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16/MHS01/093
ANATOMY
400L
HISTOPATHOLOGY ASSIGNMENT

Q1. WRITE ON CANCERS EPIDEMIOLOGY IN AFRICA GENERALLY AND NIGERIA IN PARTICULAR.

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)

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 United Nations population estimates, 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 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. 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.

In this review, we present data on the estimated burden for common cancers in Africa based on the most recent GLOBOCAN estimates of incidence and mortality for 2012.

These data are built upon results from the network of population-based cancer registries that have grown up over the last 30 years. In Africa, data from cancer registries are particularly important, as there are no accurate mortality statistics available from civil registration systems on the continental mainland. (Maxwell Parkin *at al.,* 2012)

The numbers and rates presented here were extracted from the GLOBOCAN 2012 database of the International Agency for Research on Cancer (IARC), which presents estimates of incidence of, and mortality from all cancers and 27 major types in 184 countries or territories worldwide for 2012. Of the 54 countries of Africa for which estimates are available, relatively recent cancer registry data were used for 34, while the absence of any recent data for 20 meant that estimates were based on data from neighboring countries. depicts the data sources and methods used in map form (Maxwell Parkin *at al.,* 2012)

In seven countries (Algeria, Egypt, Libya, Malawi, Tunisia, Uganda, and Zimbabwe) there were local ("regional") registries which cover less than 10% of the national population, but which were judged to be of sufficient quality for inclusion in the latest volume of "Cancer Incidence in Five Continents" (CI5; ref. (Maxwell Parkin *at al.,* 2012)

Their data were used to estimate national incidence [methods 6 (>1 registry per country) and 7 (a single registry)].

National cancer registry data were available from seven countries (Botswana, Mauritius, Namibia, Reunion, The Gambia, Swaziland, and Republic of South Africa). Although none were of a quality sufficient for inclusion in CI5, the incidence rates of six of them were used in making estimates for the country (Maxwell Parkin *at al.,* 2012)

Cancer-specific mortality statistics were available from four countries, but they were of only medium quality in two (Mauritius and Reunion) and of low quality in Egypt and Republic of South Africa (quality criteria as defined by Mathers and colleagues; ref. 5). Recent mortality rates from these counties were used for the 2012 estimates. For the remaining countries, mortality was estimated by combining the estimates of cancer incidence with survival probabilities predicted from country-specific levels of the Human Development Index (Maxwell Parkin *at al.,* 2012)

Estimates of the incidence of Kaposi sarcoma (KS) for countries in Sub-Saharan Africa were calculated by a different approach, using data on prevalence of HIV infection, as

most KS cases are HIV-related (Maxwell Parkin *at al.,* 2012)

1. The number of endemic (pre-AIDS) KS cases was first estimated, using the percentage frequency of the disease, by sex and age, based on data from Uganda, Kampala (1961–1980), and Nigeria, Ibadan (1971–1990). These percentages were applied to countries in Eastern and Western Africa, respectively. For countries in Middle and Southern Africa, a simple average of these frequencies was applied

   The number of epidemic (AIDS-related) KS cases was then estimated for both sexes combined for the year 2011, using estimates of AIDS deaths by country in 2011 (7) and an estimate of the ratio of deaths from AIDS to incident cases of KS. This ratio was based on observed KS rates in several countries (from the sentinel registries listed below, minus the endemic KS), and was specific by region (varying from 0.7% in Western Africa to 6.0% in Eastern Africa). This total number of AIDS-related KS was partitioned by sex and age using sex- and age-specific proportions in sentinel registries of Malawi, Blantyre, Uganda, Kampala and Zimbabwe, Harare (Eastern Africa), Congo, Brazzaville (Middle Africa), Botswana and Namibia (Southern Africa), Mali, Bamako and Niger, Niamey (Western Africa) (Maxwell Parkin *at al.,* 2012)

We present the results for 2012 in terms of the numbers of new cancer cases and deaths, and cumulative risk of developing, or dying from cancer before age 75, expressed as a percentage, assuming an absence of competing causes of death. (Maxwell Parkin *at al.,* 2012)

The 2012 estimates

The numbers and rates of cancer for individual countries are estimates based on data of varying quality, ranging from population-based close-to-complete and valid observed counts of cases and deaths, through estimates based on samples, to those based solely on data from neighboring countries. They represent the best estimates that can be attained given existing information sources, and, although it is often suggested that the numbers of cases are underestimates of the true situation (Maxwell Parkin *at al.,* 2012), there is no reason to suppose that this is the case. The country-specific cancer incidence rates (and mortality using the 5-year survival method) are usually based on data reported by local cancer registries that generally cover the capital city or predominantly urban areas. Adjustments are made for known causes of under-enumeration of cancer cases, but this remains a possibility, particularly in some of the unpublished datasets that have been used. Of more concern, however, is the very sparse data available for rural Africa (where life expectancy was less than 50 years in

