NAME: OKEWULONU KAREN EZICHI

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**QUESTIONS:**

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

The epidemiology of cancer has been described as the study of cancer's distribution by age, sex, economic status, and of those factors which determine its prevalence (Phillips, 1969). 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 the International Agency for Research on Cancer (IARC), about 715,000 new cancer cases and 542,000 cancer deaths occurred in 2008 in Africa, and according to United Nations population estimates (UNPD, 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 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. It may also be in part due to a lack of awareness about the magnitude of the current and future cancer burden among policy makers, the general public, and international private or public health agencies (ACS, 2012).

Sub-Saharan Africa provides several contrasts with other world regions (Stewart and Wart, 2014). Among women, this is the only region where cervical cancer is equivalent to breast cancer in terms of incidence (each constitutes approximately a quarter of the total burden) and is the most common cause of cancer death in women (23.2% of the total). The incidence and mortality rates for cervical cancer are 34.8 and 22.5 per 100,000 respectively, the highest of any world region. Among men, prostate and liver cancers are the most common forms of incident cancer and causes of cancer death. Although the leading role of prostate cancer in the cancer incidence pattern in men is shared with most other world regions, this region also has mortality rates comparable to incidence rates. The rates of 27.9 and 20.9 per 100,000 for prostate cancer incidence and mortality, respectively, stand in marked contrast to those in Europe (64.0 and 11.3 per 100,000, respectively) or North America (97.2 and 9.8 per 100,000, respectively), where incidence is much higher but mortality is much lower. The importance of liver cancer in this region should be emphasized; it is the second most common cancer in men and the third most common cancer in women. Cervical and breast cancers in women and prostate and liver cancers in men are the only cancers with sex-specific incidence or mortality rates of more than 10 per 100,000, but the high rates of Kaposi Sarcoma is the third most common cancer in men and represents 9.2% incidence rate of 7.2% of all cancer diagnoses, with an incidence rate of 7.2 per 100,000. This reflects the very high regional level of HIV infection and associated cancer sequelae before the advent of highly active antiretroviral therapy. Cervical cancer and Kaposi sarcoma also make important contributions to the pattern of 5-year prevalence in the region (Stewart and Wart, 2014).

**Epidemiology of Cancer in Nigeria:**

The burden of cancer in Nigeria is unknown; mainly because of lack of statistics or under-reporting, and this is not peculiar to only Nigeria but most parts of Africa.

In Nigeria, according to WHO cancer county profiles, household solid fuel caused 75% of cancer in 2012, tobacco smoking 6.1% in 2011 and physical inactivity 19.8% in 2010. In Nigeria, the estimated number of cancer cases of all ages is 12,079 showing the commonest with percentage. 4172 cases (Age standardized incidence rates (ASR) =4.2 per 100,000) and 3175 deaths (ASR= 3.3 per 100,000) were estimated in Nigeria in 2012 (Ferlay *et al.,* 2012).

**CANCER INCIDENCE IN NIGERIA:**

The earliest study from Nigeria was from the Ibadan Cancer Registry; 1960-69 (ICR): Edington and MacLean reported higher rates of cancer in females with age standardized rates (ASR) of 105.1 and 78 per 100,000 females and males respectively. In 1998, 74.5 per 100,000 females and 63.9 for males was recorded from the same center. In Zaria, 1976-78 data reported 1575 cases with 52% of cases in males and 48% in females; a latter study however showed more cancers in females than males (Abdulkareem, 2009).

The current data (2001-2005) 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. From Kano, of 1001 cancers recorded for period 1995-2004, male cancers accounted for 50.3% and 49.7% in females. Mandong et al (2001) recorded 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 (Globocan, 2008). 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 (Abdukareem, 2010).

**Table 1:** Cancer incidence for some states in Nigeria based on National system of cancer registries (2016) (Morounke *et al.,* 2017).

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **States** | **Years** | **Cancer cases in males** | **Cancer cases in females** | **Total** |
| Anambra | 2009-2013 | 857(42.3%) | 1167(57.7%) | 2024 |
| Bayelsa | 2009-2013 | 53(37.9%) | 87(62.1%) | 140 |
| Borno | 2009-2010 | 251(45.6%) | 299(54.4%) | 550 |
| Edo | 2009-2010 | 923(41.4%) | 1307(58.6%) | 2230 |
| Ekiti | 2009-2010 | 126(33.1%) | 225(66.9%) | 381 |
| Enugu | 2009-2012 | 1323(40%) | 1959(60%) | 3282 |
| Gombe | 2009-2013 | 298(39.1%) | 464(60.9%) | 762 |
| Kaduna | 2009-2013 | 474(40.5%) | 696(59.5%) | 1170 |
| Kogi | 2009-2013 | 103(55.1%) | 84(44.9%) | 187 |
| Kwara | 2009-2013 | 612(41.5%) | 864(58.5%) | 1476 |
| Lagos (LU) | 2009-2013 | 596(26.5%) | 1651(73.5%) | 2247 |
| Lagos (LA) | 2009-2013 | 493(25.1%) | 1469(74.9%) | 1962 |
| Nasarawa | 2009-2013 | 109(32.4%) | 227(67.6%) | 336 |
| Osun | 2009-2010 | 262(44.7%) | 325(55.3%) | 587 |
| Rivers | 2009-2013 | 526(47.0%) | 592(53.0%) | 1118 |
| Sokoto | 2013 | 60(40.8%) | 87(59.2%) | 147 |

