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Recent global burden of cervical cancer incidence and mortality, predictors, and temporal trends

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HIGHLIGHTS

- Little is known about the recent temporal trends in cervical cancer incidence and mortality.
- The mortality of cervical cancer continued to decline or remained stable from the most countries.
- Increasing trend in incidence was found from more countries, particularly among younger women.

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ABSTRACT

Backgrounds. This study investigated the global incidence and mortality of cervical cancer, its predictors, the temporal trend by country and age.

Methods. Data from Global Cancer Observatory 2020 for 185 countries was used to estimate current cervical cancer incidence and mortality and their associations with predictors by linear regression analysis. Estimated age-standardized rates (ASR) and average annual percentage changes (AAPC) from cancer registries for up to 53 countries through 2018 were used for trend analysis by joinpoint regression.

Results. Wide variations in cervical cancer were observed globally with the highest rates of incidence and mortality in East Africa (ASR, 40.1 and 28.6). The incidence and mortality of cervical cancer were positively associated with human papillomavirus, human immunodeficiency virus infection and negatively associated with cervical cancer screening coverage. In the most recent 5 years, reduction of incidence and mortality was found from 22 (AAPC, −11.2 to −0.5) and 27 countries (−21.5 to −0.3). Increase of incidence and mortality was found from 13 (1.7 to 6.5) and 5 (0.3 to 1.8) countries. Comparing to women aged above 50 years, increasing incidence were additionally found among women under age 50 years from 9 countries (ranging from 0.2 in Denmark to 3.8 in Sweden).

Conclusions. While most countries with cancer registry have shown reduction in cervical cancer incidence and mortality, the increasing incidence among younger women from some developed countries warrants further implementation of effective cancer screening.

1. Introduction

Invasive cervical cancer is the 4th most common cancer in women worldwide with an estimated 570,000 new cases and its age-standardized rate (ASR) at 13.1 per 100,000 women-years in 2018 [1]. The incidence and mortality of cervical cancer varied significantly between countries. For instance, the highest incidence (>40 per 100,000) were found in countries from eastern, southern, or western Africa, while the lowest incidence (<3 per 100,000) were found in higher income countries from North America, Europe, Australia, and New Zealand [1]. Of the 340,000 women died from cervical cancer, 90% of them occurred in low- and middle-income countries [1].

Geographical disparities in the burden of cervical cancer reflect the availability, coverage, and quality of preventive strategies, including human papillomavirus (HPV) vaccination targeting young adolescent girls aged 9–14 years as primary prevention, screening and treatment of precancerous lesions as secondary prevention, and diagnosis and treatment of invasive cervical cancer as tertiary prevention

Abbreviations: GLOBOCAN, global cancer observatory; WHO, world health organization; HPV, human papillomavirus; HIV, human deficiency virus; HDI, human development index; CI5, cancer incidence in five continents; ASR, age-standardized rate; AAPC, average annual percentage change.

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recommended by World Health Organization (WHO) [2]. It also reflected the prevalence of risk factors. The main risk factor of cervical cancer is chronic infection with HPV [3]. HPV-16 and 18 are the most common subtypes in cervical cancer and together they accounted for about 70% of cervical cancer [3]. Other known risk factors included higher parity, smoking, increasing number of sexual partners, and human immunodeficiency virus (HIV) infection [4]. Globally, it has been estimated that 4.9% of new diagnosed cervical cancer were attributable to HIV infection [4].

To meet the target to eliminate cervical cancer by 2030 [5], it is essential to investigate the recent global pattern and temporal trends of cervical cancer using cancer surveillance data of high quality. However, the previous studies were limited to certain countries, for instance 26 member states of the European Union [6], 9 selected countries from Africa, Latin America and the Caribbean and Asia [7], or used relative old data (up to 2010) [8]. Although these studies suggested decreasing trend of cervical cancer due to the national cervical cancer screening and treatment programmes [6,8], recent data indicated that the coverage of cancer screening started to decrease in some countries with well-established screening programme particularly among women aged between 20 and 49 years [9–11]. It is therefore expected that the reduction of screening along with the increased risk of sexual behavior in this age group could have impact on the incidence and mortality of cervical cancer. The increasing trend of cervical cancer incidence in recent years among younger women have been reported in some national studies from Sweden and Denmark [12,13]. However, to our knowledge, no study has examined the trend of cervical cancer using registry data by age globally. This study therefore aimed to investigate the global and regional incidence and mortality of cervical cancer, its predictors, and the recent temporal trend overall and by ages using real-world cancer registries.

2. Methods

2.1. Data sources

Incidence and mortality of cervical cancer were extracted from cancer of cervix uteri in 185 countries from the Global Cancer Observatory (GLOBOCAN) 2020 database [14]. Data were aggregated by 5-year age group and for this study, women were categorized into younger women (15 to 49 years) and older women (50+ years) to assess the burden of cervical cancer by age.

Human development index (HDIs) in 2019 was obtained for each country from United Nation Development Programme [15]. The quartiles of HDI were used to categorize the countries into the following four groups: ≤0.550 for low, 0.550–0.699 for medium, 0.700–0.799 for high, and ≥ 0.800 for very high HDIs. To quantify the association of predictors with cervical cancer, the following variables were retrieved, including smoking and coverage of national cervical cancer screening from WHO Observatory [16,17], HIV from Global Burden Disease 2019 [18], and HPV prevalence from normal cytology among women of all ages from previous meta-analysis [19]. All these risk factors except HPV were based on data from 2010.

For trend analysis, all incidence and mortality available from national or regional registries in all calendar years were retrieved for up to 53 countries through 2018 (Appendix Table 1). We extracted cancer incidence data from nation/region-specific cancer registries from Cancer Incidence in Five Continents Plus (CI5-plus) [20]. The WHO mortality database was used to extract yearly mortality data [21]. Only data from countries with a quality at least medium level were used to estimate mortality. To obtain more recent data for Northern Europe countries and the United States, the Nordic Cancer Registries (NORDCAN) [22] and the Surveillance, Epidemiology, and End Results (SEER) Programs [23] were used. Cervical cancer was identified by using International Classification of Diseases tenth edition (ICD-10) code (C53.0-C53.9). The WHO standard population was used as reference to calculate ASR.

