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Introduction to Histopathology

 ANA 404

**Q1. Write on cancers epidemiology in Africa generally and Nigeria in particular.**

In Africa, the five most frequent cancers in males, in order of decreasing age-standardised incidence are: prostate, liver, Kaposi sarcoma, oesophageal and colorectal cancer and in females, they were: cervix uteri, breast, liver, colorectal and ovarian cancers. Age-standardised mortality rates from cancers in African men in 2012 was highest for prostate cancer (20.9%), followed by liver cancer (9.6%), Kaposi Sarcoma (6.5%), Oesophageal (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. The most burden of cancer cases for all ages in women in Africa in 2012 was from breast (25.5%) and cervix uteri cancer (25.2%) .The lack of optimal screening programmes 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.

Regional Variation in Cancer Epidemiology

The populations of Africa are a heterogenous group with significant differences in social constructs, cultural norms, genetic predispositions, environmental influences and exposure to risk factors for cancers. There is therefore regional variation in both the incidence of cancers as well as mortality. (Ferlay et al. 2010) data for cancers in Africa shows that in males, liver cancer is commoner in countries of Western & Middle Africa such as Mali, Niger, Chad, Burkina Faso, Ghana, Benin, Guinea, Senegal, Gambia, Sierra Leone, Central African Republic and Congo. In contrast, oesophageal cancer is commoner in Eastern African countries such as Kenya, Tanzania and Somalia. Recent systematic reviews have explored the epidemiology in sub-Saharan Africa of oesophageal cancer (Kachala 2010) and colorectal cancer (Graham 2012). Prostate cancer was commoner in Nigeria, Cote d’Ivoire, Cameroon,

Gabon, Congo, Angola, South Africa and Madagascar. In females, the two main cancers responsible for the vast majority of cancers in Africa are cervical cancer and breast cancer. These represent the commonest cancers

in most countries in Africa

Risk Factors

Virally-Mediated Cancers

Infectious diseases are endemic in Africa. Persistent infections with

some viruses have been associated with some cancers.

Human Papilloma Virus (HPV) high risk genotypes (HPV 16 & 18 notably)

cause cervical cancer, other genital cancers (vaginal, vulvar, anal, penile) and more

recently some oropharyngeal head and neck cancers mainly in developed countries.

HPV is sexually transmitted with 70% of cervical cancers caused by persistent

infection with high risk HPV 16 and 18. (zur Hausen 2009). Cervical cancer is the

leading cause of mortality due to cancers in developing countries (Yang et al. 2004).

In Sub-Saharan Africa, cervical cancer accounts for both the highest incidence and

mortality from cancers in women with significant consequences on affected communities

Hepatitis B virus (HBV) and Hepatitis C virus (HCV) are aetiologic agents for

hepatocellular carcinoma. In the majority of cases, infection with HBV or HCV is

asymptomatic or results in acute hepatitis with resolution by a competent immune

system. In some cases however, epidemiological studies have shown chronic infection

with HBV (Beasley and Hwang 1984) and 4–7% of HCV infection

(Thomas et al. 2000) progress to hepatocellular carcinoma. The WHO estimates that

5–10% of the adult population in Sub-Saharan Africa has chronic HBV infection

compared to less than 1% in Europe and North America (WHO 2015).

Lifestyle and Dietary Factors

Tobacco smoking and excessive alcohol consumption are recognised risk factors that

work in a synergistic fashion to cause cancers generally – in particular, head and neck

cancers, lung cancers, oesophageal, gastric, colorectal, liver, pancreatic cancers.

Tobacco use accounts for about 6% of cancer deaths in Africa and 20% worldwide (Ezzati and Lopez 2004). Tobacco smoking has increased in some SSA countries due to economic growth and marketing policies employed by tobacco companies. There have been significant dietary changes in many Sub-Saharan African communities in the last few decades that have coincided with the rising incidence of some cancers. Adoption of unhealthy lifestyles such as increasing intake of more refined sugars and calorie-dense foods coupled with physical inactivity has led to a rise in non-communicable diseases. The economic revivals in many SSA countries has also brought with it increasing levels of air pollution from industrial fumes and motor vehicle exhausts. These all contribute towards cancer predisposition.

Challenges and Resources for Cancer Care

There are significant challenges to cancer diagnosis and treatment across Africa that culminate in a complex web and require urgent attention. These difficulties are replicated in most other developing regions of the world, are not peculiar to cancer care alone and invariably affect every spectrum of disease in Africa. The challenges of cancer care can be surmounted by concerted unified efforts by African governments, healthcare systems, medical and allied professions, the media, opinion leaders, non-governmental organizations and funding bodies.

