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HIGHLIGHTS

Incidence

- While germ cell, trophoblastic and other gonadal (GCTOG) tumors represented 16% of all cancers among adolescents between 15 and 19, they represented only 7% of cancer diagnoses among children younger than 20 (incidence 12.0 per million) and 3.5% of cancer diagnoses for children younger than 15 (incidence 5.4 per million) (Table X.4).
- In the US, approximately 900 children and adolescents younger than 20 years of age are diagnosed with germ cell tumors each year.
- The majority (61%) of GCTOG tumors occurring among children younger than 20 years are gonadal (ovarian or testicular) germ cell tumors (Table X.1). However, when only children younger than 15 years of age are considered, non-gonadal germ cell tumors are more common than gonadal germ cell tumors (Table X.4).
- For males, the incidence rates of testicular (Xc) and non-CNS extragonadal (Xb) germ cell tumors were similar during the first year of life at approximately 9 per million, and then declined to very low levels by age 4. Between ages 4 and 15 the rates of testicular germ cell tumors remained very low, but between ages 15 and 19 years of age, the incidence rates increased dramatically (Figure X.2).
- For females, ovarian (gonadal) germ cell tumors (Xc) began to increase in incidence at age 8-9 years and peaked at age 18 (20 per million) (Figure X.3). For males, the rate of testicular germ cell tumors (Xc) at age 19 was substantially higher than that observed for ovarian germ cell tumors among 19 year old females (44.5 versus 10.4 per million).
- White males younger than age 20 had much higher rates of testicular germ cell tumors (9.1 per million) than blacks males (1.2 per million). In contrast, white females younger than age 20 had slightly lower rates (4.5 per million) than black females (5.6 per million) for ovarian germ cell tumors (Table X.3).

Survival

- For patients younger than 20 years of age, females had slightly higher 5-year survival rates than males, and whites had somewhat higher 5-year survival rates than blacks for GCTOG tumors (Figure X.6).
- Increasing survival rates were observed between 1975-84 and 1985-94 for each subgroup of the ICCC for patients younger than 20 (Figure X.7). The overall 5-year relative survival rate for all subgroups combined increased from 77% to 87% (Figure X.6).
- The increase in survival between 1975-84 and 1985-94 was similar for ovarian and testicular germ cell tumors. Both increased from 82% to 93-94% (Figure X.7). Young males (<5 years) survived better than males aged 15-19.

Risk factors

- The etiology of malignant germ cell tumors is poorly understood. Cryptorchidism is the only confirmed risk factor for testicular germ cell tumors (see Table X.5 for references).

INTRODUCTION

Germ cell tumors are biologically diverse and histologically heterogeneous [1-3], with a substantial proportion having benign rather than malignant behavior (particularly among young children). Germ cell tumors originate in primordial germ cells, which may undergo germinomatous or embryonic differentiation. Primordial germ cells are initially detectable in the yolk sac of the four week embryo, and their migratory route during embryogenesis from the yolk sac to the gonads (either the testes or ovaries) may account for the primarily midline location of most extragonadal germ cell tumors [1].

Germ cell tumors are grouped together with trophoblastic and other gonadal neoplasms in the International Classification of Childhood Cancer (ICCC) [4]. For shorthand notation this entire group, ICCC X, will be abbreviated as GCTOG tumors. This diagnostic group is categorized into five subgroups according to the cells of origin of the cancer (germ cells, trophoblastic cells or other cells) and the location in the body of the cancer (gonads: testes or ovaries; central nervous system; or elsewhere) (see Table X.1).

In the US, approximately 900 children and adolescents younger than 20 years of age are diagnosed with germ cell tumors each year. Essential for understanding the incidence patterns for germ cell tumors of children and adolescents is recognition that the germ cell tumors of infancy and early childhood are biologically distinctive from those that arise in older children and adolescents [2,3]. Thus, tumors in the same ICCC subgroup may have very different biological characteristics and clinical behavior (Table X.2. [5]). The categorization of germ cell tumors in Table X.2 provides a

Table X.1: Average annual age-adjusted* incidence rates per million for germ cell trophoblastic and other gonadal cancers by sex and subtype, age <20 all races, SEER, 1986-95

