



## Patterns and trends of HPV-related cancers other than cervix in South Africa from 1994–2013



Admire Chikandiwa<sup>a,\*</sup>, Pedro T. Pisa<sup>a</sup>, Mazvita Sengayi<sup>b,c</sup>, Elvira Singh<sup>b,c</sup>,  
Sinead Delany-Moretlwe<sup>a</sup>

<sup>a</sup> Wits Reproductive Health and HIV Institute, Faculty of Health Sciences, University of the Witwatersrand, 22 Esselen Street, Hillbrow, Johannesburg, 2001, South Africa

<sup>b</sup> National Cancer Registry, National Health Laboratory Service, 1 Modderfontein Rd, Sandringham, Johannesburg, 2192, South Africa

<sup>c</sup> School of Public Health, University of Witwatersrand, 27 St Andrews Road Parktown, Johannesburg, 2193, South Africa

### ARTICLE INFO

#### Keywords:

Anogenital  
Head and neck  
HPV-related  
Cancer  
Incidence  
Mortality  
South Africa

### ABSTRACT

**Background:** HPV infection causes several cancers which include cervical, vaginal, vulval, penile and oropharyngeal cancer (OPC). Understanding the burden of HPV-related cancers is important for guiding cancer prevention and treatment interventions.

**Methods:** To inform policy, we analysed trends of age-standardised incidence (ASIR) and mortality (ASMR) rates for HPV-related head and neck (HNC) and anogenital cancers (AGC) in South Africa between 1994 and 2013.

**Results:** A total of 1 028 330 incident cancers and 617 044 cancer-related deaths were reported during the study period. The overall ASIR (-5.5%) and ASMR (-2.2%) for HNC declined, in part related to the anti-smoking legislation. In contrast, incidence (2.9%) and mortality (0.8%) rates for AGC increased with the rising HIV prevalence. ASIR for oral cavity cancer (OCC: -6.3%) and laryngeal cancer (LC: -11.3%) declined, including mortality associated with these cancers (OCC: -1.9%, and LC: -2.6%). However, oropharyngeal cancer showed a slower rate of decline in ASIR (-4.4%) and ASMR did not change. Compared to women, ASIR and ASMR for HNC were 3-fold higher among men. ASIR for both anal (7.5%) and vulval cancer (16.1%) increased. Median age at diagnosis of vulval cancer declined by 18 years (p-value = 0.01). Mortality rates for anal (3.9%) and vulval (2.6%) cancer increased. ASIR (-3.2%) and ASMR (-2.0%) for penile cancer declined. Rates for vaginal cancer did not change.

**Conclusions:** Anal and vulval cancers have increased over the reporting period. There is need to continuously monitor trends of these cancers. Implementation of HPV vaccination could significantly reduce the burden of HPV-related cancers.

### 1. Introduction

The overall incidence of head and neck cancers (HNC) has declined in recent years in high income countries (HIC) [1]. A closer analysis has shown two patterns: an increasing trend for HPV-related HNC that mainly arise from base of the tongue, tonsils and other oropharynx (oropharyngeal cancer [OPC]) and a declining trend for HNC from other oral sites (oral cavity cancer [OCC]) and laryngeal cancers (LC). For instance, the population-level incidence of HPV-positive OPC in the US increased by more than 200% between 1998 (0.8 per 100 000) and 2004 (2.6 per 100 000) [2]. The declining trend for OCC and LC is

consistent with the decrease in tobacco use which is a strong risk factor for these cancers [1,3,4]. Similarly, reports from HIC show increases in incidence of anal cancer [5,6]. Anal cancer incidence is estimated to be 70 per 100 000 among people living with HIV (PLHIV), but increases to 131 per 100 000 among men who have sex with men [6,7].

HPV infection is a known risk factor for OPC and anogenital cancers (AGC) including: anal, cervix, penile, vulvar and vaginal [8]. The rising OPC and anal cancer incidence may be attributable to increases in HPV prevalence associated with changes in oral and anal sex practices over time respectively [2,7]. Whilst HPV is responsible for almost all cases of cervical cancer, it is important to note that the population attributable

**Abbreviations:** AGC, anogenital cancer; APC, annual percentage change; ASIR, age standardised incidence rate; ASMR, age standardised mortality rate; HIC, high income countries; HNC, head and neck cancer; HPV, human papillomavirus; ICD-03, International Classification of Diseases for Oncology Version 3; ICD10, 10th revision of the international Classification of Disease and related health problems; LC, laryngeal cancer; LMIC, low to middle income countries; NCR, national cancer registry; OCC, oral cavity cancer; OPC, oropharyngeal cancer; SA, South Africa; Stats SA, Statistics South Africa; SILs, squamous intra-epithelial lesions

\* Corresponding author.

E-mail address: [achikandiwa@wrhi.ac.za](mailto:achikandiwa@wrhi.ac.za) (A. Chikandiwa).

<https://doi.org/10.1016/j.canep.2018.12.004>

Received 25 July 2018; Received in revised form 21 October 2018; Accepted 6 December 2018

Available online 15 December 2018

1877-7821/ © 2018 The Authors. Published by Elsevier Ltd. This is an open access article under the CC BY-NC-ND license

(<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

fraction (PAF) for the other HPV-related anogenital cancers varies [9]. The PAF for OPC, anal, penile, vulvar and vaginal cancers are estimated to be 31%, 88%, 50%, 25% and 78% respectively [8]. Other important risk factors for these cancers are smoking, alcohol, older age as well as phimosis and poor hygiene for penile cancer [4,10–12].

HIV increases the risk of HPV infection, persistence and progression to pre-neoplastic lesions [13–15]. While excess mortality associated with these cancers has not been uniformly observed in regions of high HIV prevalence [16], this can be explained by premature death from more acute causes in the absence of highly effective antiretroviral therapy (ART) early on in the epidemic [14]. With expanding access to ART we may see an increase in HPV-related cancer in countries with high HIV prevalence like South Africa, as life expectancy improves and progression to invasive cancers occurs [7,17].

There are fewer data on trends of HPV-related cancers in low and middle income countries (LMIC), particularly in sub-Saharan Africa [8]. This may be attributed to poor cancer surveillance and absence of high quality cancer registries in the region [18]. It is important to understand the patterns of HNC and AGC in South Africa over the past two decades. This period covers the transition to democracy and increasing access to health care for all race groups [19]. It was also when HIV incidence began to rise prior to widespread ART access. In addition during this period, strong anti-tobacco legislation was implemented with the goal of reducing disease burden linked to tobacco use [20]. In the absence of comprehensive population based cancer registry data, we used the pathology based cancer registry data to understand the patterns and trends of HPV-related cancers. Despite the limitations, pathology-based registries can yield very useful insights, providing the results are interpreted with due care as to its inherent biases [21]. We evaluated burden of HPV-related cancers other than cervix from 1994 through to 2013. We present trends in incidence and mortality rates stratified by age groups, gender and ethnicity.

