Original Article

Worldwide Trends in Cervical Cancer Incidence and Mortality, With Predictions for the Next 15 Years

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BACKGROUND: Cervical cancer is 1 of the most common cancers in females worldwide. Understanding the most recent global patterns and temporal trends of cervical cancer burden might be helpful for its prevention and control. **METHODS:** Data on cervical cancer (International Classification of Diseases, Tenth Revision, code C53) incidence and mortality in 2018 were extracted from the GLOBOCAN 2018 database and further analyzed for their correlations with the Human Development Index. Temporal trends were analyzed using the annual percent change with joinpoint analysis among 31 countries with highly qualified data from the Cancer Incidence in Five Continents Plus and World Health Organization mortality databases. Future trends for the next 15 years were predicted using an open-source age-period-cohort model. **RESULTS:** Cervical cancer incidence and mortality rates were both negatively correlated with the Human Development Index ($r = -0.56$ for incidence, $r = -0.69$ for mortality; $P < .001$) in cross-sectional analysis, and both remained stable in 12 countries or even decreased in 14 and 18 countries for incidence and mortality, respectively, during the most recent 10 data years. Similar findings were observed for the next 15 years. **CONCLUSIONS:** Cervical cancer burden was correlated with socioeconomic development. An overwhelming majority of countries had stable or decreasing trends in incidence and mortality rates, especially in those with effective cervical cancer screening programs and human papillomavirus vaccination. ***Cancer* 2021;127:4030-4039**. © *2021 American Cancer Society*.

LAY SUMMARY:

- The authors investigated the most up-to-date data from official databases released by the International Agency for Research on Cancer and found that cervical cancer incidence and mortality were negatively correlated with socioeconomic development.
- Among the 31 countries analyzed, most (26 countries were analyzed for incidence, and 30 were analyzed for mortality) had stable or even decreasing temporal trends over the most recent 10 years, especially in those with effective cervical cancer screening programs.
- In addition, the predicted trends for the next 15 years were basically consistent with the observed trends among most of the analyzed countries (19 countries for incidence and 26 countries for mortality).

KEYWORDS: cervical cancer, human development index, incidence, mortality, projection, temporal trend.

INTRODUCTION

Cervical cancer is the fourth most common neoplasm and the fourth leading cause of cancer death among women in the world, accounting for approximately 570,000 new cases and 311,000 deaths in 2018.[1] The distribution of cervical cancer varies widely, with >85% of the global burden occurring in low-income and middle-income countries.[2] Over the last decades, trends in cervical cancer incidence and mortality have been observed to vary in different countries.[3,4]

The Human Development Index (HDI), a summary measure of average socioeconomic development comprising life expectancy, education, and gross national income, is the most widely used criteria to differentiate the comprehensive development status of a country.[5] It has been reported to be widely correlated with cancer burden.[6] For example, it has been observed that the incidence of prostate cancer increases with the HDI level.[7] Both incidence and mortality of colorectal cancer showed a distinct gradient with increasing levels of HDI.[8] For cervical cancer, incidence and mortality reportedly rank second among females in countries with a low HDI.[1]

Persistent infection with human papillomavirus (HPV) is the main etiologic factor for cervical cancer, of which HPV types 16 (HPV16) and HPV18 are responsible globally for 71% of cervical cancers.[9] Other risk factors, such as human immunodeficiency virus (HIV) infection,[10] oral contraceptive (OC) use,[11] and high-risk sexual behaviors,[12] could have

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We thank the cancer registries that were participating investigators for having contributed their data.

Additional supporting information may be found in the online version of this article.

DOI: 10.1002/cncr.33795, **Received:** January 26, 2021; **Revised:** May 22, 2021; **Accepted:** June 11, 2021, **Published online** August 9, 2021 in Wiley Online Library (wileyonlinelibrary.com)

an effect either by influencing the acquisition of HPV infection or by severely impairing the immune response after HPV infection. Nevertheless, prophylactic vaccination and screening are often recognized as the primary and secondary methods, respectively, for the prevention of cervical cancer.[13]

Understanding the most recent trends and predicting the future burden might help to evaluate the impact of screening along with other factors that influence cervical cancer. However, previous studies were limited to specific countries or regions and did not consider the area socioeconomic development when making comparisons.[14,15] Therefore, we examined the relationships between cervical cancer incidence and mortality and the HDI, described the temporal trends for cervical cancer in 31 countries, and predicted future trends for the next 15 years using the most recent data from the GLOBOCAN, Cancer Incidence in Five Continents Plus (CI5*plus*), and World Health Organization mortality databases released by the International Agency for Research on Cancer (IARC).