**The six most common cancers in Nigeria in descending order of frequency are;**

1.Breast,

2.Cervix,

3.Prostate,

4.Colorectal

5.Liver Cancer And

6.Non-Hodgkins lymphoma (NHL). (Abdukareem, 2010).

* **Breast cancer:**

This is the commonest female cancer and most common cancer in both sexes. Studies have indicated increase in the relative frequency ratio; moving from number 2 or 3 to the number one cancer in both sexes. This increase has been attributed to increase awareness and presentation for screening. Majority of breast cancers occur in pre-menopausal women with the peak age in the 5th decade. Parity is 5.3-6 and age at first child is less than 20yrs (Abdukareem, 2010).

In Nigerian studies, only 25-50% of the tumors are reported to be estrogen or progesterone receptor positive, which is the basis for hormonal treatment. It is common practice to give anti-estrogen blindly in Nigeria without recourse to ER/PR status; this is reported to be at the risk of complication such as endometrial carcinoma, which has been reported in Nigeria (Banjo et al., 2008). For male breast cancer in Nigeria, it represents 3.7 -8.6% of all breast cancers. This is higher than the 1% recorded from other parts of the world. The higher figures in Nigeria may be due to small sample size, since the data are mainly hospital based. The peak age incidence is 40-49years; similar to that of female cancer. Majority are invasive ductal carcinoma. It is characterized by late presentation at advanced stage with attendant poor prognosis (Abdukareem, 2010).

* **Cervical cancer:**

It is the 2nd most common cancer in Nigerian women and the most common female genital cancer constituting a major cause of mortality among Nigerian females in their most productive years. It was the commonest cancer reported from Ibadan, Eruwa, Zaria, Jos, Benin and Calabar and in the early years, 2nd to breast in Enugu and Ife-Ijesha. A steady increase was reported by Babarinsa *et al*(1999) in Ibadan in between 1975-1995 which was attributed to poor screening facilities, and lack of organized national screening programme.

Recent data shows that it has however been overtaken by breast cancer; except in Kano where it was reported as the most common cancer in both sexes. In Jos, it is the most common female cancer. On the other hand, incidence of other gynae cancers such as choriocarcinoma and endometrial has reduced drastically (Babarinsa *et al.,*1999). The age range is between 17-80yrs with peak in the 5th decade. Patients are multiparous with average parity of 5.6-6.5.

* **Prostate cancer:**

Prostate cancer is the most common cancer among men in southern Africa and western Africa in which Nigeria and Cameroon are good examples (Jemal *et al.,* 2010; Hsing and Devesa, 2001). A study showed that the age standardized incidence rates (ASR) of 17.5 per 100,000 in Africa was lower than those of developed countries with 61.7 per 100,000 (Ferlay *et al.,* 2014). Ajape et al., 2010 reported low levels of awareness of prostate cancer and prostate specific antigen (PSA) screening in Africa (Ajape *et al.,* 2010). In Nigeria, prostate cancer is also the most common cancer among men. 11944 cases with ASR of 30.7 per 100,000 and 9628 deaths with ASR of 25.3 per 100,000 were estimated in 2012 (Ferlay *et al.,* 2012).

* **Colo-rectal cancer:**

Colorectal carcinoma is the commonest malignancy of the gastrointestinal tract worldwide. Previous studies had shown it to be a rare disease in Nigeria representing 3-6% of all malignant tumors in most studies. It accounts for 10-50% of all GIT malignancies in Nigeria, peak incidence-60-70years and mean age in Lagos is 50.7years (Abdukareem, 2010).When it occurs in the young, it is associated with polyposis syndrome or ulcerative colitis should be suspected, but contrary to previous report which showed it to be rare, recent report shows the incidence to be increasing; an 81% increase over a period of two decades was reported from Ibadan. A recent study from Lagos & Sagamu showed similar trend with an increase in annual frequency of this cancer from 14 cases per annum to 32.3 cases per annum. The low incidence in Nigerians was attributed to fibre rich diet which is a common practice. The age incidence of CRC in Nigeria is lower compared to developed countries; about 10 years difference has been reported in many studies and the peak age reported from Nigeria ranged between 42.9years to 53years with a mean of 46years. There has also been an increase in the proportion of young patients with CRC. Reports from various parts of Nigeria showed that 35-42% of CRC are below age 40yrs. CRC in younger age has been shown to present a diagnostic and therapeutic problem and prognosis tend to be less favorable. Generally, CRC is more common in males than females with average male: female ratio of 1.5:1 in Nigeria and 2:1 in America. Similar to reports from other parts of Nigeria, recent report from Lagos showed a mean age of 50.7 years, M:F ratio of 1.3:1 with 23% occurring below 40years. The majority (76.4%) was well to moderately differentiated adenocarcinoma. Mucinous carcinoma (10.7%) and signet ring carcinoma (1.2%) were more common in patients under 40yrs compared to well differentiated tumors and majority of CRC are located in the rectosigmoid.

