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Motlhale, Melitah, Sitas, Freddy, Bradshaw, Debbie et al. (9 more authors) (2022) Lifestyle factors associated with sex differences in Kaposi sarcoma incidence among adult black South Africans : A case-control study. Cancer Epidemiology. 102158. ISSN 1877-7821

https://doi.org/10.1016/j.canep.2022.102158

Cancer Epidemiology 78 (2022) 102158

Contents lists available at ScienceDirect

Cancer Epidemiology

journal homepage: www.elsevier.com/locate/canep

Lifestyle factors associated with sex differences in Kaposi sarcoma incidence among adult black South Africans: A case-control study

Melitah Motlhale [a,b,*], Freddy Sitas [c,d,e], Debbie Bradshaw [c], Wenlong Carl Chen [a,f], Mwiza Gideon Singini [a,b], Chantal Babb de Villiers [g], Cathryn M. Lewis [h,i], Mazvita Muchengeti [a,b,j], Tim Waterboer [k], Christopher G. Mathew [f,g,i], Robert Newton [l,m], Elvira Singh [a,b,1]

[a] National Cancer Registry, National Health Laboratory Service, Johannesburg, South Africa
[b] Division of Epidemiology and Biostatistics, School of Public Health, Faculty of Health Sciences, University of Witwatersrand, Johannesburg, South Africa
[c] Burden of Disease Research Unit, South African Medical Research Council, Cape Town, South Africa
[d] Centre for Primary Health Care and Equity, School of Population Health, University of New South Wales Sydney, Australia
[e] Menzies Centre of Health Policy, School of Public Health, University of Sydney, Australia
[f] Sydney Brenner Institute for Molecular Bioscience, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa
[g] Division of Human Genetics, School of Pathology, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa
[h] Social, Genetic and Developmental Psychiatry Centre, Institute of Psychiatry, Psychology & Neuroscience, King's College London, SE5 8AF, United Kingdom
[i] Department of Medical and Molecular Genetics, Faculty of Life Sciences and Medicine, King's College London, SE1 9RT, United Kingdom
[j] South African DSI-NRF Centre of Excellence in Epidemiological Modelling and Analysis (SACEMA), Stellenbosch University, Stellenbosch, South Africa
[k] Division of Infections and Cancer Epidemiology, German Cancer Research Center (DKFZ), Heidelberg, Germany
[l] MRC/UVRI and LSHTM Uganda Research Unit, Entebbe, Uganda
[m] University of York, York, United Kingdom

ARTICLE INFO

Keywords:
Kaposi sarcoma
HIV
Sex ratio
Johannesburg cancer study
South Africa

ABSTRACT

Kaposi Sarcoma (KS) is endemic in several countries in Southern and Eastern Africa, relatively rare worldwide but a leading cancer among people living with HIV. KS has always been more common in adult males than females. We assessed the prevalence of known cancer modifying factors (parity, hormonal contraceptive use in females, sex-partners, smoking and alcohol consumption in both sexes), and their relationship to KS, and whether any of these could account for the unequal KS sex ratios. We calculated logistic regression case-control adjusted odds ratios (OR_{adj}), and 95% confidence intervals (95%CI), between KS and each of the modifying factors, using appropriate comparison controls. Controls were cancer types that had no known relationship to exposures of interest (infection or alcohol or smoking or contraceptive use). The majority of the 1275 KS cases were HIV positive (97%), vs. 15.7% in 10,309 controls. The risk of KS among those with HIV was high in males (OR_{adj}=116.70;95%CI=71.35–190.88) and females (OR_{adj}=93.91;95%CI=54.22–162.40). Among controls, the prevalence of smoking and alcohol consumption was five and three times higher in males vs. females. 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). These associations remained positive for alcohol consumption (but with wider CIs) after stratification by sex, and restriction to HIV positive participants. We

Abbreviations: ARV, antiretroviral; CI, confidence intervals; ELISA, Enzyme-linked Immunoassay; hCG, human chorionic gonadotropin; HIV, human immunodeficiency virus; IARC, International Agency for Research on Cancer; ICD-O, International Classification of Diseases for Oncology; IQR, interquartile range; KS, Kaposi's sarcoma; KSHV, Kaposi's sarcoma-associated herpesvirus; JCS, Johannesburg Cancer Study; ORadj, Adjusted odds ratios; OR, odds ratios; SSA, sub-Saharan Africa; USA, United States of America.

* Correspondence to: National Cancer Registry, National Health Laboratory Service, Sandringham, Johannesburg, South Africa.
E-mail address: melitahm@nicd.ac.za (M. Motlhale).

[1] **Deceased**

https://doi.org/10.1016/j.canep.2022.102158
Received 16 September 2021; Received in revised form 31 March 2022; Accepted 3 April 2022
Available online 11 April 2022

found no evidence of interactions of smoking and alcohol by sex. Smoking and alcohol consumption may provide a possible explanation for the KS sex differences, given both exposures are more common in men, but confounding and bias cannot be fully ruled out. 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.

