

TOPIC: NEOPLASIA

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**Introduction**

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 (Adebamowo and Adekunle, 1999).

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 behaviours), and of certain infectious agents of importance in cancer etiology. According to United Nations population estimates (Ally *et al*., 1998), 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.

Overall, 847,000 new cancer cases (6.0% of the world total) and 591,000 cancer deaths (7.2% of the world total) were estimated to have occurred in Africa in 2012. Crude rates of incidence and mortality are much lower than the global average because of the young age of the African population (the median age in 2010 was 19.2, compared with 28.5 for the world. In terms of cumulative risk, however, the difference is much less pronounced. Indeed, cumulative mortality in African women is greater than the global average.

shows the contribution of different cancers to the total burden of incidence in Africa. In females, cancer of the breast (133,900 or 27.6% of cases) and cervix (99,000 or 20.4% of cases) are by far the most important. In Sub-Saharan Africa, the numbers of cases of these two cancers are almost equal: 94,300 (25.5% of cancers in women) and 93,200 (25.2%), respectively.

In males, cancer of the prostate dominates in terms of number of cases, both in Africa as a whole (59,500 cases, 16.4% of cancers in men), and, even more so in Sub-Saharan Africa (51,900 cases, 20.3% of the total), followed by liver cancer (38,700 cases, 10.7%) and KS (23,800 cases 6.6% of the total).

Discussion

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 neighbouring 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, 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. 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). 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. 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.

Cervical Cancer

Cancer of the cervix is the leading cancer in women in Sub-Saharan Africa with an estimated 70,700 new cases occurring in 2002 (the total in the whole continent was 78,900 cases). Estimated rates for eastern and southern Africa of 30 to 60 per 100,000 are higher than those found in the rest of Sub-Saharan Africa (20 to 35 per 100,000), but the reasons for this difference are unclear. In many developed countries, such as the United Kingdom and Sweden, mortality from cancer of the cervix declined between the early 1900s and the 1960s and then declined further as a result of the introduction of national screening programs (Bergstrom, Sparen, and Adami 1999). However, in Bulawayo between 1963 and 1977 and in Kampala in the 1960s, 1970s, and 1990s, cancer of the cervix has appeared to increase in incidence over time (Skinner et al. 1993; Wabinga *et al*., 2000). No increases over time were observed in Nigeria and South Africa (Parkin *et al*., 2003).

It was noted early that cervical cancer has quite marked differences in incidence according to classical demographic variables (social class, marital status, ethnicity, religion). Later, epidemiological studies (mainly case-control studies) showed a consistent association between risk and early age at initiation of sexual activity, increasing number of sexual partners of females or of their sexual partners, and other indicators of sexual behavior. These findings were strongly suggestive of a causative role for a sexually transmitted agent. It is now recognized that certain sexually transmitted oncogenic human papillomaviruses constitute the necessary cause of cervical cancer. However, additional independent risk factors include increasing number of pregnancies, exposure to oral contraceptives, smoking, and specific dietary patterns.

At the onset of the AIDS epidemic, cancer of the cervix was classified as an AIDS-defining cancer by the U.S. Centers for Disease Control and Prevention (CDC 1993). But it is far from clear that HIV infection really increases the risk of invasive cervical cancer. No change in cervical cancer incidence has been demonstrated in some centers like Harare, where HIV/AIDS has been endemic for some time (Chokunonga *et al*. 1999). In Kampala the increase in cervical cancer incidence began before the advent of AIDS (Wabinga *et al*., 2000). With respect to cervical intraepithelial neoplasia (CIN), most studies failed to adjust for the fact that, for obvious reasons, women infected by HIV were very often also infected by HPV (with a consequently high risk of CIN). Careful adjustment for such confounding suggests that HIV has an independent effect on risk of CIN but that it is small; there is an interaction between the effects of HIV and HPV, as might be expected, if the role of HIV is indirect, through creation of immune suppression and dysfunction (Mandelblatt *et al*., 1999).

Case-control and descriptive studies on cancer of the cervix in Africa have shown associations of the disease similar to those observed in Western countries with respect to number of partners, level of education, high parity, and steroid contraceptives; however, genital hygiene, vaginal discharge, alcohol, and male circumcision were also found in certain studies to be important (Parkin *et al.* 2003). HIV was found to be associated with cervical cancer in case-control and cohort studies in South Africa and Uganda (Mbulaiteye *et al*., forthcoming; Newton *et al*. 2001; Sitas *et al.* 2000) with odds ratios between 1.6 and 2.4; however, such a weak association could easily be due to confounding by sexual activity, and other studies have shown no association (Newton et al. 1995; Sitas *et al.,* 1997; ter Meulen *et al.* 1992).

Before the introduction of screening programs in the 1960s and 1970s, the incidence in most of Europe, North America, and Australia and New Zealand was much as we see it in Africa today: it was 38 per 100,000 in the Second National Cancer Survey of the United States, for example (Dorn and Cutler 1959). National screening programs have been responsible for the further decline in the incidence of cancer of the cervix. Pap test screening, with coverage of over 80 percent of the female population over 35 years of age appears to be the most effective method in reducing the incidence of cervical cancer. For example, if women were offered screening three times in their lifetime (at about ages 35, 45, and 55) the incidence of cancer of the cervix would be halved (Miller 1992).