* **Liver cancer:**

Liver cancer is the most common cause of cancer death in Nigeria and most common liver malignancy in Nigeria is hepatocellular carcinoma (HCC). Data from various parts of Nigeria shows that it accounts for between 1.6%- 7.2% of all cancers in both sexes and represent the second or third most common cancer in males. HCC was earlier reported to be the most common male cancer until recently when it was overtaken by prostate cancer. It is the most common malignancy on medical wards and the most common cause of liver disease in Nigeria accounting for between 29.3% - 64% of all liver biopsies in several studies (Abdukareem, 2010). The peak age incidence is between the 4th and 5th decade with M: F ratio of 2 to 1, and incidence has been found to be a decade earlier than for liver cirrhosis and hepatitis. A significant number of cases occur in association with liver cirrhosis.

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

Osteosarcoma is derived from mesenchymal tissues, and often occurs in the long bones of the body such as the distal femur, proximal tibia, and humeral metaphysis. It is most common in children and adolescents, with an annual incidence of approximately 3 per 1,000,000 (Picci, 2007; Mirabello *et al.,* 2009; Ottaviani and Jaffe, 2009). It is well known that the development of osteosarcoma involves a complex, multistep, and multifactorial process (de Alava, 2007; Bovée and Hogendoorn, 2010; Powers *et al.,* 2010). Several studies have investigated the role of cancer stem cells in osteosarcoma and their potential to cause tumors (Berger *et al.,* 2008; Osuna and de Alava, 2009), the results of which suggested that genetic factors play an important role in the development of osteosarcoma (Jia et al., 2013; He et al., 2013, 2014). Angiogenesis, the formation of new blood vessels from preexisting endothelium, is a discrete event in carcinogenesis that is related to the aggressive potential of a tumor (Hanahan and Folkman, 1996; Nakamura *et al.,* 2005). Accumulating evidence suggests that the growth of tumors is associated with increased angiogenesis and that the formation of new blood vessels is a fundamental step in tumor development and expansion (Mariani *et al.,* 2012). Vascular endothelial growth factor (VEGF) is a potent angiogenic growth factor, and the polymorphisms in VEGF have been shown to influence the expression of this gene through altering the initiation of transcription and the internal initiation of translation (Akiri *et al.,* 1998).

Several previous studies have assessed the association between gene polymorphisms in VEGF and cancer risk, but the results have been inconsistent (Chen *et al.,* 2014; Kapahi *et al.,* 2014; Yang *et al.,* 2014; Rinck-Junior *et al.,* 2015). However, only two studies have reported the association of VEGF gene variations with the risk of osteosarcoma (Tie *et al.,* 2014; Wang *et al.,* 2014). Expression of VEGF has been suggested as a means of evaluating the prognostic importance of angiogenesis in osteosarcoma (DuBois & Demetri, 2007). It is now widely accepted that both mutations of oncogenes and tumor suppressor genes lead to the switch into an angiogenic tumor. According to Gorlick et al (Gorlick *et al.,* 2003), osteosarcoma has complex unbalanced karyotypes and with alterations of the p53 and retinoblastoma pathways in most cases, thus the vasculature playing an intimate role in the progression of the pathologic development of osteosarcoma.

VEGF is a key tumor-derived angiogenic factor that has multiple functions, including stimulation of angiogenesis, vasculogenesis, inflammation, and vascular permeability, which constitutes the most important signaling pathways in tumor angiogenesis (Quan & Choong, 2006). Certain genetic and environmental factors, which cause DNA damage, have been reported to have a role in the development of osteosarcoma (Jia *et al.,* 2013; He *et al.,* 2013, 2014), and the VEGF gene was considered as one studies (Tie *et al.,* 2014; Wang *et al.,* 2014). The present hospital-based study investigated the association between VEGF genetic polymorphisms and the risk of osteosarcoma in a Chinese population, and the results suggested that the AA and CA+AA genotypes of VEGF -2578C/A were statistically correlated with an increased risk of osteosarcoma.

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