1. Introduction

Kaposi Sarcoma (KS) is endemic in several countries in Southern and Eastern Africa and relatively rare cancer worldwide, with approximately 34,000 cases and 15,000 deaths reported by GLOBOCAN in 2020. [1] KS remains the most common cancer among people living with the human immunodeficiency virus (HIV). [2,3] KS is classified as an AIDS-defining cancer and the risk of developing KS is about 50–134 fold higher among those individuals who are HIV positive in South Africa.[4,5] Regardless of HIV positivity, throughout Africa, adult males have always been at higher risk of KS than females. [6,7] In South Africa, between 1988 and 2017 the pathology-based National Cancer Registry reported that KS incidence rates doubled in males and increased about seven-fold in females. This resulted in a decline of the sex ratio from 7:1 (males versus females) in 1988–2:1 in 2017. [8–10] Even though the ratio has declined, most likely as a result of the nature of the HIV epidemic in SA which predominantly affects women, the KS sex disparities are still evident.

Kaposi sarcoma-associated herpesvirus (KSHV) is considered a necessary cause of KS. [11] Co-infection with HIV and KSHV greatly increases the likelihood of developing KS, [12] which has resulted in a large increase in KS incidence during the HIV/AIDS pandemic in SA. [10]In Africa, the seroprevalence of KSHV varies from 20% to 80%. [4,8,12–17] A recent meta-analysis of KSHV prevalence showed no difference in KSHV seroprevalence between boys and girls in SSA but found KSHV to be about 30% higher in adult males than females, which may explain some of the sex differences observed. [7] In other studies conducted in Uganda, males were twice as likely to have detectable KSHV in blood compared to females, [18–20] however in South Africa, we observed no Male: Female differences in adult KSHV seroprevalence. [12] The more than two-fold KS sex differences suggest the importance of further unknown cofactors other than KSHV in the development of KS. [9].

There is a dearth of information on KS lifestyle risk factors that could explain these sex differences. [21] The role of immunity and genomic make-up is currently uncharted. Grulich and Kaldor in 1996, at the early stages of the HIV epidemic, suggested sex hormones (e.g. during pregnancy) were not an important factor in KS pathogenesis. [22] Male hormones (androgen and testosterone) have been reported to aid KSHV infection and female pregnancy hormone human chorionic gonadotropin (hCG) inhibit the development of KS. [23–27] The role of smoking as a risk factor for KS was suggested by Goedert in 2009 to be protective in classical and epidemic KS in Sicily and the United States of America (USA). [28–30] The role of alcohol as a risk factor for KS is inconclusive. [21] These studies were, all however, small.

With some exceptions, smoking and drinking prevalences are higher in men than in women. Males are more likely to be in the heavy drinking and smoking categories as compared to females in South Africa. Peltzer and colleagues reported 41.5% men compared to 17.1% women as current alcohol users from the 2008 South African national population survey, whereas for all ethnicities, hazardous/ harmful drinking in black males and females were 15.5% and 10.0% respectively. [31] Results from the South African Smoking and Death Notification Survey (2007, aged 35–74) show black males had a smoking prevalence four times (46.3%) higher than black females (11.1%). [32].

We used data from the Johannesburg Cancer Study (JCS) to assess whether the lower incidence of KS in females (or higher incidence in males) could be attributed to any of known cancer-associated lifestyle factors such as parity, hormonal contraceptive use, lifetime sex partners, urban/rural residence, education, smoking and alcohol consumption in a black South African population.

2. Methods

2.1. Study setting and design

The JCS is an epidemiological study of over 25,000 cancer patients established by the National Cancer Registry of South Africa in 1995, at the early stages of the HIV epidemic. Data collection continued during the antiretroviral (ARV) rollout in 2004 and ended in 2016. The study aim of the JCS described in Chen et al., [33] was to investigate the relative importance of known cancer risk factors in an African population. This study utilizes an established case-control design for cancer epidemiological studies, whereby cases are individuals with the cancer of interest and controls are individuals with other cancers that are not associated with the exposures under investigation. [4,12,34].

2.2. Study population

The JCS recruited in a consecutive fashion, cancer patients of any type mainly from southern Gauteng province, attending the medical and radiation oncology departments of the largest tertiary referral public hospitals in Johannesburg (mainly Charlotte Maxeke Johannesburg Academic hospital and associated referral centres). [33] Participants were aged 18–74 years, black, resident of South Africa, with a new (incident) diagnosis of cancer, who had given written or witnessed oral informed consent. Trained nurse interviewers used a standard questionnaire to interview participants in their preferred language (usually Zulu or Sotho). Participants were interviewed within six months of diagnosis and before receiving radio- or chemotherapy.

The questionnaire covered questions on the leading, emerging and suspected risk factors for cancer such as place of birth and residence, education, ethnicity (home language of parents), method of cooking and heating, smoking by type of tobacco and amounts smoked, snuff (sniffed tobacco) use, alcohol consumption by type and amount consumed, parity, use of oral and injectable contraceptives, number of sexual partners, basic occupations, and self-reported use of ART (since 2005). Interviewers collected peripheral blood samples for HIV testing and other analyses. The serum was used for serological screening for HIV on all samples and KSHV and Human papilloma virus (HPV) in selected samples in previous studies. [4,12] HIV antibody testing was conducted using the Vironostika (HIV Uniform II plus O) micro enzyme-linked immunosorbent assay (ELISA). Cancer types were mostly (>90%) ascertained by cytology/histology[4] and coded to their topography and morphology using the International Classification of Diseases for Oncology Version 3 (ICD-O3).