## 2. Methods

### 2.1. Data sources

Sources of data were the South African National Cancer Registry (NCR) pathology-based cancer incidence reports for 1994 to 2012 and mortality reports from Statistics South Africa (Stats SA) for 1997 to 2013.

### 2.2. South African NCR methodology

The NCR is a pathology-based cancer registry. It records all laboratory diagnosed cancers from private and public healthcare laboratories in SA. The methodology of the NCR has been described previously [22]. In short, the data which include patient demographics and tumour characteristics are extracted from pathology reports. An imputation imputation is used to impute missing data on population group. [23]. The cancer cases are coded according to the International Classification of Diseases for Oncology Version 3 (ICD-O3) morphology and topography classifications [24]. An analysis has been done on the repeatability of manual coding and it has been shown to be high and within the acceptable standards [25]. From 2005 to 2010, private health laboratories withheld cancer reports owing to concerns regarding voluntary sharing of patient data. However this represented a minimal impact on overall cancer reporting, with a net decrease of less than 4% [26]. Since 2011, Regulations relating to cancer registration have ensured that reporting is more complete.

### 2.3. Stats SA methodology

Stats SA collects and disseminates statistics on the causes of death in SA using the International Statistical Classification of Diseases and Related Health Problems (ICD-10) [27]. A cancer death was defined as

any death where a cancer was recorded as the main or underlying cause of death.

### 2.4. Data analysis

The head and neck cancers (HNC) were divided into three main groups, using a classification adapted from Lam et al. [28], which were namely: OPC [*base of the tongue (C01.9), soft palate (C05.1), tonsil (C02.4; C09.0–C9.9), uvula (C05.2), oropharynx (C10.0–C10.9), Waldeyer's ring (C14.2)*]; Oral cavity cancer (OCC) [*anterior two thirds of the tongue (C02.0–3, C02.5–9), lip (C0.0–C0.9), gum (C03.0–C03.9), floor of the mouth (C04.0–C04.9), hard palate (C05.0), palate unspecified (C05.9), other oral cavity (C06.0–C06.9), pharynx not otherwise specified (14.0), overlapping lesion of the lip, oral cavity, pharynx (14.8)*]; and Laryngeal cancer (LC) [*glottis (C32.0), supraglottis (C32.1), subglottis (C32.2), laryngeal cartilage (C32.3), other larynx not specified (C32.9) and hypopharynx cases (C13) including the pyriform sinus (C12.9)*]. Anogenital cancers (AGC) were classified as *anal (C21), penile (C60), vulval (51) and vaginal (C52)*.

Age-standardised incidence rates were computed from the NCR reports from 1994 to 2012 using the direct method which allows for comparison of results across populations. Since the HNC cases were far higher in males than in females, ASIRs were also reported by population groups for men. The population groups include Black, White, Coloured and Asian/Indian. Age specific incidence rates were calculated using Stats SA mid-year population denominators for five or 10-year age categories for 4 periods viz: 1994–1998, 1999–2003, 2004–2008 and 2009–2012. The direct method of standardisation (Segi World Standard Population) was employed to calculate age-standardised mortality rates (ASMR) using the Stats SA mid-year population estimates as denominators. Sensitivity analyses were done by incorporating external data on the trends in smoking and antenatal HIV prevalence to determine if these would explain the observed trends in cancer incidence.

Annual percentage change (APC) was calculated to assess the ASIR and ASMR trends of the cancers using the linear regression:  $\log(\text{rate}_y) = b_0 + b_1y$  with  $\log(\text{rate}_y)$  being the natural log of incidence/mortality rate in year  $y$  as described previously [29]. The APCs and  $p$ -values were calculated using the formula:  $(e^{b_1} - 1) \times 100$  from the Joinpoint Regression Program, version 4.3.1.0 to quantify the magnitude of changes in cancer incidence and mortality trends over time [30]. A  $p$ -value  $< 0.05$  indicates a significant change in trend.

## 3. Ethics

The NCR was granted an ethics waiver (Number: W-AW\_220909-2) by the University of Witwatersrand Human Research Ethics Committee (Wits HREC) for research performed on its surveillance data. The current study was approved by Wits HREC (Reference: M160859).

## 4. Results

### 4.1. Incidence

During the period 1994 to 2012, a total of 1 028 330 cancers were reported to the NCR. Of these, 38 035 (3.7%) were HNC with OPC reflecting the greatest contribution (1.5%) followed by OCC (1.1%) and LC (1.0%). AGC as a group contributed 0.9% of the cases (Table 1). The overall ASIR trend for HNC combined showed three distinct phases: an initial non-significant rise from 1994 to 1996 (APC = 13.1%;  $p$ -value = 0.1), followed by a longer significant decline in incidence from 1996 to 2005 (APC = -5.5%;  $p$ -value = 0.01), and a subsequent small non-significant increase (APC = 1.1%;  $p$ -value = 0.3), from 2005 until 2012. Though the incidence of AGC is 5–8 fold lower than HNC, it increased significantly (APC = 2.9%,  $p$ -value = 0.01) over the reporting period (Fig. 1a). The rise in AGC incidence is exponentially related to the increase in HIV prevalence with an R-squared value of 0.49

**Table 1**  
Incident and mortality cases for HNC and AGC cancers.

Year	Incidence					Mortality				
	All HNCs	All AGCs	OPC	OCC	LC	All HNCs	All AGCs	OPC	OCC	LC
1994	1704	287	690	531	483	–	–	–	–	–
1995	1976	314	821	564	591	–	–	–	–	–
1996	2205	278	847	707	651	–	–	–	–	–
1997	2195	302	842	658	695	1138	121	125	505	430
1998	2219	310	844	678	697	1139	129	115	529	411
1999	2111	523	833	597	681	1194	132	122	546	437
2000	1986	575	793	563	630	1137	149	106	537	421
2001	2090	576	877	597	616	1205	154	143	549	415
2002	2019	519	846	626	547	1229	167	144	535	444
2003	1869	534	799	547	523	1230	156	131	582	406
2004	1849	555	769	538	542	1264	183	121	631	443
2005	1797	507	772	547	478	1255	187	133	636	415
2006	1950	496	839	576	535	1193	194	152	590	380
2007	1901	577	797	581	523	1113	195	135	539	375
2008	1953	630	794	591	568	1167	215	137	523	427
2009	1966	628	835	566	565	1178	202	169	525	391
2010	2041	725	793	626	622	1192	231	165	557	386
2011	1981	762	835	588	558	1204	237	160	546	412
2012	2223	845	997	653	573	1266	240	163	577	443
2013	–	–	–	–	–	1201	241	179	556	385
Totals	38035	9943	15623	11334	11078	20305	3133	2400	9463	7021

HNC: Head and neck cancer; AGC: Anogenital cancer, OPC: Oropharyngeal cancer, OCC: Oral Cavity Cancer and LC: Laryngeal cancer.

