(i) Epidemiology of bone and soft-tissue sarcomas

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Abstract

Sarcomas are malignant tumours of connective tissue and account for around 1% of all the cancer diagnoses in the UK each year. Sarcomas can be categorized as being of either bone or soft tissue in origin and both categories consist of a wide variety of histological subtypes. Most sarcomas (about 55%) affect limbs, most frequently the leg; about 15% affect the head and neck area or are found externally on the trunk, while the remainder are internal and located in the retroperitoneum or abdomen. A number of environmental factors including radiation exposure, viral infection, occupation and chemical exposure have been linked to the development of sarcomas. A number of heritable conditions, including Li—Fraumeni syndrome, neurofibromatosis, retinoblastoma and Werner's syndrome, are associated with an increased risk of sarcoma development. This article reviews the epidemiology of bone and soft-tissue sarcomas and highlights its relevance with regard to sarcoma diagnosis and the potential development of new treatments.

Keywords bone; epidemiology; sarcoma; soft-tissue

Introduction

Sarcomas are malignant tumours of connective tissue. Soft tissue sarcomas are tumours arising from mesechymal tissue, which consists of muscle, fat, blood vessels, fibrous and other supporting tissue, whereas bone sarcomas are tumours of the skeleton.[1] The incidence of soft tissue sarcoma is approximately 30 per million[2] and accounts for less than 1% of all malignant neoplasms. There are no data to suggest a change in the incidence of soft tissue sarcoma over time or any geographic variation. Bone sarcomas occur at a rate approximately one third that of their soft tissue counterparts[3] and there are approximately 300 to 400 cases a year in the UK.[4] Osteosarcoma is the most common and accounts for over 35% of primary bone sarcoma cases. Chondrosarcoma (26%) and Ewing's sarcoma (16%) are the next most common primary bone sarcomas.[3]

Several factors conspire to leave a relative paucity of information on the descriptive epidemiology of bone and soft tissue sarcomas. The main reason for this is the fact that cancer registry data are presented in terms of the primary site of the cancer rather than its histological type. The most commonly used system is the International Classification of Diseases (ICD), as used by the Office for National Statistics in compiling the cancer statistics for the UK.[4]

The ICD enables malignant bone and cartilage neoplasms to be defined as a single group, though it is impossible to further subdivide this group in order to distinguish between osteosarcoma and chondrosarcoma, for example. There are further problems when trying to interpret the statistics as regards soft tissue sarcomas. One code 'malignant neoplasm of connective and other soft tissue' includes both sarcomas and non-sarcomatous neoplasms, whilst many sarcomas can be found in other diverse groups, such as 'malignant neoplasms of the retroperitoneum' and 'malignant neoplasms of other and ill-defined sites'. This reflects the complexity of the treatment of sarcoma, with over 50 different histiological sub-types and emergence at all body sites, demanding input from a range of clinicians, each with a site-specific interest.

Age and site distribution

Soft tissue sarcoma

Three quarters of soft tissue sarcomas are located in the limbs and the median age at diagnosis is 65 years. Sarcomas are histologically classified by their presumed cell of origin. The most common types are malignant fibrous histiocytoma (MFH), leiomyosarcoma and liposarcoma. In children rhabdomyosarcoma is predominant. For all cell types combined, and for most individual types, there is a male preponderance. This is especially true for blood vessel sarcomas largely because of Kaposi's sarcoma, which has an increased incidence in white males attributable to the acquired immune deficiency syndrome (AIDS). The age related incidence depends on the histological sub-type of tumour; for example synovial sarcoma is most common in young adults whilst liposarcoma and leiomyosarcoma dominate in the elderly.

Bone sarcoma

The age-related incidence rates of bone sarcomas are bimodal. The first peak occurs in the second decade of life (Figures 1 and 2), while the second peak is after the age of sixty years. This is clearly different to the age-related incidence rates of soft tissue sarcomas, which increase gradually with increasing age (Table 1).

The most common bone sarcoma, osetosarcoma, predominates in patients under the age of twenty and the majority are located in the long bones. This predilection for the long bones tends to decrease with increasing age. Ewing's sarcoma has a similar peak incidence in the second decade of life and tends to arise in the diaphyseal areas of the long bones, as opposed to osteosarcoma, which is more frequently found in the metaphyseal areas (Figure 3). Ewing's sarcoma occurs almost exclusively in the white population, unlike osteosarcoma which is equally distributed across different racial groups. Chondrosarcoma shows a gradual increase in incidence that continues into the eighth decade of life. There is no clear difference in incidence between races and sexes.

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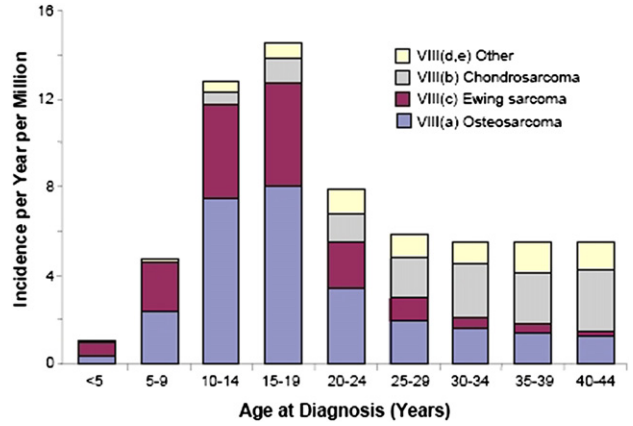

Figure 1 The incidence of bone sarcomas by type (SEER 1975–2000).[5]

Environmental factors

Radiation

There is strong evidence that radiation exposure increases the risk of developing both bone and soft tissue sarcomas. Numerous studies of patients treated with ionizing radiation have observed an increased risk of sarcoma. The incidence of sarcomas after radiotherapy ranges from one in several thousand to around one percent.