2.3. Ethics

The University of Witwatersrand Human Research Ethics Committee (Medical) approved the primary study and the current study (Clearance certificate number: M191130).

2.4. Data management

Fig. 1 shows the participants used in case-control selection. Cases for

this study were participants with a histologically confirmed diagnosis of KS (N = 1275). Controls were women and men drawn from the rest (N = 19,161) of the participants diagnosed with cancer types that have no known relationship to exposures of interest. We used the IARC 100th Monograph series and Schottenfeld and Fraumeni's Textbook (3rd and 4th editions), to assess cancer/exposure relationships to identify appropriate control cancer types. [11,33,35–37] Control selection and therefore sample size varied when assessing the effect of HIV (infection-related cancers excluded, N = 10,309 remained), smoking (smoking-related cancers excluded, N = 2170 remained), alcohol consumption (alcohol-related cancers excluded, N = 3090 remained), parity and hormonal contraceptive use (reproductive-related cancers were excluded, N = 6870 remained) (Fig. 1). A detailed list of cancers included in each control group and the sex distribution among cases and controls (Supplementary Table S1 and Table S2). To test the robustness of the smoking and alcohol-KS-ORs we performed a sensitivity analysis recalculating these ORs by removing one cancer type at a time from each of the control comparison groups. (Supplementary Fig. S1 and S2).

The explanatory variables included sex, age group at enrolment, year of interview, place of birth (by province), ethnicity, place of residence (urban/rural), education (none, secondary or tertiary) and number of sexual partners (0–1, 2–5, 6 or more), weekly alcohol consumption (none, light (1–7 drinks for females and 1–14 drinks for males), and heavy (>8 drinks for females and >14 drinks for males). Cut-offs for heavy drinking were set at 8 or more drinks per week for women, 15 or more drinks per week for men according to the Centers for Disease Control and Prevention alcohol factsheet. [38] A current smoker was defined as someone who stopped smoking 5 years before interview to minimize reverse causation, and we conservatively assumed 1 g of tobacco per unit of tobacco products (mainly cigarettes). In females only, parity was classified as 0–2, 3 or more children born alive, and contraceptive use was measured in relation to combinations of ever/never use of injectable or oral contraceptives. Period of use of antiretroviral therapy period (ART-period) was classified as pre-ART (1995–2004), early ART (2005–2009) and late ART period (2010–2016).

2.5. Statistical analysis

The descriptive summary of the socio-demographic characteristics of cases and controls are shown in Table 1. To assess whether the high M:F sex ratio was associated with any of the leading modifying factors, unconditional unmatched logistic regression models were fitted to calculate their odds ratios (ORs) and 95% CI in relation to KS overall (Table 2) and stratified by sex (Table 3). ORs were adjusted for important socio-demographic variables (sex-where appropriate, age group, year of interview, HIV status, number of sexual partners, education, place of residence and ART period). For alcohol consumption and smoking we assessed the effect of an interaction term between alcohol, smoking and sex using unmatched logistic regression models (Supplementary Table S5 and S6).

We performed a test for heterogeneity on categorical variables and a score test for trend in the ORs on ordinal categorical variables (Tables 2 and 3). To adjust for confounding associated with HIV, smoking and alcohol consumption analyses were also restricted to HIV positive cases and controls. For each set of case-control comparisons, we used appropriate control comparison groups, conscious that the sample size in each set of comparisons varied. The statistical analysis was done using STATA software version 15.0 (Stata Corp, College Station, Texas).

3. Results

The majority of the 1275 individuals diagnosed with KS were male, 675 (53.0%) (Table 1). Most of the KS cases were HIV positive (95.6% males and 96.7% females), with very little difference in HIV prevalence across all the demographic and lifestyle groups studied. The highest proportion of KS cases was between the ages of 25 and 34 years in females and 35–44 among males. The majority of the cases (95%) were from urban places of residence and had secondary/tertiary education level (72.4% males and 80% females). Males reported a median of six sexual partners (IQR=4–10) and females a median of four partners (IQR=3–5). Most males, (N = 430, 63.7%) vs females (N = 172, 28.7%) were in the heavy alcohol consumption category.

