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Population-based temporal trends and ethnic disparity of vulvar cancer mortality in South Africa: Joinpoint and age-period-cohort regression analyses (1999–2018)

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Abstract

Background: The epidemiology of vulvar cancer is rapidly changing due to changing prevalence of human papilloma virus infection, human immunodeficiency virus infection and other risk factors in South Africa and globally. We evaluated the vulvar cancer mortality trends in South Africa from 1999 to 2018.

Methods: Data collected by Statistics South Africa were utilised to conduct age-period-cohort analysis and Joinpoint regression modelling of trends in the age-standardised mortality rate (ASMR) of vulvar cancer in South Africa. Ethnic trends were also calculated and compared.

Results: From 1999 to 2018, 1,922 vulvar cancer mortalities were reported, with a decline in mean age from 57.2 years in 1999 to 50.8 years in 2018. The ASMR increased by 5.4% per annum from 0.23 deaths per 100,000 women in 1999 to 0.76 deaths per 100,000 women in 2018, $p < 0.001$. In 2018, the Indian/Asian (0.75 per 100,000 women), Blacks (0.74 per 100,000 women) and Mixed race (0.71 per 100,000 women) had relatively high ethnic-specific ASMR of vulvar cancer as compared to the ASMR among Whites (0.36 per 100,000 women). From 1999 to 2018, Blacks average annual percent change (AAPC: 7.8%, $p < 0.001$) and Whites (AAPC: 3.8, $p < 0.001$) had statistically significant annual increases in ASMR of vulvar cancer. However, Mixed race (AAPC: 2.1%, p 0.2) and Indian/Asians had non-significant increases in annual ASMR of vulvar cancer (AAPC: 1.9, p 0.3). There were significant age, period and cohort effects on vulvar cancer mortality trends in South Africa and among the Black ethnic group.

Conclusion: Our study showed significant increase in vulvar cancer mortality trends with a decline in average age at mortality in South Africa. All ethnic groups had increased vulvar mortality rates to varying degrees.

Keywords: *vulvar cancer mortality, ethnic disparity, vulvar cancer trends, Joinpoint regression, South Africa*

Research

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Introduction

Globally, vulvar cancer accounts for about 5% of all gynaecological malignancies [1, 2].About 45,240 new cases and 17,908 new deaths of vulvar cancer occurred globally [3] There has been an increasing incidence of vulvar cancer among young premenopausal women [4–9]. An increasing trend in the incidence of human papilloma virus (HPV) infection, human immunodeficiency virus (HIV) infection, unsafe sexual behaviours, early sexual debut, multiple sexual partners and smoking has been found to be related to the increasing trends in vulvar cancer especially among young adults [4, 5–8, 10, 11].

The incidence of vulvar cancer in the sub-Saharan Africa region is variable depending on the prevalence of risk factors and the risk of under-reporting [4–6, 8, 10, 12]. South Africa has the highest age-standardised incidence rate (ASIR) of vulvar cancer of 7.2/10,000 population as compared to the rates in high income countiry (HIC) with ASIR of about 0.2 to 5 per 100,000 population [5, 13]. South Africa has experienced an upward rise in both the vulvar cancer incidence and mortality, especially among the young population due to the HIV prevalence in the country. In the Southern African subregion, about 90% of women with vulvar cancer are young women living with HIV infection [8, 14]. South Africa has one of the highest prevalence of women living with HIV globally and one of the largest populations of women currently on free antiretroviral therapy (ART) [15–17].

There are two known pathways to the development of vulvar cancer [4, 18]. The non-HPV-associated pathway develops from differentiated vulvar intraepithelial neoplasia that arises from lichen sclerosus (this is the commoner pathway in elderly women) [4, 18]. The second pathway is the HPV-dependent pathway, which shares similar epidemiological factors with other HPV-related malignancies [4, 18].

There is no known screening modality to reduce the incidence and death from vulvar cancer [4, 14, 19]. However, increasing evidence from HICs suggests that HPV vaccination might be effective against vulvar premalignant and invasive cancers [4, 20]. In HICs where the uptake of HPV vaccination has been optimal, there has been a significant decline in the prevalence of HPV infection [13, 20], which might impact vulvar cancer in the future.

The complex interplay of the changing trends in the prevalence of HPV and HIV infections and other risk factors in South Africa can impact on the vulval cancer trends. This study therefore aimed to evaluate the trend in vulvar cancer mortality by age and ethnic groups in South Africa from 1999 to 2018, using both Joinpoint and age-period-cohort (APC) regression models.

Materials and methods

Data source

The national and ethnic gynaecological cancer mortality data were obtained from Statistics South Africa (Stats SA). Stats SA data published national mortality data including variables such as gender, ethnicity, age and place of residence [21]. The mid-year population was also obtained from Stats SA [11, 22]. The data published by Stats SA has been judged to be of high quality [23]. The vulvar cancer mortality was coded as C51 [18].

South Africa is a multi-ethnic country with four recognised population groups. The population groups are Blacks, Whites, Mixed race and Indian/Asians [21].

The study protocol was approved by the Human Research Ethics Committee (Medical) of the University of the Witwatersrand (Clearance certificate number: M190544).

Statistical analysis

Data were checked for missing data and consistency and then cleaned. Categorical variables were described using frequency percentages, while continuous variables such as age were described using mean (± standard deviation). The annual proportion of vulvar cancer mortality among all female breast and gynaecological cancer mortality was calculated from 1999 to 2018. We divided the annual deaths from vulvar

cancer by the mid-year population aged ≥15 years to obtain the annual crude mortality rate (CMR) of vulvar cancer. Age-specific mortality rate of vulvar cancer was also calculated by dividing the vulvar cancer mortality of each 5-year age group (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) by the mid-year population of each age category. We utilised the direct standardisation method and the 1964 SEGI world standard population to calculate the annual age-standardised mortality rate of vulvar cancer (ASMR) [24]. Analysis was stratified by ethnic groups. Stata version 16 statistical software (StataCorp, USA) was utilised for data analysis, while Excel spreadsheets were utilised for calculating and producing ASMR graphs.

Joinpoint regression

We utilised the Joinpoint regression analysis software, version 4.9.1.0 (Statistical Methodology and Applications Branch, Surveillance Research Program, National Cancer Institute, Bethesda, MD) [25, 26]to conduct robust trend analysis of vulvar cancer mortality between 1999 and 2018. Four maximum Joinpoints, with 4,499 Monte Carlo permutation tests, were allowed during the analyses [11, 22, 27]. Segmented and average annual percent change (AAPC) were obtained.

The segmental APC was calculated as

$$APC = (e^{\beta} - 1) \times 100$$

Where β = coefficient of the calendar year or the slope of the slope coefficient (β) of the log-linear regression model. The AAPC of the overall trends was calculated as the average of all the segmental APCs. All these were iteratively calculated by the Joinpoint regression software [22, 27, 28].

Positive or negative AAPC showed increased or decreased trends, respectively. We reported a stable trend when the AAPC of vulvar cancer trends was within the range of −0.5 to +0.5 and the *p*-value >0.05 [22, 27, 28].

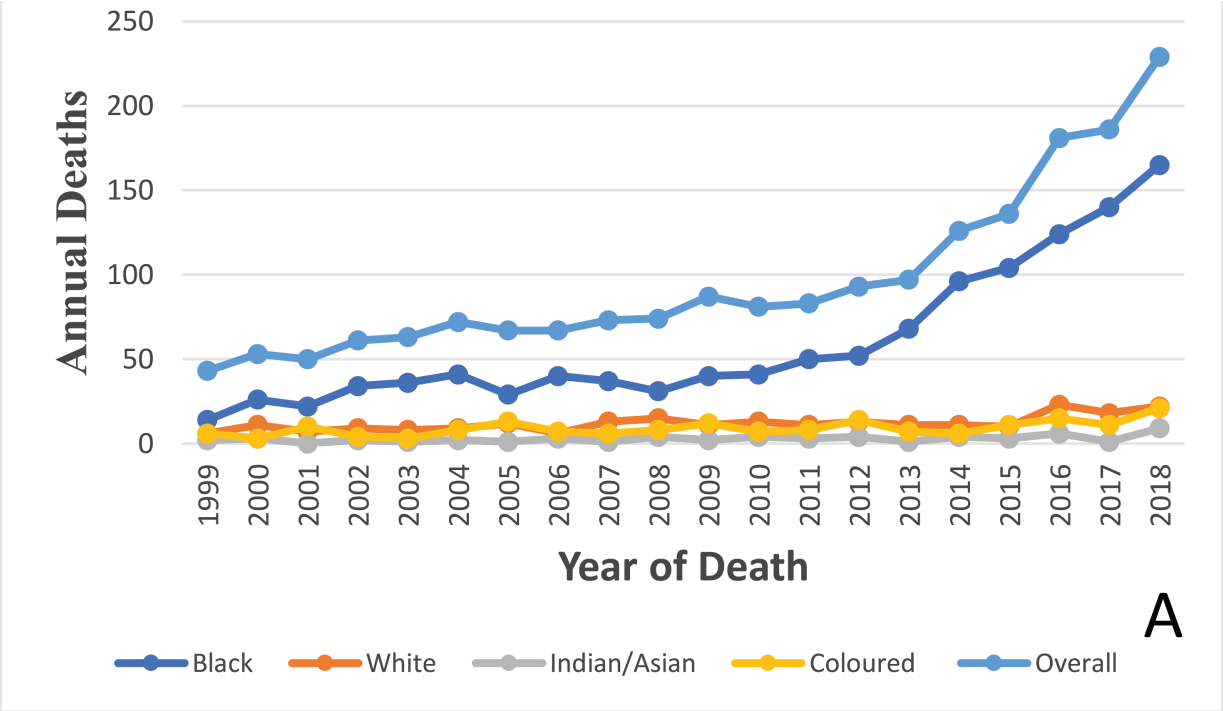
APC analysis

The effect of age, calendar period and birth cohort on vulvar cancer mortality in South Africa was evaluated using the APC regression modelling. The age effect is the impact of biologic age on vulvar cancer mortality. Calendar period effect is the impact of population-based interventions (such as vaccination of HPV, screening, improvement in access to reproductive health services and improvement in death registration), policies (such as bridging the socio-economic gaps) and environmental factors (such as pollution) on all age groups during the period of the study [11]. On the other hand, birth cohort effect is the impact of being exposed to similar mortality risks, reproductive behaviours, environmental carcinogens and socio-economic conditions by virtue of being born around the same time. For example, a cohort effect may occur among babies whose mothers were exposed to diethylstilbestrol. Diethylstilbestrol was used for the treatment of miscarriages during the era from 1940 to 1970 but was later discovered to have some carcinogenic properties [29].

Firstly, a lexis matrix was formed using the vulvar cancer mortality data and the mid-year population estimates [30]. The 5-year age category (15–19 years, 20–24 years, 25–29 years, 30–34 years, 35–39 years, 40–44 years, 45–49 years, 50–54 years, 55–59 years, 60–64 years, 65–69 years, 70–74 years, ≥75 years) was arranged as the columns while the corresponding 5-year calendar period (1999–2003, 2004–2008, 2009–2013 and 2014–2018) were the rows. Usually, the diagonal should correspond to the birth cohort. Secondly, the lexis matrix was imputed into the APC web tool [30]. Wald's chi-square test was conducted to test the statistical significance of the estimable functions (Net drift, local drift, longitudinal age drift, cohort risk ratio (RR) and period rate ratio) [11, 22, 30]. The statistical level of significance was set at *p*-value < 0.05 or 95% confidence interval.

Results

From 1999 to 2018, there were 1,922 vulvar cancer mortalities. Vulvar cancer deaths increased from 43 deaths in 1999 to 229 deaths in 2018 at about 8.5% per annum (AAPC: 8.5%, 95%CI: 7.1%–9.9%, *p*-value <0.001) (Figure 1a, Table 1).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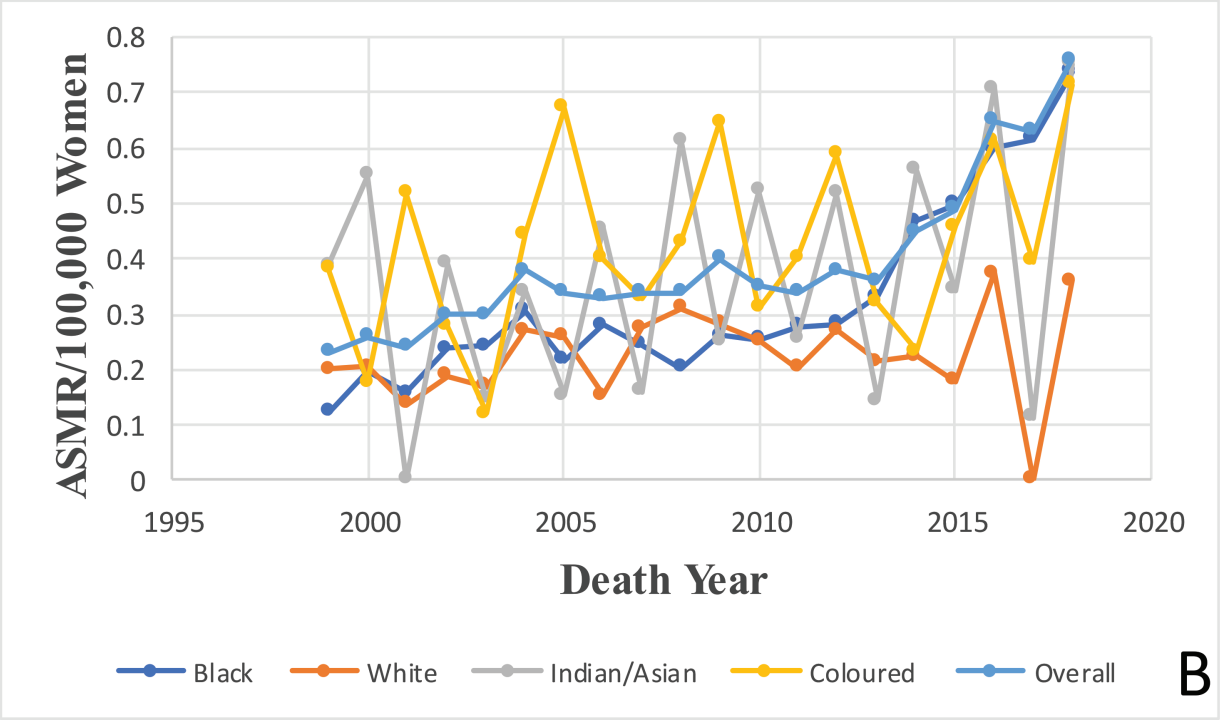
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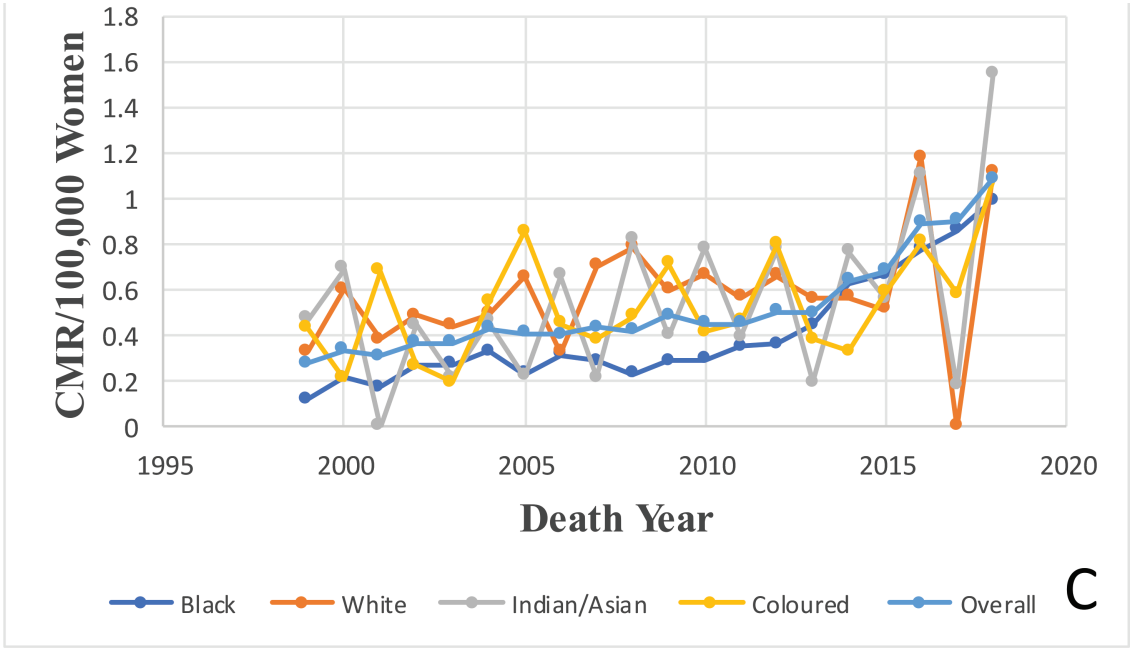