Given the complex organization of screening programs, no organized national cervical cancer screening program exists in Africa. Reasons for this include lack of good quality cytology services, difficulty of long-term follow-up in many communities, lack of education, and lack of postal facilities and infrastructure. But many countries in Sub-Saharan Africa do not have the ability to diagnose or treat CIN. In other countries some attention has been given to the value of screening by visual inspection after acetic acid impregnation of the cervix (University of Zimbabwe/JHPIEGO Cervical Cancer Project 1999). The high negative predictive value of this approach suggests that few significant lesions will be missed. If appropriately and safely treated by effective, affordable methods like cryotherapy (Chirenje *et al*. 2001), then this method may provide a useful alternative to the conventional Pap test, not least in that treatment is provided during the same visit as the screening test, thus dispensing with the requirement to recall women for diagnosis and therapy.

Vaccines against the leading HPV serotypes have now been developed, and programs may be implemented for women before they become sexually active. However, it is unclear how long the protection will last and whether the vaccine will also be effective in reducing the incidence of cancer of the cervix among women who are infected.

Breast Cancer

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

Worldwide, risk factors for female breast cancer include menstrual and reproductive factors, high body mass index (BMI), family history of breast cancer, and certain genetic mutations, including BRCA1/2. Other suggested risk factors include, to a much lesser extent, high alcohol consumption, contraceptive use, and the use of certain postmenopausal hormone replacement therapies. Reproductive and hormonal factors appear to be the most important, with risk being increased by early menarche, late menopause, late age at first birth, and low parity (Henderson, Ross, and Bernstein 1988).

Studies in Sub-Saharan Africa have also found reproductive and hormonal factors to be important, reporting increased risk with advanced age at first pregnancy and delivery, low parity, and late age at menarche (Adebamowo and Adekunle 1999; Coogan et al. 1996; Shapiro et al. 2000; Ssali, Gakwaya, and Katangole-Mbidde 1995).

In Sub-Saharan Africa, higher incidence rates and relative frequencies of breast cancer have been reported in association with urban than with rural residence (Oettlé and Higginson 1966; Schonland and Bradshaw 1968), but data are sparse. The incidence of breast cancer is much higher among white women in Africa than among black African women; for example, in Harare between 1993 and 1995, the incidence was 127.7 per 100,000 in whites and 20.4 in blacks (Chokunonga et al. 2000). These differences may be a reflection of the distribution of lifestyle factors thought to be important in the development of breast cancer, for example, low parity and high body mass.

Breast cancer risk has been associated with socioeconomic status, with women of higher social class (as measured by education, income, housing, and so forth) having a higher risk (Kogevinas *et al.* 1997). Once again, such differences are most likely a reflection of different prevalences of risk factors among social classes (for example, parity, age at menstruation and menopause, height, weight, alcohol consumption).

The effect of oral contraceptive hormones on the risk of breast cancer has been the subject of much research. There appears to be a small but detectable risk in women currently using oral contraceptives, but this diminishes when contraception ceases, and after 10 years, none of the excess risk remains (Reeves 1996). A case-control study in South Africa found that combined oral contraceptives may result in a small increase in risk, confined to women below the age of 25 years, but that injectable progesterone contraceptives did not increase risk (Shapiro et al. 2000).

Dietary fat appears to be correlated with the risk of breast cancer in interpopulation studies (Prentice and Sheppard 1990), but the association has been difficult to confirm in studies of individuals (Hunter *et al.* 1996). However, obesity in postmenopausal women has been identified as a risk factor in Europe (Bergstrom *et al*. 2001) as well as in Sub-Saharan Africa (Adebamowo and Adekunle 1999; Walker *et al.* 1989). Although traditional diets in Africa are typically low in animal products, especially fat, and high in fiber (Labadarios *et al*. 1996; Manning *et al.* 1971), this pattern is being modified by urbanization and Westernization of lifestyles, which may lead to an increase in breast cancer incidence in African populations. A case-control study in Cape Town did not find a protective effect of breastfeeding on breast cancer (Coogan *et al.* 1999). However, in a meta-analysis of 47 studies from 30 countries breastfeeding appears to be protective; based on a reanalysis of about 50,302 cases and 96,973 controls, two-thirds of the difference in rates between developed and developing countries were estimated to be attributed to breastfeeding (International Collaboration on HIV and Cancer 2002).

At least part of the familial risk of breast cancer is mediated through the major susceptibility genes BRCA1 and BRCA2 (about 2 percent of breast cancer cases in Europe). Very little is known of the prevalence of these mutations in African populations, although family history of breast cancer is also a risk factor in this setting (Rosenberg *et al.* 2002).