MATERIALS AND METHODS

Data Sources

To analyze the correlation between cervical cancer burden and the HDI, incidence and mortality estimates of cervical cancer (International Classification of Diseases, Tenth Revision, code C53) for 185 countries in 2018 were obtained from the GLOBOCAN 2018 database.[2] The HDI for each country was obtained from the United Nations Development Program,[5] from which the 2018 HDIs were available for 174 of the 185 countries. Finally, those 174 countries were included in the cross-sectional correlation analyses between cervical cancer burden and the HDI. Thirty-one countries with qualified, consecutive data were further analyzed for longitudinal correlations at the country-specific level.

To describe the temporal and projected trends of cervical cancer burden, incidence data from the CI5*plus* database[16] and mortality data from the World Health Organization mortality database,[17] both of which were released by IARC, were used (see Supporting Table 1). To ensure data quality, the IARC used high standards based on assessment of completeness, comparability, validity/accuracy, and timeliness.[18,19] In the temporal trends description, we included 31 countries that had 1) available data for ≥15 consecutive years in incidence and mortality to ensure data quality over time, 2) available data beyond 2010 to ensure contemporary meaning, and 3) available incidence data preceding mortality data to ensure temporality. Among these, 27 countries that had 1) available data from ≥3 of the most recent 5-year observed periods for incidence and mortality, and 2) sufficient cases (>10) in any age groups also had future trends predicted for the next 15 years.

Statistical Analysis

The age-standardized incidence and mortality rates (ASRs) per 100,000 were computed referring to the world standard population.[20] To clearly demonstrate the relationship between cervical cancer burden and socioeconomic development, ASRs were plotted against the HDI. Correlation coefficients (r) calculated by simple linear regression were used to quantify this association. To demonstrate the temporal trends graphically, both the observed data and the local polynomial regression smoothed data were plotted.[21] To analyze incidence and mortality trends, a joinpoint regression model[22] was used, which managed to fit a series of joined line segments to the trends of ASRs. A logarithmic transformation of the rates and a maximum of 3 joinpoints were adopted as options. To estimate the direction and magnitude of recent trends in each population, the average annual percent change and its corresponding 95% CI were calculated for the most recent available 10 years. To predict the trends of cervical cancer incidence and mortality in the next 15 years (three 5-year prediction periods), the NORDPRED age-period-cohort method developed by Moller et al was used,[23] which has been widely adopted for projecting trends into the near future.[24,25] In brief, from 3 to 5 of the most recent 5-year observed periods were extrapolated using a power function to stabilize the growth, with a projection of the recent linear trend for the last 10 years, which was attenuated by 25% and 50% in the second and third prediction periods, respectively. The trend in the last 10 years instead of the average change in the whole observed period was used as the drift component to be projected if the rates displayed significant curvature in the prediction base. Mean annual differences in the cervical cancer incidence and mortality were calculated by comparing the ASRs in the last 5 predicted years relative to those of the last 5 observed years, which were used as the index for future trends.

Data management and analyses were performed using R software (version 4.0.2). The joinpoint regression models were performed using the Joinpoint Regression Program (version 4.8.0.1). All statistical tests were 2-sided, and P values <.05 were regarded as statistically significant.