2000), and the likelihood that incidence rates for most cancers are much lower in rural areas than those reported by the cancer registries covering urban areas. If the urban:rural incidence rate ratios that are reported by Indian cancer registries were applicable to African countries, then the 2012 estimates for Africa would be overestimated, as only 40% of the population is urban (Maxwell Parkin *at al.,* 2012). The estimates presented in GLOBOCAN 2012 are the most accurate that can be made at present, although there is obviously a need for more reliable cancer registry data, especially in Sub-Saharan Africa, and promoting population-based cancer registration systems for assessing local cancer control priorities in these countries is clearly very important.

The major cancers

Breast cancer.

Breast cancer is the most commonly diagnosed cancer in Africa, and in Sub-Saharan Africa, and is also the leading cause of death from cancer (63,100 deaths in 2012). shows that breast cancer is the most commonly diagnosed cancer in women in all of North Africa, and has also become the leading cancer in women in many Sub-Saharan countries. However, the geographic pattern does not closely follow the conventional regions. Apart from the island populations of Mauritius and Reunion, the highest rates are seen in Egypt, Algeria, Nigeria, and Republic of South Africa. Although the reasons for the increasing importance of breast cancer must be speculative, they most likely include increases in the prevalence of risk factors such as early menarche, late child bearing, having fewer children, obesity, and increased awareness and detection, which are associated with urbanization and economic development. There have been rapid increases in the incidence of breast cancer in Sub-Saharan Africa; rates of increase in the last 20 years were 3.6% per year in Kampala (Uganda) and 4.9% per year in the Black population of Harare (Zimbabwe; In North Africa, the increase in Central Tunisia was 2.5% annually in the last 15 years (Maxwell Parkin *at al.,* 2012)

It has been known for some time that breast cancer among Black Americans is more likely to be early onset, higher grade, and estrogen receptor (ER) negative than is observed among White Americans and the same is true in the Black population of the United Kingdom. Early age at onset and aggressive clinical features have frequently been documented in clinical series from Africa and case series from several centers in Africa have reported that hormone receptor–negative cases are predominant, for example, only 25% of cases in a large multicenter series of patients from West Africa were ER-positive, less than half that observed in the U.S. Black population overall and in

those born in Africa (Maxwell Parkin *at al.,* 2012). However, these findings from Africa were based on archival materials and the role of antigen degradation and false negative results could not be ruled out Indeed, a more recent prospective case-series study in South African Black women found that only 35% of breast cancer cases were ER negative, which was comparable with those which had been reported in U.S. Black women (Maxwell Parkin *at al.,* 2012)

Cervical cancer.

Cervical cancer is the second most frequently diagnosed cancer in Africa (99,000 cases) and Sub-Saharan Africa (93,200, 25.2% of cancers in women) in 2012, but is much rarer in North Africa (only 5800 cases, 5.1% of cancers in women) (Maxwell Parkin *at al.,* 2012) shows cumulative incidence by country, and illustrates the very high risk in East Africa, with cumulative risk in Malawi, Zimbabwe, and Mozambique in excess of 6%, whereas in some countries of North Africa (Egypt, Sudan and Tunisia) the cumulative risk is below 1%. These high rates reflect a high prevalence of the causative virus, HPVas well as a lack of screening services for the prevention and early detection of the disease. It is noteworthy that before the introduction and wide dissemination of Pap testing in the 1960s in the United States, the incidence of cervical cancer (cumulative risk, 0–74) in ten selected metropolitan areas in 1947–48 [3.1% in whites and 6.7% in non-whites] was of the same order of magnitude as the highest rates found in Eastern Africa today. There is little evidence for any decline in incidence in recent years; incidence rates in both Kampala and Harare show persistent increases in incidence. (Maxwell Parkin *at al.,* 2012)

Prostate cancer.