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

A review of the literature indicates a deficit of studies on breast cancer risk in Sub-Saharan Africa, and further research could be beneficial. As certain groups become more Westernized and urbanized, with associated changes in diet, later childbirth, and reduced parity and periods of breast-feeding, breast cancer incidence may increase. Public health campaigns should encourage breastfeeding unless there are good reasons not to (for example, HIV-infected mothers where milk powder and sterile water are freely available). There is no organized mammography screening program in Sub-Saharan Africa.

Kaposi's Sarcoma

Prior to the HIV/AIDS era, Kaposi's sarcoma was a rare cancer in Western countries, seen mainly among immigrants from the Mediterranean littoral and African regions and in immunosuppressed transplant recipients. Meanwhile, in Africa, the incidence of Kaposi's sarcoma varied 100-fold, being most common in central and eastern Africa and rare in northern and southern Africa (IARC 1996; Oettlé 1962); in certain parts of central and eastern Africa, Kaposi's sarcoma was as common as cancer of the colon was in the West (Cook-Mozaffari et al. 1998). There appears to be some geographical association with the prevalence of human herpes virus-8, now regarded as a necessary cause for the development of Kaposi's sarcoma (Dukers and Rezza 2003). The incidence of Kaposi's sarcoma has increased over 1,000-fold in populations at high risk of HIV in some Western countries (Biggar *et al.* 1984; Rabkin, Biggar, and Horm 1991), but in the rest of the population the tumor still remains relatively rare (Grulich, Beral, and Swerdlow 1992; Rabkin, Biggar, and Horm 1991). In Africa, since the 1980s, areas like Malawi, Swaziland, Uganda, and Zimbabwe, where Kaposi's sarcoma was relatively common before the era of AIDS, the incidence of Kaposi's sarcoma has increased about 20-fold, such that it is now the leading cancer in men and the second leading cancer in women. In these cancer registries, overall age-standardized rates have increased by about 15 percent, mainly as a result of HIV-associated Kaposi's sarcoma (for example, Bassett et al. 1995; Wabinga *et al*. 1993; Wabinga *et al.* 2000).

According to the most recent estimates, 40,000 cases of Kaposi's sarcoma in males and 17,200 cases in females were estimated for 2002 for Sub-Saharan Africa; only 200 male and 65 female cases were estimated to occur in northern Africa. The region most affected is central Africa (age-standardized rates in males of 30 per 100,000) followed by eastern, southern, and lastly western Africa, in line with the background prevalence of HIV in each of these regions. With regard to the effect of HIV infection, three case-control studies from Africa showed increased risks of 30 to 50 in association with HIV, and these risks rise to 1,600 in HIV-positive individuals with high HHV8 antibody titers (Newton et al. 2002; Sitas *et al*. 1997; Sitas et al. 1999; Sitas *et al.* 2000). HHV8 in adults is associated with increasing age, low educational standard, and increasing numbers of sexual partners (Sitas *et al.* 1999). Antiretroviral therapy for treating HIV in adults has caused a decline in the incidence of Kaposi's sarcoma in Western countries (International Collaboration on HIV and Cancer 2000). HHV8 in children appears to be associated with infected mothers (Bourboulia *et al.* 1998). In countries with a high prevalence of HIV, Kaposi's sarcoma is now the leading cancer in children, causing almost a doubling in the childhood cancer incidence (Chokunonga *et al*. 1999; Wabinga *et al.* 1993). Antiretroviral drugs have now become more available in Botswana and recently in South Africa. If their use becomes widespread, then a decline in the incidence of Kaposi's sarcoma would be expected; however, it is unclear whether antiretrovirals (for example, zidovudine [AZT] or nevirapine) issued to mothers during delivery, which proved effective in reducing mother-child transmission of HIV, would cause a decline in Kaposi's sarcoma in children.

Stomach Cancer

A total of 13,800 cases of stomach cancer in males and 10,700 in females was estimated in Sub-Saharan Africa in 2002. Age-standardized incidence rates in males varied, per 100,000, from 3.4 in western Africa to 7.4 in eastern, 8.2 in southern, and 13.4 in central Africa. In western Africa, where the incidence of stomach cancer is the lowest, the male-to-female ratio is 0.9 to 1; however, there is a male predominance in all other areas. Despite the generally low incidence rate in Africa, some populations have a particularly high incidence rate. Clusters of high incidences exist among the South African mixed race, or coloured, population of 98 per 100,000. A high incidence rate is also reported in the Great Lakes region that includes Burundi, Kivu Province of the Democratic Republic of Congo, Rwanda, northwestern Tanzania, and southwestern Uganda. In Rwanda the age-standard incidence rate was found to be 13 per 100,000 males and 15 per 100,000 females (Newton et al. 1996). In western Uganda, stomach cancer was the second most common cancer, accounting for 12 percent of all male cancers and 6 percent of all female cancers (Wabinga *et al*. 2000). Bamako in Mali was another area with a high incidence rate: 18.5 per 100,000 males and 15 per 100,000 females (Bayo *et al*. 1990).