2.2. Analysis

Joinpoint regression analysis was performed for trend analysis. To fit the joinpoint regression model, the incidence and mortality data were log transformed and standard errors were obtained from a binomial approximation. Annual Percentage Change (APC), Average Annual Percent Change (AAPC) and its 95% confidence interval in the last 5-year (2007–2011 to 2014–2018, depending on the country) were estimated to show the trend of cervical cancer. The trend was considered as significant reduction if APC or AAPC and its upper estimate of 95% confidence interval (CI) were less than 0 and it was considered as significant increase if APC or AAPC and its lower estimate of 95% CI were greater than 0. Otherwise, the trend was considered as no change or stable over the period as previous study [24].

Correlation and linear regression models were used to estimate the association of incidence and mortality with potential risk factors for the 185 countries from GLOBOCAN in 2020. Correlation coefficient (r) was used to show the strength of the relationship. A forward stepwise model selection was used to decide the final variables included in the multivariable linear regression analysis. Beta coefficient (β) was presented to indicate the change in ASRs of incidence or mortality associated with 1% increase of a certain risk factor.

A sensitivity analysis of the linear regression was conducted for the 53 countries where registry data was available for the most recent year. A two-sided p value <0.05 was considered statistically significant.

3. Results

In 2020, a total of 604,127 new cervical cancer cases and 341,831 related deaths were estimated from 185 countries. The incidence and mortality rates of cervical cancer increased with age (Appendix Table 2), while they decreased with increasing level of HDIs for incidence (ASR, from 27.2 to 9.1) and mortality (from 19.8 to 3.1). The highest incidence and mortality were found in East Africa (40.1 and 28.6), Southern Africa (36.4 and 20.6) and Middle Africa (31.6 and 22.7) (Appendix Table 2 and Appendix Fig. 1).

Fig. 1 and Appendix Table 3 show the association of cervical cancer incidence and mortality in 2020 from GLOBOCAN 2020 with smoking, the prevalence of HPV, HIV, and national cervical cancer screen coverage. Of the 140 countries with known prevalence of smoking among women, smoking was negatively correlated with cervical cancer incidence ($r = -0.24$, $p = 0.005$) and mortality ($r = -0.31$, $p < 0.001$). Of the 66 countries with known prevalence of HPV from normal cytology, HPV was positively associated with increased rates of cervical cancer incidence ($r = 0.39$, $p = 0.001$) and mortality ($r = 0.37$, $p = 0.003$). Of 178 countries with known prevalence of HIV, HIV was positively associated with increased rates. Cervical cancer screening coverage was negatively associated with incidence and mortality (Fig. 1 and Appendix Table 3). However, in our multivariate linear regression analysis, incidence and mortality of cervical cancer were only positively associated with increasing prevalence of HIV ($\beta = 2.21$ $p < 0.001$; $\beta = 1.46$, $p < 0.001$; Appendix Table 3) and negatively associated with increasing coverage of cervical cancer screening ($p \leq 0.01$). In the sensitivity analysis when using the registry data from the 48 countries for incidence and 53 countries for mortality in 2018, the above associations remained overall although some statistical tests were not significant (Appendix Table 4).

Fig. 2 and Table 1 shows the long and short-term trends in cervical cancer incidence rate from 48 countries worldwide. Although the onset and magnitude of changes varied across countries, incidence rate over the entire period have shown consistent patterns. During the most recent 5 years, incidence rates increased significantly in 13 of the 48 countries, with the estimated AAPC ranging from 0.7 in Finland to