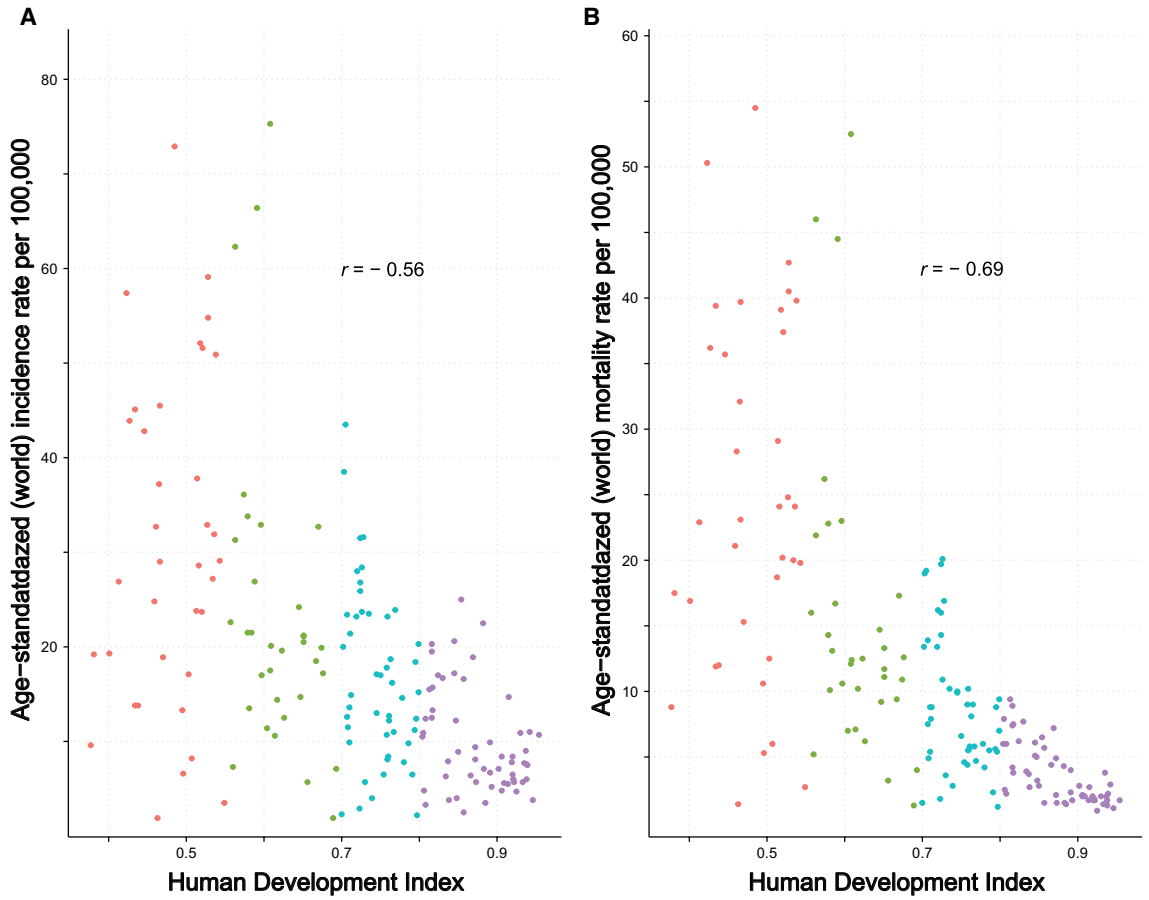

Figure 1. Correlations between the Human Development Index (HDI) and age-standardized rates per 100,000 are illustrated for cervical cancer (A) incidence and (B) mortality. Red dots indicate low HDI (<0.550); green dots, median HDI (0.550 to <0.700); blue dots, high HDI (0.700 to <0.800); purple dots, very high HDI (≥0.800).

RESULTS

Correlation Between Cervical Cancer Burden and the HDI

Simple linear regression analysis identified significantly inverse correlations between the HDI and cervical cancer incidence ($r = -0.56$; $P < .001$) and mortality ($r = -0.69$; $P < .001$) in cross-sectional analysis (Fig. 1). When analyzing the individual correlations by country, most countries had inverse relationships of the HDI with cervical cancer incidence (21 of 31 countries analyzed) and mortality (25 of 31 countries analyzed) (Table 1).

Observed Temporal Trends in Cervical Cancer Incidence and Mortality

As shown in Figure 2, among the 31 analyzed countries with eligible data that varied over the included years, the numbers that had stable, decreasing, and increasing trends over the most recent 10 years amounted to 12, 14, and 5 countries, respectively, for incidence and 12, 18, and 1, respectively, for mortality. Slovenia (−6.6 per year; 95% CI, −8.7 to −4.5 per year), Brazil (−6.1 per year; 95% CI, −7.3 to −4.8 per year), Colombia (−5.7 per year; 95% CI, −7.3 to −4.0 per year), and Chile (−5.1 per year; 95% CI, −7.8 to −2.3 per year) showed the strongest decreasing changes in incidence. New Zealand (−5.0 per year; 95% CI, −5.5 to −4.4 per year), the Republic of Korea (−4.5 per year; 95% CI, −5.3 to −3.6 per year), and Denmark (−4.3 per year; 95% CI, −4.7 to −3.8 per year) showed the greatest decreasing changes in mortality (Fig. 3).

