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REVIEW ARTICLES

Etiologic, Environmental and Inherited Risk Factors in Sarcomas

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Sarcomas are a rare group of mesenchymal tumors affecting a younger population. The etiology remains unknown in most cases. Environmental factors that increase sarcoma risk include radiation exposure and chemical carcinogens. Several familial cancer syndromes confer sarcoma predisposition, such as the Li-Fraumeni Syndrome (LFS). In this increasingly genomic focussed era of medicine, it will be clinically important to understand the genetic basis of sarcoma risk.
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KEY WORDS: familial cancer syndrome; genetic sarcoma risk; sarcoma etiology

INTRODUCTION

Sarcomas are a complex group of rare malignant connective tissue tumors, comprised of over 50 subtypes, each of which is genetically and pathologically distinct. Although precise estimates are difficult to obtain, the annual incidence of all sarcomas approximates 30/million population [1]. Importantly, sarcomas disproportionately affect a young population comprising 20% of childhood cancers, and 10% of cancers in adolescents and young adults. In particular, bone sarcomas (Ewing sarcoma and osteosarcoma) are essentially diseases of the young, while the median age of onset of soft-tissue sarcomas is somewhat older (65 years [1]). Early age of onset is a predictor of inherited or constitutive cancer risk, suggesting the importance of genetic factors in sarcoma development in general.

There is evidence for ethnic variation in the spectrum of connective tissue tumors, with Ewing sarcoma reportedly rare in African American populations [2], and giant cell tumor of bone being more common in Asians [3]. A recent survey of racial and ethnic differences in the incidence of sarcoma subtypes amongst adolescents and young adults in the United States found that Hispanics had higher incidences of liposarcoma, African Americans had a higher incidence of fibromatous sarcomas, while Caucasians had a higher incidence of synovial sarcoma [4].

There are several issues potentially limiting sarcoma data collection and analysis. Accurate population-level ascertainment of case numbers is not always easily available, and pathological subtypes are frequently misreported. Cancer incidence is often reported by topography rather than morphology leading to an under representation of sarcoma incidence in some subtypes. For example, uterine leiomyosarcoma and breast angiosarcomas are frequently coded as gynecologic and breast cancers, respectively. Additionally, some estimates suggest that 20% of sarcoma diagnoses are revised substantially on central expert review [5,6]. Assuming each subtype has a distinct genetic and environmental etiology, the rarity of individual subtypes further exacerbates challenges in identifying causal associations. For this reason, and because the classifications of sarcoma have substantially evolved over the past 20 years, there is a tendency to pool sarcoma subtypes in retrospective epidemiologic studies. Whilst this achieves statistical power, it probably results in loss of signal for subtype-specific risk factors.

On the other hand, sarcomas are sufficiently rare that their incidence is notable clinically, a feature that has paradoxically led to the mapping of many dominant Mendelian cancer syndromes, including the Retinoblastoma and Li-Fraumeni syndromes (LFS), as well as environmental risk factors such as radiation, carcinogens, and viruses. Benign connective tissue tumors are estimated to be 100 times more common than sarcomas. A subset of benign tumors, including peripheral nerve sheath tumors, giant cell tumor of bone, and some cartilage tumors, undergo malignant degeneration to true sarcoma. Moreover, distinguishing between benign and malignant tumors can be challenging because the histologic appearances can be ambiguous, and some connective tissue tumors may have "malignant" behavior while being considered "benign." For example, giant cell tumor of bone may metastasise to the lung—a characteristic usually considered diagnostic of malignancy. Finally, some connective tissue tumors have a truly "intermediate" phenotype exemplified by aggressive fibromatosis. Benign connective tissue tumors form part of the spectrum of tumors in inherited cancer syndromes.

We describe here the known heritable, environmental, and other genetic risk factors associated with sarcomas (Table I) and propose that in this era of genomic cancer medicine that understanding the genetic basis for cancer risk will be increasingly important clinically.