Of the 675 male KS cases, 13.6% (N = 92) males vs 2.5% (N = 15) of

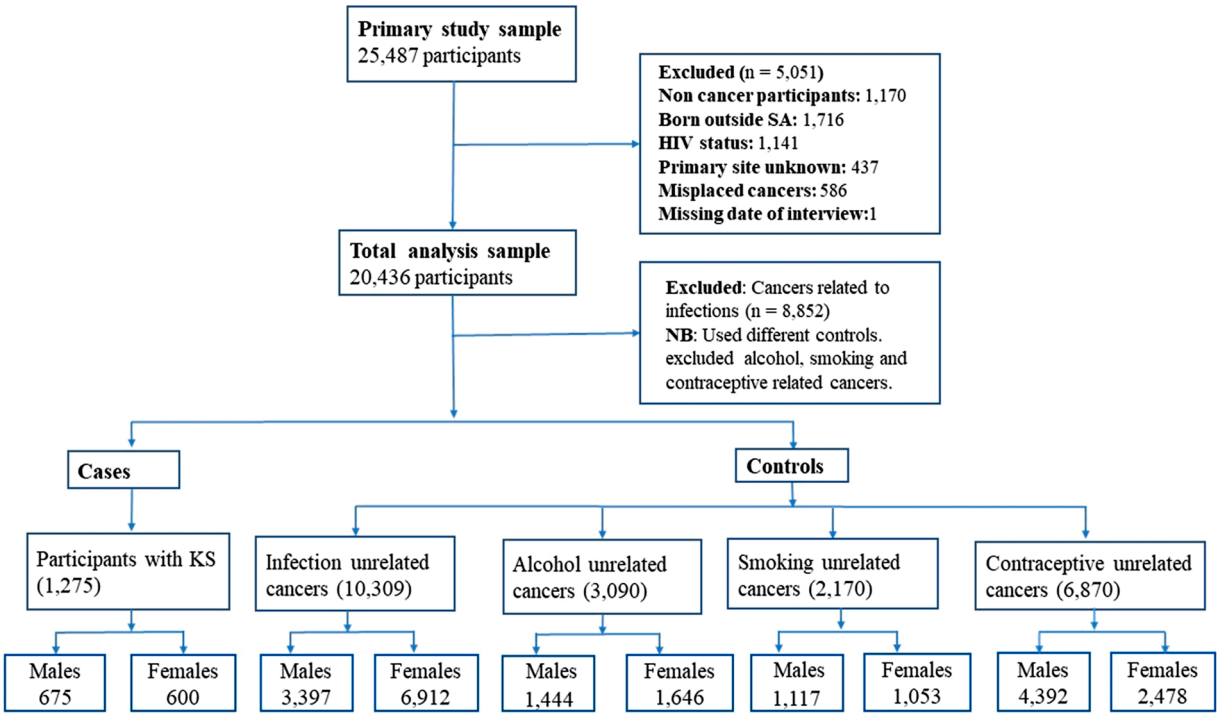

Fig. 1. Selection of study participants (cases and controls).

Table 1
Socio-demographic characteristics of study participants (cases and controls).

Characteristics	Cases (1275)		Controls (10,309[a])	
	Males	Females	Males	Females
	Total 675 (52.94) N (Col %)	Total 600 (47.06) N (Col %)	Total 3397 (32.95) N (Col %)	Total 6912 (67.05) N (Col %)
HIV status				
Negative	30 (4.44)	20(3.33)	3018 (88.84)	5674 (82.09)
Positive	645 (95.56)	580 (96.67)	379 (11.16)	1238 (17.91)
Age				
Median [IQR]	38 [33–44]	33 [29–40]	57 [49–64]	52 [43–61]
Age group (years)				
18–24	11 (1.63)	54 (9.00)	79 (2.33)	84 (1.22)
25–34	214 (31.70)	282 (47.00)	122 (3.59)	503 (7.28)
35–44	292 (43.26)	169 (28.17)	324 (9.54)	1395 (20.18)
45–54	120 (17.78)	69 (11.50)	887 (26.11)	1921 (27.79)
55–64	30 (4.44)	24 (4.00)	1197 (35.24)	1864 (26.97)
65 +	8 (1.19)	2 (0.33)	788 (23.20)	1145 (16.57)
Period of interview				
1995–1999	41 (6.07)	33 (5.50)	827 (24.35)	1057 (15.29)
2000–2004	121 (17.93)	113 (18.83)	673 (19.81)	1217 (17.61)
2005–2009	229 (33.93)	229 (38.17)	895 (26.35)	1848 (26.74)
2010–2016	284 (42.07)	225 (37.50)	1002 (29.50)	2790 (40.36)
Place of residence				
Urban	647 (95.85)	564 (94.00)	3020 (88.90)	6187 (89.51)
Rural	26 (3.85)	34 (5.67)	362 (10.66)	697 (10.08)
Missing	2 (0.30)	2 (0.33)	15 (0.44)	28 (0.41)
Education				
None	31 (4.59)	24 (4.00)	462 (13.60)	740 (10.71)
Primary	155 (22.96)	96 (16.00)	1330 (39.15)	2023 (29.27)
Secondary & Tertiary	489 (72.44)	480 (80.00)	1596 (46.98)	4130 (59.75)
Missing	–	–	9 (0.26)	19 (0.27)
Number of sexual partners				
Median [IQR]	6 [4–10]	4 [3–5]	5 [3–9]	3 [2–5]
Number of sexual partners (cat)				
0–1	16 (2.37)	24 (4.00)	153 (4.50)	655 (9.48)
2–5	207 (30.67)	333 (55.50)	1319 (38.83)	3860 (55.84)
6 or more	265 (39.26)	115 (19.17)	1176 (34.62)	674 (9.75)
Unknown	187 (27.70)	128 (21.33)	749 (22.05)	1723 (24.93)
Alcohol consumption[b]				
Never	203 (30.07)	382 (63.67)	845 (58.55)	1368 (83.11)
Light > 0–7 or > 14 drinks/week	42 (6.22)	46 (7.67)	85 (5.88)	87 (5.29)
Heavy ≥ 8 or ≥ 15 drinks/week	430 (63.70)	172 (28.67)	514 (35.57)	191 (11.60)
Smoking[c]				
Never	206 (30.52)	483 (80.50)	393 (35.18)	891 (84.62)
Ex-smoker	69 (10.22)	20 (3.33)	273 (24.44)	71 (6.74)
Current-light 1–14 g/day	308 (45.63)	82 (13.67)	348 (31.15)	83 (7.88)
Current-heavy ≥ 15 g/day	92 (13.63)	15 (2.50)	103 (9.22)	6 (0.57)
Missing	–	–	–	2 (0.19)
Parity[d]				
0–2		372 (62.00)		866 (34.94)
3 or more		153 (25.50)		1436 (57.95)
Unknown		75 (12.50)		176 (7.10)
Contraceptive use[d]				
Never oral (oc) or injectable (ic)		152 (25.33)		1318 (53.19)
Ever oc never ic		49 (8.17)		271 (10.94)
Ever ic never oc		309 (51.50)		543 (21.91)
Ever ic and ever oc		88 (14.67)		332 (13.40)
#Ever ic and/ or ever oc		446 (74.33)		1146 (46.25)
Missing		2 (0.33)		14 (0.56)
ART-period				
Pre-ART 1995–2004	162 (24.00)	146 (24.33)	1500 (44.16)	2274 (32.90)
Early ART 2005–2009	229 (33.93)	229 (38.17)	895 (26.35)	1848 (26.74)
Late ART 2010–2016	284 (42.07)	225 (37.50)	1002 (29.50)	2790 (40.36)