Projected Future Trends in Cervical Cancer Incidence and Mortality

Twenty-seven of the 31 countries also had future trends predicted for the next 15 years. As shown in Figure 4, most countries had stable or decreasing trends. Accordingly, the

TABLE 1. The Individual Correlations of Cervical Cancer Incidence and Mortality Rates with the Human Development Index by Country

Country	Incidence			Mortality		
	Study Period	r^a	P^b	Study Period	r^a	P^b
Latin America and the Caribbean						
Brazil	1993-2012	−0.90	<.001[c]	1990-2017	−0.71	<.001[c]
Chile	1998-2012	−0.76	<.001[c]	1990-2017	−0.97	<.001[c]
Colombia	1990-2012	−0.87	<.001[c]	1990-2017	−0.93	<.001[c]
Costa Rica	1990-2011	−0.91	<.001[c]	1990-2017	−0.88	<.001[c]
Northern America						
Canada	1990-2012	−0.93	<.001[c]	1990-2017	−0.88	<.001[c]
United States	1990-2012	−0.92	<.001[c]	1990-2017	0.90	<.001[c]
Asia						
China	1990-2012	−0.54	.007[c]	1990-2017	−0.86	<.001[c]
Israel	1990-2012	−0.05	.831	1990-2017	0.02	.912
Japan	1990-2012	0.48	.022[c]	1990-2017	0.81	<.001[c]
Kuwait	1998-2012	−0.41	.128	1993-2017	−0.86	<.001[c]
Republic of Korea	1993-2012	−0.98	<.001[c]	1990-2017	0.16	.420
Eastern Europe						
Bulgaria	1998-2012	0.60	.018[c]	1990-2015	0.60	.001[c]
Northern Europe						
Denmark	1990-2012	−0.89	<.001[c]	1990-2015	−0.95	<.001[c]
Estonia	1990-2012	0.57	.004[c]	1990-2018	−0.75	<.001[c]
Iceland	1990-2012	−0.22	.307	1990-2018	−0.31	.097
Ireland	1994-2012	0.48	.037[c]	1990-2015	−0.39	.050[c]
Lithuania	1990-2012	0.76	<.001[c]	1990-2018	−0.33	.085
Norway	1990-2012	−0.93	<.001[c]	1990-2016	−0.94	<.001[c]
United Kingdom	1990-2012	−0.88	<.001[c]	1990-2016	−0.99	<.001[c]
Southern Europe						
Croatia	1990-2012	−0.37	.079	1990-2017	−0.49	.008[c]
Italy	1990-2012	−0.81	<.001[c]	1990-2016	−0.77	<.001[c]
Malta	1993-2012	−0.42	.067	1990-2016	−0.42	.029[c]
Slovenia	1990-2012	−0.66	<.001[c]	1990-2017	−0.81	<.001[c]
Spain	1990-2012	−0.47	.024[c]	1990-2017	−0.72	<.001[c]
Western Europe						
Austria	1998-2012	−0.92	<.001[c]	1990-2017	−0.86	<.001[c]
France	1990-2012	−0.92	<.001[c]	1990-2016	−0.91	<.001[c]
Germany	1990-2012	−0.85	<.001[c]	1990-2017	−0.97	<.001[c]
Switzerland	1990-2012	−0.93	<.001[c]	1990-2016	−0.91	<.001[c]
The Netherlands	1990-2012	−0.54	.008[c]	1990-2017	−0.89	<.001[c]
Oceania						
Australia	1990-2012	−0.87	<.001[c]	1990-2017	−0.92	<.001[c]
New Zealand	1990-2012	−0.96	<.001[c]	1990-2015	−0.95	<.001[c]

[a]Correlation coefficients (*r*) were determined using Pearson correlation analysis.
[b]*P* values were determined using Pearson correlation analysis.
[c]These *P* values indicate a significant difference.

number of countries that had stable, decreasing, and increasing trends predicted in the next 15 years amounted to 10, 9, and 8 countries, respectively, for incidence and 16, 10, and 1 countries, respectively, for mortality. The predicted incidence rates decreased (−1% per year) in 9 countries, among which Slovenia, Brazil, and Chile showed the highest decreasing tendencies, with the ASR annual changes of −5.1%, −5.0%, and −4.5%, respectively. The predicted mortality rates decreased in 10 countries, with the greatest decreases in New Zealand (−3.9%), Denmark (−3.1%), and Switzerland (−2.2%) (see Supporting Fig. 1).

