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| ANA 404: INTRODUCTION TO HISTOPTHOLOGY |
| NEOPLASIA ASSIGNMENT |
| BYOSAMOR MICHELLE16/MHS01/213 |
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QUESTION 1

Cancer has become a major source of morbidity and mortality globally (Sylla and Wild, 2011). In 2008, there were 12.7 million new cases and 7.6 million cancer-related deaths (Ferlay and Shin, 20080). Most, 56% of these newly reported cancer cases occurred in developing countries and It is projected that by 2030, 70% of all new cases of cancer will be found in developing countries (Boyle and Levin, 2008). Most of this increase in incidence is a result of population growth and increased life expectancy (Curado and Edwards, 208).

In Nigeria, some 100 000 new cases of cancer occur every year, with high case fatality ratio (Forman and Mathers, 2008). 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 and Wild, 2011). 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 and Wild, 2011).

Despite the threat that cancer poses to public health in sub-Saharan Africa (SSA), few countries in this region have data on cancer incidence (Storm and Ferlay, 2008). Most of the cancer incidence data in SSA in recent times is based on reports from registries in The Gambia, Zimbabwe and Uganda (Storm and Ferlay, 2008). These cancer registries have consistently provided incidence data for the last 10– 20 years despite the difficulties of sustaining cancer registration in developing countries (Parkin and Wabinga, 1999; Amero and Nambooze, 2011; Chokunonga and Levy, 1999; Chirenje and Nyabakau, 2011; Bah and Whittle, 1993-1997)

.In recent times, information on cancer incidence, prevalence and mortality in Nigeria has been based on estimates from case series, medical records, mortality records, hospital based cancer registries and the Ibadan population based cancer registry (IBCR) (Hamdi-Cherif and Thomas, 2011). IBCR, located at the University College Hospital Ibadan and set up in 1962, is the first cancer registry in Nigeria. Cancer incidence data from this registry were published for the time periods 1960– 1962, 1960–1965, and 1960–1969 in the first three volumes of Cancer Incidence in 5 Continents (CIV). However, due to logistic problems the registry suffered some setbacks from the 1970s to 2000s (Bray and Edwards, 2010).

Since 2009, the Nigerian Federal Ministry of Health (FMOH) and the Institute of Human Virology Nigeria (IHVN) have initiated a program of National System of Cancer Registries to strengthen existing cancer registries and establish new ones through provision of baseline training for newly established registries; continuing education for older registries; mentoring, computer hardware and software provision and support; data management and analysis. In this paper, we present estimates of cancer incidence in Nigeria based on data from 2 population-based cancer registries in the system. These registries cover defined populations and use multiple source reporting.

The Ibadan Cancer Registry is located in one of the oldest cities in Nigeria, Ibadan, a small city in Oyo state, Southwestern Nigeria. The major ethnic group in this region is Yoruba , one of the largest ethnic groups in Africa. The common religions in this area are Islam and Christianity. The major source of income is agriculture and industries. In contrast, the Abuja Cancer Registry (ABCR) is located in the modern capital city of Abuja Nigeria which is centrally located and home to people of varied ethnic groups and religions. Abuja is the more developed of the two cities and houses major multinational companies, foreign embassies, the legislative and executive arms of government, and is attractive to young people seeking job opportunities and career advancement.

NATIONAL CANCER INCIDENCE BASED ON POPULATION BASED REGISTRIES DATA (2012-2013)

National cancer incidence statistics were derived from the Abuja and Enugu population-based cancer registries and are reported below: There were 3215 cases of cancer reported by the Abuja and Enugu population-based cancer registries in 2012-2013. Out of these 3215 cases, 1977 (61.5%) were in women and 1238 (38.5%) in men. The age standardized incidence rates (ASR) for all cancers in women was 160.2 per 100,000 and 94.2 per 100,000 in men. The five most common cancers in Nigerian women were cancers of the Breast 871 cases, ASR= 65.8 per 100,000, Cervix 290 cases ASR= 31.2 per 100,000, Ovary 86 cases ASR=6.9 per 100,000, Colo-rectal67 cases ASR 6.8 per 100,000 and Connective/ Soft Tissue 56 cases ASR 3.0 per 100,000. The five most common cancers in Nigerian men in 2012-2013 were cancers of the Prostate 412 cases ASR= 42.5 per 100,000, Colorectal 84 cases ASR= 5.9 per 100,000, Non-melanoma Skin 73 cases ASR= 4.0 per 100,000, Liver 63 cases ASR 3.9 per 100,000 and Connective/Soft Tissue 56 cases ASR 3.1 per 100,000 [29]. 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 (Way FSCSS, 2016). 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 (Way FSCSS, 2016).

