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Trends in national and ethnic burden of ovarian cancer mortality in South Africa (1999–2018): a population based, age-period-cohort and join point regression analyses

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Abstract Ovarian cancer is the most lethal and third leading cause of gynaecological cancers globally and in South Africa (SA). However, its current mortality trends have not been evaluated in most sub-Saharan African Countries including South Africa that is currently undergoing epidemiological and health transitions. We evaluate the trends in the ovarian cancer mortality rates in SA over 20 years (1999–2018).

Methods Crude (CMR) and age standardised mortality rates (ASMR) of ovarian cancer was calculated based on national mortality data of South Africa. The overall and ethnic trends of ovarian cancer mortality among women aged 15 years and older from 1999 to 2018 was assessed using the Join point regression model, while Age-period-cohort regression analysis was conducted to evaluate the underlying impact of age, period and cohort on ovarian cancer mortality.

Results In all, 12,721 ovarian cancer deaths were reported in South Africa from 1999 to 2018 and the mortality rates increased from 2.34 to 3.21 per 100,00 women at 1.8% per annum. In 2018, the overall mean age at ovarian cancer death in South Africa was 62.30 ± 14.96 years while the mean age at death among Black women (58.07 ± 15.56 years), was about 11 years earlier than among White women (69.48 ± 11.71 years). In 2018, the White ethnic group (4.93 deaths per 100,000 women) had about doubled the ovarian cancer ASMR for the non-Whites (Indian/Asians, 2.92/100,000 women, mixed race, 2.49/100,000 women and Black women (2.36/ 100,000 women). All the ethnic groups had increased ASMR with Black women (Average annual percent change, [AAPC]: 4.7%, P-value < 0.001) and Indian/Asian women (AAPC: 2.5%, P-value < 0.001) having the highest rise. Cohort mortality risk ratio of ovarian cancer increased with successive birth cohort from 0.35 among 1924–1928 birth cohorts to 3.04 among 1999–2003 cohort and the period mortality risk increased by about 13% and 7.5% from 1999 to 2003 to 2004–2008 (RR: 0.87, 95% CI: 0.80–0.94), and from 2004 to 2008 to 2009–2013 (RR: 1.075, 95% CI:1.004–1.152) respectively. The longitudinal age analysis revealed that ovarian cancer increased with age, but there was an exponential increase from 55 years.

Conclusions Our study showed that there was increasing trends in ovarian cancer mortality among all the South African ethnic groups, driven partly by increasing cohort and period mortality risks. We therefore highlight the huge burden of ovarian cancer in SA and the need for targeted intervention. Public health interventions geared towards

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reducing ovarian cancer mortality should be instituted and ethnic disparity should be incorporated in the cancer control policy.

Keywords APC analysis, Age period cohort analysis, Ovarian cancer mortality, Ethnic disparity of cancer, Gynaecological cancer trends, Join point regression, South Africa, Sub-saharan Africa

Introduction

Globally, about 207,000 deaths were due to ovarian cancer in 2020 s [1, 2]. Ovarian cancer was the eighth leading cause of female cancer but the third leading cause of female cancer deaths globally [1]. Furthermore, ovarian cancer is a lethal cancer with the highest mortality- to-incidence ratio (MIR) of 0.66 among all female reproductive cancers [1]. In sub–Saharan Africa (SSA), ovarian cancer is the fourth cause of cancer deaths among women [1]. There has been marked increase in the incidence of ovarian cancer in Africa ranging from 2.5% per annum in Bamako, Mali to 8% per annum in Eastern Cape Province of South Africa [3].

More than 90% of ovarian cancers are due to epithelial type [1, 3]. Genetic, hormonal, reproductive and environmental factors have been linked to the evolution of ovarian cancer, with majority of cases linked to ethnicity and genetic factors [1–4]. Low parity, obesity and tobacco smoking predisposes to ovarian cancer while prolonged use of combined oral contraceptive pills (COCP), multiparity, breastfeeding and bilateral tubal ligation are protective against ovarian cancer [1–7].

South Africa is a middle-income country that commenced multi-racial democracy in 1994 after dismantling apartheid rule and its socio-economic and health inequity [8–10]. The complex interactions of increased prevalence of obesity and sedentary lifestyle coupled with low fertility rate and increased use of COCPs in South Africa can impact on the ovarian cancer mortality trends in the country [6, 11, 12]. South Africa has four recognised ethnic groups namely Black, White, Indians/Asians and mixed-race population groups [13]. The percentage of the population in 2021 comprising Black, mixed race White and Indian/Asian population group were 76.4%, 9.1%, 8.9% and 2.5% respectively [13]. Marked ethnic disparity in ovarian cancer incidence, survival and mortality has been documented in the United States of America, possibly because of ethnic differences in genetics, aggressiveness of histological types, access to appropriate oncological facilities, socio-economic and reproductive behaviour, comorbidity and level of awareness [14–16]. Ethnic specific ovarian cancer research and interventions are currently being evaluated to improve prognosis and survival [14–16].

Join point regression modelling is a robust statistical software for evaluating long term cancer trends [2]. Furthermore, Age-period-cohort (A-P-C) regression modelling can provide useful information or cues and expose any racial disparity of ovarian cancer mortality in South Africa, by reporting the change in risk based on demographic and population-based change (Period), increasing biological age (Age) and generational changes (Cohort) [5, 7, 17–19]. To our knowledge, both join point regression and A-P-C analysis had not been utilised to evaluate ovarian cancer trends in South Africa and indeed, in any of the SSAs. We therefore conducted a time series analysis to evaluate the national and ethnic trends in ovarian cancer mortality in South Africa over a 20-year period (1999–2018) by utilising both Join point and A-P-C regression modelling.

Methodology

This was a trends analysis of routinely collected population based national data of all deaths in South Africa from 1999 to 2018.

Data source

Data on deaths due to cancers among female South Africans from 1999 to 2018 was obtained from Statistics South Africa (Stats SA). The Stats SA is the South African national agency that is responsible for collecting, processing and publishing official mortality data and population census in SA [20–22]. It is mandatory for all deaths in SA to be reported to the department of home affairs before burial. The utilized code for the underlying cause of death, based on the international classification of diseases, Tenth revision (ICD10), for all cancer was C00– D48, while the codes for breast and gynaecological cancers were in parenthesis: breast (C50), cervical cancer (C53), ovarian Cancer (C56), endometrial cancer (C55), vulva cancer (C51) and vagina cancer (C52). Mid-year population estimates of females (≥ 15 years) stratified by ethnicity and 5-year age group were obtained from Stats SA [20].

Data quality

The vital registration data of South Africa is reported to be one of few high-quality mortality data in SSA [23]. The data has good coverage rates, high completeness of adult death registration rate (94%), and it scores high on temporal consistency, age/sex classification (100%), timeliness (Processing time: 9 months; Time to publishing: 11 months) and sub-national availability (100% of provinces and municipalities) [21, 23, 24]. The Stats SA data is at present the only nationally representative cancer mortality records in South Africa.

Ethical considerations

Before the commencement of the study, ethical approval was obtained from the Human Research Ethics Committee (Medical) of the University of the Witwatersrand (Clearance certificate number: M190544). Confidentiality was ensured as anonymized data was utilized.

Statistical analysis

Stata version 17 (Statacorp, USA) statistical software data was utilised for statistical analysis. The frequency of categorical variables and mean (± standard deviation) of continuous variables were presented. The annual proportion of ovarian cancer in relation to all female breast and gynaecological cancer mortality was calculated. The annual crude mortality rate (CMR) of ovarian cancer was calculated by dividing the annual deaths due to ovarian cancer among women aged ≥ 15 years by the mid-year female population (≥ 15years).

Age specific mortality rate was also calculated by dividing the age stratified mortality of each 5-year age group (15–19, 20–24, 25–29……0.75+) by c mid-year population in the corresponding age group. The Annual age standardised mortality rates (ASMR) were calculated using the direct method of standardisation, based on the 1964 modified Segi world standard population as weighted population [25, 26]. The ASMR calculation was conducted among women aged 15 years and older. All rates were stratified by ethnicity (Black, mixed race, White, Indian/Asian) and expressed per 100,000 women.

Join point regression modelling

The Joinpoint regression analysis was conducted using the Joinpoint regression software, version 4.9.1.0 (Statistical Methodology and Applications Branch, Surveillance Research Program, National Cancer Institute, Bethesda, MD), to evaluate the overall and ethnic ovarian cancer mortality trends. Log-linear model with four maximum Join points and 4499 Monte Carlo permutation tests were conducted for the trends. Annual percent change (APC) of the segmental trends and the Average annual percent change (AAPC) of the overall trends were calculated. Positive, or negative AAPC with P-value < 0.05 was taken as a statistically significant increase or decrease trends. AAPCs with P-value > 0.05 was presented as a non-significant increased or decreased trend. AAPCs from − 0.5 to + 0.5 with p-value > 0.05 were reported as stable trends.

Age period cohort modelling of ovarian cancer mortality

We conducted an A-P-C regression modelling to obtain independent impact of age, period and birth cohort on ovarian cancer mortality in South Africa [18, 27, 28] The age effect of A-P-C modelling is related to the biologic impact of chronological age on health and social outcomes while the impact of population level interventions such as improvement in screening, diagnosis and treatment of diseases on the trends in health outcomes among all age groups over a time frame is known as period effect [18, 27]. People who were born about the same time are likely to be exposed to similar cohort-specific cancer risks [7, 18].

