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**An assignment submitted to the**

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1. Write on cancers epidemiology in Africa generally, and Nigeria in particular.
2. Critically examine the involvement of angiogenic genes in the development and progression of osteosarcomas.

Answers

1)Cancer is an emerging public health problem in Africa. About 715,000 new cancer cases and 542,000 cancer deaths occurred in 2008 on the continent, with these numbers expected to double in the next 20 years simply because of the aging and growth of the population. Furthermore, cancers such as lung, female breast, and prostate cancers are diagnosed at much higher frequencies than in the past because of changes in lifestyle factors and detection practices associated with urbanization and economic development. Breast cancer in women and prostate cancer in men have now become the most commonly diagnosed cancers in many Sub‐Saharan African countries, replacing cervical and liver cancers. In most African countries, cancer control programs and the provision of early detection and treatment services are limited despite this increasing burden. This paper reviews the current patterns of cancer in Africa and the opportunities for reducing the burden through the application of resource level interventions, including implementation of vaccinations for liver and cervical cancers, tobacco control policies for smoking‐related cancers, and low‐tech early detection methods for cervical cancer, as well as pain relief at the palliative stage of cancer.

The burden of cancer is increasing in Africa because of the aging and growth of the population as well as increased prevalence of risk factors associated with economic transition, including smoking, obesity, physical inactivity, and reproductive behaviours (Boyle and Levin, 2008; UNPD, 2008). According to United Nation's population estimates (UNPD, 2008), the population of Africa between 2010 and 2030 is projected to increase by 50% overall (from 1.03 billion to 1.52 billion) and by 90% for those aged ≥60 years (from 55 million to 105 million), the age at which cancer most frequently occurs.



Fig 1:Estimated numbers of new cases and deaths for leading cancer sites in Africa are shown for 2008. (Source: GLOBOCAN 2008).



Fig 2:Most common cancer sites in Africa by sex and country are shown for 2008. (Source: GLOBOCAN 2008).

In Nigeria

Cancer has become a major source of morbidity and mortality globally (Sylla and Wild, 2011). In 2008, there were 12.7 million new cases and 7.6 million cancer-related deaths (Ferlay *et al.,* 2010). Most, 56% of these newly reported cancer cases occurred in developing countries and It is projected that by 2030, 70% of all new cases of cancer will be found in developing countries (Boyle and Levin, 2008). Most of this increase in incidence is a result of population growth and increased life expectancy (Lyverly *et al.,*2011).

In Nigeria, some 100 000 new cases of cancer occur every year, with high case fatality ratio (Ferlay *et al.,* 2010). With approximately 20% of the population of Africa and slightly more than half the population of West Africa, Nigeria contributed 15% to the estimated 681,000 new cases of cancer that occurred in Africa in 2008 (Sylla and Wild, 2011). Similar to the situation in the rest of the developing world, a significant proportion of the increase in incidence of cancer in Nigeria is due to increasing life expectancy, reduced risk of death from infectious diseases, increasing prevalence of smoking, physical inactivity, obesity as well as changing dietary and lifestyle patterns (Sylla and Wild, 2011).

Despite the threat that cancer poses to public health in sub-Saharan Africa (SSA), few countries in this region have data on cancer incidence (Curado *et al.,* 2011). Most of the cancer incidence data in SSA in recent times is based on reports from registries in The Gambia, Zimbabwe and Uganda (Curado *et al.,* 2011). These cancer registries have consistently provided incidence data for the last 10–20 years despite the difficulties of sustaining cancer registration in developing countries (Parkin *et al.,* 1999; wabinga *et al.,* 2011; Chokunonga *et al.,* 1999; Chokunonga *et al.,* 2011; Bar *et al.,* 2011).

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) (Parkin *et al.,* 2011). 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 (Parkin *et al.,* 2010).