Abbreviations: IQR, Interquartile range; oc, oral contraceptive; ic, injectable contraceptive.
#Ever ic and /or ever oc: a sum of category (2–4), ever oc never ic, ever ic never oc and ever ic and ever oc.
Total number of controls for the lifestyle exposures are different: for the demographic variables, infection unrelated cancer controls were used. For alcohol consumption, the controls comprised participants with cancers that were unrelated to infectious agents and alcohol. For smoking, the controls were not related to infectious agents and smoking. Contraceptive use controls were cancers unrelated to infectious agents and hormonal contraceptives.
[a] Infection unrelated controls= 10,309
[b] Alcohol unrelated controls= 3090
[c] Smoking unrelated controls= 2170
[d] Contraceptive unrelated controls= 6870

the 600 females smoked 15 g or more of tobacco per day (current heavy smokers). Most females, 372 (62.0%) reported giving birth to 0–2 children. More than half of the females, 309 (51.5%) reported only using injectable contraceptives and 49 (8.17%) reported only using oral contraceptives. Among the controls, HIV prevalence was 11.2% in males and 17.9% in females. About three times as many males (35.6%) reported heavy alcohol consumption (8–15 or more drinks a week) vs. females (11.6%). About five times as many males (40%) reported current smoking, vs. females (8%) (Table 1). Smoking and alcohol consumption prevalences are higher in males than females in both cases and controls. Socio-demographic characteristics of study participants by HIV status were also tabulated (Supplementary Table S3).

KS risk was highest among persons who tested HIV positive, OR_{adj} of 115.42 (95% CI=79.76–167.01). We found no association between KS and number of sexual partners (P_{trend}=0.40). Persons in the heavy drinking category were more likely to develop KS with an OR_{adj} of 1.31 (95% CI=1.03–1.67) compared to never drinking category (*P*

Table 2
Unadjusted and adjusted ORs (95% CI) of developing KS.

Variables	Unadjusted OR (95% CI) using appropriate controls	Adjusted OR (95% CI) using appropriate controls
HIV status		
Negative	1.00	1.00
Positive	131.70 (98.77 – 175.60)	**115.42 (79.76 – 167.01)**
P-value (heterogeneity)	< 0.001	< 0.001
Place of residence		
Urban	1.00	1.00
Rural	0.43 (0.33 – 0.56)	0.83 (0.54 – 1.28)
P-value (heterogeneity)	< 0.001	0.181
Education		
None	1.00	1.00
Primary	1.64 (1.21 – 2.21)	0.86 (0.56 – 1.32)
Secondary & Tertiary	3.70 (2.80 – 4.89)	0.86 (0.57 – 1.31)
P-value (heterogeneity)	< 0.001	0.876
Number of sexual partners		
0–1	1.00	1.00
2–5	2.11 (1.51 – 2.93)	1.26 (0.77 – 2.08)
6 or more	4.15 (2.96 – 5.81)	1.32 (0.79 – 2.21)
Unknown	2.57 (1.83 – 3.61)	1.24 (0.73 – 2.11)
P-value (trend)	< 0.001	0.402
Alcohol consumption[b]		
Never	1.00	1.00
Light	1.94 (1.47 – 2.54)	1.33 (0.87 – 2.04)
Heavy	3.23 (2.80 – 3.72)	**1.31 (1.03 – 1.67)**
P-value (trend)	< 0.001	< 0.001
P-value (sex contribution)		< 0.001
Alcohol consumption[b] (in HIV positives only)		
Never	1.00	1.00
Light	1.38 (0.91 – 2.11)	1.32 (0.83 – 2.09)
Heavy	1.86 (1.50 – 2.32)	**1.35 (1.04 – 1.76)**
P-value (trend)	< 0.001	< 0.001
Smoking[c]		
Never	1.00	1.00
Ex-smoker	0.48 (0.38 – 0.62)	1.00 (0.65 – 1.55)
Current-light (1–14 g)	1.69 (1.43 – 1.99)	**1.41 (1.03 – 1.92)**
Current-heavy (>=15 g)	1.83 (1.38 – 2.43)	**1.82 (1.07 – 3.10)**
P-value (trend)	< 0.001	< 0.001
P-value (sex contribution)		0.013
Smoking[c] (in HIV positives only)		
Never	1.00	1.00
Ex-smoker	0.79 (0.52 – 1.18)	1.11 (0.68 – 1.81)
Current-light (1–14 g)	1.70 (1.28 – 2.26)	1.26 (0.90 – 1.77)
Current-heavy (>=15 g)	2.47 (1.41 – 4.34)	1.84 (0.99 – 3.40)
P-value (trend)	< 0.001	0.087
Parity[d] (females only)		
0–2	1.00	1.00
3 or more	0.25 (0.20 – 0.30)	0.80 (0.59 – 1.09)
Unknown	1.00 (0.74 – 1.33)	0.83 (0.41 – 1.30)
P-value (trend)	0.9578	0.4590
Contraceptive use[d] (females only)		
Never oral or injectable	1.00	1.00
Ever oc never ic	1.57 (1.11 – 2.22)	1.48 (0.89 – 2.47)
Ever ic never oc	4.93 (3.97 – 6.14)	1.19 (0.86 – 1.64)
Ever ic and ever oc	2.30 (1.72 – 3.07)	1.25 (0.81 – 1.94)
Ever ic and/ or ever oc	3.37 (2.76 – 4.12)	1.24 (0.91 – 1.68)
P-value (trend)	< 0.001	0.3575
ART-period		
Pre-ART 1995–2004	1.00	1.00
Early ART 2005–2009	2.05 (1.76 – 2.38)	1.15 (0.89 – 1.48)
Late ART 2010–2016	1.64 (1.42 – 1.91)	0.83 (0.64 – 1.09)
P-value (trend)	< 0.001	0.175

