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

 In 2011, WHO estimated cancer to be the leading global cause of death, ranking above ischemic heart disease, stroke, and lower respiratory tract infections. 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 (Parkin *et al.,* 2014). 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 (Ferlay *et al.,* 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. Data Sources and Methods 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 (Ferlay *et al.,* 2012). 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 (Parkin *et al.,* 2014). Adjustments are made for known causes of underenumeration 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 (Ferlay *et al.,* 2010) were applicable to African countries, then the 2012 estimates for Africa would be overestimated, as only 40% of the population is urban . 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 (Parkin *et al.,* 2014).

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). 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 (Wabinga *et al.,* 2013, Chokunonga *et al.,* 2013). In North Africa, the increase in Central Tunisia was 2.5% annually in the last 15 years (Missaoui *et al.,* 2012). 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 (Gukas *et al.,* 2005, Adebamowo *et al.,* 2008, Stark *et al.,* 2010), for example, only 25% of cases in a large multicenter series of patients from West Africa were ERpositive, less than half that observed in the U.S. Black population overall and in those born in Africa (Miller *et al.,* 2002, Jemal *et 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 (Adebamowo *et al.,* 2008). Indeed, a more recent prospective case-series study in South African Black women found that only 35% of breast cancer cases were ER negative (McCormack *et al.,* 2013), which was comparable with those which had been reported in U.S. Black women.

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). Figure 6A 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, HPV (de Sanjose *et al.,* 2007) as well as a lack of screening services for the prevention and early detection of the disease (Denny *et al.,* 2004). 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 (Denny *et al.,* 2004)] 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(Wabinga *et al.,* 2013, Chokunonga *et al.,* 2013).

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. 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 tomore 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 (Ferlay *et al.,* 2013), although incidence is markedly increasing in a number of African populations, for example in Kampala and in the Black population of Harare (Chokunonga *et al.,* 2013). 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] (Parkin *et al.,* 2014).

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 (Sylla *et al.,* 2012, Parkin *et al.,* 2003), 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 (Frank *et al.,* 2000).