With almost 60,000 new cases estimated in 2012, cancer of the prostate is the most frequently diagnosed cancer in men, although in North Africa, it lies in fourth position (after lung, liver, and bladder). It is the third most common neoplasm overall (after breast and cervix), both in Africa as a whole and in Sub-Saharan Africa. In the latter region, the risk of developing prostate cancer before age 75 (3.4%, affecting almost 1 in 30 men) is in fact not dissimilar to the equivalent risks for breast (3.5%) and cervical cancer (3.8%) among women (Maxwell Parkin *at al.,* 2012)

As is evident in the disease is the leading cause of cancer among men in many African countries (23 of 54). There remains however a 10-fold variation in cumulative incidence of prostate cancer in Sub-Saharan countries, with risk in 2012 ranging from 0.8% in Ethiopia to more than 8% in the Republic of South Africa. Even in the latter country, rates are modest compared with those in men of African descent in the United States and Caribbean, although incidence is markedly increasing in a number of African populations, for example in Kampala and in the Black population of Harare

(Maxwell Parkin *at al.,* 2012). Most cancer registries are situated in major cities or urban populations on the continent, and it thus remains difficult to ascribe such geographical and temporal differences to risk factors linked to increasing affluence (a westernization of lifestyle), or to inherent and well-known artifacts [enhanced diagnostic capabilities, notably via the increasing availability (and affordability) of PSA testing] (Maxwell Parkin *at al.,* 2012)

Liver cancer.

Given the poor prognosis of liver cancer, the number of new cases (58,500) and deaths (56,000) estimated in 2012 are rather similar, and in terms of both indicators, liver cancer (predominantly hepatocellular carcinoma) ranks as the fourth most frequent cancer on the African continent and in Sub-Saharan Africa, accounting for about 7% of the total cancer burden. Rates are 2-fold greater in North Africa than in Sub-Saharan Africa largely because of the very high incidence rates in Egypt and indeed liver cancer rates tends to be low elsewhere in the region; compare, for example, the cumulative incidence in Morocco (0.2%), Algeria (0.2%), and neighboring Libya (0.7%) among men with those estimated for Egypt (4.6%). The incidence and mortality rates are also elevated elsewhere, particularly in Western Africa, where liver cancer is the most common malignancy of men in 12 countries with a cumulative risk ranging from 1% to 3% in 2012.

The major risk factors in operation for liver cancer on the African continent are infections with the hepatitis viruses and aflatoxin, particularly chronic carriage of the hepatitis B virus (HBV) in Sub-Saharan Africa, with chronic hepatitis C virus (HCV) infection more prevalent in Northern Africa. This is markedly the case in Egypt, where the burden of HCV prevalence is the highest in the world and largely attributed to public health campaigns to reduce schistosomiasis via mass parenteral antischistosomal therapy (Maxwell Parkin *at al.,* 2012)

Colorectal cancer.

Colorectal cancer is the fifth most common malignancy in Africa according to estimates for 2012, with 41,000 new cases and around 29,000 deaths, and a slight preponderance of cases in men. It is certainly more common in Northern Africa where, in Algeria, it ranks second only to breast cancer in terms of incidence when both sexes are combined. In Tunisia and Libya, colorectal cancer takes second place among women, and lifetime risk (0–74) is above 1%. Cumulative risk is even higher in the Indian Ocean islands of Mauritius and Reunion, as well as in Republic of South Africa, where rates are many times greater in Whites compared with Blacks (Maxwell Parkin *at al.,* 2012)

Given the relative diagnostic biases associated with prostate and breast cancer, cancers of the large bowel may be considered a more robust marker of the extent of transition in a given population, probably linked to a number of ill-defined dietary factors as well as nutritional correlates (sedentary lifestyle and obesity).While Burkitt's review of colorectal cancer over 40 years ago revealed its rarity across Sub-Saharan Africa, cumulative incidence is now above 1% in Zimbabwe in 2012, and time trends in incidence over the 20-year period up to 2010 revealed increases in colorectal rates of around 4% per annum among both Black men and women in Harare (Maxwell Parkin *at al.,* 2012)

Kaposi sarcoma.

An estimated 37,500 cases of KS (23,800 cases in males and 13,700 cases in females were diagnosed in Africa in 2012, all but about 300 in Sub-Saharan Africa shows that the area of highest incidence is in East Africa, where in six countries it is the most common cancer in males. The incidence rates for KS rose several fold in East Africa and other parts Sub-Saharan Africa during the 1990s, consistent with the HIV/AIDS epidemic in these regions, and incidence rates still correlate, at least to some extent, with the prevalence of HIV-AIDS KS is an HIV-associated cancer caused by human herpes virus-8 (Maxwell Parkin *at al.,* 2012) Although KS continues to be a leading cause of cancer in most parts of Eastern Africa, rates are declining because of reduction in prevalence of HIV and wider availability of highly active antiretroviral therapy (Maxwell Parkin *at al.,* 2012)

Non–Hodgkin lymphoma.

