**MATRIC NUMBER:16/MHS01/177**

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**DEPARTMENT: HUMAN ANATOMY**

**COURSE CODE: ANA404**

**COURSE NAME: HISTOPATHOLOGY**

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**Questions**

**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.**

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

**Epidemiology of cancer in Africa**

Cancer is not a rare disease in Africa. Even ignoring the huge load of AIDS-related Kaposi's sarcoma, yet the facilities for providing treatment for cancer cases in most of Africa are minimal (Levin, El-Gueddari, and Meghzifene 1999).

Cancer registration in economically underdeveloped populations, such as all the countries of Sub-Saharan Africa, is a difficult undertaking for a variety of reasons (Parkin *et al.,* 2003).

The major challenge is to ensure that all new cases of cancer are identified. Cases can be found only when they come into contact with health services: hospitals, health centers, clinics, and laboratories. When resources are restricted, the proportion of the population with access to such institutions may be limited, and the statistics generated will thus not truly reflect the pattern of cancer. The ease with which the cases can be identified also depends on the extent of medical facilities available and the quality of statistical and record systems already in place (for example, pathology request forms, hospital discharge abstracts, treatment records, and so forth). It is impossible to know, without an extensive population survey, what proportion of those with cancer never come into contact with modern diagnostic or treatment services, instead making use only of traditional healers or receiving no care at all.

In the past, studies have suggested that some sections of the population may have been underrepresented in hospital statistics, particularly older women and young men, both of whom were more likely to return to their rural homes to seek care (Mitchell 1967).

The top six cancers in males were the following:

* Kaposi's sarcoma (15.9 percent)
* liver (13.3 percent)
* prostate (10.7 percent)
* esophagus (6.0 percent)
* non-Hodgkin's lymphoma (5.8 percent)
* Stomach (4.5 percent).

In females, the following were the leading cancers:

* cervix (25.4 percent)
* breast (17.4 percent)
* Kaposi's sarcoma (6.2 percent)
* liver (5.5 percent)
* stomach (3.8 percent)
* non-Hodgkin's lymphoma (3.8 percent).

**Breast cancer**

Breast cancer is the second most common cancer among women in Sub-Saharan Africa, accounting for 16.8 percent of all female cancers. Central, West, and East Africa appear to have lower incidence rates than southern Africa, the latter estimated at 33.4 per 100,000. An estimated total of 48,600 cases occurred in Sub-Saharan Africa in 2002.

About 1 percent of all breast cancer cases occur in men, with the male-to-female ratio being higher in black and African populations than among white populations (Parkin *et al.,* 2003; Sasco, Lowenfels and Pasker de Jong 1993).

**Stomach cancer**

A total of 13,800 cases of stomach cancer in males and 10,700 in females was estimated in Sub-Saharan Africa in 2002. Age-standardized incidence rates in males varied, per 100,000, from 3.4 in western Africa to 7.4 in eastern, 8.2 in southern, and 13.4 in central Africa. In western Africa, where the incidence of stomach cancer is the lowest, the male-to-female ratio is 0.9 to 1; however, there is a male predominance in all other areas.

*Helicobacter pylori* infection is now recognized as an important risk factor for cancer of the stomach (IARC 1994); however, smoking and diets low in fruit and vegetables and vitamin C, and high in salts appear to play an important role. Many studies have shown the prevalence of *H. pylori* in Africa to be about 80 percent and that infection is acquired at a younger age than in Western countries for example (Sathar *et al.,* 1994).

**Liver cancer**

Liver cancer is now the second leading cancer in men in Sub-Saharan Africa and the fourth leading cancer in women Chronic carriage of HBV or hepatitis C (HCV), causing cirrhosis, or chronic hepatitis is the leading risk factor for liver cancer. HCV transmission is probably via blood transfusion, unsterile medical and dental procedures, and traditional practices, such as scarification; sexual transmission is thought to be rare (Madhava, Burgess, and Drucker 2002).

There were an estimated total of 33,500 cases in males and 15,500 cases in females in 2002. Areas of high liver cancer incidence (mainly hepatocellular cancers) include countries like The Gambia, Guinea, and Senegal in West Africa, where liver cancers comprise a quarter or more of all cancer cases, with incidence rates ranging from 30 to 50 per 100,000 in men and 12 to 20 per 100,000 in women. Similarly, in central Africa, liver cancer is the leading cancer in Rwanda and in the Republic of Congo (Brazzaville); the estimated rate is 15.4 per 100,000 for men and 8.9 per 100,000 for women. Mozambique is reported to have high incidence rates, although the only data are old (Prates and Torres 1965).

