HIGHLIGHTS

Incidence

- Malignancies of the bone, with an average annual incidence rate of 8.7 per million children younger than 20 years of age, comprised about 6% of childhood cancer reported by SEER areas from 1975-95.
- In the US, 650-700 children and adolescents younger than 20 years of age are diagnosed with bone tumors each year of which approximately 400 are osteosarcoma and 200 are Ewing's sarcoma.
- The two types of malignant bone cancer that predominated in children were osteosarcomas and Ewing's sarcomas, about 56% and 34% of the malignant bone tumors, respectively.
- Osteosarcomas derive from primitive bone-forming mesenchymal stem cells and most often occur near the metaphyseal portions of the long bones. The Ewing's sarcomas are believed to be of neural crest origin and occur roughly evenly between the extremities and the central axis.
- For all bone cancer combined, a steady rise in incidence rates occurred with increasing age between ages 5 and 10, and a steeper rise began at age 11 until age 15 coinciding with the adolescent growth spurt. The peak incidence of bone cancer (19 per million) occurred at age 15, after which rates showed a decline (Figure VIII.2).
- Rates did not differ much by sex among younger children, but males had higher incidence than females during adolescence (Figure VIII.4).
- For osteosarcoma, black children had a higher overall rate than did white children (Figure VIII.7). For Ewing's sarcoma the racial variation in rates was dramatic: white children had an approximate 6-fold higher incidence rate than black children (Figure VIII.8).
- The most frequent site of bone cancer development was the long bones of the lower limbs for osteosarcomas and the central axis for Ewing's sarcomas (Figure VIII.9).

Survival

- The 5-year relative survival for children with bone cancer improved from 49% in the period 1975-84, to 63% in the period 1985-94. The survival rates improved between the two time periods for both osteosarcoma (Figure VIII.11) and Ewing's sarcoma (Figure VIII.12).
- Survival rates for osteosarcoma were higher than those for Ewing's sarcoma especially in the earlier time period (Figures VIII.11 and VIII.12).

Risk factors

- Although directed ionizing radiation exposure and a few genetic susceptibility syndromes are associated with increased risk of osteosarcoma, to date no factor has emerged to explain even a modest proportion of cases (Table VIII.2). Other than the important racial difference in incidence between black and white children, no environmental factor or other characteristic has yet been shown to be a strong risk factor for Ewing's sarcoma (Table VIII.3).

INTRODUCTION

This chapter describes the descriptive epidemiology of childhood bone cancer, including short discussions on survival and risk factors for occurrence. Sarcomas of the bone and cartilage are a diverse group of tumors comprising about 0.5% of all malignancies in humans. The relative magnitude of bone cancer, however, is considerably higher in children than in adults [1].

About half of bone tumors that occur among children are of nonmalignant histopathology [2]. Because SEER case reporting is limited to primary malignant neoplasms, the information presented in this report will refer only to malignancies of the bone (bone cancer). In the International Classification of Childhood Cancer (ICCC) classification system, bone cancers are categorized as osteosarcomas, Ewing's sarcomas, chondrosarcomas, 'other specified malignant bone tumors' and 'unspecified malignant bone tumors' [3]. The two types of bone cancer that predominate in children are osteosarcomas and Ewing's sarcomas. For the 21-year period of 1975-95, there were 1,657 children younger than 20 years of age in the SEER areas who were diagnosed with a primary bone malignancy. Osteosarcomas represented about 56% of these tumors and Ewing's sarcomas an additional 34%. In the US, 650-700 children and adolescents younger than 20 years of age are diagnosed with bone tumors each year of which approximately 400 are osteosarcoma and 200 are Ewing's sarcoma.

Osteosarcomas derive from primitive bone-forming mesenchymal stem cells and most often occur near the metaphyseal portions of the long bones [3]. There is a bimodal age distribution of osteosarcoma incidence, with peaks in early adolescence and in adults older than 65 years of age [1]. The Ewing's sarcomas, which include Ewing's, atypical Ewing's, and the peripheral primitive neuroectodermal tumor of bone, are believed to be of neural crest

Figure VIII.1: Percent distribution of bone cancers by histology and age group, all races, both sexes, SEER, 1975-95