Age, period and the birth cohort are linearly and perfectly related or dependent thereby leading to the identifiability problem:

$$\text{Birth cohort} = \text{period (year of death)} - \text{Age at death.}$$

[18, 29]. We used the Age-period-cohort Web Tool (Biostatistics Branch, National Cancer Institute, Bethesda, MD, USA). (Age Period Cohort Analysis Tool (cancer.gov)) to produce estimable parameters that is based on weighted least squares estimators. The A-P-C model assumes a Poisson distribution of the mortality rates (dependent variable) with age, period and birth cohort as the independent variables [18, 27, 29].

A lexis matrix was formed with 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,75years and above) as columns and the corresponding 5-year calendar period (1999–2003, 2004–2008, 2009–2013, 2014–2018) as rows. The diagonal becomes the corresponding birth cohort. The lexis matrix was imputed into the A-P-C webtool [18, 27, 29].

We obtained the following parameters from the A-P-C webtool [29]: [1] Net drift, which is equivalent to the AAPC of the ovarian cancer mortality from 1999 to 2018. Net drift also represents the log-linear trend of the combined effect of period and birth cohort of all age groups; [2] local drift, which is equivalent to the annual percent change per age group. Local drift is the log-linear trend of the combined effect of period and birth cohort for each age group; [3] Cohort risk ratio (RR) [4] Period RR [5] longitudinal age specific rates, which corresponds to the expected age-specific rates adjusted for period in the reference cohort [6] cross-sectional age specific rates (age trend – period trend). The Cohort RR are the age specific relative risk of ovarian cancer mortality among each of the successive birth cohort with median birth cohort of 1959–1963 as reference. The Period RR are the age specific relative risk of ovarian cancer mortality during the successive calendar periods (1999–2003, 2004–2008, 2009–2013, 2014–2018), with the 2004–2008 as the reference period [29]. Positive net or local drift suggest increased mortality rate, while negative drift suggest declining rates. Wald's Chi-squared test was also calculated for all the estimates to test for statistical significance. Two-tailed test of significance was assumed and P-value < 0.05 was taken as statistically significant level.

All analysis was conducted nationally and then stratified by ethnic groups.

Results

During the 20-year period from 1999 to 2018, 361,449 cancer-deaths occurred among South African females aged 15 years and older. Of these female cancer deaths, 79,150 (21.90%, 95%CI: 21.76–22.03%) were due to gynecological cancers, out of which 12,721 (16.07%, 95%CI: 15.82 – 16.33%) were caused by ovarian cancer. The proportion of ovarian cancer death out of all breast and gynaecological cancer deaths slightly increased from 9.27% in 1999 to 9.67% in 2018 (Table 1).

Trends in ovarian cancer mortality

Ovarian cancer deaths increased from 428 deaths in 1999 to 905 deaths in 2018 at about 4.2% per annum (AAPC: 4.2%, 95%CI: 3.8 – 4.6%, P-value < 0.001) (Fig. 1A; Table 1). The ASMR of ovarian cancer increased from 2.34 deaths per 100,000 women in 1999 to 3.21 deaths per 100,000 women in 2018 at 1.8% per annum. (AAPC: 1.8%, 95%CI:1.2–2.4, P-value < 0.001). (Fig. 1B; Tables 1 and 2; Fig. 2A). The CMR of ovarian cancer also increased during the study period (Fig. 1C; Table 1). There was a statistically significant increased trends of about 3.8% per annum from 1999 to 2006 (APC: 3.8%, P-value < 0.001) and a subsequent, non-statistically significant lower annual rise of 1.0% from 2006 to 20,018 (APC: 1.0%, P-value = 0.1). (Fig. 2; Table 2)

Table 1 Trends in the mortality rates and mean age at death of ovarian cancer in South Africa (1999–2018)

Year	Ovary cancer deaths (*n* = 12,721)			
	Mortality (% of gynae & breast) ≥ 15 years	Age (years) mean ± SD	CMR*	ASMR*
1999	428 (9.27)	59.80 ± 14.84	2.78	2.34
2000	402 (8.45)	60.27 ± 14.75	2.55	2.17
2001	463 (9.04)	59.41 ± 15.07	2.86	2.41
2002	508 (9.76)	60.64 ± 14.80	3.10	2.63
2003	447 (8.34)	60.17 ± 15.18	2.63	2.21
2004	509 (8.66)	61.03 ± 14.30	3.07	2.91
2005	535 (8.86)	61.55 ± 14.52	3.29	2.76
2006	573 (9.42)	61.42 ± 15.07	3.48	2.88
2007	594 (9.58)	62.15 ± 15.23	3.56	2.88
2008	610 (9.76)	59.88 ± 16.32	3.49	2.89
2009	698 (10.42)	61.57 ± 14.79	3.93	3.3
2010	642 (9.47)	61.61 ± 14.56	3.57	3.02
2011	713 (10.05)	62.19 ± 14.46	3.91	3.17
2012	668 (9.30)	61.68 ± 14.89	3.62	2.93
2013	719 (9.52)	61.61 ± 14.25	3.69	2.9
2014	749 (9.15)	61.16 ± 15.08	3.82	2.9
2015	787 (9.34)	61.05 ± 16.38	3.97	3.06
2016	835 (9.38)	62.18 ± 14.57	4.13	3.23
2017	936 (10.30)	62.45 ± 14.66	4.55	3.52
2018	905 (9.67)	62.30 ± 14.96	4.30	3.21

*Per 100,000 women; CMR: Crude mortality rate; ASMR: Age standardised mortality Rate

Ethnic trends of ovarian cancer mortality

In 2018, the White ethnic group had the highest ASMR of ovarian cancer (4.93 deaths per 100,000 women), while Indian/Asian (2.92/100,000 women), mixed race (2.49/100,000 women) and Black women (2.36/100,000 women) had about half the rates among White women. (Fig. 1B, Supplementary Table 1). All the ethnic groups had increased ASMR, with Black (AAPC: 4.7%, P-value < 0.001) and Indians/Asian (AAPC: 2.5%, P-value < 0.001) women having the highest rise while White women (AAPC: 1.0%, P-value < 0.001) and mixed race (AAPC: 1.1%, P-value = 0.1) had relatively minimal or non-significant annual increase (Table 2; Fig. 2). White women had stable trends from 2009 to 2018 (APC: -0.2, P-value = 0.8) (Fig. 2; Table 2). In 2018, the White women had CMR (13.52 per 100,000 women) of about 2.7, 3.5 and 4.9-fold as compared to the CMR among Indian/Asian women (4.99 per 100,000 women), mixed race (3.88 per 100,000 women) and Black women (2.76 per 100,000 women) respectively and throughout the study period. (Fig. 1C, Supplementary Table 1).

Trends in national and ethnic mean age at death and age specific mortality rates of ovarian cancer

In 2018, the mean age at death from ovarian cancer in South Africa was 62.30 ± 14.96 years and was between 59 years and 62 years between 1999 and 2018 (Table 1). In 2018, the youngest mean age at death from ovarian cancer occurred among the Black women (58.07 ± 15.56 years), followed by Indian/Asian women (61.8 ± 14.27 years), mixed race (62.03 ± 11.89 years) while the White women occurred about 11 years later (69.48 ± 11.71). (Supplementary Table 1). The mean age at death from ovarian cancer generally increased among the ethnic groups. (Supplementary Table 1).

Age specific death rate of ovarian cancer by ethnicity, 2018

In 2018, the White ethnic group had the highest mortality rate in all age groups from 35 to 39 years (0.67 deaths per 100,000 women) and the rates had a steep rise from 50 to 54 years (5.53 deaths per 100,000 women) till 75 years and above (42.58 deaths per 100,000 women). The mortality rate was stable among Indian/Asian women from 40 to 44 years (4.83 per 100,000 women) to 50–59 years (4.91 per 100,000 women) and dramatically increased to 17.22 per 100,000 women among the women aged 75 years and older and was the second highest rate. Black women and mixed population group generally had lower rates for most of the age groups. (Fig. 1D, Supplementary Table 2).

