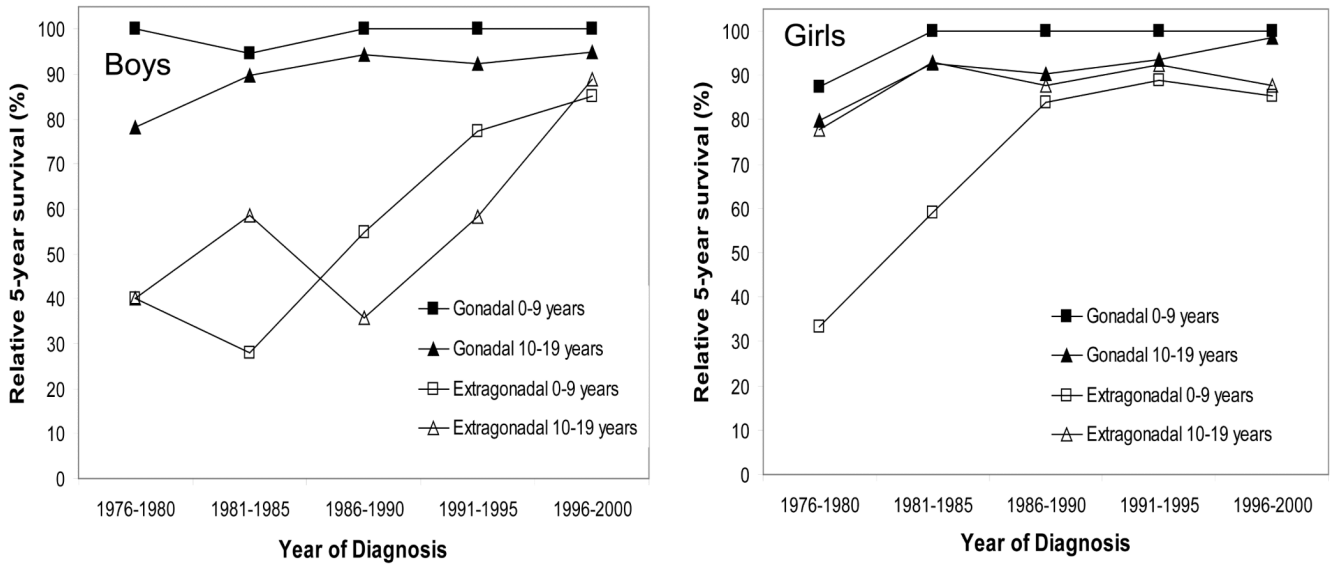

Figure 3.
Five-year relative survival rates for boys and girls for 5-year diagnostic periods by age group and tumor location

Table 1

Frequency and incidence rates of pediatric germ cell tumors by race, ethnicity, and age group in girls and boys in the NCI Surveillance, Epidemiology and End Results Registry, overall and by tumor location

	Boys						Girls					
	Overall		Gonadal		Extragonadal		Overall		Gonadal		Extragonadal	
	N[1] (%)	Incidence Rate	N[1] (%)	Incidence Rate	N[1] (%)	Incidence Rate	N[1] (%)	Incidence Rate	N[1] (%)	Incidence Rate	N[1] (%)	Incidence Rate
Age Group: 0-9 years												
Race[4]												
White	149 (76)	3.3	83 (73)	1.8	66 (81)	1.4	141 (75)	3.3	41 (84)	1.0	100 (71)	2.3
Black	17 (9)	2.1	7 (6)	0.9	10 (12)	1.2	33 (17)	4.2	5 (10)	0.6	28 (20)	3.5
American Indian/ Alaskan Native, Asian/Pacific Islander	29 (15)	4.8	24 (21)	4.02	5 (6)	0.8	15 (8)	2.7	3 (6)	0.6	12 (9)	2.1
Ethnicity[5]												
Non-Hispanic	114 (67)	3.6	58 (62)	1.8	56 (73)	1.8	126 (74)	4.2	35 (66)	1.2	91 (71)	3.0
Hispanic	56 (33)	4.3	35 (38)	2.7	21 (27)	1.6	45 (26)	3.8	18 (34)	1.7	27 (21)	2.1
Age Group: 10-19 years												
Race[4]												
White	853 (91)	18.6	787 (92)	17.1	66 (78)	1.4	384 (72)	8.8	331 (72)	7.6	53 (69)	1.2
Black	27 (3)	3.6[2]	23 (3)	3.1[2]	4 (5)	0.5[2]	89 (17)	11.8[2]	67 (15)	8.9	22 (29)	2.9[2]
American Indian/ Alaskan Native, Asian/Pacific Islander	58 (6)	10.8[2]	43 (5)	7.8[2]	15 (18)	2.7	62 (12)	11.6	60 (13)	11.2[2]	2 (3)	0.4
Ethnicity[5]												
Non-Hispanic	542 (72)	17.7	501 (72)	16.4	41 (73)	1.3	277 (69)	9.2	250 (70)	8.3	27 (64)	0.9
Hispanic	209 (28)	20.8	194 (28)	19.3	15 (27)	1.5	124 (31)	13.2[3]	109 (30)	11.5[3]	15 (36)	1.6

[1] Number of cases in SEER registry, 1975–2006

[2] Rate is significantly different than rate in white

[3] Rate is significantly different than rate in non-Hispanic

[4] Incidence data from the SEER 9 Registries, 1975-2006

[5] Incidence data from the SEER 13 Registries, 1992-2006