 Late Presentation

Late presentation of cancers and the attendant morbidity and mortality that this brings remains prevalent across the African continent. This is due in part, to a lack of access to efficient healthcare systems and trained personnel that can promptly diagnose cancers but more profoundly due to inherent cultural tendencies of African populations to seek traditional healers primarily and only turn up in hospital at terminal stages of disease. The social stigma that attends any cancer diagnosis is compelling in its impact as a cancer diagnosis is often viewed as a ‘death sentence’. Ignorance of the symptoms of cancers and the dearth of public enlightenment campaigns on diagnosis and treatment further feeds these public misgivings and perceptions. Social attitudes in Africa are sometimes deeply steeped in religious and cultural ideas propagated by religious and local opinion leaders. The admonition not to present to hospital in the face of obvious symptoms indicative of cancer, or the firm belief that the symptoms are due to other ‘*intangible unseen* *causes’* drives many a late presentation and ultimately the comparatively higher mortality in Africa from cancers

During the 65th World Health Assembly, member states of the WHO agreed to adopt a global target of a 25% reduction in premature mortality from the four major noncommunicable diseases (NCD) by the year 2025. This was in response to the growing burden of NCDs, in which, in 2011, cancer was estimated to be the leading global cause of death, ranking above ischemic heart disease, stroke, and lower respiratory tract infections (Maxwell Parkin *at al.,* 2012). 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.

### Establishing and maintaining cancer control programs in Africa

The World Health Organization has promoted the development of National Cancer Control Programmes. Their aim is to reduce the incidence and mortality of cancer and improve the quality of life of patients with cancer in a particular country or state, through the systematic and equitable implementation of evidence-based strategies for prevention, early detection, treatment, and palliation, making the best use of available resources (Maxwell Parkin *at al.,* 2012). This policy was endorsed by the member states of WHO, when, in 2005, the World Health Assembly passed a resolution on cancer prevention and control, calling on Member States to intensify action against cancer by developing and reinforcing cancer control programs Yet, in a survey carried out in 2010, WHO found that only 14 of the 47 countries in the African region responded to questionnaire survey by reporting the existence of an operational policy/strategy/action plan for cancer. In fact, this does not imply the existence of a formal national cancer control plan. In any case, rational planning is impossible without a means of identifying the main health problems, determining priorities for preventive and curative programs, evaluating whether goals are reached in the target groups, and determining what has been achieved in relation to resources expended (Maxwell Parkin *at al.,* 2012)

IN NIGERIA

Cancer Incidence In Nigeria

Nigeria recorded 102079 cases of cancer, out of which 27,304 (26.7%) cases were for breast cancer, 14089 (13.8%) for cervix uteri, 12,047 (11.8%) for liver and 11,944 (11.7%) for prostate cancer as incidence (Globocan, 2012). The age standardized incidence rates (ASR) for these common cancers; breast, cervix uteri, liver and prostate were 50.4, 29.0, 11.5, and 30.7 per 100,000 respectively. A 5-year prevalence study in Nigeria also showed almost the same trend. Breast cancer being the leading cases with 87,579 (37.7%), followed by cervix uteri 35,644 (15.4%), prostate 31062 (13.4%) and then liver 8,447 (3.7%) . The mortality as recorded by Globocan (2012) showed that breast cancer caused 13,960 (19.5%) deaths, cervix uteri 8,240 (11.5%) deaths, liver 11,663 (16.3%) deaths and prostate 9628 (13.5%) deaths in Nigeria. The ASR for mortality are; breast cancer 25.9 per 100,000, cervix uteri 17.5 per 100,000, liver 11.0 per 100,00 and prostate 25.3 per 100,000. The cumulative risk for these common cancers in Nigeria are on the high side, breast cancer being the highest followed by cervix uteri, prostate and the liver cancer. Nigeria like many other African countries lacked accurate data on cancer incidence and mortality. Some of the estimates by WHO are gotten from extrapolating data of few populations- based cancer registries in Nigeria and therefore may not be accurate. The recent publication by Nigeria National System of Cancer Registries (2016) gave the cancer incidence and pattern in Nigeria for 5 years i.e. from 2009-2013 (Morounke Saibu *et al.,* 2017)