This study describes the pattern of cancer recorded in the Kano cancer registry over a 10 year period and noted a progressive increase in number of cancer cases. This supports existing predictions that major increases in cancer incidence and mortality will occur in developing 4 countries as the population continues to expand. The 1990 cases in this study is actually an under estimation of the actual cancer burden in the area served by the KCR since at present it limits its entries only to cases of cancer attending tertiary hospitals that have been confirmed by histology or cytology. Therefore the figures only represent the 'minimal cancer' frequency rates for the area of coverage. It is however acknowledged that the most widely accepted means of evaluating quality of cancer incidence report is by the proportion of histologically confirmed diagnosis. Many cases would have been missed or died because of limited access to tertiary institutions in the area of coverage. Globally, cancers tend to demonstrate slight female preponderance. There was however a slight male preponderance in the KCR (50.2% vs.49.8%) in contrast to reports from other registries in Nigeria, where female (Ogunbiyi *et al.,* 2000, Mandong *et al.,* 2003) cases predominated. The reason for this finding is unclear, but recent estimates in Europe, show 54% of new cancers occurring in men, compared with 46% in 10 females. Cancer of the cervix was the most common cancer, comprising of 22.9% of all female cancers. This cancer is reported to be the most frequent form of cancer seen in (Parkin *et al.,* 2001, Pisani *et al.,* 2002, Thomas *et al.,* 2004) women in developing countries , even though some Nigerian studies have observed a changing trend with breast cancer superceding cervical cancer as the most common malignancy. The risk factors for cervical cancer such as infection with high risk human papilloma virus (HPV) types 16,18,31,33 e.t.c, Human Immunodeficiency Virus and other reproductive factors are well established. It is potentially preventable through institution of comprehensive cervical cancer screening programmes which detect preinvasive lesions of the cervix with potential for progression to invasive cancer. Unfortunately in Nigeria, there is no national or state cervical screening programme, and screening remains mainly opportunistic and limited to tertiary health institutions, utilizing the pap test. It may be necessary that in low resource settings alternative cost effective screening approaches such as visual inspection with acetic acid may be more applicable. This should be co-coordinated under a comprehensive national cervical cancer screening programme. The introduction of Cancer in Nigeria: A 10-Year Analysis: Mohammed A Z, Edino S T\*, Ochicha O, Gwarzo A K\*\*, Samaila A A\*\*\* HPV vaccination offers a relevant alternative for preventing cervical cancer and is already yielding promising results in some developed countries but will however take several decades to become widely (Harper *et al.,* 2004) available in developing countries. Breast cancer the leading female cancer worldwide was the second most frequent cancer in this study with a 15 mean age of 46years. Breast cancer has genetic, familial and environmental influences including high fat diet. It has been shown to be positively associated with menstrual and obstetric risk factors in a case control study in Ibadan, Nigeria similar to the finding in (Ramon *et al.,* 1996, Adebamowo *et al.,* 1999) Caucasian populations in Europe and America. Majority of our patients however did not exhibit these risk factors inconsonance with other studies in Africa and parts of the Middle East. Early detection and “cure” are obtainable in developed countries, through mammographic screening and wide application of fine needle aspiration cytology (FNAC) for diagnosis. In developing countries, there is need to incorporate programmes that promote breast self examination, clinical breast examination and FNAC into mammography based screening services. Prostate cancer was the most common cancer in men accounting for 16.5% of male cancers. Cancer registry reports from Nigeria and other parts of Africa have highlighted the emerging trend of prostate cancer as the commonest male cancer, in contrast to earlier studies that showed predominance of liver cancer. Unlike some developed countries whose rising incidence of this cancer has been partly attributed to routine screening of males which results in early detection, the vast majority of our cases were diagnosed in symptomatic men with clinical prostate cancer since routine screening is currently not practiced in our setting. The mean age of patients was 64.2 years, and we did not observe a tendency to younger age at presentation as described elsewhere. The principal factors contributing to high incidence of prostate cancer are genetic factors, increasing age, serum androgen (testosterone) levels, high fat diet and sexual factors amongst others. The importance of race is demonstrated in the higher incidence amongst African-American men when compared to Caucasians in the USA. Available screening options include digital rectal examination (DRE) which is limited by low sensitivity, prostate specific antigen assays and transrectal ultrasound scans. Nigerian Journal of Medicine, Vol.17, No.3 July-August 2008, ISSN 1115 2613 282 Non-melanoma skin cancers as a group ranked fourth representing 8.3% of all cancers. The sex ratio was, male to Female, 1.6:1. They were mainly squamous cell carcinomas and less frequently basal cell carcinomas. Skin cancer is also the most common cancer in some Arab populations and individuals of non-African descent in Africa, where exposure to sunlight is the most important risk factor. In our environment different risk factors may be operative particularly as trauma is an important event preceding the development of these cancers which commonly present as chronic ulcers that refuse to heal. Colorectal cancers in Black Africans have been suggested to represent unique molecular and clinical entities . They were the fifth commonest cancer with a male to female ratio of 2.7:1. In general, race, family history, 'westernization of diet' and genetic alterations involving several genetic loci e.g. APC, DCC and FAP 23 genes are associated with increased incidence. The frequent association with infectious agents in developing countries is remarkable and requires further (Mandong *et al.,* 2003, Ojo *et al.,* 1992) investigation. Although principally a disease of elderly individuals in developed countries, it has been shown to (Mandong *et al.,* 2003, Ojo *et al.,* 1992) affect a younger age group in Nigeria. The recorded mean age in this study was 44.4 years. In high risk individuals with a family history, surveillance by colonoscopy is essential early in life and genetic testing for gene mutations is now standard care in many (Neal *et al.,* 1996, Powell *et al.,* 1993) developed societies. Bladder cancer ranked sixth amongst the most frequent cancers. It exhibited a wide sex ratio (male to Female, 4.6:1), with 53% being of the squamous cell carcinoma histologic variety which was associated with Schistosoma haematobium in 12% of cases. This finding is consistent with the well established linkage between bladder cancer 26 and Schistosoma haematobium infection. A changing pattern towards a predominant transitional cell carcinoma histologic variety is now being recorded in other parts of 27 Nigeria. Schistosomiasis remains endemic in many parts of Africa, Asia and the Middle east where the high incidence of this parasite associated cancer documents the importance of infection-related malignancies in less developed countries. Among the less frequent cancers, liver cancer deserves special mention as it constituted only 1.6% of all cancers with a male to female ratio of 7:1. Liver cancer is associated with Hepatitis B and C viruses, exposure to aflatoxin B1 through dietary contamination and liver 6 cirrhosis of varied aetiology. This cancer is generally underestimated in histopathology based studies because of reliance upon results of clinical tests, ultrasound scans Cancer in Nigeria: A 10-Year Analysis: Mohammed A Z, Edino S T\*, Ochicha O, Gwarzo A K\*\*, Samaila A A\*\*\* Nigerian Journal of Medicine, Vol.17, No.3 July-August 2008, ISSN 1115 2613 283 and alpha-fetoprotein estimation by clinicians. This is because patients present late often with deranged 5 clotting profile. Although liver biopsy facilities are available at our institution, late presentation precludes clinicians from undertaking the procedure because of the high risk of bleeding. Postmortem examinations are also not routinely performed hence several suspected cases may be missed leading to underestimation of liver cancer. The viral aetiology of some cases of the disease provides potential for a preventive strategy through hepatitis B virus (HBV) vaccination. It is anticipated that a future decline in incidence may be seen as HBV vaccination is gradually being incorporated into the national programme on immunization in Nigeria. Of major concern is the category of metastatic cancers of unknown primary site which together constituted 5.1% of cancers. This group comprises of advanced widely disseminated cancers in which the primary site could not be ascertained. The absence of immunohistochemistry in most Nigerian institutions hinders accurate determination of the primary site. Paediatric cancers constituted 9.3% of all cancers and were dominated by lymphoreticular cancers and retinoblastoma.

