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Population risk factors for late-stage presentation of cervical cancer in sub-Saharan Africa

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ABSTRACT

Background: Cervical cancer is the most prevalent malignancy in sub-Saharan Africa (SSA) with many women only seeking professional help when they are experiencing symptoms, implying late-stage malignancy and higher mortality rates. This ecological study assesses population-level exposures of SSA women to the numerous risk factors for HPV infection and cervical cancer, against late-stage presentation of cervical cancer.

Materials and method: A literature review revealed the relevant risk factors in SSA. Open-access databases were mined for variables closely representing each risk factor. A proxy for late-stage presentation was used (ratio of incidence-to-mortality, IMR), and gathered from IARC's GLOBOCAN 2012 database. Variables showing significant correlation to the IMR were used in stepwise multiple regression to quantify their effect on the IMR.

Results: Countries with high cervical cancer mortality rates relative to their incidence have an IMR nearer one, suggesting a larger proportion of late-stage presentation. Western Africa had the lowest median IMR (1.463), followed by Eastern Africa (IMR = 1.595) and Central Africa (IMR = 1.675), whereas Southern Africa had the highest median IMR (1.761). Variables selected for the final model explain 65.2% of changes seen in the IMR. Significant predictors of IMR were *GDP* (coefficient = 2.189×10^{-6}, p = 0.064), *HIV infection* (-1.936×10^{-3}, p = 0.095), *not using a condom* (-1.347×10^{-3}, p = 0.013), *high parity* (-1.744×10^{-2}, p = 0.008), and *no formal education* (-1.311×10^{-3}, $p < 0.001$).

Conclusion: Using an IMR enables identification of factors predicting late-stage cervical cancer in SSA including: *GDP, HIV infection, not using a condom, high parity* and *no formal education.*

1. Introduction

Cervical cancer is the most prevalent malignancy among women in the developing world. It is also the most common AIDS-related cancer in women [1,2] and is responsible for the majority of cancer-related deaths within the four regions of sub-Saharan Africa (SSA) (Eastern, Central, Southern and Western) [3]. Of these, Eastern Africa reportedly has the highest incidence of cervical cancer worldwide [4]. These ominous data seem at odds with the fact that cervical cancer is the most preventable form of cancer through vaccination, screening and treatment of pre-cancerous lesions [2,5]. Central to the development of cervical cancer is infection by the sexually transmitted mucosal human papillomavirus (HPV) [6,7]. Worldwide, HPV prevalence in women with normal cervical cytology is approximately 12%, whereas in SSA the prevalence averages at 24%, ranging between 17.4% and 33.6% [8]. To date, the most effective cervical cancer control method has been screening programmes that detect women at increased risk of developing cervical cancer, followed by treatment of the pre-cancerous lesions prior to malignant transformation.

The high burden of cervical cancer in SSA is partly explained because cytology-based screening is prohibitively difficult in those countries lacking adequate health infrastructure, resources and expertise. There are currently very few SSA countries that possess both the capacity and expertise to perform cytology-based screening in a primary care setting nationwide [2,9]. In addition, due to competing demands on the healthcare system from HIV and tuberculosis, health system challenges and lack of human resources, the coverage achieved by cytology screening programmes has varied between less than 10%

Abbreviations: SSA, sub-Saharan Africa; IMR, incidence-to-mortality ratio; HPV, human papillomavirus; LMIC, low-and middle-income countries; IARC, International Agency for Research on Cancer; DHS, USAID's Demographic and Health Survey; GDP, gross domestic product

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and 50% [10–14].

Consequently, many women only seek help from healthcare professionals once they are experiencing gynaecological symptoms (unexpected vaginal bleeding, foul-smelling vaginal discharge, haematuria and abdominal pain) [13,15,16]. This symptomatic presentation means the malignancy is already at an advanced stage, resulting in a poor prognosis and increased mortality [17–19]. There are numerous risk factors, both physiological and socio-cultural, that make SSA women particularly vulnerable to developing cervical cancer. Ginsburg et al. [20] demonstrated that factors including where a woman lives, or if she is affected by poverty, largely determine whether she will develop cervical cancer and her chances of survival within low- and middle-income countries (LMICs).

In this ecological study we assessed the relationship between population-level exposure to established risk factors and potential regional differences with late-stage cervical cancer presentation.

2. Methods

2.1. SSA countries and their cervical cancer prevention programmes

Sub-Saharan Africa are those 51 countries predominantly located south of the Sahara desert, and divided into Eastern, Southern, Central and Western Africa [22]. Owing to a lack of data, five countries were omitted from the analysis: Sao Tome and Principe, Mayotte, Reunion, Seychelles, and Saint Helena. The regional groupings, adult female population size [23], presence and type of cervical cancer prevention programme and female population coverage achieved in each country, can be seen in Table 1.

2.2. Computed variables

As the stage of cervical malignancy at presentation is not routinely reported for all SSA countries, using a ratio of the incidence-to-mortality (IMR) [24,25] may provide a means of estimating the level of late-stage presentation for each country. Consequently, a ratio closer to one implies a late stage of presentation, as both the incidence and mortality values are similar i.e. a larger proportion of the population is dying from cervical cancer than is expected relative to the incidence rates. Conversely, countries yielding a higher IMR are more likely to have fewer late-stage cervical cancer presentations. The inverse of this ratio, mortality-to-incidence, has been shown as a reliable proxy for 1-survival and an important measure of completeness of cancer registry data and the quality of cancer care in both a single country [26] and in multiple countries [25]. Cervical cancer data was derived from IARC's GLOBOCAN 2012 database [4] and included age-standardised incidence and mortality rates per 100,000 of the female population. The IMR for each country is shown in Table 1.

2.3. Risk factors and data sources

A literature review of risk factors for HPV infection and the development of cervical cancer in SSA was undertaken. Population-level data for each risk factor from each SSA country were collected using open-source databanks. The risk factors and the variables used, where possible, are shown in Table 2. The World Bank Databank [23] provided the demographic, female HIV and smoking prevalence, undernourishment and parity data. UNESCO Institute for Statistics: Data Centre [32] provided education-related data, whilst sexual behaviours, marital status, contraception, STIs and additional education data was obtained from USAID's Demographic and Health Surveys (DHS) Program database [33]. Wherever possible, data was taken from 2012 in accordance with the GLOBOCAN cervical cancer data. In instances where 2012 data was not available, the nearest year in which all countries had available data was selected.

2.4. Variable selection

An initial culling of variables occurred after Table 2 was compiled, when risk factors for which there were significant missing data or no attainable variables were excluded. Demographic and Health Survey data were not available for the following regions: Central Africa (Angola, Central African Republic, Chad), Eastern (Djibouti, Mauritius, Somalia, South Sudan), Southern (Botswana) and Western (Guinea Bassau). For those risk factors with multiple variables, the variables with the most complete data were selected. Statistical analysis then determined which variables were included in the final model.

2.5. Statistical analysis

Regional IMR data, cervical cancer prevention programmes and coverage data were described through IQR boxplots, with Mood's median test and *post-hoc* Pairwise Median test performed on each. Risk factor data from the 46 countries were initially examined for normalcy and outliers, through Shapiro-Wilks test. Descriptive statistics for each variable can be seen in Table 3. The distribution of the outcome variable (IMR) was assessed, and the skewness detected was corrected through a Log_{10} transformation and confirmed with a QQ-plot. Pearson correlation coefficients for those variables of normal distribution, Spearman correlation coefficients for those non-parametric variables, and probability values (p) were generated and used to test the association between each risk factor and the logIMR. All p-values presented are two-sided with significant probability set at $\alpha < 0.05$. Co-linearity between the relevant risk factors was assessed through a scatterplot matrix. In the case of co-linearity, a single variable consisting of a large n value, high regression coefficient and a low p-value was selected from those co-linear risk factors. Of the remaining risk factors showing a statistically significant correlation with the logIMR, there were a number of missing values (14.2%). To retain as much of the data as possible, the missing values were calculated using mean imputation with additive regression (an additive cubic spline), bootstrapping and predictive mean matching. Through different bootstraps, data were randomly resampled for each of the multiple imputations, followed by fitting one of ten flexible additive models to the samples with replacements from the original data. Finally, these additive models predicted the missing values by using the non-missing values, and the results then pooled. Two categorical variables were then added to the dataset: *Region* ("Southern", Eastern", "Central" and "Western") and *Screening* ("Population-based", "Opportunistic", "No programme" and "No data"), and the complete dataset underwent a stepwise multiple linear regression to select the combination of variables to describe late-stage cervical cancer for SSA. Additionally, a stepwise regression was performed using the non-missing data and results compared with the data imputation model. Regression diagnostics of the final model was conducted using ANOVA Type II sum of squares tests assessing any interaction between variables. All data analyses were performed using R version 3.4.1 (2017-06-07) for Mac iOS with the following packages: *pastecs, MASS, psych, car, gvlma, RVAidememoire, rcompanion, RColorBrewer, rworldmap, rworldxtra* and *Hmisc*.

