The incidence and epidemiology of conjunctival squamous cell carcinoma in relation to the HIV epidemic in South Africa: a 25-year analysis of the National Cancer Registry (1994–2018)

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SYNOPSIS

There have been considerable changes in conjunctival squamous cell carcinoma incidence rates over the course of the HIV epidemic in South Africa. Declining rates coincide with notable changes in the availability of effective antiretroviral therapy.

ABSTRACT

Aims:

To describe the incidence and epidemiology of conjunctival squamous cell carcinoma (CSCC) in South Africa over a 25-year period (1994–2018), with particular reference to the human immunodeficiency virus (HIV) epidemic.

Methods:

Incident cases of histologically diagnosed CSCC were identified from the pathology-based South African National Cancer Registry. Crude and direct age-standardised incidence rates (ASIRs) per 100 000 persons (Segi World Standard Population) were calculated using national population statistics and compared by age, sex and ethnicity. Trends in the incidence and demographic features of CSCC were described and analysed. Incidence rates were compared to national HIV-related statistics for the same time period.

Results:

In total, there were 9 016 reported CSCC cases (female: 56.6%, Black: 86.8%, mean age: 41.5 years). The overall ASIR was 0.78 per 100 000. Two distinct epidemiological patterns were identified: (1) older White males, and (2) younger Black females. There was a six-fold increase in CSCC incidence rates between 1994 and 2009 with a corresponding shift from the first to the second disease profile. Despite rising HIV seroprevalence, CSCC incidence rates have declined since 2009. A strong ecological correlation (r=0.96) between CSCC incidence and widespread antiretroviral therapy (ART) provision was identified.

Conclusion:

This study highlights the evolving trends and disease burden of CSCC in South Africa. Widespread ART provision is ecologically correlated with declining CSCC rates over the last decade. These findings are in keeping with reported trends for other HIV-related cancers and have important implications for future incidence studies and public health policy.

Keywords:

Conjunctival squamous cell carcinoma, ocular surface squamous neoplasia, incidence, epidemiology, South Africa, National Cancer Registry.

What is already known on the topic:

Human immunodeficiency virus (HIV) is known to be a major risk factor for conjunctival squamous cell carcinoma (CSCC) but it is unclear what impact an evolving HIV epidemic and widespread antiretroviral therapy (ART) provision have had on temporal CSCC trends.

What this study adds:

This study provides detailed estimates of CSCC incidence in South Africa over a 25-year-period and highlights the impact the HIV epidemic has had on the epidemiological profile of the disease. It shows that, despite rising HIV-seroprevalence, the CSCC incidence rate has declined over the last decade and that this trend may be related to widespread ART provision in the country.

How this study might affect research, practice or policy:

Findings from this study strengthen the case for widespread ART provision and highlight the potential clinical and economic benefits of such a public health policy. Recognition that the CSCC disease burden is temporally related to an evolving HIV epidemic has important implications for direct comparability or pooling of estimates from different countries or time periods.

INTRODUCTION

Ocular surface squamous neoplasia (OSSN) is the most common non-pigmented tumour of the ocular surface and encompasses a spectrum of histological diagnoses, ranging from mild epithelial dysplasia to invasive carcinoma.[1] Conjunctival squamous cell carcinoma (CSCC) represents the end-stage of this disease spectrum and is the most common malignancy of the ocular surface.[2]

Globally, the annual CSCC incidence rate has been estimated at 0.18 and 0.08 per 100 000 for males and females, respectively.[3] However, there is considerable global variation, with estimates as high as 3.4 per 100 000 from sub-Saharan Africa (SSA),[3] largely attributable to regional variations in human immunodeficiency virus (HIV) prevalence, which has been associated with an eightfold increase in the risk of OSSN.[4]

CSCC is locally and regionally invasive and, left untreated, may lead to significant visual morbidity, disfigurement and even death.[5] The costs associated with the management of OSSN can be substantial, particularly in resource-limited settings, and it therefore represents an important public health consideration in areas of high HIV prevalence.[6,7] Estimates of CSCC incidence are vital for the provision and planning of healthcare services, especially in the context of an evolving HIV pandemic and advances in antiretroviral therapy (ART).

South Africa is a middle-income country with a diverse, multi-racial population of approximately 60 million.[8] It is home to the largest HIV seropositive population in the world and is one of only a few African nations with a representative national cancer registry system.[9,10] Using a combination of nationwide data sources, we investigated the incidence and epidemiology of CSCC in South Africa over a 25-year period (1994–2018), with particular reference to the HIV epidemic.

METHODS

Data sources

Data on incident cases of CSCC were obtained from the South African National Cancer Registry (NCR), a division of the National Health Laboratory Service. Established in 1986, the NCR is a pathology-based cancer registry covering nearly all public and private healthcare laboratories in South Africa. Since 2011, legislation has formally established the NCR as South Africa's main cancer surveillance agency, with obligatory reporting of all cytologically and histologically diagnosed invasive malignancies. Full details of the history and objectives of the NCR can be found elsewhere.[9,11] All NCR cancer registration methodology is based on recommendations made by the International Agency for Research on Cancer (IARC).[12]

Briefly, demographic and tumour information are extracted from all submitted pathology reports and only anonymised data are made available to external researchers. Demographic details include age, sex and ethnicity (Black, White, Coloured [mixed race] and Asian/Indian), in keeping with the classification used for the South African national census. Missing ethnicity data is allocated using a hot-deck imputation method based on known surname-ethnicity pairings, but does not always succeed in allocating this information. The International Classification of Diseases for Oncology Version 3 (ICD-O3) is used to code cancer topographies and morphologies, but exclude information on tumour clinical grade or stage. The entire dataset from inception is reviewed for duplicates to ensure only incident cancer cases are retained.