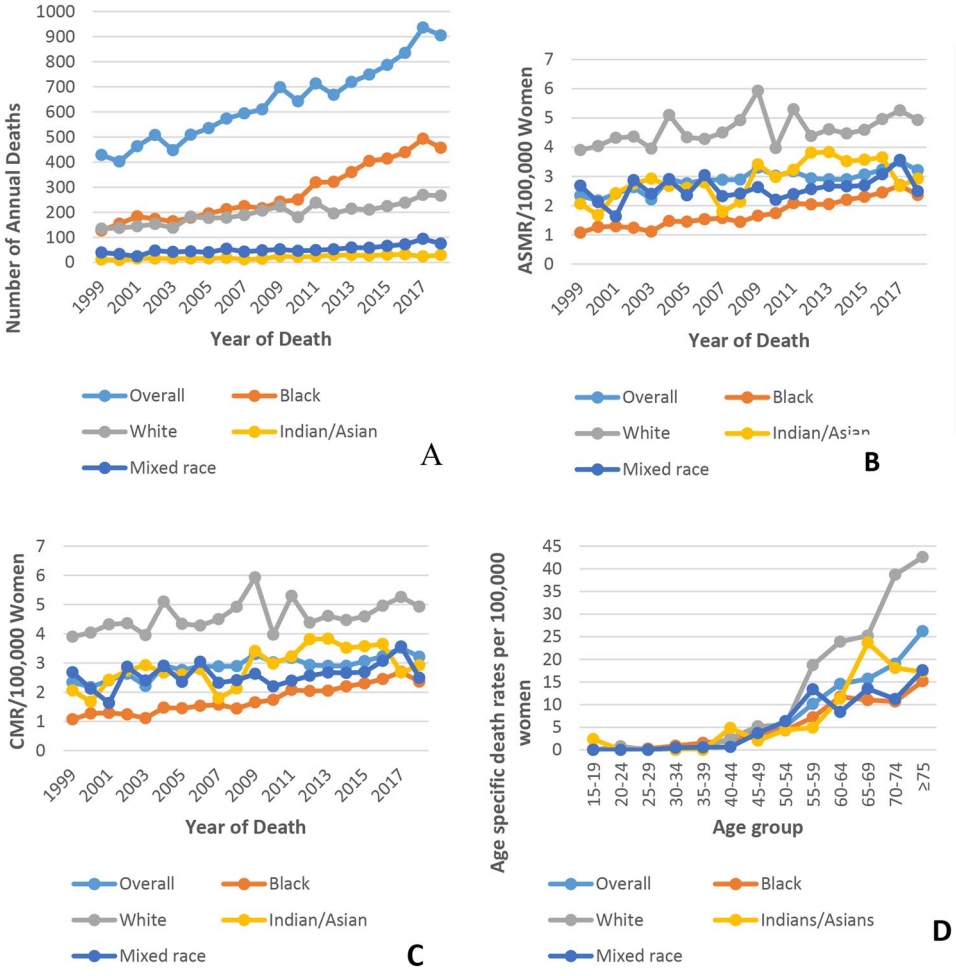


Fig. 1 Trends in national and ethnic annual deaths (**A**), Age standardized rates (**B**), Crude mortality rates (**C**), and age specific mortality rates (**D**) of ovarian cancer in South Africa (1999–2018) among women aged 15 years and older

Join point trends in the overall age specific mortality rates 1999–2018

From 1999 to 2018, women aged 15–24 years and 55 years and older had increased ovarian cancer mortality rates (AAPC range: 1.4 – 5.0%, P-value < 0.001) with teenagers having the highest increase. However, women aged 25–39 years and other women aged 50–54 years had non-significant increased ovarian cancer mortality trends (AAPC range: 0.7 to 1.8, P-value > 0.05). While women aged 40–49 years had stable trends (AAPC: 0.1 to 0.2, P-value > 0.05). (Table 3; Fig. 3a-e)

Age period cohort analysis of overall and ethnic trends in ovarian cancer mortality

Local and net drift

After correcting for cohort and period effects, the overall net drift of ovarian cancer mortality trends over the study period (1999–2018) was about 1.70% per annum (95%CI: 1.11–2.29). (Fig. 4A, Supplementary Table 3). There was a statistically significant positive net drift among Black women (5.52%, 95%CI: 4.88–6.15%) while White women (0.99% 95%CI: -1.15–3.17%) and Indian/Asian women (0.13%, 95%CI: -4.44 to 4.93) had non-statistically significant lower positive drift. On the other hand, mixed race women (-0.56%, 95%CI: -2.59–1.52%) had non-significant negative drift. (Fig. 4A, Supplementary Table 4). From the Wald's test the net drift of the overall and Black ethnic group was statistically significant. (Table 4)

All the local drift of ovarian cancer were > 0 and the trends generally depicted a U-shaped curve with the most rapid drifts occurring among teenagers, aged 15–19 years (5.77%, (95%CI:1.53–10.18%) and elders aged 75 years and above (4.43%, 95%CI:3.47–5.40%). Women aged 40–44 years (0.38%, 95%CI: -0.86–1.64%) had the lowest rise in ovarian cancer mortality. (Fig. 4B, Supplementary Table 3). All the local drifts for Black women were positive, and relatively high, showing increased ovarian cancer mortality rates. The local drift among Black women highest among women aged 75 years and older 9.09%, (95%CI: 7.49–10.71%) followed by women aged 15–19

Table 2 Join point regression estimates of the trends in age standardised mortality rates of ovarian cancers in South Africa (1999–2018), among women aged 15 years and older

Cancer Type	Trends	Year Period	APC	95%CI	*P*-value	Comment
Overall ASMR						
Segmental trend	1	1999–2006	3.8*	0.8 to 7.0	< 0.001	Statistically significant increase
Segmental trend	2	2006–2018	1.0	-0.2 to 2.2	0.1	Non-Statistically significant increase
	Full Range^	1999–2018	1.8*	1.2 to 2.4	< 0.001	Statistically significant increase
Blacks						
Segmental trend	1	1999–2018	4.7*	4.1 to 5.3	< 0.001	Statistically significant increase
	Full Range^	1999–2018	4.7*	4.1 to 5.3	< 0.001	Statistically significant increase
Indian/Asian						
Segmental trend	1	1999–2015	3.7*	1.7 to 5.6	< 0.001	Statistically significant increase
Segmental trend	2	2015 – 2018	-9.8	-28.0 to 13.1	0.3	Non-Statistically significant decrease
	Full Range^	1999–2018	2.5*	1.0 to 4.0	< 0.001	Statistically significant increase
Mixed race						
Segmental trend	1	1999–2006	2.4	-3.9 to 9.2	0.4	Non-Statistically significant increase
Segmental trend	2	2006–2010	-3.8	-24.3 to 22.3	0.7	Non-Statistically significant decrease
Segmental trend	3	2010–2018	3.8	– 1.3 to 9.1	0.1	Non-Statistically significant increase
	Full Range^	1999–2018	1.1	-0.1 to 2.3	0.1	Non-Statistically significant increase
White						
Segmental trend	1	1999–2009	2.1*	0.1 to 4.0	< 0.001	Statistically significant increase
Segmental trend	2	2009–2018	– 0.2	-2.3 to 2.0	0.8	Stable
	Full Range^	1999–2018	1.0*	0.1 to 1.8	< 0.001	Statistically significant increase

^: Full trend with zero Joinpoint * Statistically significant trend

years (6.22%, (95%CI: 2.39–10.19%), while women aged 35–39 years (3.53%, (95%CI: 1.99–5.10%) had the least drift. to. (Fig. 4B, Supplementary Table 4)

The White ethnic group aged 45–54 years had negative drifts (Though not statistically significant), while all other age groups had positive drifts. (Fig. 4B, Supplementary Table 3). Indian/Asian women aged 25–39 years, 50–59 years and mixed-race women aged 15–19 years, and 25–49 years had negative local drifts. The local drift among Indian/Asian women generally decreased from 17.92%, (95%CI: -11.70–57.46%) among women aged 15–19 years to -6.85%, 95%CI: -21.48–10.50%) among women aged 30–34 years. There was fluctuating drift with age afterwards and women aged 75 years and older had a drift of 4.20, 95%CI -1.76–10.51%). (Fig. 4B, Supplementary Table 4)

The local drift in ovarian cancer mortality among mixed race women decreased from 4.38%, (95%CI: -6.31–16.29%) among 20–24 years to -4.84%, (95%CI: -9.53–0.09%) among women aged 35–39 years and then increased to 2.71%, (95% CI: 0.41–5.06%) among women aged 65–69 years. (Supplementary Table 3, Fig. 4B). All the local drifts among Black women were statistically significant while only local drift among mixed race women aged 60–69 years and White women aged 75 years and older were statistically significant. No local drift was statistically significant among Indian/Asian women. (Supplementary Table 4, Fig. 4B)