3. Results

3.1. Incidence-to-mortality ratio

The geographic distribution of country-specific cervical cancer incidence, mortality and IMRs appear in Fig. 1a–c, with a comparison of regional and individual IMRs in Fig. 2a and b. Overall, the IMR for sub-Saharan Africa is 1.569. By region, Western Africa has the lowest median IMR at 1.463, followed by Eastern Africa (IMR = 1.595) and Central Africa (IMR = 1.675), whereas Southern Africa is highest with 1.761. The effect of cervical cancer prevention programmes on the IMR, as well as the coverage achieved, can be seen in Fig. 3a and b. The

Table 1
Sub-Sahara African countries grouped by region with their adult female population (15–64 years) in 2012, the presence of a national cervical cancer prevention programme, the programme's coverage of the eligible female population, and incidence-to-mortality ratio (IMR) of cervical cancer; *VIA = visual inspection with acetic acid, Pap = Papanicolaou smear test, vac = vaccine; *Programme started after data collection (2012) and is not reflected in the current study.*

Region	Country	Adult female population (2012) [23]	National cervical cancer prevention programme [12]	Population coverage of screening programme, % [12]	IMR
Central	Angola AGO	5,706,933	Pilot HPV vac* & population-based Pap	10–50	1.675
	Cameroon CMR	5,815,025	Pilot HPV vac* [27]	–	1.714
	Central African Republic CAF	1,315,501	Opportunistic Pap	< 10	1.373
	Chad TCD	3,128,292	Opportunistic	< 10	1.288
	Democratic Republic of Congo DRC	17,929,634	*No data*	–	1.212
	Equatorial Guinea GNQ	213,142	*No data*	–	1.780
	Gabon GAB	450,883	*No data*	–	2.369
	Republic of the Congo COG	1,154,892	–	–	1.938
Eastern	Burundi BDI	2,739,225	–	–	1.254
	Comoros COM	205,205	–	–	1.517
	Djibouti DJI	265,652	*No data*	–	1.504
	Eritrea ERI	–	Opportunistic VIA	< 10	1.328
	Ethiopia ETH	24,800,769	Opportunistic VIA	< 10	1.435
	Kenya KEN	11,692,795	Pilot HPV vac*, & opportunistic VIA	10–50	1.839
	Madagascar MDG	6,109,613	Pilot HPV vac* & population-based VIA	< 10	1.664
	Malawi MWI	3,999,277	Pilot HPV vac* & opportunistic Pap	< 10	1.521
	Mauritius MUS	445,445	*No data*	–	1.829
	Mozambique MOZ	6,835,222	Pilot HPV vac* & population-based VIA	10–50	1.321
	Rwanda RWA	3,190,312	HPV vac* [28] & population-based VIA	10–50	1.595
	Somalia SOM	2,522,215	–	–	1.662
	South Sudan SSD	2,955,693	*No data*	–	1.498
	Tanzania TZA	12,732,924	Pilot HPV vac* [27] & opportunistic VIA [29]	–	1.667
	Uganda UGA	8,667,082	HPV vac* & opportunistic VIA	< 10	1.632
	Zambia ZMB	3,756,880	Pilot HPV vac* & population-based VIA	50–70	1.602
	Zimbabwe ZWE	4,113,530	HPV vac* & population-based VIA	10–50	1.598
Southern	Botswana BWA	680,164	Population-based VIA & Pap [30]	10–50	2.075
	Lesotho LSO	614,116	HPV vac* & opportunistic Pap	10–50	1.655
	Namibia NAM	705,342	Opportunistic VIA [31]	10–50	2.130
	South Africa ZAF	17,231,517	HPV vac* & population-based Pap	50–70	1.761
	Swaziland SWZ	367,036	Population-based VIA	10–50	1.713
Western	Benin BEN	2,732,100	Pilot HPV vac*	–	1.551
	Burkina Faso BFA	4,340,346	Pilot HPV vac* & opportunistic VIA	< 10	1.253
	Cabo Verde CPV	162,662	*No data*	–	2.197
	Cote d'Ivoire CIV	5,525,042	Pilot HPV vac*	–	1.476
	Gambia, The GMB	475,430	Pilot HPV vac* & opportunistic Pap	–	1.450
	Ghana GHA	7,513,583	Pilot HPV vac* & opportunistic VIA	< 10	1.873
	Guinea GIN	3,126,218	Population-based screening*	< 10	1.376
	Guinea-Bissau GNB	480,678	*No data*	–	1.380
	Liberia LBR	1,127,338	Pilot HPV vac*	–	1.275
	Mali MLI	4,000,685	Pilot HPV vac* & population-based VIA	< 10	1.377
	Mauritania MRT	1,052,159	–	–	1.564
	Niger NER	4,172,086	Pilot HPV vac*	–	1.225
	Nigeria NGA	44,033,382	Pilot HPV vac * & opportunistic VIA	< 10	1.657
	Senegal SEN	3,814,143	Pilot HPV vac*	–	1.574
	Sierra Leone SLE	16,665,004	Pilot HPV vac*	–	1.208
	Togo TGO	1,880,301	Pilot HPV vac* & population-based VIA	< 10	1.558

median IMR does not change significantly based on the type of prevention programme present, but the coverage achieved does show a positive trend, though not statistically significant.

3.2. Risk factors and their correlations with IMR

Correlations between the thirty remaining risk factors and the IMR, as well as descriptive statistics for each, can be seen in Table 3. Those variables that showed statistically significant correlation to the IMR were selected for multivariate linear regression. The number of countries (n) for which data was present for each variable ranged from 28 to 46. Notable exclusions for statistical significant correlation included *Median age of sexual debut* (n = 35) and *Median age at first birth* (n = 36).

3.3. Multivariate linear regression

The variables selected to be included in the final model can be seen in Table 4. The resulting model has a final AIC of −286.52, p-value of 7.863×10^{-09} and adjusted R^2 of 0.6521. Thus, the model explains approximately 65% of the change seen in the IMR. In this model, *GDP* is the only protective factor with a higher GDP resulting in higher IMR values, whereas *HIV infection*, *no condom use with non-regular partner*, *percentage of rural population*, *parity* and *no formal education* all result in a lower IMR and are thus risk factors for late-stage presentation of cervical cancer. The regression diagnostic showed *no formal education* has the largest single effect on the IMR (sum of square = 0.031936, p-value = 8.941×10^{-05}), and that no significant interaction between the model variables exists. Performing the stepwise regression using only the non-missing data, the number of countries (n) decreased from 46 to 22 (a resultant 21 degrees of freedom). The model had no significant findings.

4. Discussion

Due to a paucity of histopathological staging data for cervical

Table 2
Risk factors associated with cervical cancer. **Excluded risk factors due to missing data or unattainable variables;* DHS: USAID's Demographic Health and Survey programme database .

Risk Factor	Literature source	Attainable variables	Data source
Young age of sexual debut [34–39]	Jimenez-Perez, 1999 Louie, 2009 Moreno, 1995 Williams, 1994 Thomas, 2001 Berrington de Gonzalez, 2004	Median age of first marriage % Teenage mothers/pregnant (15–19yr) Median age of first sexual intercourse	DHS World Bank DHS
Multiple sexual partners or sex with someone who has multiple partners [34,36–42]	Jimenez-Perez, 1999 Brinton, 1989 Moreno, 1995 Williams, 1994 Thomas, 2001 Bayo, 2002 Berrington de Gonzalez, 2004 Maiman, 1998	Mean no. of partners in a lifetime % Females with 1 or more co-wife % Females that don't use condom with non-regular partner	DHS DHS World Bank
Young age of first full-term pregnancy (FTP) [35,43]	Louie, 2009 Appleby, 2006	Median age of first FTP (years)	DHS
Poor genital hygiene [41]*	Bayo, 2002	N/A	
Intravaginal practices [44]*	Seay, 2016	N/A	
Female circumcision [41]*	Bayo, 2002	% Female population who are circumcised	DHS
Parity/FTP (> 26wks) [34,36–39,41,43,45–47]	Jimenez-Perez, 1999 Ruche, 1998 Brinton, 1989 Appleby, 2006 Moreno, 1995 Williams, 1994 Thomas, 2001 Bayo, 2002 Berrington de Gonzalez, 2004 Muwonge, 2016	Fertility rate (no. of births per woman)	World Bank
Marital status [21,34,47,48]	Jimenez-Perez, 1999 Mitchell, 2014 Berraho, 2012 Muwonge, 2016	% Female population: single, married, divorced, widowed	DHS
Oral and/or injectable contraceptive use [34,38,39,48–51]	Jimenez-Perez, 1999 Mitchell, 2014 Castellsague, 2003 Thomas, 2001 Djigma, 2011 Berrington de Gonzalez, 2004 Urban, 2012	% Women having ever used the oral contraceptive	DHS
Smoking tobacco [36,38,39,42,45,49,50,52–55]	Castellsague, 2003 La Ruche, 1998 Moreno, 1995 Thomas, 2001 Djigma, 2011 Roura, 2014 Guillaud, 2014 Appleby, 2006 Berrington de Gonzalez, 2004 Lacey, 2001 Maiman, 1998	% Women who use tobacco (cigarettes, pipe, chew)	World Bank
HIV infection [1,42,48,50,56,57]	Mitchell, 2014 Maiman, 1997 Djigma, 2011 Gondos, 2004 Lomalisa, 2000 Maiman, 1998	% Women who are HIV positive (15–49yr)	World Bank
Sexually transmitted infection [36,37,50,58]	Moreno, 1995 Williams, 1994 Djigma, 2011 Castellsague, 2014	% Women who have a self-reported STI (15–49yr)	DHS
Schistosomiasis haematobium infection [59–65]*	Savardekar, 2010 North, 2003 Yang, 2005 Maraj, 2013 Prabhakaran, 2004 Pillay, 2016	N/A	

(*continued on next page*)

Table 2 (*continued*)

Risk Factor	Literature source	Attainable variables	Data source
	Moubayed, 1995		
Low socioeconomic status (SES) [20,38,48,66–68]	McFarland, 2003	GDP per capita, PPP	World Bank
	Mitchell, 2014	Poverty headcount ratio at national poverty line (% of population)	World Bank
	Cutler, 2008		
	Thomas, 2001		
	Hibbitts, 2006		
	Ginsburg, 2016		
Lack of formal education [37,45,48,69–71]	Mitchell, 2014	% Illiteracy/literacy	UNESCO
	La Ruche, 1998	Cumulative dropout of girls from primary school per annum	UNESCO
	Williams, 1994	% Girls who transition from primary to secondary school	UNESCO
	Smith-Greenaway, 2015	% Population with no formal education	DHS
	Ainsworth, 1996	Female primary school completion rate, (% of age group)	World Bank
	Mlange, 2016		
Poor health literacy and lack of awareness for early attendance to a healthcare facility[71–78]	Mwaka, 2015	Knowledge of one modern contraceptive method (% female)	DHS
	RCGP, 2014	Correct knowledge of HIV transmission prevention of HIV (% female)	DHS
	Bostock, 2012		
	Berkman, 2014		
	Schrauben, 2015		
	Agurto, 2005		
	Mlange, 2016		
	Ibrahim, 2011		
Limited access to healthcare/rural dwelling [17,21,77,78]	Mwaka, 2015	% Rural population	World Bank
	Agurto, 2005		
	Ibrahim, 2011		
	Berraho, 2012		
Folate and Vitamin A deficiency [79–83]	Orr, 1985	% Undernourished population	World Bank
	Wang, 2006		
	Eleutério Jr., 2014		
	Chen, 2015		
	Jia, 2016		
Poor healthcare infrastructure[17,77]	Mwaka, 2015	No. of hospital beds per 1000 population	World Bank
	Agurto, 2005	Health expenditure per capita	World Bank
Preference for seeing traditional practitioner over standard healthcare provider [71]*	Mlange, 2016	N/A	