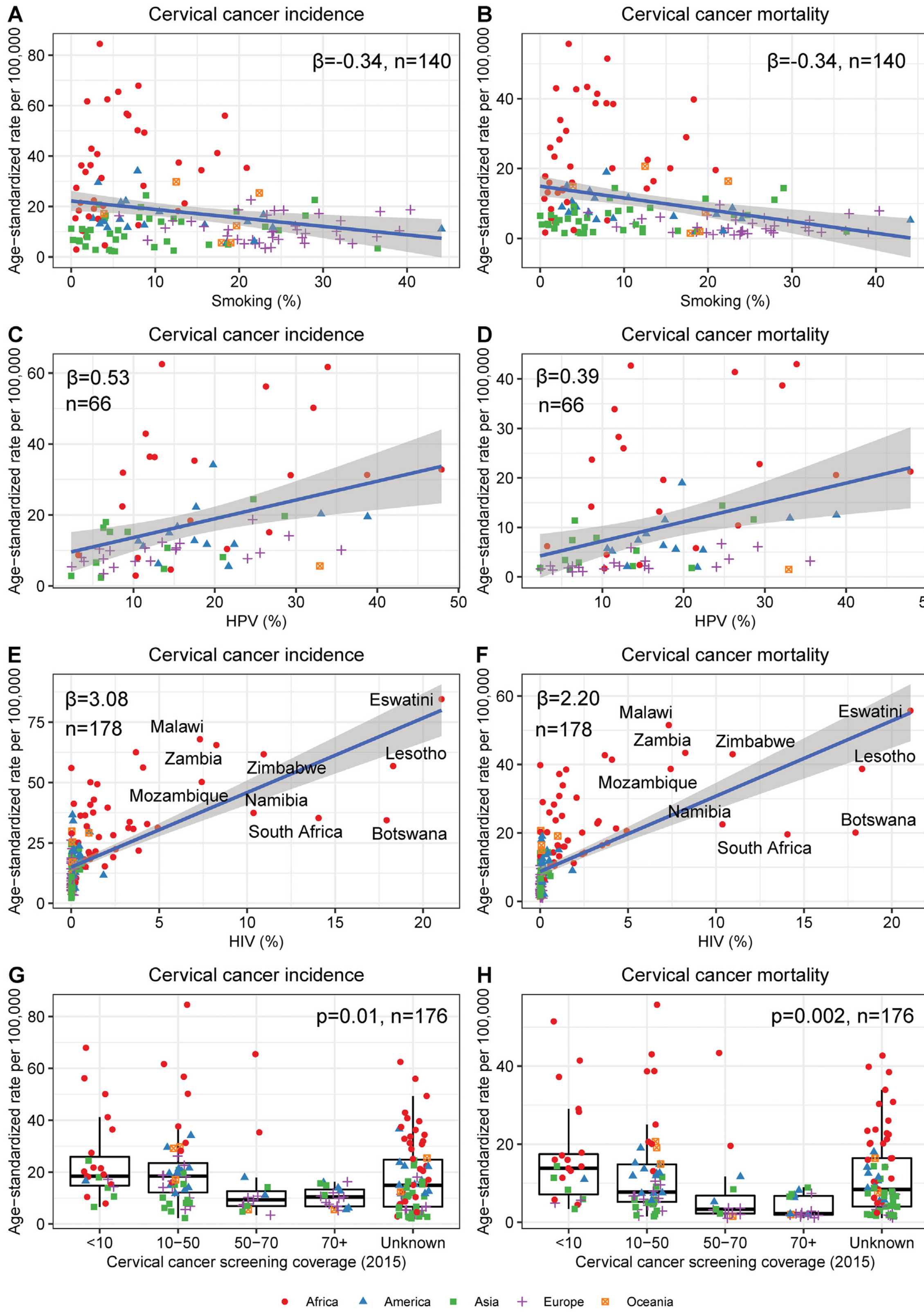

Fig. 1. Correlation of cervical cancer incidence and mortality with smoking, HPV, HIV, and cervical cancer screening coverage. Country names were added for those with prevalence of HIV >7%. In each figure, r represented correlation coefficient, β represented regression coefficient and n represented the number of country in the analysis.

8.1 in Italy. The incidence rates decreased in 22 countries (AAPC, ranging from −0.5 in Denmark to −11.2 in Thailand), whereas they remained stable in the rest 13 countries.

When comparing the trends by age (Fig. 3, Appendix Table 5, and Appendix Table 6), increasing rates were found among younger women from 9 countries (including Turkey, Australia, Denmark,

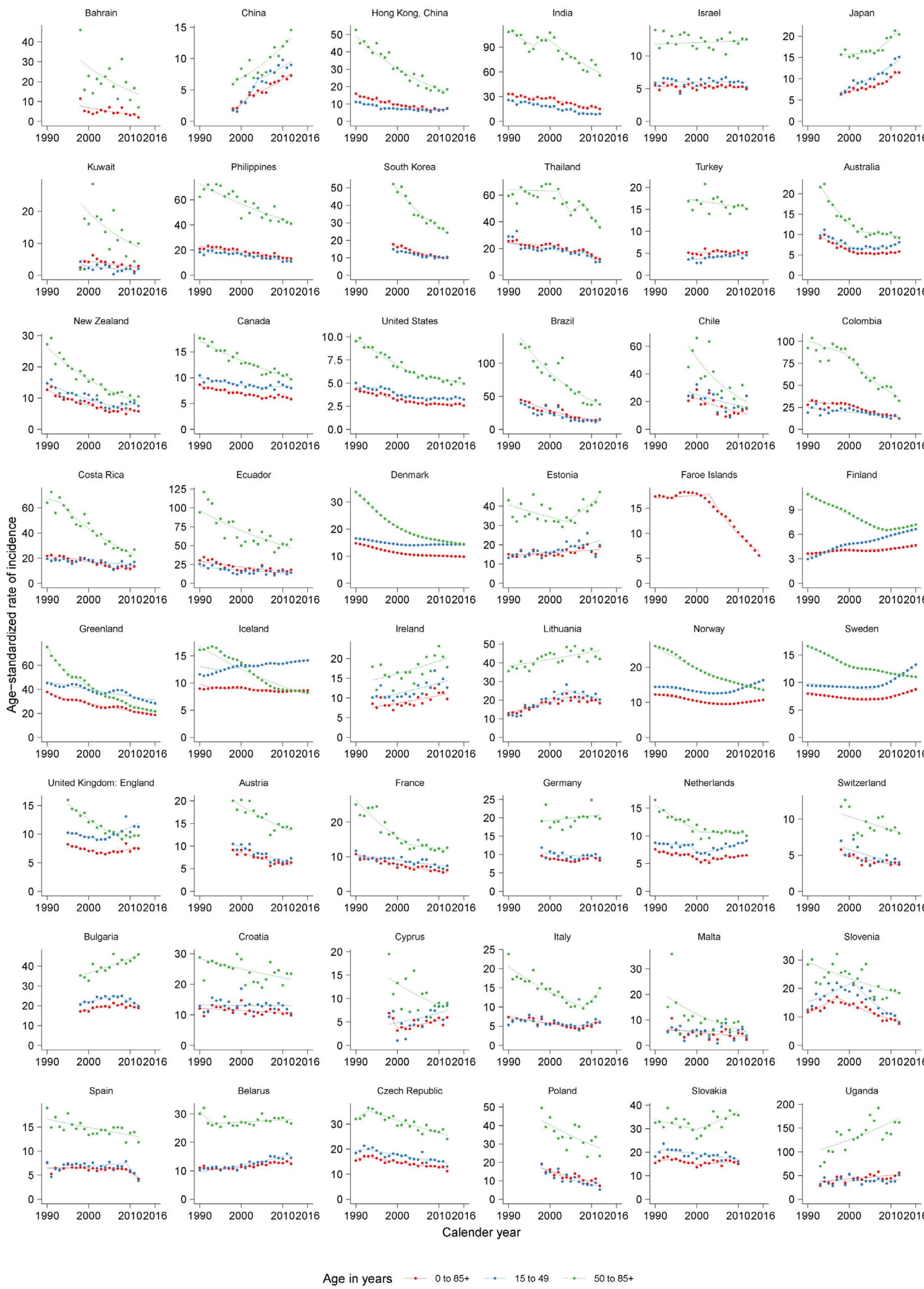

Fig. 2. Joinpoint analysis of trends in age-standardized (world population) incidence rates from cervical cancer overall and by age. Data from 48 selected countries worldwide, in all women (red), women aged 15–49 years (blue) and women aged 50–85 years (green). Solid lines represent fitted values based on joinpoint analysis. Symbols represent observed rates. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Iceland, Norway, Sweden, United Kingdom, Netherlands, and Belarus), while they decreased or remained stable among older women from these countries. Due to the increasing rates of cervical cancer among younger women, their rates approached or surpassed those among older women from 10 countries (including New Zealand, Denmark, Greenland, Iceland, Norway, Sweden, England, Cyprus, Netherlands, Malta) (Fig. 2).