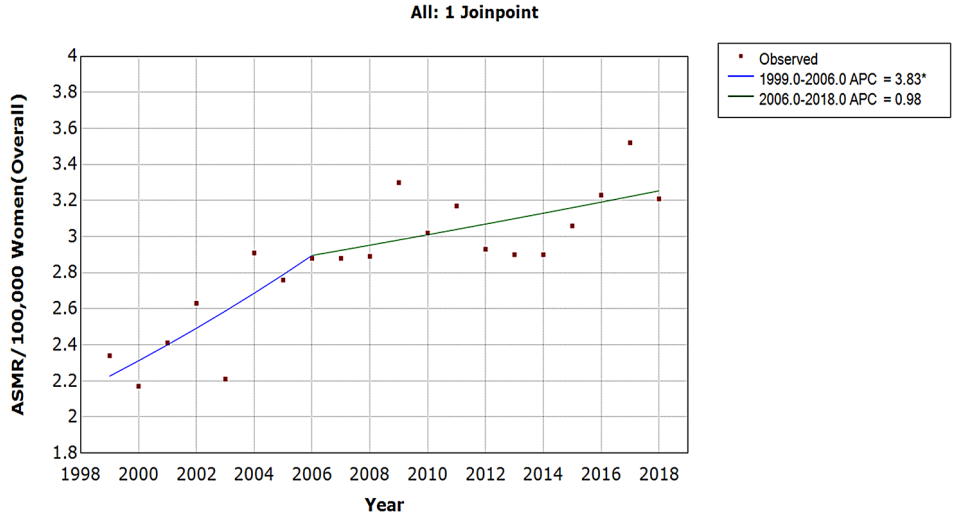
Age effect

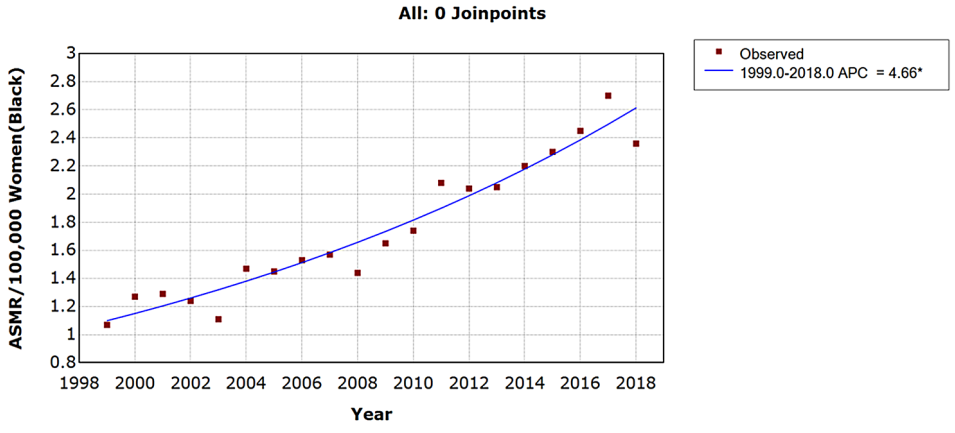
Based on the longitudinal age curve, which corresponds to the expected age-specific rates adjusted for period in the reference cohort, the relative risk of ovarian cancer mortality increased with age and there was an exponential increase from 55 years. (Fig. 5 Supplementary Table 3). The age specific rate of ovarian cancer increases with age and there was exponential increase from: 30 years for mixed race women 35 years for White and Indian/Asian women and 40 years for Black women. The Black women followed by mixed race women had the lowest ovarian cancer mortality rate from 15 to 64 years while White women followed by Indian/Asian women had the highest rate from 15 to 64 years. However, Black women followed by White women had the highest rate from 65years and above while Indian/Asian women followed by mixed race women had the lowest rates from 65 years. (Supplementary Table 4, Fig. 5A)

Period effect

The overall period risk ratio (RR) respectively increased by 13%,7.5% and 12% from 1999–2003(RR: 0.87, 95% CI: 0.80–0.94) to 2004–2008(RR:1.00); 2004–2008 to 2009–2013 (RR: 1.075, 95% CI:1.004–1.152) and from 2004 to 2008 to 2014–2018. (Supplementary Table 3, Fig. 5B). The Wald's test for period effect of overall ovarian cancer mortality trends was statistically significant (Table 4).

The Black (RR from 0.84 to 1.92) and White (RR from 0.93 to 1.08) women generally experienced increased period RR from 1999 to 2018. Women of mixed race





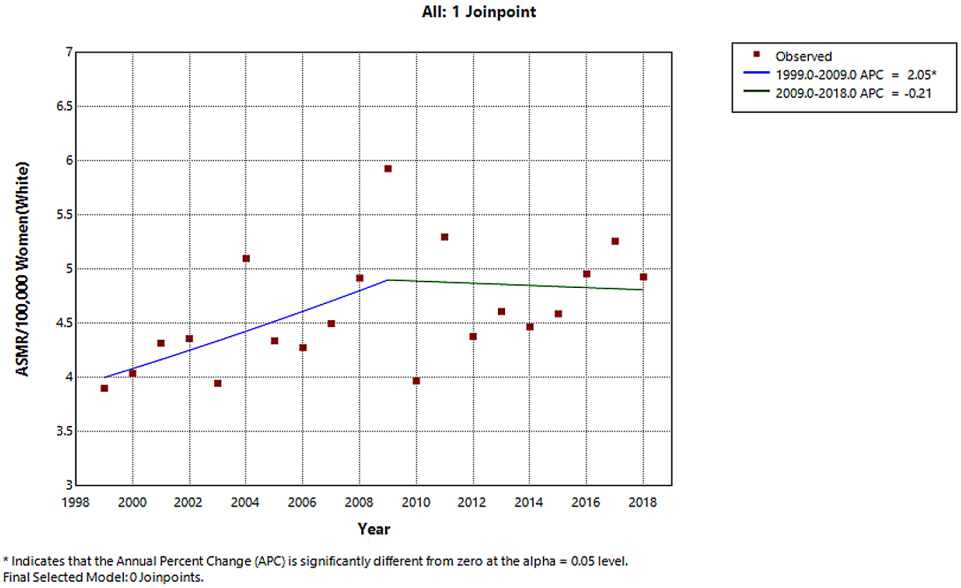
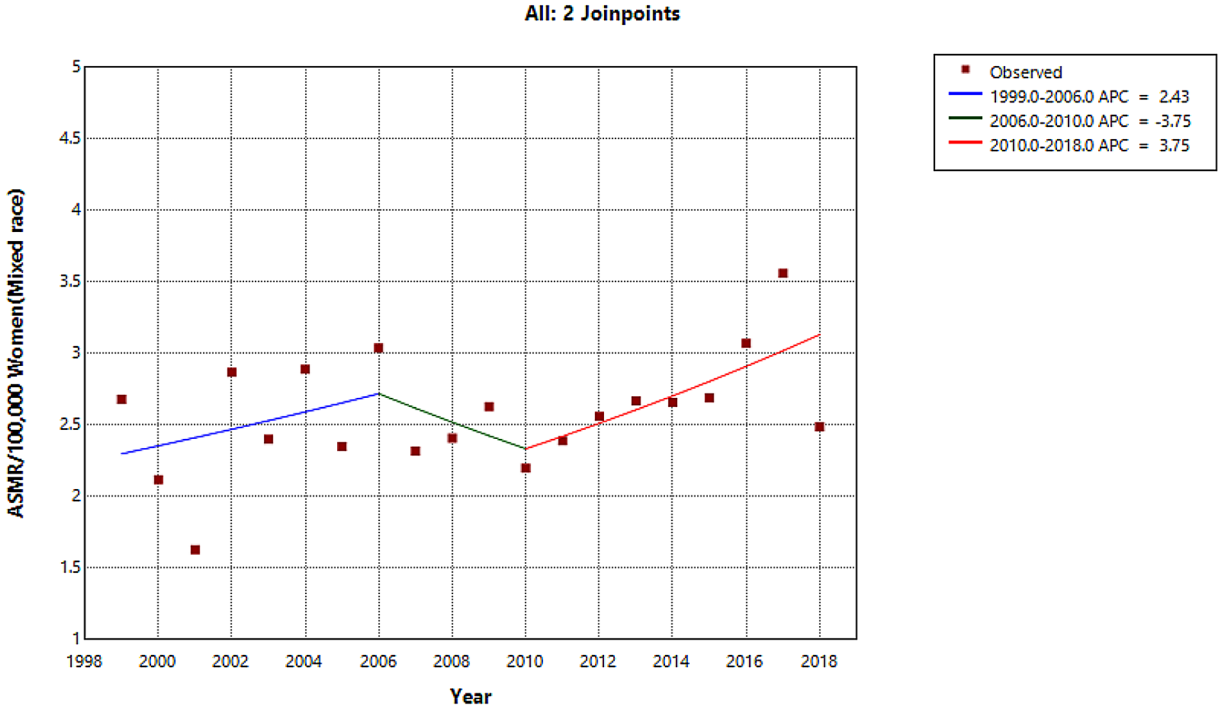
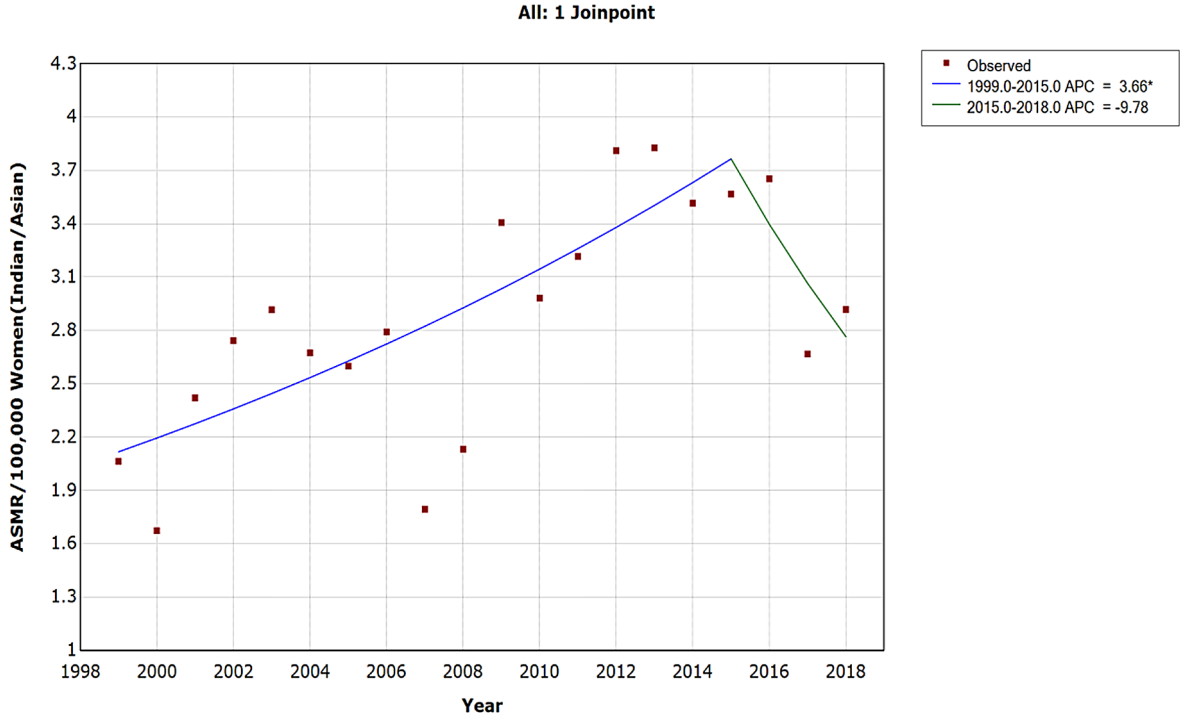


