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Trends in the incidence of cancer in Kampala, Uganda 1991–2010

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The Kampala cancer registry is the longest established in Africa. Trends in incidence rates for a 20-year period (1991–2010) for Kyadondo County (Kampala city and a rural hinterland) illustrate the effects of changing lifestyles in urban Africa, and the effects of the epidemic of HIV-AIDS. There has been an overall increase in the risk of cancer during the period in both sexes, with incidence rates of major cancers such as breast and prostate showing particularly marked increases (3.7% and 5.2% annually, respectively). In the 1960s cancer of the oesophagus was the most common cancer of men (and second in women), and incidence in the last 20 years has not declined. Cancer of the cervix, always the most frequent cancer of women, has shown an increase over the period (1.8% per year), although the rates appear to have declined in the last 4 years. HIV prevalence in adults in Uganda fell from a maximum in 1992 to a minimum (about 6%) in 2004, and has risen a little subsequently, while availability of antiretroviral drugs has risen sharply in recent years. Incidence of Kaposi sarcoma in men fell until about 2002, and has been relatively constant since then, while in women there has been a continuing decline since 2000. Other HIV related cancers—non-Hodgkin lymphoma of younger adults, and squamous cell carcinoma of conjunctiva—have shown major increases in incidence, although the former (NHL) has shown a small decline in incidence in the most recent 2 years.

Introduction

Kampala Cancer Registry (KCR) was established in 1954 with the aim of obtaining information on cancer occurrence in the population of Kyadondo County which includes Kampala city the capital of Uganda.[1] The registry is located in the Department of Pathology of the Makerere University College of Health Sciences, and achieved adequate coverage of the population in 1960. However, after 10 years, registration activity became confined to the recording of pathology diagnoses, during the period of dictatorship and civil war in the 1970s and 1980s. Full coverage of the Kyadondo population was achieved again in 1989 and has continued since then.[2] The registry provides the longest time series of cancer incidence in Africa. This makes the data of special value of cancer surveillance and research, particularly in monitoring the epidemic of HIV/AIDS and as a baseline for analytical studies and intervention studies. Screening programmes are now in existence especially for cancer of the cervix, as a consequence of the very high incidence rates recorded by the registry in previous reports.

In a previous paper[3] we presented cancer incidence data from KCR for a 16-year time period (1991–2006). Here we update this analysis, including more recent data, to identify the consistency or otherwise of the previously observed trends.

Materials and Methods

Submission to the registry is voluntary as cancer is not a notifiable disease in Uganda, and, although some cancer cases are notified to the registry by clinical staff, the registry relies for the most part on active case-finding by the two full time cancer registry staff. As well as scrutinising records of the Department of Pathology (the host institution) tumour registrars conduct regular search for cancer cases admitted to, or treated in the four main hospitals in Kampala (including the Uganda Cancer Institute and Department of Radiotherapy within Mulago Hospital, the main teaching and national referral hospital), as well as three moderate-sized mission hospitals with about 200 beds each and the Hospice Uganda. Copies of all reports mentioning cancer are received from three private pathology laboratories that deal with specimens from patients treated by private practitioners and clinics. Certification of death is only carried out for deaths in hospital, or for legal reasons, and is thus incomplete; nevertheless death certificates issued in the mortuary of Mulago Hospital are used as a source of information by the registry.

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What's new?
Little information is available on trends in cancer incidence from sub-Saharan Africa. To help rectify that situation, the authors of the present study examined cancer incidence trends over a 20-year period in Kyadondo County, which includes Kampala, the capital of Uganda, using data from the Kampala Cancer Registry. Some trends were expected, such as an increase in cancers associated with Western lifestyles. Other trends, however, such as a lack of decline in cancers of the cervix, esophagus, and stomach, which are associated with poverty, were surprising. In addition, HIV-related cancers showed only modest or no recent decline.

Data are abstracted onto notification forms, and are then entered into the registry database, using the CANREG system (http://www.iacr.com.fr/) which includes checks for consistency and validity, and permits search for potential duplicate registration.

Tumour topography and morphology were coded according to the second edition of the International Classification of Diseases for Oncology.[4] For tabulation of results, these were converted to the 10th revision of the ICD.[5] Squamous cell carcinomas of the conjunctiva (SCCC) were defined as tumours with ICD-O morphology codes M8010-M8082 of conjunctiva (ICD-O C69.0) or eye, unspecified (ICD-O C69.9); only 3% of squamous cell cancers occur at other subsites of the eye.