Cancer Patterns In Nigeria States

Cancer pattern in Nigeria as extracted from Nigeria National System of Cancer Registries (2016) is shown in Table 3 below. There were 4209 cases of cancer recoded from two registration centers in Lagos State between 2009 and 2013. 25.9% of this figure is male while 74.1% is female. The next in rank after Lagos centers is Enugu center with total cancer cases of 3282 in which 40% is male and 60% is female. Edo and Anambra are the next with 2230 and 2024 cases of cancer respectively. The least cases of cancer were recorded in Bayelsa and Kogi with 140 and 187 cancer cases respectively . The common cancer recorded in LUTH (LU), one of Lagos cancer registries, for period of 2009 to 2013 for male were prostate (7.1%) and colorectal (3.4%) while that of female were breast (41.2%), cervix (14.5%) and colorectal (3.1%). In LASUTH (LA), the second center in Lagos, prostate (5.3%), connective, soft tissue (4.4%), and colorectal (3.3%) for male and breast (38.9%), cervix (9.2%) and uterus (6.6%) were recorded. The record from Enugu cancer registry showed similar trend: prostate (33.9%) and colorectal (6.0%) and non-melanoma skin (4.1%) in male while that of female were breast (60.3%), cervix (22.2%), ovary (5.5%) and colorectal (5.3%). The most common cancers in men in Anambra for all ages were of the prostate (15.1%), colorectal (3.4%) and liver (2.6%). For women of all ages in rank order were breast (20.1%), cervix (8.3%) and ovary (4.0%). In Edo state where the lowest cancer cases were recorded within 2009-2013, the common cancers reported were prostate (13.4%), and colorectal (2.0%) for male and breast (19.6%), and cervix (3.9%) for female (Morounke Saibu *et al.,* 2017)

Conclusion

The prevalence of symptoms of cancer and cancer treatment are highly significant issues in clinical oncology. Cancer data available in Nigeria are hospital based; it is obvious that cancer incidence and deaths in Nigeria are increasing from year to year. However, majority of the Common Cancers are preventable or curable if detected early. Despite these, Nigeria government is putting very little effort towards cancer diagnosis and management. This review was conducted in order to call the attention of the government and research based organizations to use the trend of cancer in Nigeria for setting priorities in cancer control programs. It is obvious that the implementation of the National Cancer Registry could facilitate the study of the evolution of the tendency of cancer by age group in the future, to achieve an appropriate screening system and provide training to people at risk. This will help health officials monitor the disease in the community. Also, as novel cytotoxic, radiation, immunotherapy, and combination therapies evolve, there is a continued need for research evaluating strategies for preventing or mitigating the symptoms related to cancer. The evidence of efficacy of current treatment regimens needs further validation in well powered clinical trials, targeted to and specific to cancers and treatment regimens. Future studies using personalized medicine approaches for the treatment of cancer with the identification of specific gene clusters to discriminate these groups will be valuable (Morounke Saibu *et al.,* 2017)

Q2. Critically examine the involvement of angiogenic genes in the development and progression of osteosarcomas.

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 deubiquitination of von Hippel Lindau protein. Von Hippel Lindau protein releases hypoxia-inducible factor-1*α* (HIF-1*α*), allows HIF-1*α* to bind to the promoter region of the vascular endothelial growth factor (VEGF) gene (D. J. Hicklin *et al*..,2005), and upregulats it. TGF-*α*, and fibroblast growth factor (FGF) may also upregulate VEGF (H. F. 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) (M. Shibuya.,2006). VEGF-A has the broadest angiogenic effect. Upon VEGF-A binding to VEGFR2, a number of divergent signalling pathways are initiated (M. Shibuya.,2006). Nitric oxide (NO) is released by endothelial cells, leading to vasodilation and increased vascular permeability. Endothelial cell proliferation and cycling are stimulated via phospholipase C*γ* (PLC*γ*), protein kinase C (PKC), and the c-Raf-MEK-MAPK cascades (M. Shibuya.,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 (T. Matsumoto *et al*..,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-1*α* and VEGF (D. Liao  et a..,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 (P. 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 surviving, ensuring ongoing endothelial proliferation (J. 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 (S. Davis et al..,2000).

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 (M. Kaya *et al*..,2000) and lack of association (G. Kim *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 (M. 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* (B. Ren *et al*..,2006), troponin I, pigment epithelial-derived factor (PEDF) ( J. Cai *et al*..,2006), and reversion-inducing cysteine rich protein with Kazal motifs (RECK)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 (Y. Li et al..,2005)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. (K. G. Contreras 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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