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TABLE I. Risk Factors for Sarcoma Subtypes

Sarcoma	Risk factor	Heritable (H) Environ (E) Other (O)	Gene	Quality of evidence
Chondrosarcoma	Multiple osteochondromas	H	*EXT1*	High
	Maffuci syndrome	O		High
	Ollier disease	O	*PTHR1*	High
Embryonal rhabdomyosarcoma	Beckwith–Wiedemann syndrome	H	*CDKN1C*, *IGF2*	High
GIST	Familial GIST	H	*KIT*, *PDGFRA*	High
Hepatic angiosarcoma	Anabolic steroids	E	—	Very low
	Arsenic	E	—	Low
	Thorotrast	E	—	Low
	Vinyl chloride	E	—	High
Kaposi sarcoma	KSHV (HHV8)	E	—	High
KS and leiomyosarcoma	Immunosuppression	O	—	Medium
	Organ transplant	O	—	Low
Leiomyosarcoma	Epstein–Barr virus	E	—	Very low
Lymphangiosarcoma	Lymphedema	O	—	High
MPNST	Neurofibromatosis type 1	H	*NF1*	High
Malignant rhabdoid tumors	Rhabdoid predisposition syndrome	H	*SMARCB1*	High
Myogenic sarcomas	Rubinstein-Taybi syndrome	H	*CREBBP*	High
Osteosarcoma and STS	Li Fraumeni syndrome	H	*TP53*	High
	Retinoblastoma	H	*RB*	High
	Chlorophenols	E	—	Very low
	Ionising radiation	E	—	High
	Phenoxyherbicides	E	—	Very low
	Trauma	O	—	Very low
Osteosarcoma	Bloom syndrome	H	*BLM*	High
	Familial Paget disease of bone	H	*TNFRSF11A*	High
	Rothmund–Thomson syndrome	H	*RECQL4*	High
	SV-40	E	—	Very low
	Paget disease of bone	O	—	High
	Mazabraud syndrome	O	*GNAS1*	High
	McCune-Albright syndrome	O	*GNAS1*	High
Schwannomas	Neurofibromatosis type 2	H	*NF2*	High
STS and bone tumors	Werner syndrome	H	*WRN*	High

GIST, gastrointestinal stromal tumor; MPNST, malignant peripheral nerve sheath tumor; STS, soft tissue sarcomas; KS, Kaposi sarcoma

ENVIRONMENTAL RISK FACTORS

The etiology of the majority of sarcomas is unknown, but include carcinogens, viruses, as well as ionising radiation. The strongest evidence for an environmental cause relates to ionising radiation. Bone-homing radio-isotopes, such as strontium-89, cause osteosarcoma in animals [7–9]. Long-term occupational exposure to radiation increased the incidence of bone tumors [10,11]. Atomic bomb survivors have an increased incidence of many cancers including sarcomas [12]. Patients who have been treated with radiotherapy show an increased incidence of in-field soft-tissue and bone sarcomas [13,14].

The Childhood Cancer Survivor Study found the risk of secondary sarcoma was ninefold higher among this group compared to the general population and was strongly associated with radiation therapy [15]. Chemotherapy, including anthracyclines or alkylating agents also increased the risk of secondary sarcomas in these childhood survivors by ~twofold [15]. Interactions between environmental and inherited factors appear important. Some familial cancer syndromes may be particularly susceptible to radiation-induced tumorigenesis [16–19].

Animal studies suggest that various chemicals or drugs may cause sarcomas. In mice, methylcholanthrene reproducibly induces fibrosarcomas [20], while therapeutic administration of parathyroid hormone is associated with osteosarcoma in Fischer 344 rats [21,22]. Importantly, animals fundamentally differ from man, and this association has not been confirmed in man [22]. Riddelline, o-nitrotoluene, and benzophenone exposures induce sarcomas in rats and mice [23,24]. A study of occupational risk factors in Europe found significantly increased risk for bone sarcoma in woodworkers, bricklayers, blacksmiths, and toolmakers [25]. Exposure to pesticide, insecticides, and herbicides was also shown to slightly increase risk although details of chemical constituents were not included. Herbicides and pesticides containing phenoxyacetic acids may be associated with increased sarcoma rates [26,27], both contaminated [28] and free of dioxins [29], although this association has not been confirmed by other studies [30,31]. Studies of the contributions of chlorophenols and dioxins have been inconsistent [32–35]. Vinyl chloride, arsenic, anabolic steroids, and thorium may be moderately strongly associated with an increased risk of hepatic angiosarcomas [36–42]. Water fluoridation is probably not associated with an increased risk of osteosarcoma [43].