cancer across most SSA countries, the IMR is a crude yet effective approach to assess the magnitude of late-stage presentation across the region. This analysis highlights regional differences in the burden of late-stage presentation of cervical cancer, with Western Africa carrying the largest burden whilst Southern Africa shows the least. Interestingly, despite very high cervical cancer incidence and mortality, Eastern Africa does not have a high proportion of late-stage presentation relative to the rest of the continent. This demonstrates that, while East African women are commonly diagnosed with cervical cancer, the mortality rates are lower than other SSA regions. The high incidence relative to mortality rates could imply that healthcare workers in Eastern Africa are relatively adept at diagnosing cervical cancer. It may also mean these women are dying of other causes not directly related to their cervical cancer, such as complications from pregnancy and childbirth or HIV/AIDS [84–86]. Anderson and Ray (2017) calculated the extent and cause of excess female deaths amongst 15–59 year-olds in Africa: excess deaths are highest in Western Africa (450,000) followed by Eastern Africa (400,000); with HIV responsible for the most excess deaths – 800,000 across the continent, predominantly affecting Southern and Eastern Africa [87]. As these excess deaths similarly affect all regions of SSA, it is likely that the differences seen amongst regional IMRs are due to stage of cervical cancer, and not excess deaths. Conversely, while fewer women are being diagnosed with cervical cancer in Western Africa, more are presenting with late-stage disease; consequently women in Western Africa have poorer outcomes.

4.1. Screening and vaccination programmes

As expected, this study demonstrated a difference in IMR between countries with cervical cancer prevention programme coverage of < 10%, and those with coverage from 10 to 50% and 50–70% (Fig. 3b). However, this difference was not statistically significant, nor was the presence of a prevention programme selected for the multivariate regression model. If implemented correctly, screening programmes decrease cervical cancer incidence provided their coverage is extensive [88]. Without high coverage, or with existing poor awareness and management of early lesions, these prevention programmes will not reduce cervical cancer mortality rates or late-stage presentation. This may be why screening programmes do not contribute as positively in sub-Saharan Africa as they may in other developed countries. The recent introduction of pilot HPV vaccination programmes in many of these countries [12] should decrease the overall incidence, thereby having a knock-on reduction in mortality, and advanced-stage cervical cancer presentation.

4.2. Potential risk factors predicting late-stage presentation with cervical cancer

4.2.1. HIV

Populations with high HIV prevalence are more at risk of contracting HPV due to the congruent transmission patterns and their increased risk from immune compromise, thus they are at greater risk of developing cervical cancer [48,89–91]. Governments in countries with high HIV burdens, such as South Africa, may prioritise the medical

Table 3
Descriptive statistics, correlation coefficients and for each risk factor relative to the IMR. *$p < 0.05$.

Variable	Number of countries (n)	Median	IQR	Range	Pearson (C)	Spearman (S)	*p*-value
HIV prevalence 15–49yr, %	45	2.7	5	0.2–26.5		0.375	0.011*
Comprehensive HIV knowledge, %	34	28.75	20.38	13.9–67.8		0.201	0.254
Economic status, GDP per capita USD	46	1811.96	2100.27	547.32–36754.81		0.753	0.000*
Health expenditure, per capita USD	44	124.15	146.62	23.65–1170.09		0.743	0.000*
Hospital beds, per 1000 population	44	1.1	1.35	0.1–3.3		0.581	0.000*
Rural population, % total	46	60.97	22.57	13.54–88.79	−0.523		0.000*
Undernourishment, % total	39	20.2	20.4	3.6–48.1	−0.182		0.2666
Single, % women	36	27.9	8.48	7.9–59.5		0.468	0.004*
Married, % women	36	54.75	22.45	10.7–88.4	−0.696		0.000*
Common-law spouse, % women	36	9.5	14.85	0.2–34.2		0.336	0.049*
Divorced, % women	36	7.4	5.15	1.0–14.1	0.403		0.015*
Widowed, % women	36	2.5	1.75	0.6–7.5		−0.037	0.831
Median age of sexual debut	35	17.4	1.45	15.9–21.0		0.24	0.166
Median age at first marriage	40	18.85	2.2	15.5–29.1		0.622	0.000*
Median age at first birth	36	19.95	1.6	18.3–23.0	0.148		0.39
Average no. sexual partners	28	2.25	0.93	1.2–5.1		0.493	0.008*
No condom use with non-regular partner	34	64.8	21.03	34.5–95.0	−0.525		0.001*
1 or more co-wife, % women	33	18.3	21.2	1.5–343.8		−0.377	0.030*
Oral contraception, % women	36	4.1	4.45	0.7–62.2		0.297	0.078
Contraceptive knowledge, % women	35	96.4	4.65	67.3–99.7		0.468	0.005*
STI, % women	34	10.4	11.68	0.2–50.2		−0.064	0.718
Parity (average)	45	4.94	1.23	1.45–7.58	−0.601		0.000*
Smoking, % women	33	2.8	4	0.2–21.2		−0.108	0.549
Illiteracy, female 15 + yr	44	38.35	36.93	6.87–88.96		−0.708	0.000*
Transition Prim to Sec, % women	37	78.67	24.76	53.36–98.56		0.285	0.087
Cumulative primary dropout, % women	38	35.62	27.73	1.13–75.49	−0.494		0.002*
Mean years of education	33	4.4	3.99	0.99–9.02		0.792	0.000*
Education: none (%)	37	20	34.3	2.3–80.0		−0.742	0.000*
Education: primary (%)	37	33.6	30.7	9.3–68.3	0.189		0.261
Education: secondary (%)	37	27	23.5	6.5–65.2		0.568	0.000*
Education: post-secondary (%)	32	3.6	3.63	0.5–22.0		0.484	0.005*

resources for its management, as seen by the 262% increase in HIV spending by the government between 2005 and 2013 [92,93]. This may lessen the amount of money, human resources and infrastructure available for cervical cancer awareness and screening programmes [94,95], and contribute to advanced-stage presentation of cervical cancer [96]. Furthermore, cervical cancer symptoms may be mistaken for genital infections including HIV [17]. At a national level, cervical smears for all newly diagnosed HIV-positive women, especially those without effective population-based screening programmes, should be a priority in tackling presentation with late-stage disease.

4.2.2. GDP

GDP is shown to be the only protective model variable against late-stage presentation with cervical cancer, probably because countries with more disposable income can allocate healthcare sector funds to prevention strategies, such as screening programmes and education, and provide timely and effective treatment regimens for those women who are diagnosed with cancer. The need for intersectoral collaboration, which extends further than healthcare provisions, is paramount to attain population health equity [97,98]. This equity may be achieved by reducing those factors that have a negative impact on population health, such as poor housing, nutrition, water and sanitation [98,99]. Direct correlation can be seen between an increase in GDP and an increase in IMR (correlation coefficient 0.753, p-value < 0.001). This correlation is also explained from the reverse direction as a healthier population is a more effective workforce and thus able to contribute more productively to the country's economy.

4.2.3. Percentage rural population

The percentage of population that lives rurally is included in the model, though is not statistically significant. Larger rural populations might be less able to access healthcare and have limited exposure to urban marketing and information. This may result in poorer health literacy and cancer awareness, and a greater likelihood of a patient only presenting to a health centre once symptoms are considerable [78]. In addition, SSA has a large rural-to-urban migrant labour force [100,101] which may facilitate the spread of HPV on return of the labourer to their rural home.

4.2.4. No condom with non-regular partner

High incidence of unsafe sex implies a severe lack of health education, possibly a lack of health literacy, and insufficient government awareness and intervention programmes [102]. This could be due to lack of resources in countries with a low GDP, or internal conflict, corruption and misappropriation of funds, droughts and famine [103]. In addition, gender inequity resulting in female disempowerment, a common gender norm in many SSA countries, leaves women less able to negotiate condom use with their partner [104–110].

4.2.5. Parity

High parity is biologically plausible as a higher frequency of unprotected sex results in greater exposure to HPV and increased risk of developing cervical cancer [39,46,103,111]. Late-stage presentation may result from high parity potentially due to lack of contraception knowledge or access, and a lack of health literacy [112]; both possibly the result of a struggling healthcare system and limited resources [103]. High parity may also reflect inequalities between the sexes in access to education, with the negative correlation that exists between women's likelihood of childbearing and the attainment of education being well established [113]. This relationship potentially perpetuates the cycle of high parity and lack of education amongst generations of women.

4.2.6. No formal education

Populations with a larger proportion of uneducated women indicate systemic failings within almost all government sectors. Though academic education, or lack thereof, cannot directly be extrapolated to health education or health literacy, one can assume that countries unable to provide their populations with even basic education are also