There is evidence of a slight but not significant increase in the incidence of stomach cancer over time in Kampala (Wabinga *et al.* 2000). In Kivu Province of the Democratic Republic of Congo, the incidence rates of stomach cancer among males and females were 9 and 15 per 100,000, respectively, in 1956–60, but this dropped to 6 and 4.5 per 100,000 in 1983–86 (Bourdeaux *et al*. 1988; Clemmensen, Maisin, and Gigase 1962). However, in rural Kenya reported incidence increased as a result of an endoscope acquired by the main hospital there (McFarlane *et al.* 2001). Trend data from the rest of Africa are incomplete or inconsistent; however, in South Africa, between 1948 and 1964 no real change in the relative frequency of stomach cancer was observed over time in one of the country's largest hospitals serving the predominantly black population of Soweto, Johannesburg (Robertson 1969), nor was a change observed in pathology-based cancer national registrations between 1986 and 1995 (Sitas, Madhoo, and Wessie 1998).

Helicobacter pylori infection is now recognized as an important risk factor for cancer of the stomach (IARC 1994); however, smoking and diets low in fruit and vegetables and vitamin C, and high in salts appear to play an important role. Many studies have shown the prevalence of H. pylori in Africa to be about 80 percent and that infection is acquired at a younger age than in Western countries (for example, Sathar *et al.* 1994). Chronic atrophic gastritis and intestinal metaplasia of the stomach are two key lesions in the natural history of stomach cancer. Very few studies in Sub-Saharan Africa have measured the association between gastric mucosal pathology and H. pylori. In summary, even in a continent where the prevalence of H. pylori is high, differences exist in the prevalence of H. pylori between those with a normal mucosa (0–33 percent) and those with gastritis of any kind. Needless to say, the prevalence of gastritis (mild or moderate) is high, but the prevalence of severe or chronic atrophic gastritis or intestinal metaplasia is low (Parkin *et al*. 2003). Two case-control studies from Africa show an association between H. pylori and stomach cancer, but the relative risks are low, probably because the mucosa of patients with gastric cancer is unfavorable to the survival of H. pylori (Jaskiewicz *et al.* 1989; Louw *et al*. 2001). CagA positive strains, usually associated with more severe gastric pathology and outcomes, are the predominant strains in Africa (Ally *et al.* 1998), but their role in gastric carcinogenesis is unclear. Certain vacA genotypes appear to be more common in patients with gastric cancer (Kidd *et al.* 1999) and seem to be independent risk factors for the disease; however, no studies have been done in Sub-Saharan Africa on the relation between stomach cancer, host susceptibility (in relation to inflammatory cytokines), and the other risk factors known to be associated with stomach cancer (for example, diet, salt, smoking, and pickled foods) (see, for example, Coggon *et al*. 1989). There are many places in Africa where food is salted or pickled to aid preservation, but the relative importance of these risk factors in local settings is unknown.

Liver Cancer

Early observations in Africa have always noted the high occurrence of liver cancer (for example, Oettlé 1964), and it is still one of the leading cancer types in men and women, although the relative frequency has been reduced in consequence of the large increase in the number of cases of Kaposi's sarcoma resulting from the epidemic of HIV/AIDS. Liver cancer is now the second leading cancer in men in Sub-Saharan Africa and the fourth leading cancer in women. There was an estimated total of 33,500 cases in males and 15,500 cases in females in 2002. Areas of high liver cancer incidence (mainly hepatocellular cancers) include countries like The Gambia, Guinea, and Senegal in West Africa, where liver cancers comprise a quarter or more of all cancer cases, with incidence rates ranging from 30 to 50 per 100,000 in men and 12 to 20 per 100,000 in women. Similarly, in central Africa, liver cancer is the leading cancer in Rwanda and in the Republic of Congo (Brazzaville); the estimated rate is 15.4 per 100,000 for men and 8.9 per 100,000 for women. Mozambique is reported to have high incidence rates, although the only data are old (Prates and Torres 1965).

Few places in Sub-Saharan Africa have information on cancer trends over time. In Ibadan, Nigeria, between 1960–69 and 1998–99, there appears to be no change in incidence, whereas in Kampala, Uganda, between the 1960s and the 1990s there appears to be a decline of liver cancer in men but not in women. However, a decline was noted in liver cancer incidence between the 1970s and the 1980s among Mozambican miners working in South Africa (Harington, Bradshaw, and McGlashan 1983).

Prostate Cancer

For the year 2002, a total of 26,800 cases of prostate cancer were estimated, comprising 10.6 percent of cancers of men in Sub-Saharan Africa (Ferlay *et al*. 2005). The relatively high incidence (and mortality) recorded in African populations is reflected in populations of African descent elsewhere. Thus, within the United States, the black population has the highest incidence (and mortality) rates, some 72 percent higher than whites. Southern Africa appears to have the highest rates (40.5 per 100,000). Rates of histologically diagnosed prostate cancer in South Africa are 40.1 per 100,000 in whites versus 14 per 100,000 in blacks, although for blacks, access to diagnostic facilities has been limited (Parkin *et al.* 2003). In Zimbabwe (defined as being part of eastern Africa), rates for whites and blacks were 70 versus 25 per 100,000 (Parkin *et al.* 2003). Central Africa follows with rates of 24.5 per 100,000. Surprisingly, in West Africa, where the majority of African-American men originated, the incidence rate of prostate cancer was estimated as 19.3 per 100,000 in 2002, compared with about 125 per 100,000 in the United States (Ferlay *et al*. 2005). High rates are observed in other places with populations that are descended from West Africa (for example, the Bahamas, Barbados, Trinidad).