Animal studies show that viruses can cause sarcomas. The *Src* oncogene was first isolated from the Rous sarcoma virus [44], and there are many other examples. There is little evidence that viruses are associated with human sarcomas, with the exception of Kaposi sarcoma and Kaposi sarcoma-associated herpesvirus (KSHV), also known as HHV8 [45]. Kaposi sarcoma is a tumor of lymphatic endothelial cells, rather than true mesenchyme, and KSHV sequences were first isolated from AIDS-associated Kaposi sarcoma [46,47]. Perhaps most data exist for SV40 DNA sequences identified in human osteosarcoma [48,49]. In AIDS cases, leiomyosarcomas associated with Epstein–Barr virus have been reported [50,51] and have also been described in transplant recipients [52,53]. Overall, however, the evidence supporting a significant etiologic role for viruses in sarcoma development is weak.

Other risk factors for sarcoma have been reported, with varying levels of evidence. Stewart and Treves first described lymphedema, as a factor in the development of lymphangiosarcoma [54]. Whether prior trauma predisposes to sarcomas is unproven. Patients undergoing arthroplasties

have not shown an elevated incidence of sarcoma [55,56]. In elite athletes, an increased incidence of sarcoma was observed with the suggested contributory factor being prior sporting injury [57]. An early study linked high body mass index with increased sarcoma risk [58], and both diabetes and obesity are associated with an increased risk of uterine sarcomas [59]. Osteosarcoma is markedly more common during the adolescent growth spurt, suggesting a strong effect of pubertal bone growth [60].

HERITABLE RISK FACTORS

To date the heritable aspects of sarcoma have been studied to a lesser degree than other cancers with most genetic research focused on breast, bowel, and ovarian cancers, where 22–35% of the etiology is thought to be heritable [61]. Sarcomas are more common in certain familial cancer syndromes, including LFS, Retinoblastoma, Gardner's and Werner's syndromes, NF1, and some immunodeficiency conditions [62]. A third of pediatric sarcomas are associated with a significant incidence of cancer in relatives [63,64], while sarcomas are sixfold more common in relatives of children with sarcoma than age-matched controls [65]. A population-based study found that one in five sarcoma survivors developed a second cancer within 10 years, and the risk of a second sarcoma was increased 18- to 30-fold [66], with a 5.3-fold increased risk of sarcomas in parents of patients with leiomyosarcoma [67]. A recent Swiss study found that excess secondary sarcoma risk was observed after skin melanoma, breast cancer, uterine cancer, testicular cancer, thyroid cancer, Hodgkin lymphoma, and leukemias [68]. Taken together, these data strongly support a genetic component to sarcomas in particular.

KNOWN SARCOMA PREDISPOSITION SYNDROMES

LFS is a rare, dominant Mendelian cancer syndrome characterized by early onset of a variety of tumor types, most commonly sarcomas (both soft-tissue and bone), early-onset breast cancer, brain tumors, leukemia, and adrenocortical carcinoma[69,70]. The majority of mutations identified to date in families with LFS involve the *TP53* gene. Mutation carriers within LFS families are reported to have a 50% chance of developing cancer by the age of 30 years [71]. Approximately 2–4% of individuals affected by sarcoma will carry mutations in *TP53*, regardless of family history [72].

The IARC database now catalogues over 20,000 reported mutations and variants in *TP53*, which comprise over 350 pathogenic types [73]. Most mutations arise in the DNA-binding domains, but more subtle consequences may arise from variants located outside these critical domains. Specific mutations in *TP53* are associated with different penetrance and cancer types [74]. An interesting specific case is the relatively high frequency of the p.R337H mutation in Southern Brazil, where it is associated with increased risks of breast cancer and adrenocortical cancer [75].