Population

Population censuses were performed in 1991 and 2002, and for these years, the population of Kyadondo County was available by sex and 5-year age group. Intercensal estimates were prepared assuming a constant rate of change, within age–sex groups. The Uganda Bureau of Statistics in the Prime Minister's office provided an estimate (by age and sex) for 2010. The annual populations 2003–2010 were estimated assuming constant rates of change, within age–sex groups.

The population in 1991, and the estimate for 2010, are shown in Figure 1.

Statistical methods

Incidence rates were calculated for 5-year age groups, by sex, for each year (1991–2010), and for four time periods: 1991–1995, 1996–2000, 2001–2005, and 2006–2010. Age-standardized rates (ASRs) were calculated using the World Standard population.[6] Average annual percentage rates of change (AAPC) (and 95% confidence intervals) over the whole 20-year period were calculated for each sex, for those cancer sites with at least one case registered in each year, assuming a constant rate of increase or decrease in the period considered. Graphs of time trends in rates use 3-year moving average values of rates to minimize fluctuation due to small numbers of cases.

Results

During the 20 years of registration considered (1991–2010) a total of 22,494 cases (10,237 males and 12,257 females) were registered. Table 1 shows the ASRs in each of the 5-year periods, and the AAPC in incidence over the 20-year period. Incidence rates have increased in both sexes over the period; the AAPC was +2.3% (95% CI 1.4, 3.1) in males and +2.2% (95% CI 1.4, 3.2) in females.

Figure 2 shows the trends in incidence rates (3-year moving average ASRs) for the five cancers with the highest incidence rates in males, and Figure 3 the cancers with highest rates in females.

In males, the most common cancers over the period (in terms of age standardised rates) are cancers of the prostate, and Kaposi sarcoma; they show opposite trends in rates, with significant increases in the incidence of prostate cancer [5.2% (95% CI 3.0, 7.3) annually] and decreases in the incidence of Kaposi sarcoma [−2.1% annually (95% CI −0.8, −3.7)]. The incidence of cancers of the oesophagus, liver and large bowel (colon, rectum, and anus) have remained relatively constant (Fig. 2). Among the other sites with lower rates of incidence, increases are evident for cancers of the nasopharynx, non-Hodgkin lymphomas (NHL), and leukaemias, while there have been significant declines in the incidence of penile cancer [AAPC of −5.6% (95% CI −1.4, −9.9)].

In females, the most frequent cancer over the whole period was cancer of the cervix uteri. The overall trend over the 20-year period is an increase of 1.8% annually (95% CI 0.3, 3.4) (Table 1) although the highest rate recorded was around 2006, and since then rates appear to have decreased somewhat (Fig. 3). Over the 20-year period, the incidence of breast cancer has been about half that of cervix cancer, but the increase in incidence was about double at 3.7% per year (95% CI 2.3, 5.0). For both cancer of the cervix and breast, the increases in incidence are more evident at older age groups (after age 50) than among the young (Figs. 4*a* and 4*b*). The annual rate of increase of premenopausal (age <50) breast cancer was 1.3% (−0.6, 3.1) when compared with an annual rate of 5.2% (3.9, 6.6) in women aged 50 or more. Similarly, for cancer of the cervix, the rate of change under age 50 was nonsignificant [−0.7% (−2.4, 1.0)] per year. Rates of Kaposi sarcoma in females have also shown some decline in the recent years, but the decline over the whole 20-year period is not statistically significant. Among the other sites with lower rates of incidence, significant increases in rates are evident for NHL, cancers of the large bowel, eye, and leukaemia. There has been a significant rise in the incidence of