Since 2009, the Nigerian Federal Ministry of Health (FMOH) and the Institute of Human Virology Nigeria (IHVN) have initiated a program of National System of Cancer Registries to strengthen existing cancer registries and establish new ones through provision of baseline training for newly established registries; continuing education for older registries; mentoring, computer hardware and software provision and support; data management and analysis. In this paper, we present estimates of cancer incidence in Nigeria based on data from 2 population-based cancer registries in the system. These registries cover defined populations and use multiple source reporting.

Study shows that the commonest cancers in Nigeria in 2009 to 2010 were breast and cervical cancer among women and prostate cancer among men. It was found significant increase in the incidence of breast cancer compared to historical records while the incidence of cervical cancer was relatively stable. There was very little disparity in the cancer incidence reported by registries in the northern and southern parts of the country regardless of differences in ethnicity and level of urbanization.

Data suggests that the incidence of breast cancer in Nigeria has risen significantly. The age standardized incidence rates for breast cancer in the period 1960–1969 was 13.7 per 100 000 and it rose to 24.7 per 100 000 by 1998–1999 – more or less a doubling of incidence over 4 decades or approximately 25% increase in incidence per decade (Parkin *et al.,* 2011). With incidence in 2009 to 2010 at 54.3 per 100 000, this represents a 100% increase in the last decade. This is supported by the literature showing rise in breast cancer incidence rates in SSA (Forouzanfa *et al.,* 2011) In the results, the incidence rate of breast cancer in Nigeria in 2010 was higher than the GLOBOCAN 2008 estimate of 38.7 per 100 000 (Ferlay *et al.,* 2011), although the GLOBOCAN estimate is for the whole country and for a different time period. The increase in cancer incidence in women may be both apparent and real. Some of the increase noted may result from improved diagnosis, better case finding and improved access to care. Despite this, some of the increase in incidence may be real due to increasing prevalence of risk factors for these cancers in populations that hitherto had low incidence (Forouzanfar *et al.,* 2011).

Cervical cancer is the most common cancer among women in most of sub-Saharan Africa (Sitas *et al.,* 2000; Piras *et al.,* 2011). However in Nigeria, it is the second most common after breast cancer (Ferlay *et al.,* 2010). Our findings are also somewhat similar to the 2008 GLOBOCAN estimates for the whole country of 32.9 per 100 000 for the period 1998 to 2002 (Ferlay *et al.,* 2010). This suggests that the incidence of cervical cancer has remained largely stable over time. This seemingly stable incidence of cervical cancer over time could possibly be due to poor screening coverage in Nigeria.

2) Osteosarcoma is a relatively uncommon cancer although it is the most common primary malignancy to arise from bone. While incidence is low, osteosarcoma predominately affects adolescents and young adults, and if untreated it is fatal (Bielack etal., 2002).

Tumour angiogenesis is essential for sustained osteosarcoma growth and metastasis. Without a supporting vasculature, osteosarcoma cells would be unable to obtain the nutrients and oxygen necessary for proliferation. Metastasis to the lungs and bone, the most common sites for osteosarcoma spread, also relies on the formation and maintenance of blood vessels. Radiation therapies, while compromising tumour cells, also destroy the vascular component of tumours and block the supply of nutrients. So, radio- and chemotherapies act by these dual actions. This aspect is discussed below.

A balance between pro-angiogenic and antiangiogenic factors regulates angiogenesis, and this balance is tipped towards the favour of neovascularisation by tissue hypoxia, acidosis, oncogene activation, and loss of tumour suppressor gene function. A hypoxic and acidotic microenvironment exists around proliferating osteosarcoma cells, and these conditions stimulate deubiquitinations of von Hippel Lindau protein. Von Hippel Lindau protein releases hypoxia-inducible factor-1α (HIF-1α), allows HIF-1α to bind to the promoter region of the vascular endothelial growth factor (VEGF) gene (Hicklin and Eliis, 2005), and upregulats it. TGF-α, and fibroblast growth factor (FGF) may also upregulate VEGF (Dvorak 2005).

