1 Epidemiology of Bone and Soft Tissue Sarcomas

Philip J. Lupo, Logan G. Spector, Schuyler O'Brien, Joshua D. Schiffman, and Simone Hettmer

1.1 Introduction

Bone and soft tissue sarcomas are relatively rare cancers that collectively account for approximately 1% of adult solid tumors and 12% of all pediatric malignancies (Burningham et al. 2012; Ries et al. 1999). Major bone tumors include osteosarcoma and Ewing sarcoma, whereas soft tissue sarcomas are largely categorized by rhabdomyosarcoma and non-rhabdomyosarcoma soft tissue sarcomas. In spite of their relative infrequency, these tumors remain a leading cause of cancer death in individuals <20 years of age in developed countries and are a significant source of cancer-related morbidity (Ries et al. 1999). Given the suboptimal outcomes seen among those with bone and soft tissue sarcomas, these malignancies have a substantial impact on public health as measured by the average number of productive years of life lost due to cancer (Burningham et al. 2012). Thus, it is important to characterize their clinical/biological behavior and their etiologies. Epidemiologic studies help this endeavor in two ways. Descriptive studies reveal the incidence of these sarcomas and their associated mortality and survival rates with respect to histologic subtype and demographic characteristics. Analytic studies compare the risk of bone and soft tissue sarcomas in people with and without certain characteristics (cohort studies) or compare the histories of people with and without sarcomas (case-control studies) to identify and assess a wide range of possible risk factors, including exposures to radiation and hereditary cancer predisposition syndromes. Combined consideration of epidemiologic insights and progress in the molecular classification of these tumors provides greater insight into the role of tumor biology in disease progression and sensitivity to radiation treatment and chemotherapy, ultimately providing a framework for improved assessment of sarcoma risk, early tumor identification, and eventually strategies for individualized prevention and treatment of sarcomas.

P. J. Lupo (✉)
Department of Pediatrics, Section of Hematology-Oncology, Baylor College of Medicine, Houston, TX, USA
e-mail: philip.lupo@bcm.edu

L. G. Spector
Division of Pediatric Epidemiology and Clinical Research, Department of Pediatrics, University of Minnesota, Minneapolis, MN, USA
e-mail: spect012@umn.edu

S. O'Brien · J. D. Schiffman
Department of Pediatrics, University of Utah Health Sciences Center, Salt Lake City, UT, USA
e-mail: joshua.schiffman@hci.utah.edu

S. Hettmer
Division of Pediatric Hematology and Oncology, Department of Pediatric and Adolescent Medicine, University Medical Center Freiburg, University of Freiburg, Freiburg, Germany
e-mail: Simone.Hettmer@childrens.harvard.edu

C. A. S. Arndt (ed.), *Sarcomas of Bone and Soft Tissues in Children and Adolescents*, Pediatric Oncology, https://doi.org/10.1007/978-3-030-51160-9_1

1.2 Descriptive Epidemiology

1.2.1 Osteosarcoma

Osteosarcoma (OS) in the young is rare worldwide, with rates between 4 and 7 cases per million children and adolescents <25 years of age, and shows minimal international variation (Mirabello et al. 2009). In the USA, an estimated 400 cases of OS are diagnosed each year among children 0–19 years of age and accounted for about ~3% of total cancer in this age group (Ries et al. 1999; Howlader et al. 2015).

The overall rate for OS is 5.3 cases per million children ages 0–19 years in the USA (Howlader et al. 2015), but this obscures substantial variation in incidence of the tumor by age (Fig. 1.1). Notably OS is very rare in early childhood but has a markedly peaked incidence in adolescence. Males have a somewhat higher incidence than females, and, interestingly, the peak incidence in females appears 2 years earlier than in males. Incidence among young adults (20–24 years) is also appreciable but less than at the peak (Wu et al. 2003). The incidence of OS in Surveillance, Epidemiology, and End Results (SEER) program data rose significantly by 1.6% per annum between 1975 and 1993 but remained steady between 1994 and 2012 (Ries et al. 1999). OS has a distinctive pattern of tumor location, with almost 80% of OS cases occurring in the long bones of the lower limbs and only about 5% in the central axis (Ries et al. 1999).

1.2.2 Ewing Sarcoma

The incidence of Ewing sarcoma is 1 case per million for all ages and increases to 3 cases per million for those under the age of 20 years. Estimates vary, but approximately 80–90% of individuals who develop Ewing sarcoma are under the age of 24 years (Cotterill et al. 2000). For this reason, Ewing sarcoma is largely considered a childhood cancer, although it can also occur in adults. The most common primary site for Ewing Sarcoma is the pelvis and lower extremities (Cotterill et al. 2000). Males are at a slightly increased risk for developing Ewing sarcoma in comparison to females. The incidence of

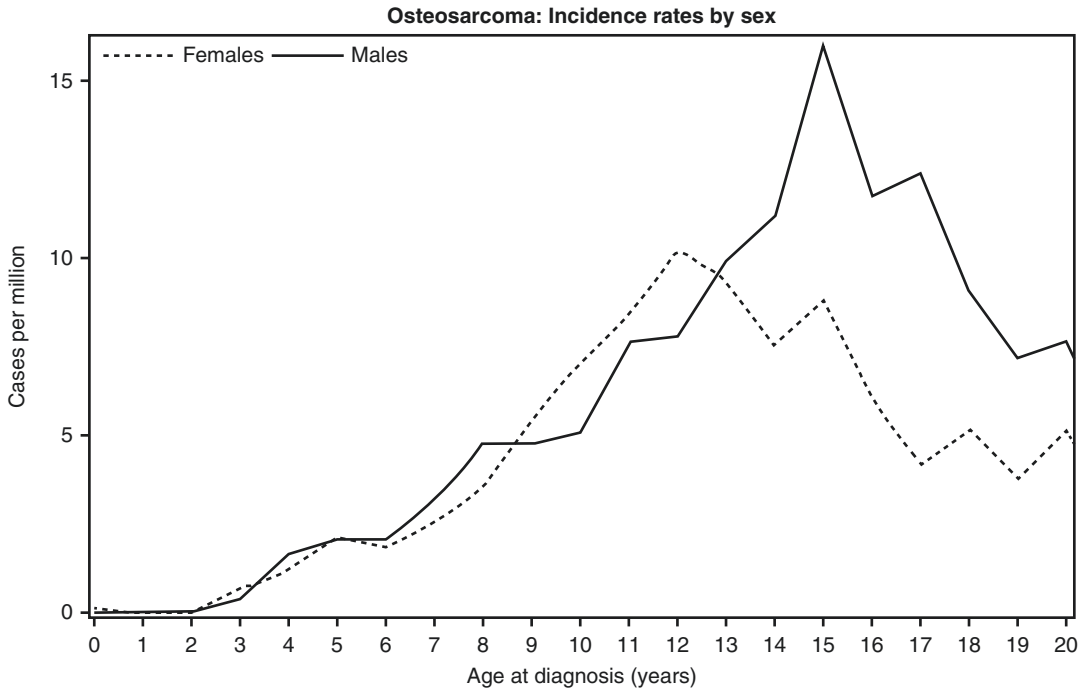

Fig. 1.1 Incidence of OS by age and sex (SEER 2000–2012)

Ewing sarcoma also varies significantly by race. Caucasians have the highest incidence, followed by Asians/Pacific Islanders, and African Americans, with incidence rates of 0.155, 0.082, and 0.017 per 100,000 individuals, respectively (Fig. 1.2) (Jawad et al. 2009). The fact that Caucasians are 9-times more likely to Ewing sarcoma compared to African Americans is a very important observation. In populations worldwide, those of European ancestry exhibit the highest incidence rates, regardless of geography. Furthermore, those with African ancestry on different continents still exhibit the lowest incidence, suggesting racial disparities in incidence are due to differences in genetics (Jawad et al. 2009; Fraumeni and Glass 1970).

1.2.3 Rhabdomyosarcoma (RMS)

RMS is the most common soft tissue sarcoma in children and adolescents, with an overall incidence rate of 4.5 cases per million among those <20 years of age. In the USA, this equates to approximately 350 new cases per year. While adult cases of RMS make up 40% of all RMS diagnoses, these tumors are considered rare in adults and are often characterized by a different histologic subtype (pleomorphic) (Sultan et al. 2009). In fact, information regarding the clinical and biologic characteristics of RMS in adults is very limited. Large, multi-institutional trials have not been performed, and only reports from single institutions have been published.

