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Thesis: EPIDEMIOLOGY OF KAPOSI SARCOMA IN A SOUTH AFRICAN ADULT BLACK POPULATION

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Abstract

Background

Kaposi sarcoma (KS) is a malignant neoplasm caused by infection with Kaposi's sarcoma associated herpesvirus (KSHV). KS is a common AIDS-defining cancer in sub-Saharan Africa. KS was endemic in South Africa even before the advent of the human immunodeficiency virus (HIV). There is a consistent male predominance of KS incidence before and after the advent of HIV. The risk of KS is amplified in HIV-immunosuppressed individuals, and antiretroviral therapy (ART) reduces KS incidence. Literature on the epidemiology of KS in adult black Africans is sparse, concentrating mainly on cancer risk in relation to KSHV and HIV among African populations. Reliable data on the relationship between these factors, especially in explaining the uneven sex ratios are lacking in African populations. The overall aim of this PhD is to investigate the epidemiology of Kaposi sarcoma in an adult (18-74 years) black South African population.

Methods

Firstly, we describe the trends in incidence of KS in sub-Saharan Africa before and after antiretroviral rollout periods using the best available KS incidence data from WHO-International Agency for Research on Cancer (IARC) and the African Cancer Registry Network (AFCRN) publications.

Data for the second and third part of the thesis came from the Johannesburg cancer study (JCS), a cancer epidemiological biobanking study of over 25,000 cancer patients recruited between 1995 and 2016 who provided answers to a short questionnaire and a blood sample. The JCS is particularly suited to answer multiple associations via case-control comparisons. Secondly, we assessed the prevalence of known cancer modifying factors (parity, hormonal contraceptive use in females, sex-partners, urban/rural status, education, smoking and alcohol consumption in both sexes) in relation to KS. Thirdly, using sera that were tested for HIV-1 and KSHV antibodies, we measured the association between KSHV seropositivity and select sociodemographic variables, measured the association between KS and seropositivity to HIV-1 and KSHV and assessed KSHV seropositivity before (1995-2004), early (2005-2009) and late (2010-2016) ART rollout periods. We calculated case-control adjusted odds ratios (OR_{adj}) using unconditional logistic regression to assess these relationships and especially whether any of these could account for the unequal KS sex ratios.

Results

Using data from 16 registries in 14 countries and a subset with some KS trend data, an increase in KS incidence was observed in four out of 16 registries throughout sub-Saharan Africa as the HIV epidemic progressed, reaching peak incidences pre-ART rollout. Between early and late rollout periods 10 out of 16 registries showed a decline in KS incidence. The overall unweighted average decline in KS incidence between early and late ART rollout periods was 27%.

In the second study, 1,275 cases and 10,309 infection unrelated controls were included, with particular attention to selecting controls that are not associated with exposures of interest. We

found a positive association between KS and heavy vs. non-drinking (OR_{adj}=1.31;95%CI=1.03–1.67), and in current heavy vs. never smokers (OR_{adj}=1.82;95%CI=1.07–3.10).

In the third study, 1,237 KS cases and 6,649 infection unrelated cancer controls were included. KSHV seropositivity among 1,237 KS cases was 98%. Among 6,649 controls, KSHV seropositivity was higher in males (OR_{adj}=1.4;95%CI=1.23–1.52), in persons with HIV, (OR_{adj}=4.2;95%CI=3.74–4.73) and lower in high school leavers (OR_{adj}=0.7;95%CI=0.59–0.83). The risk of KS among those with HIV was high, with no difference in risk between the sexes (OR_{adj}=86.96;95%CI=60.36–125.29, $P_{heterogeneity}$=0.934). Among those who were KSHV seropositive the risk of KS was also high with no difference in risk between males and females (OR_{adj}=132.21;95%CI=86.30–202.52, $P_{heterogeneity}$=0.297). Compared to HIV-1 and KSHV seronegatives, KSHV seropositives yielded an adjusted OR for KS of 26;(95%CI=11–62) in HIV-1 seronegative participants and increased 100-fold to an adjusted OR of 2501;(95%CI=1083–5776) in HIV-1 seropositive participants. KSHV seropositivity declined over the ART rollout periods (37%, 28%, 28% P_{trend}<0.001) but also coincided with increases in high school leavers over the same periods (46%, 58% and 67%, P_{trend}<0.001). HIV-1 seroprevalence increased from 10% pre-ART period to 22% in late ART period (P_{trend}<0.001).

Conclusions

ART rollout coincides with a decline in KS incidence across several regions in sub-Saharan Africa. There is a need to establish enduring and accurate cancer registration in most regions of Africa. The role of other risk factors in the published literature could not be fully ascertained. We show that smoking and alcohol consumption may provide a possible explanation for the KS sex

differences, given both exposures are more common in men, but given this is the first report of such an association in a case-control study, further, preferably cohort studies are needed to confirm this association. HIV-1 increases risks of KS in those infected with KSHV by 100-fold. Even though these modern serological assays for KSHV are highly sensitive in detecting KSHV, they are not specific in a high KSHV prevalence setting such as South Africa. Decline in KSHV seroprevalence coincide with ART rollout and with improvements in educational standards and general hygiene. Despite the decline in KS, it remains common among males and females in South Africa. The role smoking and alcohol play in relation to viral loads of HIV/KSHV, differences in immunological responses or other genetic differences between males and females warrant further studies. Further studies are also needed to improve the clinical utility of the current KSHV serological assays by improving their specificity.