VEGF is the best-characterised pro-angiogenic factor, and it stimulates the processes of endothelial cell proliferation, migration, and blood vessel maturation. A number of different VEGF molecules exist (VEGF-A through to VEGF-E), and these proteins bind to VEGF receptors (VEGFR1-3) (Shibuya and Claesson-Welsh, 2006). VEGF-A has the broadest angiogenic effect. Upon VEGF-A binding to VEGFR2, a number of divergent signalling pathways are initiated (Shibuya and Claesson-Welsh, 2006). Nitric oxide (NO) is released by endothelial cells, leading to vasodilation and increased vascular permeability (Nagy *et al.,* 2007). Endothelial cell proliferation and cycling are stimulated via phospholipase Cγ (PLCγ), protein kinase C (PKC), and the c-Raf-MEK-MAPK cascades (Shibuya and Claesson-Welsh, 2006 ). Rearrangement of the actin cytoskeleton, necessary for endothelial cell migration occurs via phosphorylation of T cell-specific adapter (TSAd) and interaction with Src, another protein kinase (Matsumoto and Mugishima, 2006). The net result of all these changes is the formation of an immature, irregular, and leaky vascular network.

The immature and inefficient nature of the vessels so produced facilitates feedback loops for further vessel formation. Upregulation of HIF-1α and VEGF (Liao and Johnson, 2007) again occurs as the leaky vasculature is unable to meet the metabolic demands of the proliferating osteosarcoma cells. Additionally, VEGF upregulates matrix metalloproteinase (MMP) and plasmin activity (Carmeliet, 2005). These proteases break down extracellular matrix, which releases any VEGF combined with heparin proteoglycan in the matrix. VEGF also induces antiapoptotic factors Bcl-2, and survivin, ensuring ongoing endothelial proliferation (Tran *et al.,* 1999). In addition to VEGF, the proliferating tumour cells release a number of other pro-angiogenic factors. These include FGF, platelet-derived growth factor (PDGF), angiopoietin1 (Ang1), and ephrin-B2 (Yancopoulos *et al.,* 2000; Lobov *et al.,* 2007) .

While it is known that osteosarcoma is a relatively vascular tumour, the prognostic significance of this is yet to be determined. There have been studies suggesting both a correlation (Kaya *et al.,* 2000; Hara *et al.,* 2006) and lack of association (Mantadakis *et al.,* 2001) between VEGF expression and osteosarcoma microvascular density and metastases at diagnosis. This may relate to a greater tumour dependence on functionally mature vessels. One study that demonstrated a survival advantage associated with increased osteosarcoma microvascular density (Kreuter *et al.,* 2004) attributed this advantage to improved tissue penetration by chemotherapeutic agents.

As previously mentioned, angiogenesis is regulated by the balance between pro-angiogenic and antiangiogenic factors. Antiangiogenic proteins such as thrombospondin 1, TGF-β (Ren *et al.,* 2006), troponin I, pigment epithelial-derived factor (PEDF) (Cai *et al.,* 2006), and reversion-inducing cysteine rich protein with Kazal motifs (RECK) (Clark *et al.,* 2007) are downregulated in osteosarcoma. These antiangiogenic molecules are particularly important for embryogenesis and physiological processes such as wound healing and menstruation; however, they also play a protective mechanism against osteosarcoma progression. For example, troponin I and PEDF are expressed predominately within the avascular zones of the cartilaginous growth plate (Quan *et al.,* 2005; Moses *et al.,* 1999) and are likely to contribute to growth plate resistance to osteosarcoma invasion from a typical metaphyseal location. In addition to inhibiting angiogenesis, PEDF exerts direct effects on osteosarcoma cells. Ek et al. (Dass *et al.,* 2007; Dass *et al.,* 2007) have demonstrated apoptosis induction in osteosarcoma cell lines treated with PEDF. Also, in a murine model of orthotopic osteosarcoma, tumour volume was reduced by PEDF, which was associated with reduced microvascular density. There was decreased tumour metastases and reduced size of metastatic tumours in lung.

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