Among the 53 countries included for the mortality trend analysis in the most recent 5 years, mortality rates increased in 5 countries, decreased in 27 countries, and stabilized in 21 countries (Fig. 4 and

Table 1
Joinpoint analysis for cervical cancer incidence for all women, from 1995 to 2016 (according to data availability).

	Trend 1		Trend 2		Trend 3		Trend 4		AAPC (95% CI)
	Period	APC	Period	APC	Period	APC	Period	APC	Last 5 yr
Asia									
Bahrain	1998–2012	−6.0*							−6.0* (−10.1 to −1.7)
China	1998–2002	19.8*	2002–2012	6.5*					6.5* (4.5 to 8.6)
Hong Kong, China	1983–2008	−4.4*	2008–2012	0.9					0.9 (−4.7 to 6.8)
India	1983–1986	4.2	1986–1992	−6.9*	1992–2000	−1.1	2000–2012	−4.9*	−4.9* (−6.0 to −3.7)
Israel	1963–1986	−0.9*	1986–1989	15.5	1989–2012	−0.1			−0.1 (−0.5 to 0.3)
Japan	1998–2008	3.0*	2008–2012	7.5*					7.5* (3.7 to 11.4)
Korea	1999–2012	−4.5*							−4.5* (−5.2 to −3.9)
Kuwait	1998–2012	−4.7*							−4.7* (−8.5 to −0.7)
Philippines	1983–2012	−2.2*							−2.2* (−2.5 to −1.9)
Thailand	1983–2002	−0.9*	2002–2005	−7.1	2005–2008	3.3	2008–2012	−11.2*	−11.2* (−15.1 to −7.2)
Turkey	1998–2012	0.3							0.3 (−0.6 to 1.2)
Oceania									
Australia	1993–2002	−6.5*	2002–2012	0.7					0.7 (−0.5 to 1.8)
New Zealand	1983–1988	2.0	1988–2006	−4.7*	2006–2012	0.3			0.3 (−3.7 to 4.6)
Northern America									
Canada	1983–2005	−1.9*	2005–2012	−0.2					−0.2 (−1.4 to 1)
United States	1975–1982	−4.6*	1982–1990	0.1	1990–2007	−2.7*	2007–2016	−0.2	−0.2 (−1.2 to 0.8)
Southern America									
Brazil	1993–2012	−6.3*							−6.3* (−7.6 to −5)
Chile	1998–2012	−5.6*							−5.6* (−8.6 to −2.5)
Colombia	1983–2000	−1.6*	2000–2012	−5.6*					−5.6* (−7.1 to −4.1)
Costa Rica	1982–2000	−1.8*	2000–2006	−6.7*	2006–2011	1.2			1.2 (−2.8 to 5.4)
Ecuador	1985–2012	−2.9*							−2.9* (−3.5 to −2.2)
Northern Europe									
Denmark	1943–1964	1.3*	1964–1983	−3.1*	1983–2003	−2.5*	2003–2016	−0.5*	−0.5* (−0.7 to −0.3)
Estonia	1983–2012	0.9*							0.9* (0.5 to 1.2)
Faroe Islands	1960–1963	24.8*	1963–1978	5.8*	1978–2003	0.3*	2003–2015	−8.1*	−8.1* (−9 to −7.3)
Finland	1953–1963	0.3	1963–1968	−1.9*	1968–1987	−6.4*	1987–2016	0.7*	0.7* (0.6 to 0.8)
Greenland	1968–1977	−0.8	1977–1982	6.4*	1982–1993	−4.3*	1993–2016	−2.4*	−2.4* (−2.6 to −2.1)
Iceland	1955–1967	3.5*	1967–1976	−5.7*	1976–1993	−2.1*	1993–2016	−0.4*	−0.4* (−0.6 to −0.1)
Ireland	1994–2012	2*							2.0* (1.0 to 3.1)
Lithuania	1988–2004	3.5*	2004–2012	−1.6					−1.6* (−3.4 to 0.3)
Norway	1953–1975	1.0*	1975–1984	−3.2*	1984–2007	−1.6*	2007–2016	1.5*	1.5* (1.1 to 1.8)
Sweden	1960–1968	−0.2	1968–1980	−4.6*	1980–2004	−1.5*	2004–2016	2.2*	2.2* (1.8 to 2.5)
United Kingdom	1995–2003	−2.7*	2003–2012	1.7*					1.7* (0.3 to 3.1)
Western Europe									
Austria	1998–2012	−3.2*							−3.2* (−4.2 to −2.2)
France	1977–2012	−3.0*							−3.0* (−3.3 to −2.8)
Germany	1998–2006	−2.1*	2006–2010	4.8*	2010–2012	−6.4*			−1.0 (−3.6 to 1.7)
Netherlands	1989–1998	−1.3*	1998–2001	−6.1	2001–2012	1.8*			1.8* (1.1 to 2.5)
Switzerland	1998–2012	−2.5*							−2.5* (−3.7 to −1.3)
Southern Europe									
Bulgaria	1998–2006	2.5*	2006–2012	−1.5					−1.5 (−3.1 to 0.1)
Croatia	1988–2012	−0.6*							−0.6* (−1.2 to 0)
Cyprus	1998–2000	−29.5	2000–2012	4.0*					4.0* (1.3 to 6.7)
Italy	1978–2008	−2.9*	2008–2012	8.1*					8.1* (0.7 to 16.1)
Malta	1993–2012	−3.3*							−3.3* (−5.9 to −0.5)
Slovenia	1983–1990	−2.5	1990–1997	5.8*	1997–2012	−4.6*			−4.6* (−5.6 to −3.5)
Spain	1976–1984	8.5	1984–2009	−0.2	2009–2012	−9.7			−7.4 (−14.3 to 0.1)
Eastern Europe									
Belarus	1983–1995	−1.4*	1995–2012	1.4*					1.4* (1.0 to 1.7)
Czech Republic	1983–1994	0	1994–2012	−1.6*					−1.6* (−2.0 to −1.3)
Poland	1998–2012	−4.5*							−4.5* (−6.1 to −2.9)
Slovakia	1971–1995	0.8*	1995–2000	−2.9	2000–2010	0.9			0.9 (−0.4 to 2.2)
Africa									
Uganda	1993–2012	1.7*							1.7* (0.5 to 2.9)

APC, annual percentage change; AAPC, average annual percentage change. * The APC or AAPC is significantly different from zero at $p < 0.05$.