Based on data from the SEER Program, we know the incidence of RMS differs both by age and histology (Fig. 1.3). Specifically, the incidence of embryonal RMS (eRMS) has a bimodal peak, with each peak occurring during key developmental periods (i.e., early development and puberty). This is not seen with alveolar RMS (aRMS), where the incidence remains constant throughout childhood and adolescence. Also using data from SEER (Ognjanovic et al. 2009), Ognjanovic et al. reported the incidence of eRMS for the period 1975–2005 has remained relatively stable. However, there has been a significant increase in the incidence of aRMS (annual per-

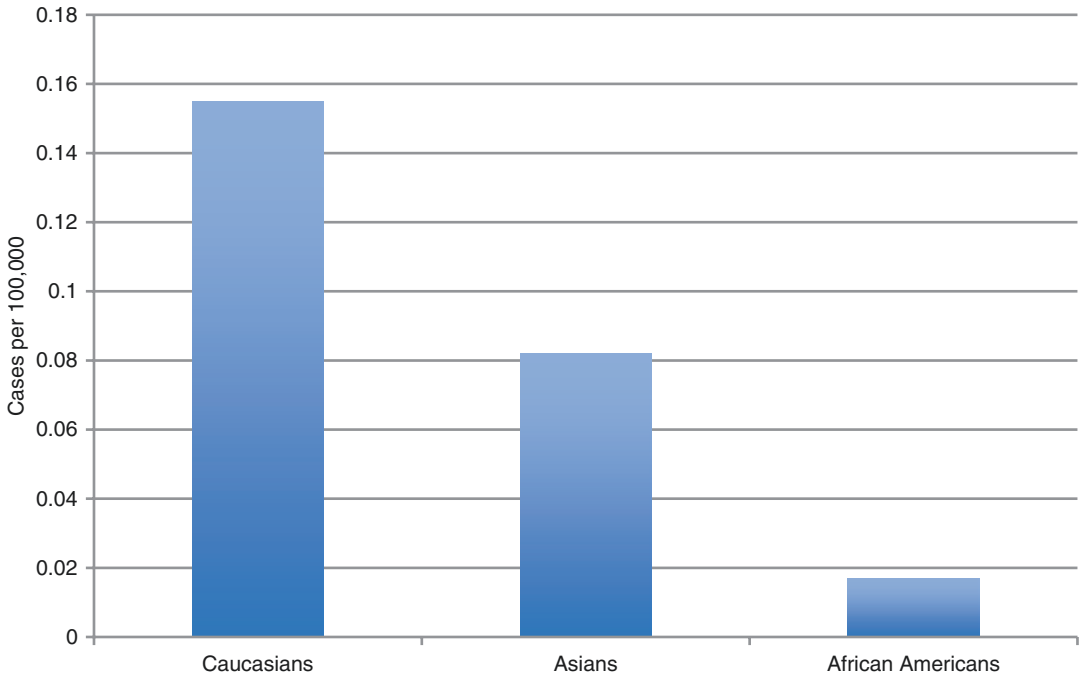

Fig. 1.2 Incidence of Ewing sarcoma by race (Jawad et al. 2009)

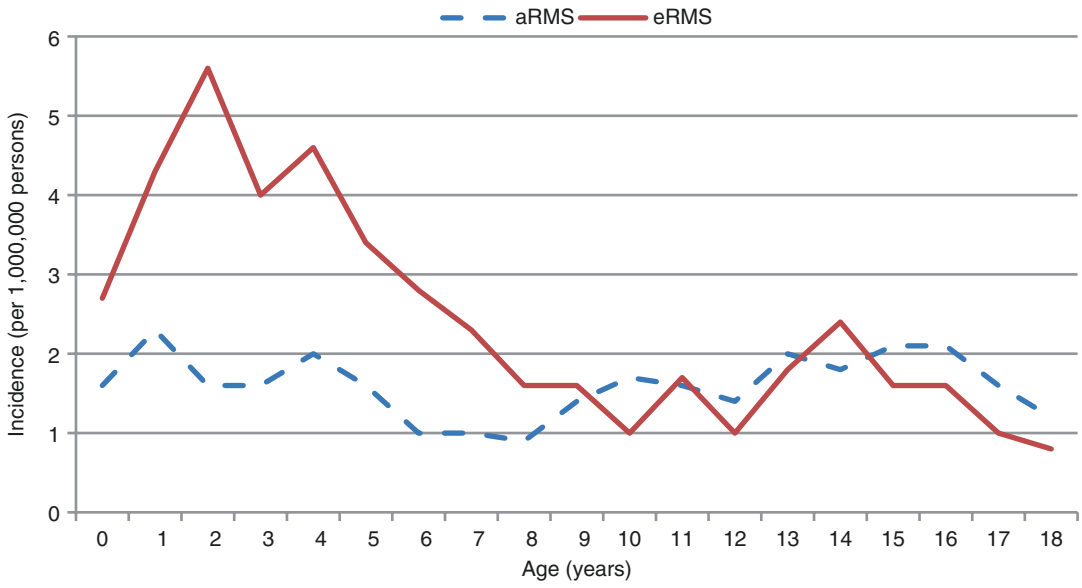

Fig. 1.3 Incidence of RMS by age and histology (SEER 1975–2011)

centage change (APC) = 4.20%, 95% confidence interval (CI): 2.60–5.82) for the same period. The authors noted that this might be attributable to changes in diagnostic criteria over time. There are also differences in incidence by gender. Males had a higher incidence of RMS compared to females, but this predominance was mainly among those diagnosed with eRMS (male/female ratio = 1.51, 95% CI: 1.27–1.80). Overall, there were no notable differences in incidence by race/ethnicity. This is consistent with a study pooling cancer registry data across five states (California, Minnesota, New York, Texas, and Washington), which indicated there were no significant differences in the risk of RMS by parental race (Chow et al. 2010). The only exception was the risk of RMS in offspring was significantly lower when both parents were of Hispanic ethnicity (OR = 0.65, 95% CI: 0.48–0.88).

1.2.4 Non-rhabdomyosarcoma Soft Tissue Sarcoma (NRSTS)

Non-rhabdomyosarcoma soft tissue sarcoma (NRSTS) incidence rates range between 1.8 and 5.0 per 100,000 individuals per year (Gustafson 1994; Levi et al. 1999; Ross et al. 1993; Storm 1994; Toro et al. 2006; Zahm and Fraumeni Jr. 1997). Differences in incidence rates between countries (e.g., 1.8 per 100,000 in Sweden (Gustafson 1994) and 4–5 per 100,000 in the USA (Toro et al. 2006; Zahm and Fraumeni Jr. 1997)) are likely due to racial differences, discrepant Kaposi sarcoma rates, and changing pathology definitions. Several reports documented increasing STS incidence rates over time (Toro et al. 2006; Zahm and Fraumeni Jr. 1997; Lahat et al. 2008), which are likely explained by improved registry systems and diagnostic tools, as well as the marked rise in Kaposi sarcoma incidence rates from 0.5 per 100,000 in 1975 to 3.3 per 100,000 during the HIV/AIDS epidemic of the late 1980s/early 1990s (Eltom et al. 2002). Incidence rates per year of specific NRSTS subtypes in the general population are summarized in Table 1.1 (Toro et al. 2006; UK CR 2008–2010).

There is a modest peak in the incidence of NRSTS among young children under the age of 5 years with a larger peak observed at approximately 60 years of age (Burningham et al. 2012; Wibmer et al. 2010). Mean age of diagnosis is 58 years, and mean age of death is 65 years (Burningham et al. 2012). However, STS

Table 1.1 Incidence rates per year of specific NRSTS subtypes

NRSTS	Yearly incidence rates per 100,000
GIST	0.68
Leiomyosarcoma	0.81–1.23
Liposarcoma	0.59–0.62
Synovial sarcoma	0.11–0.13
MPNST	0.12–0.19
Fibrosarcoma	0.18–0.65
Malignant fibrous histiocytoma	0.88
Sarcoma NOS	0.65–0.85

accounts for 7% of all cancer diagnoses in the pediatric age group and <1% of all malignancies in adults (Pappo and Pratt 1997). There are marked differences between histologies diagnosed in different age groups. Frequent NRSTS in the pediatric age group include synovial sarcomas (accounting for up to 42% of NRSTS (Dillon et al. 1992)); and fibroblastic/myofibroblastic/fibrohistiocytic tumors. In the adolescent and young adult (AYA) population, synovial sarcomas are relatively more common compared to the general adult NRSTS population and account for approximately 33% of AYA NRSTS (Herzog 2005).

Data on gender differences in STS risk are inconsistent, with male/female ratios ranging from 0.80 to 1.42 in different populations (Levi et al. 1999; Ross et al. 1993; Zahm and Fraumeni Jr. 1997; Wibmer et al. 2010). The highest NRSTS incidence rates were noted among black women, followed by black men, white men, and white women (Toro et al. 2006). Differences in black-white incidence rates were observed at all ages except childhood and driven largely by higher rates of leiomyosarcomas and dermatofibrosarcomas among non-Hispanic blacks (Toro et al. 2006). Race/ethnicity differences in STS incidence rates were also noted in another report, with incidence rates of 5.1 per 100,000 in blacks, 4.5 per 100,000 in whites, and 2.8 per 100,000 in Asians/Pacific Islanders (Burningham et al. 2012).