ICCC Group X	Description	Total	Males	Females
X a-e	Germ cell, trophoblastic and other gonadal tumors	11.6	12.0	11.1
Xa	Intracranial and intraspinal germ cell tumors	1.6	2.3	0.9
Xb	Other and unspecified non-gonadal germ cell tumors. (This category includes the tumors of infants and young children that originate in the sacrococcygeal region, as well as mediastinal tumors primarily developing in older children.)	1.6	1.5	1.8
Xc	Gonadal germ cell tumors	6.7	8.0	5.3
	Testis	4.1	8.0	-
	Ovary	2.6	-	5.3
Xd	Gonadal carcinoma	1.4	0.1	2.9
	Ovary	1.3	-	2.6
	Other	0.1	0.1	0.3
Xe	Other and unspecified malignant gonadal tumors	0.2	0.1	0.3

*Adjusted to the 1970 US standard population

Table X.2: GCTOG tumors by sub-group, age and biological characteristics [5]

GCTOG TUMORS (ICCC X)	Site	Age	Characteristics
Intracranial and intraspinal germ cell tumors (ICCC Xa)	Intracranial (especially pineal region) [2]	Older children, adolescents and adults	Some, though not all, of these tumors have biological characteristics similar to those of testicular germ cell tumors in adolescents and young adults (e.g., an isochromosome of the short of chromosome 12 as discussed below) [6-9].
Non-CNS, Non-gonadal germ cell (ICCC Xb)	Sacrococcygeal/pelvic region [2]	Infants and young children	The biological characteristics of these tumors is similar to those of testicular germ cell tumors in young boys (see below), but different from those of testicular germ cell tumors in adolescents and young adults (see below).
"	Mediastinum [2]	Older children, adolescents and adults	Some, though not all, mediastinal germ cell tumors have biological characteristics similar to those of testicular germ cell tumors in adolescents and young adults (e.g., an isochromosome of the short of chromosome 12 as discussed below) [10,11].
Gonadal germ cell (ICCC Xc)	Testicular	Infants and young boys	The biological characteristics of these tumors are distinctive from those of testicular germ cell tumors in adolescents and young adults (see below). The tumors primarily show yolk sac tumor (endodermal sinus tumor) histology and are generally diploid or tetraploid. Recurring chromosomal abnormalities include deletions of chromosome 1p and 6q, but not isochromosome of the short arm of chromosome 12 [12-15].
"	Testicular	Adolescents and young adults	These typically possess an isochromosome of the short arm of chromosome 12 [5,16-19] and are aneuploid [12,19]
"	Ovary	Adolescents and adults	These show greater biological diversity than do germ cell tumors arising in the testes, and include malignant teratomas and other malignant germ cell tumors (e.g., dysgerminomas, yolk sac tumors, and mixed germ cell tumors). Like their testicular counterparts, they commonly show increased copies of the short arm of chromosome 12 [5].
Gonadal carcinomas (Xd)	Ovary	Adolescents and adults	These carcinoma tumors are not biologically related to the germ cell tumors and develop almost exclusively in the ovary.

basis for understanding the incidence patterns and trends of germ cell tumors in children.

A total of 2,065 children younger than 20 years of age were diagnosed with GCTOG tumors during the period 1975 through 1995 in the SEER areas. This represents 7% of all neoplasms diagnosed among children younger than 20 years of age: 3.5% of all neoplasms for children younger than 15 years of age and a much higher proportion, 13.9%, for 15-19 year olds. The majority (1,260 or 61%) of GCTOG tumors occurring among children younger than 20 years of age are gonadal (ovarian or testicular) germ cell tumors (Xc). However, when only children younger than 15 years of age are considered, non-gonadal germ cell tumors (Xa and Xb) are more common than gonadal germ cell tumors.

The GCTOG tumor group (ICCC X) includes 94% of the malignant testicular tumors and 99% of the ovarian tumors among children and adolescents. Six percent of malignant testicular tumors and less than 1% of ovarian tumors are sarcomas and are grouped under ICCC IX (soft tissue sarcomas). Excluding the sarcomas, nearly all of the testicular tumors in male children and adolescents were germ cell tumors, 98%. Excluding the small number of ovarian sarcomas, the histologic types of ovarian tumors in female children and adolescents were 64% germ cell (Xc), 33% carcinomas (Xd), and 3% other and unspecified (Xe).

INCIDENCE

Sex-specific incidence

Table X.1 shows the incidence of GCTOG tumors by sex for children younger than 20 years of age for the years 1986 to 1995. The incidence for males (12.0 per million) slightly exceeded that for females (11.1 per million). For males, the subgroup with the highest incidence was testicular germ cell tumors (8.0 per million). For females, ovarian germ cell tumors had the highest rate (5.3 per million). Intracranial and intraspinal germ cell tumors (ICCC Xa) were more common in males (2.3 per million) than in females (0.9 per million), and accounted for about 14 percent of all GCTOG tumors among those younger than 20 years of age. Non-gonadal germ cell tumors arising outside of the central nervous system (CNS), ICCC Xb, occurred with similar frequency among males and females. In contrast gonadal carcinomas were almost exclusively seen among females and most of these were ovarian gonadal carcinomas.