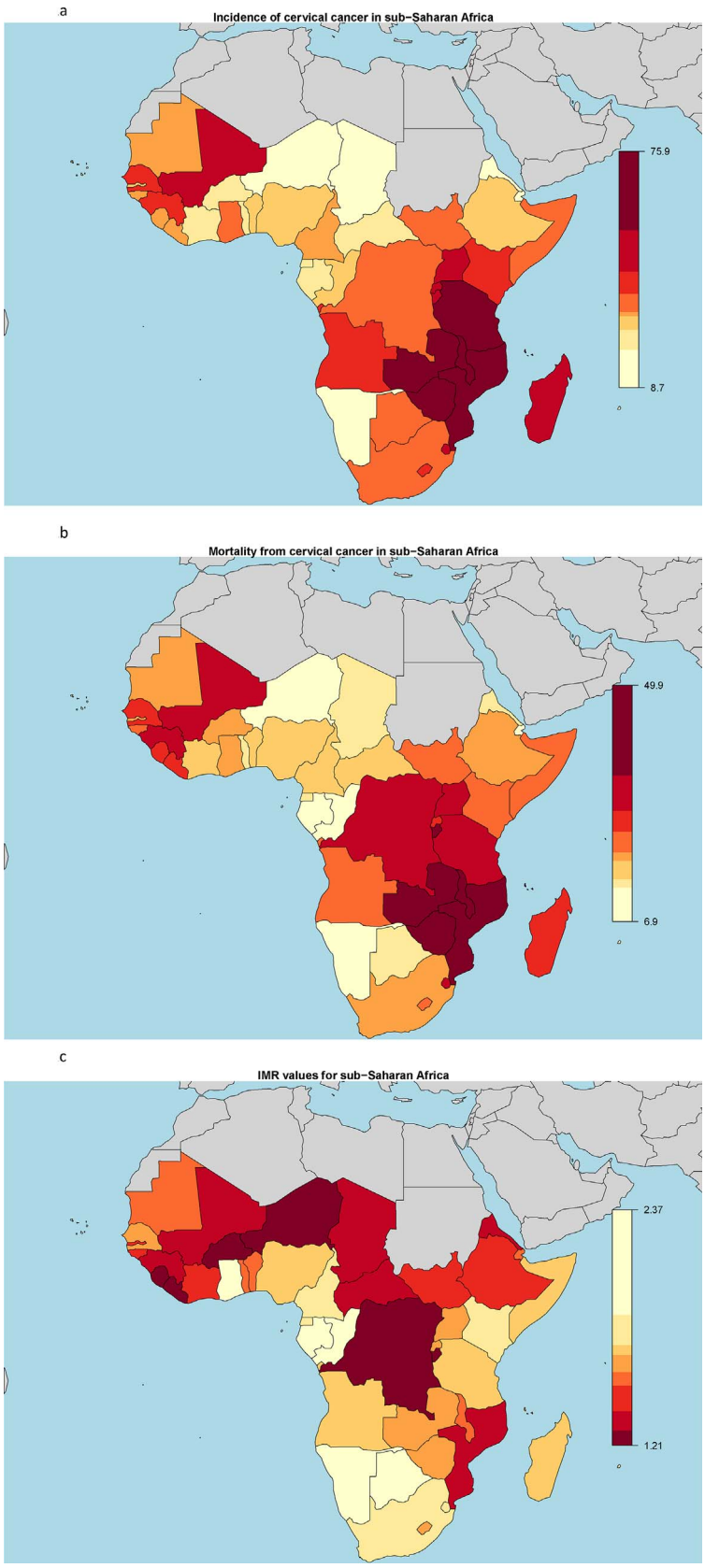

Fig. 1. a–c: Maps of Africa showing age-standardised rates of cervical cancer incidence (a), mortality (b) and the ratio of incidence-to-mortality (IMR) (c). Rates are highest in Eastern Africa for the former two indices, whereas IMR values are closer to one for countries in Central and Western Africa: Democratic Republic of Congo, Niger, Burkina Faso, Liberia and Sierra Leone.

unlikely to provide population-based screening and prevention programmes for cervical cancer [98].

4.3. Strengths and limitations

To the best of our knowledge, this study is the first of its kind to assess late-stage presentation of cervical cancer in SSA and the

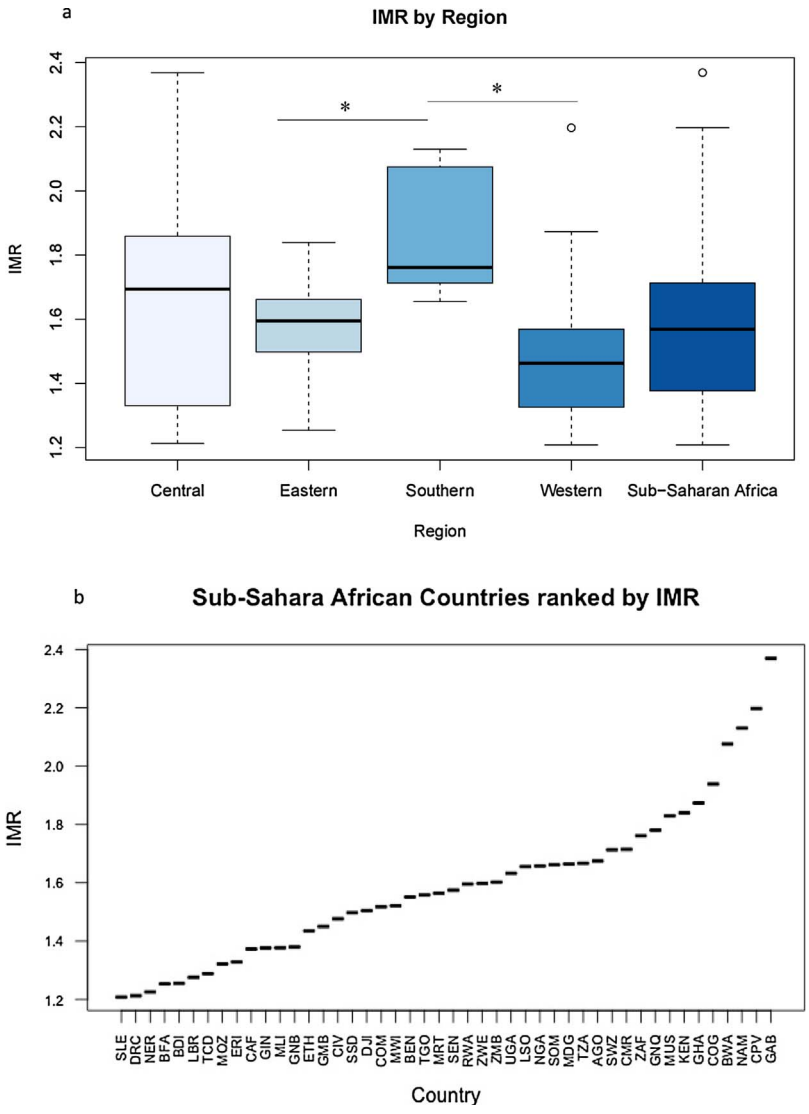

Fig. 2. a & b: Median and interquartile range of incidence-to-mortality ratios for each region and for sub-Saharan Africa (a), countries ranked by IMR (b). *$p < 0.05$ for Mood's median test and *post hoc* pairwise median test.

population risk factors thereof. It also collates types of cervical cancer prevention programmes and coverage information for the majority of these countries with the resulting burden of late-stage presentation. Although drawing causal relationships between predictor and outcome variables, and the inference of population-level data at an individual level ('ecological fallacy' [114]), is prevented in ecological studies, this study retains a number of positive attributes [115,116]. The public health potential of ecological studies includes 'group effects' in which groups of individuals acquire collective properties that are greater than the sum of their individual parts, which may be lost using only individual observations [117]. The main limitations are the variations in data availability and quality across the sub-Saharan countries, partly due to the lack of African cancer registries. Additionally, the missing DHS and screening programme data affected the study methodology, necessitating imputation prior to statistical analysis. This may dilute the associations we can draw, despite the robust methods used. However, the missing data itself provides valuable information: the need for systematic data collection regarding all aspects of cervical cancer programmes and coverage within SSA. One cannot monitor the progress of future interventions without knowing the extent of the problem. The missing data highlight the scale of the challenges facing many SSA countries, which need to be acknowledged when attempting to implement cervical cancer prevention strategies.

5. Conclusion

Through using a proxy for late-stage presentation of cervical cancer (the IMR), we were able to determine potential population risk factors that could contribute to this phenomenon within SSA. *HIV prevalence*, *high parity*, *no formal education, no condom use with non-regular partner* and a *high percentage rural population* are shown to be population risk factors for late-stage presentation of cervical cancer. In contrast, *higher GDP* was associated with higher IMRs, and thus protective against symptomatic presentation.

Authorship contribution

All authors reviewed and revised the paper critically for important intellectual content, gave final approval of the version to be published, and are accountable for all aspects of the work. In addition: TSS: conceptualisation, data collection, statistics, interpretation, original draft writing, editing; FMW: supervisor, conceptualisation, interpretation, editing; JM: content input regarding South Africa, statistics, interpretation, editing.

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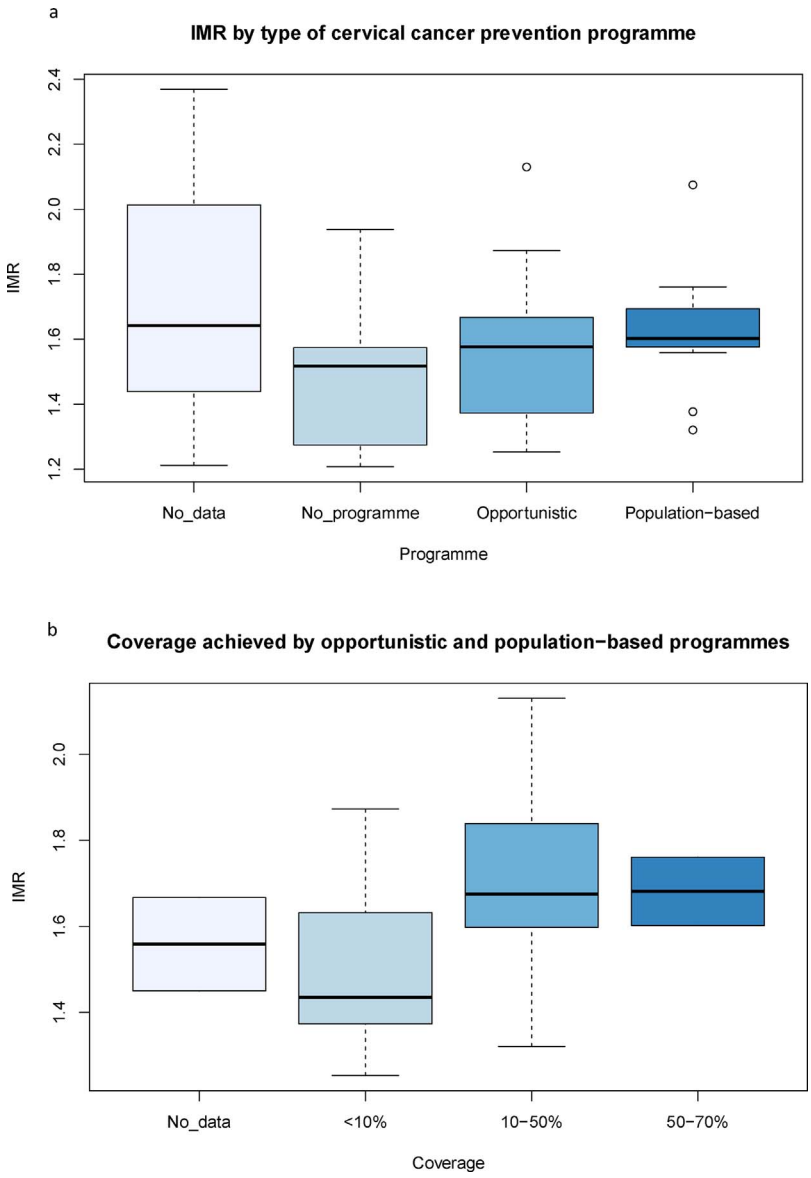

Fig. 3. a & b: Types of screening and prevention programmes present (a), and population coverage achieved by opportunistic and population-based screening programmes (b), and the resulting incidence-to-mortality ratio of each.