**Prostate cancer**

For the year 2002, a total of 26,800 cases of prostate cancer were estimated, comprising 10.6 percent of cancers of men in Sub-Saharan Africa (Ferlay *et al.,* 2005). Rates of histologically diagnosed prostate cancer in South Africa are 40.1 per 100,000 in whites versus 14 per 100,000 in blacks, although for blacks, access to diagnostic facilities has been limited (Parkin *et al.,* 2003).

In Zimbabwe rates for whites and blacks were 70 versus 25 per 100,000 (Parkin *et al.,* 2003). Central Africa follows with rates of 24.5 per 100,000. Surprisingly, in West Africa, where the majority of African-American men originated, the incidence rate of prostate cancer was estimated as 19.3 per 100,000 in 2002, compared with about 125 per 100,000 in the United States (Ferlay *et al.,* 2005). High rates are observed in other places with populations that are descended from West Africa (for example, the Bahamas, Barbados, Trinidad).

**Non-Hodgkin's Lymphomas**

The non-Hodgkin's lymphomas are composed of an extremely heterogeneous group of lymphoproliferative malignancies displaying distinct behavioral, prognostic, and epidemiological characteristics.

 A total of 14,500 cases in males (5.8 percent of all cancers) and 10,600 cases in females (3.8 percent of all female cancers) were estimated for 2002 in Sub-Saharan Africa. In most African populations non-Hodgkin's lymphoma is relatively rare, but the relative frequency is above the world average in North and Sub-Saharan Africa because of the high incidence of Burkitt's lymphoma in children in the tropical zone of Africa. As in Western countries, most non-Hodgkin's lymphomas in Africa are of B-cell type. In adults, clinical series show an excess of high-grade lymphomas and a deficit of nodular lymphomas. Human T-cell lymphotrophic viruses (for example, HTLV-I) are common in tropical Africa (IARC 1996) and are a cause of T-cell lymphomas; however, the incidence of these in Africa is low.

**Cancer of the esophagus**

In 2002 a total of 15,150 cases of cancer of the esophagus were estimated to occur in males in Sub-Saharan Africa and 7,200 cases in females. Certain areas of high risk have been reported from Kenya and the former Transkei homeland in the Eastern Cape Province of South Africa, where incidence rates as high as 76.6 per 100,000 in males and 36.5 per 100,000 in females were reported between 1991 and 1995 (Somdyala *et al.,* 2003). Cancer of the esophagus shows a remarkable geographic distribution, being one of the leading cancers in southern and East Africa (average incidence in males about 19 per 100,000) but rare in West Africa (1 to 2 cases per 100,000).

**Cancer of the cervix**

Cancer of the cervix is the leading cancer in women in Sub-Saharan Africa with an estimated 70,700 new cases occurring in 2002 (the total in the whole continent was 78,900 cases). Estimated rates for eastern and southern Africa of 30 to 60 per 100,000 are higher than those found in the rest of Sub-Saharan Africa (20 to 35 per 100,000), but the reasons for this difference are unclear. In Kampala the increase in cervical cancer incidence began before the advent of AIDS (Wabinga *et al.,* 2000).

**Kaposi's sarcoma**

According to the most recent estimates, 40,000 cases of Kaposi's sarcoma in males and 17,200 cases in females were estimated for 2002 for Sub-Saharan Africa; only 200 male and 65 female cases were estimated to occur in northern Africa.

**Cancer in Nigeria**

In Nigeria, some 100 000 new cases of cancer occur every year, with high case fatality ratio 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 & Wild 2012). 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 & Wild 2012)

A total of 4 521 cases of invasive cancer in both registries, 2 985 (66%) in females and 1 536 (34%) in males. Most, 3 393 (75.0%) cancers were reported by the IBCR, with1 155 (34.0%) among males and 2 238 (66.0%) in females. In Abuja over the same period, 1 128 (25.0%) invasive cancers was reported, 381 (33.8%) in males and 747 (66.2%) in females.

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

**Angiogenesis in Osteosarcoma**

Osteosarcoma is a malignant tumor of mesenchymal origin and primarily occurs in children, adolescents, and young adults. This pleiomorphic tumor of the bone, based on animal model systems (Gorlick, Anderson *et al.,* 2003) depends on new blood vessel development, also known as angiogenesis, for tumor growth and metastasis.

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. 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. 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. 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.

 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. Whereas one report by Wang et al. showed evidence for decreased overall survival in osteosarcoma patients with high MVD. failed to demonstrate a correlation between intratumoral neovascularization and long-term outcome in patients with nonmetastatic osteosarcoma. Experimental studies on the role of tumor MVDs revealed a significant correlation between MVD and pulmonary metastasis. Increased pretherapeutic 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. 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.

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