This analysis utilised NCR data from 1994 (the first year of democracy and unsegregated access to healthcare in South Africa) to 2018 (the latest data available at the time of analysis).

Mid-year population estimates for the study period (stratified by age, sex, and ethnicity) were obtained from published Statistics South Africa (SSA) reports (https://www.statssa.gov.za). SSA is South Africa's national statistical services agency and the country's official source of demographic, economic, and social census data.

Detailed estimates of national HIV prevalence and ART uptake were obtained from published Thembisa Project reports (https://www.thembisa.org). The Thembisa Project is a mathematical model of the South African HIV epidemic, designed to answer policy questions relating to HIV prevention and treatment.[13] It is also acts as a projection model and source of demographic statistics and, since 2017, is the source on which official Joint United Nations Programme on HIV/AIDS (UNAIDS) estimates for South Africa are based.

Case definition

In keeping with previous pathology-based studies,[14] we defined cases of CSCC according to ICD-O3 codes as:

- Topography 69.0 (conjunctiva), plus Morphology 8050–8084 (squamous cell carcinomas) or 8000–8041 (tumours, not otherwise specified);
- Topography 69.9 (eye, not otherwise specified), plus Morphology 8050–8084 (squamous cell carcinomas).

This definition therefore includes conjunctival cancers of unspecified cell type and all squamous cell carcinomas of the eye, allowing for the inclusion of advanced CSCC cases in which the primary anatomical site could not be identified as the conjunctiva.

Statistical analysis

Incident cases of CSCC were identified and extracted from the NCR database. Frequencies and proportions were calculated according to age, sex and ethnicity. Age at diagnosis was expressed as mean (standard deviation, SD) and compared across groups with a two-sample *t*-test (for sex) or pairwise comparison of means (for ethnicity).

For descriptive purposes, the overall study period was divided into five 5-year time periods: 1994–1998, 1999–2003, 2004–2008, 2009–2013 and 2014–2018. Annual crude age-specific incidence rates with 95% confidence intervals (CIs) were calculated using mid-year population estimates as the denominators for each 5-year age group. In order to account for known differences in the age structure of the population over time, and to allow for meaningful comparisons across population sub-groups, direct age-standardised incidence rates (ASIRs) were then calculated.[15] In keeping with IARC recommendations, the Segi World Standard was used as the reference population, allowing for the comparison of cancer incidence rates across different countries.[12,16] Incidence rates were further stratified and compared by sex and ethnicity. When calculating age-, sex- and ethnicity-specific incidence rates, the pro rata method of allocating cancers was used to handle missing demographic data.[12] This method allocates cancers proportionately according to the observed frequency of missing demographic parameters in the remaining dataset.

To assess ecological correlations, we plotted national HIV and ART related frequency estimates (from the Thembisa Project) together with confirmed CSCC cases (from the NCR) for each year of the study period and calculated the Pearson correlation coefficient (r). Since CSCC is a relatively rare cancer, we used 3-year moving averages to smooth year-on-year variability and aid visual assessment of long-term annual trends, as is commonly performed.[17]

Incidence rate ratios and comparative incidence figures (the ratio of two ASIRs) were calculated as measures of relative risk (RR).[15]

All incidence rates are expressed as cases per 100 000 persons with 95% CIs. Analyses were conducted using Microsoft Excel (Microsoft Corp. 2019. Redmond, WA, USA) and Stata (Version 17.0. StataCorp LLC. 2021. College Station, TX, USA). Trend analysis was performed using Joinpoint Regression Program (Version 4.9.0.0. Statistical Methodology and Applications Branch, Surveillance Research Program, National Cancer Institute. 2021. Bethesda, MD, USA),[18] assuming logarithmic trends and uncorrelated standard errors.

Ethical considerations

This study was conducted using anonymised participant data and population statistics freely available in the public domain. The research adhered to the tenets of the Declaration of Helsinki and ethical approval was granted by the Health Sciences Research Ethics Committee, University of the Free State (UFS-HSD2020/0611/2605-0001).

RESULTS

Newly registered cases

Between 1994 and 2018, a total of 9 016 cases of CSCC were reported to the NCR, ranging from 64 cases in 1994 to 651 cases in 2010. A majority of reported cases occurred in females (n=5 105, 56.6%) and Black individuals (n=7 823, 86.8%). Overall, the mean age at diagnosis was 41.5 years, although this differed significantly by sex (female: 39.9 years; male: 43.5 years; $P<0.001$) and ethnicity (White: 55.0 years; compared to Black: 40.4 years; Coloured: 43.8 years; Asian/Indian: 41.1 years; $P<0.001$ for all). Full details of newly registered cases by age, sex, and ethnicity are available in **Supplementary Table S1**.

