Epidemiology and risk factors of osteosarcoma

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ABSTRACT

Osteosarcoma is a rare tumor diagnosed at any age; however younger age is a common risk factor. In addition, multiple factors are believed to contribute to higher rates of osteosarcoma, particularly race and gender. Although diagnosed worldwide, osteosarcoma is found to be more prevalent in Africa with high numbers of cases reported in Nigeria, Uganda, and Sudan. Additionally, higher rates are detected in African Americans, suggesting a genetic predisposition linked to race. This review focuses on identifying high risk factors of osteosarcoma with an emphasis on sarcoma epidemiology and risk factors in African countries.

1 Introduction

Osteosarcoma is a primary bone tumor, characterized by deposition of an immature osteoid matrix (1). The incidence rates vary depending on age, race, sex and a number of other factors. The rates vary throughout the world from 3-5 per million in males to 2-4 per million for females (2). In general is around 5.2 for children aged 0-19 years, per year per millions of people (3). It is ranked the eighth highest childhood cancers at around 2.4% of tumors diagnosed. Despite being a rare type of tumor, a number of risk factors have been identified, including race and sex; with indigenous African and African American males being disproportionately more affected (4). Age is also a key factor with those aged 10-14 years old most likely to be affected and a second peaks occurring at adults older than 65 years old (2, 5, 6). Treatment usually concentrates on surgery to remove the tumor and metastasis, often in combination with chemotherapy (7). Surgery may involve limb amputation or limb salvage techniques depending on the grade of tumor. Over the years many differing treatment protocols and in vitro and in vivo models have been described and developed. In addition, work into immunotherapy-based treatments and pharmacogenomics has been undertaken but to date outcomes for patients diagnosed with high grade osteosarcoma remain poor (8-10). Given this, it is essential to conduct research further exploring key risk factors to understand the pathogenesis of the disease and to develop more effective treatment plans, which is the primary focus of the current review.

Clinically, osteosarcoma can be divided into two stages: localized and metastatic. Localized osteosarcoma refers to the cancer, affecting only the bone and the tissues in which it developed. It can then further be split into resectable and non-resectable stages, based on the viability of surgically removing the tumor. The metastatic stage of osteosarcoma shows that the cancer has spread from the original site to other organ sites, making it more difficult to treat.

The two most common classification systems, used in this review, are the Enneking Staging System and Broder's classification. The named classification systems are important in treatment planning, providing insight into prognosis, assisting in evaluating treatment results, facilitating effective inter-institutional communication, and contributing to investigation of human malignancies (Jawad and Scully 2010). The Enneking Staging System includes benign and malignant mesenchymal tumors such as osteosarcoma (11). This system includes three categories for benign tumors: latent, active, and aggressive. With regards to malignant tumors, the Enneking Staging System considers grade (G1, G2), local extent of tumor (T, T1, T2), and the

presence or absence of metastasis (M0, M1). Stage I includes low-grade (G1) and intra/extracompartmental tumors (T1 and T2) without metastasis (M0). Stage II tumors are characterized by high-grade (G2) and intra/extracompartmental tumors (T1 and T2) without metastasis. Stage III includes any grades and any sites with regional and distant metastasis (11).

While the Enneking Staging System characterizes benign and malignant tumors, Broder's classification focuses specifically on classifying the differentiations in squamous cell carcinomas (11, 12). According to Broder's classification, tumor grades from 1 to 4 reflect the presence of anaplasia. Low-grade tumors are characterized by low mitotic rates, low nuclear to cytoplasmic ratio, and limited pleomorphism. However, high-grade lesions (3 and 4) have a higher incidence of metastasis and are characterized by mitosis, prominent nucleoli, and pleomorphism (13).

Generally, metaphysis of the long bones is the most common site of origin for osteosarcoma in adults (14), with femur (42%), tibia (19%) and humerus (10%) frequently found to be affected by the tumor (Figure 1). Other less frequent locations include the skull or jaw (8%) and pelvis (8%) (14). While osteosarcoma is most common in the long bones of the extremities, in older patients other bones are also identified as tumor sites. Cranial, facial, and axial tumors increase in frequency with age, with about 40% of all osteosarcomas localized in patients aged 60 years or older (4). The overall 5-year survival rate for osteosarcoma is 70% (4, 14), which varies depending on the type of pathology as follows: chondroblastic 54%, fibroblastic 73%, and telangiectatic 59% (4).