Histology of the prostate in elderly men often reveals latent malignant cells, and clearly, advances in diagnostic and screening methods can cause artificial increases in reporting. This is illustrated by a fourfold increase in the incidence of histologically verified prostate cancer among whites in South Africa (most whites were covered by private health insurance) compared with no change in incidence in blacks between 1986 and 1995 (Sitas, Madhoo, and Wessie 1998). Notably, in Cape Town in the 1950s prostate cancer appeared to be more common in blacks than in whites (Muir-Grieve 1960). Increases over time have also been noted in Kampala and in Ibadan, but it is unclear how much of these increases represents a greater risk and how much can be attributed to increased awareness or a greater readiness to perform prostatectomy for urinary symptoms in elderly men (Parkin *et al.* 2003).

The consumption of fat and red meat has been implicated as a risk factor for prostate cancer in studies in developed countries, even though adjustment for total caloric intake was not always done. Associations with vegetable consumption have been inconclusive. Associations with anthropometric measures or a link with obesity have been inconclusive, and so have associations with numbers of sexual partners and history of sexually transmitted diseases, or STDs (Hayes *et al*. 2000; Key 1995; Kolonel 1996). In one case-control study from South Africa, prostate cancer was associated with high intake of fat, meat, and eggs; eating out of the house; and a low consumption of vegetables (Walker *et al*. 1992).

Sex hormones, modulated by polymorphisms on the long arm of chromosome X, play an important role in the development of prostate cancer (for example, Ross et al. 1998; Shibata and Whittemore 1997). Polymorphisms on the androgen receptor gene may vary by ethnic group and may provide some explanation for the geographic variation observed. However, no studies have been done on interethnic variations in androgen receptor polymorphisms in Africa.

Non-Hodgkin's Lymphoma

The non-Hodgkin's lymphomas are composed of an extremely heterogeneous group of lymphoproliferative malignancies displaying distinct behavioral, prognostic, and epidemiological characteristics. Advances in molecular biology, genetics, and immunology have resulted in extensive changes in the classification of lymphoid tumors in the last few decades. The WHO classifies tumors according to cell lineage defined by immunophenotype (Jaffe *et al.* 2001). Three broad categories are now recognized: B-cell neoplasms, T/NK-cell neoplasms, and Hodgkin's lymphoma. Lymphocytic leukemias fall within the B-cell neoplasm group.

A total of 14,500 cases in males (5.8 percent of all cancers) and 10,600 cases in females (3.8 percent of all female cancers) were estimated for 2002 in Sub-Saharan Africa. In most African populations non-Hodgkin's lymphoma is relatively rare, but the relative frequency is above the world average in North and Sub-Saharan Africa because of the high incidence of Burkitt's lymphoma in children in the tropical zone of Africa. As in Western countries, most non-Hodgkin's lymphomas in Africa are of B-cell type. In adults, clinical series show an excess of high-grade lymphomas and a deficit of nodular lymphomas.

Human T-cell lymphotrophic viruses (for example, HTLV-I) are common in tropical Africa (IARC 1996) and are a cause of T-cell lymphomas; however, the incidence of these in Africa is low. Although Epstein-Barr virus DNA may be found in a small proportion of lymphomas, its role in causing non-Hodgkin's lymphomas is unclear (IARC 1997). HCV infection has been implicated in B-cell non-Hodgkin's lymphomas in some studies; the postulated mechanism being through the stimulation of polyclonal proliferation of B cells (reviewed by Parkin *et al.* 2003). HIV infection has been associated with 60-fold increased risks of developing non-Hodgkin's lymphomas in Western countries (for example, Beral *et al*. 1991); approximately 5 to 10 percent of HIV-infected persons will develop a lymphoma, and non-Hodgkin's lymphoma is the AIDS-defining illness in about 3 percent of HIV-infected patients (Remick 1995). In Africa, however, the association between HIV and non-Hodgkin's lymphoma has been in the region of 2.3 to 12.3 (Mbulaiteye *et al*., forthcoming; Newton *et al.* 2001; Parkin *et al*. 2003; Sitas *et al*. 1997; Sitas *et al*. 2000). The reason for the discrepancy in the association between HIV and non-Hodgkin's lymphoma between developed countries and Africa is unclear. Non-Hodgkin's lymphomas were increasing in incidence in Western populations before the advent of HIV but have increased dramatically in high-risk groups affected by HIV (see, for example, Schultz, Boshoff, and Weiss 1996). In Harare, Zimbabwe (Chokunonga *et al*. 1999), and in Kampala, Uganda, there is now evidence of an increase in incidence between earlier cancer registration periods and periods in the 1990s (Parkin *et al*. 1999; Parkin *et al*. 2003).