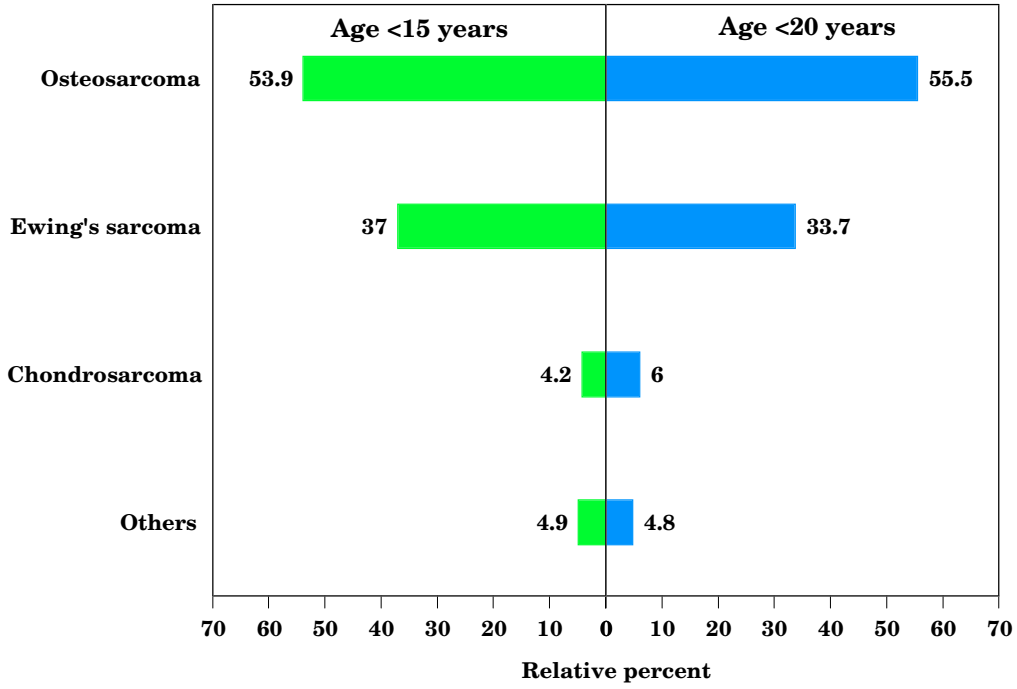
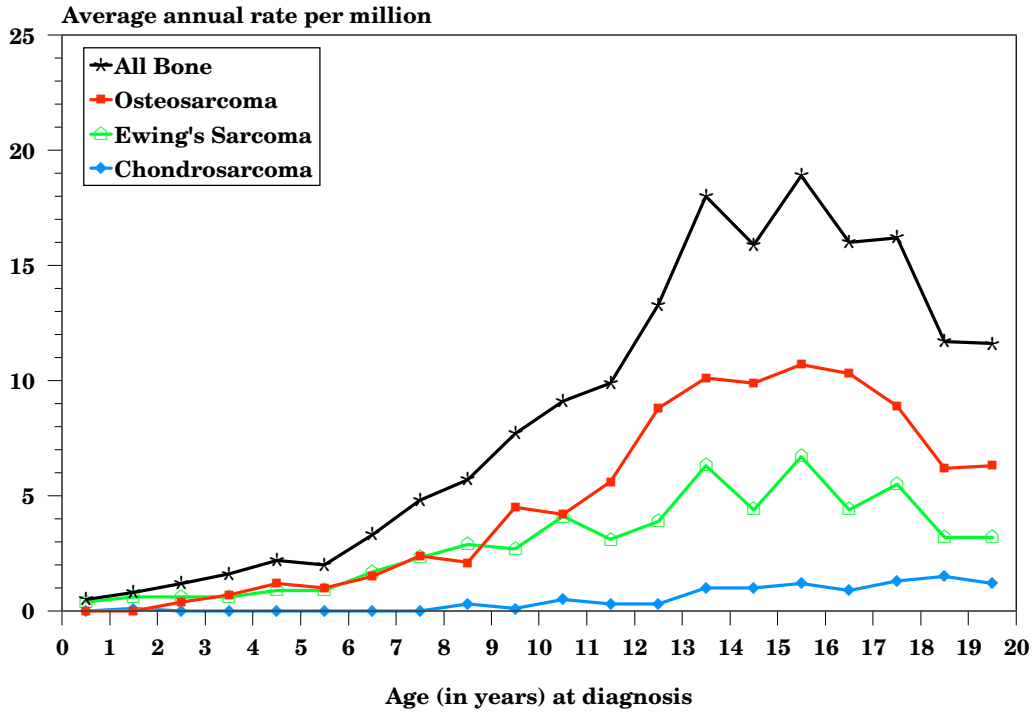


Figure VIII.2: Bone cancer age-specific incidence rates by histology all races, both sexes, SEER, 1976-84 and 1986-94 combined



origin and occur roughly evenly between the extremities and the central axis [5]. Ewing's sarcoma is a disease primarily of childhood and young adults; occurrence in older adults is extremely rare [1]. Chondrosarcomas, which after osteosarcomas are the most common of the bone malignancies among adults [1], are very rare in children. Figure VIII.1 presents the relative distribution of bone cancer by histologic types, both for children younger than 15 years of age and younger than 20 years of age.