Carriers of mutations in *TP53* experience an estimated second cancer risk of 57% at 30 years after a first cancer diagnosis [18,76], up to 83 times higher than the population at large. Two recent studies suggest that screening may be useful in early cancer detection in LFS patients, including children [77,78]. Breast screening with MRI is now recommended from 25 years for female *TP53* mutation carriers [79]. Avoidance of unnecessary ionising radiation in mutation carriers is important if possible without compromising care. Minimising unnecessary computed tomographic or X-ray surveillance is also sensible [80].

Fully 30% of LFS and up to 80% of Li Fraumeni like kindreds are due to hereditary events not involving *TP53* itself [73]. *CHK2* variant 1100delC has been reported in 2/44 families with LFS/LFL, but interestingly these families were considered atypical because of lack of sarcomas [81], and the role of *CHK2* is controversial [82,83].

The Retinoblastoma syndrome (RB) is a rare autosomal dominant familial cancer syndrome. RB is associated with the childhood tumor, retinoblastoma. Survival rates following retinoblastoma are excellent (90% at 10 years [17]). In survivors of childhood retinoblastoma, the second most commonly reported cancer type is osteosarcoma, with a standardized incidence ratio of 360 compared to the population at large [84,85]. There is also an increased risk of soft-tissue sarcomas, with a cumulative risk of 13.1% at 50 years follow up. Both chemotherapy and radiotherapy exposure are associated with an increased risk [85].

There are two forms of neurofibromatosis, NF1 and NF2. NF1 is a relatively common autosomal dominant disease, occurring in up to 1/2500 live births [86]. Clinical manifestations include café au lait pigmentation, Lisch nodules, neurofibromas, optic pathway gliomas, and bony dysplasias in the context of a family history [86]. The neurofibromas are prone to malignant degeneration, with a 1/10 lifetime chance of developing malignant peripheral nerve sheath tumors [87]. Overall, patients with NF1 have a 34-fold increased risk of dying with a malignant connective tissue of soft-tissue neoplasm, exacerbated by exposure to radiotherapy [19,88]. Malignant transformation is associated with a poor prognosis, and close surveillance is recommended to facilitate effective surgical treatment of these tumors [89].

NF2 is less common, affecting 1/25,000 live births [86]. The incidence of clinical disease is less common, because some individuals do not develop symptoms until adulthood, and many die in childhood. The clinical features of NF2 include a family history, bilateral vestibular schwannomas, meningiomas, gliomas, or neurofibromas. Most cases present clinically in early adulthood, but there is great variability [90]. Treatment for these tumors is essentially surgical, but radiotherapy may be considered. There appears to be increased risk for radiation-induced malignancy in NF2 patients, although the risk of malignant degeneration appears less common than that seen with NF1 [87]. The increased mortality associated with NF2 is mostly due to progressive, benign intracranial disease, or complications of treatment. There are guidelines for surveillance of patients with NF2 [91].

Gastrointestinal stromal tumors (GIST) are rare connective tissue tumors arising within the gastrointestinal tract, and may occur in a syndromic fashion. The causal mutation in GIST most commonly activates KIT, a receptor tyrosine kinase [92] and less commonly, activating mutations occur in *PDGFRA*. Germ-line KIT mutations have been reported in several families and are characterised by GISTs, hyperpigmentation, urticaria pigmentosa, and dysphagia [93–95]. Interestingly, there seems to be overlap with heritable intestinal NF, which has been associated with *PDGFRA* mutations [96]. It has been proposed that intestinal NF may be a form of GIST. Intestinal nerve sheath tumors have been reported concurrently with GIST in four patients. Three of these cases had NF1 mutations, suggesting phenotypic similarities resulting from inherited *KIT*, *PDGFR*, and *NF1* mutations [97].

Carney triad is a syndrome of GIST, pulmonary chondroma, and paraganglioma for which a genetic cause has not been identified [98]. On the other hand, Carney Stratakis syndrome is an autosomally dominant inherited syndrome characterised by GIST and paragangliomas thought to be due in some cases to mutations in SDHB, SDHC, and SDHD [99,100].