DIAGNOSIS AND TREATMENT OF CANCER IN NIGERIA

Early diagnosis is very important to the control of cancer. Standard screening methods are available for detecting different types of cancers. These methods include mammography for breast cancer, fecal occult blood testing and sigmoidoscopy/ colonoscopy for colorectal cancer, and Pap smear for cervical cancer (Lambert and Sauvaget, 2009). Whereas pap smear-based screening program was unsuccessful in Africa, other approaches like on visual inspection using Lugol’s iodine or acetic acid, and low-cost DNA tests to detect HPV infections, have been shown to be feasible and effective in many parts of Africa, including Kenya and South Africa (Louie and DeSanjose, 2009; Denny and Kuhun, 2005). Screening one or two times in life time between the ages of 35-55 years would reduce cancer by about 30% (Goldie and Gaffikin, 2005). Increasing public awareness of early signs and symptoms of cancers of the breast, cervix, oral cavity, urinary bladder, colorectal, and prostate should increase the detection of these diseases at earlier stages when there are more effective options for treatment leading to better prognosis (Curado and Edwards, 2007). Different treatment options are available.

Four common types are:

1. Chemotherapy: The use of a combination of drugs to destroy cancer cells to cure or to control cancer.

2. Radiation therapy: The use of various forms of radiation to safely and effectively treat cancer and other diseases. Radiation therapy remains an important component of cancer treatment with approximately 50% of all cancer patients receiving radiation therapy during their course of illness; it contributes towards 40% of curative treatment for cancer (Baskar and lee, 2012). The main goal of radiation therapy is to deprive cancer cells of their multiplication (cell division) potential.

3. Surgery: Removal of the tumor and the area surrounding the tumour.

4. Antologous/allogenic Bone Marrow Transplant: Used to treat diseases that damage or destroy the bone marrow; also used to restore bone marrow that has been damaged during cancer treatment (International Agency for Research on Cancer, 2003).

Cancer treatment is facing serious challenges in Nigeria. The treatment facilities are inadequate or unavailable, especially radiotherapy machines. Most of the few ones in Nigeria are in bad conditions without hope of repairing them. This has contributed to high cancer deaths recorded in Nigeria. Therefore, the government of Nigeria need to show more commitment towards fighting this deadly disease called cancer. Cancer treatment needs urgent improved funding and research from government and other stakeholders.

The prevalence of symptoms of 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 wellpowered 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.

QUESTION 2

Principles of angiogenesis

Angiogenic processes are deﬁned as the formation of new vessels. To date, at least three processes contribute to the growth of new blood vessels: angiogenesis, vasculogenesis and arteriogenesis (Yancopoulos *et al*., 2000; Battegay *et al*., 2003; Kutryk and Stewart, 2003). Angiogenesis – formation of new capillary blood vessels from existent microvessels – occurs in physiological and pathological states. It is a multistep process depending on a multitude of angiogenic and antiangiogenic molecules that plays a crucial role in the development of vascular supply in normal tissue, for example, in reproduction and wound healing, as well as in pathology. Inefﬁcient angiogenesis is involved in many ischemic diseases like heart disease, peripheral vascular disease, rheumatoid arthritis, and tumor growth and metastasis.

Apart from angiogenesis, vasculogenesis is known as the development of new vessels from blood stem cells and this process is well recognized in embryogenesis. Blood vessels are derived from mesoderm by differentiation of angioblasts. The third known angiogenic process is arteriogenesis, which refers to the formation and modelling of new arteries possessing fully organized tunica media. Often, this process is described as the maturation of pre-existing collaterals. Angiogenic processes formulate a complex cascade of events, (Yancopoulos *et al*., 2000; Battegay *et al*., 2003; Kutryk and Stewart, 2003) controlled by a multitude of positive and negative regulators. Apart from angiogenic cytokines, many of the extracellular enzymes such as metalloproteinases facilitate angiogenesis by extracellular matrix remodelling (Davidson and Reich, 2002; Kuzuya and Iguchi, 2003). Traditionally, angiogenesis starts with injured tissues (or tumor) that produce and release angiogenic factors that bind to speciﬁc receptors located on the endothelial cells of pre-existing blood cells (for VEGF there are VEGFR1, VEGFR2 and VEGFR316,35) and activate them to proliferation and migration. The activated endothelial cells migrate to the source of proangiogenic factors (injured tissues, tumor). In the ﬁnal step, sprouting endothelial cells roll up to organize a blood vessel tube, loops and, ﬁnally, matured vessels, stabilized mainly by smooth muscle cells.

