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1. **Write on cancers epidemiology in Africa generally, and Nigeria in particular.**

**1.1 Epidemiology of cancer in Africa**

Cancer is an increasing problem in Africa because of aging and growth of the population as well as increased prevalence of risk factors associated with economic transition (including smoking, alcohol, obesity, physical inactivity, and reproductive behaviors), and of certain infectious agents of importance in cancer etiology According to United Nations population estimates in 2012, the population of Africa between 2010 and 2030 is projected to increase by 60% overall (from 1.03 billion to 1.63 billion) and by 90% for those 60 and older (from 55 million to 103 million), the age at which cancer most frequently occurs. Despite this growing burden, cancer continues to receive a relatively low public health priority in Africa, largely because of limited resources and other pressing public health problems, including communicable diseases such as Acquired Immune Deficiency Syndrome (AIDS)/Human Immunodeficiency Virus (HIV) infection, malaria, and tuberculosis. Another factor may be a general lack of awareness among policy makers, the general public, and international private or public health agencies, concerning the magnitude of the current and future cancer burden on the continent and its economic impact. Focusing on specific types of cancer, research has shown the following data,

**Breast cancer:** Breast cancer is the most commonly diagnosed cancer in Africa, and in Sub-Saharan Africa, and is also the leading cause of death from cancer (63,100 deaths in 2012). Studies show that breast cancer is the most commonly diagnosed cancer in women in all of North Africa, and has also become the leading cancer in women in many Sub-Saharan countries. However, the geographic pattern does not closely follow the conventional regions. Apart from the island populations of Mauritius and Reunion, the highest rates are seen in Egypt, Algeria, Nigeria, and Republic of South Africa. Although the reasons for the increasing importance of breast cancer must be speculative, they most likely include increases in the prevalence of risk factors such as early menarche, late child bearing, having fewer children, obesity, and increased awareness and detection, which are associated with urbanization and economic development.

**Prostate Cancer:** With almost 60,000 new cases estimated in 2012, cancer of the prostate is the most frequently diagnosed cancer in men, although in North Africa, it lies in fourth position (after lung, liver, and bladder). It is the third most common neoplasm overall (after breast and cervix), both in Africa as a whole and in Sub-Saharan Africa. In the latter region, the risk of developing prostate cancer before age 75 (3.4%, affecting almost 1 in 30 men) is in fact not dissimilar to the equivalent risks for breast (3.5%) and cervical cancer (3.8%) among women (Parkin *et al*., 2014).

**Liver Cancer:** Given the poor prognosis of liver cancer, the number of new cases (58,500) and deaths (56,000) estimated in 2012 are rather similar, and in terms of both indicators, liver cancer (predominantly hepatocellular carcinoma) ranks as the fourth most frequent cancer on the African continent and in Sub-Saharan Africa, accounting for about 7% of the total cancer burden. The major risk factors in operation for liver cancer on the African continent are infections with the hepatitis viruses and aflatoxin (Sylla and wild, 2012), particularly chronic carriage of the hepatitis B virus (HBV) in Sub-Saharan Africa, with chronic hepatitis C virus (HCV) infection more prevalent in Northern Africa. This is markedly the case in Egypt, where the burden of HCV prevalence is the highest in the world and largely attributed to public health campaigns to reduce schistosomiasis via mass parenteral antischistosomal therapy (Parkin *et al*., 2014).