(Supplementary Fig. 1).

The ASIR trends for the three individual HNC mirror the overall trend of HNC as a group with relatively slower decline for OPC (APC 1996–2005 = -4.4%,  $p$ -value = 0.01) compared to OCC (APC 1996–2004 = -6.3%,  $p$ -value = 0.01) or LC (APC 1999–2003 = -11.3%,  $p$ -value = 0.01; Fig. 1b).

The individual AGC show different patterns with an increase for anal cancer (APC 2005–2012 = 7.5%,  $p$ -value = 0.01) and vulval cancer (APC 1994–2012 = 16.1%,  $p$ -value = 0.01). The median age at diagnosis of vulval cancer has declined by 18 years (from 64 years in 1994 to 46 years in 2012,  $p$ -value = 0.01). Age specific incidence rates for vulval cancer have increased among women younger than 50 years (e.g. 0.1 in the 1994–1998 period vs 1.7 per 100 000 in the 2009–2012 period among women aged 30–39) (Supplementary Fig. 2). There was a decline in incidence of penile cancer (APC 1994–2012 = -3.2%,  $p$ -value = 0.01) and no significant change for vaginal cancer (APC 1994–2012 = 2.3%,  $p$ -value = 0.6; Fig. 1c).

HNC incidence is 3–5 fold higher among men compared to women. Among men, all three HNC declined with a pattern similar to that for each individual HNC showing a slower decline for OPC (APC 1996–2005 = -4.6% vs. APC 1996–2004 = -6.8% for OCC and APC 1997–2003 = -9.1% for LC). Results from sensitivity analysis suggest that the declining trends in HNC among men are largely related to decline in smoking prevalence among men (Supplementary Fig. 3a). In contrast, there was no significant change in HNC incidence among women and this trend also mirrors the prevalence of smoking among women which has been static (Fig. 2a & b; Supplementary Fig. 3b). Among men, the median age at diagnosis for OPC (range 55–58 years) was 4 years earlier than for LC (range 59–61 years). However, anal cancer ASIR increased in both men (APC = 6.6%,  $p$  = 0.01) and women (APC = 7.2%,  $p$  = 0.01) between 2006 and 2012 (Fig. 2a & b).

Further analysis show that, among men, the ASIRs for all the HNC were highest among Coloured males followed by White males, Black males and Asian males. ASIRs for Black males, show a sharp increase 2–4 years after 1994 and the overall incidence did not decline significantly thereafter for the three HNC. Rates for White males decreased significantly for all the three HNC (OPC: APC 1994–2006 = -3.1%;  $p$ -value = 0.01; OCC: APC 1994–2012 = -2.2%;  $p$ -value = 0.01 and LC: APC 1994–2006 = -4.9%;  $p$ -value = 0.01). No clear inferences on trends could be made for Asian males due to smaller numbers (Supplementary

Fig. 4 a–c).

#### 4.2. Mortality

Of the total 617 044 cancer-related deaths reported during the 1997 to 2013 period, 20 305 (3.3%) were attributable to HNC. The greatest number of deaths were from OCC (1.5%) or LC (1.4%) with fewer deaths observed for OPC (0.4%). AGC combined contributed slightly more deaths (0.5%) than OPC alone (Table 1). The overall ASMR for the HNC declined by 2.2% (1997–2013;  $p$ -value = 0.01). However the rate plateaued at 3 per 100 000 from 2007 until 2013. AGC had a modest increase (APC 1997–2013 = 0.8%,  $p$ -value = 0.01) but the absolute rate is low (Fig. 3a). Mortality rates for OPC were 4-fold lower than OCC or LC and did not change during the reporting period. OCC (APC 1997–2013 = -1.9%,  $p$ -value = 0.01) and LC (APC 1997–2013 = -2.6%,  $p$ -value = 0.01) rates declined (Fig. 3b). Anal cancer (APC 1997–2013 = 3.9%,  $p$ -value = 0.01) and vulval cancer (APC 1997–2013 = 2.6%,  $p$ -value = 0.01) rates increased whilst those of penile cancer declined (APC 1997–2013 = -2.0%,  $p$ -value = 0.01). Mortality rates for vaginal cancer did not change (Fig. 3c).

There were gender differences in mortality rates. The ASMR among males for all the three categories of HNC was 2–6 fold higher compared to that of females. Among males, mortality rates for OCC (APC 1997–2013 = -5.6%,  $p$ -value = 0.01) and LC (APC = 1997–2013 = -2.6%,  $p$ -value = 0.01) declined whilst the rates for OPC were static (APC 1997–2013 = 0.2%,  $p$ -value = 0.7). For females, the ASMR for LC (APC 1997–2013 = -3.2%,  $p$ -value = 0.01) declined but those for OPC and OCC did not change. The mortality rates for anal cancer increased among females (APC 1997–2013 = 5.9%,  $p$ -value = 0.01) but not for males (APC 1997–2013 = 2.2%,  $p$ -value = 0.1) (Fig. 4a & b).

The ASMR for all the three HNC were highest among Coloured males followed by Black males, White males and Asian males. Black men had an initial decline from higher rates in the 1997–1999 period, however the rates did not change significantly after 2003 for all the 3 HNC. White men had lower mortality than Black men (despite having higher incidence). The rates amongst White men have declined for OCC (APC 2005–2013 = -4.2%,  $p$ -value = 0.01) and LC (APC 2000–2013 = -2.0%,  $p$ -value = 0.01) but not for OPC (APC 1997–2013 = 0.1%,  $p$ -value = 0.01). Mortality rates for Asian males were difficult to interpret due to small numbers (Supplementary Figure 5 a–c).