Table X.3: Average annual age-adjusted* incidence rates per million for germ cell trophoblastic and other gonadal cancers by race, sex, and subtype age <20, SEER, 1975-95

ICCC Group X	ICCC Germ Cell Tumor Category	White Male	Black Male	White Female	Black Female
X a-e	All	12.3	3.2	9.0	10.8
Xc	Gonadal germ cell tumors	9.1	1.2	4.5	5.6
	Testis	9.1	1.2	-	-
	Ovary	-	-	4.5	5.6
X a,b,d,e	Other than gonadal germ cell tumors	3.2	2.0	4.5	5.2

*Adjusted to the 1970 US standard population

Black-white differences in incidence

Black children had a lower incidence of germ cell tumors than white children (7.0 vs. 10.7 per million). This difference was primarily the result of a lower rate of gonadal germ cell tumors among blacks than whites. Table X.3 shows the incidence rates for gonadal germ cell tumors for children younger than 20 years of age for the years 1975 to 1995 by race and sex. Remarkably, the lower rates of gonadal germ cell tumors among black children were restricted to males. For children younger than 20 years of age, black males had a rate of testicular germ cell tumor that was only one-seventh that for white males (1.2 versus 9.1 per million), while black females had slightly higher rates of ovarian germ cell tumors than white females (5.6 versus 4.5 per million). The low rate of testicular germ cell tumors observed among young black males is consistent with the reported low incidence for testicular cancer among adult black males [20-22].

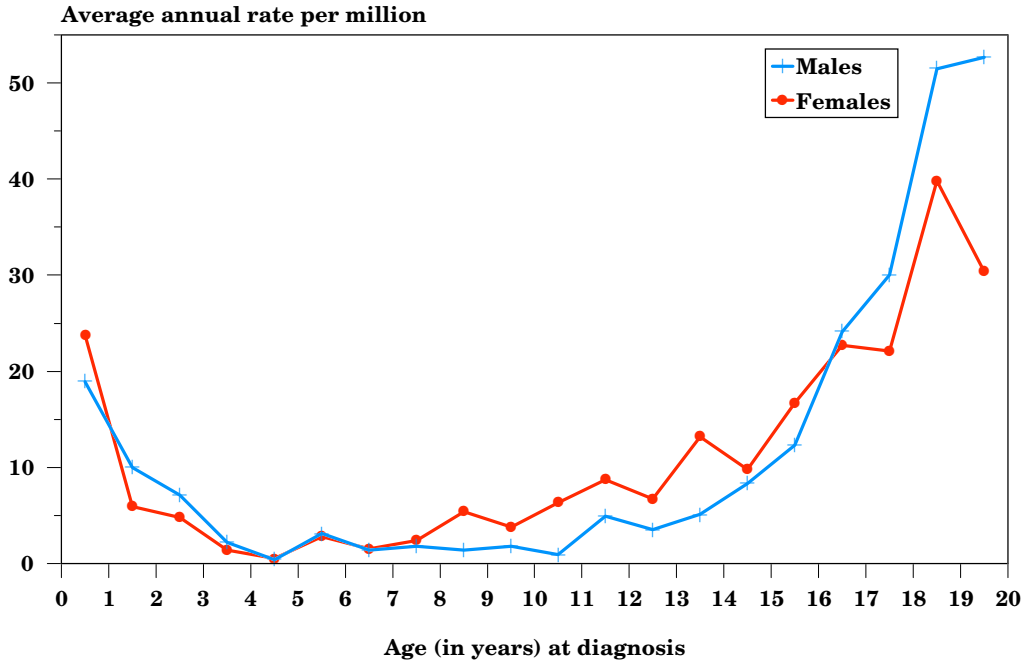
Age-specific incidence

Figure X.1 shows the age-specific incidence of GCTOG tumors by single year of age and sex.[1] Rates were relatively high in the first year of life and then declined to very low levels before increasing at age 8-12 years for females and at age 11-14 years for males. Incidence continued to increase for both males and females up through age 19. The distribution of tumor types by age was distinctive for males and females.