The epidemiology of certain NRSTSs is notable for specific features: classic gastrointestinal stromal tumors (i.e., GIST,which harbor *C-KIT* or *PDGFRA* pathogenic variants (Miettinen et al. 2005)) typically presents with a male/female ratio of 1.5 and affects individuals over 50 years of age (Tran et al. 2005), whereas its wild-type form (*C-KIT*/*PDGFRA*-negative) more commonly occurs in younger age groups and females (Nannini et al. 2013; Pappo and Janeway 2009). Finally, EBV-associated leimyosarcomas in immunodeficient individuals occur at any age, with a distinct age peak in children aged 0–9 years, whereas leiomyosarcoma rates in the general population increase with age and peak over the age of 50 years (Bhatia et al. 2012).

1.3 Environmental (Non-genetic) Risk Factors

1.3.1 Osteosarcoma

1.3.1.1 Growth and Development

The descriptive epidemiology of osteosarcoma strongly suggests an etiology related to growth and development. The age-incidence curve of OS closely follows that of the childhood growth curve (Fraumeni 1967), especially with respect to peak incidence in females reflecting their earlier growth spurts. Moreover, OS occurs most frequently at the metaphyseal region of long bones which are sites that contribute the most to vertical growth during the adolescent growth spurt (Price 1958).

Consequently, many studies have attempted to ascertain whether patients with OS attain greater height, grow faster, or reach puberty earlier than the general pediatric population. The largest analysis of height at diagnosis of OS pooled 1067 cases from seven studies to find that people in the 51st to 89th percentiles and those with ≥90th percentile of height had significantly increased risk of OS (odds ratio [OR] = 1.35, 95% confidence interval [CI]: 1.18–1.54 and OR = 2.60, 95% CI: 2.19–3.07, respectively) (Mirabello et al. 2011a). The same analysis pooled birth weight data from four studies to find that birth

weight ≥4046 g resulted in a greater risk of OS (OR = 1.35, 95% CI:1.01–1.79), although a subsequent, population-based, fairly sizable Scandinavian study did not replicate the finding (Troisi et al. 2014).

Some investigations have sought to quantify the rate of growth in OS cases and controls (Buckley et al. 1998; Gelberg et al. 1997; Operskalski et al. 1987), while others have examined the age at appearance of secondary sexual characteristics (Buckley et al. 1998; Gelberg et al. 1997). No correlation has been found with risk for OS.

The epidemiology of canine OS also points to a role for growth in the etiology of the tumor. It has been known since the 1960s that OS is more common in large dog breeds than in small ones (Tjalma 1966). One study in Rottweilers indicated that endogenous hormone exposure, and not simply growth, drives OS (Cooley et al. 2002). Investigators found that earlier age of gonadectomy raised the risk of OS significantly both male and female dogs, independent of size.

1.3.1.2 Exogenous Exposures

Most investigations of exogenous exposures and OS have been unrevealing, with previous treatment for cancer being a prominent exception. Radiation and alkylating agents each raise risk of OS independently with risk increasing by dose (Hawkins et al. 1996; Tucker et al. 1987). However, only about 1% of childhood cancer survivors developed OS within 20 years of their primary diagnosis in one cohort (Hawkins et al. 1996).

Because fluoride and radium are deposited in the bones, and especially because the latter is radioactive, several ecologic or case-control studies have examined exposures to these elements, especially in drinking water, in relation to OS. One case-control study that comprehensively reconstructed fluoride exposure across the lifespan found risk increased at higher levels of exposure among males, but not females (Bassin et al. 2006); direct measurement of fluoride in bone samples from OS patients in this study showed no difference compared to controls with other tumors (Kim et al. 2011), suggesting the previous finding was by chance. Moreover, other studies of OS and fluoride have been mostly null (Moss et al. 1995; Blakey et al. 2014; Levy and Leclerc 2012; Gelberg et al. 1995; McGuire et al. 1991). Although high doses of ingested radium caused OS in an historical cohort of radium dial painters (Fry 1998), there is little evidence that radium at the levels present in drinking water raises the risk of disease (Moss et al. 1995; Finkelstein 1994; Finkelstein and Kreiger 1996; Guse et al. 2002).

Few population studies have directly addressed the topic of OS and infections although some evidence indirectly supports an association. Simian virus 40 (SV40), JC, and BK viruses comprise the polyomavirus family and have in common a T antigen which interferes with the function of the *TP53* and *RB1* tumor suppressor genes (Fanning 1998; Barbanti-Brodano et al. 1998), which are the frequent targets of somatic mutation in OS. SV40 induces OS in hamsters (Diamandopoulos 1973) and has been detected in OS tissue (Yamamoto et al. 2000; Mendoza et al. 1998; Carbone et al. 1996). On the other hand, studies in cohorts of children who received early batches of poliovirus vaccine contaminated by SV40 have not supported an increased risk of OS (Engels et al. 2003; Carroll-Pankhurst et al. 2001; Fisher et al. 1999; Strickler et al. 1998; Olin and Giesecke 1998). One case-control study of OS did not indicate an association with childhood or maternal infections. Little evidence supports the spatiotemporal clustering of OS cases (Ross et al. 1999; Silcocks and Murrells 1987; McNally et al. 2006, 2012; Basta et al. 2010), which can occur in the presence of a causative infection.

Lastly there have been several exploratory analyses of putative exogenous risk factors, which have generated few positive associations with OS. Risk factors examined to date include parental smoking (Hartley et al. 1988a), medications taken by mother or child (Hartley et al. 1988a), and in utero or postnatal diagnostic X-rays (Operskalski et al. 1987; Hartley et al. 1988a). One study suggested an association with bone fracture, particularly at the tumor site (Operskalski et al. 1987), but this was not replicated in another study (Buckley et al. 1998).

Studies of parental occupation and OS have also produced only isolated reports of associations with OS (Buckley et al. 1998; Gelberg et al. 1997; Operskalski et al. 1987; Hartley et al. 1988a; Hum et al. 1998).

1.3.2 Ewing Sarcoma

To date, there are no well-documented environmental risk factors for Ewing sarcoma. A handful of environmental association studies have found a correlation between farming-related environments and an increased risk for developing the disease. Specifically, parental exposure to pesticides and other chemicals associated with agriculture have been linked to Ewing sarcoma (Holly et al. 1992; Stiller et al. 1991; Valery et al. 2002). A few studies have associated both inguinal and umbilical hernias with an increased risk for the disease (Cope et al. 2000; Valery et al. 2003, 2005). The possible association between these two factors makes analyzing them in the context of Ewing sarcoma somewhat challenging. Ewing sarcoma and hernias do share common embryological pathways. Therefore, it is possible that the two may share or have an overlapping genetic predisposition. However, this has not been demonstrated in a molecular context. More work is clearly needed to determine how farming related environments, and/or hernias may contribute to the development of Ewing sarcoma.

Patient stature and pubertal growth patterns have also been investigated as risk factors for Ewing sarcoma. Studies have been somewhat conflicting with no clear trends emerging (Cotterill et al. 2000; Fraumeni 1967; Bacci et al. 1992; Pui et al. 1987; Winn et al. 1992). Part of the difficulty in evaluating these variables likely comes from alterations in normal development due to treatment (Cotterill et al. 2000).