2 Pathogenesis

The pathogenesis of osteosarcoma remains largely unknown; however, correlation between bone growth during childhood/puberty and tumor risk diagnosis suggest that growth factors could play a role in the onset of the disease (15, 16). Osteoid is commonly found in osteosarcoma, suggesting that osteoblasts can be involved in the tumor development (17). However, genetic and epigenetic changes in osteosarcoma cells imply their primitive origin (18-20). Another important feature of these cells is their ability to differentiate into multiple cell types including osteoblasts (21). There are currently two primary competing hypotheses regarding the cellular origin of osteosarcoma: mesenchymal stem cell (MSC) and the osteoblast (22-25). Both hypotheses are based on results from in-vitro and in-vivo studies.

The MSCs origin of osteosarcoma is supported by findings indicating that genetic mutations in progenitors are linked to failure of osteoblast maturation and development of osteosarcoma-like tumors in animal models. Spontaneous transformation of MSCs is shown to promote formation of osteosarcomas in animal models (26, 27). The malignant transformation of MSCs is accompanied by accumulation of chromosomal instability and various mutations (28, 29). Additionally, the Rb1 gene deletion in MSCs causes overexpression of c-MYC, which could promote the osteosarcoma-like properties and express osteosarcoma markers CD99, ALP, osteonectin, and osteocalcin (30). These MSCs also metastasize into the lung, which is a key clinical feature of osteosarcoma in humans.

Supporters of the osteoblast origin of sarcoma argue that osteoblasts, obtained from osteosarcoma patients, and not MSCs, maintain in-vitro and in-vivo tumorigenesis, thus playing a role in the pathogenesis of osteosarcoma (22). Supporting this notion, activation of the intracellular domain of Notch1 in transgenic mice promotes immature osteoblast proliferation and induces osteosarcomagenesis (31). Both MSCs and osteoblast hypotheses can explain pathogenesis of osteosarcoma. It is possible that both cell types contribute to tumor onset.

Osteosarcoma can metastasize by dissemination through the circulatory route. Lungs are the most common site of metastasis (32). The survival rate of osteosarcoma patients with lung metastases remains low, even when metastases are surgically removed (33). However, there is evidence suggesting that resection of pulmonary metastases improves the survival of these patients (34, 35). In contrast, other studies demonstrate that chemotherapy has limited effect on the prognosis of osteosarcoma outcome in patients with lung metastasis (36). Major setbacks of chemotherapy are based on low tumor cell sensitivity to the treatment and subsequent side effects (37, 38). Patients with lung metastasis have a higher risk of tumor relapse and fatal outcome (39, 40). Axial locations with a tumor diameter larger than 5 cm were linked to a higher risk of lung metastasis.

3 Epidemiology

Osteosarcoma is diagnosed worldwide, however incidence rates vary in different countries and populations. In the United States, osteosarcoma occurrence was reported to be higher in young Asian/Pacific Islander and black patients (average rates of 5.3 and 5.1 respectively for 0-24 year olds) in comparison to non-Hispanic White, Hispanic and American Indian/Alaska Native populations which saw rates of 3-4.9 per million (4). A similar trend is documented among the younger age groups in South Europe (Stiller et al., 2009), especially in Italy (41). While confirming the high rate of osteosarcoma in Italy, Mirabello et al. reported even higher numbers of cases diagnosed among Latin populations (rates of 7.0–7.6 for males and 3.5–4.9 for females). This work also highlighted particularly high incidence levels in the Philippines and Ecuador (rates up to up to 11.4 and 8.2 respectively)(2). Interestingly, overall a high incidence of osteosarcoma was reported in African countries, predominantly in Sudan and Uganda, as compared to those in Europe (2, 41).