DISCUSSION

By describing the most up-to-date data, our study demonstrates negative correlations of the HDI with the incidence and mortality rates of cervical cancer. Among the 31 included countries, most (26 countries for incidence and 30 countries for mortality) had stable or decreasing temporal trends over the most recent 10 years. Furthermore, the predicted trends in the next 15 years basically were consistent with the findings in the observed temporal trends among the 27 analyzed countries (19 countries for incidence and 26 countries for in mortality).

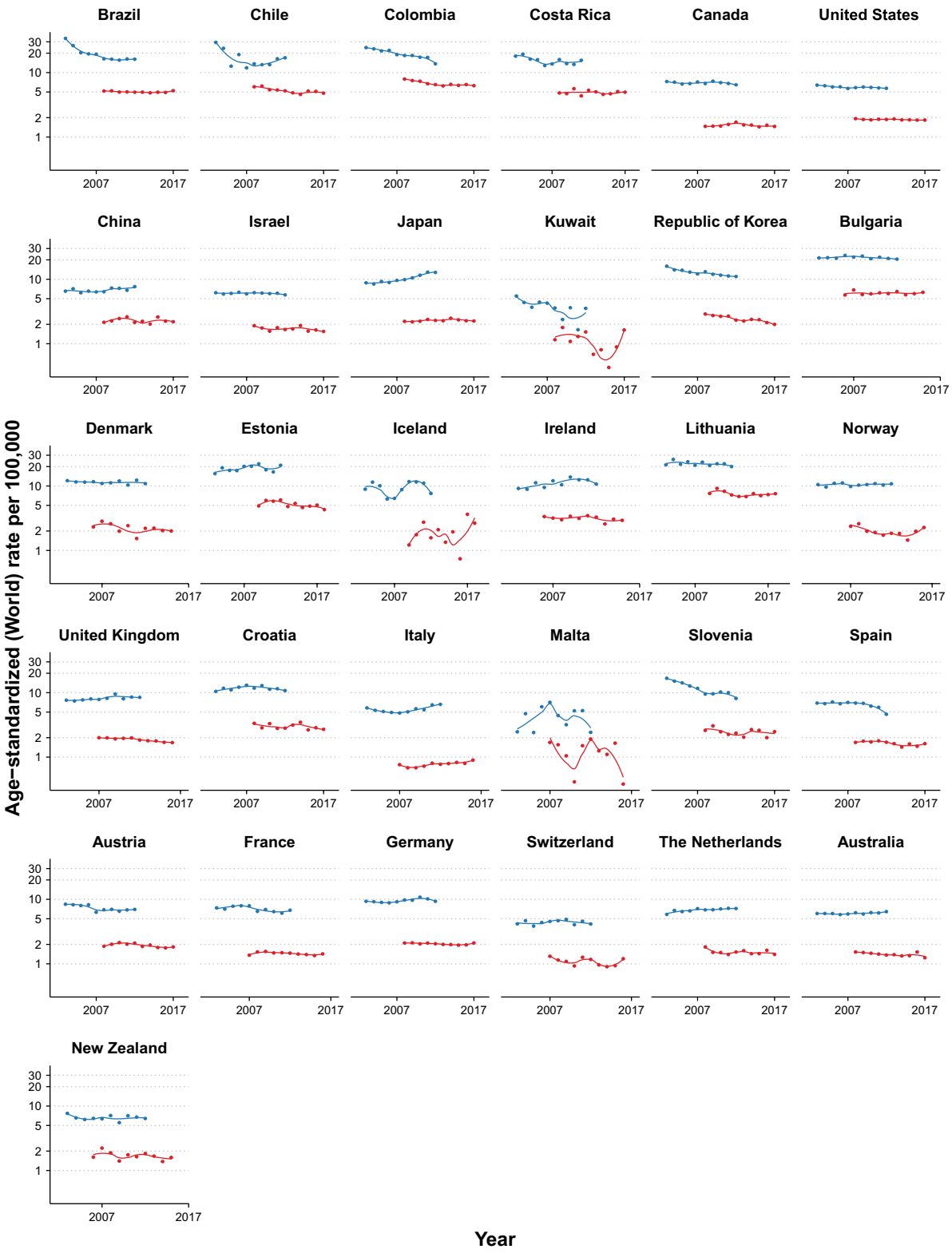

Figure 2. Temporal trends for cervical cancer incidence (blue lines) and mortality (red lines) are illustrated by country. All data are expressed as the age-standardized rate per 100,000.

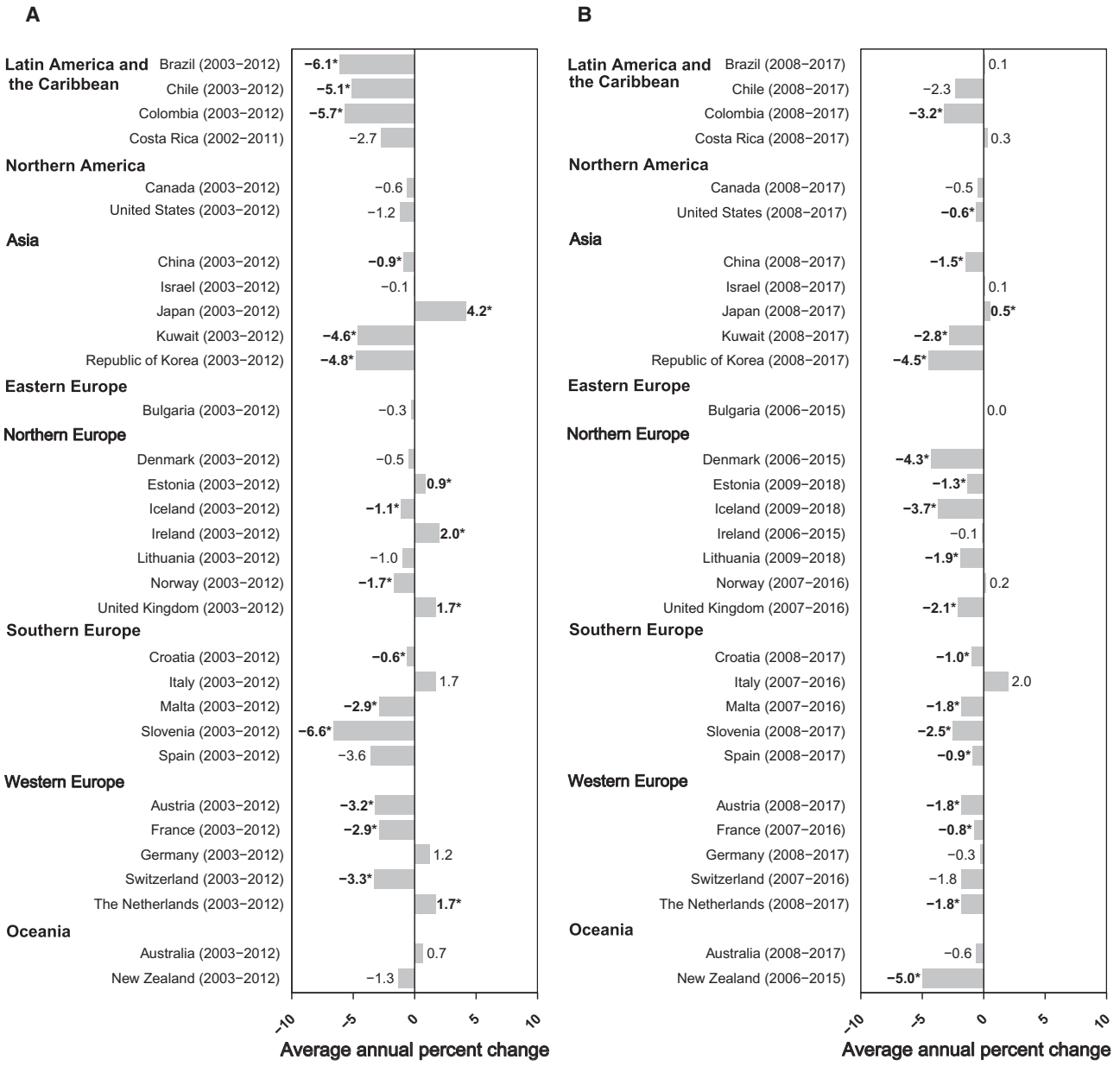

Figure 3. The average annual percent changes in cervical cancer (A) incidence and (B) mortality are illustrated for the most recent 10 years. Asterisks indicate a statistically significant difference.