Table 4
Coefficients, standard error, t-value statistic and probability of the selected variables in the final model. The F-statistic is 15.06 on 6 and 39 DF, and a p-value of 7.863×10^{-09}. The residual standard error is 0.04142 on 39 degrees of freedom and adjusted R^2 is 0.6521.

Coefficients:	Estimate	Std. Error	t value	p value
(Intercept)	4.426×10^{-01}	4.908×10^{-02}	9.018	4.39×10^{-11} ***
HIV	-1.936×10^{-03}	1.130×10^{-03}	−1.713	0.095 .
GDP	2.189×10^{-06}	1.147×10^{-06}	1.909	0.065 .
Rural	-6.078×10^{-04}	4.328×10^{-04}	−1.404	0.168
No condom use	-1.347×10^{-03}	5.194×10^{-04}	−2.594	0.013 *
Parity	-1.744×10^{-02}	6.220×10^{-03}	−2.804	0.008 **
No education	-1.311×10^{-03}	3.039×10^{-04}	−4.315	0.0001 ***

Significance codes: '***' < 0.001; '**' < 0.01; '*' < 0.05; '.' < 0.1; ' ' < 1

agencies in the public, commercial, or not-for-profit sectors.

Conflicts of interest

None.

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References

[1] M. Maiman, R.G. Fruchter, M. Clark, C.D. Arrastia, R. Matthews, E.J. Gates, Cervical cancer as an AIDS-defining illness, Obstet. Gynecol. 89 (1997) 76–80 (Accessed 22 February 2016), http://www.ncbi.nlm.nih.gov/pubmed/8990442.

[2] S.L. van Schalkwyk, J.E. Maree, S.C. Dreyer Wright, Cervical cancer: the route from signs and symptoms to treatment in South Africa, Reprod. Health Matters 16 (2008) 9–17, http://dx.doi.org/10.1016/S0968-8080(08)32399-4.

[3] World Health Organization, Cervical Cancer: Fact Sheets by Population, Int. Agency Res. Cancer, 2012 (Accessed 8 November 2015), http://globocan.iarc.fr/Pages/fact_sheets_population.aspx.

[4] [dataset] J. Ferlay, I. Soerjomataram, M. Ervik, R. Dikshit, S. Eser, C. Mathers, M. Rebelo, D. Parkin, D. Forman, F. Bray, GLOBOCAN 2012 v1.0, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 11 [Internet]. Int. Agency Res. Cancer. (2013). 10.1002/ijc.29210.

[5] B. Fonn, M. Bloch, S. Mabina, H. Carpenter, C. Cronje, M. Bennun, G. du Toit, I. de Jonge, G. Manana, Prevalence of pre-cancerous lesions and cervical cancer in South Africa – a multicentre study, South Afr. Med. J. 92 (2016) 148–156 (Accessed 22 February 2016), http://www.ncbi.nlm.nih.gov/pubmed/11894653.

[6] N. Munoz, F.X. Bosch, S. de Sanjose, R. Herrrero, X. Castetellaasague, et al., Epidemiologic classification of human papillomavirus types associated with cervical cancer, N. Engl. J. Med. 348 (2003) 518–527.

[7] L. Denny, S. de Sanjose, M. Mutebi, B.O. Anderson, J. Kim, J. Jeronimo, R. Herrero, K. Yeates, O. Ginsburg, R. Sankaranarayanan, Interventions to close the divide for women with breast and cervical cancer between low-income and middle-income countries and high-income countries, Lancet 6736 (2016) 21–30, http://dx.doi.org/10.1016/S0140-6736(16)31795-0.

[8] L. Bruni, M. Diaz, X. Castellsagué, E. Ferrer, F.X. Bosch, S. de Sanjosé, Cervical human papillomavirus prevalence in 5 continents: meta-analysis of 1 million women with normal cytological findings, J. Infect. Dis. 202 (2010) 1789–1799, http://dx.doi.org/10.1086/657321.

[9] L. Denny, M. Quinn, R. Sankaranarayanan, Screening for cervical cancer in developing countries, Vaccine 24 (2006), http://dx.doi.org/10.1016/j.vaccine.2006.05.121.

[10] L. Denny, Prevention of cervical cancer, Reprod. Health Matters 16 (2008) 18–31, http://dx.doi.org/10.1016/S0968-8080(08)32397-0.

[11] J. Moodley, M. Kawonga, J. Bradley, M. Hoffman, Challenges in implementing a cervical screening program in South Africa, Cancer Detect. Prev. 30 (2006) 361–368, http://dx.doi.org/10.1016/j.cdp.2006.07.005.

[12] [dataset] Global Health Observatory, Global Health Observatory data repository: Primary and secondary prevention of cancer, WHO Website. (2016). http://apps.who.int/gho/data/node.main.A914?lang=en, (Accessed 9 April 2017).

[13] M. Momberg, M.H. Botha, F.H. Van der Merwe, J. Moodley, Women's experiences with cervical cancer screening in a colposcopy referral clinic in Cape Town, South Africa: a qualitative analysis, BMJ Open 7 (2017) e013914, http://dx.doi.org/10.1136/bmjopen-2016-013914.

[14] C. Day, A. Gray, Health and related indicators, in: A. Padarath, J. King, R. English (Eds.), South African Heal. Rev. 2014/15, Health Systems Trust, Durban, 2015, pp. 207–329, , http://dx.doi.org/10.1007/s13398-014-0173-7.2.

[15] A.D. Mwaka, H.R. Wabinga, H. Mayanja-Kizza, Mind the gaps: a qualitative study of perceptions of healthcare professionals on challenges and proposed remedies for cervical cancer help-seeking in post conflict northern Uganda, BMC Fam. Pract. 14 (2013) 193, http://dx.doi.org/10.1186/1471-2296-14-193.

[16] L.W. Kivuti-Bitok, G.P. Pokhariyal, R. Abdul, G. McDonnell, An exploration of opportunities and challenges facing cervical cancer managers in Kenya, BMC Res. Notes 6 (2013) 136, http://dx.doi.org/10.1186/1756-0500-6-136.

[17] A.D. Mwaka, E.S. Okello, H. Wabinga, F.M. Walter, Symptomatic presentation with cervical cancer in Uganda: a qualitative study assessing the pathways to diagnosis in a low-income country, BMC Womens Health 15 (2015) 1–13, http://dx.doi.org/10.1186/s12905-015-0167-4.

[18] K. Mishra, A. Desai, S. Patel, M. Mankad, K. Dave, Role of percutaneous nephrostomy in advanced cervical carcinoma with obstructive uropathy: a case series, Indian J. Palliat. Care 15 (2009) 37–40, http://dx.doi.org/10.4103/0973-1075.53510.

[19] M.L. Hicks, O.W.S. Yap, R. Matthews, G. Parham, Disparities in cervical cancer screening, treatment and outcomes, Ethn. Dis. 16 (2006) 3–63.

[20] O. Ginsburg, F. Bray, M.P. Coleman, V. Vanderpuye, A. Eniu, S.R. Kotha, M. Sarker, T.T. Huong, C. Allemani, A. Dvaladze, J. Gralow, K. Yeates, C. Taylor, N. Oomman, S. Krishnan, R. Sullivan, D. Kombe, M.M. Blas, G. Parham, N. Kassami, L. Conteh, The global burden of women's cancers: a grand challenge in global health, Lancet 0 (2016) 743–800, http://dx.doi.org/10.1016/S0140-6736(16)31392-7.

[21] M. Berraho, M. Obtel, K. Bendahhou, A. Zidouh, H. Errihani, A. Benider, C. Nejjari, Sociodemographic factors and delay in the diagnosis of cervical cancer in Morocco, Pan Afr. Med. J. 12 (2012) 14.

[22] [dataset] The World Bank: IBRD – IDA, Sub-Saharan Africa | Data, World Bank Data Sub-Saharan Africa. (2017). http://data.worldbank.org/region/sub-saharan-africa, (Accessed 26 August 2017).

[23] [dataset] World Bank Group, The World Bank: DATA, World Bank Website. (2016). http://data.worldbank.org/, (Accessed 2 March 2016).

[24] V. Sunkara, J.R. Hébert, The colorectal cancer mortality-to-incidence ratio as an indicator of global cancer screening and care, Cancer 121 (2015) 1563–1569, http://dx.doi.org/10.1002/cncr.29228.

[25] F. Asadzadeh Vostakolaei, H.E. Karim-Kos, M.L.G. Janssen-Heijnen, O. Visser, A.L.M. Verbeek, L.A.L.M. Kiemeney, The validity of the mortality to incidence ratio as a proxy for site-specific cancer survival, Eur. J. Public Health 21 (2011) 573–577, http://dx.doi.org/10.1093/eurpub/ckq120.

[26] D.M. Parkin, F. Bray, Evaluation of data quality in the cancer registry: principles and methods Part II. Completeness, Eur. J. Cancer 45 (2009) 756–764, http://dx.doi.org/10.1016/j.ejca.2008.11.033.

[27] PATH, Report of an African Regional Meeting on Cervical Cancer Improved Cervical Cancer Prevention: Planning Now for a Better Future, September 14–15 2010, Kampala, Uganda, Seattle, 2010.

[28] A. Binagwaho, C.M. Wagner, M. Gatera, C. Karema, C.T. Nutt, F. Ngabo, Atteinte d'un niveau de couverture élevé pour le programme national Rwandais de vaccination contre le papillomavirus humain, Bull. World Health Organ 90 (2012) 623–628, http://dx.doi.org/10.2471/BLT.11.097253.

[29] ICAP, ICAP Scales up Integrated Cervical Cancer Screening Programs in Mozambique, Tanzania and Kenya | News | ICAP at Columbia University, ICAP Website, 2013 (Accessed 31 March 2017), http://icap.columbia.edu/news-events/detail/icap-scales-up-integrated-cervical-cancer-screening-programs-in-mozambique/.