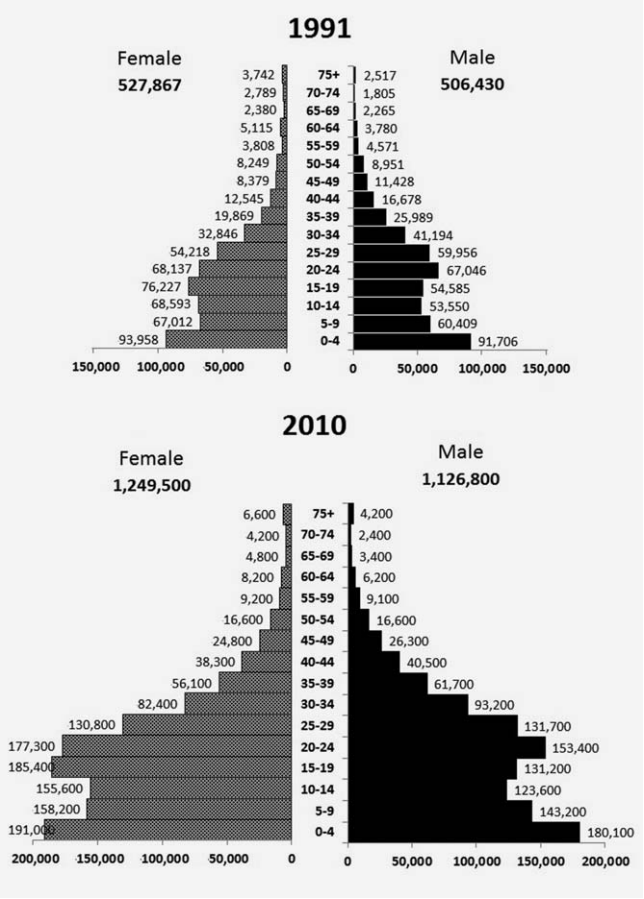

Figure 1. Population of Kyadondo County, by age and sex, census of 1991 and estimate for 2010.

lung cancer in females over the 20-year period [AAPC 14.3% (95% CI 7.6, 20.9)], so that the incidence in the last decade is similar to that of males.

Figure 5 shows the age-specific incidence rates of Kaposi sarcoma in four time periods, in males (Fig. 5*a*) and females (Fig. 5*b*). In both sexes, there has been a decline in incidence of KS in the youngest age group (0–4). In males, the decrease in incidence has concerned particularly the high rates noted in the early 1990s at ages 30–44. In females, in contrast, the main change appears to be a decrease in rates in younger women (aged 15–34). As a result, there has been some increase in mean age at diagnosis, and narrowing of the age differential between males and females, although it remains statistically significant. The mean age at diagnosis in 1991–1995 was 33.1 in men and 27.8 in women (a difference of 5.4), and this increased to 35.5 and 32.5 in men and women, respectively, in 2006–2010 (difference of 3.0 years).

Figure 6 shows the trends in age standardised incidence rates (3-year moving average) of two other cancers that have been associated with infection with HIV: squamous cell carcinoma of the conjunctiva (SCCC) and non-Hodgkin lymphomas (NHL) in young adults (age 15–49). For NHL, incidence has increased until about 2004, and since 2008 there has been a small decline in rates. This is not evident for SCCC, for which there appears to be a steady increase in incidence over time, with no suggestion of any recent decline.

In the childhood age range (0–14) 2020 cancers were registered in the 20-year period, the most common being lymphomas (35.8%), Kaposi sarcoma (25.1%), leukaemias (6.9%) nephroblastoma (Wilms' tumour) (6.2 %), and retinoblastoma (4.8%). Within the lymphoma group, about 55% were Burkitt lymphomas (19.8 % of all childhood cancers). The profile of childhood cancer changed over the period. Kaposi sarcoma was the most frequently diagnosed in 1991–2000 (ASR 46.1 per million), but the incidence had fallen to 34.2 per 10^6 by 2001–2010. Conversely incidence rates of Burkitt lymphoma increased by 27% between the two periods (from 26.8 to 34.1 per 10^6) as did the incidence rates of leukaemia (+33%) and nephroblastoma (+45%).

Discussion

Accurate evaluation of trends in incidence, based on cancer registry data, requires completeness of registration to be similar throughout the period under consideration. In recent years (since 1991) we believe that registration has been relatively complete. Evaluation by independent case ascertainment for the period 1994–1996 suggested that the registry had identified 90% of incident cancers.[7] Results from the registry have been published in Cancer Incidence in Five Continents volumes VII (1991–1993), VIII (1993–1997) and IX (1998–2002),[8–10] and have been accepted for publication in volume X (2003–2007). Accurate rates also require that the population at risk is correct. For Kyadondo County, census counts (by age group and sex) of the population were available for 1991 and 2002, and we made use of an official projection for 2010 and 2012, with interpolations for the other years. There must be some question as to the accuracy of the person-years at risk estimates—especially in the years since 2002, and particularly with respect to the composition of the population by age.

In common with much of urban Africa, lifestyles in Kampala are changing rapidly, as the population evolves from one comprising relatively recent immigrants from village life, to one of second or third-generation inhabitants, engaged in wage–earning or the informal economy, and purchasing foodstuffs and other necessities, rather than producing them themselves. This demographic transition is accompanied by familiar trends in patterns of health and illness, with a decrease in maternal and infant mortality, fertility, and a rise in the importance of noncommunicable diseases.[11] It is therefore not surprising to note a steady increase in the incidence of cancer in both sexes. One might reasonably expect the changes to relate to an increase in the cancers that are particularly common in "western" populations (Europe and North America)—lung, prostate, large bowel and breast, and a decrease in those more familiar in the so-called developing world (cancers of the stomach, oesophagus, liver, and cervix uteri), but these preconceptions not always borne out.