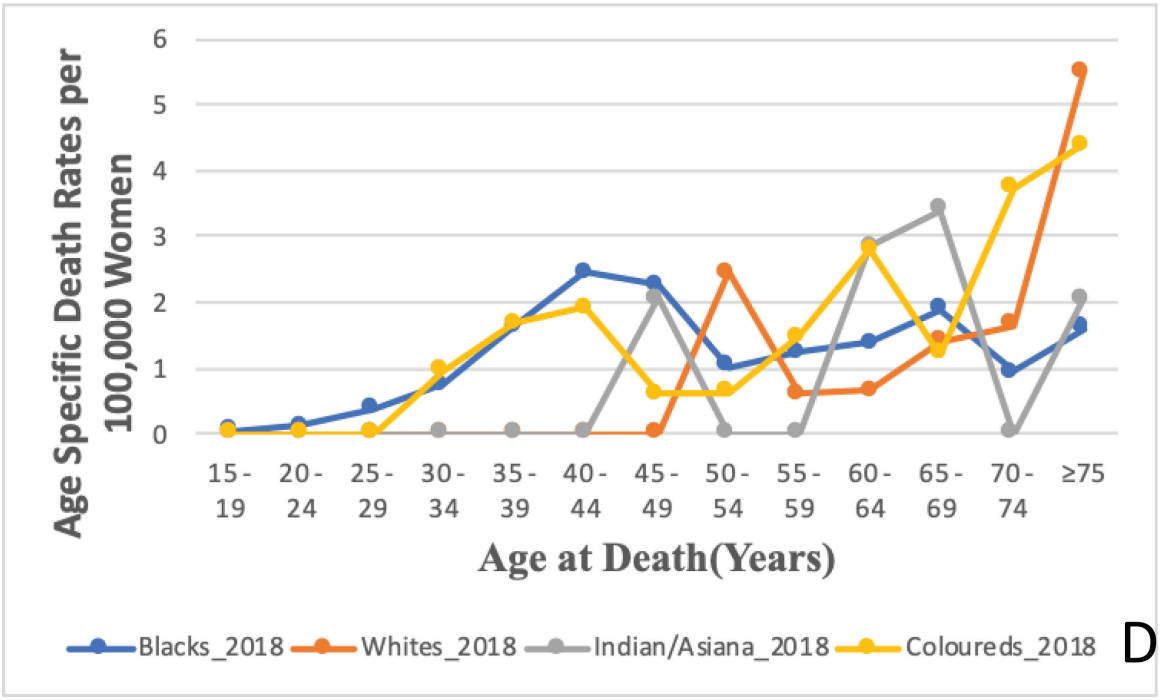


Figure 1. Trends in overall and ethnic (a): Deaths (b): ASMR (c): CMRs of vulvar cancer in South Africa 1999–2018. (d): Age-specific death rate of vulvar cancer by ethnicity, 2018.

Table 1. Trends in mean age at death, mortality rates and proportion of vulvar cancer in South Africa (1999–2018).

Year	Vulvar cancer (*n* = 1922)			
	Mortality	Age (mean ± SD)	CMR	ASMR
1999	43	57.16	0.28	0.23
2000	53	58.81	0.34	0.26
2001	50	60.10	0.31	0.24
2002	61	58.64	0.37	0.3
2003	63	58.38	0.37	0.3
2004	72	54.78	0.43	0.38
2005	67	59.09	0.41	0.34
2006	67	54.75	0.41	0.33
2007	73	58.63	0.44	0.34
2008	74	55.96	0.42	0.34
2009	87	57.18	0.49	0.4
2010	81	57.25	0.45	0.35
2011	83	57.52	0.46	0.34
2012	93	52.76	0.50	0.38
2013	97	50.32	0.50	0.36
2014	126	48.94	0.64	0.45
2015	136	50.38	0.69	0.49
2016	181	53.49	0.90	0.65
2017	186	48.06	0.90	0.63
2018	229	50.84	1.09	0.76

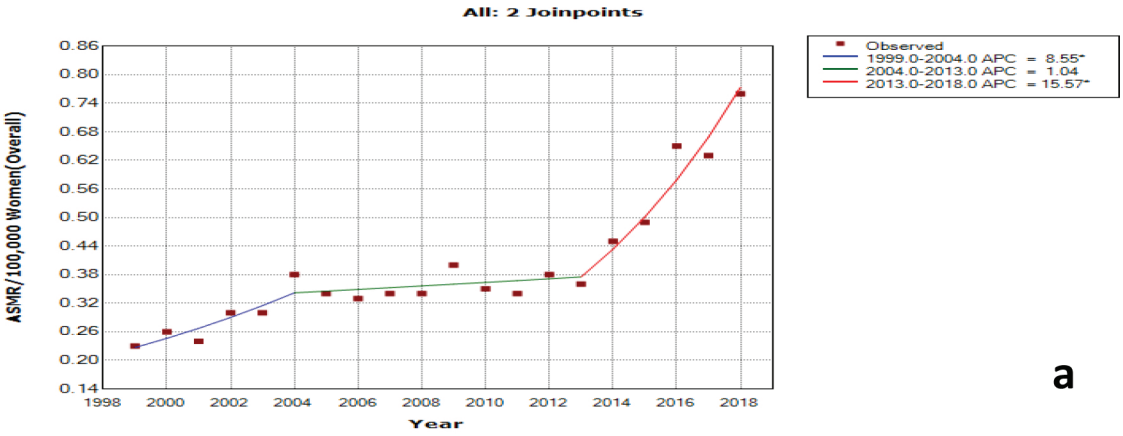
Joinpoint trends in mortality rates of vulvar cancer

The ASMR of vulvar cancer increased from 0.23 deaths per 100,000 women in 1999 to 0.76 deaths per 100,000 women in 2018 at an average increase of 5.4% per annum (AAPC: 5.4%, 95%CI: 4.2%–6.7%, *p*-value <0.001) (Figures 1b and 2a, Table 1 and Supplementary Table 1). Joinpoint regression analysis of the trends in the ASMR of vulvar cancer showed three trends: the first trend was a statistically significant increase of about 8.5% per annum from 1999 to 2004 (APC: 8.5%, *p*-value <0.001). Subsequently, there was a non-statistically significant lower annual rate of 1.0% from 2004 to 2013 (APC: 1.0%, *p*-value = 0.4). The third trend showed a statistically significant increase of 15.6% per annum from 2013 to 2018 (Figure 2a, Supplementary Table 1). The CMR of vulvar cancer also increased from 0.28 deaths per 100,000 women to 1.09 deaths per 100,000 women, and the CMR was slightly higher than the ASMR throughout the study period (Figure 1c, Table 1).

Ethnic trends in vulvar cancer mortality

Black women recorded the highest number of annual vulvar cancer deaths during the study period, increasing from 14 deaths in 1999 to 165 deaths in 2018. In comparison, annual deaths remained substantially lower among White women (6–22 deaths), Mixed-race women (6–21 deaths) and Indian/Asian women (2–9 deaths) (Figure 1a).

Between 1999 and 2018, the number of vulvar cancer deaths increased significantly across all ethnic groups. The largest average annual increases were observed among Black women (AAPC = 11.9%, $p < 0.001$) and Indian/Asian women (AAPC = 7.4%, $p < 0.001$), followed by Mixed-race women (AAPC = 5.2%, $p < 0.001$) and White women (AAPC = 5.0%, $p < 0.001$).



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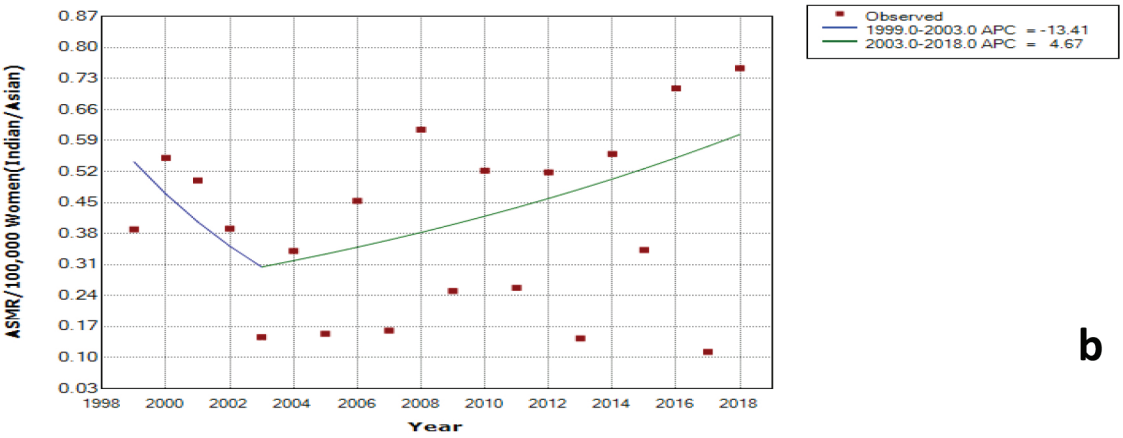

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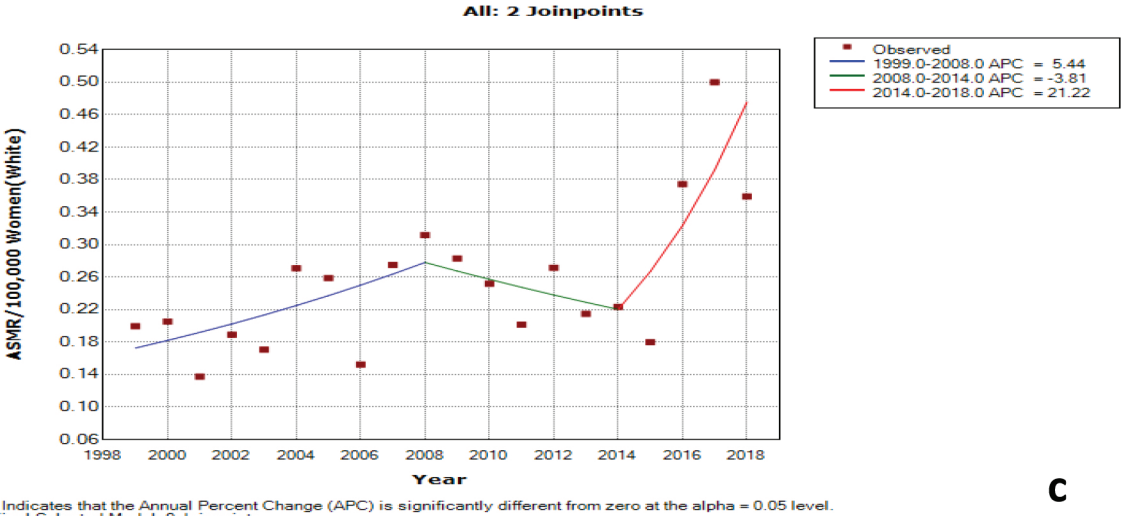

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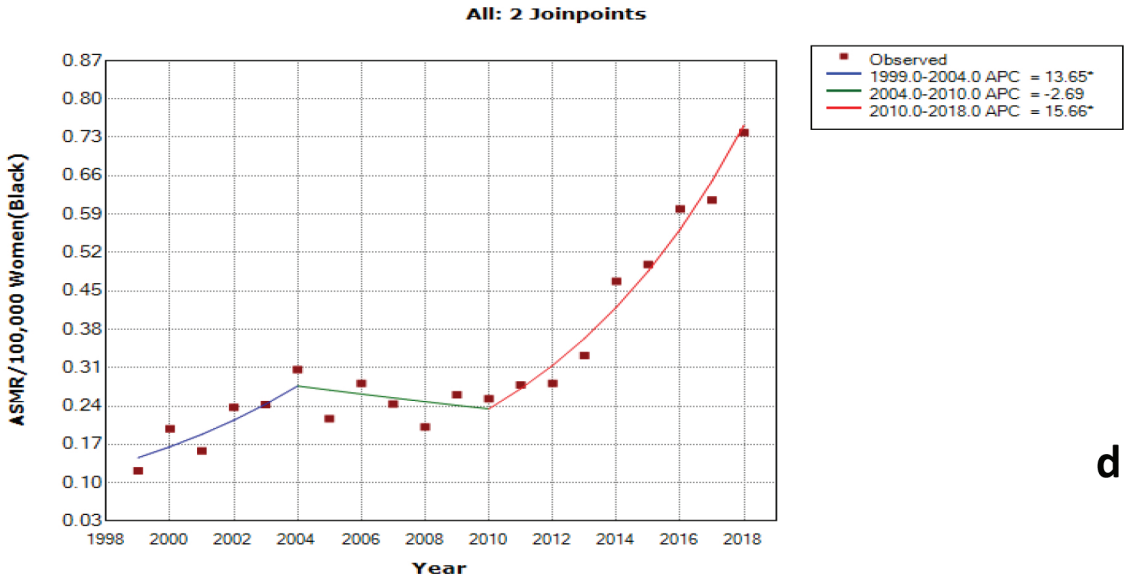

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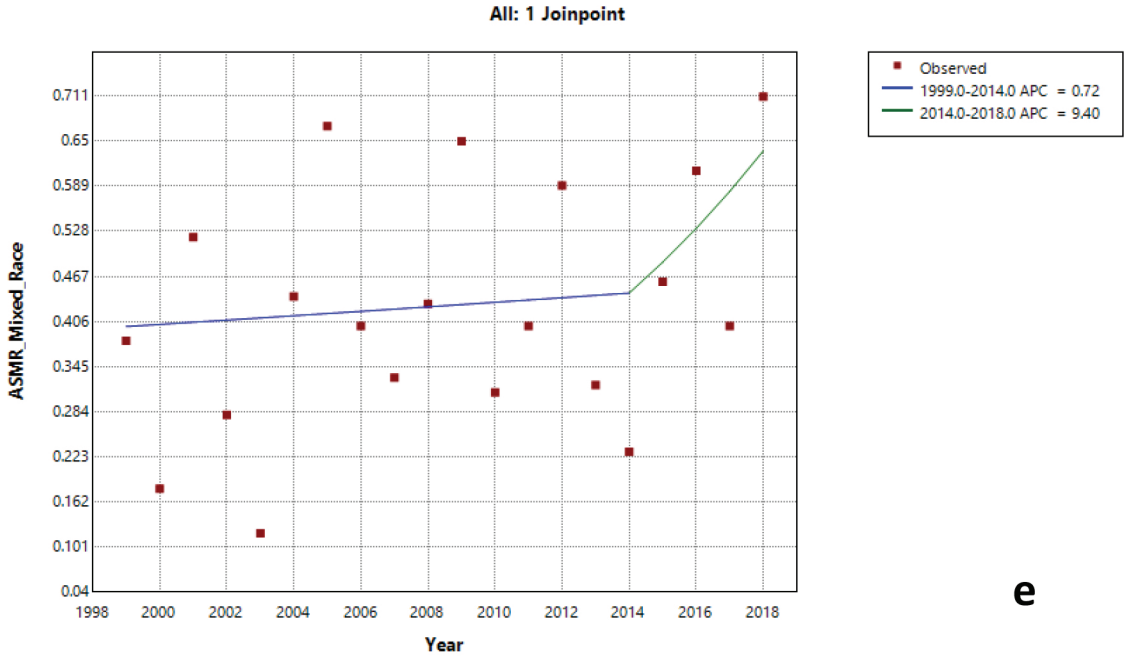

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Figure 2. (a–e): Joinpoint regression trends in the annual ASMR from vulvar cancer(Overall (a), among Indian/Asian (b),Whites (c), Black (d), and Mixed (e) population group of South Africa (1999–2018).