1.3.3 RMS

Several environmental exposures have been explored in relation to RMS risk among children, including paternal cigarette smoking (Grufferman et al. 1982), prenatal X-ray exposure (Grufferman et al. 2009), advanced maternal age (Grufferman et al. 2009), maternal antibiotic use (Grufferman et al. 1993), and parental recreational drug use (Grufferman et al. 1993). The majority of these assessments were based on the largest epidemiologic case-control study of RMS to date. Specifically, cases were collected from patients enrolled on the IRS-III study, coordinated by the Intergroup Rhabdomyosarcoma Study Group, whose protocols enrolled 80–85% of all childhood RMS cases in North America (Grufferman et al. 1984). Cases (n = 322) were 0–20 years old at the time of their RMS diagnosis from April 1982 to July 1988. Central expert pathology review confirmed all RMS diagnoses, as well as histologic subtype (i.e., embryonal, alveolar, or other). Controls (n = 322) were identified by random-digit dialing during the same period (1982–1988) (Grufferman et al. 1993, 2009). Controls were pair-matched to cases on race, sex, and age. Key findings from this study are presented in Table 1.2. While some notable associations were reported, few have been confirmed in

Table 1.2 Review of factors evaluated in IRS-III case-control study of RMS

Factor (reference)	OR (95% CI)
Birth defects (Yang et al. 1995)	2.4 (0.9–6.5)
Prenatal X-ray exposure (Grufferman et al. 2009)	1.9 (1.1–3.4)
Parental drug use (Grufferman et al. 1993)	
Maternal	3.1 (1.4–6.7)
Paternal	2.0 (1.3–3.3)
Allergies (Lupo et al. 2014a)	0.6 (0.4–0.9)
Maternal and birth characteristics (Lupo et al. 2014b)	
Fertility medications	0.7 (0.2–2.3)
Vaginal bleeding during pregnancy	1.8 (1.1–2.7)
Premature birth	2.5 (0.7–8.5)
Family history of cancer (Lupo et al. 2015)	
First-degree relative (eRMS)	2.4 (1.5–3.9)[a]
First-degree relative (aRMS)	1.0 (0.3–3.5)
Paternal exposure to agent Orange (Grufferman et al. 2014)	1.7 (0.6–5.4)

OR odds ratio, *CI* confidence interval
[a]Combined with data from the Utah Population Database

independent assessments. Unfortunately, germline DNA was not collected as part of this study, making the evaluation of genetic susceptibility of gene-environment interactions impossible. Other epidemiologic studies of RMS evaluating the role of environmental exposures have been relatively small (<100 cases). Novel and larger studies are needed to validate previous findings and explore other potential risk factors. Additionally, much work is needed to identify risk factors for RMS among adults.

1.3.4 NRSTS

NRSTS have been associated with a number of non-genetic risk factors, including virus infections conferring NRSTS susceptibility in immunodeficient patients. Elevated rates of Kaposi sarcomas and leiomyosarcomas in transplant recipients and individuals with HIV/AIDS first linked these sarcomas with immunosuppression (Bhatia et al. 2012). HIV/AIDS patients and transplant recipients also experience an excess of leiomyomas and leiomyosarcomas (Bhatia et al. 2012). The majority of leiomyosarcoma and leiomyoma cells in these patients contain EBV (Bhatia et al. 2012), which was also detected in smooth muscle tumors from individuals with congenital immunodeficiency syndromes (Hatano et al. 2006). Yet, EBV does not appear to be a general requirement for the development of leiomyosarcomas, because tumors arising in immunocompetent individuals do not contain the virus (Bhatia et al. 2012; Fernandez et al. 2010).

Most studies aimed at evaluating NRSTS-relevant environmental exposures have employed small case-control studies covering groups of NRSTS subtypes and a wide range of exposures/oncogenic factors (Burningham et al. 2012). Consequently, findings are prone to bias and should be interpreted with caution. Gardeners (Balarajan and Acheson 1984; Wingren et al. 1990), farmers (Balarajan and Acheson 1984), building caretakers, and military personnel (Pukkala et al. 2009) appear to experience an increased risk for developing NRSTS. More specifically, high-intensity occupational exposures to chlorphenol and cutting oils (Hoppin et al. 1999) and dioxin exposure from incinerators (Comba et al. 2003; Viel et al. 2000) were associated with STS risk. There is no known association between STS risk and exposure to solvents, wood dust, asbestos, DDT, or benzene (Burningham et al. 2012; Hoppin et al. 1999).

Finally, excess risk of developing NRSTS has been reported in cancer survivors in relation to therapeutic radiation (Burningham et al. 2012; Rubino et al. 2005; Menu-Branthomme et al. 2004; Virtanen et al. 2006). STS risk in a large cohort of survivors of childhood solid cancer was increased 19-fold compared to the general population after radiation alone (Menu-Branthomme et al. 2004). The same study reported a 113-fold increase in STS rates after radiation plus chemotherapy (Menu-Branthomme et al. 2004). Of note, there is no known association between STS risk and birth weight (Schuz and Forman 2007) or growth/development in early adolescence (Burningham et al. 2012).

1.4 Germline Genetic Risk Factors

1.4.1 Osteosarcoma

As with most childhood cancers a small proportion of cases are due to inherited, high-penetrance genetic variation. Li-Fraumeni (Li et al. 1988), hereditary retinoblastoma (Wong et al. 1997; Hansen et al. 1985), and Rothmund-Thomson syndromes (Leonard et al. 1996; Wang et al. 2003), which result from germline variants in *TP53, RB1*, and *RECQL4*, respectively, each raise the risk of OS substantially in carriers. Somatic mutations of the former two genes are commonly found in sporadic OS (Miller et al. 1996), while those in the latter are not (Nishijo et al. 2004). The advent of next-generation sequencing is now bringing the prevalence of these syndromes in OS into greater focus. One study in which 765 OS cases were sequenced at the *TP53* locus found that nearly 10% of harbored known or likely Li-Fraumeni variants (3.8%) or rare exonic

variants of unknown significance (5.7%) (Mirabello et al. 2015a). Another recent study which performed whole exome sequencing on 39 cases found that 7 (17.9%) had pathogenic or likely pathogenic variants in one of 21 known autosomal dominant cancer-predisposition genes (Zhang et al. 2015).

The role of common variation on OS risk has also been evaluated. There have been a number of candidate gene studies of OS (Musselman et al. 2012; Mirabello et al. 2011b; Ruza et al. 2003; Savage et al. 2006); however none appeared significantly associated with OS in the sole genome-wide association study conducted to date (Savage et al. 2013). Rather, the only two variants which reached genome-wide significance were rs1906953 near the *GRM4* gene and rs7591996 in an intergenic region of 2p25.2; the function of these variants has not been investigated to date. A second genome-wide study also identified the rs7034162 variant in the *NFIB* gene which more than doubled the likelihood of metastasis at diagnosis (OR = 2.43; 95% CI: 1.83–3.24); this finding was supported by in vitro experiments which showed cell lines with the variant behaved more aggressively (Mirabello et al. 2015b).

1.4.2 Ewing Sarcoma

At present, Ewing sarcoma is not considered to be part of any hereditary cancer syndrome. Given its rarity, the occurrence of Ewing sarcoma in siblings is slightly suggestive of an unknown genetic predisposition. Given this lack of evidence, the diagnosis of Ewing sarcoma cannot yet be considered to be part of a larger hereditary cancer syndrome requiring clinical genetic testing.

Parental age has been found to be a potential risk factor for some childhood cancers (Dockerty et al. 2001; Johnson et al. 2009; Olson et al. 1993; Yip et al. 2006). While unclear, the reason for this may be related to an increase in de novo germline mutations or epimutations (Johnson et al. 2009; Olson et al. 1993; Dryja et al. 1997). In the case of Ewing sarcoma, epimutations seem more likely given the paucity of mutations observed in tumor samples (Tirode et al. 2014).

A number of other studies have aimed at identifying a genomic region responsible for the racial disparities in incidence for Ewing sarcoma. One candidate that has been identified is an intron near a frequent breakpoint region in the *EWS/ETS* translocation. This region has been observed to be smaller in African American populations, making it an appealing possibility. Other work has identified polymorphic repeat region binding sites referred to as (GGAA) microsatellites for the EWS/ETS fusion protein as potential candidates (Beck et al. 2012; Gangwal et al. 2008; Monument et al. 2014; Zucman-Rossi et al. 1997). These regions also show variation that can be specific to races and therefore offer a potential explanation for Ewing sarcoma incidence. An important finding in recent years comes from the first genome-wide association study (GWAS) of Ewing sarcoma (Postel-Vinay et al. 2012). Two notable risk loci were identified. The first is located upstream of *TARDBP* ($P = 1.4 \times 10^{-20}$; (OR = 2.2) and the second upstream of *EGR2* ($P = 4.0 \times 10^{-17}$; OR = 1.7). Interestingly, *EGR2* also contains a (GGAA) microsatellite with a Ewing sarcoma-associated SNP that appears to alter *EWS/FLI1* binding (Grünewald et al. 2015). The authors also showed that *EGR2* knockdown induced regression of Ewing sarcoma xenografts, increasing its plausibility as a candidate for contributing to disease development. While it is somewhat unclear how these candidates would fit in with Ewing sarcoma development, the risk haplotypes were less prevalent in African Americans. Future studies will hopefully shed more light on these candidate genomic regions and their possible role in Ewing sarcoma development.