Crude incidence rates

Over the study period, age-specific incidence rates exhibited a bimodal distribution with peaks observed at the 40–45 year (2.24 per 100 000) and 80+ year (1.50 per 100 000) age groups. There were significant differences in sex-specific rates according to age group, with higher rates observed in females at younger ages and in males at older ages. The female:male incidence rate ratio decreased from >2.0 in those aged <30 years to <0.5 in those aged ≥75 years (**Figure 1A**). The bimodal age distribution was observed for all ethnicities, although the first peak (40–45 years) was more marked for Black individuals (2.81 per 100 000) while the second peak (80+ years) was more marked for White individuals (1.83 per 100 000) (**Figure 1B**).

Age-standardised incidence rates

The overall ASIR for the study period was 0.78 per 100 000. Sex-specific rates were 0.82 and 0.75 per 100 000 for females and males, respectively (RR 1.10, 95% CI 1.06–1.14). Ethnicity-specific rates were 0.94, 0.37, 0.22 and 0.15 per 100 000 for Black, White, Coloured and Asian/Indian participants, respectively. There was considerable variation in both overall and stratified rates according to time period, with the highest rates observed in 2009–2013 for both sexes and all ethnicities. Full details of overall, sex- and ethnicity-stratified ASIRs by time period and the overall study period are presented in **Tables 1–2**.

Table 1. Number of cases, age-standardised incidence rates and mean age at diagnosis of conjunctival squamous cell carcinoma in South Africa by sex and time period (1994–2018).

Time period	Overall				Female				Male				RR (95% CI)
	Cases	ASIR	95% CI	Age	Cases	ASIR	95% CI	Age	Cases	ASIR	95% CI	Age	
1994–1998	386	0.24	(0.22, 0.26)	51.4	165	0.19	(0.17, 0.22)	50.4	207	0.31	(0.28, 0.34)	52.0	0.63 (0.56, 0.70)
1999–2003	952	0.44	(0.42, 0.47)	40.7	494	0.42	(0.38, 0.46)	39.0	453	0.48	(0.44, 0.51)	41.9	0.89 (0.81, 0.96)
2004–2008	2 303	1.01	(0.97, 1.05)	39.9	1 417	1.16	(1.10, 1.22)	38.3	879	0.86	(0.81, 0.91)	42.2	1.36 (1.25, 1.46)
2009–2013	3 058	1.21	(1.17, 1.26)	40.9	1 813	1.34	(1.28, 1.41)	39.5	1 231	1.09	(1.03, 1.15)	42.9	1.23 (1.12, 1.35)
2014–2018	2 317	0.82	(0.79, 0.85)	42.8	1 216	0.81	(0.76, 0.86)	41.2	1 100	0.85	(0.80, 0.90)	44.3	0.95 (0.87, 1.04)
1994–2018	9 016	0.78	(0.76, 0.80)	41.5	5 105	0.82	(0.80, 0.85)	39.9	3 870	0.75	(0.73, 0.77)	43.5	1.10 (1.06, 1.14)

ASIR, age-standardised incidence rate (Segi World Standard Population); CI, confidence interval; RR, relative risk (female:male ratio).
Figures reported in the 'Age' column represent the mean age of cases at the time of diagnosis.

Table 2. Number of cases, age-standardised incidence rates and mean age at diagnosis of conjunctival squamous cell carcinoma in South Africa by ethnicity and time period (1994–2018).

Time period	Black				White				Coloured				Asian/Indian			
	Cases	ASIR	95% CI	Age	Cases	ASIR	95% CI	Age	Cases	ASIR	95% CI	Age	Cases	ASIR	95% CI	Age
1994–1998	253	0.22	(0.20, 0.25)	46.5	105	0.37	(0.29, 0.47)	61.8	9	0.08	(0.05, 0.11)	61.7	6	0.13	(0.05, 0.24)	43.4
1999–2003	774	0.50	(0.47, 0.53)	38.3	101	0.34	(0.26, 0.43)	53.7	33	0.18	(0.12, 0.24)	41.6	7	0.11	(0.03, 0.22)	37.7
2004–2008	1 985	1.23	(1.18, 1.28)	39.0	115	0.41	(0.32, 0.52)	53.2	60	0.28	(0.21, 0.36)	40.1	10	0.16	(0.07, 0.28)	41.5
2009–2013	2 711	1.51	(1.45, 1.56)	40.3	124	0.44	(0.34, 0.54)	50.4	70	0.30	(0.23, 0.37)	43.7	19	0.25	(0.13, 0.40)	40.6
2014–2018	2 100	0.99	(0.95, 1.03)	41.9	113	0.33	(0.24, 0.43)	57.1	58	0.22	(0.17, 0.29)	46.5	10	0.12	(0.04, 0.22)	42.7
1994–2018	7 823	0.94	(0.92, 0.96)	40.4	558	0.37	(0.33, 0.41)	55.0	230	0.22	(0.19, 0.25)	43.8	52	0.15	(0.11, 0.20)	41.1

ASIR, age-standardised incidence rate (Segi World Standard Population); CI, confidence interval.
Figures reported in the 'Age' column represent the mean age of cases at the time of diagnosis.

Demographic and incidence trends

Mean age at diagnosis demonstrated a marked decline from 51.4 years in 1994–1998 to 39.9 years in 2004–2008 and has shown a steady increase in recent years. This trend is consistent across both sexes and all ethnicities, although absolute values varied (**Tables 1–2**). The female:male incidence ratio has shown a similar trend over the study period with a switch from male predominance (RR 0.63, 95% CI 0.56–0.70) in 1994–1998 to female predominance (RR 1.36, 95% CI 1.25–1.46) in 2004–2008. Thereafter, a similar reversal is noted with a slight male predominance (RR 0.95, 95% CI 0.85–1.04) reached by 2014–2018 (**Table 1**).