Table 2). In general, most of the countries have shown reduction (AAPC, ranging from −0.3 in Belarus to −21.5 in Greenland) and increasing rates were only found from Japan, Faroe Islands, Latvia, Italy, and Russia. When comparing the mortality rates by age, similar trends were found from the majority of countries included (Appendix Fig. 2, Appendix Table 7, and Appendix Table 8). Increasing mortality was only found among younger women from Philippines, Latvia, and Russia and among older women from Latvia, Bulgaria, Croatia, and Italy. And the mortality rates from the rest countries decreased or stabilized among these two age groups in the most recent five years.

Of the 44 countries for which both recent incidence and mortality trends were available (Appendix Fig. 3), incidence and mortality rates increased in Japan and Italy, decreased in 16 countries. Another 6 countries showed increase in incidence but reduction in mortality, including United

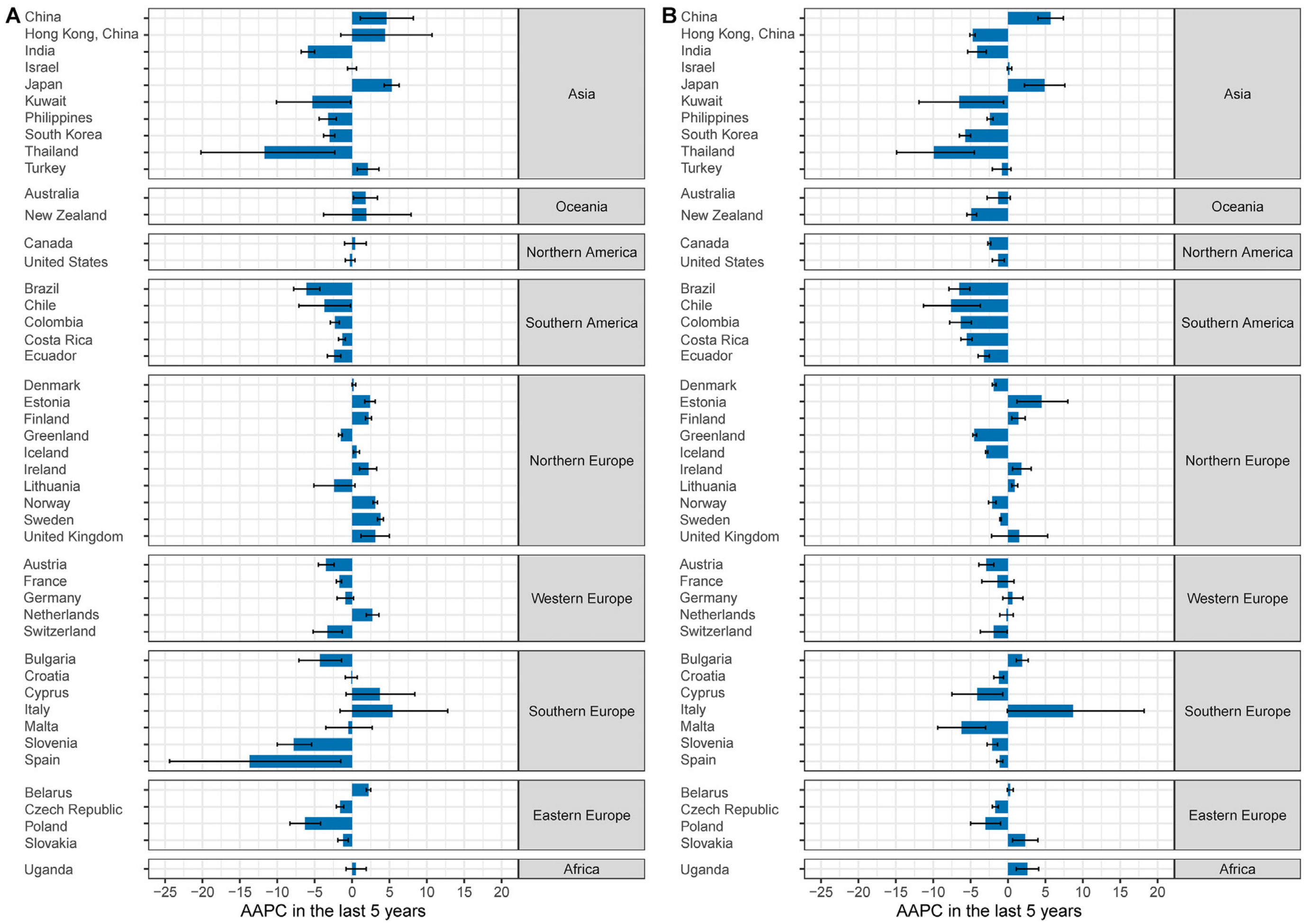

Fig. 3. Estimated Annual Average Change of Percentage of cervical cancer incidence in the past five years by age. (A) incidence among younger women aged between 15 and 49 years (B) incidence among older women aged between 50 and 85 years. AAPC, annual average change of percentage.

Kingdom, Finland, Estonia, Sweden, Netherlands, and Belarus. Rates of incidence and mortality were stable for the remaining 20 countries.

4. Discussion

This study provides the most recent global patterns in the incidence and mortality of cervical cancer, its predictors, and temporal trends overall and by age. The increasing absolute number of cases of cervical cancer worldwide in GLOBOCAN from 471,000 in 2000 to 604,127 in 2020 could be driven by the global growth of aging population but the incidence rate tended to decrease (ASR, 16.2 in 2002 to 13.3 in 2020) [1]. Consistent with previous studies [1], substantial geographical disparities were found in 2020 with the lowest incidence and mortality in regions with very high and high HDIs, and the highest in regions with medium and low HDIs. The remarkable geographical disparities reflect serious inequalities in access to cervical cancer screening and effective cancer treatment facilities as well as the exposure to risk factors.