In the United States, osteosarcoma was more often diagnosed in children and adolescents who were Asian/Pacific Islander, followed by African American (age 25–59 years), and Caucasian (age 60+ years)(42). In two consecutive studies conducted by the National Cancer Institute SEER Program, higher annual rates of osteosarcoma in children and young adolescents were found in African American populations, while lower rates were present among Caucasian Americans, based on data published for the years 1975–1995 (43). In a more recent study, an increased number of osteosarcoma incidence was again detected in African Americans, as well as Hispanics, compared to Caucasian American populations (44). Similar trends persisted in older age groups, with a higher rate of osteosarcoma diagnosis reported in African Americans as compared to Caucasians (45). This was supported by rates of 4.6 cases per million people in Black people compared to 3.7 for non-Hispanic White, 3.0 for Hispanic people, 2.9 in American Indian/Alaska Native and 1.9 for Asian/Pacific Islanders aged 60+ years old (4). It is important

to note that the highest incidence in this report was Asian/Pacific Islanders when aged 0-24 but by 25-59 and 60+ years they represented the least likely group to be affected.

It appears that juvenile osteosarcoma is more often diagnosed in South Europe, Africa, Asia, South America, and the Pacific Islands, while late age of tumor onset is more prevalent in Northern Europe, US, and Australia (2). Mirabello et al. suggested that osteosarcoma in elderly patients could be a result of malignant transformation of Paget's disease (2). To support this argument, the authors discussed a striking geographic variation in the prevalence of Paget's disease. High prevalence of the disease is documented in the United Kingdom, Australia, and North America, with a lower frequency present in Asia and the Middle East (46, 47). This distribution is consistent with osteosarcoma diagnosis in elderly populations.

While most available data on disease epidemiology comes from industrially developed countries, there is very little information about the rest of the world, including Africa. This can skew the results of studies that compare disproportionally larger data sets from more developed countries with smaller data sets from other countries. There are, however, a few studies that prioritize underrepresented countries. In a comprehensive study by Parkin et al., the systematic review of childhood cancers focused exclusively on three African countries: Nigeria, Uganda, and Zimbabwe (41). The overall cancer incidence rate in African countries was the lowest as compared to the rest of the world. However, when incidence rates of individual tumors were analyzed, osteosarcoma cases appeared high in Nigeria and Uganda (Figure 2). High rates of osteosarcoma were also reported among African Americans, suggesting the presence of a genetic predisposition linked to the race of the patient. Furthermore, the relative frequency of osteosarcoma in African countries was higher (Sudan 5.3% and Uganda 6.4%) when compared to European countries (2%-3%). In a more recent study, Aina et al. demonstrated that primary bone tumors accounted for 1.26% of the total malignant neoplasms diagnosed between 1991 and 2003 in Ile-Ife, South West Nigeria (48). This frequency is similar to that reported in Ibadan (1.28%), another province in South West Nigeria (49). However, relatively higher osteosarcoma rates were demonstrated in Zaria, Northern Nigeria (3.6%) (50), and Kenya (2.5%) (51).

In the analysis of 117 patients with primary bone tumors, Pillay et al. revealed that osteosarcoma was the most common primary malignant bone tumor, accounting for 72.6% of all cases admitted to the Department of Orthopaedic Surgery, Grey's Hospital, South Africa (52). In accordance with findings reported in previous studies, the authors also confirmed the higher male to female ratio and younger age of patients, (4, 28, 53, 54). In addition, Pillay et al identified that osteosarcoma is diagnosed in African patients at a much younger age (18 years Nigeria; 25 years South Africa), compared to patients from the USA (36 years) and United Kingdom (40 years) (52, 55). A decade-long multicenter analysis of bone tumor incidence in Cameroon showed that osteosarcoma was the most frequent form of primary malignant bone tumor (56). The authors suggested that the high incidence rate of osteosarcoma in young patients could be explained by the larger proportion of young people in the population, where 56% of Cameroonian citizens are children or teenagers, and only 4% are elderly (56). A number of other hospital-based cross-sectional studies, conducted in Nigeria, Ethiopia and Northern Tanzania similarly reported it being predominantly diagnosed in young patients (57). Notably, many

patients in Tanzania were admitted to the hospital with advanced stages of metastatic osteosarcoma only after seeking help from a local healer first.