For males, the incidence rates of testicular (Xc) and non-CNS extragonadal (Xb) germ cell tumors were similar during the first year of life at approximately 9 per

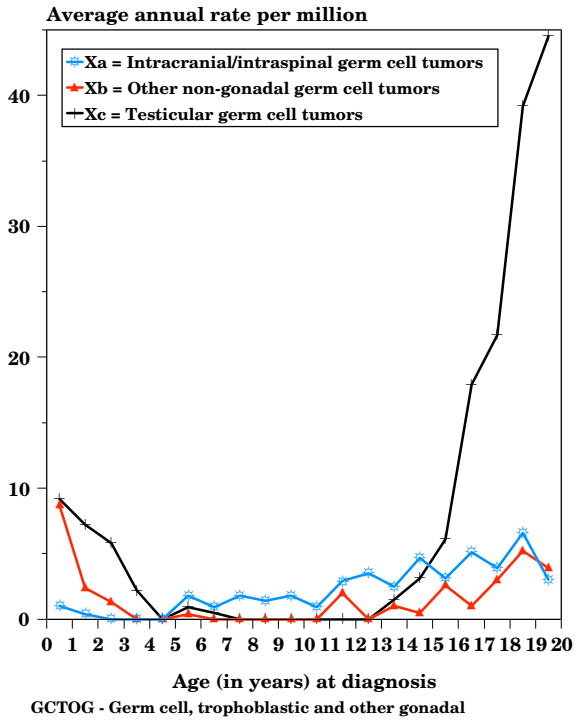
[1] Enumeration of the population at risk by single years of age was available only for the census year 1990. The US Bureau of the Census provides intercensal population estimates by 5-year age groups, but not by single years of age. Therefore, the population estimates for 1990 were used in rate calculations for cases diagnosed from 1986-94.

Figure X.1: GCTOG age-specific incidence rates by sex, all races, SEER, 1986-94



GCTOG - Germ cell, trophoblastic and other gonadal

Figure X.2: GCTOG age-specific incidence rates by selected ICCC subgroups, males all races, SEER, 1986-94



million, and then declined to very low levels by age 4 years (Figure X.2). Between ages 4 and 15 the rates remained very low, but between ages 15 and 19 years of age, the incidence rates increased dramatically.

For females, non-CNS extragonadal germ cell tumors (Xb) accounted for the vast majority of cases in the first year of life, with ovarian germ cell tumors (Xc) being extremely rare (Figure X.3). Most of the extragonadal germ cell tumors arising in the first year of life occurred in pelvic soft tissue (e.g., the sacrococcygeal region) and in the retroperitoneum. Gonadal germ cell tumors (Xc) began to increase in incidence for females at age 8-9 years, while gonadal carcinomas (Xd) began to increase after age 12. By age 19, the rate of gonadal carcinomas (Xd) was similar to ovarian germ cell tumors (Xc) in females. For males, the rate of testicular germ cell tumors (Xc) at age 19 was substantially higher than that observed for ovarian germ cell tumors among 19 year old females (44.5 versus 10.4 per million for age 19).

TRENDS

The age-adjusted incidence rates for GCTOG tumors increased between 1975-79 and 1990-95 from 3.7 to 5.4 per million for children younger than 15 years of age and from 8.5 to 12.0 per million for those younger than 20 years of age (Table X.4). For both males and females younger than 15 years of age, the increase in incidence primarily resulted from higher rates for intracranial and intraspinal germ cell tumors (Xa) and for non-CNS extragonadal germ cell tumors (Xb), while the rates of gonadal germ cell tumors (Xc) did not increase. The increased incidence of non-CNS extragonadal tumors (Xb) for both males and females was due in large measure to an increase in incidence in the first

Figure X.3: GCTOG age-specific incidence rates by selected ICCC subgroups females, all races, SEER, 1986-94