An estimated 36,700 new cases and 26,400 deaths from non–Hodgkin lymphoma (NHL) occurred in Africa in 2012. Incidence rates in both sexes are rather higher than the world average (cumulative risk 0.54%) in North Africa (cumulative risk 0.70%) but lower in Sub-Saharan Africa (cumulative risk 0.37%). NHL encompasses a variety of histologically distinct forms (Maxwell Parkin *at al.,* 2012). Burkitt lymphoma (BL) is a very common cancer of children in parts of tropical Africa, where it may account for up to three-quarters of all childhood cancers. In the zone of high incidence of childhood BL in central Africa, almost all cases are associated with Epstein–Barr virus (EBV), as demonstrated by the presence of either EBV nuclear antigen (EBNA) or EBV DNA in the tumor cells. Intense (holoendemic) malaria infection is a cofactor: BL cases have evidence of more frequent or intense infection with malaria than control children. The

risk of adult NHL is increased by HIV infection, although the relative risk in HIV-positive subjects in Africa is lower than in Europe and North America, and the association between endemic BL and HIV is even less clear. In 2002, it was estimated that about one quarter of NHL cases in Sub-Saharan region were associated with AIDS

Lung cancer.

About 30,300 new lung cancer cases and 27,000 deaths were estimated to have occurred in 2012 in Africa, with men accounting for over 70% of the total cases and deaths. There is over a 30-fold difference in incidence and mortality rates between countries in both males and females, with the lowest rates found in the Western Africa and Middle Africa and the highest rates in Southern and Northern Africa. Notably, lung cancer is the most commonly diagnosed cancer among males in most countries in Northern Africa, including Tunisia, Libya, Morocco, and Algeria (Maxwell Parkin *at al.,* 2012)

Data on time trends in lung cancer rates in Africa are sparse. Chokunonga and colleagues reported that lung cancer incidence rates decreased from 1991 through 2010 in Black population of Harare, Zimbabwe, in both men and women (Maxwell Parkin *at al.,* 2012)

. In South Africa, Bello and colleagues documented decreasing lung cancer mortality rates in men but increasing rates in women from 1995 through 2006, and an increasing incidence in women has also been noted in Kampala (Uganda; ref. The decrease in men may reflect reduction in tobacco use due to antitobacco policies over the past decades, including increased excise tax on cigarettes and banning smoking in public places. In general, tobacco consumption and lung cancer rates are expected to increase in many parts of Africa because of continued tobacco promotion and lack of comprehensive tobacco control policies in the region. According to data from the Global Youth Tobacco Survey, initiation of smoking increased from 1999 to 2008 in some African countries (Maxwell Parkin *at al.,* 2012)

Esophageal cancer.

About 27,500 new cancer cases and 25,200 deaths from esophageal cancer were estimated to have occurred in Africa in 2012, 89% of these in Sub-Saharan Africa. It is more common in males than females (sex ratio = 1.4) and incidence rates are particularly high in East Africa. Exceptionally high incidence rates have been recorded in the East Cape Province (former Transkei) area of South Africa. Almost all of the esophageal cancers in these high risk areas are squamous cell carcinomas. The reasons for the high burden of esophageal cancers in several parts of Eastern Africa and Southern Africa are not fully understood. Tobacco and alcohol are, as elsewhere, clear risk factors, but obviously do not explain the dramatic regional variation within

Africa. Many other hypotheses have been advanced, including nutritional deficiencies secondary to poor dietary patterns such as consumption of a maize-based diet that is low in fruits and vegetables, and the contamination of maize with fungi that produces fumonisins, a cancer-initiating agent in experimental animals (Maxwell Parkin *at al.,* 2012). Although a small decline in registered death rates from esophageal cancer in males was recorded in the Republic of South Africa between 1999 and 2006, no decline in incidence has been seen in cancer registries in the high risk populations of the Eastern Cape Harare, Zimbabwe and Kampala, Uganda (Maxwell Parkin *at al.,* 2012)

Bladder cancer.

Bladder cancer is the fourth most common cancer of men in North Africa, with a cumulative risk of 1.1% , but the incidence elsewhere in Africa is much lower. Incidence and mortality rates among men in Northern Africa are twice as high as those in Southern Africa, which has the second highest regional rates (cumulative risk 0.8%). Egyptian men have by far the highest bladder cancer incidence rates in Africa (cum risk 2.6%). A large proportion of bladder cancer cases in Africa are squamous cell carcinoma, and between 30% and 60% of all bladder cancer cases in this region are caused by chronic infection with the parasite *Schistosoma haematobium*. Treatment of schistosomiasis with the drug praziquantel coupled with lower infection rates (probably because of urbanization) are thought to have contributed to the substantial decrease in incidence of Schistosoma-associated bladder cancer in Egypt over the past few decades (Maxwell Parkin *at al.,* 2012)