Burkitt's lymphoma affects mainly children between the ages of five and nine. The jaw is affected 50 to 60 percent of the time. Burkitt's lymphoma shows a peculiar geographic distribution and has been reviewed by others (for example, Burkitt 1969; Williams *et al*. 1978; Wright 1973). It accounts for about a quarter to a half of childhood cancers in the eastern and central parts of Africa and in tropical West Africa, and less frequently in other places. Burkitt identified a striking distribution 15 degrees north and south of the equator, with a southern tail into Mozambique. But even within this area Burkitt's lymphoma was rarer in higher altitudes. The areas where it was most common were typified by rainfalls over 50 centimeters per year and an average of the coolest month of greater than 15.6°C, which seem associated with the distribution of malaria endemicity (Burkitt 1969; O'Conor 1970). Low socioeconomic status, family clustering, and proximity to the plant species Euphorbia tirucalli have been suggested as important factors in the etiology of Burkitt's lymphoma; however, the leading agent has been infection with Epstein-Barr virus (IARC 1997).

In a follow-up study of 42,000 children, those who developed Burkitt's lymphoma had higher titers of antiviral capsid antigen than in matched controls (de Thé *et al*. 1978; Geser *et al*. 1982). The link with malaria appears to be a result of the loss of cytotoxic T-cell control due to dysfunction of a subset of CD4 cells responsible for the induction of suppressor-cytotoxic CD8 cells. This may result in uncontrolled proliferation of B cells containing the Epstein-Barr virus and resultant malignant transformation (for example, Pagano *et al.* 1992; Whittle *et al*. 1990). In a five-year period of malaria suppression (when chloroquine was issued to children under 10), Burkitt's lymphoma appeared to decline in incidence. Incidence returned to the original level after the five-year program was completed (Geser, Brubaker, and Draper 1989). Burkitt's lymphoma is much rarer in adults, although Burkitt-like (or high-grade Burkitt-like) lymphomas appear to be occurring with increased frequency as a result of HIV (Sitas *et al.* 2000).

A prevention program for non-Hodgkin's lymphomas can be carried out only after the taxonomy and causes are further elucidated. It appears that antimalarial programs may have a significant impact on Burkitt's lymphoma in children, and as in Western countries, widespread antiretroviral therapy of HIV-positive individuals would cause a decline in the incidence of non-Hodgkin's lymphoma.

Cancer of the Esophagus

In 2002 a total of 15,150 cases of cancer of the esophagus were estimated to occur in males in Sub-Saharan Africa and 7,200 cases in females. Cancer of the esophagus shows a remarkable geographic distribution, being one of the leading cancers in southern and East Africa (average incidence in males about 19 per 100,000) but rare in West Africa (1 to 2 cases per 100,000). Certain areas of high risk have been reported from Kenya and the former Transkei homeland in the Eastern Cape Province of South Africa, where incidence rates as high as 76.6 per 100,000 in males and 36.5 per 100,000 in females were reported between 1991 and 1995 (Somdyala *et al*. 2003). Several studies between the 1950s and the 1990s in South Africa, Uganda, and Zimbabwe have demonstrated that cancer of the esophagus has increased in incidence. But the latest available data from cancer registries in these countries show a declining trend in esophageal cancer incidence, particularly in males after 1990 (Parkin *et al*. 2003; Somdyala *et al*. 2003).

Tobacco and alcohol consumption, known risk factors for the development of esophageal cancer in many countries, have also been documented as important in Africa in studies conducted from the 1980s onward; earlier studies found no such association, probably because of the low alcohol concentration of noncommercial drinks. The net effect of increasing commercial alcohol consumption, combined with increases in some places of tobacco consumption, on esophageal cancer trends is to date unclear. There is no consistent evidence of an effect of homemade brews and esophageal cancer risk in Africa.

Esophageal cancer also appears to occur in areas of extreme poverty and poor nutritional status. The high incidence of esophageal cancer in the Transkei region of the Eastern Cape Province has been associated with the monotonous consumption of corn, which contains low levels of niacin, riboflavin, vitamin C, zinc, calcium, and magnesium (Van Rensburg 1981) and is sometimes contaminated with fungal toxins produced by Fusarium spp. Certain studies in this region have shown a geographical association with the presence of Fusarium moliniforme, a common fungal contaminant of poorly stored corn. Other risk factors reported in the Transkei include infections with Candida albicans and the consumption of a green, leafy plant weed, Solanum nigrum (Sammon 1992).

Other HIV-associated Cancers

Aside from Kaposi's sarcomas and non-Hodgkin's lymphomas, other cancers that appear to be associated with HIV immune suppression are cancer of the conjunctiva and possibly cancers of the cervix, vulva or vagina, anus, and liver (IARC 1996). However, except for conjunctival cancers, the data, at least from Sub-Saharan Africa, are not yet conclusive (IARC 1996; Parkin *et al.* 2003). Conjunctival cancers are increasing in incidence in Malawi (Banda *et al*. 2001);Uganda (Newton *et al*. 2001; Parkin *et al*. 1999), and Zimbabwe (Chokunonga *et al.* 2000); these countries have some of the most prolonged and highest levels of HIV prevalence in Africa, and it is anticipated that these cancers will increase in time in other places in Africa that are affected by HIV.