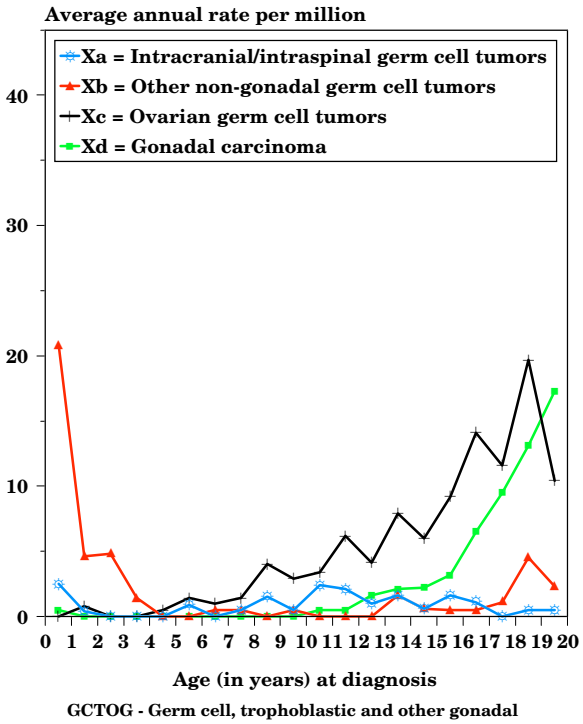


Table X.4: Average annual age-adjusted[1] incidence rates per million for germ cell trophoblastic, and other gonadal cancers by sex, age, subtype, and time period, all races, SEER, 1975-95

Sex/Age Group	Years	X(total)	Xa[2]	Xb[2]	Xc[2]	Xd[2]	Xe[2]
Total <15	1975-79	3.7	0.5	0.7	2.2	0.1	0.2
	1980-84	4.8	0.9	1.1	2.6	0.1	0.1
	1985-89	4.8	0.7	1.3	2.7	0.1	0.1
	1990-95	5.4	1.5	1.4	2.1	0.3	0.0
Males <15	1975-79	3.1	0.5	0.6	1.8	0.1	0.1
	1980-84	4.1	1.2	0.9	2.0	0.0	0.0
	1985-89	4.1	1.1	0.8	2.2	0.0	0.1
	1990-95	4.4	1.9	1.1	1.4	0.0	0.0
Females <15	1975-79	4.3	0.4	0.8	2.6	0.2	0.4
	1980-84	5.5	0.6	1.3	3.3	0.2	0.2
	1985-89	5.6	0.4	1.8	3.2	0.1	0.1
	1990-95	6.4	1.2	1.9	2.7	0.7	0.0
Total <20	1975-79	8.5	0.6	1.4	5.4	0.8	0.3
	1980-84	9.6	0.9	1.5	6.4	0.7	0.2
	1985-89	10.7	1.1	1.7	6.6	1.1	0.2
	1990-95	12.0	1.9	1.6	6.8	1.6	0.2
Males <20	1975-79	9.1	1.0	1.2	6.9	0.1	0.1
	1980-84	11.0	1.2	1.5	8.1	0.1	0.1
	1985-89	11.4	1.7	1.6	7.8	0.1	0.1
	1990-95	12.2	2.6	1.3	8.1	0.1	0.1
Female <20	1975-79	7.8	0.3	1.6	3.9	1.5	0.6
	1980-84	8.1	0.6	1.5	4.5	1.3	0.3
	1985-89	10.0	0.4	1.8	5.3	2.2	0.3
	1990-95	11.7	1.1	1.8	5.3	3.2	0.3

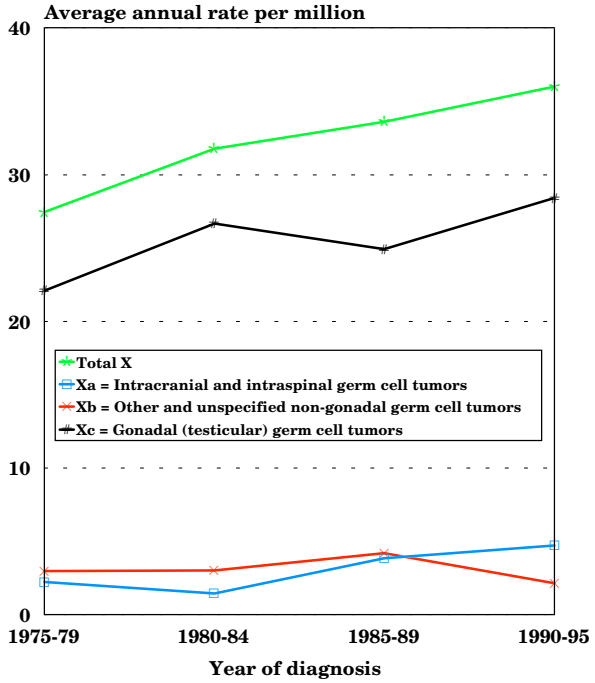
[1] Adjusted to the 1970 US standard population

[2] Xa = Intracranial and intraspinal germ cell tumors; Xb = Other and unspecified non-gonadal germ cell tumors; Xc = Gonadal (ovarian and testicular) germ cell tumors; Xd = Gonadal carcinoma; Xe = Other and unspecified malignant gonadal tumors.

year of life. This increase in non-CNS extragonadal malignant tumors among infants must be interpreted with caution, because non-malignant sacrococcygeal teratomas diagnosed in the newborn period outnumber malignant teratomas [3,23-25], and because careful inspection of mature and immature sacrococcygeal teratomas may show microscopic foci of yolk sac tumor [26,27]. Since nonmalignant sacrococcygeal teratomas are not reported and yolk sac tumors are reported, the increase in incidence in the first year of life may be the result of increasing recognition by pathologists of the need for careful scrutiny of apparently non-malignant sacrococcygeal teratomas. Almost all of the increase in the first year of life for females was in malignant teratomas/embryonal teratomas.