[30] S. Grover, M. Raesima, M. Bvochora-Nsingo, S.P. Chiyapo, D. Balang, N. Tapela, O. Balogun, M.K.A. Kayembe, A.H. Russell, B. Monare, S. Tanyala, J. Bhat, K. Thipe, M. Nchunga, S. Mayisela, B. Kizito, A. Ho-Foster, B.E. Gaolebale, P.A. Gaolebale, J.A. Efstathiou, S. Dryden-Peterson, N. Zetola, S.M. Hahn, E.S. Robertson, L.L. Lin, C. Morroni, D. Ramogola-Masire, Cervical cancer in Botswana: current state and future steps for screening and treatment programs, Front. Oncol. 5 (2015) 239, http://dx.doi.org/10.3389/fonc.2015.00239.

[31] J. Kangmennaang, N. Thogarapalli, P. Mkandawire, I. Luginaah, Investigating the disparities in cervical cancer screening among Namibian women, Gynecol. Oncol. 138 (2015) 411–416, http://dx.doi.org/10.1016/j.ygyno.2015.05.036.

[32] [dataset] UNESCO, Education, UNESCO Institute of Statistics Website. (2016). http://data.uis.unesco.org/Index.aspx?DataSetCode=EDULIT_DS&popupcustomise=true&lang=en, (Accessed 2 March 2016).

[33] [dataset] USAID, The DHS Program – Data, Demogr. Heal. Surv. Website. (2011). https://dhsprogram.com/data/, (Accessed 14 March 2016).

[34] M. Jimenez-Perez, D.B. Thomas, Has the use of Pap smears reduced the risk of invasive cervical cancer in Guadalajara, Mexico? Int. J. Cancer 809 (1999) 804–809.

[35] K. Louie, S. de Sanjose, M. Diaz, X. Castellsague, R. Herrero, C.J. Meijer, K. Shah, S. Franceschi, K.S. Louie, S. De Sanjose, M. Diaz, X. Castellsague, C. Rica, Early age at first sexual intercourse and early pregnancy are risk factors for cervical cancer in developing countries, Br. J. Cancer (2009) 1191–1197, http://dx.doi.org/10.1038/sj.bjc.6604974.

[36] V. Moreno, N. Muiioz, F.X. Bosch, S. De Sanjos, L. Tafur, M. Gili, I. Izarzugaza, C. Navarro, P. Viladiu, N. Ascunce, Factors for progression of cervical intraepithelial grade III to invasive cervical neoplasm, Cancer Epidemiol. Biomark. Prev. 4 (1995) 459–467.

[37] M.A. Williams, P.R. Kenya, J.K. Mati, D.B. Thomas, Risk factors for invasive cervical cancer in Kenyan women, Int. J. Epidemiol. 23 (1994) 906–912 (Accessed 9 March 2016), http://www.ncbi.nlm.nih.gov/pubmed/7860170.

[38] D.B. Thomas, R.M. Ray, A. Koetsawang, N. Kiviat, J. Kuypers, Q. Qin, R.L. Ashley, S. Koetsawang, Human papillomaviruses and cervical cancer in Bangkok. I. Risk factors for invasive cervical carcinomas with human papillomavirus types 16 and 18 DNA, Am. J. Epidemiol. 153 (2001) 723–731, http://dx.doi.org/10.1093/aje/153.8.723.

[39] A. Berrington de González, S. Sweetland, J. Green, Comparison of risk factors for squamous cell and adenocarcinomas of the cervix: a meta-analysis, Br. J. Cancer 90 (2004) 1787–1791, http://dx.doi.org/10.1038/sj.bjc.6601764.

[40] L.A. Brinton, W.C. Reeves, M.M. Brenes, R. Herrero, E. Gaitan, F. Tenorio, R.C. de Britton, M. Garcia, W.E. Rawls, The male factor in the etiology of cervical cancer among sexually monogamous women, Int. J. Cancer. 44 (1989) 199–203 (Accessed 11 March 2016), http://www.ncbi.nlm.nih.gov/pubmed/2547727.

[41] S. Bayo, F. Bosch, S. De Sanjose, N. Muñoz, A. Combita, P. Coursaget, M. Diaz, A. Dolo, A. Van Den Brule, C. Meijer, Risk factors of invasive cervical cancer in Mali, Int. J. Epidemiol. 31 (2002) 202–209, http://dx.doi.org/10.1170/134.

[42] M. Maiman, R. Fruchter, A. Sedis, J. Feldman, P. Chen, R. Burk, H. Minkoff, Prevalence risk factors, and accuracy of cytologic screening for cervical intraepithelial neoplasia in women with the human immunodeficiency virus, Gynecol. Oncol. 68 (1998) 233–239.

[43] P. Appleby, V. Beral, D. Colin, S. Franceschi, J. Green, C. La Vecchia, J. Peto, G. Randi, R. Herrero, A. Hildesheim, C. La Vecchia, D. Skegg, Cervical carcinoma and reproductive factors: collaborative reanalysis of individual data on 16 563 women with cervical carcinoma and 33,542 women without cervical carcinoma from 25 epidemiological studies, Int. J. Cancer 1124 (2006) 1108–1124, http://dx.doi.org/10.1002/ijc.21953.

[44] J.S. Seay, M. Mandigo, J. Kish, J. Menard, S. Marsh, E. Kobetz, Intravaginal practices are associated with greater odds of high-risk HPV infection in Haitian women, Ethn. Health 0 (2016) 1–9, http://dx.doi.org/10.1080/13557858.2016.1246423.

[45] G. La Ruche, B. You, I. Mensah-Ado, C. Bergeron, C. Montcho, R. Ramon, K. Tour??-Coulibaly, C. Welffens-Ekra, F. Dabis, G. Orth, Human papillomavirus and human immunodeficiency virus infections: relation with cervical dysplasia-neoplasia in African women, Int. J. Cancer 76 (1998) 480–486, http://dx.doi.org/10.1002/(SICI)1097-0215(19980518)76:4<480:AID-IJC6>3.0.CO;2-N.