[a] Demographic characteristics were compared to infection unrelated controls.
[b] Alcohol comparisons used alcohol unrelated controls
[c] Smoking comparisons used smoking unrelated controls
[d] Contraceptive use and parity analysis for females only using reproductive factor unrelated controls.
All ORs were adjusted for sex, HIV status, age group, year of interview, place of birth, ethnicity, place of residence, education, number of sexual partners and ART period.

$_{trend}$<0.001). We found a strong statistical effect of sex in the overall model (Table 2, P_{value}<0.001).

3.1. Additional analyses

After restricting the analysis to persons who were HIV positive (remaining N = 1225 KS, 1617 controls- i.e. losing approx. 80% of the controls) the odds of developing KS remained unchanged (OR_{adj}=1.35 (95%CI=1.04–1.76, P_{trend} <0.001)) in the heavy drinking category (Table 2). Those in the current heavy smoking category were more likely to develop KS (OR_{adj} 1.82 (95% CI=1.07–3.10, P_{trend}<0.001) compared to never smoking (Table 2). We found a strong statistical effect of sex in the overall model (Table 2, P_{value}<0.013). Stratification of the data by sex is shown in Table 3. We found no evidence of sex*smoking (P-value 0.7) or sex*alcohol interactions (P-value=0.8) (Supplementary Table S5 and S6). We also tested the robustness of the smoking and alcohol KS associations by removing sex specific cancer controls from these analyses. We found no material differences in the ORs before and after removal (results not shown).

HIV positive males were similarly likely to develop KS as compared to HIV infected females (OR_{adj}=116.70; 95%CI=71.35–190.88 versus OR_{adj}=93.91; 95%CI=54.22–162.40) (Table 3). The association between smoking and KS remained positive in males for both smoking (P_{trend}=0.034) and alcohol consumption (p-trend=0.01). In females, elevated ORs were observed in the heavy drinking and smoking categories (OR=1.21 and 2.03) but the p-trend is no longer significant (P_{trend}=0.1, 0.6 respectively) perhaps because of reduced sample sizes.

4. Discussion

We attempted to identify potential lifestyle explanations for the well described excess male to female sex ratio in KS. We found that as in previous JCS study[4] being HIV positive increased significantly the risk of KS development. In contrast to some previous studies (see below) we found an association between increased smoking intensity and KS and heavy alcohol consumption and KS particularly in males. Smoking and alcohol consumption may provide a possible explanation for the KS sex differences. We found no association between KS and parity or hormonal contraceptive use, reconfirming the hypothesis stated by Grulich and Kaldor. [22] In a study estimating the prevalence of KSHV in females, de Sanjose and colleagues also reported that KSHV was not associated with the number of children, or patterns of oral contraceptive use. [39] Additional studies of the potential mechanisms for sex-related differences in KS are necessary to evaluate further the roles of sex-specific factors such as parity and female sex hormones in KS pathogenesis. [40].

As regards smoking, we found an association between increasing smoking intensity and KS, (Table 3). The association was evident in both sexes and in males alone, with sample sizes in females becoming being too low to draw clear inferences. The literature regarding the role of smoking is mixed. An inverse association between cigarette smoking and infection with KSHV or KS development has been reported in some studies, but these results were not adjusted for education and other confounding factors. [29,30,41] In one study in Uganda (N = 458 KS cases) and another in Cameroon (N = 266 cases), smoking was positively associated with HIV-related-KS; both studies adjusted for education and occupation associated with affluence. [42,43] Our study based on over 1000 KS cases and after adjustment for a range of confounders

Table 3
Unadjusted and adjusted OR (95%CI) of developing KS stratified by sex.