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

Osteosarcoma is a relatively uncommon cancer, accounting for 5% of childhood cancers and 8.9% of cancer-related deaths in children (Yang *et al.,* 2013). The overall incidence is five cases per million persons per year. Despite modern multidisciplinary treatments including chemotherapy and surgery, the 5-year survival rate of osteosarcoma patients remains 60–70% [1,2]. Osteosarcoma pathogenesis is complex and may involve genetic aberrations of the VEGF, mTOR, and Wnt signaling pathways; inactivation of p53, Rb, and WWOX; and amplification of APEX1, Myc, RECQL4, RPL8, HDMX, and VEGFA (Yang *et al.,* 2013). Recent translational studies that have shed light on new molecular targets for osteosarcoma have investigated genetic aberrations, tumorigenic pathways, key transcription factors, growth factors, miRNAs, and factors involved in tumor cell migration and invasion, proliferation and apoptosis, angiogenesis, osteoclast function, and drug sensitivity (Yang *et al.,* 2013). Several miRNAs (such as miR-215) and their target genes are potential novel biomarkers or therapeutic targets for osteosarcoma (Yang *et al.,* 2013) biology and include altered chromosomes and genes; regulators of cell migration and invasion, proliferation and apoptosis, angiogenesis, osteoclast function, and drug sensitivity; growth factors and signaling pathways; transcription factors; and microRNAs (miRNAs) (Yang *et al.,* 2013). Some aberrations are correlated with clinical prognosis or are involved in important signal pathways, suggesting they partly result in tumorigenesis or progression. Kyoto Encyclopedia of Genes and Genomes pathway enrichment analysis of osteosarcoma revealed several key signaling networks in which multiple genes were altered at the chromosomal level. These include the vascular endothelial growth factor (VEGF) and mammalian target of rapamycin (mTOR) signaling pathways, in which amplifications occur, and the wingless-type MMTV integration site family (Wnt), cellular adhesion molecules, and Hedgehog signaling pathways, in which deletions occur. Further investigation of the VEGF pathway revealed that VEGFA gene amplification is a poor prognostic factor for tumor-free survival of osteosarcoma patients (Yang *et al.,* 2011). When used in combination with chemotherapy, the anti-VEGF antibody bevacizumab significantly improved the survival and response rates in patients with metastatic colorectal cancer. Thus, antivascular therapymay hold promise for patients with osteosarcoma (Hicklin *et al.,* 2005).

Regulators Of Angiogenesis: The anti-VEGF antibody bevacizumab significantly improved survival and response rates in colorectal cancer patients (Hicklin *et al.,* 2005). VEGFA is abundantly expressed in 74.1% of osteosarcoma cases, and patients with VEGFA-positive osteosarcomas had significantly worse tumor-free survival rates than patients with VEGFA-negative osteosarcomas (Yang *et al.,* 2011).

Growth Factors and Signaling Pathways: Recently, investigated cell surface receptor expression patterns in standard and patientderived osteosarcoma cell lines. Insulin-like growth factor (IGF)-2R was consistently overexpressed on the cell surface across all tested cell lines. Substantial expression of met proto-oncogene (hepatocyte growth factor receptor), v-erb-b2 erythroblastic leukemia viral oncogene homolog 2 (HER-2), IGF-1R, fms-related tyrosine kinase 4, insulin receptor (IR), and platelet-derived growth factor receptor, beta polypeptide was also detected, suggesting that these receptors may contribute to the aggressiveness and biological heterogeneity of osteosarcoma and may serve as potential targets for osteosarcoma patients. Similarly, Wang et al. reported that siRNA-mediated IGF-1R down-regulation suppressed osteosarcoma cell growth rates in vitro and reduced tumorigenicity in vivo. More specifically, IGF-1R down-regulation caused G0/G1 arrest and induced apoptosis via caspase-3 activation. Further study showed that co-targeting IGF-1R and IR-A is more effective than targeting IGF-1R alone in inhibiting osteosarcoma growth (Wang *et al.,* 2009)

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