This study identified some predictors associated with the incidence and mortality of cervical cancer at a country level, including smoking, infections with HPV, HIV, and coverage of cervical cancer screening. These findings are generally consistent with previous studies. The sexually transmitted infection of high-risk HPV types is considered to be the main aetiological factor for cervical cancer in individual level [3]. However, the prevalence of HPV from women with normal cytology was only available from 66 countries in the meta-analysis and the data on high-risk HPV was far less till now [19]. By using the most recent HPV prevalence data from these countries, the positive association was found for both incidence and mortality of cervical cancer with HPV from women with normal cytology. Although the detection of HPV among women with normal cytology is indicative of screening practices in the population by which some active infections could be removed in well-screened populations, HPV test has only been used for 14 countries in national cervical cancer screening program till 2019 [25]. In addition, of the 78 studies included in the meta-analysis for the prevalence of HPV, only about 4% (6226/157879) of the women tested were from Africa [19], suggesting the majority of women with HPV from Africa not screened for HPV. With the utilization of HPV test as the universal screening method in the future for more countries, the risk of HPV could be removed thus reducing the incidence and mortality of cervical cancer.

The strong and positive association of cervical cancer with HIV in our study reflected the significant role of HIV infection in cervical cancer. Due to synergistic actions of HIV and HPV, the cervical cancer burden is substantially increased [3]. Consistent with previous estimation about 21% of cervical cancer in Africa attributable to HIV infection [4], the highest incidence and mortality of cervical cancer in this study were clustered in African countries with high prevalence of HIV and HPV. These data highlighted the importance of HIV prevention measures on the burden of cervical cancer in Africa in the era of cervical cancer elimination. In addition, this study showed that most African countries did not have cervical cancer screening or have very low

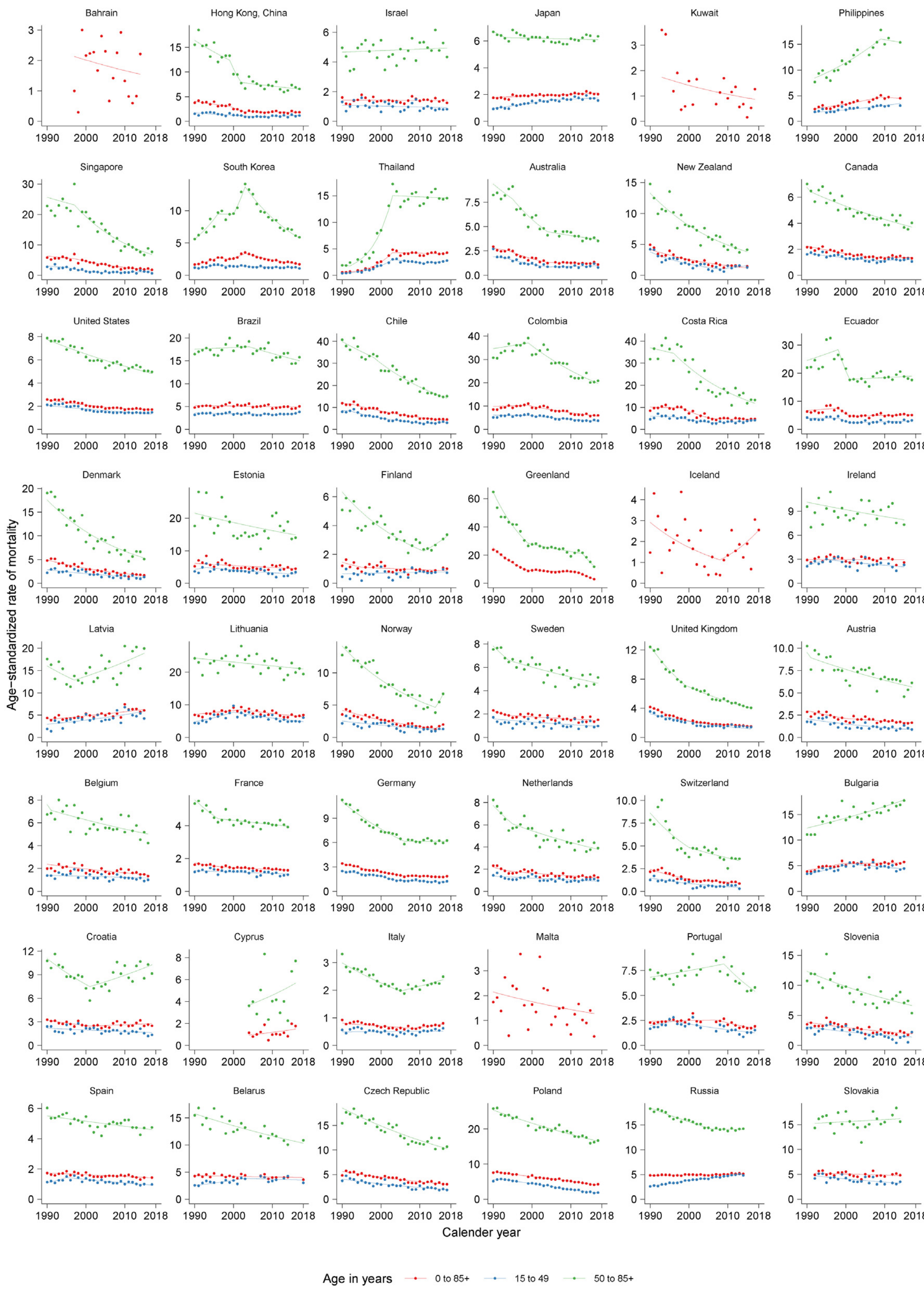

Fig. 4. Joinpoint analysis of trends in age-standardized (world population) mortality rates from cervical cancer overall and by age. Data from 48 selected countries worldwide, in all women (red), women aged 15–49 years (blue), and women aged 50–85 years (green). Solid lines represent fitted values based on joinpoint analysis. Symbols represent observed rates. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

coverage of screening program. Such low implementation of cervical cancer screening also contributed to the burden of cervical cancer in African countries [26], as population-wide screening is the main strategy to reduce cervical cancer by detecting and treating precancerous lesions so far [8]. Furthermore, the negative association of smoking with cervical cancer in this study is expected as the prevalence of smoking among women is very low in some lower and middle income countries where cervical cancer is very high [27].

Table 2
Joinpoint analysis for cervical cancer mortality at all ages, from 1995 to 2016 (according to data availability).