Table 1. Age standardized incidence rates (per 100,000) in three four-year periods, and average annual percentage change in age standardised rates in period 1991–2010

			Males					Females				
			Age standard rate (per 100,000)					Age standard rate (per 100,000)				
Site	ICD-10	No. of cases	1991–1995	1996–2000	2001–2005	2006–2010	Annual percent change (95% confidence interval)	1991–1995	1996–2000	2001–2005	2006–2010	Annual percent change (95% confidence interval)
Nasopharynx	C11	264	0.8	2.8	2.2	2.4	**7.0% (0.9:13.2)**	0.9	1.5	1.6	1.3	12.4% (−1.0:25.7)
Oesophagus	C15	1062	16.0	12.1	16.2	24.8	3.3% (0.2:6.3)	11.4	9.2	10.2	13.5	1.6% (−1.2:4.4)
Stomach	C16	494	5.5	7.2	6.7	8.5	3.7% (−0.7:8.0)	3.7	6.3	7.7	3.9	2.5% (−1.8:6.8)
Large bowel	C18–21	706	7.8	7.8	7.6	8.8	1.6% (−0.9:4.1)	5.2	8.4	9.2	8.8	**4.1% (1.2:7.0)**
Liver	C22	901	9.0	8.3	9.7	12.2	2.8% (−1.0:6.6)	5.2	6.0	7.3	9.6	**4.0% (0.8:7.1)**
Lung	C33–34	342	3.5	4.9	5.7	4.1	1.8% (−4,2:7.9)	0.7	3.9	4.4	5.1	**14.3% (7.6:20.9)**
Kaposi sarcoma	C46	6003	39.7	36.0	28.9	29.3	**−2.1% (−0.8:−3.3)**	18.2	20.5	21.5	16.1	−0.3% (−1.8:1.2)
Breast	C50	1572	1.2	1.5	1.5	2.5		18.0	22.9	29.6	31.2	**3.7% (2.3:5.0)**
Cervix uteri	C53	2701						38.1	44.7	48.9	50.2	**1.8% (0.3:3.4)**
Corpus uteri	C54	175						3.5	3.8	4.3	4.5	0.6% (−3.4:4.6)
Ovary	C56	417						6.5	6.4	8.5	6.4	1.2% (−1.2:3.3)
Penis	C60	110	3.1	3.3	3.0	1.2	**−5.6% (−1.4:−9.9)**					
Prostate	C61	1158	25.7	42.5	38	58.0	**5.2% (3.0:7.3)**					
Bladder	C67	164	2.5	2.8	3.7	1.5	−4.5% (−4.5:−13.9)	1.3	1.5	1.8	1.6	
Eye	C69	598	2.4	2.3	2.7	3.2	**1.9% (0.07:3.8)**	2.3	2.1	2.6	3.1	**3.0% (0.4:5.7)**
Brain, nervous system	C70–72	161	0.4	0.8	1.1	2.6		0.4	0.6	0.6	1.8	
Thyroid	C73	213	0.6	0.8	1.3	1.1		3.1	3.2	2.1	2.9	
Hodgkin disease	C81	252	1.0	1.4	1.7	1.5		0.5	1.4	2.0	1.1	
Non-Hodgkin lymphoma	C82–C85	1426	3.9	6.7	8.1	9.0	**5.4% (3.3:7.5)**	2.1	5.0	6.3	6.4	**7.0% (3.0:10.9)**
Multiple Myeloma	C90	110	0.4	0.5	2.4	2.2		0.5	1.1	1.1	2.2	
Leukaemia	C91–95	382	0.7	1.4	2.1	3.5	**11.5% (7.6:15.4)**	1.1	1.5	2.0	2.7	**5.5% (2.0:8.9)**
All sites		22494	149	166.3	168.9	212.3	**2.3% (1.4:3.2)**	146.3	173.3	199.9	201.7	**2.2% (1.4:3.1)**

Prostate cancer became the most common cancer of men (in terms of age standardised incidence) in 2006, and there has been a major increase in incidence: 5.2% annually on average over the 20-year period. By 2010, the age standardized incidence rate (65.0 per 10^5) was one of the highest observed in Africa.[12] Most of this increase is in elderly men—aged 65 or over. The increase is certainly not due to screening, although it is quite likely that increased awareness, a greater readiness to perform prostatectomy for urinary symptoms in elderly men, and histological examination of operative biopsies have played a role. An even more dramatic increase in incidence—6.4% annually—was seen in Harare, Zimbabwe, over the same time period (1991–2010).[13]