4 Risk factors

4.1 Age. Osteosarcoma is characterized by bimodal age distribution, with the first diagnosis peak associated with young children and adolescents, and the second peak documented in geriatric patients (54). While the early age incidence rate of osteosarcoma diagnosis is relatively consistent around the world (3 to 4.5 cases/million population/year) (2, 53, 54, 58), more variations (1.5 to 4.5 cases/million population/year) were documented among ages of 60 and over (2, 4). Even though the patient's age is generally agreed to be one of the risk factors and a potential prognostic marker for osteosarcoma, it cannot be applied to the African population due to inaccurate or unavailable demographic data (59). Many of the studies show incidence for older patients but most show a 60+ years rate. Average incidence rates of 1-7 have been observed in males aged 75+ worldwide some countries such as Australia, Canada and the UK saw even higher levels (15-18, 10-11 and 11.6 respectively) (2).

4.2 Gender. Multiple studies, including of the African population, have demonstrated a gender-specific osteosarcoma association, stronger pronounced among males, than females (4, 43, 45, 49, 60-62). It has also been reported that females under the age of 15, have slightly higher cancer rates than males in the same age group (4, 41, 42, 63-68). In adolescents, incidence peaks at a later age and is higher among males (age 15–19, peak rate of 9–15 cases/million population) compared to females (age 10–14, peak rate of 6–10 cases/million population) (4, 41), suggesting that bone growth, hormonal changes, and/or development associated with puberty may be involved in osteosarcoma etiology. In elderly patients, osteosarcoma prevails among African Americans (42) and females, particularly those with a prior history of cancer (4). In general the older age groups (60+ years old) also show less disparity between the sexes, with male-to-female ratios of 1.01:1(2) worldwide and 0.9:1 in the United States. This increases to 1.43:1 (male:female) in those under 24 years old and 1.28:1 in those aged 25-59. This data may further support the pubertal changes theories in relation to younger patients.

4.3 Socio-economic status. It appears that patients from lower socioeconomic groups have higher incidence rates of osteosarcoma and mortality (69). Socioeconomic status, including education, income, and occupation, was shown to be a strong predictor of morbidity and mortality, with education having the strongest impact on the patient's survival. Individuals and caregivers with low or lack of education may have difficulty in understanding the full seriousness of the disease. This can cause delays in seeking or refusal of medical attention in favor of such alternative methods as local bonesetters. Traditional bonesetters are commonly preferred by locals for treating many musculo-skeletal diseases, however, 34% patients withdrew from treatment according to Oboirien et al.'s study from West Nigeria due to the "lack of improvement" (60). Since many patients are living in rural areas, traditional bonesetters are often the only available and affordable source of treatment in that region (Oboirien and Khalid 2013). Therefore, educating traditional bonesetters in bone tumor awareness is essential to improving survival rates among osteosarcoma patients.

4.4 Height. The earliest observation of positive correlation between patient's height and risk of osteosarcoma was published by Fraumeni in the 60-s (61) and was later confirmed by multiple studies (62, 64, 65). Meta-analysis demonstrated that "taller-than-average" and "very tall" individuals are at an increased risk of developing osteosarcoma (66). The same study also showed that individuals with high birth weights had increased risks. Furthermore, Longhi et al. showed a strong correlation between height and osteosarcoma diagnosis in growing individuals (64). These correlations suggest that growth factors and/or rapid bone growth both in puberty and *in utero* could play a role in the cancer pathogenesis.

4.5 Genetics. The etiology of osteosarcoma is complex and not well understood. Studies have identified several genetic risk markers, including hereditary retinoblastoma (Rb) (67, 68), Rothmund–Thomson syndrome (70, 71), and Li Fraumeni syndrome (72). Mutations in the Rb gene have a strong association with predispositions to osteosarcoma (73-75), where the loss of heterogeneity in the Rb gene could indicate unfavorable disease outcome (76). Additionally, altered p53 loci was reported in 10–39% of osteosarcoma cases (77-80). Combined mutations in Rb and p53 show synergistic tumorigenic properties (79, 81, 82).