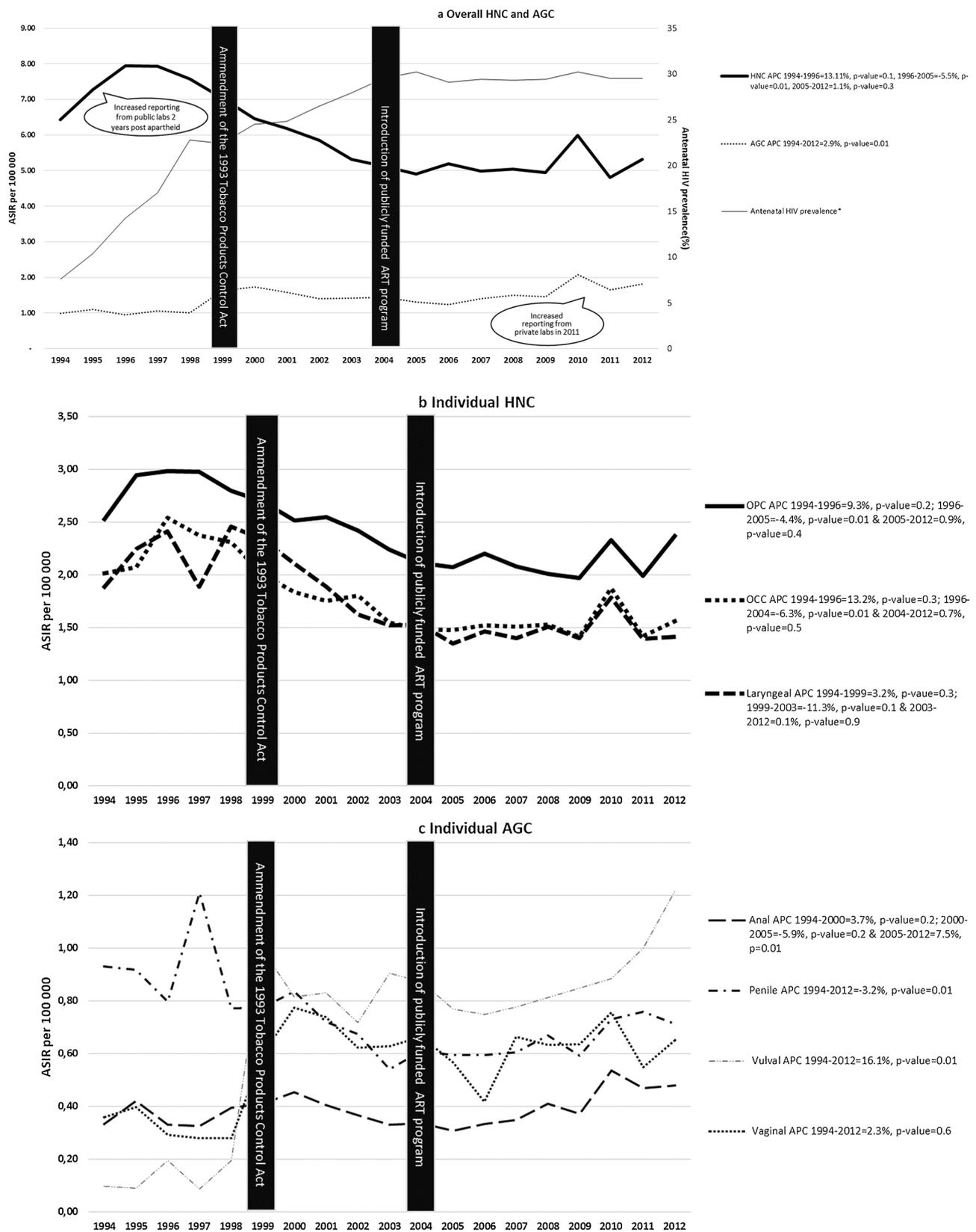


Fig. 1. Age Standardised Incidence Rates (ASIR) between 1994 and 2012. (a) Overall; (b) Individual HNC; (c) Individual AGC. APC: Annual Percentage Change; ART: Anti-Retroviral Therapy; LC: Laryngeal cancer; OCC: Oral Cavity Cancer; OPC: Oropharyngeal Cancer. \*HIV prevalence obtained from the National Antenatal HIV Surveys.

5. Discussion

As reported in other settings, a decrease in overall incidence and mortality rates for HNC was observed [31]. However, the overall ASIR

and ASMR for AGC increased. We hypothesise that trends for HNC are related to the declines in tobacco smoking as a result of the anti-tobacco legislation in SA since the alcohol consumption per capita has remained stable at 8 liters [20,32,33]. However the increase in AGC