Over the 20-year period, the incidence of breast cancer in women has also shown a rather rapid increase (3.7%

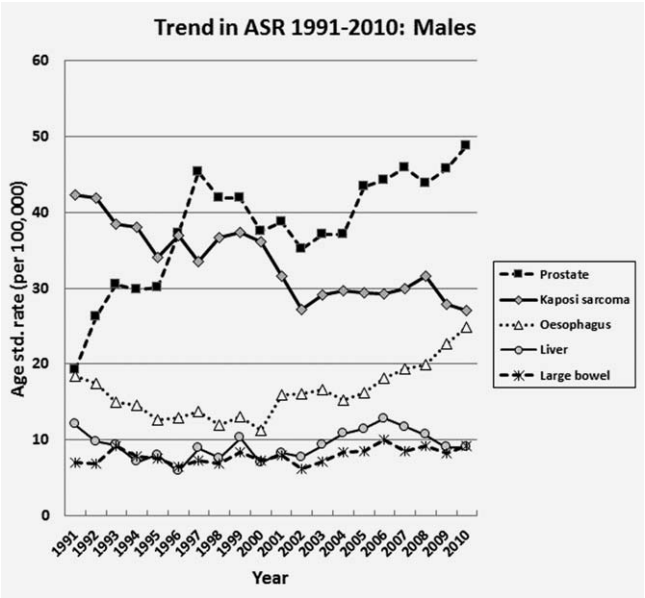

Figure 2. Trends in age standardised incidence rates of the most common cancers of males, 1991–2010 (3-year moving averages).

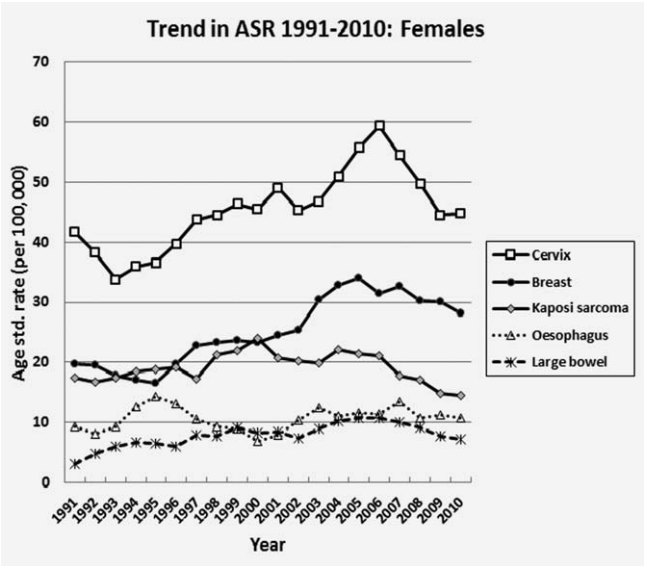

Figure 3. Trends in age standardised incidence rates of the most common cancers of females, 1991–2010 (3-year moving averages).