[46] L.A. Brinton, W.C. Reeves, M.M. Brenes, R. Herrero, R.C. de Britton, E. Gaitan, F. Tenorio, M. Garcia, W.E. Rawls, Parity as a risk factor for cervical cancer, Am. J. Epidemiol. 130 (1989) 486–496.
[47] R. Muwonge, L. Ngo Mbus, T. Ngoma, C. Gombe Mbalawa, A. Dolo, M. da Ganda Manuel, H. Nouhou, M. Nacoulma, J. Mwaiselage, M. Koulibaly, S. Bayo, J. Nsonde Malanda, H. De Vuyst, R. Herrero, R. Sankaranarayanan, N. Keita, A. Dolo, S. Bayo, M. Tour??, B. Keita, C. Gombe Mbalawa, J. Kokolo, J. Nsonde-Malanda, N. Keita, M. Koulibaly, I. Kabba, T. Ngoma, R. Muwonge, J. Mwaiselage, J. Kawegere, P. Bukori, M. da Ganda Manuel, A.P. Filipe, J. Bernardo Dumas, M. Ranque Frank, R. Sankaranarayanan, E. Lucas, B. Fontanière, L. Frappart, L. Ngo Mbus, H. De Vuyst, R. Herrero, M. Nayama, H. Nouhou, M. Nacoulma, B. Sakande, Socio-demographic and reproductive determinants of cervical neoplasia in seven sub-Sahara African countries, Cancer Causes Control 27 (2016) 1437–1446, http://dx.doi.org/10.1007/s10552-016-0823-5.
[48] S.M. Mitchell, M. Sekikubo, C. Biryabarema, J.J.K. Byamugisha, M. Steinberg, J. Jeronimo, D.M. Money, J. Christilaw, G.S. Ogilvie, Factors associated with high-risk HPV positivity in a low-resource setting in sub-Saharan Africa, Am. J. Obstet. Gynecol. 210 (2014) 81, http://dx.doi.org/10.1016/j.ajog.2013.08.038 e1–81. e7.
[49] X. Castellsague, N. Munoz, Chapter 3: Cofactors in human papillomavirus carcinogenesis—role of parity, oral contraceptives, and tobacco smoking, J. Natl. Cancer Inst. Monogr. 31 (2003) 20–28.
[50] F.W. Djigma, C. Ouédraogo, D.S. Karou, T. Sagna, C. Bisseye, M. Zeba, D. Ouermi, C. Gnoula, V. Pietra, N.W. Ghilat-Avoid-Belem, K. Sanogo, J. Sempore, S. Pignatelli, A.M. Ferri, J.B. Nikiema, J. Simpore, Prevalence and genotype characterization of Human Papillomaviruses among HIV-seropositive in Ouagadougou, Burkina Faso, Acta Trop. 117 (2011) 202–206, http://dx.doi.org/10.1016/j.actatropica.2010.12.007.
[51] M. Urban, E. Banks, S. Egger, K. Canfell, D. O'Connell, V. Beral, F. Sitas, Injectable and oral contraceptive use and cancers of the breast, cervix, ovary, and endometrium in black south african women: case-control study, PLoS Med. 9 (2012) 1–11, http://dx.doi.org/10.1371/journal.pmed.1001182.
[52] E. Roura, X. Castellsagué, M. Pawlita, N. Travier, T. Waterboer, N. Margall, F.X. Bosch, S. De Sanjosé, J. Dillner, I.T. Gram, A. Tjønneland, C. Munk, V. Pala, D. Palli, K.T. Khaw, R.V. Barnabas, K. Overvad, F. Clavel-Chapelon, M.C. Boutron-Ruault, G. Fagherazzi, R. Kaaks, A. Lukanova, A. Steffen, A. Trichopoulou, D. Trichopoulos, E. Klinaki, R. Tumino, C. Sacerdote, S. Panico, H.B. Bueno-De-Mesquita, P.H. Peeters, E. Lund, E. Weiderpass, M.L. Redondo, M.J. Sánchez, M.J. Tormo, A. Barricarte, N. Larrañaga, J. Ekström, M. Hortlund, D. Lindquist, N. Wareham, R.C. Travis, S. Rinaldi, M. Tommasino, S. Franceschi, E. Riboli, Smoking as a major risk factor for cervical cancer and pre-cancer: results from the EPIC cohort, Int. J. Cancer 135 (2014) 453–466, http://dx.doi.org/10.1002/ijc.28666.
[53] M. Guillaud, T.P.H. Buys, A. Carraro, J. Korbelik, M. Follen, M. Scheurer, K.A. dler Storthz, D. van Niekerk, C.E. MacAulay, Evaluation of HPV infection and smoking status impacts on cell proliferation in epithelial layers of cervical neoplasia, PLoS One 9 (2014) e107088, http://dx.doi.org/10.1371/journal.pone.0107088.
[54] P. Appleby, V. Beral, A. Berrington De González, D. Colin, S. Franceschi, A. Goodill, J. Green, J. Peto, M. Plummer, S. Sweetland, Carcinoma of the cervix and tobacco smoking: collaborative reanalysis of individual data on 13 541 women with carcinoma of the cervix and 23,017 women without carcinoma of the cervix from 23 epidemiological studies, Int. J. Cancer 118 (2006) 1481–1495, http://dx.doi.org/10.1002/ijc.21493.
[55] J.V. Lacey, M. Frisch, L.A. Brinton, F.M. Abbas, W.A. Barnes, P.E. Gravitt, M.D. Greenberg, S.M. Greene, O.C. Hadjimichael, L. McGowan, R. Mortel, P.E. Schwartz, R.J. Zaino, A. Hildesheim, Associations between smoking and adenocarcinomas and squamous cell carcinomas of the uterine cervix (United States), Cancer Causes Control 12 (2001) 153–161 (Accessed 12 March 2016), http://www.ncbi.nlm.nih.gov/pubmed/11246844.
[56] A. Gondos, E. Chokunonga, H. Brenner, D.M. Parkin, R. Sankila, M.Z. Borok, Z.M. Chirenje, A.M. Nyakabau, M.T. Bassett, Cancer survival in a southern African urban population, Int. J. Cancer 112 (2004) 860–864, http://dx.doi.org/10.1002/ijc.20471.
[57] P. Lomalisa, T. Smith, F. Guidozzi, Human immunodeficiency virus infection and invasive cervical cancer in South Africa, Gynecol. Oncol. 77 (2000) 460–463, http://dx.doi.org/10.1006/gyno.2000.5775.
[58] X. Castellsagué, M. Pawlita, E. Roura, N. Margall, T. Waterboer, F.X. Bosch, S. De Sanjosé, C.A. Gonzalez, J. Dillner, I.T. Gram, A. Tjønneland, C. Munk, V. Pala, D. Palli, K.T. Khaw, R.V. Barnabas, K. Overvad, F. Clavel-Chapelon, M.C. Boutron-Ruault, G. Fagherazzi, R. Kaaks, A. Lukanova, A. Steffen, A. Trichopoulou, D. Trichopoulos, E. Klinaki, R. Tumino, C. Sacerdote, A. Mattiello, H.B. Bueno-De-Mesquita, P.H. Peeters, E. Lund, E. Weiderpass, J.R. Quirõs, M.J. Sánchez, C. Navarro, A. Barricarte, N. Larrañaga, J. Ekström, M. Hortlund, D. Lindquist, N. Wareham, R.C. Travis, S. Rinaldi, M. Tommasino, S. Franceschi, E. Riboli, Prospective seroepidemiologic study on the role of Human Papillomavirus and other infections in cervical carcinogenesis: evidence from the EPIC cohort, Int. J. Cancer 135 (2014) 440–452, http://dx.doi.org/10.1002/ijc.28665.
[59] L.S. Savardekar, D. Balaiah, B.N. Mali, Association of Schistosoma haematobium and human papillomavirus in cervical cancer: a case report, Acta Cytol. 54 (2010) 205–208 (Accessed 14 November 2016), http://www.ncbi.nlm.nih.gov/pubmed/20391981.
[60] M. North, I. Dubinchik, A. Hamid, S. Elderiny, R. Sayegh, Association between cervical schistosomiasis and cervical cancer. A report of 2 cases, J. Reprod. Med. 48 (2003) 995–998 (Accessed 14 November 2016), http://www.ncbi.nlm.nih.gov/pubmed/14738030.
[61] H. Yang, K. Yang, a Khafagi, Y. Tang, T.E. Carey, a W. Opipari, R. Lieberman, P. a Oeth, W. Lancaster, H.P. Klinger, a O. Kaseb, a Metwally, H. Khaled, D.M. Kurnit, Sensitive detection of human papillomavirus in cervical, head/neck, and schistosomiasis-associated bladder malignancies, Proc. Natl. Acad. Sci. U. S. A. 102 (2005) 7683–7688, http://dx.doi.org/10.1073/pnas.0406904102.
[62] K. Chin, H. Maraj, A. Elmardi, D. Bhattacharjee, S. Meti, F. Hakim, J. Dixon, P548 Cervical schistosomiasis – an increasing presentation in the developed world, Int. J. Gynecol. Obstet. 107 (2009) S569, http://dx.doi.org/10.1016/S0020-7292(09)62038-5.
[63] V.C. Prabhakaran, L.J.R. Brown, Cervical schistosomiasis and neoplasia in HIV-infected patients, Int. J. Gynecol. Pathol. 23 (2004) 403–404, http://dx.doi.org/10.1097/01.pgp.0000132205.41604.95.
[64] P. Pillay, L. van Lieshout, M. Taylor, M. Sebitloane, S. Zulu, E. Kleppa, B. Roald, E. Kjetland, Cervical cytology as a diagnostic tool for female genital schistosomiasis: correlation to cervical atypia and Schistosomapolymerase chain reaction, Cytojournal 13 (2016) 10, http://dx.doi.org/10.4103/1742-6413.180784.
[65] P. Moubayed, A. Ziehe, J. Peters, H. Mwakyoma, D. Schmidt, Carcinoma of the uterine cervix associated with schistosomiasis and induced by human papillomaviruses, Int. J. Gynecol. Obstet. 49 (1995) 175–179, http://dx.doi.org/10.1016/0020-7292(95)02332-7.
[66] D. McFarland, Cervical cancer and Pap smear screening in Bostwana: knowledge and perceptions, Int. Nurs. Rev. 50 (2003) 167–175.
[67] D.M. Cutler, A. Lleras-Muney, T. Vogl, Socioeconomic Status and Health: Dimensions and Mechanisms, (2008), http://dx.doi.org/10.1017/CBO9781107415324.004 Cambridge M.A.
[68] S. Hibbitts, G.C. Rieck, K. Hart, N.G. Powell, R. Beukenholdt, N. Dallimore, J. McRea, A. Hauke, A. Tristram, A.N. Fiander, Human papillomavirus infection: an anonymous prevalence study in South Wales, UK, Br. J. Cancer 95 (2006) 226–232, http://dx.doi.org/10.1038/sj.bjc.6603245.
[69] E. Smith-Greenaway, Are literacy skills associated with young adults' health in Africa? Evidence from Malawi, Soc. Sci. Med. (2015) 124–133, http://dx.doi.org/10.1016/j.socscimed.2014.07.036.
[70] M. Ainsworth, K. Beegle, A. Nyamete, The impact of women's schooling on fertility and contraceptive use: a study of fourteen sub-Saharan African countries, World Bank Econ. Rev. 10 (1996) 85–121 (Accessed 17 February 2016), http://www-wds.worldbank.org/external/default/WDSContentServer/WDSP/IB/2013/05/14/000333037_20130514150628/Rendered/PDF/771160JRN0WBER0Box0377291B00PUBLIC0.pdf.
[71] R. Mlange, D. Matovelo, P. Rambau, B. Kidenya, Patient and disease characteristics associated with late tumour stage at presentation of cervical cancer in northwestern Tanzania, BMC Womens Health (2016) 1–6, http://dx.doi.org/10.1186/s12905-016-0285-7.
[72] A. Mwaka, C.G. Orach, E.M. Were, G. Lyratzopoulos, H. Wabinga, M. Roland, Awareness of cervical cancer risk factors and symptoms: cross-sectional community survey in post-conflict northern Uganda, Health Expect (2015) 1–14, http://dx.doi.org/10.1111/hex.12382.
[73] G. Rowlands, J. Protheroe, H. Price, B. Gann, I. Rafi, Health Literacy Report from an RCGP-lead Health Literacy Workshop, London, 2014.
[74] S. Bostock, A. Steptoe, Association between low functional health literacy and mortality in older adults: longitudinal cohort study, BMJ 344 (2012) e1602, http://dx.doi.org/10.1136/bmj.e1602.
[75] N.D. Berkman, S.L. Sheridan, K.E. Donahue, D.J. Halpern, K. Crotty, Annals of internal medicine review low health literacy and health outcomes: an updated systematic review, Ann. Intern. Med. 155 (2014) 97–107.
[76] S.J. Schrauben, D.J. Wiebe, Health literacy assessment in developing countries: a case study in Zambia, Health Promot. Int. (2015) 1–7, http://dx.doi.org/10.1093/heapro/dav108.
[77] I. Agurto, S. Arrossi, S. White, P. Coffey, I. Dzuba, A. Bingham, J. Bradley, R. Lewis, Involving the community in cervical cancer prevention programs, Int. J. Gynecol. Obstet. 89 (2005) 38–45, http://dx.doi.org/10.1016/j.ijgo.2005.01.015.
[78] A. Ibrahim, V. Rasch, E. Pukkala, A.R. Aro, Predictors of cervical cancer being at an advanced stage at diagnosis in Sudan, Int. J. Womens Health 3 (2011) 385–389, http://dx.doi.org/10.2147/IJWH.S21063.
[79] J.W. Orr, K. Wilson, C. Bodiford, A. Cornwell, S.J. Soong, K.L. Honea, K.D. Hatch, H.M. Shingleton, Nutritional status of patients with untreated cervical cancer. II. Vitamin assessment, Am. J. Obstet. Gynecol. 151 (1985) 632–635 (Accessed 14 January 2018), http://www.ncbi.nlm.nih.gov/pubmed/3919585.
[80] J. Wang, X. Ma, Y. Cheng, L. Ding, Q. Zhou, [A case-control study on the association between folate and cervical cancer], Zhonghua Liu Xing Bing Xue Za Zhi 27 (2006) 424–427 (Accessed 14 January 2018), http://www.ncbi.nlm.nih.gov/pubmed/16981341.
[81] J. Eleutério Jr., P.C. Giraldo, A.K. Gonçalves, R.M.N. Eleutério, R. de, C.C. Barbosa, D.I.M. Cavalcante, The risk of high-grade squamous intraepithelial lesions in women with low serum levels of Vitamin A, Gynecol. Obstet. Invest. 78 (2014) 235–238, http://dx.doi.org/10.1159/000363741.
[82] X. Chen, J. Wang, L. Bai, L. Ding, T. Wu, L. Bai, J. Xu, X. Sun, [Interaction between folate deficiency and aberrant expression related to fragile histidine triad gene in the progression of cervical cancerization], Zhonghua Liu Xing Bing Xue Za Zhi 36 (2015) 387–392 (Accessed 14 January 2018), http://www.ncbi.nlm.nih.gov/pubmed/25975556.
[83] W.L. Jia, L. Ding, Z.Y. Ren, T.T. Wu, W.M. Zhao, S.L. Fan, J.T. Wang, Effects of both folic acid, p16 protein expression and their interaction on progression of cervical cancerization, Zhonghua Liu Xing Bing Xue Za Zhi 37 (2016) 1647–1652, http://dx.doi.org/10.3760/cma.j.issn.0254-6450.2016.12.018.
[84] WHO, UNICEF, UNFPA, World Bank Group, and the United Nations Population Division, Maternal Mortality Ratio (modeled Estimate, Per 100,000 Live Births) | Data, World Bank Data, (2015) (Accessed 3 September 2017), https://data.

