**ANA 404: INTRODUCTION TO HISTOPATHOLOGY (NEOPLASM)**

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16/MHS01/046

**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 such as; smoking, alcohol, obesity, physical inactivity, and reproductive behaviors, and of certain infectious agents of importance in cancer etiology (Parkin *et al.,* 2014).

According to United Nations population estimates, the population of Africa between 2010 and 2030 is projected to increase by 60% overall (1.03 billion to 1.63 billion) and by 90% for those 60 and older (55 million to 103 million), the age at which cancer most frequently occurs (Adedeji, 2017). 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 (Adedeji, 2017). 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 (Parkin *et al.,* 2014).

GLOBOCAN is a database of the International Agency for Research in Cancer (IARC) that provides estimated incidence, mortality and prevalence of cancers worldwide. In 2012, it reported that there were 14.1 million new cancer cases worldwide, 8.2 million cancer-related deaths and 32.6 million people living with cancer (within 5 years of initial diagnosis). Alarmingly, 57% (8 million) of new cancer cases and 65% (5.3 million) of mortality occurred in the less developed countries of the world in 2012. There is regional variation in cancer incidence and mortality across continents with some cancers commoner in some parts of the world. Genetic susceptibility, cancer biology, environmental and risk factors’ exposures can explain the geographic differences observed.

In the WHO Africa region, in 2012, the estimated age-standardized incidence rates for all cancers (excluding non-melanoma skin cancer) were 645 per 100,000 population (both sexes), 265 per 100,000 in males and 381 per 100,000 in females (Adedeji, 2017). The changes in population dynamics, lifestyles and diet across Africa have coincided with the increasing cancer burden. Life expectancy is improving in developing countries so more people live longer with disease (Adedeji, 2017). In Sub-Saharan Africa, the five most frequent cancers in males, in order of decreasing age-standardized incidence are: prostate, liver, Kaposi sarcoma, esophageal and colorectal cancer and in females, they were: cervix uteri, breast, liver, colorectal and ovarian cancers (Adedeji, 2017).

**1.1.1: Male Epidemiology**

Prostate cancer accounted for the highest estimated number of cancer cases for all ages in males in 2012 with 20.3% of the overall cancer burden, followed by liver cancer (9.7%), Kaposi sarcoma (9.2%), Non-Hodgkin lymphoma (5.7%) and Colorectal cancer (5.6%). In prostate cancer, there is genetic predisposition and patients in SSA tend to present late. Liver cancer is associated with hepatitis B & C infection and alcohol consumption including local spirits (Davies, 1963). Kaposi sarcoma is linked to the Human Herpes Virus 8 (HHV8; also known as Kaposi Sarcoma Associated Herpes-Virus (KSHV)) infection and AIDS with on-going epidemics of the latter in SSA. Dietary and lifestyle changes with a trend towards those of the developed world has contributed towards the colorectal cancer proportions. Men tend to be younger at presentation with colorectal cancer in South Africa with median age of 59 years compared with 71 years in North America (Parkin *et al.,* 2014). Age-standardized mortality rates from cancers in Sub-Saharan African men in 2012 was highest for prostate cancer (20.9%), followed by liver cancer (9.6%), Kaposi Sarcoma (6.5%), Esophageal (6.4%), Colorectal (4.9%) and lung (4.3%) cancers. The high mortality rates for these cancers are often due to late presentation, lack of diagnostic and treatment facilities and an immunocompromised state (especially with Kaposi sarcoma). In comparison to the rest of the world regions, mortality rates from prostate cancer, for example, is disproportionately higher (Parkin *et al.,* 2014).

**1.1.2: Female Epidemiology**

The most burden of cancer cases for all ages in women in SSA in 2012 was from breast (25.5%) and cervix uteri cancer (25.2%). The lack of optimal screening programs for these cancers, papanicolaou smears or HPV DNA screening for cervical cancer and mammography for breast cancer drives late presentation which ultimately leads to poor quality of life and high mortality (Adedeji, 2017). In 2012, the age-standardized mortality rate from cervix uteri cancer was highest in SSA at 22.5%, compared to 2.6% in North America and mortality from breast cancer was 17.2% compared to 14.8% in North America (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) (Abdulkareem, 2009). 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 (Abdulkareem, 2009).

Data from Ibadan showed increasing incidence and the Age-standardized Rate (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 (Jedy-Agba *et al.,* 2012).

* 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%)
* 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-Globocan (Jedy-Agba *et al.,* 2012). 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 (Jedy-Agba *et al.,* 2012).

**2.1: Angiogenesis in Osteosarcoma**

The concept that malignant tumor development, growth, spread and invasion depend on angiogenesis is widely recognized and accepted. 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 (Quan & Choong, 2006). 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. In initial tumor development, known as in situ carcinoma, there appears to be a prolonged dormant period during which the tumor is not angiogenic, and is restricted in growth to a few cubic millimeters. 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 (Peng *et al.,* 2013).

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 (Peng *et al.,* 2013). 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 (Chen *et al.,* 2012). 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 (Chen *et al.,* 2012). 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 (Kreuter *et al.,* 2004).

 Osteosarcoma is the most frequent primary malignant bone tumor. The inclusion of cytotoxic polychemotherapy in multimodal treatment strategies has led to dramatic prognostic improvements in patients with osteosarcoma, with survival rates reaching 50% to 80%. Recent reports have identified tumor site and size, primary metastases, response to chemotherapy, and surgical remission as independent prognostic factors in osteosarcoma. However, the role of angiogenesis in osteosarcoma still remains a matter of debate (Kreuter *et al.,* 2004). Whereas one report showed evidence for decreased overall survival in osteosarcoma patients with high Micro vessel Density (MVD) failed to demonstrate a correlation between intra-tumoral neovascularization and long-term outcome in patients with non-metastatic osteosarcoma (Kreuter *et al.,* 2004). Experimental studies on the role of tumor MVDs revealed a significant correlation between MVD and pulmonary metastasis. Increased pre-therapeutic levels of vascular endothelial growth factor (VEGF), a well-known proangiogenic factor, in patients with osteosarcoma correlated with MVD and metastasis. Moreover, VEGF overexpression in osteosarcoma was associated with reduced disease-free and overall survival (Mikulić *et al.,* 2004). First experimental studies on the effect of anti-VEGF antibodies in osteosarcoma in a chick embryo chorioallantoic membrane model resulted in growth arrest of tumor xenografts and decreased MVD. Furthermore, expression of the VEGF co-receptor neuropilin-2 correlated with increased vascularity and poor prognosis in osteosarcoma patients (Mikulić *et al.,* 2004).

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