Opportunities for cancer prevention and control

Opportunities for reducing suffering and death from cancer in Africa exist across all stages of the cancer control spectrum. Recent reviews have described the current status and future opportunities with respect to cancer treatment and palliative care in Africa (Maxwell Parkin *at al.,* 2012). Here, we focus on the prospects for cancer prevention, based on our understanding of etiology and the nature history, and applicable resource-dependant approaches to early detection strategies
Prevention is rightly proposed as of primary importance as it is undoubtedly more logical, and cost-effective to prevent disease that to deal with it once it has occurred. The benefits of preventive interventions take a long time to be manifest, and the more urgent needs of alleviating suffering among patients with cancer will take priority, but this should not preclude relatively modest investments to reduce the size of the problem to be dealt with in future.

It has been estimated that at least 32.7% of cancers in Sub-Saharan Africa are caused by infectious agents including cervix, liver, and bladder cancers and KS—but excluding

some that result from infection with HIV. A substantial proportion of these cancers is potentially preventable by vaccination, improved hygiene, sanitation, and/or treatment. (Maxwell Parkin *at al.,* 2012)

Vaccination against Hepatitis B (responsible for the majority of liver cancers in Sub-Saharan Africa), has been available since the early 1980s and has been recommended as part of routine national infant immunization programs since 199 Although almost all African countries have included the vaccine as part of their national infant immunization schedule, vaccination coverage was less than optimal (<80%) in at least 20 countries in 2012 (Maxwell Parkin *at al.,* 2012)

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)

The need for a functional cancer surveillance system is explicit in all of the documents relating to cancer control planning, as is, in the context of low and middle income countries, the essential role of cancer registries in this respect. Cancer-specific incidence data (per 100, 000) from (population-based) cancer registries is one of the core indicators promoted by WHO as part of the framework for NCD surveillance in the Global Status Report on Non-Communicable Diseases. It is disappointing that at present only 20 of the countries of Sub-Saharan Africa have a functioning population-based cancer registry (Maxwell Parkin *at al.,* 2012). Cancer registration is always a feasible system to introduce in a country and does not need to cover an entire national population—a common misapprehension, unless the country is small or wealthy, most

cancer surveillance needs can be met in a cost-effective manner through registration of a sample of the population from which national estimates can be derived (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 (Figure 4) (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%) (Figure 5). 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 (Figure 6). 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)

BREAST CANCER

Breast cancer (BC) is a global disease of significant burden and its incidence continues to rise especially in the sub-Saharan Africa [13]. It was described as the most common cancer in women worldwide [14]. It accounted for 24.45% of all the cancer types (Figure 3). Huge differences have been observed in the behavior of the tumour, clinical manifestation, treatment response and prognosis across the various regions of the world especially between the developed and the developing world incidence data from two population based cancer registries in Nigeria suggested substantial increase in incidence of breast cancer in recent times [18]. Recent observations also showed that the frequency of breast cancer had risen over that of cervical cancer in Nigeria [19]. In 2012, WHO also estimated 27,304 cases with age standardized incidence rates (ASR) of

50.4 per 100,000 and 13960 deaths with ASR 25.9 per 100,000. Nggada et al., in 2008 suggested public enlightenment, were screening all women at risk, early detection of the lesion, and proper management in our health institution as the ways to slow down the progressive increase in breast cancer cases and deaths in our environment, Nigeria (Morounke Saibu *et al.,* 2017)

CERVICAL CANCER

Cervical cancer is a cancer of the women. Its frequency in Africa is second to breast cancer and it is the leading cause of cancer death (50,300) in women with ASR of 25.2 cases per 100,000 [3]. North America on the other hand had 7.7 per 100,000 as its ASR [20]. This value is low when compared with that of Africa. In Nigeria, the incidence and the trend are not different. In 2012, WHO also named cervical cancer as the second common cancer in Nigerian women with estimated 14,080 cases and ASR of 29.0 per 100,000 and 8,240 deaths and ASR of 17.5 per 100,000 [21]. Cervical cancer is caused by Human papilloma virus infection which is transmitted during sexual intercourse. So, it is preventable and remains one of the most preventable cancers. Its slow development offers an opportunity for easy identification and treatment when detected early. Some of the risk factors in African women are early age of sexual initiation and multiple sex partners (Morounke Saibu *et al.,* 2017)