**1.2 Epidemiology of cancer in Nigeria**

In recent times, information on cancer incidence, prevalence and mortality in Nigeria has been based on estimates from case series, medical records, mortality records, hospital based cancer registries and the Ibadan population based cancer registry (IBCR). IBCR, located at the University College Hospital Ibadan and set up in 1962, is the first cancer registry in Nigeria. Cancer incidence data from this registry were published for the time periods 1960– 1962, 1960–1965, and 1960–1969 in the first three volumes of Cancer Incidence in 5 Continents (CIV). However, due to logistic problems the registry suffered some setbacks from the 1970s to 2000s. Data from Ibadan showed increasing incidence and the ASR for all cancers as 81.6 per 100,000 for males and 115.1 per 100,000 for females with 65.9% and 34.1% in females and males respectively 7. From Kano, of 1001 cancers recorded for period 1995-2004, male cancers accounted for 50.3% and 49.7% in females10, 1162 and 1657 cancer cases respectively for males and females for the period between 1995 and 2002 from the Cancer Registry in Jos University Teaching Hospital. Report from University of Benin Teaching Hospital showed 2258 cases over a 20year period with female cancers predominating (64%) while that from Calabar showed a total of 588 cancers between 2004-2006 with 50.9% and 49.1% respectively for males and females. The WHO estimated incidence of cancer from all sites in 2002 for Nigeria was 90.7 and 100.9 per 10,000 for males and females respectively while mortality rates were 72.2 and 76 respectively-Globocan15. This is comparable to 89.1 and 104.1/100,000 incidence for males and females and 72.2 and 79.6 crude mortality rates recorded for Ghana but much less than figures recorded for United Kingdom and USA Generally cancer incidence in Nigeria appears low compared to developed countries which may not truly reflect the burden. Similar to reports from other parts of the world, it is slightly higher in female.

1. **Critically examine the involvement of angiogenic genes in the development and progression of osteosarcomas.**

Osteosarcoma is a primary malignant tumor of the skeleton characterized by the direct formation of immature bone or osteoid tissue by the tumor cells. It is an extremely aggressive malignancy that arises mostly in the long bones (DuBois and Demetri, 2007). Angiogenesis, the formation of new blood vessels from preexisting ones, is involved in the growth, maintenance, and metastasis of most solid tumors. In contrast to carcinomas derived from epithelial cells and hematologic malignancies, few data are available regarding the relevance of angiogenesis and its prognostic impact in osteosarcoma. Osteosarcoma is the most frequent primary malignant bone tumor (Kreuter *et al*., 2004). Tumor cells, like normal cells, require the delivery of oxygen and nutrients by blood vessels in order to survive and grow. In most normal adult tissues, vessels are quiescent due to the presence of equal or higher levels of inhibitors relative to inducers of angiogenesis. In pathological angiogenesis, the balance of mediators shifts so that inducers predominate, either due to increased secretion of inducers or decreased secretion of inhibitors, or a combination of both. When sufficient tumor cells have switched to the angiogenic phenotype from a quiescent phenotype, neovascularization may begin, and hence rapid tumor growth and metastasis can proceed. This process, known as the “angiogenic switch,” is complex and remains incompletely understood. It can be triggered by various signals, including metabolic stress such as hypoxia, acidosis and hypoglycemia, mechanical stress such as pressure, immune or inflammatory response, and is often a consequence of the genetic alterations that drive tumor progression. Tumors become angiogenic by increasing the local expression of pro-angiogenic factors, such as vascular endothelial growth factor (VEGF), basic fibroblast growth factor (bFGF), platelet-derived growth factor (PDGF) and transforming growth factor (TGF)-β (Xie and Guo, 2017). These factors may be mobilized from the extracellular matrix, or produced by recruited host macrophages and mast cells or the tumor cells themselves. Tumor cells also secrete proteolytic enzymes that degrade basement membrane and extracellular matrix, thus allowing angiogenesis to proceed. The angiogenic factors stimulate quiescent endothelial cells to degrade and migrate into extracellular matrix, and to proliferate and organize themselves into new capillaries. As tumors grow, internal areas of hypoxia develop, which further stimulate production of pro-angiogenic factors. The importance of the production of pro-angiogenic factors in osteosarcoma pathogenesis and progression has been highlighted by numerous studies that have shown VEGF expression to be correlated with increased tumor vascularity and metastatic potential, and poorer prognosis in osteosarcoma. Serum VEGF levels were five times increased in pediatric patients with malignant solid tumors, including osteosarcoma, compared to normal healthy controls. These studies advocate a role for inhibition of tumor angiogenesis using anti-VEGF methods. Other angiogenic factors such as TGF-β1 have similarly been associated with the more aggressive phenotype in osteosarcoma. Recent studies, however, have given conflicting results as to whether increased tumor angiogenesis is associated with worse clinical prognosis in osteosarcoma .

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