Tobacco-related Cancers

Tobacco smoking is by far the most important cause of lung cancer. The evidence has been reviewed many times (IARC 1986, 2004). In 1985 it was estimated that about 76 percent of all lung cancer worldwide (84 percent of cases in men and 46 percent in women) could be attributed to tobacco smoking (Parkin *et al*. 1994). However, in Africa, because smoking is a relatively recent habit in most areas, the proportion of tobacco-attributed lung cancers is low.

Only where the smoking habit has been established in a significant percentage of the population for a prolonged period of time is the proportion of tobacco-attributable cancers also significant—85 percent of cases in males in certain southern African populations and 68 percent in northern Africa, for example (Parkin and Sasco 1993).

Because of the lower incidence of lung cancer in Africa (and the low prevalence of tobacco consumption in most places in Africa) there is a widespread misconception that the hazards of tobacco are only relevant in developed countries. However, it appears that tobacco consumption, particularly of manufactured cigarettes, is increasing in Africa. Figure 20.3 shows the distribution of per capita consumption of cigarettes in Africa in countries where data exist. It is notable that aside from southern and northern Africa, consumption is low. Typical per capita consumption in the United States, for example, is 2,255 cigarettes, and in China, 1,791, per year. In a WHO survey it was found that between two decades, 1970–72 and 1990–92, 15 countries in Africa increased their consumption of cigarettes, 6 decreased, and 5 remained unchanged (WHO 1997). Data were unavailable for the rest of Africa. Adult smoking rates also vary significantly; prevalence in Africa among men varies from 10 to 50 percent, and among women from 1 to 10 percent (WHO 1997). An exception may be the mixed-race population of South Africa, where there has been a high prevalence (currently 40 to 50 percent) of smoking among women, and, indeed, lung cancer rates (and rates for other tobacco-associated cancers such as oral and esophageal cancers) are higher in southern Africa than the rest of Africa.

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. 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 (64) 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.

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 1992. 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. More recently, effective vaccines against the oncogenic subtypes of the human papillomavirus (HPV) have become available. They provide protection against HPV-16 and -18 that cause 70% of cervical cancer in Africa. The strategy to date has aimed to vaccinate girls at around age 11 to 13 years, and the practicalities of this, in addition to cost, could be a major impediment in the wide application of the vaccines in the region.

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. 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.

Conclusion

The number of new cancer cases will increase by 70% between 2012 and 2030, faster than any other region of the world, simply because of population growth and ageing (3). The increase is likely to be even greater, given the ongoing urbanization of Africa, with associated changes in lifestyles (30). This tide of disease demands a coordinated approach to improving the extent and quality of services for cancer control and better surveillance systems with which they can be planned and monitored.

Osteosarcoma

Osteosarcoma is the most common primary bone malignancy, with a high incidence rate in children and adolescents compared to other age groups. Tumours most often arise in the long bones from osteoid-producing neoplastic cells adjacent to the growth plates, occurring less commonly in the axial skeleton and other nonlong bones (Raymond, 2002). Survival rates for osteosarcoma have remained at 60–70% for localised disease for decades despite ongoing studies. Unlike many sarcomas which are characterised by specific chromosome translocations, complex genomic rearrangements involving any chromosome characterise individual osteosarcoma cells. Because of this few consistent genetic changes that may indicate effective molecular targets for treatment have been reported.

Decades' worth of molecular cytogenetics studies and genomic analyses of osteosarcomas have been completed through karyotyping, comparative genomic hybridisation (CGH), fluorescence in situ hybridisation, quantitative PCR, and single-strand conformation polymorphism analysis, among others. Genome-wide association studies utilising single-nucleotide polymorphisms (SNPs) have been used more recently to learn more broadly about osteosarcoma genomics. Resolution of alterations has increased from visualisation at the chromosome level to point mutations, but the genetic etiology of osteosarcoma is still unknown. One consistent finding, however, is the higher incidence of osteosarcoma relative to the general population in individuals with familial Li-Fraumeni syndrome (germline TP53 inactivation), hereditary retinoblastoma (germline RB1 inactivation), Rothmund-Thomson syndrome (germline RECQL4 inactivation), or Bloom or Werner syndrome (germline BLM or WRN inactivation, resp.). The genes associated with all of these familial syndromes encode protein products necessary to stabilise the genome, and their impairment can manifest in defective maintenance of DNA.

Genomic Instability in Osteosarcoma

Osteosarcoma is characterised by a high level of genomic instability, in particular one subcategory of instability known as chromosomal instability (CIN). Microsatellite instability (MIN) and CpG island methylator phenotype (CIMP) are two other forms of genomic instability, and they have been described extensively and predominantly in colorectal cancer. CIN is the elevated rate of gain or loss of entire chromosomes or sections of chromosomes and it appears to be significant in the pathogenesis of osteosarcoma tumours, resulting in complicated structural and numerical aberrations and wide variability between cells.