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 [9,24]. A study showed that the ASR of 17.5 per 100,000 in Africa was lower than those of developed countries with 61.7 per 100,000. Ajape et al., 2010 reported low level of awareness of prostate cancer and prostate specific antigen (PSA) screening in Africa [25]. 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 (Morounke Saibu *et al.,* 2017)

LIVER CANCER

Liver cancer is common to both male and female. It is ranked as the second common cancer and the leading cause of death in men and the third common cancer and the third leading cause of cancer death women in Africa. The ASR of 11.6 per 100,000 in Africa was higher than that of the developed countries with 8.2 per 100,000 [3]. Middle Africa had the highest incidence and mortality rates while western African was next in rank [3]. Incidence rate was also common in western Africa countries like Gambia and Guinea [26]. In Nigeria, 12047 cases of liver cancer were estimated in 2012 (ASR=11.5

per 100,000), out of which 7,875 were males and 4,172 were females. Also a total of 11663 deaths with ASR of 11.0 per 100,000 were estimated for both sexes in the same year (Morounke Saibu *et al.,* 2017)

COLORECTAL CANCER

The rate of colorectal cancer in Africa was not as high as that of developed countries as recorded in 2008. The ASR for Africa was 6.9 per 100,000 compared to 37.7 per 100,000 for the developed countries. In central Tunisia, colorectal cancer accounted for 8.4% of all the cancers with significant increase between 1993 and 2007. Some risk factors like smoking, alcohol consumption, and unhealthy diets that are high in excess calories such as meats, starches, fats, and sugars are associated with development of colorectal cancer (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 (Table 3). 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 [29]. 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.

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 (Lu Xie *et al.,* 2017) depends on new blood vessel development, also known as angiogenesis, for tumor growth and metastasis. Although modern multimodality treatment has significantly improved tumor resectability and the long-term outcome of these patients, 25–35% of patients with initially non-metastatic disease subsequently develop metastasis and this remains the major cause of death (Lu Xie *et al.,* 2017). At the same time, axial skeletal osteosarcoma preliminarily responds poorly to chemotherapy and has been proven to have an even more dismal

prognosis. From the review of van Maldegem *et al* and Lagmay *et al*, we concluded that in the past two decades, published phase I/II clinical trials on chemotherapy for osteosarcoma failed to make significant progress in refractory cases. With the study of oncogenesis and pathobiological behavior of osteosarcoma, we know that new blood vessel formation (angiogenesis) is fundamental to tumor growth, invasion, and metastatic dissemination (Lu Xie *et al.,* 2017)

Several groups have evaluated tumor micro-vessel density and outcome in osteosarcoma (5–7). Expression of VEGF has been suggested as a means of evaluating the prognostic importance of angiogenesis in osteosarcoma (8). Monotherapy with second-generation broad-spectrum VEGF receptor tyrosine kinase inhibitors (TKIs) in sarcoma has now become an area of active research and application beyond gastrointestinal stromal tumors (GISTs). Within all of those preclinical experiments and clinical trials (6, 9–13), the milestone of the treatment on advanced osteosarcoma should count on the application of anti-angiogenesis TKIs sorafenib on refractory cases from the Italian Sarcoma Group (13), which officially raised the 4-month progression-free survival (PFS) from <30–46% for the first time. However, things had seemed not to change as dramatically as was expected since then. The main hurdle that researchers need to get over should be sensitivity and drug-resistance (Lu Xie *et al.,* 2017)

The goals of this review are: a) to review representative agents in *in vitro* and *in vivo* experiments that showed promise for osteosarcoma based on anti-angiogenesis therapy; b) to summarize the current phase I and II trials of anti-angiogenensis therapies that have been explored in advanced osteosarcoma patients; and c) to focus on targeting the action towards VEGFR and to discuss current hurdles and future perspectives.

Angiogenesis is the process of new blood vessel development, which is critical in both physiological development and pathological processes, such as tumor progression, wound healing, and cardiovascular, inflammatory, ischemic, and infectious diseases (15). In response to hypoxia, tumor tissues produce and release angiogenic growth factors, such as vasculo-endothelial growth factor (VEGF), the acidic and basic

fibroblast growth factors (aFGF and bFGF), and the platelet-derived endothelial cell growth factor (PD-ECGF) to recruit new blood vessels by angiogenesis and vasculogenesis (16). 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* (1), osteosarcoma has complex unbalanced karotypes 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 (Lu Xie *et al.,* 2017)

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 (7). According to Niu *et al* (16), the whole VEGF family has been identified to comprise 8 members with a common VEGF homology domain: VEGF-A, VEGF-B, VEGF-C, VEGF-D, VEGF-E, VEGF-F, and placenta growth factor (PIGF)-1 and −2. As shown in Fig. 1, VEGFs signal through 3 tyrosine kinase receptors, known as Flt-1 (VEGFR-1), Flk-1/KDR (VEGFR -2), and VEGFR-3 (17), which were previously thought to be predominantly expressed by endothelial cells, but in actual fact are also in sarcoma cell lines with limited study (18–21). It has been reported that both VEGFR-1 and −2 can promote angiogenesis and VEGFR-3 stimulation leads to lymphangiogenesis (22).