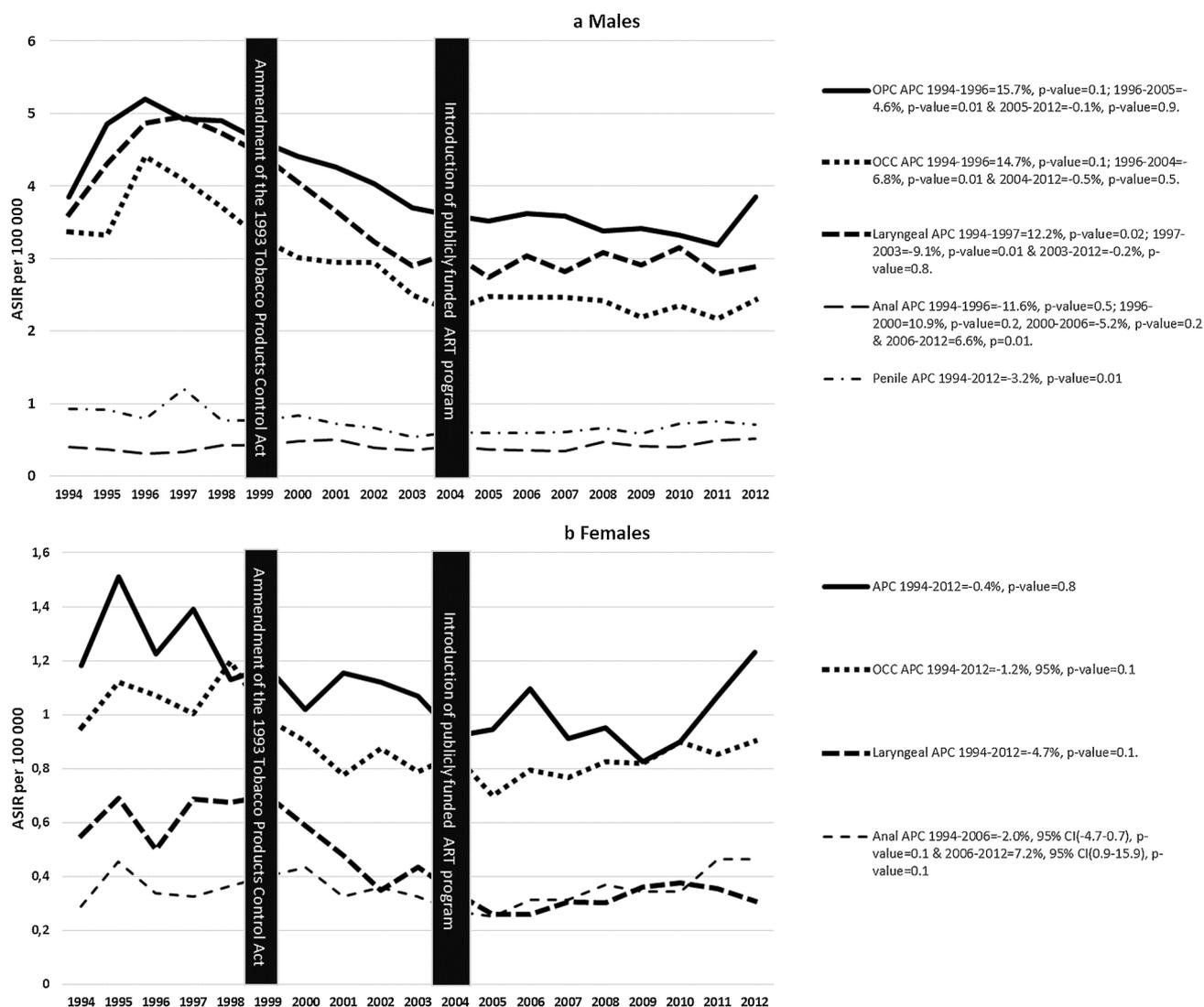


Fig. 2. Age Standardised Incidence Rates (ASIR) between 1994 and 2012. (a) Males; (b) Females. APC: Annual Percentage Change; LC: Laryngeal cancer; OCC: Oral Cavity Cancer; OPC: Oropharyngeal Cancer.

is possibly related to the rising HIV prevalence which is known to increase the risk of HPV infection, persistence and progression cancer [14]. The overall ASIR for HNC are similar to what has been reported previously in SA and other sub-Saharan African countries [34,35].

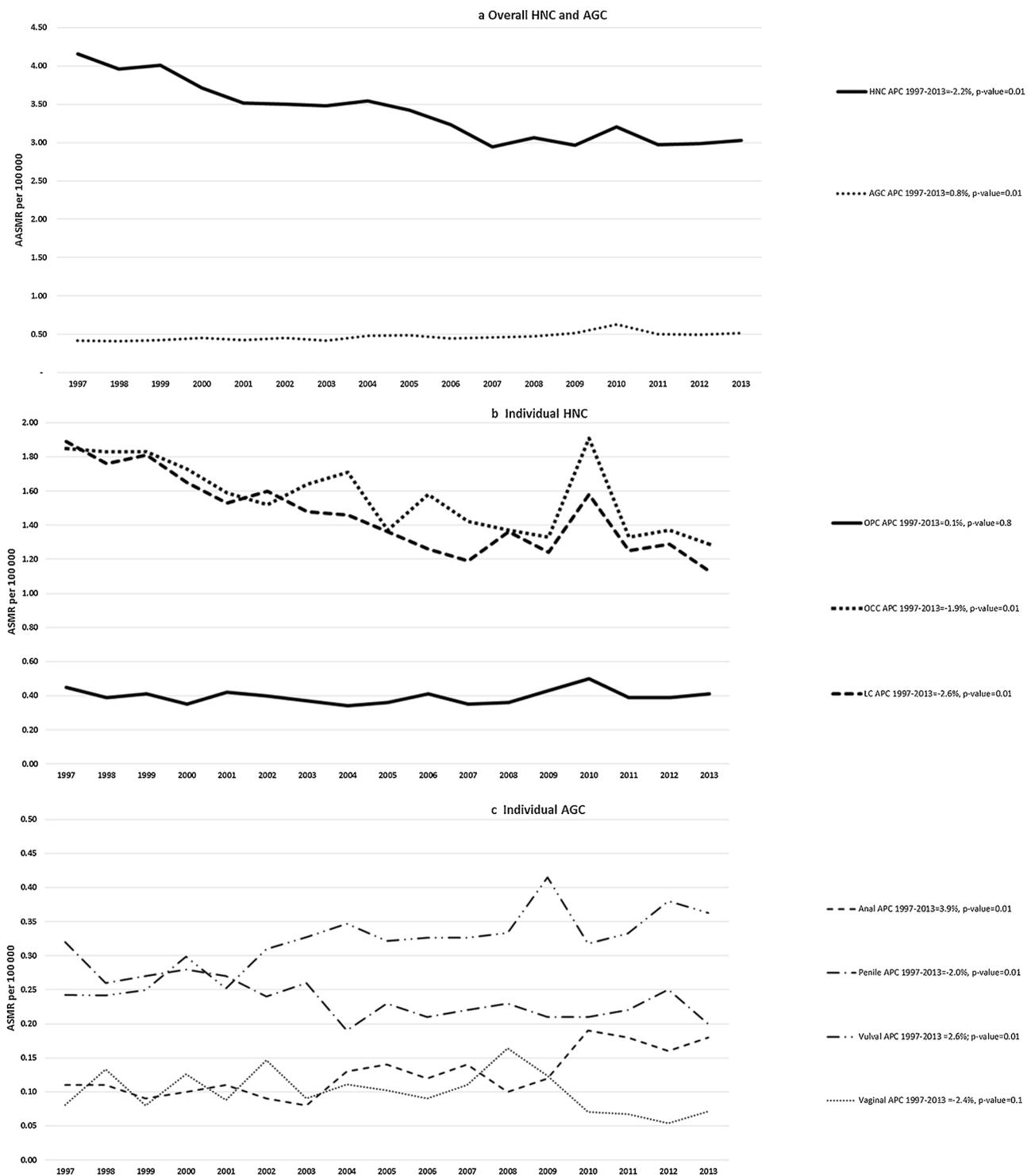
For the individual HNC, as reported by studies in HIC, there was a trend towards declines in ASIR of OCC and LC, and a similar reduction in ASMR for these cancers [31,36]. However, with OPC the pattern was different to the increases in incidence reported in HIC [2]. While there were declines in incidence, these occurred at a relatively slower rate whilst the ASMR was lower and did not change. The reason for this difference is not clear but could be in part related to the causal role of HPV in OPC. Available data suggests that HPV-related OPC has better prognosis [37]. The ASIR for all three HNC plateaued from 2005 after the introduction of the ART program. This is likely due to improved survival which also provides more time for development of cancer [38]. It is also possible that this was related to the stabilisation of the smoking prevalence rates [33].

Our finding of increased incidence and mortality rates for anal cancer among both males and females confirms reports from HIC [5,6]. This might be related to the concurrent high cervical HPV infection in women and high HIV prevalence [39,40]. As reported elsewhere, rates have continued to increase after the introduction of ART [17]. This may mean that pre-cancerous lesions which are established prior to ART

initiation are not reversed by ART and are more likely to persist and accumulate genetic changes. Furthermore, improved survival due to ART provides sufficient time for these lesions to progress undetected in the absence of clear screening guidelines for anal cancer [7].

The ASIR and ASMR for vulval cancers increased, especially among women aged less than 50 years, which confirms previous reports [41]. This suggests an increased role of HPV, exacerbated by the rising HIV prevalence since HPV-related vulval cancers are common in young women [42]. Similar to other settings, the incidence and mortality due to penile cancer has declined [43]. These declines could be related to improvements in penile hygiene secondary to improved access to basic social amenities in the post-apartheid era and reduced prevalence of smoking among men [19,44]. Further future declines are anticipated with the recent expansion of voluntary medical male circumcision.