worldbank.org/indicator/SH.STA.MMRT?end=2016&locations=ZF-ET-BI-ER-RW-ZW-ZM-UG-MZ-TZ-MU-KM-SS&start=1980&view=chart.
[85] M. Moodley, Reduction in prevalence of invasive cervical cancer in KwaZulu-Natal, South Africa: impact of the human immunodeficiency virus epidemic, Int. J. Gynecol. Cancer 16 (2006) 1036–1040.
[86] Y. Melaku, B. Weldearegawi, A. Aregay, F. Tesfay, L. Abreha, S. Abera, A. Bezabih, Causes of death among females–investigating beyond maternal causes: a community-based longitudinal study, BMC Res. Notes 7 (2014) 629, http://dx.doi.org/10.1186/1756-0500-7-629.
[87] S. Anderson, D. Ray, Excess Female Mortality in Africa, Helsinki, (2017) https://www.wider.unu.edu/publication/excess-female-mortality-africa.
[88] World Health Organization, Comprehensive Cervical Cancer Control: A Guide to Essential Practice, Second edition, (2014) Geneva.
[89] C.L. Langley, E. Benga-De, C.W. Critchlow, I. Ndoye, M.D. Mbengue-Ly, J. Kuypers, G. Woto-Gaye, S. Mboup, C. Bergeron, K.K. Holmes, N.B. Kiviat, HIV-1, HIV-2, human papillomavirus infection and cervical neoplasia in high-risk African women, AIDS 10 (1996) 413–417 (Accessed 19 February 2016), http://www.ncbi.nlm.nih.gov/pubmed/8728046.
[90] S. Odafe, K. Torpey, H. Khamofu, E. Oladele, O. Adedokun, O. Chabikuli, H. Mukaddas, Y. Usman, B. Aiyenigba, M. Okoye, Integrating cervical cancer screening with HIV care in a district hospital in Abuja, Nigeria, Niger. Med. J. 54 (2013) 176–184, http://dx.doi.org/10.4103/0300-1652.114590.
[91] R.G. Ghebre, S. Grover, M.J. Xu, L.T. Chuang, H. Simonds, Cervical cancer control in HIV-infected women: past, present and future, Gynecol. Oncol. Rep. 21 (2017) 101–108, http://dx.doi.org/10.1016/j.gore.2017.07.009.
[92] Health Policy Project, Health Financing Profile – South Africa, Heal. Policy Proj. 2012–2013, (2016) http://www.healthpolicyproject.com/pubs/7887/Botswana_HFP.pdf.
[93] N. Ndlovu, M. Vilakazi, M. Majozi, F. Sithole, K. Mbatha, T. Guthrie, Trends in National and Provincial Health and HIV/AIDS Budgeting and Spending in South Africa, Cape Town, (2013) http://www.health-e.org.za/wp-content/uploads/2014/01/Occasional_Paper_2013-1_SA-Trends_in_National_and_Provincial_Health_HIV_Spending_6Dec13. pdf.
[94] A. Jemal, F. Bray, D. Forman, M. O'Brien, J. Ferlay, M. Center, D.M. Parkin, Cancer burden in Africa and opportunities for prevention, Cancer 118 (2012) 4372–4384, http://dx.doi.org/10.1002/cncr.27410.
[95] R.I. Anorlu, Cervical cancer: the sub-Saharan African perspective, Reprod. Health Matters 16 (2008) 41–49, http://dx.doi.org/10.1016/S0968-8080(08)32415-X.
[96] S. Jordaan, P. Michelow, K. Richter, C. Simoens, J. Bogers, A review of cervical cancer in South Africa: previous, current and future, Heal. Care Curr. Rev. 4 (2016), http://dx.doi.org/10.4172/2375-4273.1000180.
[97] S. Mtenga, I.M. Masanja, M. Mamdani, Strengthening national capacities for researching on Social Determinants of Health (SDH) towards informing and addressing health inequities in Tanzania, Int. J. Equity Health 15 (2016) 23, http://dx.doi.org/10.1186/s12939-016-0308-x.
[98] J. Varughese, S. Richman, Cancer care inequity for women in resource-poor countries, Rev. Obstet. Gynecol. 3 (2010) 122–132, http://dx.doi.org/10.3909/riog0107.
[99] F.A.S. Bokhari, Y. Gai, P. Gottret, Government health expenditures and health outcomes, Health Econ. 16 (2007) 257–273, http://dx.doi.org/10.1002/hec.1157.
[100] J. Gonzalez-Garcia, E. Hitaj, M. Mlachila, A. Viseth, M. Yenice, Sub-Saharan African Migration: Patterns and Spillovers, (2016) Washington, D.C.
[101] S. Barrios, L. Bertinelli, E. Strobl, Climatic change and rural-urban migration: the case of sub-Saharan Africa, J. Urban Econ. 60 (2006) 357–371, http://dx.doi.org/10.1016/j.jue.2006.04.005.
[102] J. Shepherd, G. Peersman, R. Weston, I. Napuli, Cervical cancer and sexual lifestyle: a systematic review of health education interventions targeted at women, Health Educ. Res. 15 (2000) 681–694, http://dx.doi.org/10.1093/HER/15.6.681.
[103] A. Ntekim, Cervical cancer in sub Sahara Africa, in: R. Rajamanickam (Ed.), Top. Cerv. Cancer With an Advocacy Prev. InTech, Ibadan, 2012, pp. 51–75, , http://dx.doi.org/10.5772/27200.
[104] K. Fladseth, M. Gafos, M.L. Newell, N. McGrath, The impact of gender norms on condom use among HIV-positive adults in KwaZulu-, PLoS One 10 (2015) e0122671, http://dx.doi.org/10.7796/INDEPTH.ZA031.
[105] E. Ghanotakis, D. Peacock, R. Wilcher, The importance of addressing gender inequality in efforts to end vertical transmission of HIV, J. Int. AIDS Soc. 15 (2012) 1–10, http://dx.doi.org/10.7448/IAS.15.4.17385.
[106] M. Mbonye, W. Nalukenge, S. Nakamanya, B. Nalusiba, R. King, J. Vandepitte, J. Seeley, Gender inequity in the lives of women involved in sex work in Kampala, Uganda, J. Int. AIDS Soc. 15 (Suppl. 1) (2012) 1–9, http://dx.doi.org/10.1186/1758-2652-15-1.
[107] K. Shannon, K. Leiter, N. Phaladze, Z. Hlanze, A.C. Tsai, M. Heisler, V. Iacopino, S.D. Weiser, Gender inequity norms are associated with increased male-perpetrated rape and sexual risks for HIV infection in Botswana and Swaziland, PLoS One 7 (2012), http://dx.doi.org/10.1371/journal.pone.0028739.
[108] G.R. Gupta, How men's power over women fuels the HIV epidemic: it limits women's ability to control sexual interactions, BMJ Br. Med. J. 324 (2002) 183–184, http://dx.doi.org/10.1136/bmj.324.7331.183.
[109] S. Zierler, N. Krieger, Reframing women's risk: social inequalities and HIV infection, Annu. Rev. Public Health 18 (1997) 401–436, http://dx.doi.org/10.1146/annurev.publhealth.18.1.401.
[110] H. Amaro, Sex love, and power considering women's realities in HIV prevention, Am. Psychol. 50 (1995) 437–447, http://dx.doi.org/10.1037/0003-066X.50.6.437.
[111] V. Gawande, S.N. Wahab, S.P. Zodpey, N.D. Vasudeo, Parity as a risk factor for cancer of the cervix, Indian J. Med. Sci. 52 (1998) 147–150.
[112] L. Sharp, J. Zurawski, P. Roland, C. O'Toole, J. Hines, Health literacy, cervical cancer risk factors, and distress in low-income African-American women seeking colposcopy, Ethn. Dis. 12 (2002) 541–546 http://www.ishib.org/journal/ethn-12-04-541.pdf.
[113] D.J. Adamchak, P.G. Ntseane, Gender, education, and fertility: a cross-national analysis of sub-Saharan African nations, Sociol. Spectr. Off. J. Mid-South Sociol. Assoc. 12 (1992) 167–182, http://dx.doi.org/10.1080/02732173.1992.9981994.
[114] H.C. Selvin, Durkheim's suicide and problems of empirical research, Am. J. Sociol. 63 (1958) 607–619 http://www.jstor.org/stable/2772991.
[115] S. Schwartz, The fallacy of the ecological fallacy: the potential misuse of a concept and the consequences, Am. J. Public Health 84 (1994) 819–824, http://dx.doi.org/10.2105/AJPH.84.5.819.
[116] D. Lubinski, L.G. Humphreys, Seeing the forest from the trees: when predicting the behavior or status of groups, correlate means, Psychol. Public Policy Law 2 (1996) 363–376, http://dx.doi.org/10.1037/1076-8971.2.2.363.
[117] M. Susser, The logic in ecological: I. The logic of analysis, Am. J. Public Health 84 (1994) 825–829, http://dx.doi.org/10.2105/AJPH.84.5.825.