There is a general consensus that VEGFR-2 is the dominant receptor in mediating the pro-angiogenic functions of VEGF-A and this pathway has been prioritized for the development of antiangiogenic therapies (16, 23). Though VEGFR-1 has a 10-fold higher binding affinity for VEGF-A, its activation has less impact on the activation of intracellular signaling intermediates than VEGFR-2 (23).

Recognition of the VEGF pathway as a key regulator of angiogenesis has led to the development of several VEGF-targeted agents, including agents that prevent VEGF-A binding to its receptors (24), antibodies that directly block VEGFR-2 (25), and small molecules that inhibit the kinase activity of VEGFR-2 thereby block growth factor signaling (26). Some of them have been approved by the FDA of the US for clinical applications (16). Previous representative anti-angiogenic compounds (10,27–39) are summarized in Table I with median inhibition concentration (IC_{50}) noted for comparison (Lu Xie *et al.,* 2017)

Moreover, Broadhead *et al* (40–43) repeatedly reported that pigment epithelium-derived factor (PEDF), co-localized with VEGF in tumor tissue, was probably important in the fine-tuning of tumor vasculature and aggression. However, the clinical application of this agent is under investigation (NCT00702494) (Lu Xie *et al.,* 2017)

Fundamental study of angiogenesis in osteosarcoma and other related cellular signaling pathways

Geller and Gorlick (44) reviewed HER-2 targeted treatment of osteosarcoma. The results showed that HER-2 expression as a prognostic factor in osteosarcoma remained controversial and a comparison of the results is difficult because of variables, including the handling and preparation of material, tissue heterogeneity, fixation techniques, storage conditions, antibody characteristics, scoring scheme, and staining interpretation due to single-institution, retrospective studies that were limited in size. Abdeen *et al* (45) stated in 2009 that there was a negative correlation between VEGFR-3 and both overall survival and event-free survival of osteosarcoma, and VEGF-B was correlated with a poor histologic response to chemotherapy. In 2011, Yang *et al* (46) reported that vascular endothelial growth factor (VEGF) pathway genes collectively were amplified, and alterations of this pathway were validated by fluorescence *in situ* hybridization (FISH) and immunohistochemistry analyses in 58 formalin-fixed, paraffin-embedded osteosarcoma archival tissues that had clinical follow-up information. Lammli *et al* (47) in 2012 demonstrated that there was a significant positive correlation between VEGF expression and tumor stages among these cases ($P<0.01$). The data also suggested a higher cancer recurrence and more frequent cases of remote metastasis in the high-VEGF group compared to the low-VEGF group. The expression of VEGF has been used as a more objective means of evaluating the prognostic importance of angiogenesis in osteosarcoma. One group found that 63% of osteosarcoma samples demonstrated VEGF immunohistochemical staining in tumor cells (8).

In 2013, Chen *et al* (48) completed a meta-analysis of published studies and performed a systematic review to provide a comprehensive assessment of the prognostic role of VEGF expression. They included 12 studies with a total of 559 osteosarcoma patients in the systematic review and meta-analysis. Compared with osteosarcoma patients with low or negative VEGF expression, patients with high VEGF expression were obviously associated with lower disease-free survival (OR=0.25, 95% CI 0.11–0.58, P=0.001, I^2=56.4%). In addition, patients with high VEGF expression were obviously associated with lower overall survival (OR=0.22, 95% CI 0.13–0.35, $P<0.001$, I^2=0.0 %). Therefore, the findings from this systematic review suggested that VEGF expression was an effective biomarker of prognosis in patients with osteosarcoma. However, different

from soft tissue sarcoma (49), osteosarcoma has not been classified by which subtypes of VEGFR expression correlate with prognosis. Kampmann *et al* (49) reported in 2015 that the high expression of VEGFR1-3 and PDGFR-β was significantly correlated with higher grading (G2 vs. G3, $P<0.05$), and high VEGFR-2 was significantly correlated with decreased patient survival ($P<0.001$).