INCIDENCE

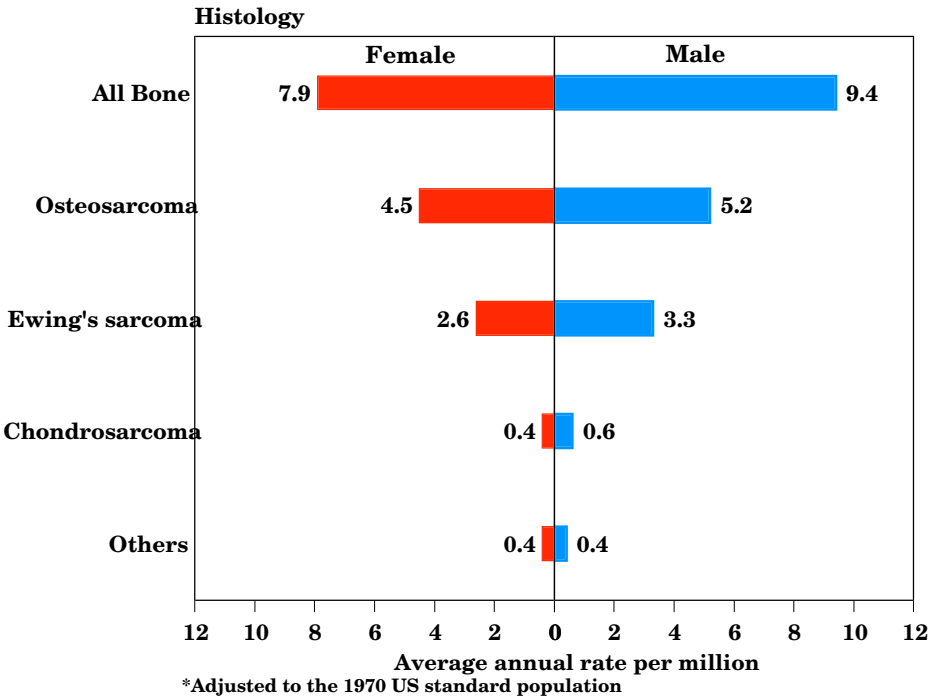
Malignancies of the bone, with an average annual incidence rate of 8.7 per than 20 years, unless otherwise noted). The histology-specific rates were 4.8 per million for osteosarcoma, 2.9 per million for Ewing's sarcoma and 0.5 per million for chondrosarcoma.

Age-specific incidence

Bone cancer represented only 0.5% of all malignancies among children younger than 5 years, compared with 5% for those 5-9 years, 11% for those 10-14 years, and 8% for adolescents 15-19 years. Figure VIII.2 shows 1-year age-specific rates for all bone cancer combined and for specific histologic subtypes. [1] For all bone cancer combined, a steady rise in rates occurred from ages 5 through 10, and a steeper rise began at age 11. The increase in rates among older children appeared to coincide with the adolescent growth spurt. The peak incidence of bone cancer (19 per million) occurred at age 15, after which rates showed a decline. Incidence of chond-

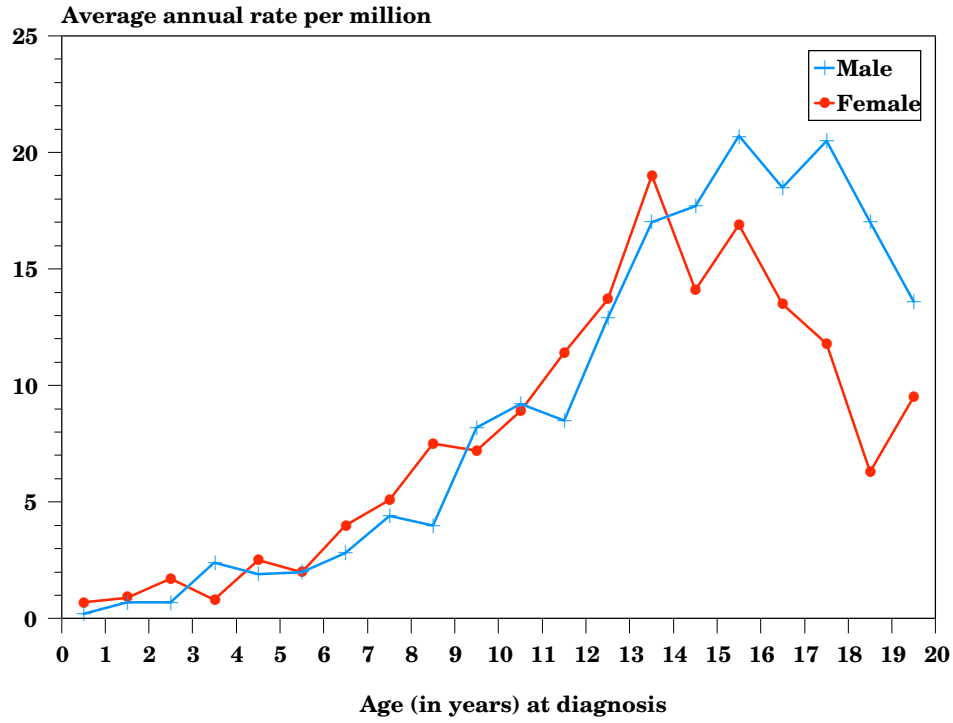
[1] Enumeration of the population at risk by single years of age was available only for the census years 1980 and 1990. The US Bureau of the Census provides intercensal population estimates by 5-year age groups, but not by single years of age. Therefore, the population estimates for 1980 were used in rate calculations for cases diagnosed from 1976-84 and the 1990 estimates were used for cases diagnosed from 1986-94.