1.4.3 RMS

As opposed to OS (Savage et al. 2013) and Ewing sarcoma (Postel-Vinay et al. 2012), there has not been a genome-wide associations study (GWAS) of RMS. Additionally, while there have been whole exome and whole genome sequencing efforts to identify somatic mutations in RMS tumors (Shern et al. 2014), to date, there have few

studies characterizing the role of germline DNA on disease susceptibility, especially among seemingly sporadic cases. There is, however, a great deal of literature to support the hypothesis that genetic susceptibility plays a role in RMS development. Numerous reports consistently highlight the fact that children with certain genetic syndromes develop RMS more frequently than their unaffected peers. The syndromes that are most commonly seen among those with eRMS are Li-Fraumeni (Diller et al. 1995), NF1 (Hartley et al. 1988b; Yang et al. 1995), Costello (Estep et al. 2006; Kratz et al. 2011); Noonan (Kratz et al. 2011), and DICER1 (Doros et al. 2012). The genes and syndromes previously identified among RMS cases are included in Table 1.3. DICER1 is particularly notable as this is a recent discovery in terms of germline genetic susceptibility to RMS. Based on smaller clinic-based studies, only about 5% of RMS cases are thought to be associated with these syndromes (Plon and Malkin 2010). Additionally, cancer predisposition syndromes appear to be more frequent in eRMS cases compared to those with aRMS (Yang et al. 1995; Estep et al. 2006; Kratz et al. 2011; Ognjanovic et al. 2012). However, there have been no large-scale population-based efforts to systematically characterize the prevalence of these variants among children with RMS.

Table 1.3 RMS predisposition syndromes and genes

Syndrome	Gene
Li-Fraumeni	*TP53*
Neurofibromatosis type 1	*NF1*
DICER1	*DICER1*
Costello	*HRAS*
Noonan	*BRAF* *KRAS* *NRAS* *PTPN11* *RAF1* *SOS1*

1.4.4 NRSTS

Several well-described cancer-predisposing germline mutations confer STS susceptibility (Table 1.4): *NF1* germline mutations (associated with Neurofibromatosis type 1) confer a 10% cumulative lifetime risk of developing MPNST (Burningham et al. 2012; Pollack and Mulvihill 1997). *RB1* germline mutations have been linked to STS, most notably leiomyosarcomas (Kleinerman et al. 2007). *DICER1* germline mutations confer pleuropulmonaryblastoma susceptibility (Slade et al. 2011). *SMARCB1*/*SMARCA4* germline mutations are associated with rhabdoid tumor predisposition (Sredni and Tomita 2015). Finally, *TP53* germline mutations (associated with Li-Fraumeni syndrome (Gonzalez et al. 2009; Li and Fraumeni Jr. 1969)); and spontaneous chromosomal instability in Werner syndrome, an autosomal recessive disorder of premature age more commonly reported in Japan than elsewhere (Goto et al. 1996), are associated with a predisposition to develop various STS types, including RMS and NRSTS.

NRSTS arising in the setting of a cancer predisposition syndrome may exhibit specific features that distinguish them from similar, spontaneous sarcomas. Familial forms of GIST,

Table 1.4 NRSTS predisposition syndromes and genes

NRSTS	Syndrome	Gene
MPNST	Neurofibromatosis type 1	*NF1*
Leiomyosarcoma	Retinoblastoma syndrome	*RB1*
Pleuropulmonaryblastoma	Pleuropulmonaryblastoma syndrome	*DICER1*
Rhabdoid tumor		*SMARCB1*/*SMARCA4*
Wild-type GIST	Neurofibromatosis type 1	*NF1*
	Carney triad	
	Carney-Stratakis syndrome	*SDHB*
Various NRSTS	Li-Fraumeni	*TP53*
Various NRSTS	Werner syndrome	

accounting for approximately 85% of pediatric and 15% of adult GISTs (Nannini et al. 2013; Corless et al. 2004), typically lack *C-KIT* or *PDGFRA* mutations (wild-type GIST (Miettinen et al. 2005)). Familial GISTs develop in individuals with neurofibromatosis type 1 (Nannini et al. 2013; Bajor 2009) and Carney triad, first described in 1977 as a triad of gastric leiomyosarcoma, extra-adrenal paraganglioma, and pulmonary chondroma (Carney et al. 1977; Matyakhina et al. 2007). Of note, familial GISTs in Carney-Stratakis syndrome, a familial predisposition to develop multifocal GISTs and multifocal paragangliomas, have been linked to succinate dehydrogenase B (*SDHB*) germline mutations (Carney and Stratakis 2002; McWhinney et al. 2007).

1.5 Conclusion

Even when using large population-based registries, the sensitivity of identifying an elevated risk of uncommon cancers depends on the categorization of cancer types, the magnitude of the association, and the incidence of these cancers in the general population. The rarity and heterogeneity of bone and soft tissue sarcomas represents a major challenge in epidemiologic studies aimed at illuminating etiologic factors. Nevertheless, descriptive epidemiology has already yielded important insights into the origins and manifestations of bone and soft tissue sarcomas and continues to provide a window into the etiologies of these malignancies. It is likely that the greatest gains in understanding the etiology of bone and soft tissue sarcomas in the near future will come from "omics" studies seeking to understand innate and exogenous factors that contribute to susceptibility. It will also be important to identify interactions between genetic and environmental factors and to conduct studies that integrate germline and somatic tumor data to determine how germline variation influences tumor mutation profiles and prognosis. For progress in these areas to occur, a coordinated investment in systematic collection of clinically annotated biological specimens (both tumor and normal) from a large number of bone and soft tissue sarcoma cases should be an international priority since cancer is a leading cause of death in children and bone and soft tissue sarcomas have very high rates of mortality and morbidity.

Acknowledgments This chapter is dedicated to our dear friend and colleague, Schuyler O'Brien (1991-2019). Schuyler was a committed scientist who worked tirelessly with the conviction that all data had the potential to become an important stepping-stone in cancer research. He was not content to make just a small contribution to the field of cancer research. Rather, he was singularly intent on dedicating all of himself to finding a cure, specifically a cure for Ewing sarcoma, a cancer he began battling at 12 years old that relapsed multiple times during his short lifetime. Facing so many relapses gave Schuyler a unique perspective, and he enjoyed gently and insightfully challenging his peers to work harder and better to understand the origins of childhood cancer. Somehow, despite years of physical suffering and intellectual exertion, Schuyler maintained a bewildering optimism and steadfast confidence in the power of science and in his ability to push through any difficulty to achieve his goals. Even though Schuyler was often—silently and unflinchingly—in pain from his multiple cancer treatments, he masterfully conducted his work over the years with an obsessive and somehow joyful passion. Schuyler never hesitated to patiently listen or lend a helping hand to his colleagues and friends. We are honored to have shared in his good-natured scientific zeal and marvel at his ability to conduct his life, like most cancer patients do, with simultaneous cynicism and hope, agony and joy. We dedicate this chapter, which Schuyler helped to write, to this young scientist who continues to serve as inspiration to all who knew him.

References

Bacci G, Ferrari S, Rosito P, et al (1992) [Ewing's sarcoma of the bone. Anatomoclinical study of 424 cases]. Minerva Pediatr 44:345–59

Bajor J (2009) [Gastrointestinal stromal tumors in neurofibromatosis type 1]. Orv Hetil 150:149–53

Balarajan R, Acheson ED (1984) Soft tissue sarcomas in agriculture and forestry workers. J Epidemiol Community Health 38:113–116

Barbanti-Brodano G, Martini F, De Mattei M, Lazzarin L, Corallini A, Tognon M (1998) BK and JC human polyomaviruses and simian virus 40: natural history of infection in humans, experimental oncogenicity, and association with human tumors. Adv Virus Res 50:69–99

Bassin EB, Wypij D, Davis RB, Mittleman MA (2006) Age-specific fluoride exposure in drinking water and osteosarcoma (United States). Cancer Causes Control 17:421–428

Basta NO, James PW, Craft AW, McNally RJ (2010) Season of birth and diagnosis for childhood cancer in Northern England, 1968-2005. Paediatr Perinat Epidemiol 24:309–318

Beck R, Monument MJ, Watkins WS et al (2012) EWS/FLI-responsive GGAA microsatellites exhibit polymorphic differences between European and African populations. Cancer Genet 205:304–312

Bhatia K, Shiels MS, Berg A, Engels EA (2012) Sarcomas other than Kaposi sarcoma occurring in immunodeficiency: interpretations from a systematic literature review. Curr Opin Oncol 24:537–546

Blakey K, Feltbower RG, Parslow RC et al (2014) Is fluoride a risk factor for bone cancer? Small area analysis of osteosarcoma and Ewing sarcoma diagnosed among 0-49-year-olds in Great Britain, 1980-2005. Int J Epidemiol 43:224–234

Buckley JD, Pendergrass TW, Buckley CM et al (1998) Epidemiology of osteosarcoma and Ewing's sarcoma in childhood: a study of 305 cases by the Children's Cancer Group. Cancer 83:1440–1448

Burningham Z, Hashibe M, Spector L, Schiffman JD (2012) The epidemiology of sarcoma. Clin Sarcoma Res 2:14

Carbone M, Rizzo P, Procopio A et al (1996) SV40-like sequences in human bone tumors. Oncogene 13:527–535