Fig. 2 Joinpoint regression trends of the annual age standardized mortality rate of Ovarian cancer in South Africa (1999–2018) among women aged 15 years and older for: (**A**) Overall (**B**) Black women (**C**) White women (**D**) mixed race (**E**) Indian/Asian ethnic groups



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



* Indicates that the Annual Percent Change (APC) is significantly different from zero at the alpha = 0.05 level.
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Fig. 2 (continued)

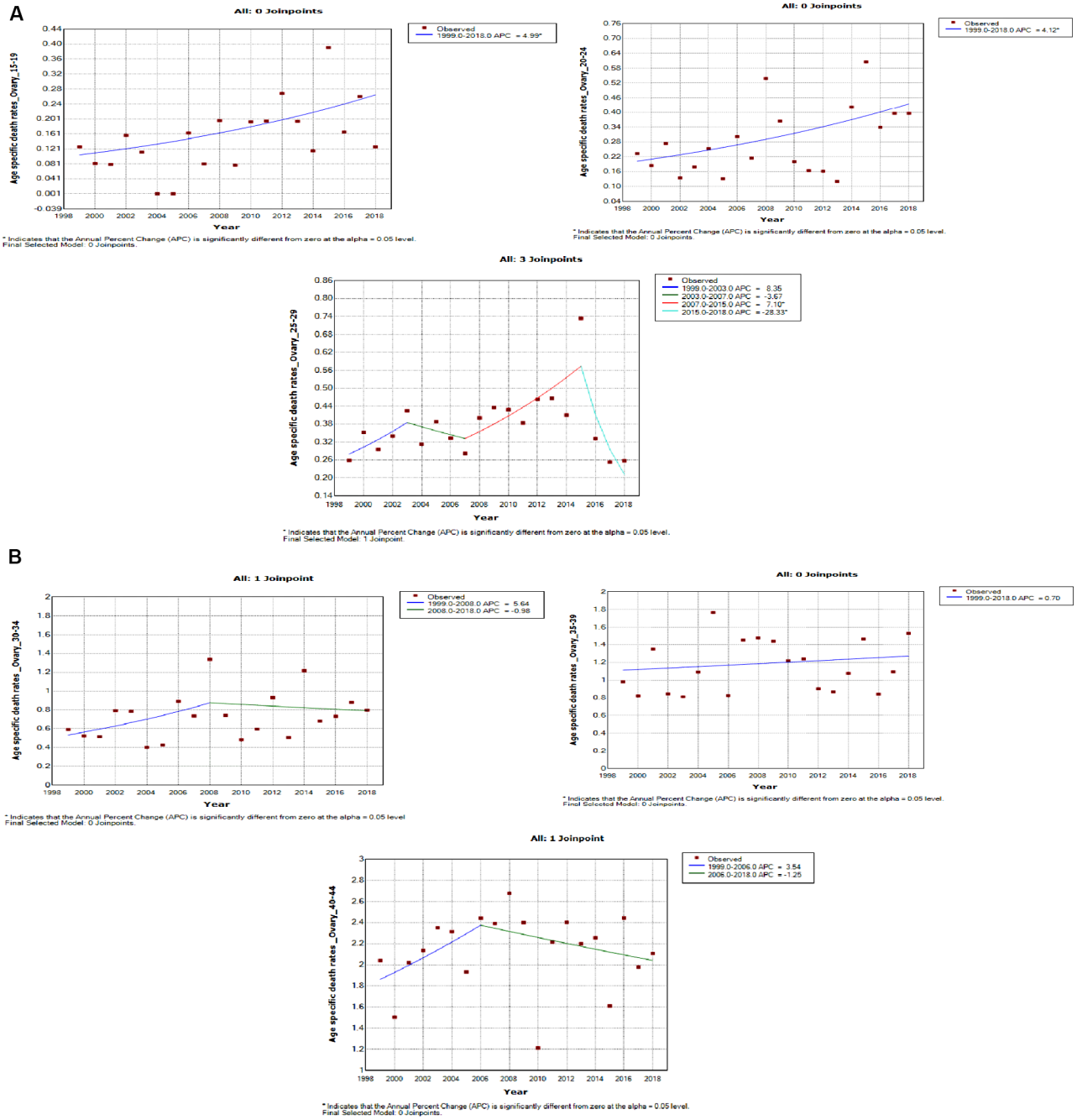

Fig. 3 Join point trends of age specific death rates of Ovarian cancer in South Africa among women aged 15 years and older. 1999–2018

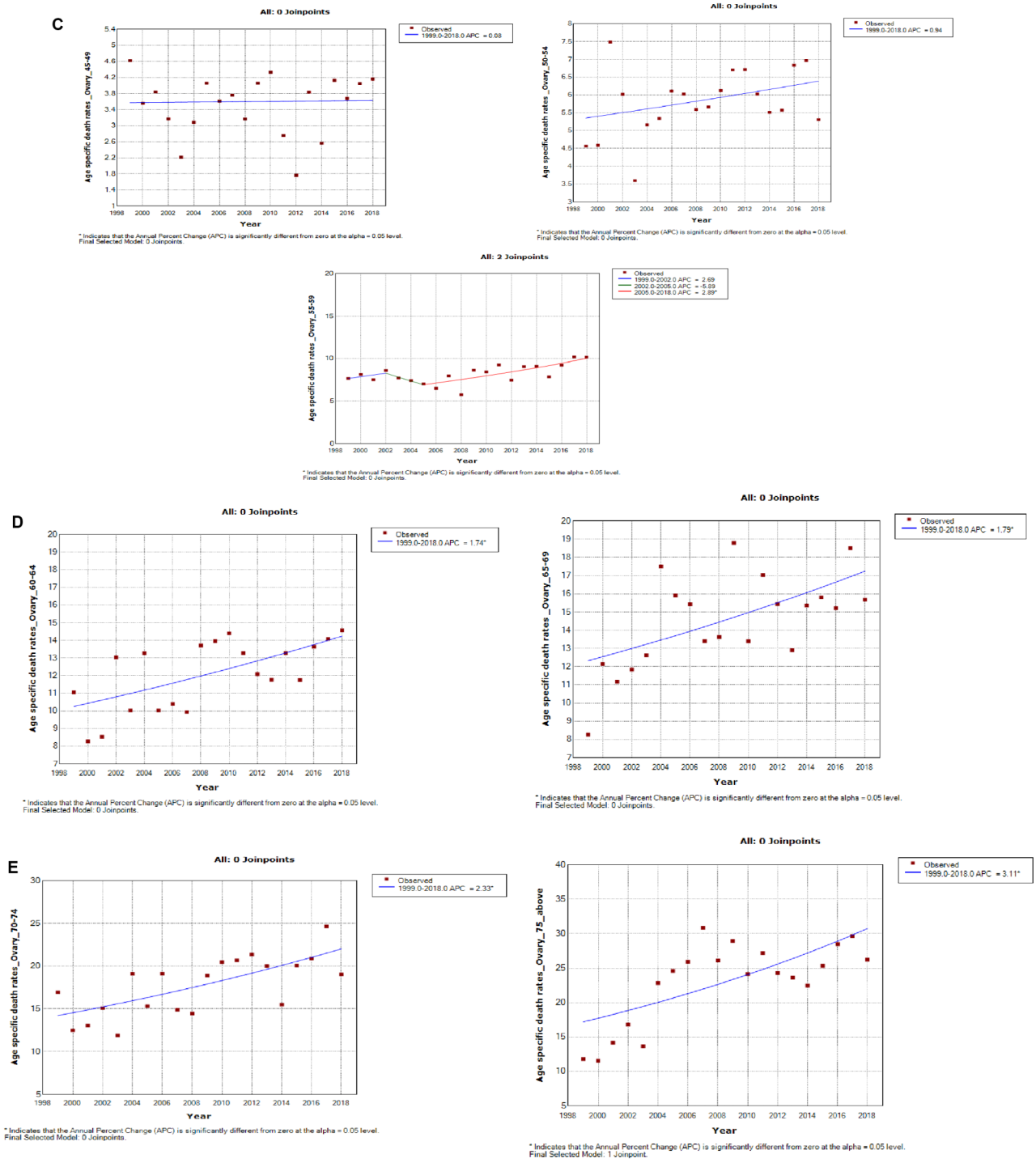

Fig. 3 (continued)

had nearly stable period RR between 1999 and 2003 and 2004–2008 (0.995 to 1.00) and subsequently had a decrease in RR from 2004 to 2008 to 2009–2013 (1.00 to 0.88) and an increase to 0.95 in 2014–2018. Indian/Asian women had a decline in period RR from 1999 to 2003 to 2004–2008 (1.35 to 1.00) and fluctuating RR trends from 2009 to 2018 (Supplementary Table 4, Fig. 5B). The Wald's test showed that period effect on ovarian cancer trends was statistically significant for only Black women (Table 4).