In 2018, the highest age-standardised mortality rates (ASMRs) were recorded among Indian/Asian women (0.75 per 100,000 women), Black women (0.74 per 100,000 women) and Mixed-race women (0.71 per 100,000 women), whereas White women had the lowest ASMR (0.36 per 100,000 women) (Figure 1b; Supplementary Table 2).

Over the study period, ASMR increased significantly among Black women (AAPC = 7.8%, $p < 0.001$) and White women (AAPC = 3.8%, $p < 0.001$). Although ASMR also increased among Mixed-race women (AAPC = 2.5%, $p = 0.30$) and Indian/Asian women (AAPC = 1.9%, $p = 0.30$), these trends were not statistically significant (Figure 2b–e; Supplementary Table 2).

From 1999 to 2013, Black women had the lowest ethnic-specific CMR despite experiencing the largest increase in mortality over time (Figure 1c).

Trends in mean age at death by ethnicity

The mean age at death from vulvar cancer in South Africa declined from 57.2 ± 16.3 years in 1999 to 50.8 ± 16.8 years in 2018 (Supplementary Table 1).

In 2018, Indian/Asian women had the highest mean age at death (73.6 ± 12.4 years), followed by White women (71.5 ± 11.8 years). In contrast, Mixed-race women (55.0 ± 16.4 years) and Black women (45.8 ± 13.8 years) died at considerably younger ages (Supplementary Table 3).

Over the study period, the mean age at death decreased among Black women, from approximately 53 to 45 years. Conversely, the mean age at death increased among White women (61 to 71 years) and Indian/Asian women (68.5 to 73.5 years). Among Mixed-race women, the mean age fluctuated markedly, ranging between 49 and 67 years.

Age-specific mortality rates by ethnicity

In 2018, Black women experienced the highest vulvar cancer mortality rates among younger age groups, beginning from ages 15–19 years. Mortality peaked among women aged 40–44 years and subsequently declined in older age groups.

Mixed-race women exhibited a similar mortality pattern, with rates comparable to those of Black women between ages 30–34 years. Two mortality peaks were observed among Mixed-race women, occurring at ages 40–44 years and 60–64 years.

Among White women, mortality rates were generally low before age 50 years and fluctuated thereafter. In Indian/Asian women, vulvar cancer mortality was observed from ages 45–49 years and increased among women aged 60–64 years and older (Figure 1d).

Joinpoint trends in the overall age-specific mortality rates of vulvar cancer, 1999–2018

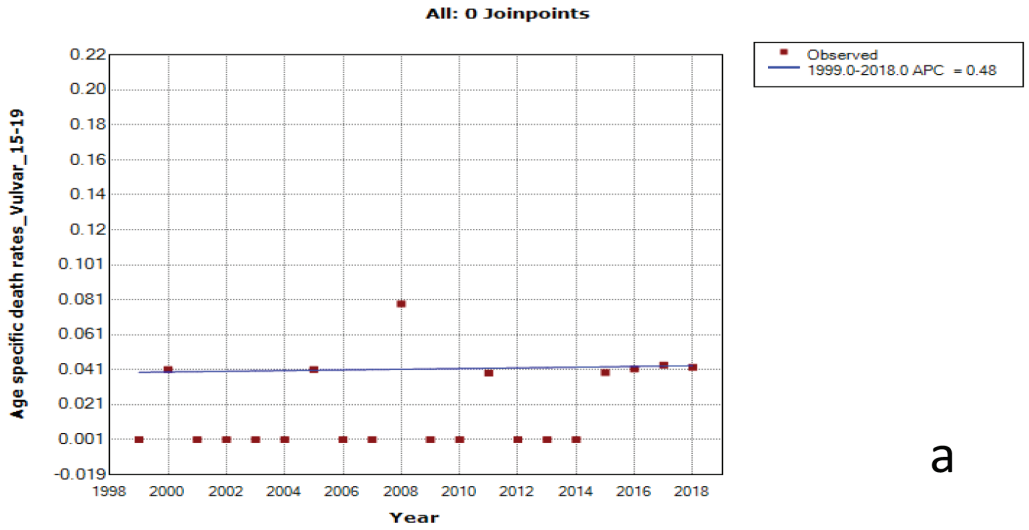
From 1999 to 2018, women aged 30–49 years (AAPC range: 8.1%–14.1%, p-value <0.001); 60–64 years (AAPC: 2.4, p-value <0.001) and 75 years and older (AAPC: 2.8%, p-value <0.001) had statistically significant increases in annual mortality rates of vulvar cancer. However, there was a non-significant increase in the annual mortality rates of vulvar cancer among women aged 20–24 years (AAPC: 3.5%, p-value = 0.1), 50–59 years (AAPC range: 1.9–2.8, p-value >0.05) and 65–69 years (2.9%, p-value >0.05), while there was non-significant decline in the annual mortality rates among women aged 25–29 years (−0.9%, p-value = 0.8). Women aged 15–19 years (AAPC: 0.5%, p-value = 0.9) and 70–74 years (AAPC: 0.2, p-value = 0.9) had stable trends (Figure 3, Supplementary Table 3).

APC analysis of vulvar cancer

Local and net drift

The overall net drift of vulvar cancer trends over the study period (1999–2018) was positive, showing an increase of 6.56% (95%CI: 5.47% to 7.65%) per annum. (Supplementary Table 4, Supplementary Figure 1). All the ethnic groups had positive net drift with Blacks (9.49%, 95% CI:7.96%–11.05%) having the highest followed by Indian/Asian (3.10% 95%CI: −7.71% to 15.17%), Mixed race (1.15%, 95%CI: −6.07% to

8.94%) and Whites (1.15%, 95%CI: −6.07% to 8.94%) (Figure 4a, Supplementary Figure 2a–d; Supplementary Table 5). From the Wald's test, net drift of overall and Blacks was statistically significant (Supplementary Table 6).



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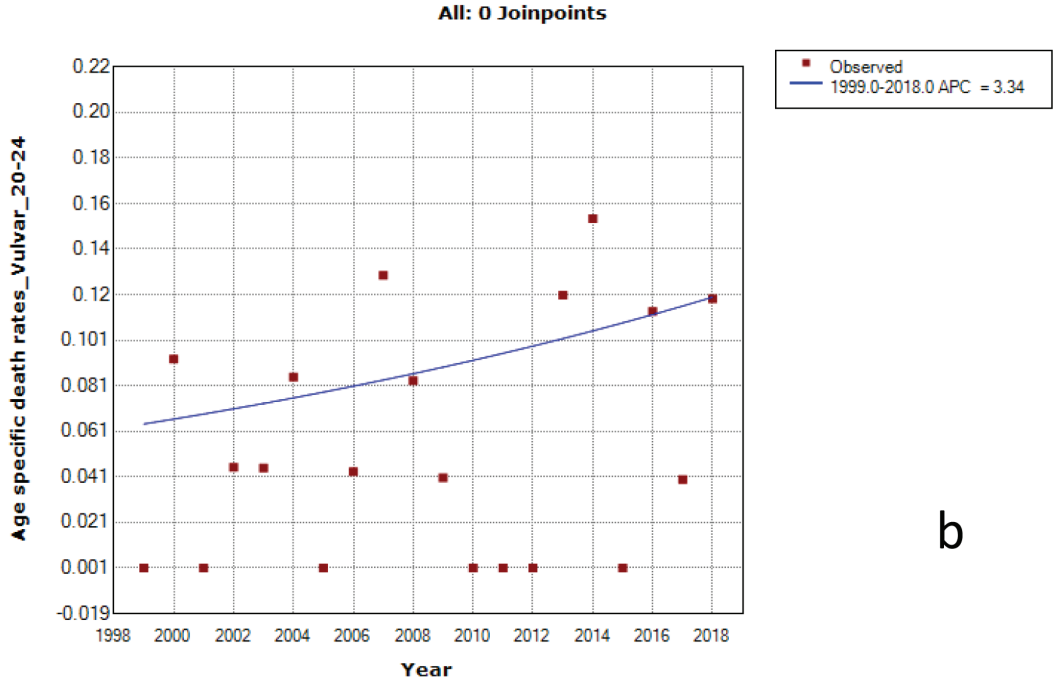

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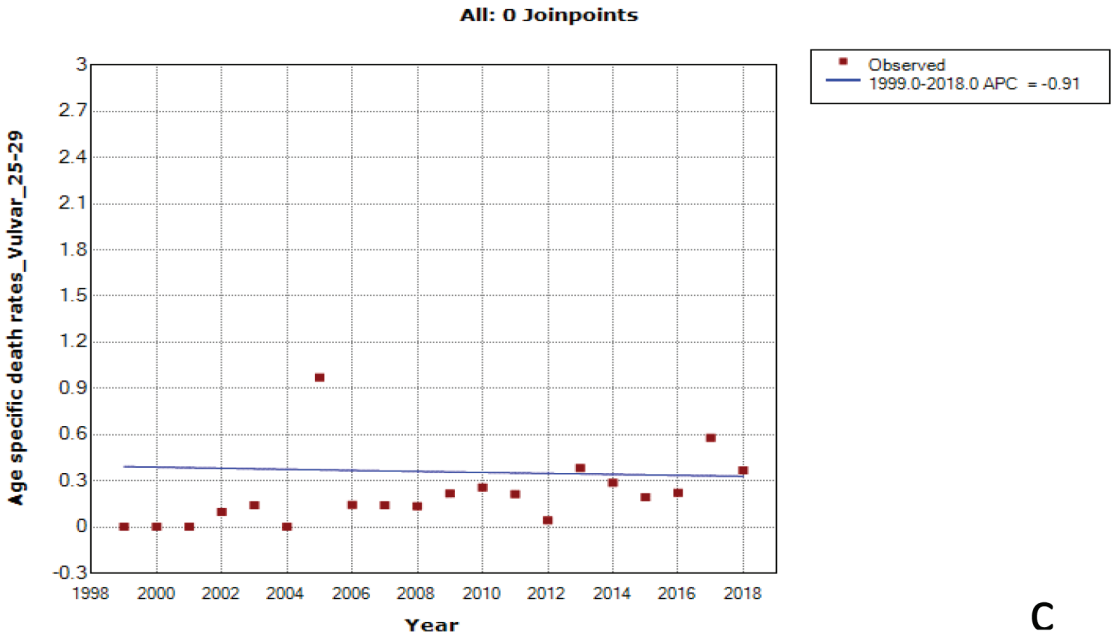

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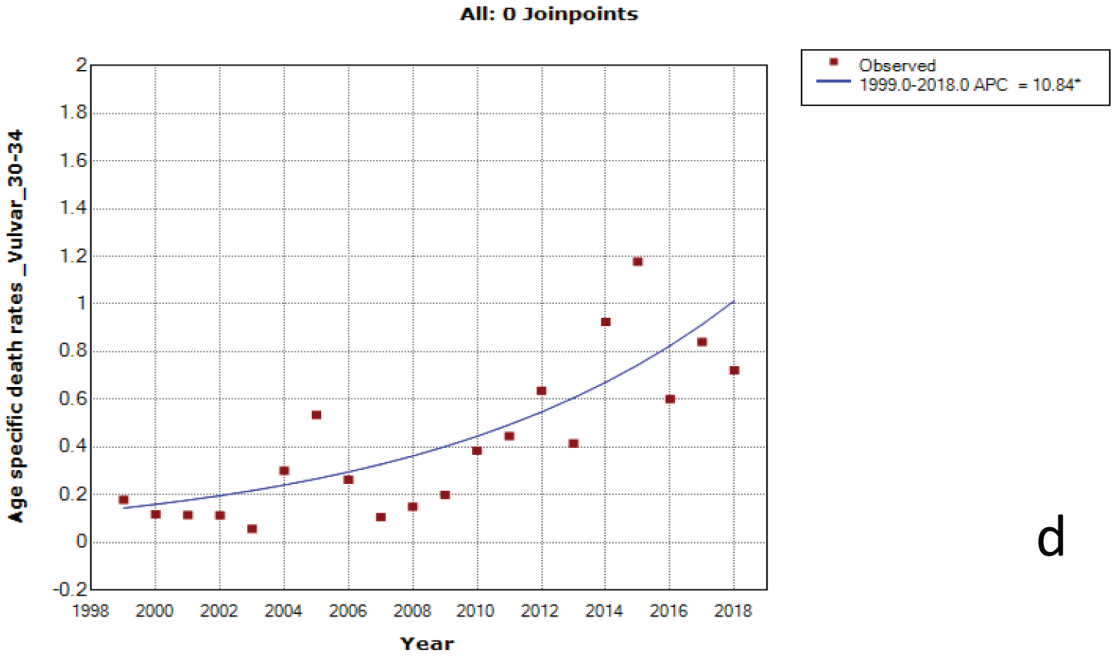

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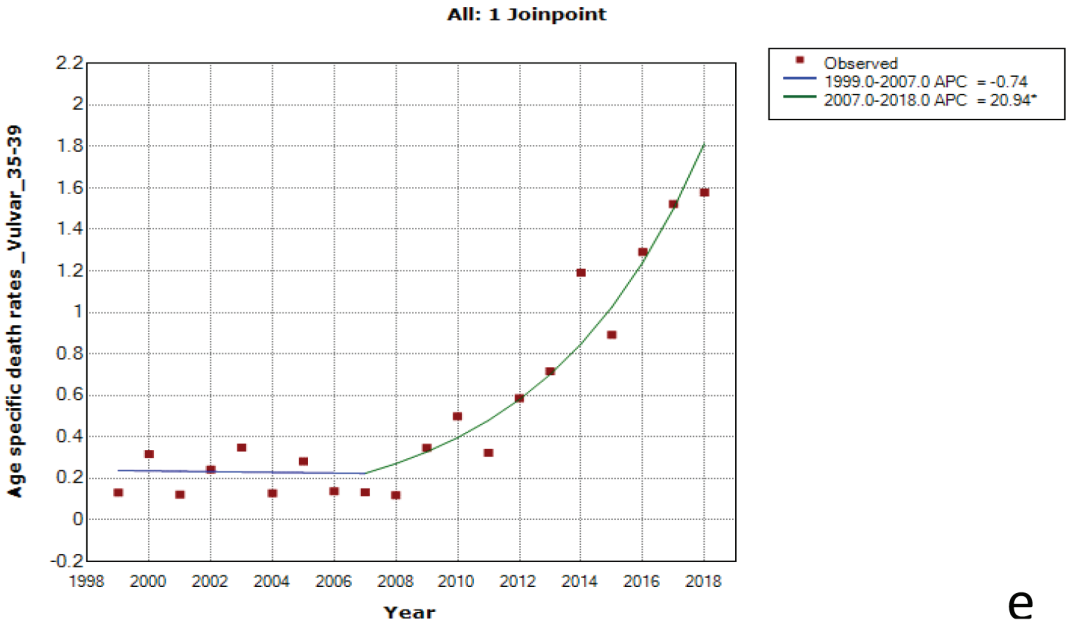