Annual CSCC ASIRs demonstrated a similar pattern to the demographic trends described above (**Figure 2)**. Trend analysis identified a significant reversal in national incidence rates in 2009. Between 1994 and 2009, there was an almost six-fold increase in the ASIR of CSCC (from 0.22 to 1.28 per 100 000), representing an annual percentage change (APC) of 15.4%. By 2018, the incidence had declined to 0.56 per 100 000, representing a 56% reduction from 2009, and an APC of -7.8% for this period.

Although all ethnicities experienced the same general trend in the ASIR of CSCC over the 25-year study period, this has been most marked for Black individuals (586% increase between 1994–1998 and 2009–2013) and least marked for White individuals (19% increase between 1994–1998 and 2009–2013) (**Table 2**). Trend analyses stratified by sex and ethnicity are presented in **Supplementary Figures 1–2**.

Relationship to HIV epidemic

Despite rising HIV prevalence, the trend of the annual number of CSCC cases in South Africa closely mirrored that of the estimated number of South African HIV positive individuals not on ART for the same time period (Pearson correlation coefficient, $r = 0.96$), which has also demonstrated a trend reversal and downward trajectory in recent years (**Figure 3**).

DISCUSSION

This study provides histologically-based estimates of CSCC incidence in South Africa from 1994 to 2018, including detailed age-, sex-, and ethnicity-specific rates. Overall, a bimodal age distribution was observed, with younger cases tending to be Black and female, and older cases more likely to be White and male. From 1994 to 2009, there was an almost six-fold increase in the ASIR of CSCC in South Africa. During this period, there was a disproportionate increase in CSCC rates observed in females and Black individuals, accompanied by a decline in the mean age at diagnosis of more than a decade. Importantly, CSCC incidence rates were found to have declined steadily over the last decade, with a corresponding reversal of the demographic trends observed prior to 2009. Additionally, a strong ecological correlation between CSCC incidence and widespread ART provision was observed, providing suggestive evidence for the beneficial effect of ART on HIV-associated cancers on a population level.

Prior to the HIV pandemic, CSCC was typically a rare, slow-growing tumour of elderly males, predominantly related to chronic ultraviolet-radiation (UVR) exposure.[3] This classical pattern of disease persists in most temperate nations, where the reported annual ASIR of CSCC is generally less than 0.1 per 100 000.[3,19-21]

There is strong evidence that HIV represents a major risk factor for CSCC and the onset of the global HIV pandemic resulted in a significant increase in cases and shift in the epidemiological disease profile, especially in countries with a larger burden of disease.[3] In southern and eastern Africa, 6 to 10-fold increases in the ASIR of CSCC were observed, with annual rates as high as 3.5 per 100 000.[22,23]

In contrast to classical descriptions of CSCC which follow a relatively benign clinical course and demonstrate successful therapeutic outcomes, HIV-related CSCC is associated with increased disease severity, local invasion, advanced presentation, a greater likelihood of bilateral disease, poorer prognosis and higher rates of recurrence after treatment.[3,4,6,24] CSCC may also be the presenting feature of HIV-positivity in up to 50% of individuals and is the most common indication for orbital exenteration in many African centres.[3,25-27] It therefore represents a significant public health consideration in areas of high HIV prevalence.

Consistent with previous reports from SSA, we found a relatively young age at presentation and a female predominance. The overall ASIR of 0.78 per 100 000 is lower than previously reported estimates from the region, although this figure is based on a considerably longer time period than previous studies, including an early period of sustained low incidence in the 1990s. Estimates from 2004–2008 and 2009–2013, however, closely resemble previously published figures.[3,14] In keeping with similar regional studies, we observed an almost six-fold increase in the ASIR of CSCC between 1994 and 2009, although this increase occurred significantly later than in Uganda and Zimbabwe.[22,23] Notably, the ASIR of CSCC in South Africa has demonstrated a sustained decline since 2009, a trend not previously reported elsewhere.

In 1994–1998, during the early stages of the South African HIV epidemic, the overall CSCC rate was relatively low and the epidemiological profile resembled that of temperate countries. The subsequent increase in CSCC rates over the following 10–15 years was accompanied by a dramatic shift in this disease profile and corresponded with rising national HIV-seroprevalence.[28] By 2004–2008, age at presentation had dropped by more than a decade with a reversal of the sex ratio; and by 2009–2013, the overall ASIR had increased to 1.21 per 100 000, with the highest rates observed in Black individuals. Young, Black South African women are disproportionately affected by HIV and the trends observed in this study may be driven by the high prevalence of HIV-seropositivity in this population.[24,28] A reversal of all these trends has been noted during the last 5–10 years of the study, corresponding to an overall decline in CSCC incidence rates. Together, these findings highlight the epidemiological transition of CSCC in South Africa over a 25-year period, from a largely outdated classical definition to a predominantly HIV-associated malignancy.