An increase in the age-adjusted incidence for GCTOG tumors was also observed for both sexes among those younger than 20 years of age. For males younger than 20 years of age, the increase in incidence was from 9.1 to 12.2 per million, with most of the increase attributed to intracranial and intraspinal germ cell tumors (Category Xa) and to testicular germ cell tumors (Category Xc). For females, the increase was from 7.8 to 11.7 per million, with most of the increase attributable to ovarian germ cell tumors

Figure X.4: Trends in GCTOG age-specific incidence rates by selected ICCC subgroups age 15-19, males, all races, SEER 1975-95



GCTOG - Germ cell, trophoblastic and other gonadal

(Category Xc) and to ovarian carcinomas (Category Xd). Because of the larger number of cases in the 15-19 year group compared to the younger than 15 year group, the trends for those younger than 20 years of age are primarily determined by trends for the 15-19 year age group.

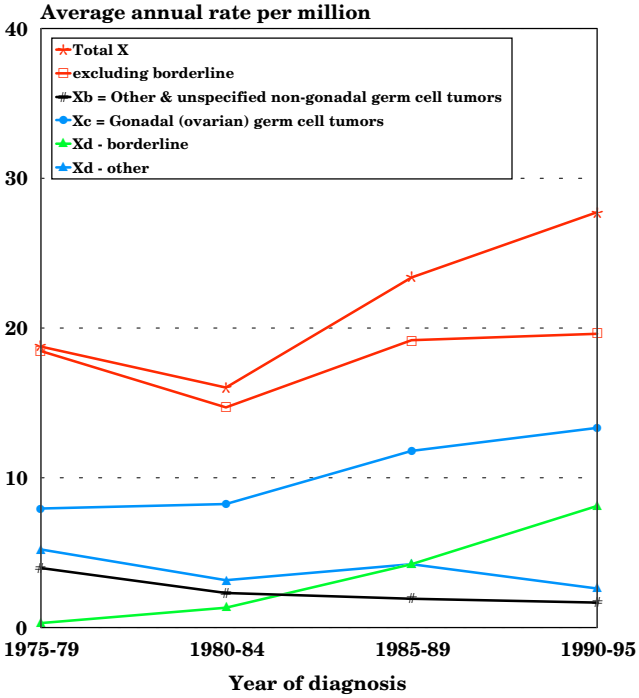
Figure X.4 illustrates the increase in incidence of testicular germ cell tumors (Xc) for the 15-19 year age group between 1975-79 (22 per million) and 1990-1995 (28 per million). The increase in incidence of testicular germ cell tumors for those 15-19 years of age is reminiscent of the increase in testicular cancer among adult males. Over the past 30-40 years, increased rates of testicular cancer have been reported from developed countries throughout the world, including the United States [21,22], European countries [28], Australia [29], and New Zealand [30].

The overall rate of GCTOG tumors for females aged 15-19 increased markedly from 1975-79 to 1990-95 (Figure X.5), but much of the increase was attributable to the inclusion of borderline tumors of the ovary which were not reportable cancers for the entire time period. Figure X.5 shows the overall rate for ICCC X for females both with and without the borderline tumors. With the borderline tumors excluded, the overall rate increased only slightly between 1975-79 and 1990-95 (Figure X.5), and this increase was driven by an increased incidence of ovarian germ cell tumors (8 per million for 1975-79 to 13 per million for 1990-95). An increased incidence for ovarian germ cell tumors in adults has also been reported [31,32].