This association was first noticed in the early 20th century by Beck, who commented on an unusually high incidence of sarcomas in patients who had previously been irradiated for tuberculous arthritis.[6] Further work from Martland and Humphreys[7] in 1929 went further to confirming the causal link. They reported 42 bone sarcomas in 1468 female watch-dial painters, representing an incidence of 2.8%. Over the following years there were several more reports of sarcomas in patients who had previously been irradiated, and in 1948, Cahan[8] proposed a series of diagnostic criteria for radiation-induced sarcoma of bone, which have since been modified by Arlen.[9] These criteria include the need for histologically proven sarcoma development after an appropriately long latent period (3–5 years) in an irradiated area that was without evidence of such tumour before the irradiation.

The majority of post-radiation sarcomas occur in bone, though soft tissue sarcomas may also occur following radiation.

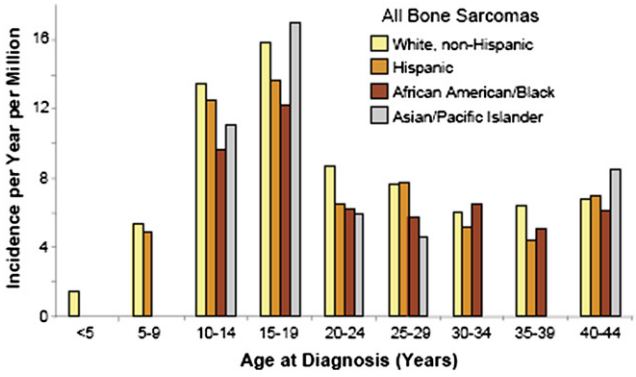

Figure 2 Incidence of All Bone Sarcomas by Race/Ethnicity, SEER 1990–2000.[5]

A review of 344 cases of post-radiation sarcoma[10] revealed osteosarcoma to be the most common, followed respectively by malignant fibrous histiocytoma and lymphangiosarcoma. It was hypothesized that the high incidence of bone tumours was related to a greater absorption of radiation by bone. A large number of these post-radiation sarcomas presented relatively late and the prognosis was generally poor. The incidence of soft tissue sarcoma following radiotherapy in the treatment of breast cancer has been studied by Karlsson et al.[11] Over 100 000 women from the Swedish Cancer Register were followed up for soft tissue sarcoma, and it was found that, for all sarcomas other than angiosarcoma, the integral dose of radiotherapy was a predictor of risk. Other studies have suggested that young children may be more susceptible to the carcinogenic effects of radiation. Ron et al.[12] observed 10 834 children who had received radiotherapy to the scalp for the treatment of ringworm over a twelve year period from 1948 to 1960. Six of these children developed bone or soft tissue sarcomas, with five of the six occurring in the irradiated field.

Viral infection and immunodeficiency

Kaposi's sarcoma is a very rare malignancy except in association with human immunodeficiency virus 1 (HIV-1) infection, when its risk of occurrence is increased by up to seventy thousand times. Human herpes virus 8 (HHV-8) has been found to be associated with all forms of Kaposi's sarcoma and is necessary for the development of this tumour.[13] Some evidence suggests that HIV-1 plays a more indirect role in the aetiological process by causing immunosuppression and facilitating coninfection with HHV-8, though other data supports a more direct involvement of HIV-1 in the tumour development process.[14]

An increased risk of soft tissue sarcoma has been reported among patients receiving therapeutic immunosuppression for renal transplants and other conditions. Soft tissue sarcoma is also excessively common amongst patients with primary immunodeciciency syndromes, certain lymphoproliferative conditions and some autoimmune diseases. Epstein Barr virus has been associated with smooth muscle tumours in immunodeficient patients. Stewart-Treves syndrome indicates the development of angiosarcoma in patients with long-standing chronic lymphoedema and some authors have attributed this phenomenon to acquired regional immunodeficiency.

Occupational and chemical

Soft tissue sarcomas have been associated with phenoxyherbicides, chlorophenols and dioxin exposure. However, not all studies have found elevated risks associated with exposure to these agents.[15] Specifically, malignant fibrous histiocytoma and leiomyosarcoma appear to be the soft tissue sarcomas that are most associated with the aforementioned agents. Occupational factors linked to soft tissue sarcomas include woodworking, construction work, solvent exposure, farming and leather tanning. Carpentry, medical research, arsenic exposure, meat packing and oil refinery work have all been linked to bone sarcoma. The inconsistent evidence in this area may well be as a result of different disease aetiologies across the sarcoma subtypes.

Various implant materials, including chromium, nickel, cobalt, titanium and polyethylene, have been suspected as risks