We found that incidence and mortality rates for HNC were higher (at least 2-fold) among men compared to women. This confirms previous reports [35]. Higher rates among men can be explained by the higher prevalence of smoking and alcohol use in men compared to women [4,33]. Indeed, our results for sensitivity analysis showed that the decline in HNC in men was largely related to the decline in smoking prevalence. Studies also show that oropharyngeal HPV infections mirror the gender patterns of OPC [45]. Men have a higher risk of oropharyngeal HPV infection as they are more likely to smoke, with



**Fig. 3.** Age Standardised Mortality Rates (ASMR) between 1997 and 2013. (a) Overall; (b) Individual HNC; (c) Individual AGC. APC: Annual Percentage Change; LC: Laryngeal cancer; OCC: Oral Cavity Cancer; OPC: Oropharyngeal Cancer.

smoking interfering with mucosal immunity, raising their susceptibility to HPV infection [46]. Also, women are more likely to generate antibodies following genital HPV infection than men, with these antibodies offering some protection against oropharyngeal HPV infection [47]. In addition, women have higher genital HPV viral loads, making transmission higher with male-female oral sex than female-male [45]. This implies that men have a higher risk of HPV infection from oral sex when compared to females. The role of HPV in OPC is partly supported by our finding that the median age at diagnosis of OPC was 4 years lower than

that of LC as HPV-related OPC is common among younger men [31,37]. We showed that among males, the ASIR and ASMR for HNC varied by population group with Coloured men having the highest incidence and mortality rates. This confirms a previous NCR report [35], and studies in other countries [48]. This may be related to the higher prevalence rates of tobacco smoking among Coloured men compared to men of other population groups in the country [49]. White men had lower mortality rates compared to Black men despite having higher incidence rates than Black men. Quite likely, this relates to better access

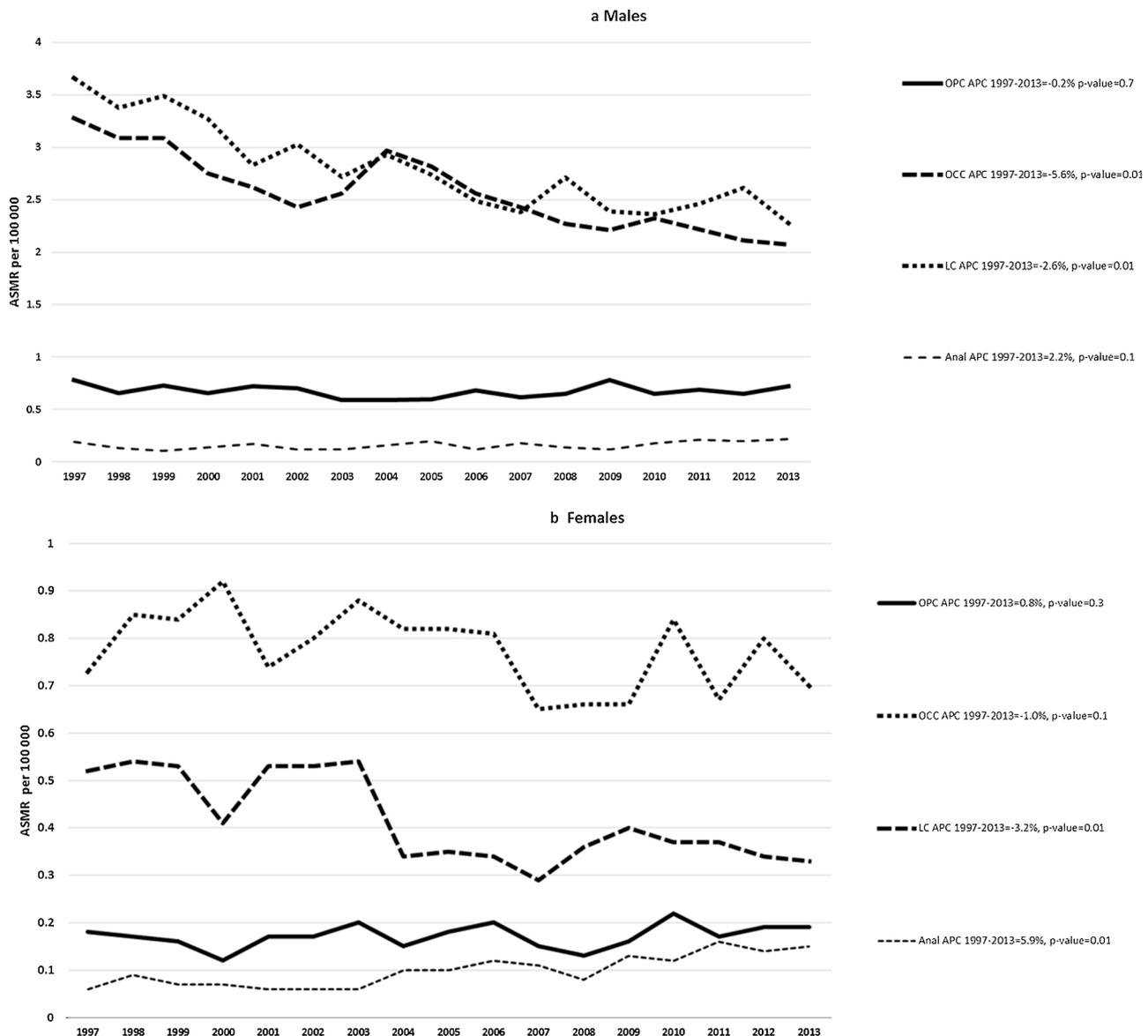


Fig. 4. Age Standardised Mortality Rates (ASMR) between 1997 and 2013. (a) Males and (b) Females. APC: Annual Percentage Change; LC: Laryngeal cancer; OCC: Oral Cavity Cancer; OPC: Oropharyngeal Cancer.

to healthcare among White men compared to Black men which results in early detection of cancer and thus better prognostic outcomes [50]. Prior to 1994, access to healthcare was determined by race; in the post-apartheid era legal restrictions have changed but race is still an indicator of socio-economic access [19].