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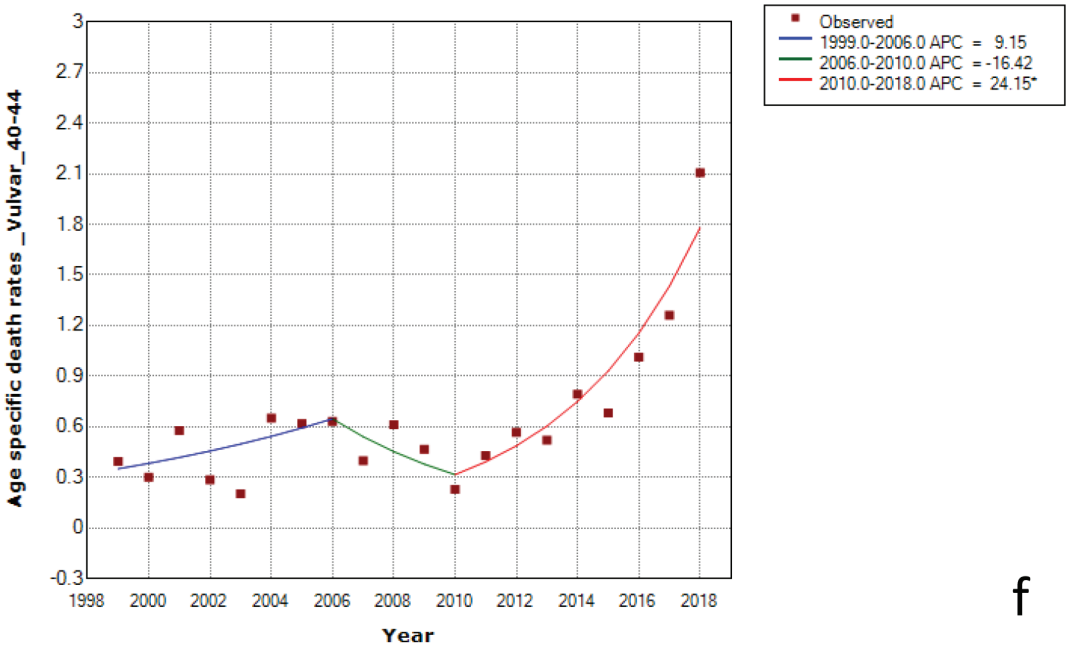

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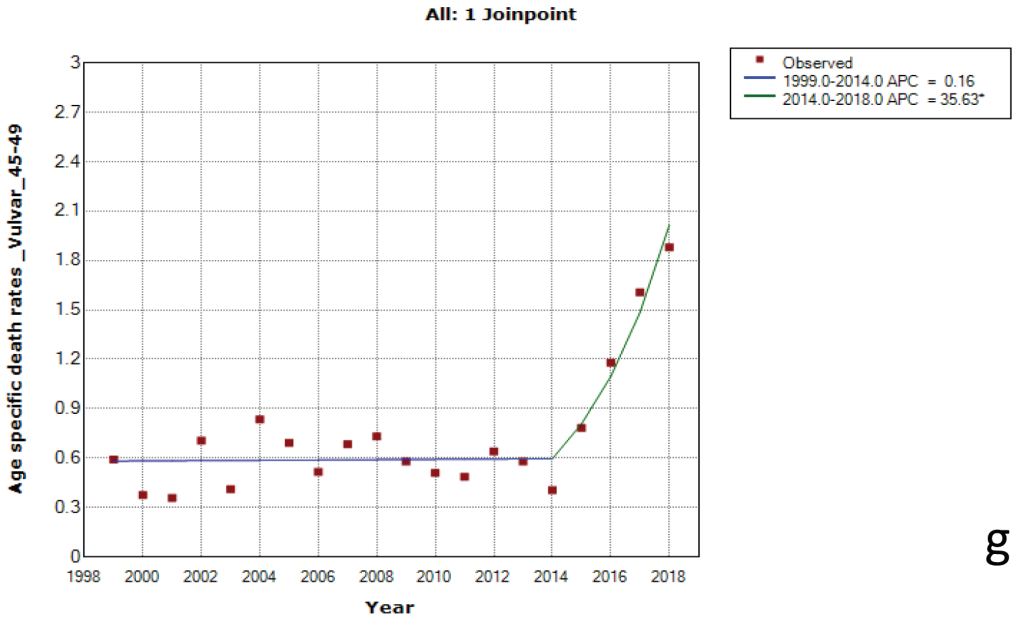

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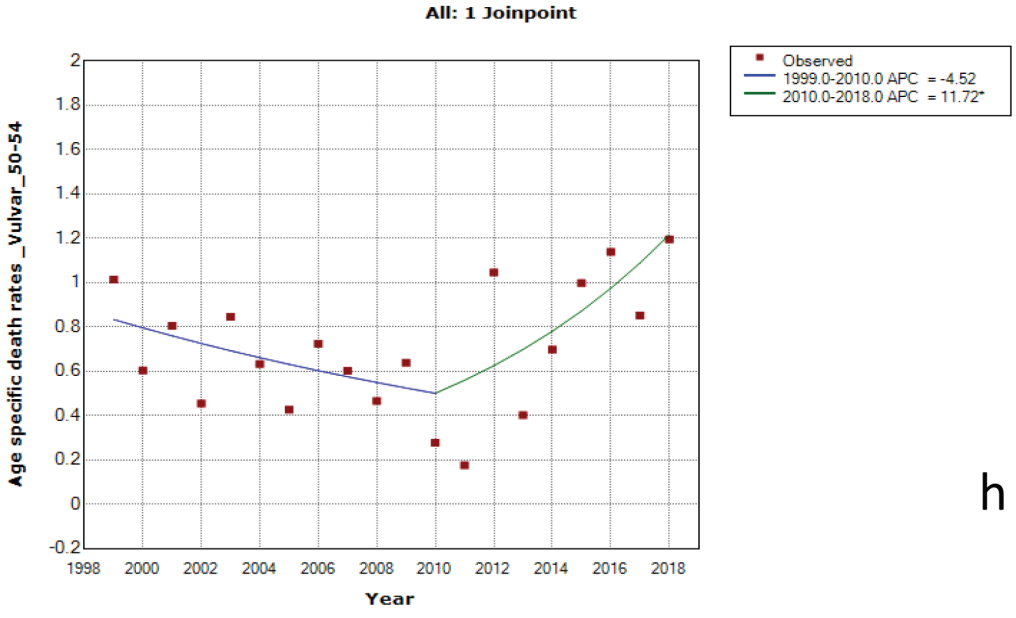

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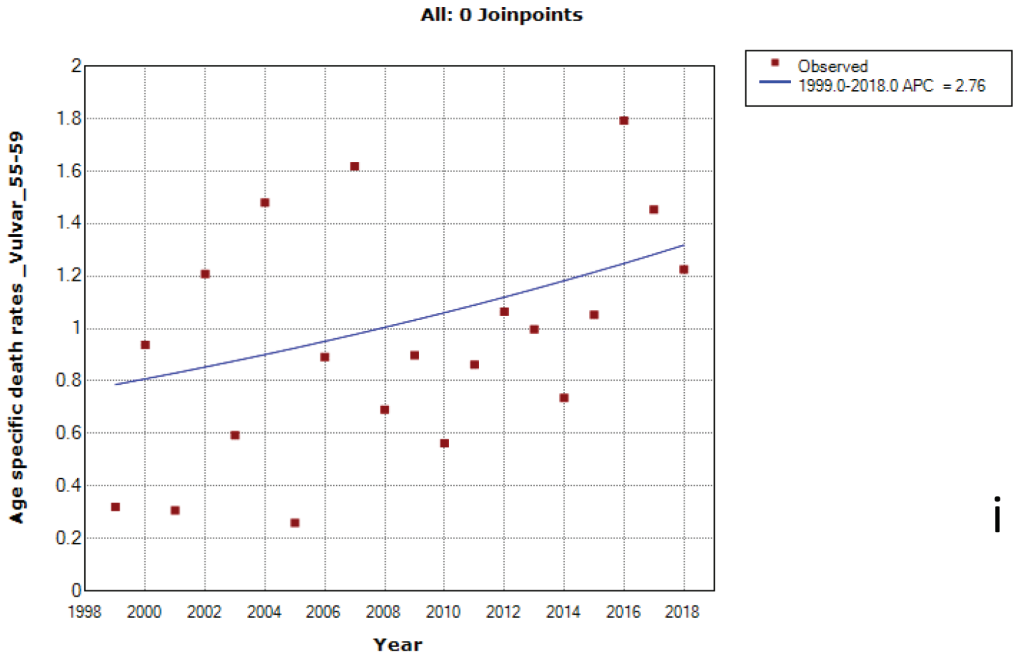

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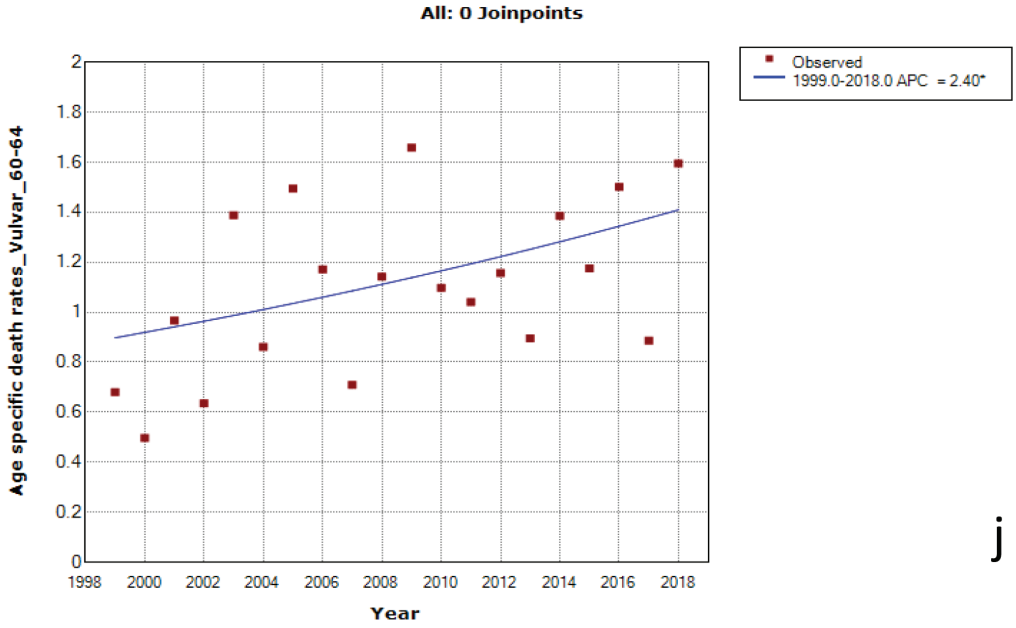

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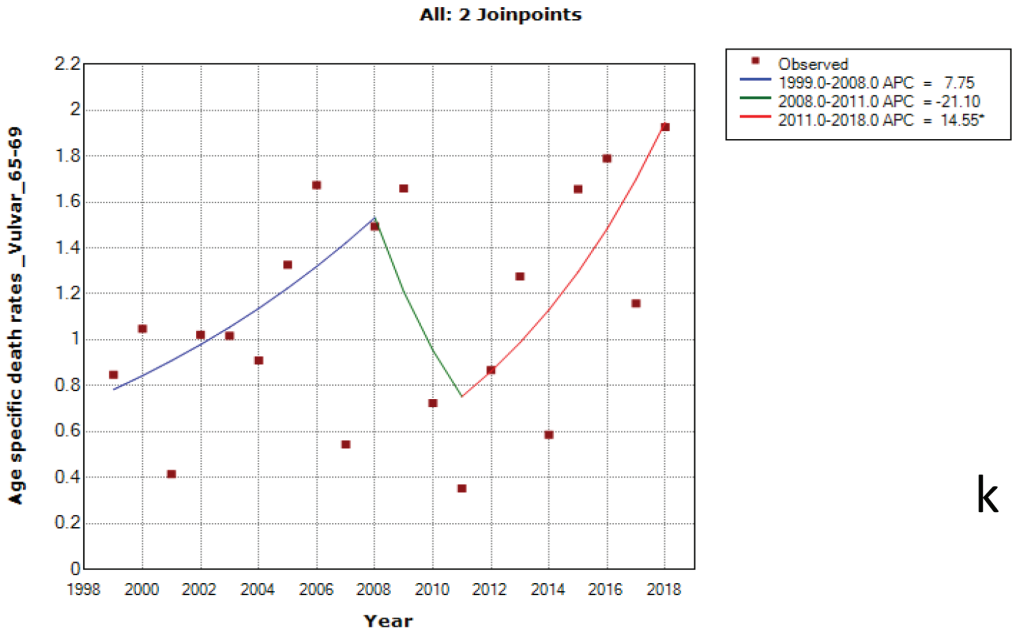

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* Indicates that the Annual Percent Change (APC) is significantly different from zero at the alpha = 0.05 level.
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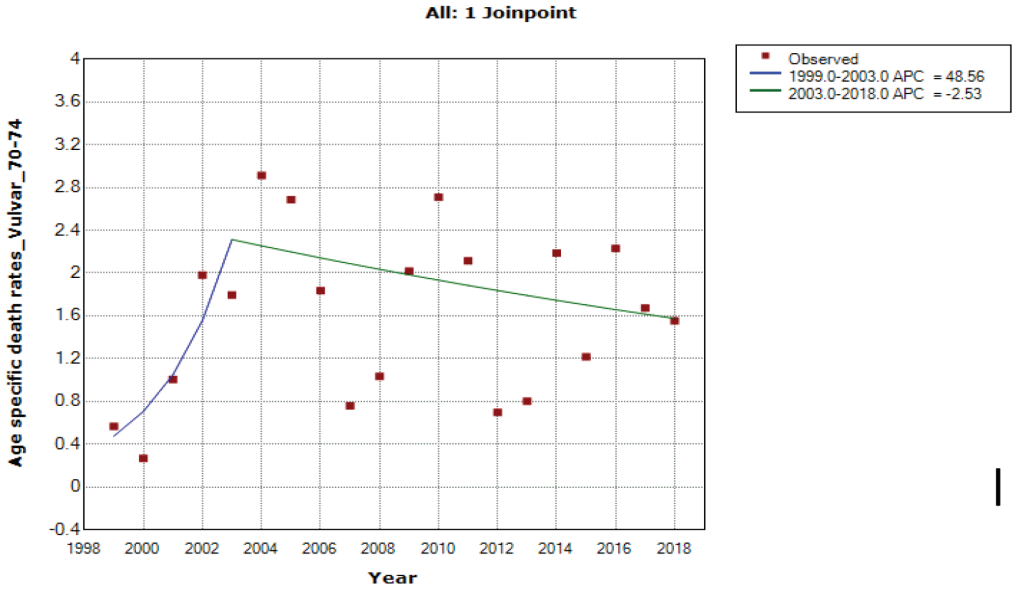

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* Indicates that the Annual Percent Change (APC) is significantly different from zero at the alpha = 0.05 level.
Final Selected Model: 0 Joinpoints.