Figure VIII.3: Bone cancer age-adjusted incidence* rates by type and sex, age <20, all races, SEER, 1975-95



*Adjusted to the 1970 US standard population

Figure VIII.4: Bone cancer age-specific incidence rates by sex, all races, SEER, 1976-84 and 1986-94

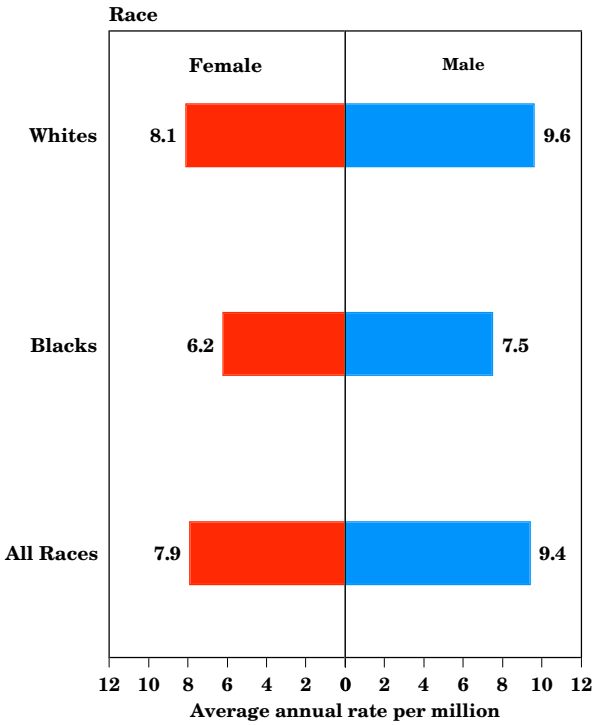


rosarcoma was very low at all ages. Rates of osteosarcoma and Ewing's sarcoma were similar until about age 10, when substantially higher rates of osteosarcoma became apparent.

Sex-specific incidence

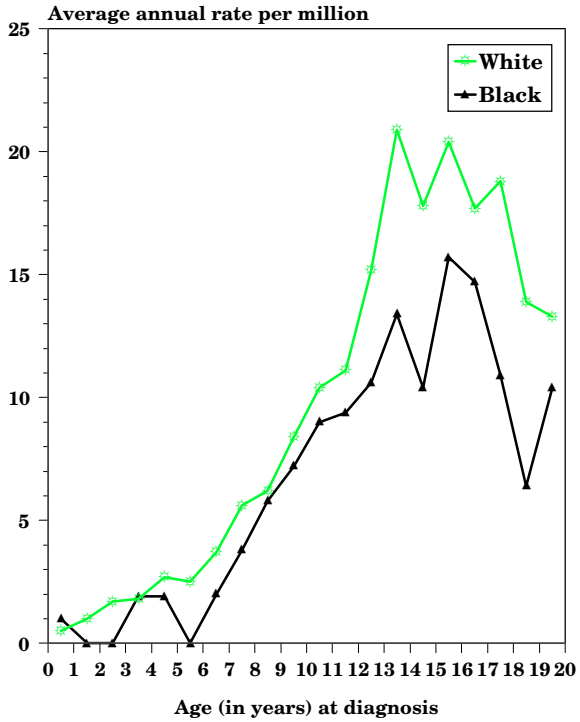
The incidence rates of osteosarcoma and Ewing's sarcoma were slightly higher for males relative to females, albeit the absolute differences in rates were quite small (Figure VIII.3). Figure VIII.4 presents 1-year age and sex specific incidence rates for all bone cancer combined. The incidence pattern by age is similar for males and females, although from age 14 through 19 male rates are higher than female rates. For females, rates of bone cancer peaked at age 13, while the highest rates for males occurred from ages 15 through 17.

Figure VIII.6: Bone cancer age-adjusted* incidence rates by race and sex, age <20, SEER, 1975-95