Importantly, the incidence of CSCC in South Africa has shown a steady decline in recent years and was found to be highly correlated with the number of ART-naïve individuals in the country, despite rising national HIV seroprevalence.[28] Given the lack of early evidence for an effect of ART on CSCC incidence, it has been suggested that CSCC rates could be expected to increase in future and that a key research question was whether scale-up of ART in Africa would impact these rates.[3] This study suggests that ART may have significant potential benefits on CSCC rates on a population level. It is important to emphasise, however, that this association is ecological in nature and, while suggestive, may be biased and would need to be explored further using individual-level data.

South African ART treatment guidelines have undergone multiple revisions over the study period,[29] and although this study demonstrates a turning point in 2009, this probably reflects the cumulative contribution of numerous changes rather than a single intervention. It is likely that a threshold minimal proportion of individuals on ART needed to be reached before this decline started. Similar results have been demonstrated for Kaposi sarcoma, another HIV-related cancer, further reinforcing this hypothesis.[30] Ultimately, HIV viral load may prove to be the single best predictor of HIV-associated CSCC risk, with HIV viral suppression shown to be associated with a significant reduction in both AIDS-defining and non-AIDS-defining cancers in a US cohort.[31]

The strengths of this analysis include its long study period, spanning more than two decades and encompassing a significant portion of the HIV epidemic in South Africa. It is also nationally representative and based on histologically-confirmed data from the NCR, the most comprehensive and reliable source of cancer surveillance in the country. Additionally, the size and temporal scope of the study allow for reliable estimates, population stratification and trend analysis. To the best of our knowledge, it represents the largest and longest study of its kind from a single nation to date.

It is important, however, to acknowledge various limitations. Firstly, results from pathology-based registries can only be considered to represent the bare minimum disease burden in a population, since they exclude cases which are diagnosed clinically or radiologically, and our findings are therefore almost certainly an underestimation of true incidence. This may limit comparability to studies with different methodology but may not necessarily affect the internal validity of the trends described.

Secondly, only invasive CSCC cases, which represent the end-stage of the OSSN disease spectrum, are reported to the NCR. While this allows for a well-defined clinical entity based on objective criteria, it also means that our results are biased towards advanced disease. Changes in the management of both HIV and CSCC over the study period, including improved case management, early clinical detection, specialist treatment, and trends towards non-surgical management are all factors which may have shifted the OSSN burden towards earlier disease, thereby contributing to declining CSCC rates independent of ART.[6,7,29] Similarly, improved capacity building and strengthening of the South African healthcare system in general may be contributory factors. However, similar trends have not been demonstrated for non-HIV-related ocular cancers in the same population and over the same time period, suggesting a true decline.[32]

Thirdly, the South African NCR has experienced numerous challenges since its inception, including financial, administrative, record keeping, and reporting difficulties, which may limit the reliability of early data.[9] This may have resulted in a further underestimation of CSCC incidence, especially in the first time period of our study, although it would not account for declining trends observed in recent years. Additionally, the effects of these challenges have been shown to have had a minimal impact on estimates of cancer incidence during our study period.[11]

Lastly, the study is limited by the lack of clinical information attached to each registered CSCC case, most notably HIV status, and any ecological associations noted on a population-level may not necessarily translate to valid individual-level inferences. It would be important for these patterns to be assessed and confirmed with individual-level data before drawing firm conclusions. This may now be possible through a recent nationwide record-linkage project.[33]

The findings of this study may have several important implications for future incidence studies, public health policy, risk communication, and the planning and provision of healthcare services. It demonstrates that demographic profiles and estimates of CSCC incidence in Africa are highly variable and may be largely related to an evolving HIV epidemic. These factors should be considered when performing meta-analyses or comparing CSCC incidence figures from different countries or time periods. Additionally, it provides suggestive evidence for a beneficial effect of ART on the risk of HIV-related cancers. This may result in a reduction in healthcare costs and resource allocation associated with the management of CSCC in future, especially with improvements in national HIV treatment programs.