We observed inverse correlations of the HDI with cervical cancer incidence and mortality rates. In line with our findings, Arbyn et al[26] reported that countries with a low HDI had the highest rates (incidence, 26.7; mortality, 20.0), whereas those with a very high HDI had the lowest rates (incidence, 9.6; mortality, 3.0) in 2018. Lower incidence and mortality rates in countries with a higher HDI may be the consequence of a lower prevalence of known risk factors related to HPV infection,[9] HIV-related immunodeficiency,[27] and OC use[11]; whereas cervical cancer screening[28] and HPV vaccination[29] are known protective factors (see Supporting Table 2).

HPV infection has been reported to play an important role in cervical cancers.[9] Persistent HPV16 (57%) and HPV18 (16%) infections were the 2 most common types identified in patients with cervical cancer, which were estimated to account for 70% to 76% of cervical cancers.[30] Moreover, a moderate or high HPV load could accelerate the progression of cervical precancers.[31] The HPV infection prevalence varied from the highest in the Caribbean

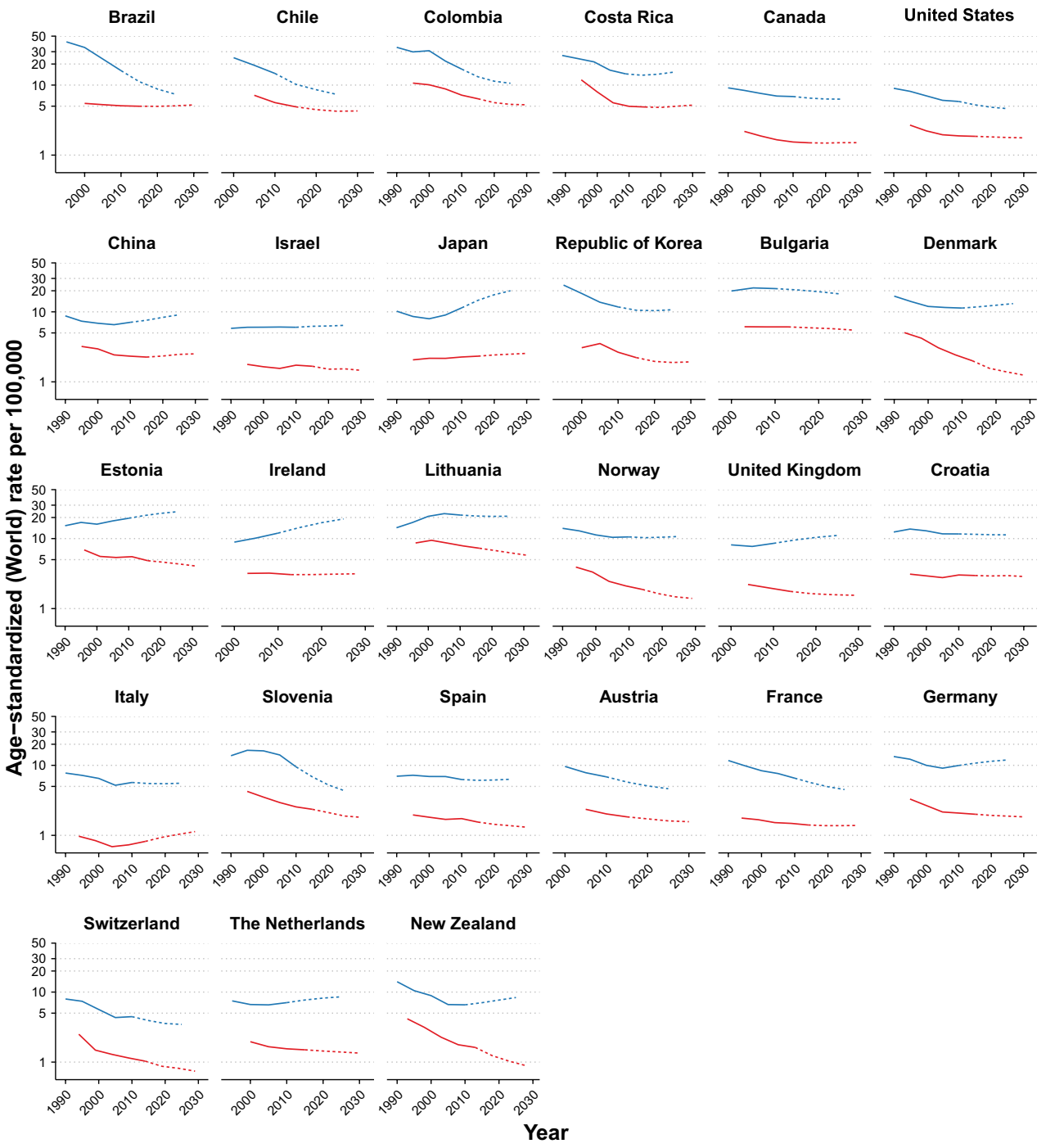

Figure 4. Predicted trends for cervical cancer incidence (blue lines) and mortality (red lines) are illustrated by country for the next 15 years. Solid lines indicate the observed incidence and mortality rates, and dashed lines indicate the predicted rates.

(35.4%) and Eastern Africa (33.6%) to the lowest in Northern America (4.8%) and Western Asia (2.2%), and this regional disparity is basically consistent with the cervical cancer prevalence in 2018.[26,32]

HIV-related immunodeficiency might have an unfavorable impact on cervical cancer development, which is associated with the increased acquisition and persistence of HPV infection.[27] Among individuals living with HIV,

the risk of HPV incidence was approximately doubled, whereas the clearance rate was approximately halved.[27] A pooled analysis showed that the prevalence of anal HPV16 was 11% in HIV-positive women versus 2% in HIV-negative women.[33] Correspondingly, HIV-positive women have a higher risk of cervical precancerous lesions and cancers, largely because of the synergistic effect between HIV and HPV infection.[34]