### 6. Public health implications of the findings

The significant decline in incidence and mortality rates for OCC and LC, whose main risk factor is tobacco smoking, suggests that the anti-smoking legislation is yielding positive outcomes and should be further strengthened. On the other hand, the rising incidence and mortality rates of anal, vulval cancer and the relatively slower decline in incidence rates for OPC, highlight the need for regular monitoring of the trends of these cancers. This is particularly important now as ART access is widespread and the resulting increased life expectancy coupled to changes in sexual behaviour might result in an increased burden of these cancers [7]. The current girls-only HPV vaccination program, could provide more benefit for cervical cancer, however these data suggest that there is need to consider inclusion for boys. This is because

of the absence of effective screening especially for men and the emerging evidence which suggest that the impact and herd immunity of a girls-only program will likely be reduced [51,52]. Modelling studies are required to understand the cost-effectiveness of including boys. In addition, studies investigating effectiveness of single dose HPV vaccine compared to the current two doses could remove the cost obstacle and make it feasible for the HPV vaccine programme to include boys

This study has some limitations. Data from a NCR could have underestimated cancer incidence as cases that are not biopsied are excluded. Mortality data from Stats SA could have missed deaths that were not registered. For this analysis, HPV-related cancers were defined based on the anatomic sites in which HPV DNA is frequently found, however all these cancers may not necessarily be HPV-positive because no testing was conducted. The antenatal HIV prevalence which was used as a proxy for monitoring the HIV epidemic overestimates the national prevalence as pregnant women are likely to be at higher risk of HIV infection. Despite these limitations, this study provides an important contribution to the epidemiology of HPV-related cancers in the country [53].

## 7. Conclusions

There have been significant overall declines in both the incidence and mortality for HNC and penile cancer during the study period. While the distinct trends observed in relation to OPC in HIC are not as obvious in SA, the data show declines in OCC and LC potentially attributable to reduction in tobacco use. In contrast, the incidence and mortality rates for anal and vulval cancer have increased. There is need to continuously analyse trends of these cancers to inform screening and prevention programmes and also help monitor current and future interventions. Vaccination of boys could be considered if cost effective and feasible by reducing HPV vaccination to one dose especially in areas where coverage is low and benefits may not be derived from herd immunity.

## Authors' contributions

AC; PTP, SD, MS and ES conceptualised the study. MS, PTP, SD and ES supervised the data collection, cleaning, coding, analysis and manuscript development. AC, PTP, SD and MS developed the analysis plan and analysed the data. AC wrote the first draft of the manuscript and all authors provided critical review.

## Funding

AC has funding as part of the EDTCP2 programme supported by the European Union. However the information or views in this manuscript are those of the authors and EDTCP Association is not responsible for any use that may be made of the information contained in this publication. AC also received funding from the Consortium of Advanced Research Training in Africa (CARTA). CARTA is jointly led by the African Population and Health Research Center and the University of the Witwatersrand and funded by the Carnegie Corporation of New York (Grant No–B 8606.R02), Sida (Grant No:54100029), the DELTAS Africa Initiative (Grant No: 107768/Z/15/Z). The DELTAS Africa Initiative is an independent funding scheme of the African Academy of Sciences (AAS)'s Alliance for Accelerating Excellence in Science in Africa (AESA) and supported by the New Partnership for Africa's Development Planning and Coordinating Agency (NEPAD Agency) with funding from the Wellcome Trust (UK) (Grant No: 107768/Z/15/Z) and the UK government. The statements made and views expressed are solely the responsibility of the fellow. AC was funded in part by the National Research Foundation (NRF) of South Africa (Grant number: 110807). The views expressed in this publication is that of the authors and the NRF accepts no liability whatsoever in this regard.

## Conflicts of interests

The authors declare that they have no competing interests.

## Acknowledgements

The authors acknowledge the National Cancer Registry and Statistics South Africa for availing the data for the period 1994–2012 and 1997–2013 respectively. The staff at these two institutions are recognised for processing the data.

## Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:<https://doi.org/10.1016/j.canep.2018.12.004>.