SURVIVAL

For the period from 1985 to 1994, the 5-year survival rate for patients

Figure X.5: Trends in GCTOG age-specific incidence rates by selected ICCC subgroups age 15-19, females, all races, SEER, 1975-95



GCTOG - Germ cell, trophoblastic and other gonadal

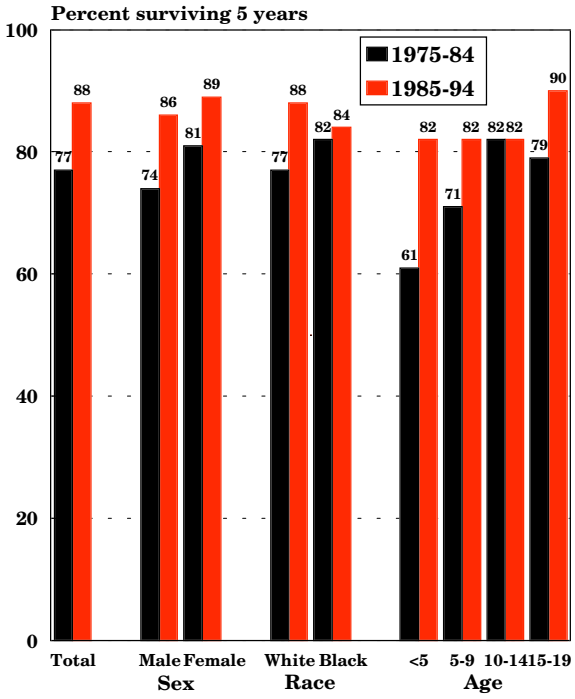
younger than 20 years of age with germ cell tumors was 87% (Figure X.6). Survival rates were better for the 15-19 year olds (5-year survival, 90%) than for the younger than 15 year olds (5-year survival, 84%). Other observations about outcome for children with germ cell tumors are illustrated in Figures X.6 and X.7 and include:

- For those younger than 20 years of age, females had slightly higher 5-year survival rates than males, and whites had somewhat higher 5-year survival rates than blacks (Figure X.6).

- Survival for patients younger than 20 years of age was better for gonadal germ cell tumors (ICCC Xc) than for tumors arising at "other and unspecified" sites (ICCC Category Xb), with 5–year survival rates of 94% and 71%, respectively in 1985-1994. Outcome was similar for patients younger than 20 years of age with intracranial germ cell tumors (ICCC Xa) and with tumors arising at "other and unspecified" sites (ICCC Xb), with both groups having survival rates for 1985-94 of approximately 70% (Figure X.7).

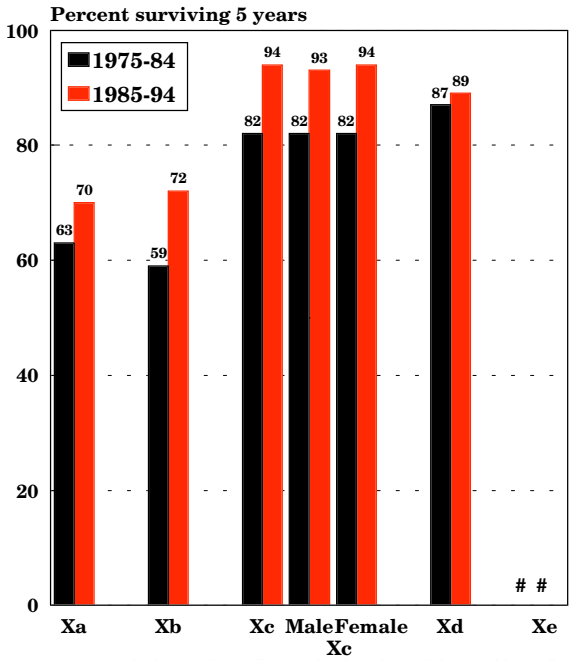
- Increasing survival rates were observed between 1975-84 and 1985-94 for each subgroup of the ICCC for patients younger than 20 years if age. The overall 5-year relative survival rate for all subgroups combined increased from 77% to 87% (Figure X.6). The largest increase in survival was for tumors arising at other and unspecified sites (ICCC Xb): 58 percent compared to 72 (Figure X.7).

Figure X.6: Germ-cell tumor 5-year relative survival rates by sex, race, age, and time period SEER (9 areas), 1975-84 and 1985-94



GCTOG - Germ cell, trophoblastic and other gonadal

Figure X.7: GCTOG tumor 5-year relative survival rates by sub-group, sex and time period, all races SEER (9 areas), 1975-84 and 1985-94



Xa = Intracranial and intraspinal germ cell tumors; Xb = Other and unspecified non-gonadal germ cell tumors; Xc = Gonadal (ovarian and testicular) germ cell tumors; Xd = Gonadal carcinoma; Xe - Other and unspecified malignant gonadal tumors.