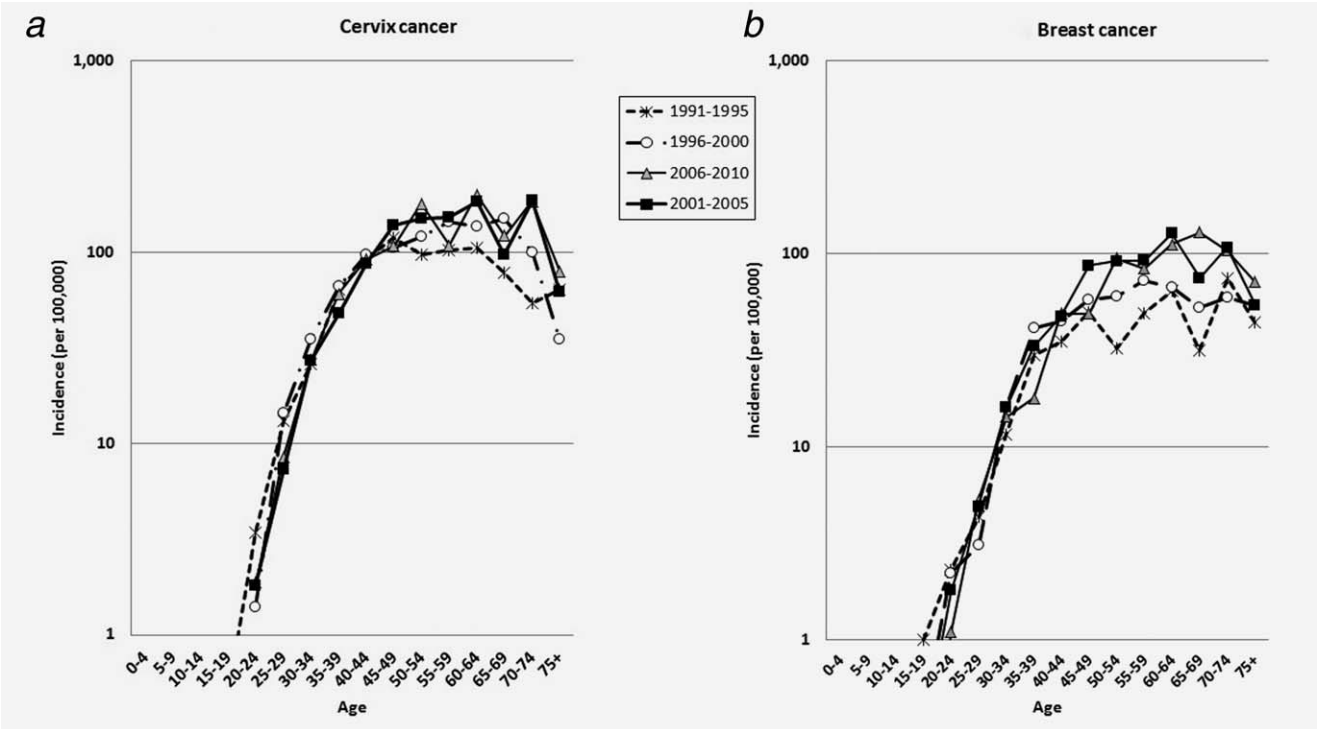

Figure 4. Age-specific incidence rates of cancers of the cervix (*a*) and breast (*b*) in 1991–1995, 1996–2000, 2001–2005, and 2006–2010.

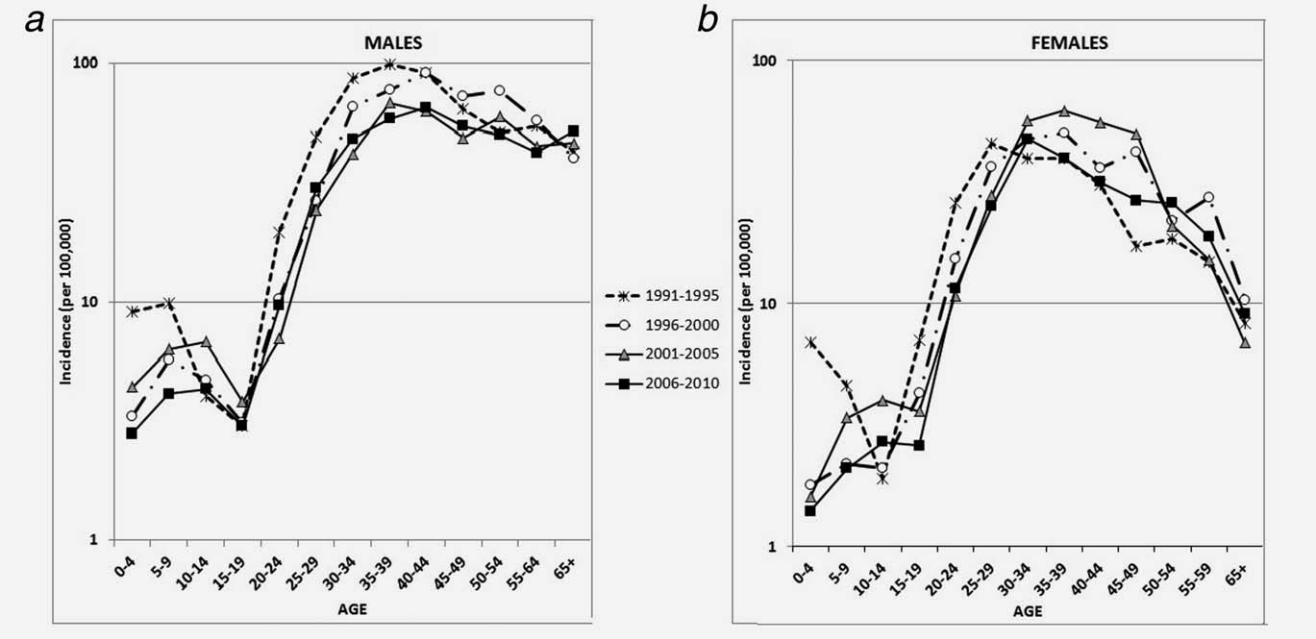

Figure 5. Age-specific incidence rates of Kaposi sarcoma in males (*a*) and females (*b*) in 1991–1995, 1996–2000, 2001–2005, and 2006–2010.

