

Epidemiology and risk factors of osteosarcoma

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22 **ABSTRACT**

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

30

31 **1 Introduction**

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

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

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

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

66 While the Enneking Staging System characterizes benign and malignant tumors, Broder's
67 classification focuses specifically on classifying the differentiations in squamous cell carcinomas
68 (11, 12). According to Broder's classification, tumor grades from 1 to 4 reflect the presence of
69 anaplasia. Low-grade tumors are characterized by low mitotic rates, low nuclear to cytoplasmic
70 ratio, and limited pleomorphism. However, high-grade lesions (3 and 4) have a higher incidence
71 of metastasis and are characterized by mitosis, prominent nucleoli, and pleomorphism (13).

72 Generally, metaphysis of the long bones is the most common site of origin for osteosarcoma in
73 adults (14), with femur (42%), tibia (19%) and humerus (10%) frequently found to be affected
74 by the tumor (Figure 1). Other less frequent locations include the skull or jaw (8%) and pelvis
75 (8%) (14). While osteosarcoma is most common in the long bones of the extremities, in older
76 patients other bones are also identified as tumor sites. Cranial, facial, and axial tumors increase
77 in frequency with age, with about 40% of all osteosarcomas localized in patients aged 60 years
78 or older (4). The overall 5-year survival rate for osteosarcoma is 70% (4, 14), which varies
79 depending on the type of pathology as follows: chondroblastic 54%, fibroblastic 73%, and
80 telangiectatic 59% (4).

81

82 **2 Pathogenesis**

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

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

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

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

117 **3 Epidemiology**

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

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

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

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

152 While most available data on disease epidemiology comes from industrially developed countries,
153 there is very little information about the rest of the world, including Africa. This can skew the
154 results of studies that compare disproportionately larger data sets from more developed countries
155 with smaller data sets from other countries. There are, however, a few studies that prioritize
156 underrepresented countries. In a comprehensive study by Parkin et al., the systematic review of
157 childhood cancers focused exclusively on three African countries: Nigeria, Uganda, and
158 Zimbabwe (41). The overall cancer incidence rate in African countries was the lowest as
159 compared to the rest of the world. However, when incidence rates of individual tumors were
160 analyzed, osteosarcoma cases appeared high in Nigeria and Uganda (Figure 2). High rates of
161 osteosarcoma were also reported among African Americans, suggesting the presence of a genetic
162 predisposition linked to the race of the patient. Furthermore, the relative frequency of
163 osteosarcoma in African countries was higher (Sudan 5.3% and Uganda 6.4%) when compared
164 to European countries (2%-3%). In a more recent study, Aina et al. demonstrated that primary
165 bone tumors accounted for 1.26% of the total malignant neoplasms diagnosed between 1991 and
166 2003 in Ile-Ife, South West Nigeria (48). This frequency is similar to that reported in Ibadan
167 (1.28%), another province in South West Nigeria (49). However, relatively higher osteosarcoma
168 rates were demonstrated in Zaria, Northern Nigeria (3.6%) (50), and Kenya (2.5%) (51).

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

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

185 **4 Risk factors**

186 **4.1 Age.** Osteosarcoma is characterized by bimodal age distribution, with the first diagnosis
187 peak associated with young children and adolescents, and the second peak documented in
188 geriatric patients (54). While the early age incidence rate of osteosarcoma diagnosis is relatively
189 consistent around the world (3 to 4.5 cases/million population/year) (2, 53, 54, 58), more
190 variations (1.5 to 4.5 cases/million population/year) were documented among ages of 60 and
191 over (2, 4). Even though the patient's age is generally agreed to be one of the risk factors and a
192 potential prognostic marker for osteosarcoma, it cannot be applied to the African population due
193 to inaccurate or unavailable demographic data (59). Many of the studies show incidence for older
194 patients but most show a 60+ years rate. Average incidence rates of 1-7 have been observed in
195 males aged 75+ worldwide some countries such as Australia, Canada and the UK saw even
196 higher levels (15-18, 10-11 and 11.6 respectively) (2).

197 **4.2 Gender.** Multiple studies, including of the African population, have demonstrated a
198 gender-specific osteosarcoma association, stronger pronounced among males, than females (4,
199 43, 45, 49, 60-62). It has also been reported that females under the age of 15, have slightly higher
200 cancer rates than males in the same age group (4, 41, 42, 63-68). In adolescents, incidence peaks
201 at a later age and is higher among males (age 15–19, peak rate of 9–15 cases/million population)
202 compared to females (age 10–14, peak rate of 6–10 cases/million population) (4, 41), suggesting
203 that bone growth, hormonal changes, and/or development associated with puberty may be
204 involved in osteosarcoma etiology. In elderly patients, osteosarcoma prevails among African
205 Americans (42) and females, particularly those with a prior history of cancer (4). In general the
206 older age groups (60+ years old) also show less disparity between the sexes, with male-to-female
207 ratios of 1.01:1(2) worldwide and 0.9:1 in the United States. This increases to 1.43:1
208 (male:female) in those under 24 years old and 1.28:1 in those aged 25-59. This data may further
209 support the pubertal changes theories in relation to younger patients.