GCTOG - Germ cell, trophoblastic and other gonadal # - < 25 cases - rate not shown

Table X.5: Current knowledge on causes of childhood malignant germ cell tumors (MGCT)

Exposure or Characteristic	Comments	References
Known risk factors		
Cryptorchidism	Risk is increased 2.5 - 11-fold. The contralateral as well as ipsilateral testis is at increased risk.	34-36
Factors for which evidence is suggestive but not conclusive		
High maternal hormone levels during pregnancy	Use of oral contraceptives during pregnancy, high pre-pregnancy weight, bleeding, hyperemesis and spotting indicate high hormone levels.	34,35,37-39
Family history of germ cell tumor	When malignant germ cell tumors occur in the same family, they are usually of the same histologic type.	40,41
Hernia	Central nervous system and genitourinary anomalies have also been observed in germ cell tumor patients.	34,35,42
Pre-term birth	Excess risk was not explained by cryptorchidism.	43,44
Trauma	The causality of this association is not clear. Trauma may result in closer scrutiny and earlier detection of an existing tumor.	45-47
Factors for which evidence is inconsistent or limtied		
Virus infection, e.g., mumps, cytomegalovirus, Epstein-B virus, and parvovirus B19		48-52
High birth weight		35,43,44
Prenatal X-ray exposure		43,53
Parental occupation	Associations have been observed with maternal employment in the medical field, paternal employment in service stations and aircraft industry, and paternal exposure to x-rays, maternal exposure to solvents, plastic and resin fumes.	44,54,55
Constitutional chromosome abnormalities, particularly sex chromosome abnormalities (e.g., Klinefelter syndrome (47,XXY), inverted Y)		56-60

The increase in survival for this subgroup, ICCC Xb, was dramatic for children younger than 5 years of age; the survival rate increased from 38% to 86%.

- The increase in survival between 1975-84 and 1985-94 was similar for ovarian and testicular germ cell tumors (Figure X.7). Both increased from 82% to 93-94%.

The improvement in outcome observed in the more recent period for children with germ cell tumors likely represents the widespread application of platinum-based chemotherapy, which is particularly effective against germ cell tumors [33].

RISK FACTORS

The etiology of malignant germ cell tumors is poorly understood. Cryptorchidism is the only confirmed risk factor for testicular germ cell tumors (see Table X.5 for references). Although rare, testicular cancer coincidence in father and son, and in male siblings has been reported, implying a genetic contribution in the disease origination. Suggested risk factors for malignant germ cell tumors, mainly based on findings from studies of testicular cancer among adult populations, include maternal exogenous hormone use and high endogenous hormone level during pregnancy, pre-term birth, high birth weight, hernia, trauma, pre-natal X-ray exposure, virus infection, parental occupation and occupational exposures, and certain constitutional chromosome abnormalities.

SUMMARY

The ICCC Diagnostic Group X for GCTOG tumors represents less than 4% of tumors among children younger than 15 years of age. However, for the 15-19 year age group, these tumors account for a much higher proportion (approximately 16%) of cancer cases. The age-incidence pattern for the group of GCTOG tumors is characterized by relatively high rates in the first year of life, followed by much lower rates until puberty, when incidence begins to increase and reaches rates greater than those in the first year of life. For males, the majority of testicular cancers occurring before age 15 years are diagnosed in the first 4 years of life. However, because the incidence of testicular germ cell tumors increases rapidly after age 15, the vast majority of testicular cancer cases among those younger than 20 years of age develop among 15-19 year olds. Black males have a much lower incidence of testicular germ cell tumors than white males, while black females and white females have similar rates for ovarian germ cell tumors.

The distinctive nature of the germ cell tumors of infants and young children compared to those of adolescents and young adults complicates analyses of trends in incidence for the children younger than 20 years of age. However, over the past 20 years there has been a small absolute increase in incidence for germ cell tumors for children younger than age 15 years, with most of the increase due to higher rates for extragonadal germ cell tumors. Among children younger than 20 years of age, the incidence of GCTOG tumors has increased. The increase has been primarily driven by higher rates for gonadal germ cell tumors among 15-19 year olds and by higher rates for gonadal carcinomas among 15-19 year old females. The latter increase is attributable to changes in reporting of ovarian tumors during this time period, specifically inclusion of borderline tumors of the ovary. The increases in gonadal germ cell tumors for adolescents 15-19 years of age mirrors that observed for young adults with germ cell tumors. The onset of higher rates in males and females at the time of puberty as well as results from epidemiological studies suggest a contributory role

for hormonal influences, although the nature of these influences remains to be elucidated.

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