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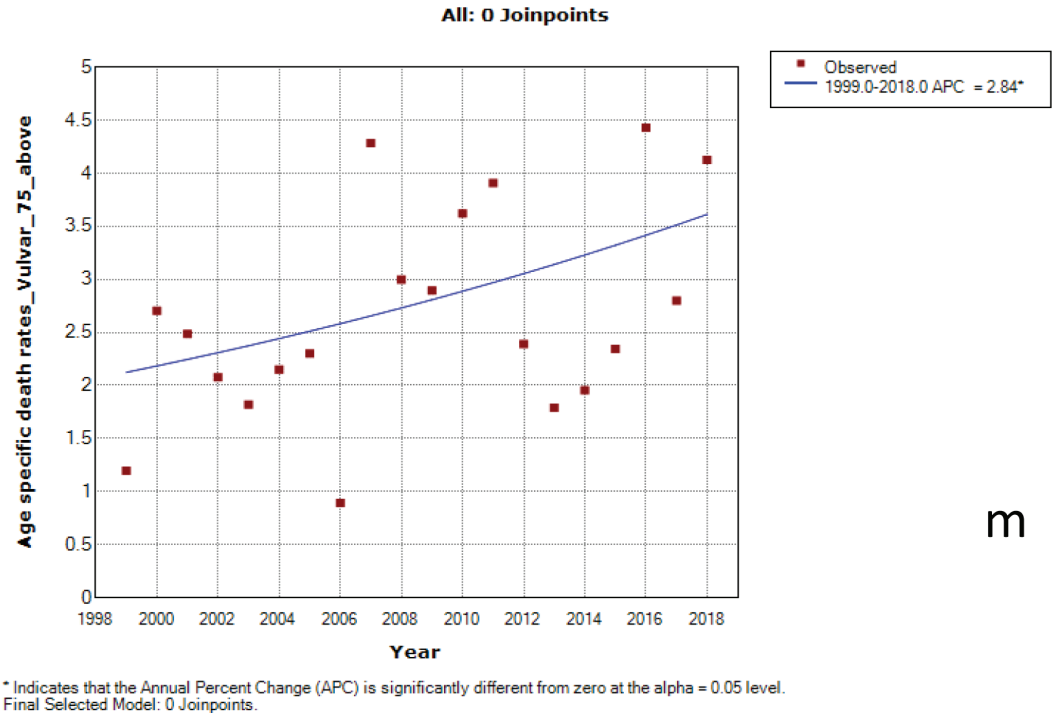

m

Figure 3. (a-m). Join point trends of age specific death rates of vulvar cancer in South Africa 1999–2018. (a): Age specific join point trends for women aged 15–19 years. (b): Age specific join point trends for women aged 20–24 years. (c): Age specific join point trends for women aged 25–29 years. (d): Age specific join point trends for women aged 30–34 years. (e): Age specific join point trends for women aged 35–39 years. (f): Age specific join point trends for women aged 40–44 years. (g): Age specific join point trends for women aged 45–49 years. (h): Age specific join point trends for women aged 50–54 years. (i): Age specific join point trends for women aged 55–59 years. (j): Age specific join point trends for women aged 60–64 years. (k): Age specific join point trends for women aged 65–69 years. (l): Age specific join point trends for women aged 70–74 years. (m): Age specific join point trends for women aged 75 years and above.

All the local drifts of vulvar cancer mortality were >0, and the drifts for women aged 25–39 years were the highest (peaked), ranging between 12.78% and 16.83% per annum. All the local drifts were statistically significant except for the 70–74-year age group (Supplementary Table 4, Supplementary Figure 1).

The local drift was >0 for Blacks and Mixed race of all ages, with women aged 25–49 years having the very high rates ranging from 9.6% to 19.5%. White women younger than 40 years had negative drift, while the net drift decreased from 5.44% among White women aged 45–49 years to 0.95% among women aged 75 years and older. Indian/Asian women aged 20–24 and 35–54 years had positive drift. The local drift among Blacks increased with increasing age from −12.41% at 20–24 years to a peak, with women aged 40–49 years having the highest drift of about 15.6%–18.10% per annum (Figure 4b, Supplementary Table 5, Supplementary Figure 2a–d).

Age effect

The RR of vulvar cancer mortality increased with age, and the pattern depicted a *J*-curve (from 0.001 at 15–19 years to 4.92 at ≥75 years). (Figure 5a, Supplementary Figure 1, Supplementary Table 4). Similarly, all ethnic groups had a *J*-curve pattern of the RR of age (Figure 5a, Supplementary Figure 2a–d, Supplementary Table 5).

Period effect

The RR for vulvar cancer mortality increased from 0.68 in 1999–2003 to1.89 in 2014–2018. (Figure 5b, Supplementary Table 4, Supplementary Figure 1). The Wald's test for period effect of overall vulvar cancer mortality trends was statistically significant (Supplementary Table 6).

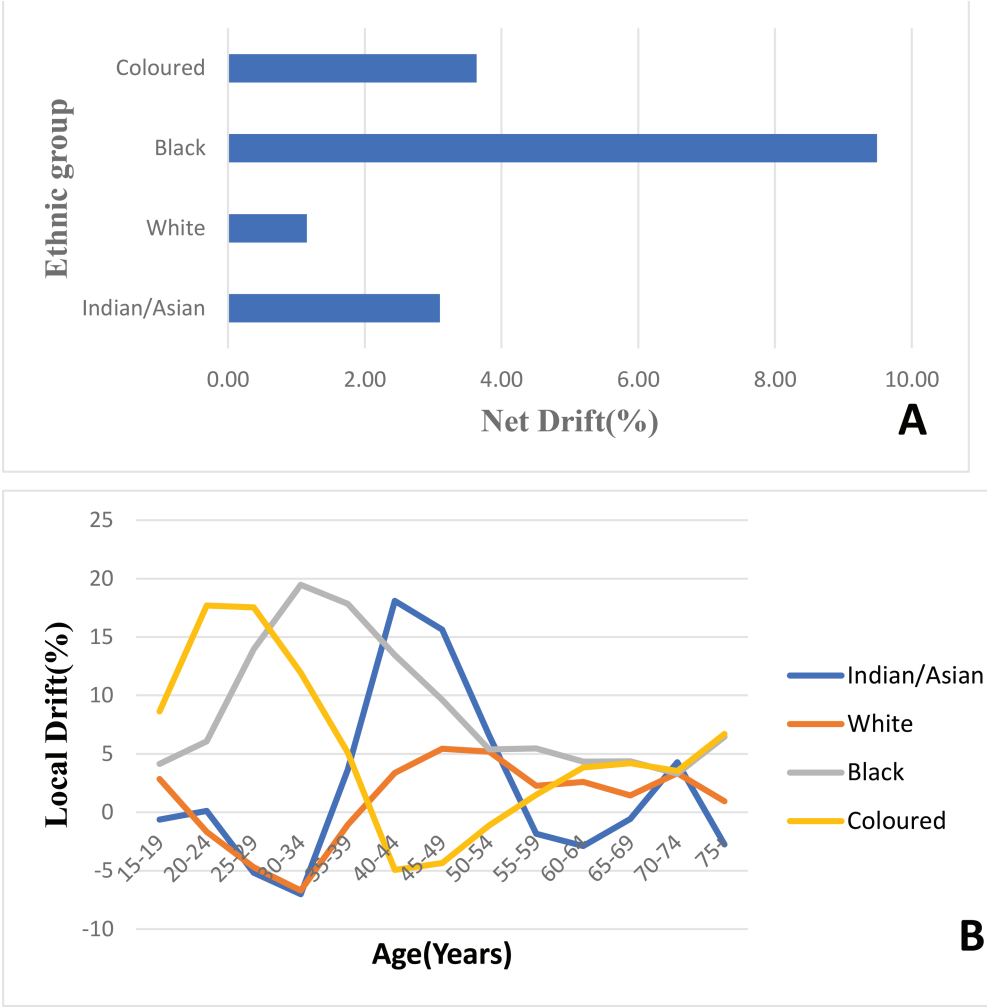

Figure 4. (a): Net drifts of vulvar cancer mortality in South Africa (1999–2018). (b): Local drifts of vulvar cancer mortality in South Africa (1999–2018).

Blacks (RR from 0.69 to 2.95), Indian/Asians (RR from 0.95 to 1.50) and Mixed race (RR from 0.71 to 1.25) generally experienced increased period RR with increasing year from 1999 to 2018. White increased from 0.78 in 1999–2003 to 1.00 in 2004–2008, then declined to 0.88 in 2009–2013 and then slightly increased to 0.98 in 2014–2018 (Figure 5b, Supplementary Table 5, Supplementary Figure 2a–d).

Wald's test showed that the period effect on vulvar cancer trends was only statistically significant among the Black ethnic group (Supplementary Table 6).

Cohort effect

The cohort mortality RR of vulvar cancer generally increased among successive birth cohorts from the earliest cohort (1924–1928) to the latest cohort (1999–2003). (RR increased from 0.18 to 75.06) (Figure 5c, Supplementary Table 5, Supplementary Figure 1). The Wald's test showed that the cohort effect was statistically significant for overall and Black women (Supplementary Table 6).

The ethnic cohort RR of vulvar cancer mortality showed that Black women had the highest RR as compared to other ethnic groups, and the RR increased among successive birth cohorts from 0.18 to 75.06. Mixed race also had increased cohort RR (0.18) from the earliest cohort to the cohort born in 1959–1963 (RR:100) then declined to 1.61 among the 1979–1983 cohort. The RR of the Mixed race then increased

till the youngest cohort of 1999–2003. The RR of Indian/Asian fluctuated among the earliest cohorts from 1924 to 1953. However, the RR then increased steadily from 0.61 among the 1949–1953 cohort to 3.60 among the youngest cohort (1999–2003). The White ethnic group generally had an increased RR among its earliest birth cohort until 1979–1983 before a decline till 1994–1998 birth cohort. (Figure 5c, Supplementary Table 5, Supplementary Figure 2a–d). The Wald's test showed that the cohort effect was not statistically significant among all the non-black ethnic groups (Supplementary Table 6).

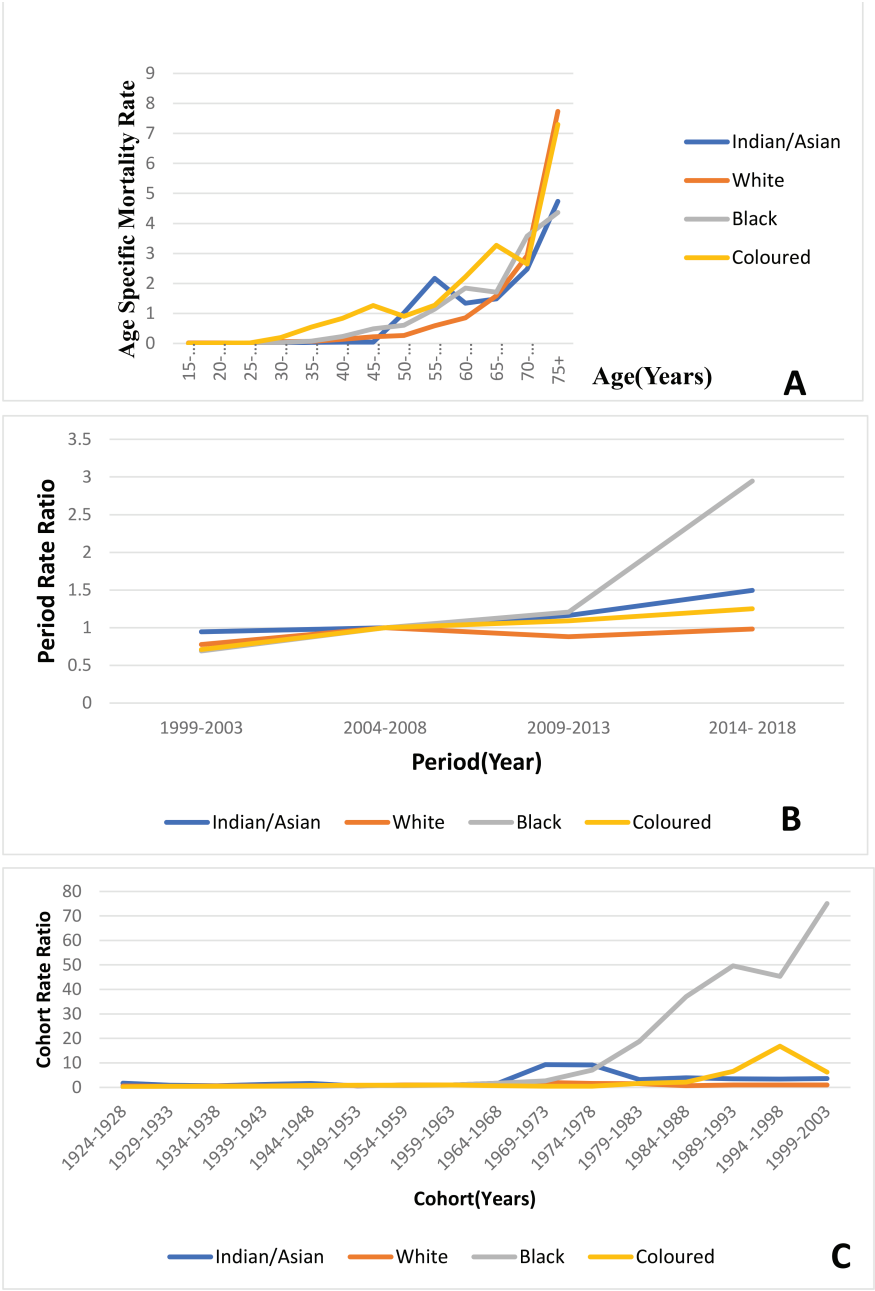

Figure 5. Mortality RR of vulvar cancer in South Africa due to (a): Age, (b): Period, and (c): Cohort after the APC analysis.

Discussion

We evaluated the trends in vulvar cancer mortality in South Africa over a 20-year period and stratified by age and ethnicity using APC and Joinpoint regression modelling. To our knowledge, this study is the first to utilise both statistical modelling techniques to describe the vulvar cancer trends in South Africa, and sub-Saharan Africa [31].

We found that the mortality rate of vulvar cancer increased by about 5.4% per annum from 0.23 deaths per 100,000 women in 1999 to 0.76 deaths per 100,000 women in 2018. This increased trend mirrors the reported increased incidence rate of vulvar cancer in the Southern African region [5, 10]. Our report is in line with reports from other low and middle income countries (LMICs) and some HICs. This is because there has been an increase in the prevalence of HIV infections over this study period (1999–2018). Despite the increased uptake in ART in South Africa since its national deployment in 2004, the vulvar cancer mortality rate is still increasing. The reason for this may be that ART uptake may not have been optimal and there might have been late diagnosis of HIV in the population [32]. Thus, early diagnosis and prompt treatment of HIV might help to reduce the vulvar cancer mortality trends. Nonetheless, HIV positive women with vulvar cancer have been reported to have a worse prognosis even while on ART, possibly because of defective immunity [14].