210 **4.3 Socio-economic status.** It appears that patients from lower socioeconomic groups have
211 higher incidence rates of osteosarcoma and mortality (69). Socioeconomic status, including
212 education, income, and occupation, was shown to be a strong predictor of morbidity and
213 mortality, with education having the strongest impact on the patient's survival. Individuals and
214 caregivers with low or lack of education may have difficulty in understanding the full
215 seriousness of the disease. This can cause delays in seeking or refusal of medical attention in
216 favor of such alternative methods as local bonesetters. Traditional bonesetters are commonly
217 preferred by locals for treating many musculo-skeletal diseases, however, 34% patients withdrew
218 from treatment according to Oboirien et al.'s study from West Nigeria due to the "lack of
219 improvement" (60). Since many patients are living in rural areas, traditional bonesetters are often
220 the only available and affordable source of treatment in that region (Oboirien and Khalid 2013).
221 Therefore, educating traditional bonesetters in bone tumor awareness is essential to improving
222 survival rates among osteosarcoma patients.

223 **4.4 Height.** The earliest observation of positive correlation between patient’s height and risk
224 of osteosarcoma was published by Fraumeni in the 60-s (61) and was later confirmed by multiple
225 studies (62, 64, 65). Meta-analysis demonstrated that “taller-than-average” and “very tall”
226 individuals are at an increased risk of developing osteosarcoma (66). The same study also
227 showed that individuals with high birth weights had increased risks. Furthermore, Longhi et al.
228 showed a strong correlation between height and osteosarcoma diagnosis in growing individuals
229 (64). These correlations suggest that growth factors and/or rapid bone growth both in puberty
230 and *in utero* could play a role in the cancer pathogenesis.

231 **4.5 Genetics.** The etiology of osteosarcoma is complex and not well understood. Studies
232 have identified several genetic risk markers, including hereditary retinoblastoma (Rb) (67, 68),
233 Rothmund–Thomson syndrome (70, 71), and Li Fraumeni syndrome (72). Mutations in the Rb
234 gene have a strong association with predispositions to osteosarcoma (73-75), where the loss of
235 heterogeneity in the Rb gene could indicate unfavorable disease outcome (76). Additionally,
236 altered p53 loci was reported in 10–39% of osteosarcoma cases (77-80). Combined mutations in
237 Rb and p53 show synergistic tumorigenic properties (79, 81, 82).

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

243 **4.6 Environmental factors.** Environmental conditions were also named as risk factors of
244 osteosarcoma. Vu et al. have shown that the risk of osteosarcoma is a linear function of local
245 doses of radiation (90). Similar data was presented by Arlen et al., who showed that residents of
246 areas with radiation ranging from 1,200 rads/few weeks to 24,000 rads/2 years were more likely
247 to develop osteosarcoma (91). Additionally, a link between radiation exposure and osteosarcoma
248 was reported among radium dial workers (92). Accordingly, treatment using teriparatide, a
249 parathyroid hormone peptide, was suggested to increase the risk of radiation-induced
250 osteosarcoma (93). Bassin et al. also proposed that exposure to fluoridated water was a potential
251 risk factor for osteosarcoma (94). Similar observations were published by Gandhi et al., which
252 suggested that fluoride-induced oxidative and inflammatory stress contribute to the pathogenesis
253 of osteosarcoma (95). Other chemical risk factors include methylcholanthrene and chromium
254 salts (96), beryllium oxide (97), zinc beryllium silicate (98), asbestos, and aniline dyes (99).

255 **5 Conclusion**

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

264

265 **Conflict of Interest**

266 The authors report no conflicts of interest.

267 **Author Contributions**

268 All authors wrote the manuscript and reviewed the final draft.

269

270 **Figure Legends**

271 Figure 1. Osteosarcoma locations within the skeleton.

272 Figure 2. Osteosarcoma in Africa. The frequency rate of osteosarcoma in Sudan (5.3%), Nigeria
273 (3.6% - 1.28%), Uganda (6.4%), Kenia (2.5%), Tanzania (61%), Cameroon (39%), Zambia
274 (55.3%), Rwanda (8.2%) and South Africa (72.6%).

275

276 **Contribution to the Field**

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

284

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