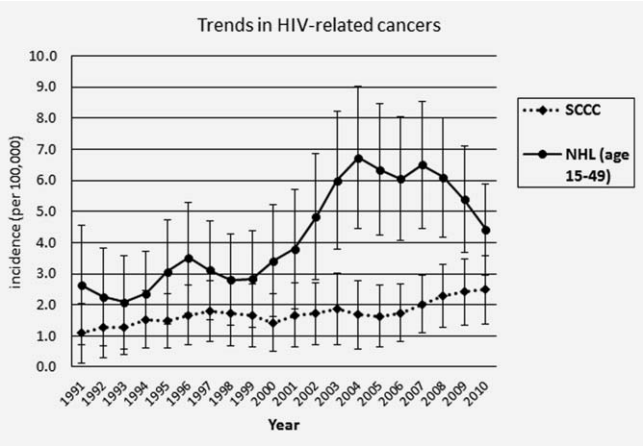

Figure 6. Age standardized incidence rate per 100,000 (with 95% confidence interval), of squamous cell conjunctival cancers (SCCC), and non-Hodgkin lymphoma (ages 15–49) by year (3-year moving average).

annually), although the absolute incidence rate (ASR of 31.2 per 10^5 in 2006–2010) remains relatively low by world standards.[12] The increase appears to have been confined to the first 15 years, with an apparent small decrease since 2005. The age-specific incidence curve shows the typical steep increase in incidence in premenopausal women, after which it is relatively flat. Unlike observations in some west African series, where the age-incidence curve showed a curious bimodal pattern, and increases in incidence occurred only in premenopausal women,[14] most of the increase in incidence in Kampala has been in postmenopausal women (Fig. 4*a*). This is what might be anticipated if the increase were related to changes in lifestyle factors, such as fertility and overweight/obesity. There have been declines in fertility in recent years in Uganda, especially among younger women, with a trend towards later age at marriage, first intercourse, and first birth; moreover, fertility in Kampala is about half that of the country as a whole.[15] Nationally, some 19% of women were overweight or obese in 2010/2011, but the proportion was much higher in Kampala (40%).[13]

Cancer of the large bowel is rather rare (as noted by Burkitt[16]), although there are increases occurring, especially among women. Likewise, cancers of the lung remain relatively rare although incidence is increasing in women. This may relate to improved diagnosis, and to increases in smoking prevalence. Comprehensive studies of prevalence of tobacco use in Uganda are limited. The 2006 Uganda Demographic Health Survey[17] indicated that cigarette smoking prevalence among adults is at 23% for males and 4% for females. However, in the Global Youth Tobacco Survey of 2007 among secondary school students (about one half from Kampala), 16.6% were current tobacco users, with no statistical difference between male and female students.[18]

These increases in incidence of cancers associated with a "western" lifestyle (breast, prostate, large bowl, lung) are not, however, being accompanied by major declines in the cancers traditionally associated with East Africa. Cancer of the oesophagus was the most common cancer of men in the 1950s and 1960s.[2] The reasons are not well understood, but suspected risk factors include alcohol intake, poor dietary patterns such as consumption of a maize-based diet that is low in fruits and vegetables and contamination of maize with fungi that produce fumonisins, a cancer-initiating agent in

experimental animals.[19] However, there has been no decline in oesophageal cancer rates in the last 20 years, and even an increase in rates, especially in men, since 2000, while one might have expected the diseases associated with nutritional deficiency (or contamination) to have declined.

Similarly, there is no sign of a decline in the incidence of stomach cancer, as is consistently reported from western countries (there are in fact nonsignificant increases in rates). It is possible that the rates may have been influenced by improvements in diagnosis, but it is unlikely to be due to differential allocation of oesophageal cancers (at the gastro-oesophageal junction) since the latter are also increasing. Prevalence of infection with *Helicobacter pylori* in adults in Kampala was 87% in a recent study, and, interestingly, there was a significantly higher prevalence in younger subjects than those over 50.[20]

As noted in an earlier report, the incidence of liver cancer appears to be increasing, especially among women.[21] The reasons are not immediately clear; there is no evidence for an increase in prevalence of infection with HBV, or increasing contamination of food with aflatoxins. Possibly it related to increasing obesity or alcohol consumption.[21] Liver cancer risk was not significantly related to HIV infection in a cohort study in Kampala.[22]