	Trend 1		Trend 2		Trend 3		Trend 4		AAPC (95% CI)
	Period	APC	Period	APC	Period	APC	Period	APC	Last 5 yr
Asia									
Bahrain	1997–2014	−1.9							−1.9 (−6.8 to 3.4)
Hong Kong, China	1979–1999	−3.0*	1999–2003	−11.0	2003–2017	−0.3			−0.3 (−1.4 to 0.9)
Israel	1975–2017	0							0 (−0.4 to 0.3)
Japan	1950–1952	−8.0	1952–1959	18.8*	1959–1987	−2.8*	1987–2017	0.7*	0.7* (0.4 to 0.9)
Kuwait	1975–2017	−2.8*							−2.8* (−4.2 to −1.5)
Philippines	1963–2009	3.8*	2009–2014	−1.1					−0.3 (−3.4 to 3.0)
Singapore	1963–1997	−2.0*	1997–2017	−5.6*					−5.6* (−6.5 to −4.8)
South Korea	1985–1996	9.0*	1996–1999	−3.8	1999–2003	8.6*	2003–2017	−4.8*	−4.8* (−5.4 to −4.1)
Thailand	1979–1992	−5.6*	1992–2003	20.2*	2003–2017	−0.4			−0.4 (−1.4 to 0.6)
Turkey	2009–2016	−0.4							−0.4 (−2.8 to 2.1)
Oceania									
Australia	1950–1962	0.8	1962–1994	−2.7*	1994–2004	−6.3*	2004–2017	−0.6	−0.6 (−1.7 to 0.5)
New Zealand	1950–1988	−1.2*	1988–2015	−4.8*					−4.8* (−5.5 to −4.2)
Northern America									
Canada	1950–1968	−1.9*	1968–1980	−6.0*	1980–2006	−2.9*	2006–2017	−0.3	−0.3 (−1.6 to 1.1)
United States	1950–1963	−2.0*	1963–1980	−4.9*	1980–2007	−1.9*	2007–2017	−0.8	−0.8 (−1.6 to 0.1)
Southern America									
Brazil	1979–2017	−0.2*							−0.2* (−0.4 to −0.1)
Chile	1955–1973	3.7*	1973–1993	−2.0*	1993–2017	−4.1*			−4.1* (−4.4 to −3.8)
Colombia	1953–1964	10.8*	1964–1999	0.5*	1999–2017	−3.3*			−3.3* (−3.8 to −2.7)
Costa Rica	1961–1972	−4.1*	1972–1998	−0.5	1998–2006	−8.3*	2006–2017	−0.5	−0.5 (−2.7 to 1.9)
Ecuador	1979–1998	1.5*	1998–2001	−14.5	2001–2017	0.6			0.6 (−0.4 to 1.6)
Northern Europe									
Denmark	1951–1961	4.3*	1961–1981	−2.4*	1981–2015	−4.4*			−4.4* (−4.8 to −4.0)
Estonia	1981–2016	−1.2*							−1.2* (−1.7 to −0.7)
Faroe Islands	1983–1988	23.6*	1988–2002	2.3	2002–2007	−51.2*	2007–2013	90.3*	90.3* (71.1 to 111.7)
Finland	1952–1964	3.4*	1964–1995	−5.3*	1995–2017	−1.1			−1.1 (−2.3 to 0)
Greenland	1983–1990	3.8*	1990–1999	−10.7*	1999–2012	−1.1*	2012–2016	−21.2*	−21.2* (−24.3 to −18)
Iceland	1986–2008	−5.2*	2008–2018	8.5					8.5 (−2.2 to 20.4)
Ireland	1951–1972	4.1*	1972–1976	−8.3	1976–2015	0			0 (−0.4 to 0.4)
Latvia	1980–1991	−2.6*	1991–2015	1.8*					1.8* (1.1 to 2.5)
Lithuania	1981–2002	1.5*	2002–2018	−1.8*					−1.8* (−2.6 to −1)
Norway	1951–1953	15.0	1953–1991	−1.5*	1991–2014	−4.5*	2014–2016	18.8	6.5 (−9.5 to 25.4)
Sweden	1951–1960	9.4*	1960–1970	−0.9	1970–1994	−4.3*	1994–2017	−1.1*	−1.1* (−1.7 to −0.5)
United Kingdom	1950–1964	−0.9*	1964–1989	−1.6*	1989–2001	−5.9*	2001–2016	−2.2*	−2.2* (−2.7 to −1.7)
Western Europe									
Austria	1955–1973	3.2*	1973–2000	−3.4*	2000–2017	−1.5*			−1.5* (−2.5 to −0.5)
Belgium	1954–2016	−1.9*							−1.9* (−2 to −1.7)
France	1950–1956	7.5*	1956–1968	−0.4	1968–1997	−2.1*	1997–2014	−0.8*	−0.8* (−1.3 to −0.3)
Germany	1990–2006	−3.6*	2006–2017	−0.5					−0.5* (−1.1 to 0)
Netherlands	1950–1969	−0.4	1969–1994	−4.3*	1994–2017	−1.7*			−1.7* (−2.2 to −1.2)
Switzerland	1951–1954	56.3*	1954–1981	−2.4*	1981–2002	−5.6*	2002–2013	−2.3	−2.3* (−4.7 to 0)
Southern Europe									
Bulgaria	1964–1981	1.3*	1981–1999	3.2*	1999–2015	0.2			0.2 (−0.4 to 0.8)
Croatia	1985–2001	−2.4*	2001–2017	0.8					0.8 (−0.5 to 2.1)
Cyprus	2004–2016	3.8							3.8 (−2.1 to 10.1)
Italy	1951–1959	7.4*	1959–1984	−3.4*	1984–2008	−1.5*	2008–2016	2.9*	2.9* (0.1 to 5.8)
Malta	1965–2016	−2.0*							−2* (−2.8 to −1.1)
Portugal	1980–2007	0.4	2007–2017	−4.1*					−4.1* (−5.9 to −2.2)
Slovenia	1985–2017	−2.6*							−2.6* (−3.1 to −2.1)
Spain	1951–1969	8.3*	1969–1973	−4.8	1973–1990	4.8*	1990–2017	−0.8*	−0.8* (−1.1 to −0.4)
Eastern Europe									
Belarus	1981–2018	−0.3*							−0.3* (−0.6 to −0.1)
Czech Republic	1986–2017	−2.3*							−2.3* (−2.5 to −2.1)
Poland	1980–1991	−0.7*	1991–2007	−2.0*	2007–2017	−3*			−3* (−3.6 to −2.5)
Russia	1980–1990	−2.7*	1990–2014	0.3*					0.3* (0.2 to 0.4)
Slovakia	1992–2014	−0.4							−0.4 (−1 to 0.1)

APC, annual percentage change; AAPC, average annual percentage change; CI, confidence interval. * The APC or AAPC is significantly different from zero at $p < 0.05$.