Variables	Unadjusted OR (95% CI)		Adjusted OR (95%CI)	
	Males	Females	Males	Females
HIV status[a]				
Negative	1.00	1.00	1.00	1.00
Positive	**171.21 (116.93 – 250.68)**	**132.91 (84.75 – 208.44)**	**116.70 (71.35 – 190.88)**	**93.91 (54.22 – 162.64)**
P-value (heterogeneity)	< 0.001	< 0.001	< 0.001	< 0.001
Alcohol consumption[b]				
Never	1.00	1.00	1.00	1.00
Light drinking	**2.06 (1.38 – 3.07)**	**1.89 (1.30 – 2.75)**	1.29 (0.68 – 2.46)	1.41 (0.79 – 2.50)
Heavy drinking	**3.48 (2.85 – 4.25)**	**3.22 (2.55 – 4.08)**	**1.46 (1.03 – 2.06)**	1.21 (0.85 – 1.72)
P-value (trend)	< 0.001	< 0.001	0.070	0.148
Alcohol consumption[b] **(HIV positives)**				
Never	1.00	1.00	1.00	1.00
Light drinking	1.00 (0.54 – 1.85)	1.73 (0.96 – 3.14)	1.08 (0.54 – 2.16)	1.63 (0.86 – 3.07)
Heavy drinking	**1.84 (1.33 – 2.57)**	**1.48 (1.07 – 2.05)**	**1.52 (1.04 – 2.23)**	1.21 (0.84 – 1.76)
P-value (trend)	< 0.001	0.012	0.034	0.100
Smoking[c]				
Never	1.00	1.00	1.00	1.00
Ex-smoker	**0.48 (0.35 – 0.66)**	**0.52 (0.31 – 0.86)**	0.87 (0.52 – 1.47)	1.49 (0.64 – 3.45)
Current-light	**1.69 (1.34 – 2.12)**	**1.82 (1.32 – 2.52)**	**1.51 (1.01 – 2.26)**	1.21 (0.72 – 2.04)
Current-heavy	**1.70 (1.23 – 2.37)**	**4.61 (1.78 – 11.96)**	**1.83 (1.00 – 3.35)**	2.03 (0.51 – 8.12)
P-value (trend)	< 0.001	< 0.001	0.010	0.621
Smoking[c] **(HIV positives)**				
Never	1.00	1.00	1.00	1.00
Ex-smoker	0.73 (0.44 – 1.24)	0.68 (0.31 – 1.49)	1.19 (0.65 – 2.17)	1.13 (0.46 – 2.76)
Current-light	**1.73 (1.15 – 2.61)**	1.17 (0.72 – 1.90)	1.48 (0.94 – 2.31)	0.97 (0.57 – 1.65)
Current-heavy	**2.14 (1.12 – 4.10)**	2.81 (0.64 – 12.43)	1.98 (0.98 – 3.99)	2.43 (0.52 – 11.26)
P-value (trend)	< 0.001	0.283	0.077	0.630

[a] For males and females, demographic characteristics used infection unrelated controls and adjusted for HIV status, age group, year of interview place of birth, ethnicity, place of residence, education, number of sexual partners and ART period.

[b] Alcohol using alcohol unrelated controls and adjusted for sex, age group, year of interview, education, HIV status, place of residence, number of sexual partners and ART period.

[c] Smoking using smoking unrelated controls and adjusted for sex, age group, year of interview, education, HIV status, place of residence, number of sexual partners and ART period.

including education, does support the hypothesis that smoking increases the risk of developing KS, and also given male smoker rates are about five times those of females, this could provide a possible explanation for the KS sex differences. Larger sample size studies, meta- analyses or cohort studies are needed to confirm this hypothesis as smoking makes a partial contribution to the KS sex difference.

While the initial analysis of the association between KS and alcohol is interesting, a crude 3-fold OR among those (in both sexes combined) in the heavy drinking category was reduced to 1.31 after adjustment, so significant confounding appears to be involved (Table 2). After stratifying by sex, those in the heavy drinking category (vs. non-drinking) were associated with increased KS risk in males but the association became weaker in females (Table 3). Restricting the analysis further to HIV positive participants indicated that heavy alcohol consumption was still associated with increased odds of KS in males and the effect being less important in females (although this could be due to reduced sample size). In this study, it seems plausible that alcohol consumption is another possible explanation for the KS sex ratios, especially given alcohol consumption is three times more prevalent in males. The relationship between KS and alcohol consumption is complex as the behavioral patterns associated with alcohol consumption may influence the probability of exposure to KSHV as stated by Mbulaiteye et al. [44] In a case-control study of KS in HIV positive Ugandan patients, Ziegler et al. and Nansseu et al. found no associated risk between alcohol consumption and KS. [42,43] KSHV seropositivity was also not associated with alcohol consumption in the study of Ugandan HIV-negative KS patients.[44,45].

Other explanations for the KS sex differences include genetic make-up along with unmeasured hormonal differences [46] and immune system functions.[47] Androgens aid KSHV infection and this may be why KS is more common in males than females. [27] Androgen receptor (found in both males and females) expression in males is high and has been identified as a KSHV entry factor and subsequently promotes KSHV infection in cells. [23,48] In females, the pregnancy hormone, human chorionic gonadotropin (hCG) has been reported to have shown anti-KS properties and this results in the reduction of KS tumor growth and inhibition of growth of other angiogenic tumors. [26] This hormone has also been shown to inhibit the growth of KS cell lines in vitro. [25] However, to the extent that we could measure (parity, hormonal contraception) we found no association between those factors in females and KS risk.