Carney JA, Stratakis CA (2002) Familial paraganglioma and gastric stromal sarcoma: a new syndrome distinct from the Carney triad. Am J Med Genet 108: 132–139

Carney JA, Sheps SG, Go VL, Gordon H (1977) The triad of gastric leiomyosarcoma, functioning extra-adrenal paraganglioma and pulmonary chondroma. N Engl J Med 296:1517–1518

Carroll-Pankhurst C, Engels EA, Strickler HD, Goedert JJ, Wagner J, Mortimer EA Jr (2001) Thirty-five year mortality following receipt of SV40- contaminated polio vaccine during the neonatal period. Br J Cancer 85:1295–1297

Chow EJ, Puumala SE, Mueller BA et al (2010) Childhood cancer in relation to parental race and ethnicity: a 5-state pooled analysis. Cancer 116:3045–3053

Comba P, Ascoli V, Belli S et al (2003) Risk of soft tissue sarcomas and residence in the neighbourhood of an incinerator of industrial wastes. Occup Environ Med 60:680–683

Cooley DM, Beranek BC, Schlittler DL, Glickman NW, Glickman LT, Waters DJ (2002) Endogenous gonadal hormone exposure and bone sarcoma risk. Cancer Epidemiol Biomarkers Prev 11:1434–1440

Cope JU, Tsokos M, Helman LJ, Gridley G, Tucker MA (2000) Inguinal hernia in patients with Ewing sarcoma: a clue to etiology. Med Pediatr Oncol 34:195–199

Corless CL, Fletcher JA, Heinrich MC (2004) Biology of gastrointestinal stromal tumors. J Clin Oncol 22:3813–3825

Cotterill SJ, Ahrens S, Paulussen M et al (2000) Prognostic factors in Ewing's tumor of bone: analysis of 975 patients from the European Intergroup Cooperative Ewing's Sarcoma Study Group. J Clin Oncol 18:3108–3114

Diamandopoulos GT (1973) Induction of lymphocytic leukemia, lymphosarcoma, reticulum cell sarcoma, and osteogenic sarcoma in the Syrian golden hamster by oncogenic DNA simian virus 40. J Natl Cancer Inst 50:1347–1365

Diller L, Sexsmith E, Gottlieb A, Li FP, Malkin D (1995) Germline p53 mutations are frequently detected in young children with rhabdomyosarcoma. J Clin Invest 95:1606–1611

Dillon P, Maurer H, Jenkins J et al (1992) A prospective study of nonrhabdomyosarcoma soft tissue sarcomas in the pediatric age group. J Pediatr Surg 27:241–244; discussion 4–5

Dockerty JD, Draper G, Vincent T, Rowan SD, Bunch KJ (2001) Case-control study of parental age, parity and socioeconomic level in relation to childhood cancers. Int J Epidemiol 30:1428–1437

Doros L, Yang J, Dehner L et al (2012) DICER1 mutations in embryonal rhabdomyosarcomas from children with and without familial PPB-tumor predisposition syndrome. Pediatr Blood Cancer 59:558–560

Dryja TP, Morrow JF, Rapaport JM (1997) Quantification of the paternal allele bias for new germline mutations in the retinoblastoma gene. Hum Genet 100:446–449

Eltom MA, Jemal A, Mbulaiteye SM, Devesa SS, Biggar RJ (2002) Trends in Kaposi's sarcoma and non-Hodgkin's lymphoma incidence in the United States from 1973 through 1998. J Natl Cancer Inst 94:1204–1210

Engels EA, Katki HA, Nielsen NM et al (2003) Cancer incidence in Denmark following exposure to poliovirus vaccine contaminated with simian virus 40. J Natl Cancer Inst 95:532–539

Estep AL, Tidyman WE, Teitell MA, Cotter PD, Rauen KA (2006) HRAS mutations in Costello syndrome: detection of constitutional activating mutations in codon 12 and 13 and loss of wild-type allele in malignancy. Am J Med Genet A 140:8–16

Fanning E (1998) Introduction to simian virus 40: getting by with more than a little help from its host cell. Dev Biol Stand 94:3–8

Fernandez MP, Krejci-Manwaring J, Davis TL (2010) Epstein-Barr virus is not associated with angioleiomyomas, or other cutaneous smooth muscle tumors in immunocompetent individuals. J Cutan Pathol 37:507–510

Finkelstein MM (1994) Radium in drinking water and the risk of death from bone cancer among Ontario youths. CMAJ 151:565–571

Finkelstein MM, Kreiger N (1996) Radium in drinking water and risk of bone cancer in Ontario youths: a second study and combined analysis. Occup Environ Med 53:305–311

Fisher SG, Weber L, Carbone M (1999) Cancer risk associated with simian virus 40 contaminated polio vaccine. Anticancer Res 19:2173–2180

Fraumeni JF (1967) Stature and malignant tumors of bone in childhood and adolescence. Cancer 20:967–973

Fraumeni JF, Glass AG (1970) Rarity of Ewing's sarcoma among U.S. Negro children. Lancet (London, England) 1:366–367

Fry SA (1998) Studies of U.S. radium dial workers: an epidemiological classic. Radiat Res 150:S21–S29

Gangwal K, Sankar S, Hollenhorst PC et al (2008) Microsatellites as EWS/FLI response elements in Ewing's sarcoma. Proc Natl Acad Sci U S A 105:10149–10154

Gelberg KH, Fitzgerald EF, Hwang SA, Dubrow R (1995) Fluoride exposure and childhood osteosarcoma: a case-control study. Am J Public Health 85: 1678–1683

Gelberg KH, Fitzgerald EF, Hwang S, Dubrow R (1997) Growth and development and other risk factors for osteosarcoma in children and young adults. Int J Epidemiol 26:272–278

Gonzalez KD, Noltner KA, Buzin CH et al (2009) Beyond Li Fraumeni syndrome: clinical characteristics of families with p53 germline mutations. J Clin Oncol 27:1250–1256

Goto M, Miller RW, Ishikawa Y, Sugano H (1996) Excess of rare cancers in Werner syndrome (adult progeria). Cancer Epidemiol Biomarkers Prev 5:239–246

Grufferman S, Wang HH, DeLong ER, Kimm SY, Delzell ES, Falletta JM (1982) Environmental factors in the etiology of rhabdomyosarcoma in childhood. J Natl Cancer Inst 68:107–113

Grufferman S, Delzell E, Delong ER (1984) An approach to conducting epidemiologic research within cooperative clinical trials groups. J Clin Oncol 2:670–675

Grufferman S, Schwartz AG, Ruymann FB, Maurer HM (1993) Parents' use of cocaine and marijuana and increased risk of rhabdomyosarcoma in their children. Cancer Causes Control 4:217–224

Grufferman S, Ruymann F, Ognjanovic S, Erhardt EB, Maurer HM (2009) Prenatal X-ray exposure and rhabdomyosarcoma in children: a report from the Children's Oncology Group. Cancer Epidemiol Biomarkers Prev 18:1271–1276

Grufferman S, Lupo PJ, Vogel RI, Danysh HE, Erhardt EB, Ognjanovic S (2014) Parental military service, agent orange exposure, and the risk of rhabdomyosarcoma in offspring. J Pediatr 165(6):1216–1221

Grünewald TGP, Bernard V, Gilardi-Hebenstreit P et al (2015) Chimeric EWSR1-FLI1 regulates the Ewing sarcoma susceptibility gene EGR2 via a GGAA microsatellite. Nat Genet 47:1073–1078

Guse CE, Marbella AM, George V, Layde PM (2002) Radium in Wisconsin drinking water: an analysis of osteosarcoma risk. Arch Environ Health 57:294–303

Gustafson P (1994) Soft tissue sarcoma. Epidemiology and prognosis in 508 patients. Acta Orthop Scand Suppl 259:1–31

Hansen MF, Koufos A, Gallie BL et al (1985) Osteosarcoma and retinoblastoma: a shared chromosomal mechanism revealing recessive predisposition. Proc Natl Acad Sci U S A 82:6216–6220

Hartley AL, Birch JM, McKinney PA et al (1988a) The inter-regional epidemiological study of childhood cancer (IRESCC): case control study of children with bone and soft tissue sarcomas. Br J Cancer 58:838–842

Hartley AL, Birch JM, Marsden HB, Harris M, Blair V (1988b) Neurofibromatosis in children with soft tissue sarcoma. Pediatr Hematol Oncol 5:7–16

Hatano M, Takada H, Nomura A et al (2006) Epstein-Barr virus-associated bronchial leiomyoma in a boy with cellular immunodeficiency. Pediatr Pulmonol 41:371–373

Hawkins MM, Wilson LM, Burton HS et al (1996) Radiotherapy, alkylating agents, and risk of bone cancer after childhood cancer. J Natl Cancer Inst 88:270–278