*Adjusted to the 1970 US standard population

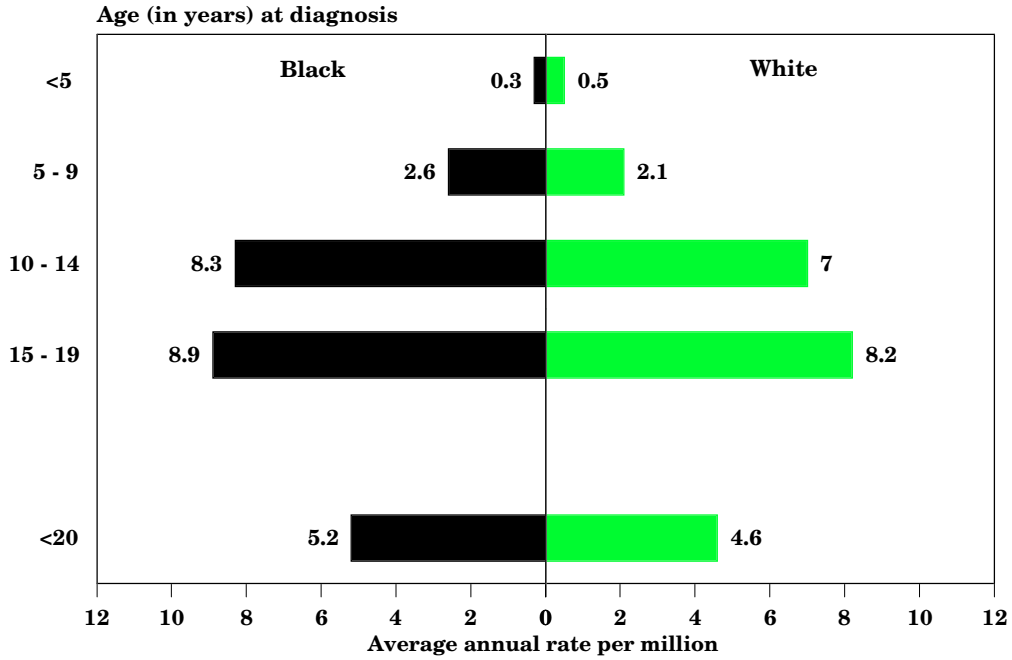
Figure VIII.5: Bone cancer age-specific incidence rates by race, both sexes, SEER, 1976-84 and 1986-94 combined



Black-white differences in incidence

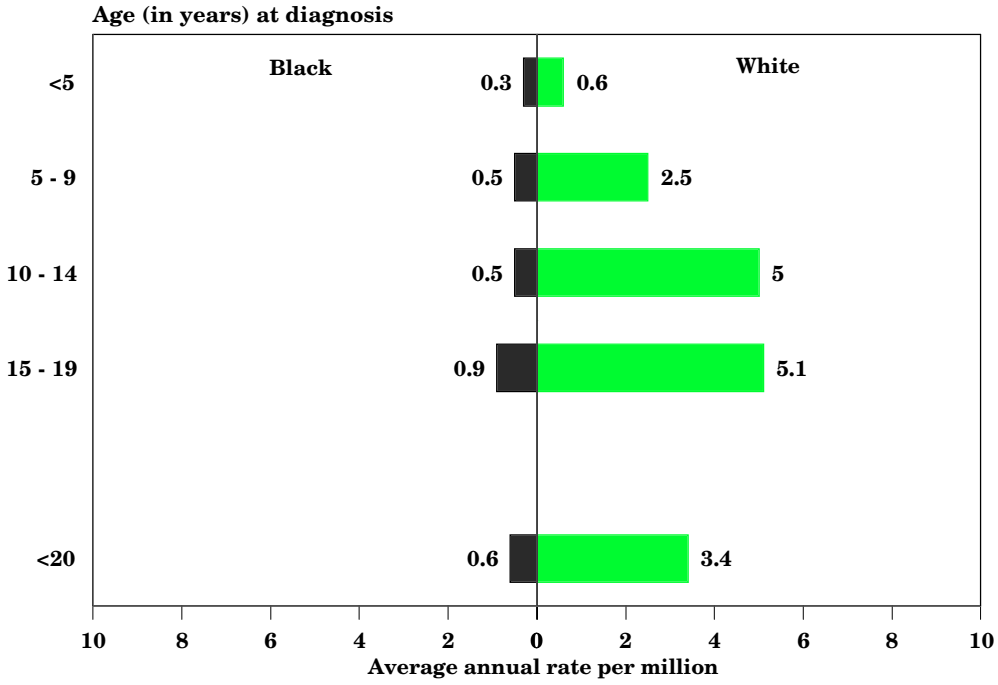
One-year age specific incidence rates of bone cancer are shown in FigureVIII.5 for white and black children. The age pattern of bone cancer incidence was quite similar by race, although higher rates among whites were seen at virtually all ages. The overall incidence rate among white children was 8.8 per million compared with 6.8 per million for black children. Figure VIII.6 shows that both white males and females had higher rates than blacks of the same sex, at about the same ratios. This racial disparity in bone cancer incidence was not consistent across histologic subtypes. For osteosarcoma, black children had a higher overall rate than did white children (Figure VIII.7). Rates were slightly higher in blacks than in whites for each age group except for those younger than 5 years of age. For Ewing's sarcoma the racial varia-

Figure VIII.7: Osteosarcoma age-adjusted* incidence rates by age group and race, both sexes, SEER, 1975-95