5. Limitations

Our study must be considered in light of possible limitations inherent in case-control studies and in this situation using people with a range of other cancers as controls. Cancer incidence in the South African black population is higher in females (National Cancer Registry data for 2017: 18,814 vs 13,116) and thus they are also more frequently represented in the JCS (7,512 vs 4,072). [10] This unusual situation, dominated by cancer of the cervix, distorts odds ratio calculations of M:F KS differences. In the analysis of risk factors, however, careful selection of controls unrelated to exposures of interest allows for valid comparisons. Population prevalence estimates for smoking and alcohol, or reproductive factors that are comparable with the 18–74-year-old black, urban population comprising the JCS study which collected data over a 20-year period, situated in southern Gauteng province are sparse. With that limitation in mind, national surveys[31] show prevalences of alcohol drinking of 35% in males and 10% in females with higher urban prevalences (in keeping with our observed prevalence of 41% and 17% in our mainly urban controls). Similarly, national current smoking prevalence in South African blacks is 50% in males and 12% in females, [32] in keeping with our observed 56% and 8% prevalence in our controls, HIV prevalence in Gauteng province is 14%, [39] again comparable to what

is observed in our controls (11% in males 18% in females).

Recall of past exposures such as number of sexual partners, alcohol consumption and smoking could be subject to recall or desirability bias. JCS collected data from radiotherapy and oncology departments and therefore, cases that were not referred to these departments (such as surgery only or palliative care) were missed. There may be possible residual confounding of lifestyle factors and HIV. Since 97% of all KS patients were HIV positive, there may be possible associations with high-risk behaviors such as number of sexual partners, smoking and alcohol drinking which are known to be associated with HIV, and the age pattern (reproductive age group). We accounted for HIV confounding by restricting the analysis for smoking and alcohol consumption to those who were HIV positive. Despite these limitations, these data remain an important source to understand sex disparities in KS among the adult black South African population.

6. Strengths

Both cases and controls are people with incident cancers, thus interviewer and recall bias is minimized (and is non-differential) by interviewing cases and controls with diseases of similar severity. Referral biases are also minimized because both cases and controls are likely to be come from the same catchment areas and referred through the same process and departments (as a precaution we adjust for Urban/Rural residence). Over 95% of the cancers were histologically verified. [4] Controls for this analysis were carefully selected, comprising cancer types not known to be associated with the exposures of interest (infectious agents, alcohol consumption smoking and hormonal contraceptive use). Sensitivity analysis of the controls used (Supplement Fig. S1 and S2) shows control selection was robust.

7. Conclusion

We have assessed, in a systematic fashion, whether selected lifestyles that are known to cause cancer are associated with KS development and whether these can explain the greater male to female KS ratio. In this study, being HIV positive increased the risk of KS in both sexes by 100-fold but the prevalence of HIV in controls was higher in females. compared to males (18 vs 11%). Parity and hormonal contraception use were not associated with KS among females. We found increased risks of KS (in both sexes combined) in relation to smoking and alcohol, and these risks remained positive after sex stratification and restriction to HIV positive participants. While confounding and biases cannot be fully ruled out, tobacco smoking and alcohol are therefore possibly responsible for the uneven KS sex ratios, given drinking and smoking was three to five times more common in males. While this is the largest case-control study to investigate these factors, reductions in sample size by restricting to HIV positives and by sex reduced our precision but the OR estimates remained about the same. Further comparative research, preferably from large cohort studies is needed to elucidate whether smoking and alcohol act independently or whether they modify the role of HIV and KSHV, the two viruses responsible for KS, especially their viral loads, immunological responses and in identifying other genetic differences in the way the two sexes respond to HIV/KSHV infection.

Grant sponsor

Original seed funding for this study was provided by National Health Laboratory Service, Professor Valerie Beral (Cancer Research UK, Cancer Epidemiology Unit) and the SA Medical Research Council. Currently the study has been supported by the South African Medical Research Council (with funds received from the South African National Department of Health) and the UK Medical Research Council (with funds from the UK Government's Newton Fund) (MRC-RFA-SHIP 01–2015). The authors are solely responsible for the contents of this publication and do not necessarily represent views of the funders.

Data sharing

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author contribution

Melitah Motlhale, Freddy Sitas and Elvira Singh conceptualised the study. **Melitah Motlhale:** performed data analysis, Writing – original draft; review and editing. **Freddy Sitas and Elvira Singh:** validation, resources, supervision writing - review and editing. **Debbie Bradshaw, Wenlong Carl Chen, Mwiza Gideon Singini, Chantal Babb de Villiers, Cathryn M. Lewis, Mazvita Muchengeti, Tim Waterboer, Christopher G. Mathew, Freddy Sitas and Elvira Singh and Robert Newton** are the members of Evolving Risk Factors for Cancers in African Populations (ERICA-SA) collaborative group. All authors read and provided feedback (writing: review and editing) to improve the final version of the manuscript.

Declaration of Competing Interest

The authors declare that there are no conflicts of interest.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.canep.2022.102158.

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