Angiogenesis and cancer in the early 1970s, Folkman described that tumor growth and metastasis formation are tightly dependent on angiogenesis and that tumor vascularization is a process necessary for the progression of cancer from a small, well-localized tumor to a larger neoplastic mass (Holleb and Folkman, 1972; Holgmen and O’Reilly, 1995). Adult endothelium is quiescent, but in response to physiological or pathological stimuli like tumors the endothelial cells may start proliferation, migration and organize preliminary vessels (Holgmen and O’Reilly, 1995; Bohle and Kalthoff, 1999; Szala and Radzikwoski, 1997). A tumor induces vascular response from host vessels by altering the balance between angiogenic and antiangiogenic factors. Very often, the speciﬁc angiogenic switch is postulated for the growth of the tumors. The role of oncogenes like Ras and Raf for angiogenis switch and tumor growth have been the subject of intensive studies (Sheta and Harding, 2000; Yu *et al*., 2004).

(Rak *et al*., 2004 and 2002) postulated that mutations in Ras or Raf are essentially important for tumor angiogenesis. So far, it is acceptable knowledge that a tumor cannot grow without new vessels when they are bigger than a few millimeters in diameter. Consequently, great effort is focused on understanding the processes involved in angiogenesis and many studies concern the evaluation of strategies of antiangiogenic therapy for inhibition of tumor growth and metastasis formation (Scapaticci *et al*., 2002; Zhang *et al*., 1998; Feldman *et al*., 2000). Folkman’s observations led many studies about preventing the angiogenesis process and ﬁnding a therapeutic approach. Inhibition of angiogenesis is a promising cancer gene therapy strategy (Feldman *et al*., 2000; Rak *et al*., 2002; Brand et al., 2002; Semenza *et al*., 2003); to date, the numbers of preclinical and clinical experiments concerning antiangiogenic therapy are essentially increasing. A multitude of endogenous inhibitors of angiogenesis have also been described and some of them are used in gene therapy (Feldman *et al*., 2000). Antiangiogenic therapies have already been proved to be sufﬁcient in a number of experimental models (Feldman *et al*., 2000; Semenza *et al*., 2003; Hoshida *et al*., 2002) . The inhibitor used possess the ability to suppress tumor growth and limit metastasis. The antiangiogenic gene constructs have also entered clinical trials (Zhang *et al*., 1998; Feldman *et al*., 2000). These facts were possible because of a few reasons. First of all, side effects associated with the antiangiogenic gene therapy have not been precisely reported. Secondly, antiangiogenic therapy may be effective in a large types of solid tumors because the main target of this strategy are the endothelial cells. Finally, there is no real evidence that cancer develops resistance to this form of therapy (Takayama *et al*., 2000).

Gene therapy and angiogenesis – rationales Angiogenesis is a multistep process involved in many physiological and pathological phenomena. The formation of new vessels is postulated to be a crucial point for tumorigenesis and metastasis, whereas deterioration of the arterial system is one of the reasons for ischemic diseases (Scapaticci *et al*., 2002; Carmeliet *et al*., 2000) Therefore, manipulation of angiogenesis in vivo may be a successful gene therapy strategy (Scapaticci *et al*., 2002). In the last decade, signiﬁcant development of the angiogenic gene therapy methods and applications of various expression vectors encoding angiogenic factors for the treatment of heart or hind limb ischemia has been observed (Scapaticci *et al*., 2002; Boehm *et al*., 1997). Preclinical and clinical trials based on plasmids or viral vectors encoding angiogenic cytokines have revealed that the gene preparations stimulate collateral vessel formation, improve blood supply and the clinical state of patients (Harjai *et al*., 2002; Yla-Harttuala *et al*., 2003). The second side of the gene manipulations based on angiogenesis is antiangiogenic strategy directly devoted to the treatment of cancer (Zhang *et al*., 1998; Feldman *et al*., 2000).

The inhibition of angiogenesis termed as antiangiogenic gene therapy, seems to be a promising method for cancer therapy. The angiogenesis process observed in tumors may be suppressed by a variety of antiangiogenic factors that limit new vessel formation and/or block the function of mature, existing vessels (Zi-Lai *et al*., 2003; Feldman *et al*., 2000). Antiangiogenic gene therapy is a very promising method because this strategy is thought to be safe and efﬁcient in in vivo conditions. To date, no serious side effects, toxic effects associated with administration and expression of antiangiogenic factors (usually divided into a few group upon mechanism of action, molecular size or origin) have been reported. Furthermore, antiangiogenic therapy may be useful for a variety of types of tumors because the endothelium and vessels are the main targets for antiangiogenic stimulators. Finally, no resistance to the therapy has been reported (Feldman *et al*., 2000; Takayama *et al*., 2000). The main expected advantages of antiangiogenic gene therapy are the shrinking of the tumor volume and limiting metastasis formation by the suppression of new vessel formation and/or inhibition of the function of the existing vasculature.

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