It appears that osteosarcoma is associated with a rapid genotype modification, complicating the identification of potential therapeutic targets (83, 84). Nevertheless, a variety of macromolecular biomarkers with potential clinical implications have been identified including ErbB-2 (85, 86), cathepsin D (87), FBXW7 (88), and miR-421 (89). However, as of yet, the true diagnostic, etiologic, and clinical significance of these biomarkers is ongoing and controversial.

4.6 Environmental factors. Environmental conditions were also named as risk factors of osteosarcoma. Vu et al. have shown that the risk of osteosarcoma is a linear function of local doses of radiation (90). Similar data was presented by Arlen et al., who showed that residents of areas with radiation ranging from 1,200 rads/few weeks to 24,000 rads/2 years were more likely to develop osteosarcoma (91). Additionally, a link between radiation exposure and osteosarcoma was reported among radium dial workers (92). Accordingly, treatment using teriparatide, a parathyroid hormone peptide, was suggested to increase the risk of radiation-induced osteosarcoma (93). Bassin et al. also proposed that exposure to fluoridated water was a potential risk factor for osteosarcoma (94). Similar observations were published by Gandhi et al., which suggested that fluoride-induced oxidative and inflammatory stress contribute to the pathogenesis of osteosarcoma (95). Other chemical risk factors include methylcholanthrene and chromium salts (96), beryllium oxide (97), zinc beryllium silicate (98), asbestos, and aniline dyes (99).

5 Conclusion

Osteosarcoma is a rare tumor, more often diagnosed among young patients. Multiple factors have been shown to contribute to developing osteosarcoma, most commonly race, gender and age. A higher incidence rate of the diagnosis is registered among young males of African origin, which was supported by the research findings conducted in Nigeria, Uganda, and Sudan. Additionally, high cancer rates are detected among African Americans, suggesting genetic and racial predispositions to osteosarcoma. Identifying genetic markers is essential to developing novel therapeutics and diagnostics. Further studies on osteosarcoma genetic markers among the African population could help to better understand the pathogenesis of the disease.

Conflict of Interest

The authors report no conflicts of interest.

Author Contributions

All authors wrote the manuscript and reviewed the final draft.

Figure Legends

Figure 1. Osteosarcoma locations within the skeleton.

Figure 2. Osteosarcoma in Africa. The frequency rate of osteosarcoma in Sudan (5.3%), Nigeria (3.6% - 1.28%), Uganda (6.4%), Kenia (2.5%), Tanzania (61%), Cameroon (39%), Zambia (55.3%), Rwanda (8.2%) and South Africa (72.6%).

Contribution to the Field

Osteosarcoma is a rare tumor, which affects young and elderly patients. Incidence rates not only change with age but also with race and gender. Males living in parts of Africa are more likely to be affected, as are African Americans, thus indicating a potential genetic predisposition. Other races have differing incidence rates but some change depending on the age and gender of the patient group. This review also looks at the treatments, genetic markers and the ongoing work to develop therapeutics and diagnostic techniques. It also highlights the need for more research into differing populations and environmental factors in relation to osteosarcoma risk.

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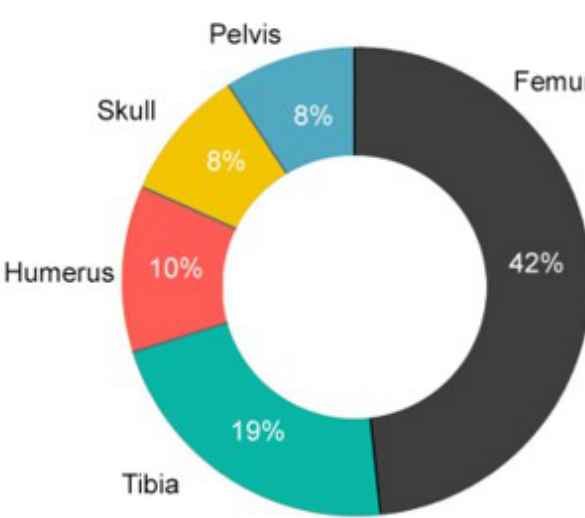
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