## References

- [1] S. Franceschi, et al., Comparison of cancers of the oral cavity and pharynx worldwide: etiological clues, *Oral Oncol.* 36 (1) (2000) 106–115.
- [2] A.K. Chaturvedi, et al., Human papillomavirus and rising oropharyngeal Cancer incidence in the United States, *J. Clin. Oncol.* 29 (32) (2011) 4294–4301.
- [3] W.J. Blot, et al., Oral and pharyngeal cancers, *Cancer Surv.* 19–20 (1994) 23–42.
- [4] E.M. Sturgis, P.M. Cinciripini, Trends in head and neck cancer incidence in relation to smoking prevalence: an emerging epidemic of human papillomavirus-associated cancers? *Cancer* 110 (7) (2007) 1429–1435.
- [5] A.M. Bouvier, et al., Trends of incidence and survival in squamous-cell carcinoma of the anal canal in France: a population-based study, *Eur. J. Cancer Prev.* 25 (3) (2016) 182–187.
- [6] R.A. Nelson, et al., Changing patterns of anal canal carcinoma in the United States, *J. Clin. Oncol.* 31 (12) (2013) 1569–1575.
- [7] J. Palefsky, Anal cancer, in: R. Yarchoan (Ed.), *Cancers in People With HIV and AIDS*, Springer, New York, 2014, pp. 273–288.
- [8] C. de Martel, et al., Worldwide burden of cancer attributable to HPV by site, country and HPV type, *Int. J. Cancer* (2017).
- [9] C. de Martel, et al., Cancers attributable to infections among adults with HIV in the United States, *AIDS* 29 (16) (2015) 2173–2181.
- [10] J.R. Roberts, L.L. Siekas, A.M. Kaz, Anal intraepithelial neoplasia: a review of diagnosis and management, *World J. Gastrointest. Oncol.* 9 (2) (2017) 50–61.
- [11] B.S. Madsen, et al., Risk factors for squamous cell carcinoma of the penis—population-based case-control study in Denmark, *Cancer Epidemiol. Biomarkers Prev.* 17 (10) (2008) 2683–2691.
- [12] P. Boyle, B. Levin, *World Cancer Report 2008*, IARC Press, International Agency for Research on Cancer, Lyon, 2008 510 pp.
- [13] D.C. Beachler, et al., Risk factors for acquisition and clearance of oral human papillomavirus infection among HIV-infected and HIV-uninfected adults, *Am. J. Epidemiol.* 181 (1) (2015) 40–53.
- [14] M.S. Shiels, et al., Impact of the HIV epidemic on the incidence rates of anal Cancer in the United States, *JNCI* 104 (20) (2012) 1591–1598.
- [15] S. Delany-Moretlwe, A. Chikandiwa, J. Gibbs, Human papillomavirus infection and disease in men: impact of HIV, *South. Afr. J. HIV Med.* 14 (4) (2013) 183–188.
- [16] K.R. Dahlstrom, E.M. Sturgis, Other HPV-associated cancers, in: R. Yarchoan (Ed.), *Cancers in People With HIV and AIDS*, Springer, New York, 2014, pp. 289–290.
- [17] C. Picketty, et al., Lack of regression of anal squamous intraepithelial lesions despite immune restoration under cART, *AIDS* 27 (3) (2013) 401–406.
- [18] C. Ndiaye, et al., The role of human papillomavirus in head and neck cancer in Senegal, *Infect Agent Cancer* 8 (1) (2013) 14.
- [19] R.C. Nnadozie, Access to basic services in post-apartheid South Africa: what has changed? Measuring on a relative basis, *Afr. Stat. J.* 16 (2013) 91–103.
- [20] P. Reddy, et al., A decade of tobacco control: the South African case of politics, health policy, health promotion and behaviour change, *S. Afr. Med. J.* 103 (11) (2013) 835–840.
- [21] D.M. Parkin, L.D. Sanghvi, Patsy Jensen (Ed.), Chapter: Cancer Registration in Developing Countries in *Cancer Registration: Principles and Methods*, IARC, Lyon, France, 1991, pp. 185–198.
- [22] E. Singh, et al., South African National Cancer registry: effect of withheld data from private health systems on cancer incidence estimates, *S. Afr. Med. J.* 105 (2) (2015) 107–109.
- [23] R. Little, D. Rubin, *Modern Methods of Data Analysis: the Analysis of Social Science Data With Missing Values*, Sage, London, 1990.
- [24] WHO, *International Classification of Diseases for Oncology*, World Health Organisation, Geneva, 2013.
- [25] N.M. Dube, et al., Repeatability of manual coding of cancer reports in the South African National Cancer registry, 2010, *South. Afr. J. Epidemiol. Infect.* 28 (2013) 157–165.
- [26] E. Singh, et al., South African National Cancer Registry: Effect of withheld data from private health systems on cancer incidence estimates vol. 105, (2015) 2015.
- [27] WHO, *International Classification of Disease and Related Health Problems, Tenth Revision ICD-10*, World Health Organisation, Geneva, 2010.
- [28] J.O. Lam, et al., Incidence, trends and ethnic differences of oropharyngeal, anal and cervical cancers: singapore, 1968–2012, *PLoS One* 10 (12) (2015) e0146185.
- [29] T.Z. Hwang, et al., Incidence trends of human papillomavirus-related head and neck cancer in Taiwan, 1995–2009, *Int. J. Cancer* 137 (2) (2015) 395–408.
- [30] Joinpoint Regression Program and Version 4.3.1.0, Statistical Research and Applications Branch, Editor, National Cancer Institute, Bethesda, USA, 2016.
- [31] A.K. Chaturvedi, et al., Worldwide trends in incidence rates for oral cavity and oropharyngeal cancers, *J. Clin. Oncol.* 31 (36) (2013) 4550–4559.
- [32] K. Peltzer, S. Ramlagan, Alcohol use trends in South Africa, *J Soc Sci* 18 (1) (2009) 1–12.
- [33] V. Winkler, N.J. Mangolo, H. Becher, Lung cancer in South Africa: a forecast to 2025 based on smoking prevalence data, *BMJ Open* 5 (3) (2015).
- [34] A. Korir, et al., Incidence of cancer in Nairobi, Kenya (2004–2008), *Int. J. Cancer* 137 (9) (2015) 2053–2059.
- [35] O.A. Ayo-Yusuf, R. Lalloo, N.W. Joghanson, Trends and ethnic disparities in oral and oro-pharyngeal cancers in South Africa, 1992–2001, *SADJ* 68 (4) (2013) 168–173.
- [36] M. Blomberg, et al., Trends in head and neck cancer incidence in Denmark, 1978–2007: focus on human papillomavirus associated sites, *Int. J. Cancer* 129 (3) (2011) 733–741.
- [37] A.M. Hong, et al., Squamous cell carcinoma of the oropharynx in Australian males induced by human papillomavirus vaccine targets, *Vaccine* 28 (19) (2010) 3269–3272.
- [38] S. Franceschi, et al., Changing patterns of cancer incidence in the early- and late-HAART periods: the Swiss HIV Cohort Study, *Br. J. Cancer* 103 (3) (2010) 416–422.
- [39] A.G. Nyitray, et al., Prevalence of and risk factors for anal human papillomavirus infection in men who have sex with women: a cross-national study, *J. Infect. Dis.* 201 (10) (2010) 1498–1508.
- [40] L. Simbayi, et al., South African National HIV Prevalence, Incidence and Behaviour

- Survey, 2012, Human Sciences Research Council, Pretoria, 2014.
- [41] E.L. Barlow, et al., Changing trends in vulvar Cancer incidence and mortality rates in Australia since 1982, *Int. J. Gynecol. Cancer* 25 (9) (2015) 1683–1689.
- [42] D.M. Parkin, F. Bray, Chapter 2: the burden of HPV-related cancers, *Vaccine* 24 (Supplement 3) (2006) S11–S25.
- [43] J.S. Barnholtz-Sloan, et al., Incidence trends in primary malignant penile cancer, *Urol. Oncol.* 25 (2007) 361–367.
- [44] C. van Walbeek, Recent trends in smoking prevalence in South Africa—some evidence from AMPS data, *S. Afr. Med. J.* 92 (6) (2002) 468–472.
- [45] A.R. Giuliano, et al., EUROGIN 2014 roadmap: differences in human papillomavirus infection natural history, transmission and human papillomavirus-related cancer incidence by gender and anatomic site of infection, *Int. J. Cancer* 136 (12) (2015) 2752–2760.
- [46] Xi, L.F., et al., Relationship between cigarette smoking and human papillomavirus type 16 and 18 DNA load. *Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology*, 2009. 18(12): p. 3490-3496.
- [47] M. Safaeian, et al., Epidemiological study of anti-HPV16/18 seropositivity and subsequent risk of HPV16 and -18 infections, *J. Natl. Cancer Inst.* 102 (21) (2010) 1653–1662.
- [48] C. Ragin, et al., Prevalence of HPV Infection in Racial-Ethnic Subgroups of Head and Neck Cancer Patients. *Carcinogenesis*, (2016).
- [49] P. Reddy, et al., Prevalence of tobacco use among adults in South Africa: results from the first south african national health and nutrition examination survey, *S. Afr. Med. J.* 105 (8) (2015) 648–655.
- [50] Z.R. Kon, N. Lackan, Ethnic disparities in access to care in post-apartheid South Africa, *Am. J. Public Health* 98 (12) (2008) 2272–2277.
- [51] M. Ronn, et al., Population-level impact of HPV vaccination program in high HIV prevalence settings, *International Papilloma Virus* (2017).
- [52] B. Donovan, et al., Quadrivalent human papillomavirus vaccination and trends in genital warts in Australia: analysis of national sentinel surveillance data, *Lancet Infect. Dis.* 11 (1) (2011) 39–44.
- [53] D.M. Parkin, The role of cancer registries in cancer control, *Int. J. Clin. Oncol.* 13 (2) (2008) 102–111.