Cohort effect: The cohort mortality risk ratio of ovarian cancer mortality among women born during

Table 3 Join point estimates of the national age specific mortality rates for ovarian cancers in South Africa, 1999–2018

Ovary (Years)	Trend	Lower Endpoint - Upper Endpoint	AAPC	Lower CI - Upper CI	Test Statistic~	*P*-Value~	Comment
15–19	Full Range^	1999–2018	5.0*	1.4 to 8.7	2.9	< 0.001	Statistically significant increase
20–24	Full Range^	1999–2018	4.1*	0.7 to 7.7	2.5	< 0.001	Statistically significant increase
25–29	1	1999–2003	8.4	-3.7 to 21.9	1.5	0.2	Non-Statistically significant increase
Segmental trend	2	2003–2007	-3.7	-19.6 to 15.4	-0.5	0.6	Non-Statistically significant decrease
Segmental trend	3	2007–2015	7.1*	2.7 to 11.7	3.7	< 0.001	Statistically significant increase
Segmental trend	4	2015–2018	-28.3*	-40.7 to -13.3	-4.0	< 0.001	Statistically significant decrease
	Full Range^	1999–2018	1.8	-0.5 to 4.2	1.6	0.1	Non-Statistically significant increase
30–34	1	1999–2008	5.6	-2.6 to 14.6	1.4	0.2	Non-Statistically significant increase
Segmental trend	2	2008–2018	-1.0	-7.3 to 5.7	-0.3	0.8	Non-Statistically significant decrease
	Full Range^	1999–2018	1.8	-0.9 to 4.6	1.4	0.2	Non-Statistically significant increase
35–39	Full Range^	1999–2018	0.7	-1.4 to 2.9	0.7	0.5	Non-Statistically significant increase
40–44	1	1999–2006	3.5	-3.6 to 11.2	1.0	0.3	Non-Statistically significant increase
Segmental trend	2	2006–2018	-1.3	-4.2 to 1.7	-0.9	0.4	Non-Statistically significant decrease
	Full Range^	1999–2018	0.2	-1.2 to 1.6	0.3	0.8	Stable
45–49	Full Range^	1999–2018	0.1	-1.6 to 1.8	0.1	0.9	Stable
50–54	Full Range^	1999–2018	0.9	-0.3 to 2.2	1.6	0.1	Stable
55–59	1	1999–2002	2.7	-13.8 to 22.4	0.3	0.7	Non-statistically significant increase
Segmental trend	2	2002–2005	-5.9	-33.8 to 33.8	-0.4	0.7	Non-statistically significant decrease
Segmental trend	3	2005–2018	2.9*	1.1 to 4.7	3.5	< 0.001	Statistically significant increase
	Full Range^	1999–2018	1.4*	0.5 to 2.3	3.2	< 0.001	Statistically significant increase
60–64	Full Range^	1999–2018	1.7*	0.7 to 2.8	3.4	< 0.001	Statistically significant increase
65–69	Full Range^	1999–2018	1.8*	0.5 to 3.1	2.9	< 0.001	Statistically significant increase
70–74	Full Range^	1999–2018	2.3*	1.1 to 3.5	4.1	< 0.001	Statistically significant increase
75+	Full Range^	1999–2018	3.1*	1.3 to 4.9	3.7	< 0.001	Statistically significant increase

^: Full trend with zero Join point

1924–1928 (RR: 0.35, 95%CI: 0.29–0.42) was the least and the risk increased among successive cohorts till the last birth cohort of 1999–2003 (RR: 3.04, 95%CI: 1.00–9.27). (Supplementary Table 3, Fig. 5B). The Wald's test showed that cohort effect was statistically significant (Table 4).

With respect to ethnic cohort variations of ovarian cancer mortality, the Black women (RR:0.07, 95%CI: 0.05–0.09) had relatively low RR among the birth cohorts of 1924–1928 and the risk increased monotonically among successive birth cohorts, becoming the highest among successive birth cohorts from 1964 to 1998, after which RR was the second highest among the most recent birth cohort (1999–2003). The cohort RR among women of mixed race (RR:0.49, 95%CI: 0.27–0.87) increased from 1924 to 1928 till 1964–1968 birth cohorts, after which there was generally slight decline in RR among recent birth cohorts of mixed-race women. The White women had the third highest ovarian cancer mortality RR among the cohort born in 1924–1928 and except for a decline among birth cohorts of 1964–1973, there was generally increased RR among successive cohort till the recent cohort. Indian/Asian women had the highest RR (0.74 95%CI: 0.25–2.20) among women born between 1924 and 1928 and the RR generally increased among successive cohorts until the birth cohort of 1969–1973 after which successive cohort experienced declining RR till the 1984–1988 birth cohort. The RR increased in the most recent cohort (1989–1993). (Supplementary Table 4, Fig. 5B). The full output of A-P-C webtool is as depicted in Supplementary Figs. 1–5. The Wald's test showed that the cohort effect was statistically significant only among Black and White women. Table 4.

Discussion

This study evaluated for the first time in South Africa and in SSA, the national and ethnic trends of ovarian cancer mortality over twenty years (1999–2018), using both Join point and A-P-C regression modelling. Our study showed that the ASMR of ovarian cancer increased at an average of 1.8% per annum and the reported ovarian cancer deaths doubled between 1999(428 deaths) and 2018(905 deaths) and.We also found that the mortality rates among the White ethnic group doubled the rates among other non-White ethnic groups (Indian/Asian, mixed race, and Black women), but Black and Indian/Asian women had nearly 5% and 3% rise per annum from 1999 to 2018 while White women and women of mixed race had nearly stable trends. The age effect occurred

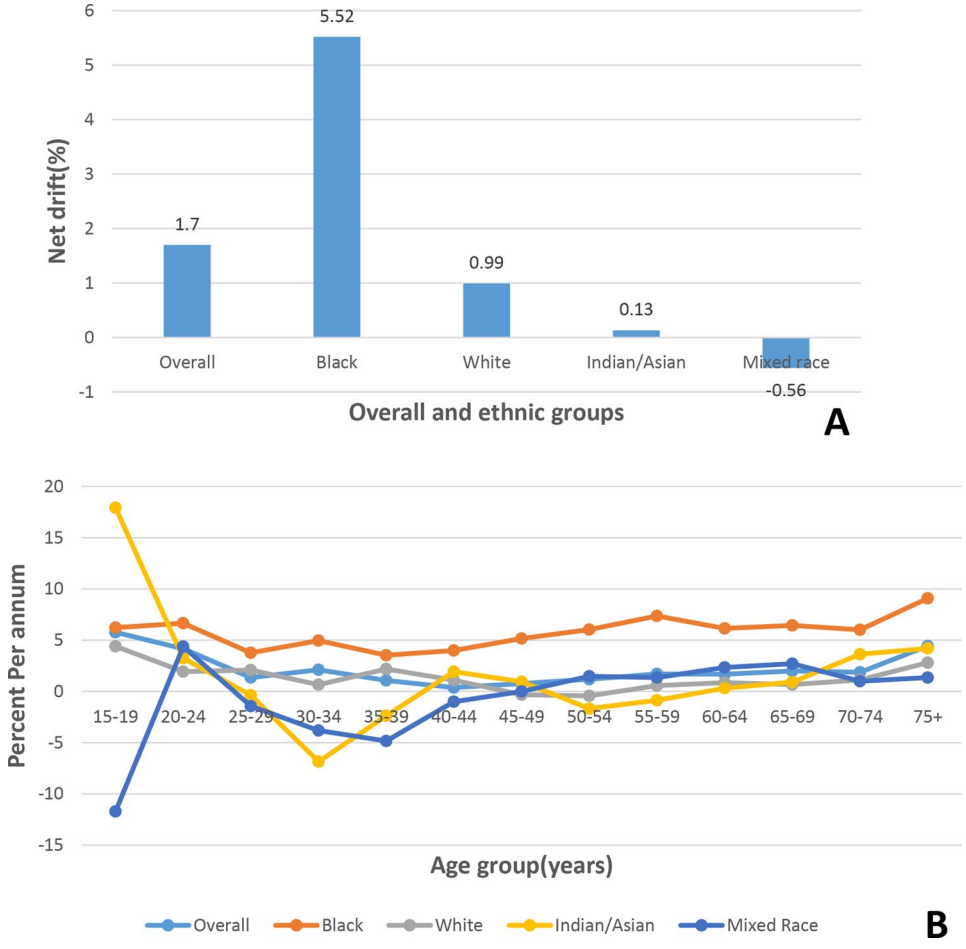

Fig. 4 Net drift (**A**), and Local drift (**B**) of Ovarian Cancer mortality in South Africa, overall and by ethnic group, 1999–2018

Table 4 Wald Chi-square test for estimable functions of age period cohort model in the overall and ethnic trends of mortality of ovarian cancer in South Africa (1999–2018)

Gynaecological cancer type	Net Drift = 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
Ovary								
Overall	32.71	< 0.0001*	33.55	< 0.0001*	149.22	< 0.0001*	49.08	< 0.0001*
Black	306.01	< 0.0001*	413.08	< 0.0001*	567.11	< 0.0001*	48.02	< 0.0001*
White	0.81	0.37	1.03	0.79	26.55	0.03*	14.52	0.338
Indian/Asian	0.0031	0.96	4.36	0.23	9.05	0.87	8.47	0.81
Mixed race	0.28	0.60	1.78	0.62	18.36	0.24	18.68	0.32

*Statistically significant at P-value < 0.05

among all ethnic groups, while cohort effect occurred only among Black and White women, and period effect occurred only among Black women, with a reported net drift of about 5.0%.