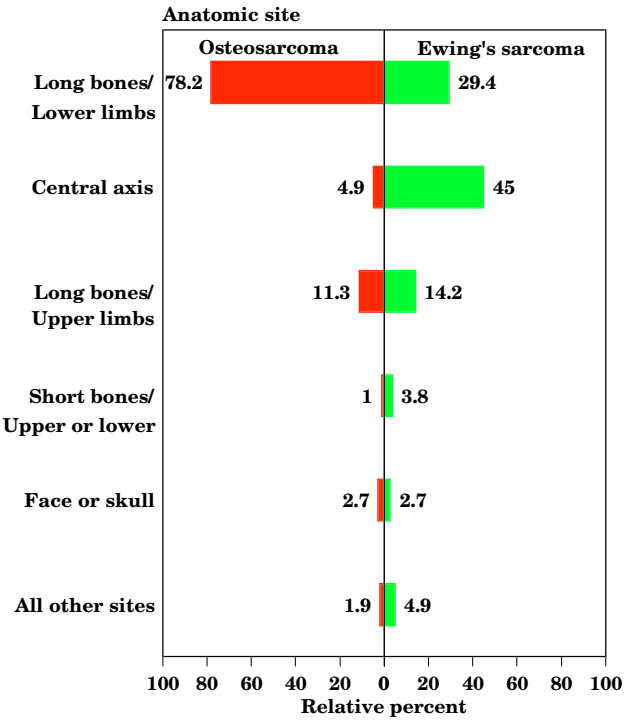
*Adjusted to the 1970 US standard population

Figure VIII.8: Ewing's sarcoma age-adjusted* incidence rates by age group and race, both sexes, SEER, 1975-95



*Adjusted to the 1970 US standard population

Figure VIII.9: Anatomic site distribution of bone cancer by histology, age <20, all races, both sexes SEER, 1975-95



tion in rates was dramatic: white children had an approximate 6-fold higher incidence rate than black children (Figure VIII.8), thus entirely accounting for the white preponderance in overall bone cancer rates. This strong racial difference was apparent in all age groups. The fact that black children in the US rarely develop Ewing's sarcoma has been observed for many years, but the protective etiology has yet to be elucidated. It is interesting to note that in several African countries the ratio of Ewing's sarcoma to osteosarcoma is very similar to that of US blacks [6].

Bone cancer location

The most frequent site of bone cancer development (57%) was the long bones of the lower limbs. The site distribution of Ewing's sarcomas, however, differed substantially from that of osteosarcomas (Figure VIII.9). The long bones of the lower limb were the site of 78% of osteosarcomas, but only 29% of Ewing's sarcomas. The central axis (vertebral column; rib, sternum, and clavicle; pelvic, sacrum, and coccyx) was the most frequent site for Ewing's sarcomas (45%), where osteosarcomas are relatively unusual.

Table VIII.1: Average age-adjusted* incidence rates per million children for bone cancer all races, both sexes, age<20, SEER 1975-95

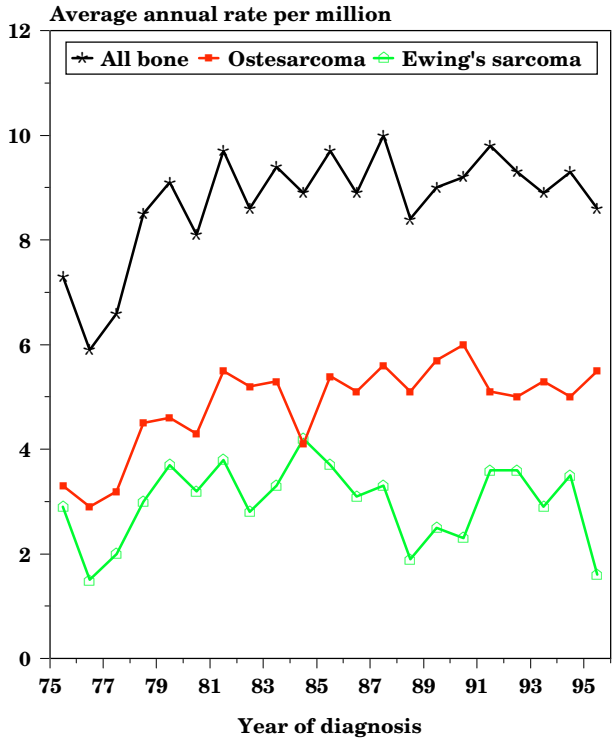
	1975-79	1980-84	1985-89	1990-95
Osteosarcoma	3.7	4.9	5.4	5.3
Ewing's Sarcoma	2.6	3.4	2.9	2.9
All Bone Cancer	7.4	9.0	9.2	9.2