The increase in the prevalence of other risk factors such as increased sexual permissiveness, early sexual debut and unprotected sexual exposure might also contribute to increased prevalence of HPV associated with vulvar cancer [4–6, 33]. This is also suggested, as there was an increasing cohort-specific RR of vulvar cancer, with the youngest cohort having the highest RR. Thus, this may suggest that some deleterious behaviours among the recent cohort might be implicated. Furthermore, the increased vulvar cancer mortality in South Africa may be linked to the increasing prevalence of obesity in South Africa, as emerging evidence linked obesity with vulvar cancer [34, 35]. South Africa is currently undergoing an epidemiological transition with an increased rate of obesity [36, 37].

The expansion of access to reproductive health services in the country might lead to an increased rate of diagnosis of vulvar cancer, thereby reducing the rate of under-reporting of vulvar cancer mortality [38–40]. There might have also been improvement in the rate of death notifications to the Stats SA over time. All these might have led to an increased vulvar cancer rate in South Africa. However, the survival rate of vulvar cancer is lower than what is obtained in HICs because the majority of the patients present at advanced stages of the disease [4, 5, 9, 10, 33, 41].

Although there are no established screening schedules for vulvar cancer, it is believed that increased preventive interventions for cervical cancer should impact vulvar cancer rates, since they are both HPV-associated cancers [4, 20, 42]. South Africa has implemented cervical cancer control programs such as population-based Pap smear screening in 2002 and HPV vaccination of schoolgirls from 2004 [11, 17, 43]. These programs might have impacted the relative mortality trends of cervical cancer in contrast to the trends of vulvar cancer over the same period, as the net drift of cervical cancer was 1.5% as compared to 5.7% for vulvar cancer over the same period in South Africa [11, 32]. The public health interventions for cervical cancer in South Africa might not have a similar impact on vulvar cancer in the country. The marked differences in the trends may also partly be that vulvar cancer patients present at later stages than cervical cancer patients [28, 41, 44]. Furthermore, while the aetiology of cervical cancer is linked to high-risk HPV in >99% of cases, the prevalence of HPV-associated vulvar cancer is variable in the literature due to the rarity of the cancer and paucity of research addressing vulvar cancer epidemiology [4, 42, 45–48]. Thus, HPV-related interventions based on the epidemiology of cervical cancer may not lead to the desired reduction in the burden of vulvar cancer in the country. Further research is needed to investigate the epidemiology and clinicopathological processes of vulvar cancer to aid prevention and eradication through vaccination and early detection.

Our study found that the average age at death of vulvar cancer declined from 57.2 years in 1999 to 50.8 years in 2018. Furthermore, we found that there was a dramatic increase in the vulvar cancer mortality among women younger than 50 years during the study period. Vulvar cancer was traditionally noted to be a disease of the elderly [4, 12, 49]. However, our report is in line with contemporary reports from both LMICs and HICs that demonstrated an increased mortality rate among young women [4, 20, 47, 49]. This trend may be because of the increased prevalence of unsafe sexual behaviours that increased the global prevalence of HPV and its associated cancers, as well as the late diagnosis of HIV among some women [4, 17]. The increased drift, period and cohort RRs suggested that current public health interventions have not impacted on the risk of vulvar cancer death in the country.

Ethnic disparity of vulvar cancer trends

We found ethnic disparity in the vulvar cancer mortality rates in South Africa. The mortality rate of vulvar cancer among the White ethnic group was 0.36 per 100,000 women, which was similar to the rates in other HICs but about half of the rates among non-White ethnic groups in South Africa. Similarly, the White ethnic group had the lowest cervical cancer mortality during a similar period in South Africa [11, 17]. This low rate may be related to less risky sexual behaviour that may reduce the risk of HPV transmission and high health-seeking behaviour

leading to early-stage disease presentation and increased survival rates. HIV infection is also higher among Blacks and Mixed race, thereby leading to a higher predisposition to vulvar cancer incidence and mortality. However, the relatively high vulvar cancer rate among the Indian/Asians is surprising, as the risk factors and prevalence of HPV among them is low. Black women had the highest rate of increase in vulvar cancer mortality rates of about 7.8% per annum. An explanation for this may be because this trend mirrors the increasing HIV infection prevalence among them [17]. Increased rate of reporting as the civic registration laws are strengthened in South Africa may also be another reason for the increased rate. A surprising result was the marked increase in the annual percentage change of vulvar cancer rates among Whites at about 3.8% per annum. This calls for further interrogation as there may be a shift in the risk factor for vulvar cancer among the White ethnic group. The non-statistically significant increase in Indian/Asian and Mixed race may be because of small numbers. Nonetheless, the apparent increase in vulvar cancer rates among all the ethnic groups calls for multi-ethnic public health interventions.

The average age at death among Indian/Asians and Whites was in the 8th decade, while Mixed race and Blacks had relatively lower average age at death in the 6th and 5th decades of life, respectively. This ethnic disparity in the average age at death may suggest that prognosis and survival rates were better among White and Indian/Asians as compared to Blacks and Mixed race. This may be because the Whites and Indian/Asians had access to sexual and reproductive health services and had access to optimum oncological care [38, 39, 50]. HPV-independent vulvar cancer type may be more common among Whites and Indian/Asians since such variants occurred insidiously after a long time in the elderly [4, 20]. Whereas Blacks and Mixed race had a high prevalence rate of HIV infection and may be predisposed to HPV associated vulvar cancer at an early age [41, 51]. Thus, aggressive HIV screening and treatment can help to reduce the incidence and mortality from vulvar cancer. Pap smear screening might probably be commoner among the whites and Indian/Asian and may also lead to increased vulvar cancer detection rate. The mean age at death from vulvar cancer generally decreased among the Blacks (53 to 45 years), while the mean age among Whites (61 to 71 years) and Indian/Asians (68.5 to 73.5 years) increased and markedly fluctuated among the Mixed race (between 67 and 49 years) during the study period. This may further suggest that Whites and Indian/Asian gained from the improved oncological care of vulvar cancer. Urgent efforts are therefore necessary to reverse the poor survival rates among Blacks and Indian/Asians.

Limitations and strengths of the study

This study has some limitations that should be considered when interpreting the findings of this study. First, although we used national mortality data over a 20-year period; however, the number of vulvar cancer deaths per annum was relatively low. Thus, our further sub-group trend analyses related to age and ethnicity should be interpreted with caution because of the wide confidence intervals of the estimates. Secondly, the Stats SA mortality data do not contain some variables that can aid interpretation and further understanding of the vulvar cancer trends analysis. Such variables of interest include histological type and stage of the vulvar cancer cases at diagnosis. The trends in type of oncological treatment received and associated prevalence of HPV and HIV status among the vulvar cancer women who died may also be useful in understanding the underlying drivers of the overall and sub-group trends of the cancer. Thirdly, since Stats SA mortality data were routinely collected, data errors in death certifications or underreporting of vulvar cancer deaths may impact the reported vulvar cancer trends.

Despite these limitations, the study has some strengths: This study utilised the only national data on vulvar cancer deaths in South Africa. This study is the first to utilise both APC and Joinpoint regression analysis to extensively evaluate national vulvar cancer trends and highlight its key ethnic disparities in South Africa. The study provides useful evidence for further research on preventive interventions for vulvar cancer in South Africa.

Conclusion

In conclusion, our study demonstrated an increased vulvar cancer mortality rate in South Africa, with younger women having the largest increase. The youngest cohorts had the highest vulvar cancer risks. All the ethnic groups had increased vulvar cancer rates, and Whites and Indians/Asians had average deaths in the 8th decade, while it was in the 5th and 6th decades for Blacks and Mixed race, suggesting HIV infection as a driving force. Efforts geared towards investigating and controlling this disease are needed.

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We acknowledge Stats SA for supplying the data for the study.

Conflicts of interest

All authors declare that they have no conflicts of interest to declare.

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Consent for publication

Not applicable as publicly available anonymised data was utilised.

Ethical approval and consent to participate

The study protocol was approved by the Human Research Ethics Committee (Medical) of the University of the Witwatersrand (Clearance certificate number: M190544) dated: 31/10/2019. The study was performed in accordance with the Helsinki Declaration. Since the study was secondary data analysis, consent to participate was not necessary.

Data availability

Publicly available datasets were analysed in this study. These data can be obtained from Statistics South Africa.

Author contributions

Conceptualisation and study design: GO, EM, EL, OCE; data acquisition: GO, EM, EL; data management and data analysis: GO, AES; data interpretation: GO, EM, EL, OCE, AES; writing original draft: GO; critical review of manuscript and acceptance on the manuscript submission: GO, EM, EL, OCE, AES; supervision of the project: EM, EL, OCE. All authors contributed to the article and approved the submitted version.

Disclosure statement

The authors declare that they do not have any conflicting interests.

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SUPPLEMENTARY TABLES FOR VULVAR CANCER TRENDS STUDY

Supplementary Table 1. Joinpoint regression estimates of the trends in ASMR of vulva cancer in South Africa (1999–2018).

Vulvar	Trends	Year period		APC	95%CI		*p*-value
Overall ASMR							
	1	1999	2004	8.5*	2.4	15.1	0.0
	2	2004	2013	1.0	−1.4	3.6	0.4
	3	2013	2018	15.6*	11.1	20.2	0.0
	Full range	1999	2018	5.4*	4.2	6.7	0.0
Blacks							
	1	1999	2004	13.6*	2.3	26.3	0.0
	2	2004	2010	−2.7	−11.2	6.6	0.5
	3	2010	2018	15.7*	11.9	19.6	0.0
	Full range	1999	2018	7.8*	6.0	9.7	0.0
Indian/Asian							
	1	1999	2003	−13.4	−43.7	33.2	0.5
	2	2003	2018	4.7	−1.2	10.9	0.1
	Full range	1999	2018	1.9	−1.6	5.7	0.3
Mixed race							
	1	1999	2014	0.7	−27.6	75.5	0.8
	2	2014	2018	9.4	−26.6	52.9	0.2
	Full range	1999	2018	2.5	−1.91	8.6	0.3
White							
	1	1999	2008	5.4	−2.3	13.8	0.2
	2	2008	2014	−3.8	−19.0	14.2	0.6
	3	2014	2018	21.2	−4.0	53.1	0.1
	Full range	1999	2018	3.8*	1.7	6.0	0.0

*APC show a statistically significant trend at *p*-value <0.05

Supplementary Table 2. Trends in mortality rate and mean age at death of vulvar cancer among ethnic groups in South Africa, 1999–2018.

Year	Black (*n* = 1,190)				White (*n* = 239)				Mixed race (*n* = 180)				Asian (*n* = 56)			
	Mortality (% of gynaecological and breast cancer) ≥ 15 year	Age mean ± SD	CMR	ASMR	Mortality (% of gynaecological and breast cancer) ≥ 15 year	Age mean ± SD	CMR	ASMR	Mortality (% of gynaecological and breast cancer) ≥ 15 year	Age mean ± SD	CMR	ASMR	Mortality (% of gynaecological and breast cancer) ≥ 15 year	Age mean ± SD	CMR	ASMR
1999	14	53.57 ± 11.55	0.12	0.12	6	61.67 ± 19.30	0.33	0.20	6	58.00 ± 13.78	0.43	0.38	2	68.50 ± 13.44	0.47	0.39
2000	26	48.81 ± 16.09	0.22	0.20	11	79.55 ± 5.70	0.61	0.21	3	67.67 ± 30.53	0.21	0.18	3	64.00 ± 18.36	0.70	0.55
2001	22	64.73 ± 15.31	0.18	0.16	7	77.71 ± 13.90	0.39	0.14	10	47.80 ± 7.39	0.68	0.52	0	0.00	0.00	0.00
2002	34	51.62 ± 14.84	0.27	0.24	9	76.56 ± 12.47	0.49	0.19	4	61.75 ± 4.99	0.27	0.28	2	65.50 ± 13.44	0.45	0.39
2003	36	56.25 ± 15.82	0.27	0.24	8	78.50 ± 9.27	0.44	0.17	3	43.00 ± 5.29	0.20	0.12	1	55.00 ± 0.00	0.22	0.15
2004	41	52.07 ± 15.66	0.33	0.31	9	60.33 ± 16.48	0.49	0.27	8	51.75 ± 14.74	0.55	0.44	2	69.00 ± 19.80	0.46	0.34
2005	29	56.83 ± 16.48	0.23	0.22	12	76.50 ± 9.23	0.66	0.26	13	50.31 ± 13.11	0.86	0.67	1	82.00 ± 0.00	0.22	0.15
2006	40	52.40 ± 13.48	0.32	0.28	6	68.33 ± 13.05	0.33	0.15	7	60.71 ± 17.48	0.46	0.40	3	61.00 ± 11.14	0.66	0.45
2007	37	51.81 ± 17.51	0.29	0.24	13	73.31 ± 13.84	0.71	0.27	6	63.00 ± 13.58	0.38	0.33	1	63.00 ± 0.00	0.22	0.16
2008	31	47.87 ± 17.23	0.23	0.20	15	69.87 ± 12.74	0.79	0.31	8	63.38 ± 12.59	0.49	0.43	4	70.75 ± 10.50	0.82	0.61
2009	40	54.50 ± 18.40	0.29	0.26	11	71.09 ± 11.74	0.60	0.28	12	58.00 ± 10.33	0.72	0.65	2	57.50 ± 26.16	0.40	0.25
2010	41	52.78 ± 19.43	0.30	0.25	13	73.62 ± 16.19	0.67	0.25	7	57.71 ± 15.33	0.41	0.31	4	61.50 ± 10.60	0.79	0.52

Continued

Supplementary Table 2. Trends in mortality rate and mean age at death of vulvar cancer among ethnic groups in South Africa, 1999–2018. *Continued*

Year	Black (*n* = 1,190)				White (*n* = 239)				Mixed race (*n* = 180)				Asian (*n* = 56)			
	Mortality (% of gynaecological and breast cancer) ≥ 15 year	Age mean ± SD	CMR	ASMR	Mortality (% of gynaecological and breast cancer) ≥ 15 year	Age mean ± SD	CMR	ASMR	Mortality (% of gynaecological and breast cancer) ≥ 15 year	Age mean ± SD	CMR	ASMR	Mortality (% of gynaecological and breast cancer) ≥ 15 year	Age mean ± SD	CMR	ASMR
2011	50	50.20 ± 19.49	0.36	0.28	11	75.18 ± 12.98	0.57	0.20	8	62.00 ± 8.88	0.46	0.40	3	61.67 ± 21.08	0.39	0.26
2012	52	47.10 ± 14.52	0.37	0.28	13	69.54 ± 10.24	0.66	0.27	14	53.43 ± 11.34	0.80	0.59	4	65.50 ± 12.66	0.78	0.52
2013	68	45.38 ± 15.23	0.45	0.33	11	73.45 ± 13.95	0.56	0.21	7	61.43 ± 11.56	0.39	0.32	1	68.00 ± 0.00	0.19	0.14
2014	96	45.74 ± 15.71	0.63	0.47	11	69.09 ± 14.71	0.57	0.22	6	49.67 ± 20.52	0.33	0.23	4	69.00 ± 3.46	0.77	0.56
2015	104	46.36 ± 16.16	0.67	0.50	10	71.70 ± 13.57	0.51	0.18	11	58.45 ± 14.02	0.59	0.46	3	63.00 ± 8.66	0.56	0.34
2016	124	48.29 ± 15.36	0.78	0.60	23	74.83 ± 10.84	1.19	0.37	15	61.20 ± 15.18	0.81	0.61	6	55.00 ± 4.10	1.11	0.71
2017	140	43.36 ± 13.29	0.86	0.62	18	69.56 ± 14.49	0.00	0.00	11	53.09 ± 17.97	0.59	0.40	1	54.00 ± 0.00	0.18	0.11
2018	165	45.80 ± 13.81	1.00	0.74	22	71.50 ± 11.79	1.12	0.36	21	54.95 ± 16.38	1.09	0.71	9	73.56 ± 12.41	1.55	0.75