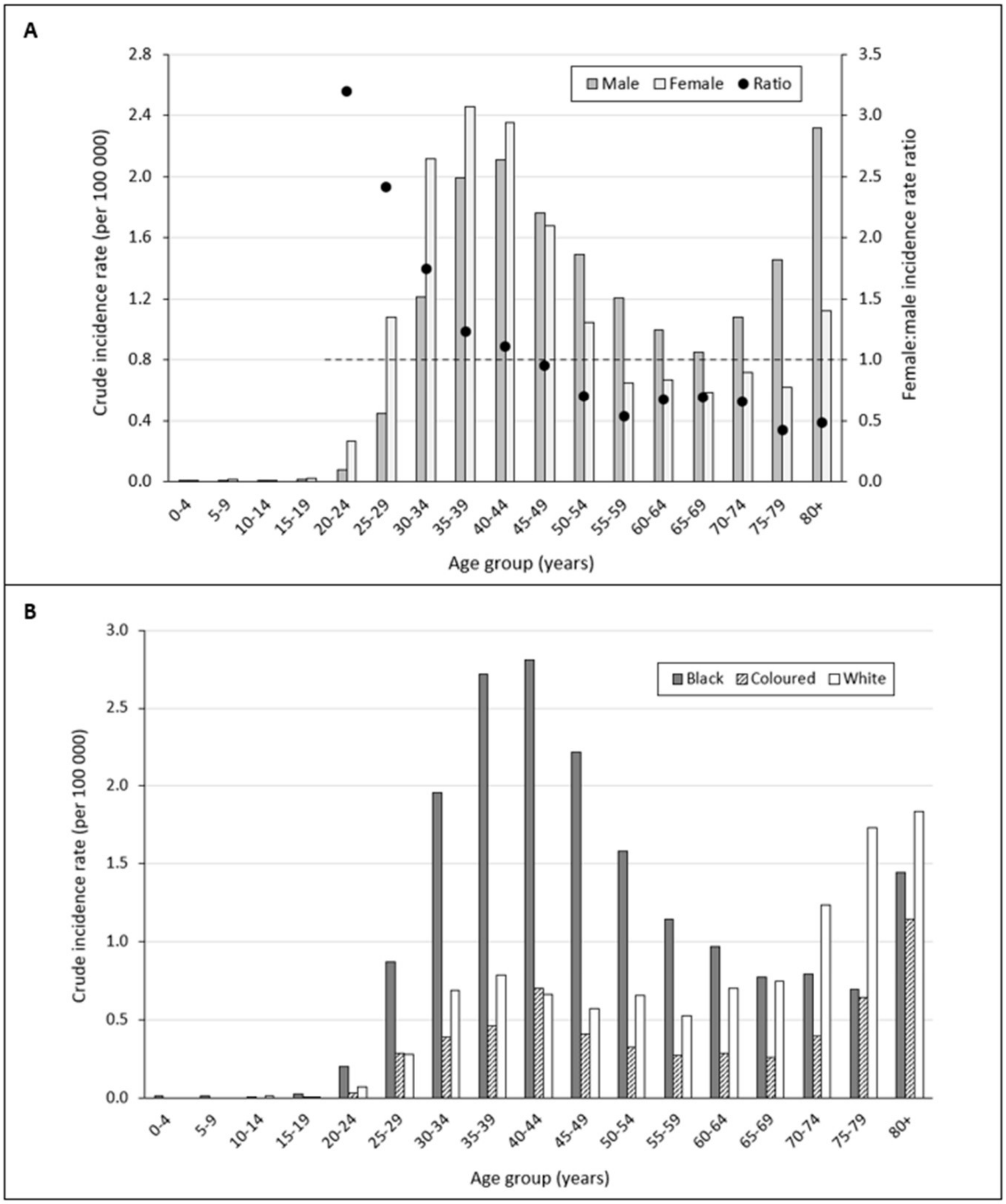
Future research will need to confirm the results of this study, especially as ART coverage continues to expand and South Africa moves towards achieving the UNAIDS 90-90-90 treatment targets.[10,28] Consideration should also be given to further investigation into the effect of ART on CSCC incidence through individual-level data or record-linkage studies, with a particular focus on the effect of HIV viral load suppression.