South African ovarian cancer mortality trends

In 2018, the mortality rate of ovarian cancer in South Africa (3.21 deaths per 100,000) was at par with the average rates among Southern African countries [1]. However, we reported that the mortality rate of ovarian cancer in South Africa was lower than the ovarian cancer mortality rate in Nigeria, East Africa, Asia and central Europe with rates in excess of 5 deaths per 100,000 [1, 30, 31]. Our study showed that there was a strong period effect on the ovarian cancer mortality in South Africa with a positive net drift of about 1.7% per annum from 1999 to 2018. The increased ovarian cancer mortality trends in South Africa appears to mirror the rising

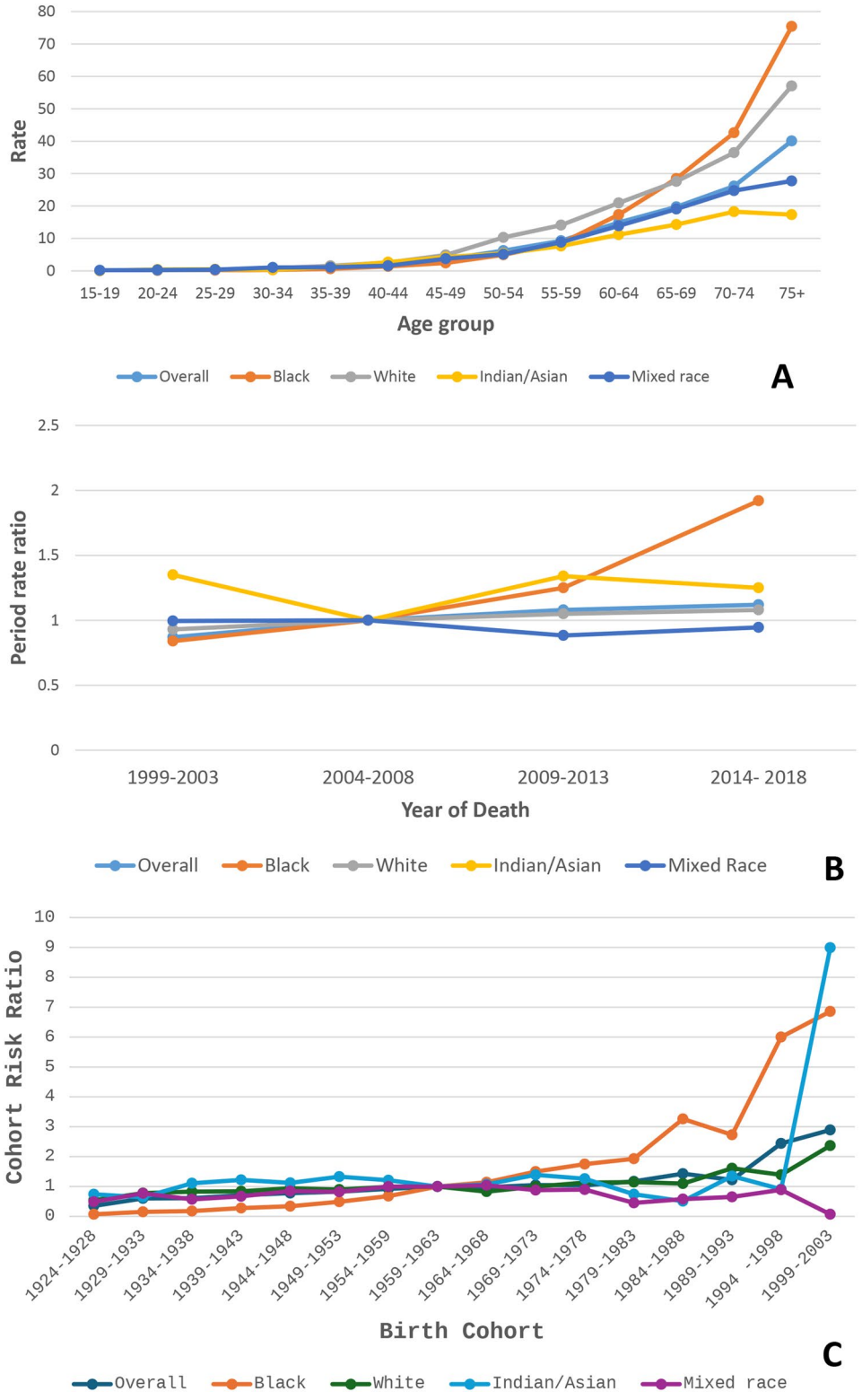

Fig. 5 Longitudinal age effect (**A**), Period effect (**B**) and Cohort effect (**C**) of Ovarian Cancer mortality in South Africa, overall and by ethnic group, 1999–2018

ovarian cancer incidence in SSA over similar period [3]. The usual lag period between cancer incidence and mortality may not be observed in South Africa because of the fatal nature of ovarian cancer, as majority of patients usually present at late stage [2, 4, 32, 33]. Similar increase in the incidence and mortality of ovarian cancer occurred in Low- and Middle-income countries (LMICs) such as Thailand, and Belarus [2].

In contrast, majority of the countries in Northern America and Europe that traditionally had high incidence of ovarian cancer now experienced declining ovarian cancer incidence and mortality, possibly because of increased use of COCPs, decreased use of hormone replacement therapy, slight increase in fertility rates in some countries and reduced female smoking rate [2, 7, 31, 33–36]. Awareness among high-risk individuals, increased prevalence of bilateral tubal ligation for contraception, and prophylactic surgery of total abdominal hysterectomy and bilateral salpingoophorectomy among high-risk women have also contributed to the reduction in incidence and mortality from ovarian cancer in High income countries (HICs) [2, 7, 33–36]. Furthermore, improved index of suspicion, improved diagnostic tools (such as radiological and tumour markers), improved surgical techniques and introduction of novel anti-cancer drugs have increased the survival rates [2, 3, 7, 33–36]. However, the global increasing prevalence of obesity has the potential to reverse the declining global trends of ovarian cancer incidence and mortality [3, 32]. The increased urbanization and prevalence of obesity in South Africa, can also explain the increased ovarian cancer mortality in South Africa [4, 9, 11, 17, 36–38].

In South Africa, the rise in ovarian cancer mortality slowed from 3.8% per annum during 1999–2006 to 1.0% per annum from 2006 to 2018, possibly because of improved access to qualitative healthcare, and health education in South Africa after the commencement of multi-racial democracy from 1994 [10]. However, the quality of population-based death registration generally improves with time and then stabilizes [21]. This might partly be responsible for the initial rise in ovarian cancer mortality rate from 1999 to 2006 [5, 7].

Cohort effect of ovarian cancer mortality

There was strong cohort effect of ovarian mortality in South Africa, with increased cohort mortality risk among majority of successive birth cohorts from 1924 to 2003. In contrast, the cohort mortality risk of ovarian cancer has been declining among successive birth cohorts in Asia, Europe and North America especially from 1960s [17, 36, 39]. Successive South African cohorts have been exposed to increased prevalence of obesity and declining fertility without commensurate exposure to early diagnosis and optimum oncological treatment of ovarian cancer [9–11, 40–42]. Unlike other HICs with high prevalence of COCP use, successive South African cohorts mainly accepted Depo medroxyprogesterone acetate injection which was not proven to be protective of ovarian cancer [6, 7, 36, 39, 40] Indeed, one of the unintended consequences of promoting long-acting reversible contraceptives in place of COCP may be an increase in the incidence of ovarian cancer. Reduction in the prevalence of tobacco smoking among successive South African cohort might not have impacted the overall cohort mortality of ovarian cancer since only the minority ethnic groups (mixed race and White ethnic groups) had high smoking rates [22, 43].

Age effect of ovarian cancer mortality trends

In line with global reports, the mean age at death of ovarian cancer in South Africa was in the sixth decade and it apparently increased from 59 years in 1999 to 62 years in 2018 [1, 2, 4, 32]. This may suggest some improvement in the survival rate of ovarian cancer at the population level [36]. The strong age effect of ovarian cancer was also reported by other authors as majority of ovarian cancers occurred among post-menopausal women [1, 2, 4, 17, 32]. Aside women aged 44–49 years, all other age groups in South Africa had a rise in ovarian cancer mortality rate. Although, previous epidemiological studies suggested that ovarian tumors at young age are likely to be benign, the current rise in mortality showed that health practitioners should always rule out ovarian malignancy among young women [44]. Our join point regression analysis showed that 5-year age group may contain smaller numbers for ovarian cancer, thereby reducing its efficiency. However, this report was useful in demonstrating the similarities between local drifts of A-P-C analysis and the AAPC of the join point regression of similar age groups.

Ethnic disparity of ovarian cancer trends

There was ethnic disparity in ovarian cancer mortality in South Africa and non-Whites (Black, mixed race, Indian/Asian women) had about half the mortality rates among White population group. The White population group generally had the highest ovarian cancer incidence in South Africa [45]. In the United States of America, the Hispanics had the highest ovarian cancer incidence, while their Black counterparts had the highest ovarian cancer mortality in the country [15]. The reason for the pattern in the USA was because Hispanics had higher prevalence of ovarian cancer risks including genetic predisposition but had better awareness of cancer symptoms and improved access to optimum cancer care as compared to the Black Americans [15].