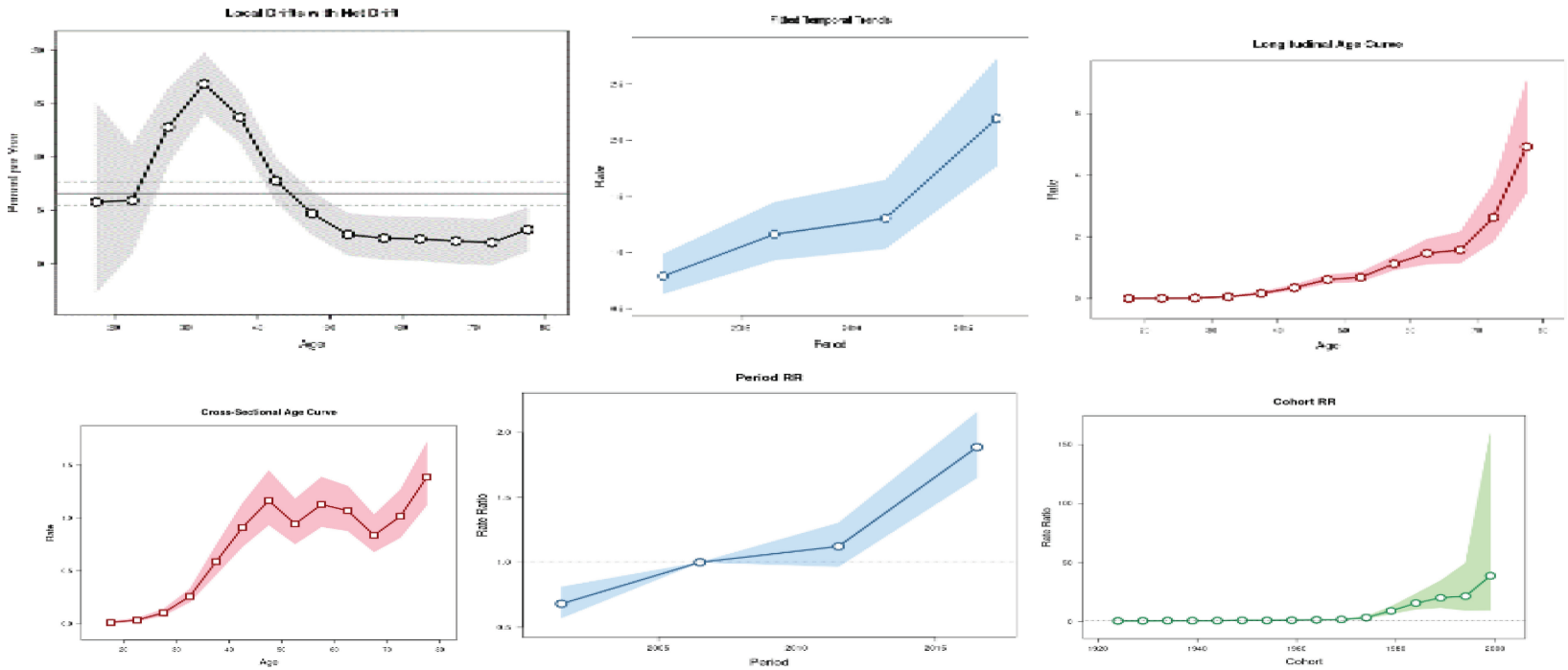
Supplementary Table 3. Joinpoint trends in the national and ethnic age-specific mortality rates of vulvar cancer in South Africa 1999–2018.

Vulvar	Range	Lower endpoint	Upper endpoint	AAPC	Lower CI	Upper CI	Test statistic~	*p*-value~
15–19	Full range	1999	2018	0.5	−5.5	6.8	0.2	0.9
20–24	Full range	1999	2018	3.3	−1.2	8.1	1.5	0.1
25–29	Full range	1999	2018	−0.9	−7.8	6.5	−0.3	0.8
30–34	Full range	1999	2018	10.8*	6.5	15.4	5.4	0.0
35–39	1	1999	2007	−0.7	−15.0	15.9	−0.1	0.9
	2	2007	2018	20.9*	14.7	27.5	7.6	0.0
	Full range	1999	2018	14.1*	10.7	17.6	9.2	0.0
40–44	1	1999	2006	9.1	−4.1	24.3	1.5	0.2
	2	2006	2010	−16.4	−49.9	39.4	−0.8	0.5
	3	2010	2018	24.1*	14.8	34.2	6.0	0.0
	Full range	1999	2018	8.1*	4.8	11.5	5.2	0.0
45–49	1	1999	2014	0.2	−2.9	3.3	0.1	0.9
	2	2014	2018	35.6*	16.4	58.0	4.3	0.0
	Full range	1999	2018	6.3*	3.3	9.3	4.6	0.0
50–54	1	1999	2010	−4.5	−10.6	1.9	−1.5	0.2
	2	2010	2018	11.7*	0.6	24.1	2.3	0.0
	Full range	1999	2018	1.9	−0.9	4.8	1.4	0.2
55–59	Full range	1999	2018	2.8	−0.7	6.3	1.7	0.1
60–64	Full range	1999	2018	2.4*	0.1	4.8	2.2	0.0
65–69	1	1999	2008	7.7	−3.1	19.8	1.5	0.2
	2	2008	2011	−21.1	−74.0	139.5	−0.5	0.7
	3	2011	2018	14.5*	0.3	30.8	2.2	0.0
	Full range	1999	2018	2.9	−0.2	6.0	1.9	0.1
70–74	1	1999	2003	48.6	−11.2	148.6	1.6	0.1
	2	2003	2018	−2.5	−6.9	2.1	−1.2	0.3
	Full range	1999	2018	0.2	−3.8	4.4	0.1	0.9
75+	Full range	1999	2018	2.8*	0.1	5.7	2.1	0.0

*AAPC had a statistically significant trend at *p*-Value <0.05

Supplementary Table 4. APC effect estimates of trends in vulva cancer mortality in South Africa, 1999–2018.

Factor	Overall					
	Longitudinal RR(adjusted for period effect)	95%CI	Cross sectional RR (Adjusted for cohort effect)	95%CI	Local drift(%)	95%CI
Age						
15–19	0.001	0.000–0.002	0.01	0.004–0.023	5.77	−2.69–14.96
20–24	0.004	0.002–0.007	0.03	0.02–0.05	5.91	0.99–11.08
25–29	0.02	0.01–0.02	0.10	0.07–0.14	12.78	9.35–16.32
30–34	0.05	0.04–0.08	0.26	0.20–0.33	16.83	14.03–19.70
35–39	0.16	0.12–0.23	0.59	0.46–0.74	13.70	11.38–16.07
40–44	0.35	0.27–0.45	0.91	0.73–1.14	7.76	5.75–9.80
45–49	0.61	0.50–0.76	1.16	0.93–1.45	4.69	2.71–6.71
50–54	0.68	0.55–0.86	0.94	0.75–1.18	2.72	0.80–4.68
55–59	1.12	0.92–1.37	1.13	0.92–1.39	2.38	0.39–4.41
60–64	1.46	1.11–1.93	1.07	0.88–1.30	2.31	0.29–4.37
65–69	1.57	1.15–2.16	0.84	0.68–1.03	2.11	0.02–4.25
70–74	2.63	1.85–3.74	1.02	0.81–1.27	1.98	−0.12–4.11
75+	4.92	3.43–7.06	1.39	1.12–1.71	3.19	1.16–5.25
Net drift (%)					6.56	5.47–7.65
Period	**Rate Ratio**	**95%CI**				
1999–2003	0.68	0.57–0.81				
2004–2008	1.00	1.00–1.00				
2009–2013	1.12	0.97–1.30				
2014–2018	1.89	1.65–2.16				
Cohort	**Rate Ratio**	**95%CI**				
1924–1928	0.41	0.27–0.65				
1929–1933	0.47	0.31–0.72				
1934–1938	0.64	0.44–0.94				
1939–1943	0.63	0.45–0.88				
1944–1948	0.66	0.49–0.89				
1949–1953	0.90	0.69–1.16				
1954–1959	0.83	0.66–1.06				
1959–1963	1.00	1.00–1.00				
1964–1968	1.32	1.04–1.68				
1969–1973	1.63	1.25–2.12				
1974–1978	3.24	2.41–4.36				
1979–1983	8.93	6.30–12.66				
1984–1988	15.53	10.25–23.52				
1989–1993	20.00	11.55–34.63				
1994–1998	21.39	9.25–49.45				
1999–2003	38.67	9.38–159.44				



Supplementary Figure 1. Age, period and cohort effects of vulva cancer mortality in South Africa (1999- 2018) due to (local drift, fitted temporal trends, longitudinal age curve, cross-sectional age curve, period effect and cohort effect were depicted for each cancer).

Supplementary Table 5. APC effect estimates of trends in vulva cancer mortality in South Africa, 1999–2018.

Factor	BLACK			WHITE			ASIAN			COLOURED		
	Longitudinal RR (adjusted for period effect (95%CI)	Cross-sectional RR (Adjusted for cohort effect (95%CI)	Local drift (%) (95%CI)	Longitudinal RR (adjusted for period effect (95%CI)	Cross-sectional RR (Adjusted for cohort effect (95%CI)	Local drift (%) (95%CI)	Longitudinal RR (adjusted for period effect (95%CI)	Cross-sectional RR (Adjusted for cohort effect (95%CI)	Local drift(%) (95%CI)	Longitudinal RR(adjusted for period effect (95%CI)	Cross sectional RR (Adjusted for cohort effect (95%CI)	Local drift (%) (95%CI)
Age												
15–19	0.006 (0.001–0.037)	0.008 (0.002–0.032)	−5.30 (−20.74 to 13.15)	0.074 (0.000–55.112)	0.0162 (0.0003–0.8027)	1.67 (−37.57 to 65.60)	0.21 (0.00–432.70)	0.04 (0.00–2.35)	0.17 (−38.66 to 63.60)	0.002 (0.000–0.116)	0.0047 (0.0001–0.1587)	8.64 (−31.19 to 71.52)
20–24	0.006 (0.001–0.030)	0.007 (0.002–0.030	−12.41 (−33.53 to 15.41)	0.085 (0.000–30.495)	0.023 (0.001–0.770)	0.95 (−32.34 to 50.64)	0.20 (0.00–225.22)	0.05 (0.00–2.25)	−0.67 (−33.46 to 48.27)	0.005 (0.000–0.209)	0.013 (0.001–0.253)	17.70 (−9.33 to 52.78)
25–29	0.010 (0.003–0.038)	0.013 (0.004–0.039)	−0.73 (−9.87 to 9.34)	0.097 (0.001–17.896)	0.032 (0.001–0.944)	2.04 (−30.41 to 49.62)	0.18 (0.00–112.00)	0.07 (0.00–2.69)	−3.11 (−34.01 to 42.26)	0.014 (0.001–0.367)	0.029 (0.002–0.419)	17.53 (−4.94 to 45.31)
30–34	0.03 (0.01–0.08)	0.04 (0.02–0.08)	1.13 (−6.41 to 9.29)	0.060 (0.001–4.985)	0.024 (0.001–0.656)	−9.97 (−36.86 to 28.35)	0.14 (0.00–51.20)	0.09 (0.00–3.39)	−5.90 (−35.41 to 37.09)	0.20 (0.05–0.86)	0.35 (0.11–1.13)	11.94 (0.82 to 24.28)
35–39	0.06 (0.03–0.14)	0.07 (0.03–0.14)	6.37 (−0.17 to 13.33)	0.19 (0.02–1.81)	0.09 (0.01–1.08)	−15.16 (−37.11 to 14.44)	0.26 (0.00–27.96)	0.24 (0.01–6.62)	−13.29 (−36.68 to 18.75)	0.54 (0.20–1.47)	0.80 (0.30–2.10)	5.10 (−2.28 to 13.05)
40–44	0.09 (0.05–0.18)	0.10 (0.05–0.20)	4.92 (−0.49 to 10.63)	0.20 (0.03–1.36)	0.11 (0.02–0.82)	−12.27 (−31.38 to 12.16)	0.07 (0.00–5.95)	0.09 (0.00–4.55)	−9.45 (−35.69 to 27.48)	0.84 (0.46–1.52)	1.03 (0.44–2.37)	−4.93 (−11.25 to 1.83)
45–49	0.11 (0.06–0.20)	0.12 (0.06–0.23)	0.02 (−5.21 to 5.53)	0.10(0.03–0.39)	0.07 (0.01–0.38)	−5.25 (−16.49 to 7.49)	0.03 (0.00–1.99)	0.07 (0.00–3.35)	−13.91 (−39.02 to 21.54)	1.27 (0.74–2.18)	1.30 (0.65–2.61)	−4.35 (−10.01 to 1.66)
50–54	0.13 (0.06–0.27)	0.13 (0.07–0.25)	-3.84 (−9.34 to 2.00)	0.15 (0.04–0.49)	0.13 (0.04–0.41)	−3.13 (−13.67 to 8.71)	0.06 (0.00–2.83)	0.21 (0.01–3.62)	−1.61 (−31.80 to 41.96)	0.91 (0.49–1.66)	0.78 (0.40–1.52)	−1.12 (−6.69 to 4.77)
55–59	0.19 (0.10–0.36)	0.20 (0.11–0.34)	−0.28 (−5.59 to 5.32)	0.19 (0.06–0.57)	0.20 (0.07–0.56)	−2.86 (−12.06 to 7.31)	0.07 (0.00–3.67)	0.36 (0.02–8.27)	−8.61 (−35.54 to 29.56)	1.28 (0.70–2.32)	0.92 (0.49–1.72)	1.50 (−3.87 to 7.18)

Continued

Supplementary Table 5. APC effect estimates of trends in vulva cancer mortality in South Africa, 1999–2018.