*Adjusted to the 1970 US standard population

Trends in incidence rates

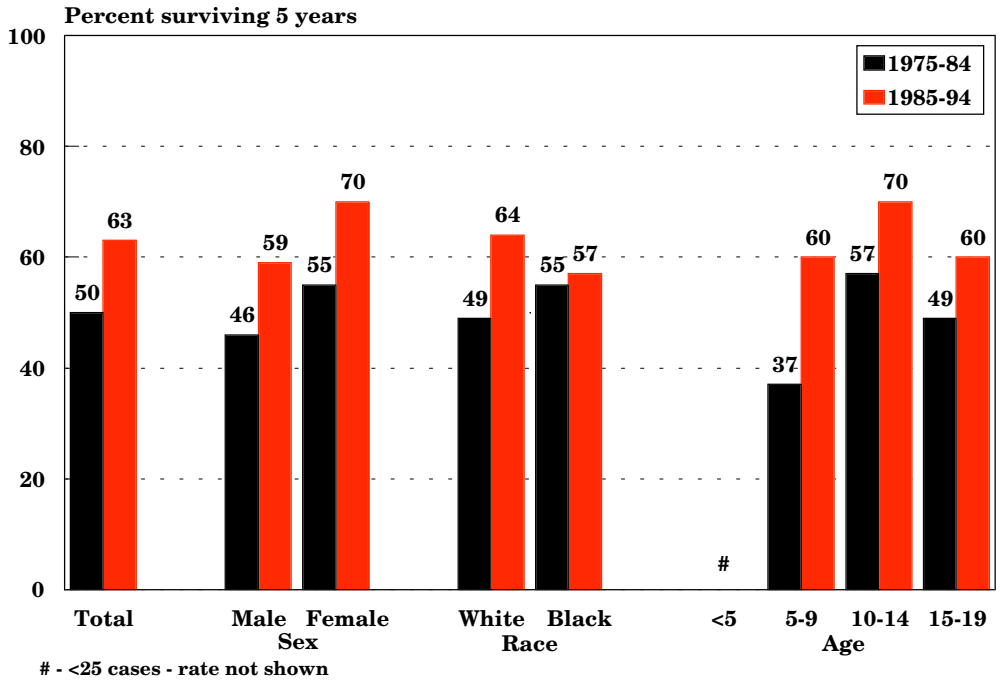
Figure VIII.10 shows histology-specific incidence rates by single year of diagnosis from 1975-95. It is unclear why rates of both osteosarcoma and Ewing's sarcoma were lower from 1975-78 than in later years. Table VIII.1 shows the average rates of bone cancer during the time periods of this study.

Figure VIII.10: Trends in bone cancer age-adjusted* incidence rates by histology, age <20 all races both sexes, SEER, 1975-95



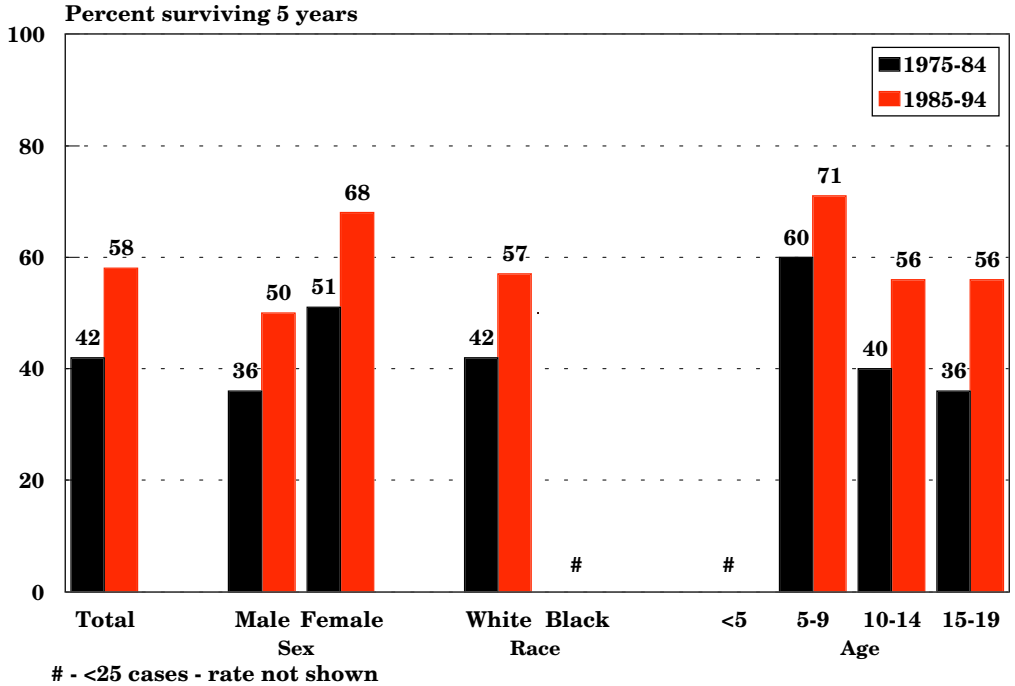
*Adjusted to the 1970 US standard population

Figure VIII.11: Osteosarcoma 5-year relative survival rates by sex, race, age and time period, SEER (9 areas), 1975-84 and 1985-94



- <25 cases - rate not shown

Figure VIII.12: Ewing's sarcoma 5-year relative survival rates by sex, race, age and time period, SEER (9 areas), 1975-84 and 1985-94



- <25 cases - rate not shown

SURVIVAL

The 5-year relative survival for children with bone cancer improved from 49% in the period 1975-84, to 63% in the period 1985-94. The time period for relative survival is 1985-94 unless otherwise noted. Females had better 5-year survival probability (70%) than males (59%) and there was only a slight difference in survival between blacks (60%) and whites (63%). No notable survival differences were observed across 5-year age groups. For osteosarcoma the 5-year relative survival was 63% (59% for males, 70% for females). Prognosis for Ewing's sarcoma was somewhat poorer than for ostoesarcoma. The overall 5-year relative survival for Ewing's sarcoma was 58%, and again there was a notable difference by sex (50% for males, 68% for females). Although survival did not differ substantially by tumor site for osteosarcoma, children with Ewing's sarcoma of the pelvic, sacrum, or coccyx has survival probabilities of under 35%.