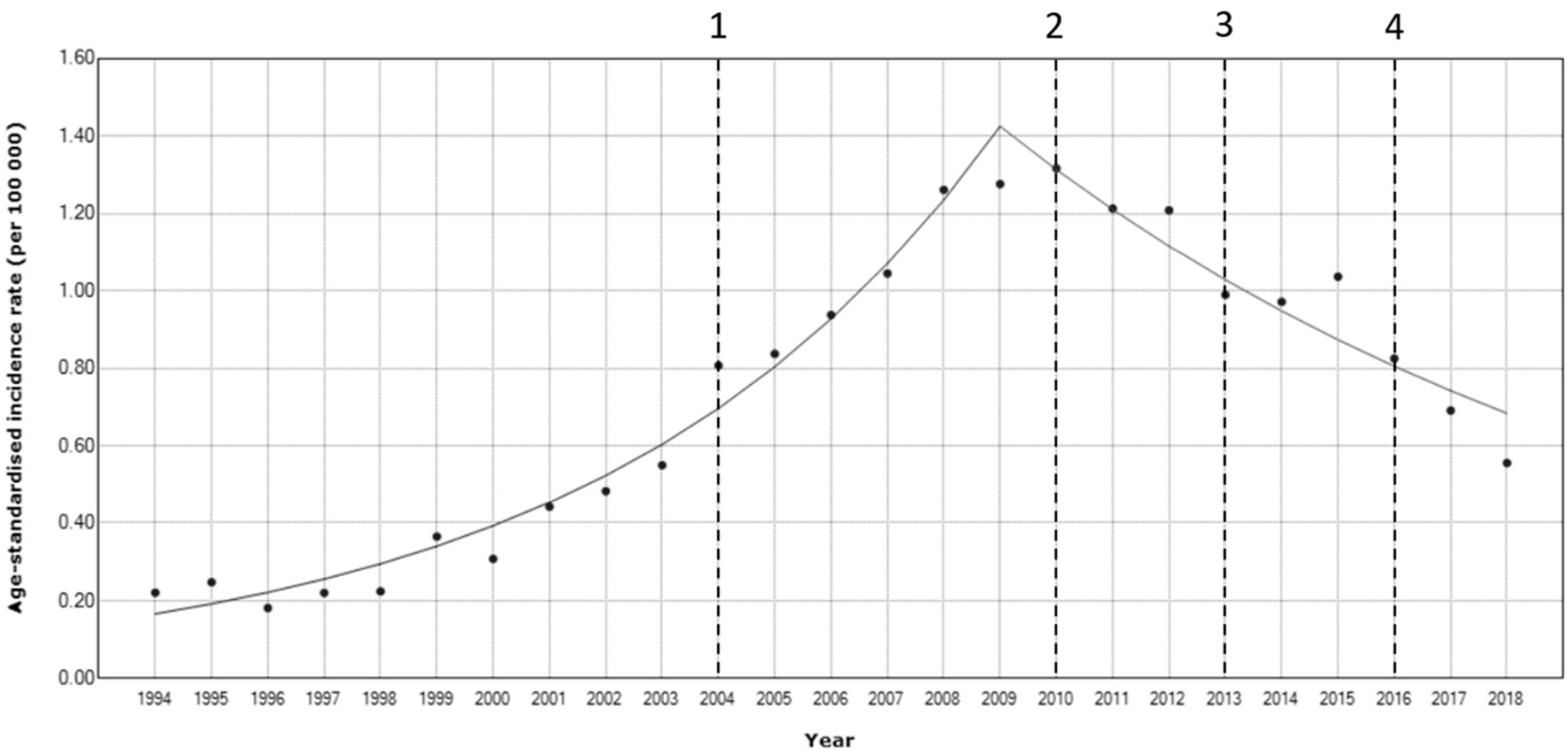
FIGURE LEGENDS

Figure 1. Crude incidence rates of conjunctival squamous cell carcinoma in South Africa (1994–2018) by **A)** age and sex, and **B)** age and ethnicity.
[Incidence rate ratios for ages <20 years and incidence rates for Asian/Indian individuals not displayed due to small case numbers. The dotted horizontal line represents a female:male incidence rate ratio of 1.]

Figure 2. Trend analysis of the age-standardised incidence rate of conjunctival squamous cell carcinoma in South Africa (1994–2018).
[Vertical dashed lines indicate significant changes in the South African national antiretroviral therapy (ART) guidelines: (1) ART was first introduced in 2004 to those with a CD4 count <200 or World Health Organisation (WHO) clinical stage III/IV disease. (2) In 2010, the guidelines were expanded to include individuals with HIV/TB co-infection and pregnant women with a CD4 count <350. (3) In 2013, all individuals with a CD4 count <350 were eligible for ART. (4) Universal ART for all HIV-positive individuals, regardless of CD4 count, was introduced in 2016.]

Figure 3. Comparison of annual number of conjunctival squamous cell carcinoma cases, estimated total number of HIV-positive individuals, and estimated number of HIV-positive individuals not on ART (3-year moving averages) in South Africa (1994–2018).
[ART, antiretroviral therapy; HIV, human immunodeficiency virus; CSCC, conjunctival squamous cell carcinoma.]


A
Male
Female
Ratio
Crude incidence rate (per 100 000)
Female:male incidence rate ratio
0-4
5-9
10-14
15-19
20-24
25-29
30-34
35-39
40-44
45-49
50-54
55-59
60-64
65-69
70-74
75-79
80+
Age group (years)
B
Black
Coloured
White
Crude incidence rate (per 100 000)
Age group (years)



1
2
3
4
Age-standardised incidence rate (per 100 000)
1.60
1.40
1.20
1.00
0.80
0.60
0.40
0.20
0.00
1994
1995
1996
1997
1998
1999
2000
2001
2002
2003
2004
2005
2006
2007
2008
2009
2010
2011
2012
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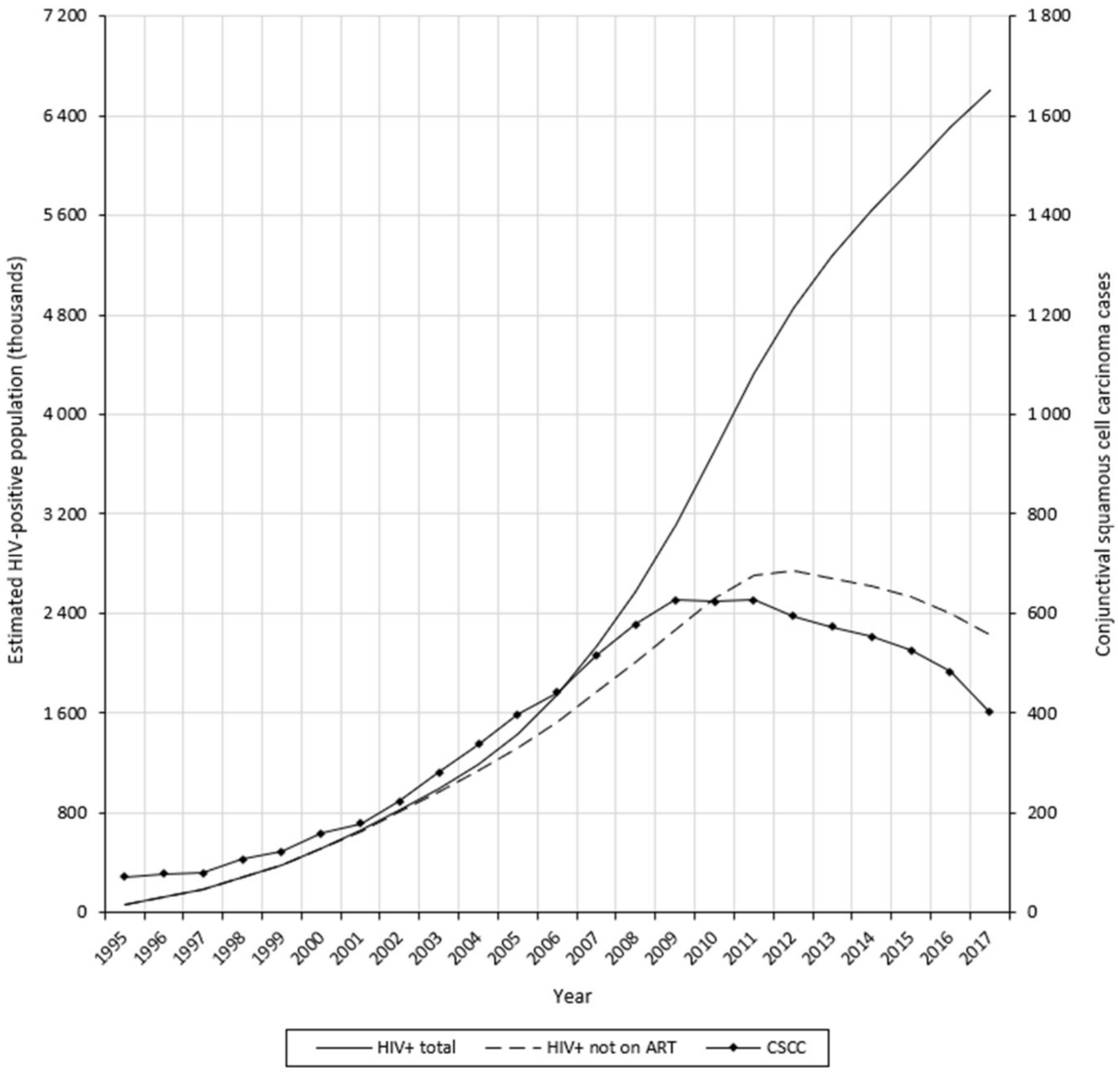
2014
2015
2016
2017
2018
Year