Several other syndromes provide substantial evidence for genetic drivers of sarcoma [1]. Werner's, Bloom's and Rothmund-Thompson syndromes are due to heritable defects in helicases and are associated with an increased risk of sarcomas. Multiple exostosis syndromes due mostly to *EXT1*, *EXT2*, or *EXT3* mutations have a risk of malignant transformation estimated at 0.5–50% of cases [101,102]. An inherited predisposition to benign tumors, such as Ollier's or Mafucci's disease, is associated with an increased risk of secondary bone sarcomas although the genetic causes are unknown. Whilst most cases appear sporadic, familial patterns have been reported [103]. Paget's disease is associated

with an increased risk of osteosarcoma estimated to be below 1% but interestingly osteosarcoma patients over the age of 60 years have an up to 50% incidence of Paget's disease [104].

Understanding inherited risk is clinically important for several reasons. Many sarcoma patients are in their reproductive years, and effective strategies now exist for antenatal and pre-gestational diagnosis if a cancer predisposition gene is identified [105]. Approximately 60% of patients diagnosed with sarcoma are cured, even in *TP53* [72] mutation carriers. Surveillance programs for LFS and other multi-organ cancer prone syndromes may modify subsequent cancer risk. Finally, ionizing radiation increases cancer risks synergistically in the presence of mutations in sarcoma genes such as *Rb* and *TP53* [16,76,106]. Diagnostic and therapeutic radiation exposure is modifiable in high-risk individuals, provided such mutations are identified. Taken together, the pace of recent developments in genomic screening and screening programs suggests that the issue of genetic testing and management will become an increasingly important area for research.

OTHER GENETIC RISK FACTORS IN SARCOMA

The advent of massively parallel sequencing is ushering in a new era of cancer genetics, for several reasons. The first is that, outside of well-designed germline genetic studies, somatic mutation testing is increasingly being applied with a view to personalized therapies. In the course of these assays, germline genetic variation is being identified in the absence of a familial context, raising important questions as to the meaning of known variants in this setting. As significantly, the parallel testing of multiple genes is uncovering polygenic influences on individual cancer risk, for which the clinical genetics community are not well prepared. It is likely that polygenic contributions to cancer risk represent a significant component of cancer risk, both conceptually and quantitatively.

Genome-wide association studies (GWAS) represent an important advance over the study of Mendelian dominant syndromes in mapping the architecture of cancer risk in the population at large. The power of GWAS is in identifying novel biological contributors to cancer biology, relevant to human cancer. The largest osteosarcoma GWAS performed to date recently identified two novel susceptibility loci [107], *GRM4* and a locus on chromosome 2. *GRM4* encodes the glutamate metabotropic receptor 4, which involves the cyclic AMP pathway. The cAMP-dependent protein kinase 1A was recently shown to have tumor suppressor functions in osteosarcoma [108], while parathyroid hormone, which mediates its activity via intracellular cAMP levels, causes osteosarcoma in Fisher 344 rats [109]. GRM4 is associated with increased tumor recurrence in colorectal cancer [110]. A second set of signals implicated a locus in a gene desert on chromosome 2, about which nothing more is known [107]. GWAS loci typically identify regions associated with modest increases in cancer risk, and the region within *GRM4* conferred an odds ration of 1.57, while the region on chromosome 2 had an odds ratio of 1.39 [107].

SUMMARY

Sarcomas are a group of rare tumors affecting a young population and displaying ethnic variation in subtype incidence. The rarity of the disease and the multiple subtypes presents challenges in understanding the etiologies. Environmental risk factors include radiation exposure and chemical carcinogens. Genetic predisposition to sarcoma has been well characterized in some familial cancer syndromes. It increasingly appears that inherited cancer risk is important in sarcoma families. In this era of increasing sequencing capacity it is important that we continue to elucidate these heritable mechanisms. This will lead to improved outcomes for sarcoma families by increasing options for reproductive decision making, treatment, surveillance, and clinical management.

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