Relatively consistent trends in incidence and mortality of cervical cancer were found across countries within the same continent from data through 2018. Of 16 countries with significant reduction of both incidence and mortality, it was most likely due to the screening strategy as most of them were high-income countries with long and well-established screening program in place [8]. Together with the significant impact of screening program in these countries, HPV vaccination has also been implemented in some countries since 2006 [26] and it started to show some impact on invasive cervical cancer among younger women in few countries recently [28,29]. The Swedish study reported the reduced risk of cervical cancer following universal HPV vaccination program among girls and women aged 10–30 years [28]. Another Finnish study based on cohort trials suggested the protective effectiveness against cervical cancer albeit with small number of invasive carcinomas ($n = 10$ in unvaccinated and $n = 0$ in vaccinated) among women aged 16–17 years followed up to 7-year time-periods [29]. Therefore, some reduction of cervical cancer incidence among younger women is expected from countries with universal HPV vaccination program implemented in early years. Nevertheless, only 30 countries have started universal HPV vaccination among teenagers from 2006 to 2010, although 81 countries have implemented HPV vaccination up to 2018 [26]. Given the average age at diagnosis of cervical cancer at 53 years, the impact of HPV vaccination among general population will not be observed until at least another 20 years.

Of few countries with consistent increase of incidence and mortality (Japan and Italy) or where only incidence (China and Uganda) or mortality data (Russia) were available, the increasing trend might be associated with low screening uptakes, high prevalence of HPV, and increased smoking [30]. Of notice, although only Uganda from Africa was included in our analysis, another study using ten population-based cancer registries in eight African countries found increased incidence in all registries [31]. However, only three of them were based on national data and none of them did submit consistent data to CI5 [20]. Therefore, there is an urgent need for government ownership and support for cancer registration in Africa to monitor future trends as an essential component of all cancer control programmes.

In our study, contrasting patterns of decreasing mortality and increasing incidence were found from Belarus, Estonia, Finland, Netherland, Sweden, and United Kingdom in the most recent five years. The reduction of mortality may be related to increasing awareness, early detection, and treatment of the cervical cancer in these countries, resulting in better oncological control [32]. In contrast, the increasing incidence might be explained by the inadequate uptake and insufficient quality of the cancer screening program as reported in Estonia [33], Belarus [34], or less intensive screening in more recent years in Netherlands [35].

Of importance, increase of incidence rate was only found among younger women from Australia, Belarus, Denmark, Iceland, Netherlands, Norway, Sweden, United Kingdom, and Turkey, which was consistent with previous reports [11,36]. These might be associated with rises in the prevalence of high risk HPV infection following the changing aspects of sexual behavior, including earlier age at first sexual intercourse and multiple partners in their lifetime [37]. More importantly, a willful lack of screening was reported by the Finnish Mass Screening Registry that less than 60% of women younger than 40 years of age accepted the invitation to be screened in 2003 and only 20% of the women 25–30 years of age participated in the screening programme [11]. Similarly cervical screening coverage is falling at higher degree year on year among younger women than that among older women in Australia [10], England [9], Denmark and Sweden [38]. Another reason for the increasing trend might be related to loss to follow-up when implementing a screening strategy with a secondary test. Studies have suggested the proportion of loss to follow-up of women with normal cytology at baseline was about 30% and the proportion was substantially higher among those aged <40 years than those aged 40–65 years with approximately 3 years apart (39% vs 29%) [39]. Lack of follow-up has been associated with both patient and system-related barriers. Therefore, effective interventions in patient level could improve follow-up rates including telephone reminders, telephone counseling, print educational interventions as suggested early [40]. In practice level, an electronic general practitioner reminder system showed the potential to improve the quality of cervical cancer screening through reduced loss to follow-up [41]. Because the increasing incidence rates of cervical cancer among younger women, our findings suggested that cervical cancer screening programmes should be further implemented among younger women aged less than 50 years in these countries in both patient and practice levels.

This study is the most recent analysis on global burden of cervical cancer, and its predicators, as well as its temporal trends by country and age based on high quality datasets. However, the major limitation of this study is that our results are limited by the availability of high-quality cancer data in certain areas of the world. Although African countries have documented highest incidence and mortality of cervical cancer in GLOBOCAN 2020, consistent high-quality data in long term are lacking from these countries, precluding temporal trends analysis. In addition, cautions should be taken when interpretating the association of country-level risk factors with burden of cervical cancer, because ecological fallacy might exist in the analysis. It is also difficult to obtain global data on other risk factors of cervical cancer, for instance parity, oral contraceptive use, and high-risk HPV. The lack of data on high-risk HPV might explain why we only found positive association of HPV infection with cervical cancer in univariate analysis but not in the multivariate analysis. Finally, the reduction of cervical cancer among younger women from some of these countries might also be partially attributable to the universal HPV vaccination programme. However, such programme won't have a clear impact on cervical cancer on a global scale in a short term, given it has only been started from 2006 in few countries [26] and the average age at diagnosis of cervical cancer at 53 years [1]. Therefore, it is of importance to assess the impact of HPV vaccination on cervical cancer globally in the future.

5. Conclusions

African countries continued to have the highest burden of cervical cancer, attributable to high prevalence of HPV, HIV infection, and low coverage of cervical cancer screening. While the reduction of mortality from most of the countries with cancer registries are promising, the increasing incidence of cervical cancer among women aged 15 to 49 years in recent year in developed countries warrants further implementation of screening programme in younger women.

Ethics approval

This study used secondary data publicly available. Only aggregated data were used and therefore ethics was not required.

Consent for publication

None.

Data availability

The data used in this article are freely available at the Global Cancer Observatory 2020 (https://gco.iarc.fr/today/home), Cancer Incidence in Five Continents (https://ci5.iarc.fr/CI5plus/Default.aspx), World Health Organization Mortality (https://www.who.int/data/gho/data/themes/mortality-and-global-health-estimates/download-the-raw-data-files-of-the-who-mortality-database), and Global Health Data Exchange (http://ghdx.healthdata.org/gbd-results-tool).

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Declaration of Competing Interest

None.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ygyno.2021.10.075.

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