7 200
6 400
5 600
4 800
4 000
3 200
2 400
1 600
800
0
Estimated HIV-positive population (thousands)
1 800
1 600
1 400
1 200
1 000
800
600
400
200
0
Conjunctival squamous cell carcinoma cases
1995
1996
1997
1998
1999
2000
2001
2002
2003
2004
2005
2006
2007
2008
2009
2010
2011
2012
2013
2014
2015
2016
2017
Year
HIV+ total
HIV+ not on ART
CSCC

Supplementary Table S1. Newly registered cases of conjunctival squamous cell carcinoma in South Africa by age, sex and ethnicity (1994–2018)

Age group (years)	Female					Male					Unknown	TOTAL
	B	W	C	A	U	B	W	C	A	U		
0–9	15	0	0	0	0	11	0	0	0	0	1	27
10–19	21	1	0	0	1	11	0	0	0	0	0	34
20–29	670	11	23	1	28	248	14	5	4	12	4	1 020
30–39	1 852	54	40	15	79	1 203	51	29	7	54	9	3 393
40–49	1 177	46	29	5	43	990	50	43	8	43	6	2 440
50–59	339	25	7	1	17	414	61	18	7	24	4	917
60–69	155	28	6	0	5	150	51	7	0	7	3	412
70–79	74	29	3	2	4	51	64	6	1	5	1	240
80+	46	22	1	0	2	30	29	6	0	2	1	139
Unknown	203	7	3	1	14	133	11	2	0	8	12	394
TOTAL	4 552	223	112	25	193	3 241	331	116	27	155	41	9 016

Abbreviations: B, Black; W, White; C, Coloured; A, Asian/Indian; U, Unknown.

STATEMENTS

Publication:

This submission has not been published anywhere previously and it is not simultaneously being considered for any other publication.

Meeting presentation:

This paper was presented in part at the 38th World Ophthalmology Conference (WOC 2022), 9–12 September 2022, China (virtual), and the 18th International Conference on Malignancies in HIV/AIDS (ICMH 2022), 24–26 September 2022, National Cancer Institute, National Institutes of Health, Bethesda, MD, USA (virtual).

Financial support:

KVS is in receipt of a UCL Overseas Research Scholarship and is supported by grants from Fight for Sight (London) (1956A) and The Desmond Foundation (unrestricted).

Competing interests:

None of the authors have any proprietary interests or conflicts of interest related to this submission.

Contributorship:

KS and DS were responsible for the conception and design of the work. KS, DS and MM were responsible for data acquisition. KS, DS and AL were responsible for data analysis, with input from RH and MM. KS was responsible for drafting the work, with input from all authors. All authors were responsible for critically revising the work and providing final approval. All authors agree to be accountable for all aspects of the work.

Data availability:

National Cancer Registry data supporting the findings of this study are available on request from the South African NCR (https://www.nicd.ac.za/centres/national-cancer-registry/). Population statistics were derived from published Statistics South Africa reports (https://www.statssa.gov.za). HIV and ART data were derived from published Thembisa Project reports (https://thembisa.org).

Abbreviations and acronyms:

AIDS, acquired immunodeficiency syndrome; ART, antiretroviral therapy; ASIR; age-standardised incidence rate; CI, confidence interval; CSCC, conjunctival squamous cell carcinoma; HIV, human immunodeficiency virus; NCR, National Cancer Registry; OSSN, ocular surface squamous neoplasia; RR, relative risk; SSA, Statistics South Africa; UNAIDS, Joint United Nations Programme on HIV/AIDS.

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