According to Aurby *et al* (50), angiogenesis inhibitors can be divided into 2 classes: direct inhibitors and indirect inhibitors. Direct inhibitors target endothelial cells by arresting proliferation and migration of these cells or by inducing their apoptosis. Indirect angiogenesis inhibitors act on the signaling pathways induced by angiogenic stimuli, by sequestering the angiogenic factors secreted by tumor cells, or by blocking the signal transduction pathways that are activated when binding factors meet their receptors on endothelial cells. The first direct inhibitor was endostatin, which was an internal fragment of the carboxy-terminus of collagen XVIII (51). It is a paradigm of a broad-spectrum endogenous anti-angiogenic molecule, through which the results of *in vitro* experiments are satisfactory. However, methods of resolubilization gave very low yields of active proteins, which makes it hard to be a mature pharmaceutical and obstructs its further development. Bevacizumab (52) neutralizes all isoforms of human VEGF and inhibits VEGF-induced proliferation of endothelial cells *in vitro* with an ED_{50} of approximately 50 ng/ml. It was tested in combination with several chemotherapeutic drugs, such as doxorubicin, topotecan, paclitaxel, and docetaxel, showing an additive antitumor effect (28,53,54). However, as for osteosarcoma, clinical application did not prove as effective as the experiments (53). With innovation from the VEGF-A aptamer (55) to VEGF trap (56), more focus has been given to the VEGFR tyrosine kinase inhibitors (TKIs) (7,16).

Protein kinases are key enzymes in the regulation of various cellular processes that catalyse transfer of a phosphate group from ATP to a hydroxyl group of a serine or a threonine. Among the 90 identified genes encoding proteins with tyrosine kinase activity, 58 encode receptors divided into 20 subfamilies (57). Of these, EGFR/ErbB (class I), the receptor for insulin (class II), PDGF (class III), FGF (class IV), VEGF (class V), and HGF (MET, class VI) are strongly associated with oncological diseases (58). Unlike bevacizumab, VEGF Trap, and pegaptanib, which target extracellular VEGF, TKIs target the intracellular signaling pathways of VEGF receptors as well as a variety of receptors that rely on a tyrosine kinase component to function properly, including PDGF receptor, FMS-like tyrosine kinase 3 (FLT3), RAF, and c-KIT receptors (16). In Table I, we summarize the classic TKIs compounds in preclinical experiments for osteosarcoma and their main targeted region. Sunitinib and sorafenib share a similar mechanism of action and primarily target tumor angiogenesis by inhibiting a variety of tyrosine kinases (36,59,60). Pazopanib is an oral, second-generation multi-targeted tyrosine

kinase inhibitor targeting VEGF-1, −2, and −3 receptors, PDGF-α and-β receptors, and c-kit, which exhibited good potency against all of the human VEGFRs and closely related tyrosine receptor kinases *in vitro* (30,31,61). Besides TKIs, antibodies blocking VEGFR2 have also been developed (Lu Xie *et al.,* 2017)

In addition to anti-angiogenesis drugs, there are some other cellular signaling pathways that should be mentioned as they are always used in combination with anti-angiogenesis target drugs in clinical trials of osteosarcoma. A signal transduction pathway through insulin-like growth factor (IGF) receptor signaling, which is also an attractive therapeutic target for the treatment of osteosarcoma, is the mammalian target of the rapamycin (mTOR) pathway (63). mTOR technically does not belong to anti-angiogenesis therapy according to Hanahan *et al* (64). Under conditions favorable for cell growth, mTOR activates ribosomal protein translation (via S6K1) and cap-dependent translation (via eIF4E), allowing G_1 to S phase cell cycle progression. This signal pathway was not originally activated in most sarcoma patients, but after using anti-angiogenesis TKIs for a while, many sarcomas show secondary activated pathway, which makes this target as a supplement to TKIs for long-term use.At the same time, the involvement of the IGF/IGF1-R axis in tumorigenesis makes it an attractive target for anticancer therapeutics, especially in Ewing's sarcoma. A human IgG1 type monoclonal antibody directed against the human IGF-IR, has been developed to antagonize IGF-IR signaling ((Lu Xie *et al.,* 2017)

Conclusion

For advanced osteosarcoma, due to its increased mutation burden and intratumor heterogeneity, therapy based on comprehensive molecular profiling has not been successfully proven. At present, anti-angiogenesis TKIs showed promising initial results for this group of patients compared to other second-line chemotherapy, but the results are still not satisfactory. Based on the limited options of effective agents, the algorithm of choosing optimal target drugs is still understudied. The anti-angiogenesis TKIs therapy of other solid tumors may shed light on the treatment for advanced OS (Lu Xie *et al.,* 2017)

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