Factor	BLACK			WHITE			ASIAN			COLOURED		
	Longitudinal RR (adjusted for period effect (95%CI)	Cross-sectional RR (Adjusted for cohort effect (95%CI)	Local drift (%) (95%CI)	Longitudinal RR (adjusted for period effect (95%CI)	Cross-sectional RR (Adjusted for cohort effect (95%CI)	Local drift (%) (95%CI)	Longitudinal RR (adjusted for period effect (95%CI)	Cross-sectional RR (Adjusted for cohort effect (95%CI)	Local drift(%) (95%CI)	Longitudinal RR(adjusted for period effect (95%CI)	Cross sectional RR (Adjusted for cohort effect (95%CI)	Local drift (%) (95%CI)
Age												
60–64	0.14 (0.06–0.34)	0.14 (0.07–0.26)	1.59 (−3.69 to 7.15)	0.25 (0.06–0.97)	0.31 (0.13–0.74)	8.61 (−0.29 to 18.30)	0.06 (0.00–10.86)	0.45 (0.03–6.44)	−10.54 (−35.00 to 23.13)	2.22 (1.05–4.71)	1.33 (0.74–2.40)	3.83 (−2.15 to 10.16)
65–69	0.27 (0.11–0.67)	0.25 (0.14–0.46)	7.00 (0.72 to 13.68)	0.44 (0.09–2.16)	0.68 (0.22–2.07)	5.54 (−4.15 to 16.20)	0.05 (0.00–19.12)	0.59 (0.03–11.54)	−19.22 (−40.38 to 9.45)	3.27 (1.39–7.69)	1.64 (0.86–3.13)	4.19 (−2.19 to 10.99)
70–74	0.58 (0.23–1.48)	0.53 (0.29–0.97)	2.08 (−2.82 to 7.21)	0.50 (0.09–2.78)	0.93 (0.21–4.11)	2.25 (−5.82 to 11.01)	0.05 (0.00–19.29)	0.86 (0.08–9.34)	−5.04 (−25.72 to 21.39)	2.64 (0.84–8.34)	1.11 (0.45–2.75)	3.54 (−4.04 to 11.73)
75+	0.72 (0.25–2.02)	0.63 (0.32–1.22)	2.39 (−4.12 to 9.34)	1.68 (0.29–9.54)	3.77 (0.69–20.64)	−3.74 (−9.48 to 2.35)	0.06 (0.00–25.56)	1.73 (0.13–22.41)	11.33 (−24.19 to 63.49)	7.30 (2.38–22.42)	2.56 (1.06–6.20)	6.71 (−2.79 to 17.14)
Net Drift (%)			0.75 (−2.28 to 3.87)			-3.80 (−12.68 to 5.98)			−8.12(−20.92 to 6.76			3.64 (−0.61 to 8.07
Period	**Rate Ratio**	**(95%CI)**		**Rate Ratio**	**(95%CI)**		**Rate Ratio**	**(95%CI)**		**Rate Ratio**	**(95%CI)**	
1999–2003	0.93	0.60–1.45		1.01	0.39–2.62		1.15	0.15–8.81		0.71	0.40–1.25	
2004–2008	1.00	1.00–1.00		1.00	1.00–1.00		1.00	1.00–1.00		1.00	1.00–1.00	
2009–2013	0.68	0.42–1.08		0.76	0.30–1.94		0.49	0.09–2.69		1.09	0.68–1.74	
2014–2018	1.21	0.80–1.81		0.58	0.19–1.73		0.36	0.04–3.13		1.25	0.76–2.07	
Cohort												
1924–1928	0.46	0.12–1.81		0.93	0.15–5.59		5.03	0.00–29201.20		0.18	0.03–1.06	

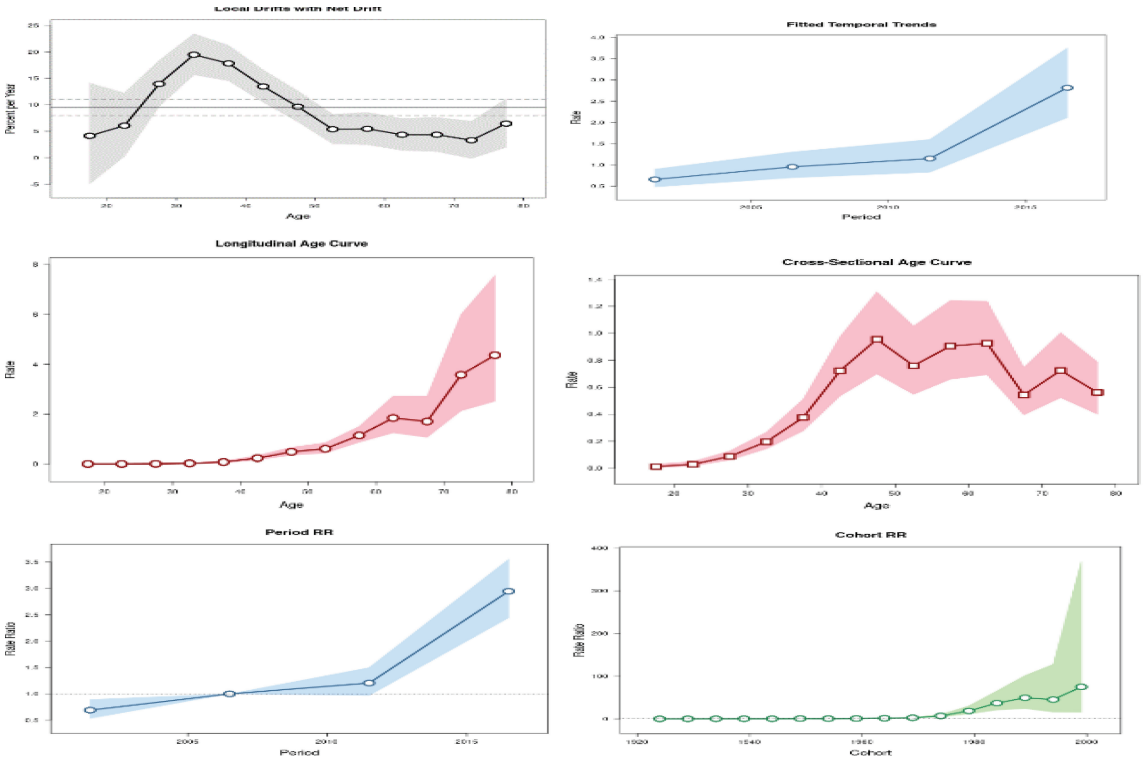
Continued

Supplementary Table 5. APC effect estimates of trends in vulva cancer mortality in South Africa, 1999–2018. *Continued*

Factor	BLACK			WHITE			ASIAN			COLOURED		
	Longitudinal RR (adjusted for period effect (95%CI)	Cross-sectional RR (Adjusted for cohort effect (95%CI)	Local drift (%) (95%CI)	Longitudinal RR (adjusted for period effect (95%CI)	Cross-sectional RR (Adjusted for cohort effect (95%CI)	Local drift (%) (95%CI)	Longitudinal RR (adjusted for period effect (95%CI)	Cross-sectional RR (Adjusted for cohort effect (95%CI)	Local drift(%) (95%CI)	Longitudinal RR(adjusted for period effect (95%CI)	Cross sectional RR (Adjusted for cohort effect (95%CI)	Local drift (%) (95%CI)
Age												
1929–1933	0.96	0.33–2.78		1.24	0.18–8.41		18.23	0.03–10735.94		0.44	0.11–1.84	
1934–1938	0.40	0.13–1.24		0.82	0.12–5.45		30.01	0.08–11555.32		0.51	0.17–1.56	
1939–1943	0.92	0.36–2.36		0.56	0.11–2.91		25.50	0.06–10236.58		0.50	0.18–1.43	
1944–1948	1.03	0.44–2.42		2.04	0.41–10.12		8.12	0.04–1674.85		0.79	0.34–1.85	
1949–1953	1.20	0.55–2.61		1.31	0.35–4.92		1.25	0.01–216.08		0.87	0.42–1.82	
1954–1959	1.14	0.56–2.31		2.59	0.81–8.28		7.43	0.16–344.79		0.91	0.47–1.78	
1959–1963	1.00	1.00–1.00		1.00	1.00–1.00		1.00	1.00–1.00		1.00	1.00–1.00	
1964–1968	0.65	0.29–1.47		1.06	0.17–6.68		1.87	0.02–167.08		0.70	0.37–1.33	
1969–1973	1.31	0.64–2.69		1.04	0.15–6.92		0.50	0.00–72.83		0.49	0.22–1.07	
1974–1978	1.76	0.76–4.08		0.11	0.00–6.71		0.30	0.00–73.15		0.48	0.16–1.44	
1979–1983	1.65	0.60–4.56		0.14	0.00–15.78		0.21	0.00–89.54		1.61	0.51–5.13	
1984–1988	1.62	0.44–5.96		0.17	0.00–43.65		0.20	0.00–172.75		2.15	0.37–12.48	
1989–1993	1.57	0.28–8.66		0.15	0.00–82.49		0.18	0.00–278.72		6.50	0.19–220.89	
1994–1998	0.18	0.00–18.68		0.17	0.00–242.12		0.19	0.00–693.37		16.83	0.30–935.90	
1999–2003	1.34	0.09–20.53		0.21	0.00–1845.41		0.20	0.00–3831.43		6.23	0.00–11944.21	

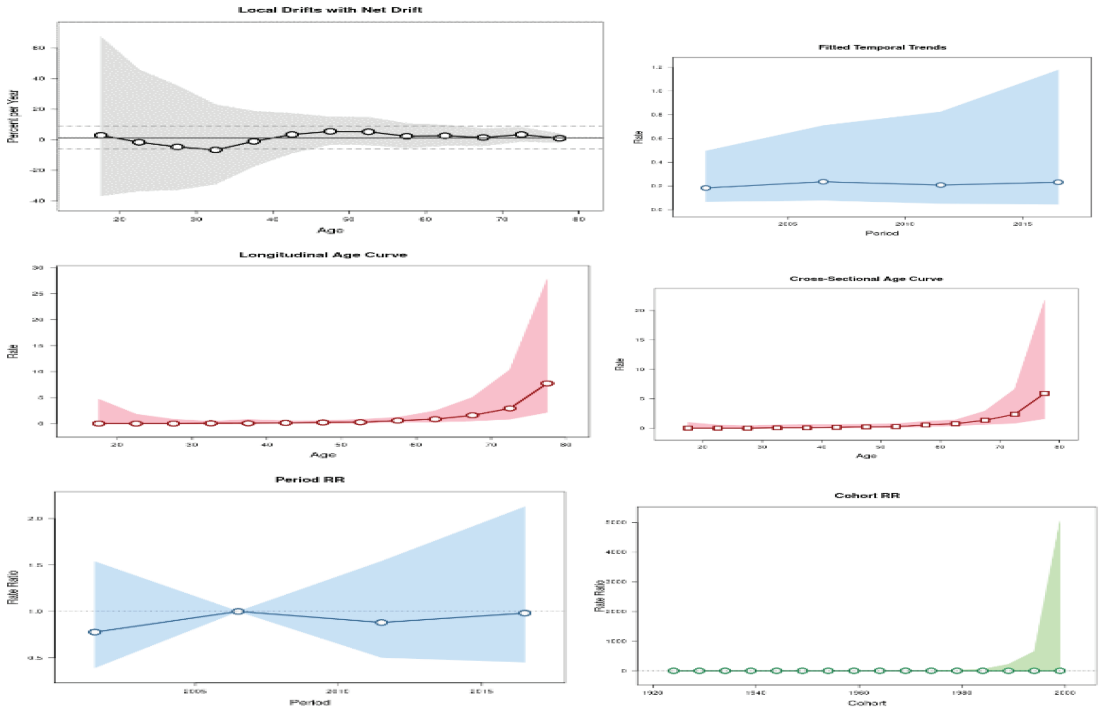
Black

A



White

B



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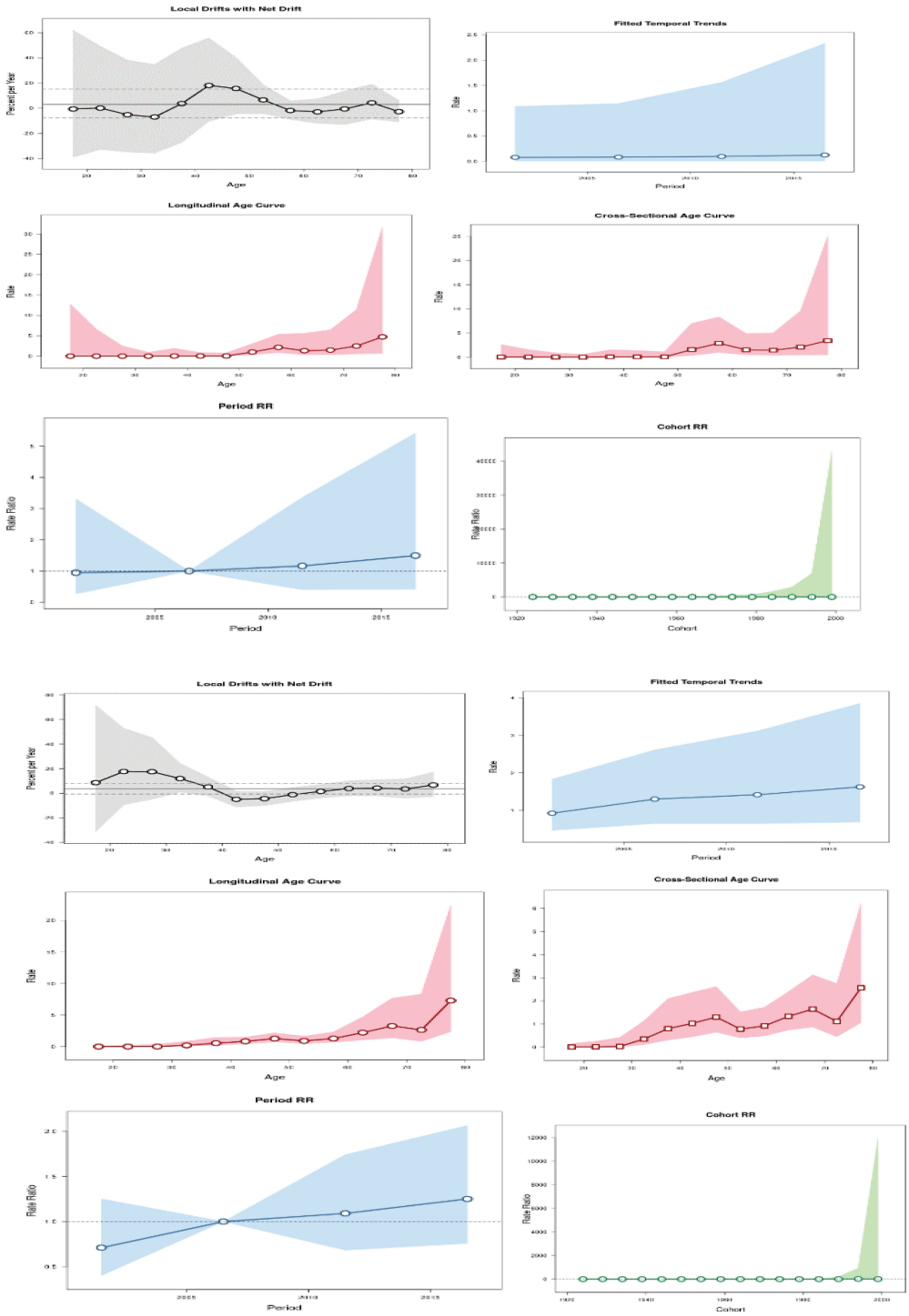

Supplementary Figure 2. Age, period and cohort effects of ethnic trends in vulva cancer mortality in South Africa (1999–2018) among (a): (Blacks), (b): Whites. (c): Indian/Asian and (d): Mixed race.

Supplementary Table 6. Wald chi-square test for estimable functions of APC model in the overall and ethnic trends of vulva cancer mortality in South Africa (1999–2018).

Vulvar cancer	NetDrift = 0		All period RR = 1		All cohort RR = 1		All local drifts = Net drift	
	Chi-square	*p*-value	Chi-square	*p*-value	Chi-square	*p*-value	Chi-square	*p*-value
Overall	148.10	4.54×10^{-34}*	209.46	3.81×10^{-45}*	248.14	3.00×10^{-44}*	115.16	1.82×10^{-18}*
Black	5.00	1.57×10^{-36}*	285.91	1.12×10^{-61}*	225.99	1.06×10^{-39}*	71.91	3.56×10^{-10}*
White	0.09	0.76	0.80	0.85	4.14	1.00	2.51	0.99
Indian/Asian	0.29	0.59	0.42	0.94	6.44	0.97	5.56	0.96
Coloured	2.80	0.09	2.92	0.40	16.43	0.35	14.96	0.31

RR: Risk ratio

*Statistically significant at *p*-value <0.05