Cancer of the cervix uteri is the most common cancer of women as it has been since the 1950s.[1] Over the 20-year period, the average increase in incidence was 1.8% a year, a trend quite the opposite of the decrease in incidence of cervix cancer in Uganda over the period 1990–2010 estimated by the Institute for Health Metrics and Evaluation.[23] The risk of cancer of the cervix in Kampala, as elsewhere, is increased by HIV infection,[22] due to the high risk for human papillomavirus (HPV) infection, HPV DNA persistence, and progression of HPV lesions to cervical cancer in women infected with HIV.[24] However, the prevalence of HIV infection in Uganda decreased from a peak of about 13% in 1992 to 6.2% in 2004 (although it has risen to about 7% subsequently[25]), and most of the increase in incidence has been in older (postmenopausal) women (Fig. 4*b*) who are less likely than younger women to be infected with HIV.[26] A more likely explanation is an increase in prevalence of HPV infection, changes in family structures, and social mores may have favoured the spread of HPV (like other sexually transmitted diseases), resulting in increasing risk of cervical cancer. Infections with high risk (Types 16 and 18) HPV genotypes is very common in Uganda, particularly among HIV positive individuals and young women irrespective of HIV status.[27] Against the background of an overall increase in the 20-year period, Figure 3 suggests that there may have been some fall in incidence rates in the last 4 years. One possibility is the increasing availability of antiretroviral therapy (ART) in the last 5 years,[25] although there is little evidence that use of ARTs in HIV positive women results in a decreased risk of invasive cervix cancer.[28] Several programmes offering screening for precancerous lesions of the cervix using visual inspection, and preventative treatment by cryotherapy have been in operation since 2006[29,30] and these may have contributed to reducing the number of incident cancers in the city.

In our previous report,[3] we described the decline in the incidence of KS in males since the early 1990s, and a similar fall in women in more recent years. It now appears that the decline in the incidence in males has ceased (since about 2002), while the rather modest decline in incidence in women (since around 2004) has continued, and, in the last 5 years, seems to have concerned women aged 30–49 (Fig. 5*b*). In the past, it was possible to correlate age-specific trends with prevalence of HIV infection, but with the widespread availability of ARTs, this is likely to be more difficult. National surveys show that the prevalence of HIV is generally higher among women than men (in 2004/2005 it was 7.5% for women and 5.0% for men, and in 2011 was 7.7% for women, and 6.7% for men); prevalence is higher in urban than rural areas.[31] Over this recent period (2004/2005 to 2011), prevalence decreased among adults aged 25–34, but increased among those in 15–24 and 35–49 age groups. There has also been a rapid expansion in availability of ART, which in 2011 was available to 68% of eligible women and 54% of eligible men (eligibility = CD4 count $<$350 and/or active TB). ART reduces the risk of both KS and NHL among individuals with HIV.[32,33] Non-Hodgkin lymphoma among young adults (15–49) has increased progressively until 2004, and there appears to be a small decrease in incidence more recently (most NHL in the under 15 age group are Burkitt lymphoma, which is not associated with HIV infection in Uganda[34]).

Squamous cell carcinoma of the conjunctiva (SCCC) has been shown to be associated with HIV infection in African populations,[35] and the incidence in the Kampala population has increased more than tenfold between 1960–1971 and 1995–1997.[2] HPV infection is present in up to half of the cases.[36] There appears to have been no reduction in the steady increase in incidence in Kampala, despite modest declines in HIV prevalence, and increasing use of ART. It has been observed that in addition to human papilloma virus, sunlight exposure in equatorial region is a major aetiological factor of SCCC in patients with severe immune-suppression.[37]

Conclusion

Long time series of real, high quality data on cancer from sub-Saharan Africa are a precious resource. Much published information on global cancer patterns and trends relies on modelling, whereby predictions are based on trends in demographic, economic and lifestyle parameters, so that, with supposed declines in mortality from infectious and nutritional disease, corresponding changes in cancer incidence will follow, and such models therefore predict declines in cancers linked to poverty and malnutrition, such as cervix, oesophagus, and stomach, with rises in "cancers of affluence", such as breast, large bowel, and prostate. The results from

Kampala show that such expectations are not always borne out in reality. Neither do the cancers with a strong link to infection with HIV-AIDS (KS, NHL, and SCCC) show similar temporal patterns, as one might expect. Observations such as these should prompt further research into local causes, and into trends in exposure to those causative agents known from studies elsewhere. They also underline that, in predicting disease patterns and trends, there is no substitute for real data, and the patient, painstaking work of cancer registration is vital to our knowledge of cancer, and for planning and evaluation of programmes for control of the disease.

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