Herzog CE (2005) Overview of sarcomas in the adolescent and young adult population. J Pediatr Hematol Oncol 27:215–218

Holly EA, Aston DA, Ahn DK, Kristiansen JJ (1992) Ewing's bone sarcoma, paternal occupational exposure, and other factors. Am J Epidemiol 135:122–129

Hoppin JA, Tolbert PE, Flanders WD et al (1999) Occupational risk factors for sarcoma subtypes. Epidemiology 10:300–306

Howlader N, Noone AM, Krapcho M et al (eds) (2015) SEER Cancer statistics review, 1975–2012. National Cancer Institute, Bethesda

Hum L, Kreiger N, Finkelstein MM (1998) The relationship between parental occupation and bone cancer risk in offspring. Int J Epidemiol 27:766–771

Jawad MU, Cheung MC, Min ES, Schneiderbauer MM, Koniaris LG, Scully SP (2009) Ewing sarcoma demonstrates racial disparities in incidence-related and sex-related differences in outcome: an analysis of 1631 cases from the SEER database, 1973-2005. Cancer 115:3526–3536

Johnson KJ, Carozza SE, Chow EJ et al (2009) Parental age and risk of childhood cancer. Epidemiology 20:475–483

Kim FM, Hayes C, Williams PL et al (2011) An assessment of bone fluoride and osteosarcoma. J Dent Res 90:1171–1176

Kleinerman RA, Tucker MA, Abramson DH, Seddon JM, Tarone RE, Fraumeni JF Jr (2007) Risk of soft tissue sarcomas by individual subtype in survivors of hereditary retinoblastoma. J Natl Cancer Inst 99: 24–31

Kratz CP, Rapisuwon S, Reed H, Hasle H, Rosenberg PS (2011) Cancer in Noonan, Costello, cardiofaciocutaneous and LEOPARD syndromes. Am J Med Genet C Semin Med Genet 157C:83–89

Lahat G, Lazar A, Lev D (2008) Sarcoma epidemiology and etiology: potential environmental and genetic factors. Surg Clin North Am 88:451–481, v

Leonard A, Craft AW, Moss C, Malcolm AJ (1996) Osteogenic sarcoma in the Rothmund-Thomson syndrome. Med Pediatr Oncol 26:249–253

Levi F, La Vecchia C, Randimbison L, Te VC (1999) Descriptive epidemiology of soft tissue sarcomas in Vaud, Switzerland. Eur J Cancer 35:1711–1716

Levy M, Leclerc BS (2012) Fluoride in drinking water and osteosarcoma incidence rates in the continental

United States among children and adolescents. Cancer Epidemiol 36:e83–e88

Li FP, Fraumeni JF Jr (1969) Rhabdomyosarcoma in children: epidemiologic study and identification of a familial cancer syndrome. J Natl Cancer Inst 43: 1365–1373

Li FP, Fraumeni JF Jr, Mulvihill JJ et al (1988) A cancer family syndrome in twenty-four kindreds. Cancer Res 48:5358–5362

Lupo PJ, Zhou R, Skapek SX et al (2014a) Allergies, atopy, immune-related factors and childhood rhabdomyosarcoma: a report from the Children's Oncology Group. Int J Cancer 134:431–436

Lupo PJ, Danysh HE, Skapek SX et al (2014b) Maternal and birth characteristics and childhood rhabdomyosarcoma: a report from the Children's Oncology Group. Cancer Causes Control 25:905–913

Lupo PJ, Danysh HE, Plon SE et al (2015) Family history of cancer and childhood rhabdomyosarcoma: a report from the Children's Oncology Group and the Utah population database. Cancer Med 4:781–790

Matyakhina L, Bei TA, McWhinney SR et al (2007) Genetics of carney triad: recurrent losses at chromosome 1 but lack of germline mutations in genes associated with paragangliomas and gastrointestinal stromal tumors. J Clin Endocrinol Metab 92:2938–2943

McGuire SM, Vanable ED, McGuire MH, Buckwalter JA, Douglass CW (1991) Is there a link between fluoridated water and osteosarcoma? J Am Dent Assoc 122:38–45

McNally RJ, Alexander FE, Bithell JF (2006) Space-time clustering of childhood cancer in great Britain: a national study, 1969-1993. Int J Cancer 118:2840–2846

McNally RJ, Blakey K, Parslow RC et al (2012) Small-area analyses of bone cancer diagnosed in Great Britain provide clues to aetiology. BMC Cancer 12:270

McWhinney SR, Pasini B, Stratakis CA (2007) Familial gastrointestinal stromal tumors and germ-line mutations. N Engl J Med 357:1054–1056

Mendoza SM, Konishi T, Miller CW (1998) Integration of SV40 in human osteosarcoma DNA. Oncogene 17:2457–2462

Menu-Branthomme A, Rubino C, Shamsaldin A et al (2004) Radiation dose, chemotherapy and risk of soft tissue sarcoma after solid tumours during childhood. Int J Cancer 110:87–93

Miettinen M, Sobin LH, Lasota J (2005) Gastrointestinal stromal tumors of the stomach: a clinicopathologic, immunohistochemical, and molecular genetic study of 1765 cases with long-term follow-up. Am J Surg Pathol 29:52–68

Miller CW, Aslo A, Won A, Tan M, Lampkin B, Koeffler HP (1996) Alterations of the p53, Rb and MDM2 genes in osteosarcoma. J Cancer Res Clin Oncol 122:559–565

Mirabello L, Troisi RJ, Savage SA (2009) International osteosarcoma incidence patterns in children and adolescents, middle ages and elderly persons. Int J Cancer 125:229–234

Mirabello L, Pfeiffer R, Murphy G et al (2011a) Height at diagnosis and birth-weight as risk factors for osteosarcoma. Cancer Causes Control 22:899–908

Mirabello L, Yu K, Berndt SI et al (2011b) A comprehensive candidate gene approach identifies genetic variation associated with osteosarcoma. BMC Cancer 11:209

Mirabello L, Yeager M, Mai PL et al (2015a) Germline TP53 variants and susceptibility to osteosarcoma. J Natl Cancer Inst 107:djv101

Mirabello L, Koster R, Moriarity BS et al (2015b) A genome-wide scan identifies variants in NFIB associated with metastasis in patients with osteosarcoma. Cancer Discov 5:920–931

Monument MJ, Johnson KM, McIlvaine E et al (2014) Clinical and biochemical function of polymorphic NR0B1 GGAA-microsatellites in Ewing sarcoma: a report from the Children's Oncology Group. PLoS One 9:e104378

Moss ME, Kanarek MS, Anderson HA, Hanrahan LP, Remington PL (1995) Osteosarcoma, seasonality, and environmental factors in Wisconsin, 1979-1989. Arch Environ Health 50:235–241

Musselman JR, Bergemann TL, Ross JA et al (2012) Case-parent analysis of variation in pubertal hormone genes and pediatric osteosarcoma: a Children's Oncology Group (COG) study. Int J Mol Epidemiol Genet 3:286–293

Nannini M, Biasco G, Astolfi A, Pantaleo MA (2013) An overview on molecular biology of KIT/PDGFRA wild type (WT) gastrointestinal stromal tumours (GIST). J Med Genet 50:653–661

Nishijo K, Nakayama T, Aoyama T et al (2004) Mutation analysis of the RECQL4 gene in sporadic osteosarcomas. Int J Cancer 111:367–372

Ognjanovic S, Linabery AM, Charbonneau B, Ross JA (2009) Trends in childhood rhabdomyosarcoma incidence and survival in the United States, 1975-2005. Cancer 115:4218–4226

Ognjanovic S, Olivier M, Bergemann TL, Hainaut P (2012) Sarcomas in TP53 germline mutation carriers: a review of the IARC TP53 database. Cancer 118:1387–1396

Olin P, Giesecke J (1998) Potential exposure to SV40 in polio vaccines used in Sweden during 1957: no impact on cancer incidence rates 1960 to 1993. Dev Biol Stand 94:227–233

Olson JM, Breslow NE, Beckwith JB (1993) Wilms' tumour and parental age: a report from the National Wilms' Tumour Study. Br J Cancer 67:813–818

Operskalski EA, Preston-Martin S, Henderson BE, Visscher BR (1987) A case-control study of osteosarcoma in young persons. Am J Epidemiol 126:118–126

Pappo AS, Janeway KA (2009) Pediatric gastrointestinal stromal tumors. Hematol Oncol Clin North Am 23:15–34, vii

Pappo AS, Pratt CB (1997) Soft tissue sarcomas in children. Cancer Treat Res 91:205–222

Plon SE, Malkin D (2010) Childhood cancer and heredity. In: Pizzo PA, Poplack DG (eds) Principles and practice of pediatric oncology, 6th edn. Lippincott Williams & Wilkins, Philadelphia, p 1600