CIN is categorised in two subtypes, numerical CIN (N-CIN) and structural CIN (S-CIN). Processes underlying N-CIN are those leading to copy number alterations. N-CIN is manifested in polyploidy, caused by errors in mitosis, aneuploidy, segmental amplifications, or deletions, and unbalanced translocations. S-CIN can result from ineffective DNA damage response mechanisms following exogenous insults or replication errors, leading to aberrant genomic rearrangements, chromosomal breakages, and usually, but not necessarily, gene copy number alterations. Karyotypic complexity in tumours, an end product of CIN, is correlated with higher expression of survival- and tissue invasion-related genes and lower expression of those involved in checking cell cycle regulation and ensuring DNA repair.

Mutations or deregulation of genes important for mitotic checkpoints is thought to be the underlying cause of CIN. For example, inactivation of the tumour suppressor proteins p53 and pRB cause CIN in vivo. Additionally, mutation of TP53 is significantly correlated with high levels of genomic instability in osteosarcoma while mutation of RB1 contributes to mitotic missegregation and loss of heterozygosity (LOH) in mice. In a study of 18 osteosarcomas, an association was made between overexpression of RECQL4, a gene which encodes a DNA helicase, and S-CIN. Whether mutator mutations are in fact required to induce carcinogenesis by increasing the rate of genetic change is still in question.

Telomere maintenance, or lack thereof, is another potential source of the instability typical of osteosarcoma, in addition to reducing the likelihood of favourable outcome in patients with the disease. Telomerase activation is a mechanism by which human cells can bypass their theoretical life span defined by the number of cell divisions required to critically deplete telomere length (the Hayflick limit), thereby avoiding senescence. Rather than activation of the telomerase subunit genes, the alternative lengthening of telomeres' (ALTs) mechanism of preserving telomeres is more frequently observed in sarcomas. Telomerase activation and ALT both contribute to telomere maintenance in osteosarcoma, but ALT seems to be the predominant process. Interestingly, ALT is more common in sarcomas not associated with specific translocations and therefore may be associated with more complex chromosomal aberrations in some tumours, including osteosarcomas. In females, shorter telomere length is associated with increased risk of osteosarcoma. Additionally, cellular telomere maintenance is associated with poor outcome for osteosarcoma patients, but enzymes facilitating ALT may have potential as therapeutic targets.

Genetic Alterations by Osteosarcoma Subtype

The vast majority of studies have been descriptions of osteosarcomas focused on the conventional, high-grade subtypes including the chondroblastic, fibroblastic, and osteoblastic variants. These are the most frequently occurring types of osteosarcoma. The rarer subtypes include telangiectatic, small cell, periosteal, high-grade surface, and low-grade osteosarcoma. These forms often present with distinguishing genetic features infrequent in conventional tumours.

Conventional Osteosarcoma

Complex and largely inconsistent genetic alterations are typical of conventional osteosarcoma. Unfortunately, for many of the alterations described in this paper there exist wide ranges of observed frequencies among published reports. These can be due to inconsistencies between materials and methodology used by groups, including differences in the resolution of cytogenetic techniques and platforms, variation between tumour cohorts with respect to staging, histological subtype, and sample size, and whether specimens have been exposed to chemotherapy (chemotherapy drugs may induce DNA damage). The low incidence rate of osteosarcoma exacerbates the limitations on genetic studies of this disease because it lowers the availability of samples. Furthermore, a high level of chromosomal instability is thought to cause the profound intra- and intertumoural heterogeneity observed in and among specimens, in which abnormalities such as heterogeneously staining regions, double-minute chromosomes, and dicentric chromosomes are not uncommon.

Osteosarcoma is characterised by extensive and heterogeneous genetic complexity, which is reflected in the similarly complex epigenetic and expression alterations in tumours and is visually apparent in the results of quantitative research. Mechanisms of genomic instability may be facilitated by the repetitive DNA sequences ubiquitous in the human genome, particularly low copy repeats, but this area still requires further study. Unfortunately, even though several alterations are relatively consistent across cohorts of tumours, the accumulated knowledge of genetic changes in osteosarcoma has yet to significantly impact survival rates. Clinical markers continue to be the most reliable indicators for prognostication. Overall, the multitude of genetics studies of osteosarcoma serves to illustrate the extremes to which DNA alterations in cancer can reach, but it is hoped that accurate biomarkers and targeted therapies will soon be revealed for this disease.

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In this paper, we have collected studies of the genetics of osteosarcoma to illustrate the heterogeneity and complexity of this tumour type at the level of the chromosome and gene. Osteosarcoma-specific epigenetic changes, mRNA and protein level aberrations, and changes to microRNA (miRNA) will not be described extensively in this paper. Other publications on these topics exist and offer more thorough descriptions of the epigenetic, expression, and miRNA profiling of osteosarcoma. To understand the molecular dynamics of this disease at any level, it is important to first recognize the fundamental role of the disruption of cellular mechanisms intended to maintain genomic instability.

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