Table VIII.2: Current knowledge on causes of osteosarcoma

Exposure or Characteristic	Comments	References
Known risk factors		
Prior treatment for childhood cancer with radiation therapy and/or chemotherapy	There is an increased risk following radiotherapy for childhood cancer. Independent of radiotherapy, treatment with alkylating agents increases the risk of developing osteosarcoma.	7-9
Hereditary retinoblastoma, Li-Fraumeni syndrome, and Rothmund-Thomson syndrome	Increased risk is well documented for these genetic conditions.	10-13
Radium	High doses of the radioisotope radium are known to cause osteosarcoma in adults. Whether the low levels sometimes found in drinking water confer risk to children or adults is unknown.	1,14
Factors for which evidence is limited or inconsistent		
Growth and development	There has been some suggestion that taller stature is associated with an increased risk, but the results of more recent studies do not support this finding. One study showed an association with earlier age at onset of secondary sex characteristics in females and lower weight gain during pubertal growth spurt in males.	15-19
Prior trauma to tumor site	One study found a small positive association between damage to the tumor site and increased risk of osteosarcoma.	16
Prenatal exposure and development	Short birth length and fetal x-rays were associated with an increased risk in a single study.	16
Parental exposures	An association with chicken farming and another with gardening with fertilizer, herbicides or pesticides have been reported in single studies.	20-21
Fluoride in drinking water	The few epidemiologic studies as well as ecologic and time trend analyses suggest that fluoride is unlikely to cause osteosarcoma.	22-25

Table VIII.3: Current knowledge on causes of Ewing's Sarcoma (ES)

Exposure or Characteristic	Comments	References
Known risk factors		
Race	ES is almost exclusively a disease of white children. Rates in whites are approximately 9 times those in blacks.	18,26,27
Risk factors for which evidence is limited or inconsistent		
Growth	As for osteosarcoma, recent studies have not found a consistent association with increased height or weight, or age at pubertal growth spurt.	15,18,27-30
Hernia	An association was found between hernias and increased risk in one study.	29
Paternal occupation	Paternal occupation in agriculture has been associated with increased risk in two studies, although only in one were the results statistically significant.	29,30
Ingestion of poison or overdose of medication	A prior poisoning episode was more common among cases than controls in a single study.	30
Family history of cancer	ES has been reported in several pairs of siblings. However, more than one family member with ES is rare. In a study of over 200 cases, none had a relative with ES. Unlike osteosarcoma, ES is not part of the Li-Fraumeni syndrome.	12,31-32

RISK FACTORS

Unfortunately, the current state of knowledge regarding the causes of bone cancer is limited. Table VIII.2 briefly summarizes results from a number of epidemiologic studies that have been conducted on children with osteosarcoma. Although directed ionizing radiation exposure and a few genetic susceptibility syndromes are associated with increased risk of osteosarcoma, to date no factor has emerged to explain even a modest proportion of cases. The same is true for Ewing's sarcoma. Other than the important racial difference in incidence between black and white children, no environmental factor or other characteristic has yet been shown to be a strong risk factor for Ewing's sarcoma (TableVIII.3).

SUMMARY

In this descriptive analysis of the population-based SEER data, bone cancer represented about 6% of malignancies in children younger than age 20 years, with an average annual incidence rate of 8.7 cases per million children from 1975-95 (9.2 per million from 1990-95). Incidence increased with increasing age until late adolescence. Rates did not differ much by sex among younger children, but males had higher incidence than females during adolescence. Osteosarcoma and Ewing's sarcomas were the most common malignancies of bone in children. Black children had slightly higher rates of osteosarcoma relative to white children, while incidence of Ewing's sarcoma was dramatically higher among white compared with black children. The most common site for development of

osteosarcoma was the long bones of the lower limbs, while Ewing's sarcoma most frequently developed in bones of the central axis. Except for the first few years of the data collection, incidence rates of bone cancer have been stable. The etiology of bone cancer remains uncertain and the few risk factors that have been identified explain only a very small proportion of the incidence of these diseases. The 5-year relative survival for children with bone cancer improved from 49% in the period 1975-84, to 63% in the period 1985-94. In general, 5-year relative survival for osteosarcoma was slightly better than for Ewing's sarcoma. For both diseases, however, females had notably better survival than males.

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