Pollack IF, Mulvihill JJ (1997) Neurofibromatosis 1 and 2. Brain Pathol 7:823–836

Postel-Vinay S, Veron AS, Tirode F et al (2012) Common variants near TARDBP and EGR2 are associated with susceptibility to Ewing sarcoma. Nat Genet 44:323–327

Price CH (1958) Primary bone-forming tumours and their relationship to skeletal growth. J Bone Joint Surg Br 40-B:574–593

Pui CH, Dodge RK, George SL, Green AA (1987) Height at diagnosis of malignancies. Arch Dis Child 62:495–499

Pukkala E, Martinsen JI, Lynge E et al (2009) Occupation and cancer—follow-up of 15 million people in five Nordic countries. Acta Oncol 48:646–790

Ries LA, Smith MA, Gurney JG et al (1999) Cancer incidence and survival among children and adolescents: United States SEER program 1975–1995. National Cancer Institute, SEER Program, Bethesda. Report No.: 99-4649

Ross JA, Severson RK, Davis S, Brooks JJ (1993) Trends in the incidence of soft tissue sarcomas in the United States from 1973 through 1987. Cancer 72:486–490

Ross JA, Severson RK, Swensen AR, Pollock BH, Gurney JG, Robison LL (1999) Seasonal variations in the diagnosis of childhood cancer in the United States. Br J Cancer 81:549–553

Rubino C, Shamsaldin A, Le MG et al (2005) Radiation dose and risk of soft tissue and bone sarcoma after breast cancer treatment. Breast Cancer Res Treat 89:277–288

Ruza E, Sotillo E, Sierrasesumaga L, Azcona C, Patino-Garcia A (2003) Analysis of polymorphisms of the vitamin D receptor, estrogen receptor, and collagen Ialpha1 genes and their relationship with height in children with bone cancer. J Pediatr Hematol Oncol 25:780–786

Savage SA, Modi WS, Douglass CW, Hoover RN, Chanock SJ (2006) Identification of a haplotype block in IGF2R associated with increased risk for osteosarcoma. American Association of Cancer Research Annual Meeting, Washington, DC

Savage SA, Mirabello L, Wang Z et al (2013) Genome-wide association study identifies two susceptibility loci for osteosarcoma. Nat Genet 45:799–803

Schuz J, Forman MR (2007) Birthweight by gestational age and childhood cancer. Cancer Causes Control 18:655–663

Shern JF, Chen L, Chmielecki J et al (2014) Comprehensive genomic analysis of rhabdomyosarcoma reveals a landscape of alterations affecting a common genetic axis in fusion-positive and fusion-negative tumors. Cancer Discov 4:216–231

Silcocks PB, Murrells T (1987) Space-time clustering and bone tumours: application of Knox's method to data from a population-based cancer registry. Int J Cancer 40:769–771

Slade I, Bacchelli C, Davies H et al (2011) DICER1 syndrome: clarifying the diagnosis, clinical features and management implications of a pleiotropic tumour predisposition syndrome. J Med Genet 48:273–278

Sredni ST, Tomita T (2015) Rhabdoid tumor predisposition syndrome. Pediatr Dev Pathol 18:49–58

Stiller CA, McKinney PA, Bunch KJ, Bailey CC, Lewis IJ (1991) Childhood cancer and ethnic group in Britain: a United Kingdom Children's Cancer Study Group (UKCCSG) study. Br J Cancer 64:543–548

Storm HH (1994) Cancers of the soft tissues. Cancer Surv 19–20:197–217

Strickler HD, Rosenberg PS, Devesa SS, Hertel J, Fraumeni JF Jr, Goedert JJ (1998) Contamination of poliovirus vaccines with simian virus 40 (1955-1963) and subsequent cancer rates. JAMA 279:292–295

Sultan I, Qaddoumi I, Yaser S, Rodriguez-Galindo C, Ferrari A (2009) Comparing adult and pediatric rhabdomyosarcoma in the surveillance, epidemiology and end results program, 1973 to 2005: an analysis of 2,600 patients. J Clin Oncol 27:3391–3397

Tirode F, Surdez D, Ma X et al (2014) Genomic landscape of Ewing sarcoma defines an aggressive subtype with co-association of STAG2 and TP53 mutations. Cancer Discov 4:1342–1353

Tjalma RA (1966) Canine bone sarcoma: estimation of relative risk as a function of body size. J Natl Cancer Inst 36:1137–1150

Toro JR, Travis LB, Wu HJ, Zhu K, Fletcher CD, Devesa SS (2006) Incidence patterns of soft tissue sarcomas, regardless of primary site, in the surveillance, epidemiology and end results program, 1978-2001: an analysis of 26,758 cases. Int J Cancer 119:2922–2930

Tran T, Davila JA, El-Serag HB (2005) The epidemiology of malignant gastrointestinal stromal tumors: an analysis of 1,458 cases from 1992 to 2000. Am J Gastroenterol 100:162–168

Troisi R, Stephansson O, Jacobsen J et al (2014) Perinatal characteristics and bone cancer risk in offspring—a Scandinavian population-based study. Acta Oncol 53:830–838

Tucker MA, D'Angio GJ, Boice JD Jr et al (1987) Bone sarcomas linked to radiotherapy and chemotherapy in children. N Engl J Med 317:588–593

UK CR (2008–2010) Soft tissue sarcoma incidence statistics. https://www.cancerresearchukorg/health-professional/cancer-statistics/statistics-by-cancer-type/soft-tissue-sarcoma/incidence

Valery PC, McWhirter W, Sleigh A, Williams G, Bain C (2002) Farm exposures, parental occupation, and risk of Ewing's sarcoma in Australia: a national case-control study. Cancer Causes Control 13:263–270

Valery PC, McWhirter W, Sleigh A, Williams G, Bain C (2003) A national case-control study of Ewing's sarcoma family of tumours in Australia. Int J Cancer 105:825–830

Valery PC, Holly EA, Sleigh AC, Williams G, Kreiger N, Bain C (2005) Hernias and Ewing's sarcoma family of tumours: a pooled analysis and meta-analysis. Lancet Oncol 6:485–490

Viel JF, Arveux P, Baverel J, Cahn JY (2000) Soft-tissue sarcoma and non-Hodgkin's lymphoma clusters around a municipal solid waste incinerator with high dioxin emission levels. Am J Epidemiol 152:13–19

Virtanen A, Pukkala E, Auvinen A (2006) Incidence of bone and soft tissue sarcoma after radiotherapy: a cohort study of 295,712 Finnish cancer patients. Int J Cancer 118:1017–1021

Wang LL, Gannavarapu A, Kozinetz CA et al (2003) Association between osteosarcoma and deleterious mutations in the RECQL4 gene in Rothmund-Thomson syndrome. J Natl Cancer Inst 95:669–674

Wibmer C, Leithner A, Zielonke N, Sperl M, Windhager R (2010) Increasing incidence rates of soft tissue sarcomas? A population-based epidemiologic study and literature review. Ann Oncol 21:1106–1111

Wingren G, Fredrikson M, Brage HN, Nordenskjold B, Axelson O (1990) Soft tissue sarcoma and occupational exposures. Cancer 66:806–811

Winn DM, Li FP, Robison LL, Mulvihill JJ, Daigle AE, Fraumeni JF (1992) A case-control study of the etiology of Ewing's sarcoma. Cancer Epidemiol Biomarkers Prev 1:525–532

Wong FL, Boice JD Jr, Abramson DH et al (1997) Cancer incidence after retinoblastoma. Radiation dose and sarcoma risk. JAMA 278:1262–1267

Wu XC, Chen VW, Steele B et al (2003) Cancer incidence in adolescents and young adults in the United States, 1992-1997. J Adolesc Health 32:405–415

Yamamoto H, Nakayama T, Murakami H et al (2000) High incidence of SV40-like sequences detection in tumour and peripheral blood cells of Japanese osteosarcoma patients. Br J Cancer 82:1677–1681

Yang P, Grufferman S, Khoury MJ et al (1995) Association of childhood rhabdomyosarcoma with neurofibromatosis type I and birth defects. Genet Epidemiol 12:467–474

Yip BH, Pawitan Y, Czene K (2006) Parental age and risk of childhood cancers: a population-based cohort study from Sweden. Int J Epidemiol 35:1495–1503

Zahm SH, Fraumeni JF Jr (1997) The epidemiology of soft tissue sarcoma. Semin Oncol 24:504–514

Zhang J, Walsh MF, Wu G et al (2015) Germline mutations in predisposition genes in pediatric cancer. N Engl J Med 373:2336–2346

Zucman-Rossi J, Batzer MA, Stoneking M, Delattre O, Thomas G (1997) Interethnic polymorphism of EWS intron 6: genome plasticity mediated by Alu retroposition and recombination. Hum Genet 99:357–363