We showed that there was strong cohort effect of ovarian cancer mortality among Black and White South Africans. The Black ethnic group had a more dramatic rise in cohort mortality risk from 0.07 among the 1924–1928

birth cohort to around 7.0 among the youngest cohort (1999–2003). However, mortality risk increase among White cohorts was not as marked rising from 0.54 among 1924–1928 birth cohorts to around 2.4 among 1999–2003 birth cohorts. Historically, the Black South African culture supports or promotes early/teenage pregnancy, and high parity [40, 41, 46]. However, the apartheid regime in South Africa before 1994 promoted vigorous contraception among the Black women ostensibly to curtail their population thereby reducing their fertility rate [40, 41, 46]. Furthermore, injectable contraceptives were made available to the Black South Africans because it was cheaper and easy to administer [6]. Thus, the reduced fertility rate coupled with the poor utilization of COCPs could account for the increased cohort mortality risk of ovarian cancer during the Apartheid era.

During the post-apartheid era from 1994, the low fertility rate among Black South Africans persisted even though women's sexual rights and autonomy were being promoted [20, 40, 41, 47]. The new democratic government expanded access to sexual and reproductive health services among the previously marginalized Black population [9, 10]. Education of the girl child was promoted which may delay childbearing among them as they pursue white collar career. Furthermore, the improved socioeconomic status and adoption of western diet coupled with increased sedentary lifestyle among Black South Africans also led to increased risk of obesity among them [11]. All the forgoing could cause increased mortality risk of ovarian cancer among women of the Black ethnic group, even during the post-apartheid era. Late presentation and poor access to optimum health facility especially during the apartheid era can also increase the cohort mortality rates among Black women [16, 37]. Government should promote ovarian cancer awareness among Black South African so that they know their risk and therefore present early to the hospital since screening is not yet recommended at the population level.

Early White South African cohorts from 1924 to 1928 had the highest ethnic mortality risk of ovarian cancer possibly because they historically had low fertility rates and increased prevalence of obesity [11, 40, 41, 46]. However, successive cohorts of White South Africans were exposed to COCPs from the mid-1960s, thereby reducing the risk of ovarian cancer incidence and mortality among them [48, 49]. Furthermore, awareness of ovarian cancer risks, early presentation and high access to optimum oncological care among the White population might have reduced the rising cohort morality risks among the younger cohorts [16].

Though not statistically significant, the ovarian cancer mortality risks among early cohorts (1924–1954) of women of the mixed race were as high as that of Whites, possibly because of high tobacco smoking rates among them [22, 43]. Surprisingly, the cohort ovarian cancer risk among women of mixed race declined from 1954 to 2003 despite declining fertility rate and increased obesity prevalence among them [11, 50]. Increased smoking rates may partly explain the decline in cohort RR among the mixed-race women. The fluctuating trends, possibly due to small numbers may not allow meaningful interpretation of the cohort mortality trends among the Indian/Asian ethnic group. Thus, modifiable cohort specific interventions may not impact the ovarian cancer risks among Indian/Asian population group of South Africa.

There was period effect of ovarian cancer mortality among only Black South Africans from 1999 to 2018, with rapid drift of about 5.5% per annum. Furthermore, period RR of ovarian cancer among Black South Africans also doubled from 0.84 in 1999–2003 to 1.92 in 2014–2018. This may suggest that rapid urbanization, coupled with improved socio-economic status that led to educational advancement, obesity and low fertility rates among Black women after the commencement of multi-racial democracy in 1994, without commensurate access to ovarian cancer care among Black ethnic group may explain the increased ovarian cancer mortality rates from 1999 to 2018 [9, 10, 37, 38, 50]. Furthermore, the expansion of access to the healthcare facilities for the previously marginalized Black South Africans can increase the diagnosis of ovarian cancer among them, thereby increasing the registration of ovarian cancer deaths among the Black ethnic group [10, 38].

However, the period effect of ovarian cancer mortality was not statistically significant among non-Black ethnic group, and they had relatively low/stable (Whites 0.99%, Indians/Asians 0.13) and declining net drifts (Mixed race: -0.56). Indeed, White and Indian/Asian women had access to private health facility with optimum oncological facilities that is comparable to healthcare services in HICs [51, 52]. Thus, sociopolitical, and public health interventions by South African government after the apartheid era may not impact on risks and outcome of ovarian cancer care among them. Indeed, South African Whites apparently had access to early ovarian cancer diagnosis and similar international preventive interventions that led to a decline in ovarian cancer mortality in North America and Europe as the join point regression modelling suggest that South African Whites also had negative but stable trends (-0.2%) of ovarian cancer mortality from 2009–2018 [2, 31]. However, future studies will confirm the non-statistically significant decline in ovarian cancer mortality in the latter period (2015–2018) among the Indian/Asian ethnic group. The lack of period and cohort effect on ovarian cancer mortality trends among women of the mixed race despite changes in their reproductive and socioeconomic status calls for further research.

There was strong age effect of ovarian cancer mortality among all the ethnic groups (especially from 40 years) and in 2018, the mean age at ovarian cancer mortality among non-Black ethnic group (Mixed race, 62.03years; Indian/Asians, 61.8years Whites, 69.48 years) was in the 6th decade while Black women (58.07 years) died at younger age. This pattern may suggest poorer survival among the Black ethnic group [36]. The high CMR of ovarian cancer as compared to ASMR among non-Black ethnic group further suggested that older age played biologic roles in their mortality pattern. All ages among women of the Black ethnic group experienced a rise in ovarian cancer mortality rate from 1999 to 2018 while only older White women (75 years and older) and older women of mixed race (60–69 years) had statistically significant mortality rise. Thus, ovarian tumors among young Black women should be properly investigated as it might be malignant and the ovarian cancer deaths among White South African can be related to co-morbidity in the elderly [36, 44].

Strength and limitation

This study is the first in SSA to conduct A-P-C and Join point regression analyses of the trends in ovarian cancer mortality over 20 years, using a high-quality vital registration data [21, 23]. A modern A-P-C method with pragmatic estimable parameters was also utilized. The study also utilized one of the three high quality death registration databases in SSA. We also conducted for the first time, the analysis ethnic disparity of ovarian cancer data in South Africa to aid ethnic specific interventions.

The limitation of this study includes the lack of information on histological types of ovarian cancer that may further aid the conclusion of the study [13, 53]. Another limitation of the study is that some deaths may occur outside health facility and may not be reported to the authorities. However, such under-reporting may be minimal as there is a law in South Africa prohibiting burial without reporting the death [54]. However, there may be differential under-reporting based on ethnicity. Under reporting of ovarian cancer may be higher among the Black and mixed-race women as compared to the White and Indian/Asian women. This is because a greater proportion of Black and mixed-race women live in the rural areas with poor access to health facilities. Furthermore, misclassification may also occur more frequently among Black and mixed-race women because of poor access to healthcare facilities. The nature and insidious nature of ovarian cancer disease progression can also lead to misdiagnosis especially in rural areas with poor access to radiological investigations to confirm the diagnosis.

Conclusion

In conclusion, our study showed a strong age, period and cohort effect on the overall mortality trends of ovarian cancer in South Africa. The ovarian cancer mortality rate increased at nearly 2% per annum with increased mortality risk among successive cohorts. Ethnic disparity is noted in the trends of ovarian cancer mortality with Whites having doubled the rates as compared to non-White South African. Black South African had increased Ovarian mortality rates and successive birth cohort had increased ovarian mortality risk. However, White women had stable trends from 2009 to 2018 but generally had increased cohort mortality risks of ovarian cancer. The average age at death was in the sixth decade except for Black women that was lower, thereby suggesting a poorer survival among the Black ethnic group. This study highlights the huge burden of ovarian cancer in South Africa and showed the need to evaluate ethnic specific interventions of ovarian cancer in South Africa. To our knowledge this is the first A-P-C and Join point analyses of national and ethnic data of ovarian cancer mortality in SSA.

Brief policy implications

The South African government promotes access to sexual and reproductive health and places emphasis on the quadruple health burden in South Africa [9, 10, 52, 55]. Furthermore, the South African national breast and cervical cancer control program were launched in 2017 [56, 57]. However, this study highlights the burden and ethnic disparity in ovarian cancer. Therefore, there is an urgent need for a more comprehensive control plan for all sexual and reproductive cancers in the country [56, 57]. We recommend that Governement should promote research on ovarian cancer, especially on its modifiable risk factors to aid interventions. Public enlightenment campaigns on ovarian cancer should be done and high risk women should have a defintive pathway for screening and treatment.

Abbreviations

AAPC	Average annual percent change
A-P-C	Age period cohort
ASMR	Age standardized mortality rate
CI	Confidence interval
CMR	Crude mortality rate
COCP	Combined oral contraceptive pills
SA	South Africa
SSA	Sub Saharan Africa
Stats SA	Statistics South Africa
MIR	Mortality to incidence ratio
RR	Risk ratio

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12885-025-13735-7.

Supplementary Material 1

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Author contributions
Conceptualization and study design: GO, EM, EL, OCE; Data curation: GO, EM, EL. Investigation and methodology: GO, with the guidance of EM, EL, OCE; Data management and formal analysis: GO. Data interpretation: GO, EM, EL, OCE; Writing original draft: GO; Critical review of manuscript and accepted that manuscript should be submitted: GO, EM, EL, OCE; Supervision of the project: EM, EL, OCE.

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Data availability
The data for this study can be accessed from Statistics South Africa.

Declarations

Ethics approval and consent to participate
Before the commencement of the study, ethical approval was obtained from the Human Research Ethics Committee (Medical) of the University of the Witwatersrand (Clearance certificate number: M190544). Confidentiality was ensured as anonymized data was utilized. The consent of the individuals were waived. All experiments were performed in accordance with relevant guidelines and regulations.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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