OC use could also increase the risk of cervical cancer and may affect the transition from HPV infection to cervical precancer.[11] Among women with current OC use, the risk for high-risk HPV persistence significantly increased, which was the prerequisite for cervical cancer development.[35] Ten years of OC use was estimated to increase the cumulative incidence from 7.3 to 8.3 per 1000 in less developed countries and from 3.8 to 4.5 per 1000 in more developed countries.[36] Moreover, the risk of invasive cervical cancer increased with increased duration of use among current users but declined after use ceased.[36]

Cervical cancer is potentially a preventable disease.[37] Screening may decrease incidence by identifying and treating cervical precancerous lesions[28] and may decrease mortality by detecting cancerous lesions at an earlier stage.[38] In the current study, the stable and even decreasing tendencies in incidence and mortality rates shown for most countries in our analysis probably are related to the improving quality and coverage of cervical cancer screening programs.[39] For example, the incidence trend in Brazil demonstrated the most evident decreases, whereas the mortality trend remained steady, which might be attributed to the early implementation of organized screening programs (1968) and improvements in screening, diagnosis, and treatment.[40,41] Japan was the only population that had increases in both incidence and mortality in our study, consistent with previous reports.[42,43] The observed increasing trends might be caused in part by the low coverage of cervical cancer screening in Japan, at approximately 40%.[42,43]

HPV vaccination may be another efficient way to prevent cervical cancer.[44] Since 2006, HPV vaccines have been introduced in many countries, mainly targeting young adolescent girls aged 10 to 14 years through national immunization programs.[45] In a prospective study, Baldur-Felskov et al[44] observed a reduced risk of cervical lesions 6 years after licensure of the quadrivalent HPV vaccine in Denmark. Bivalent and quadrivalent HPV vaccines were introduced into the Japanese national immunization program for girls aged 12 to 16 years in 2013, but the uptake has remained <1% since then,[46] which might partly contribute to the continuing increasing cervical cancer burden in the future 15 years in our projection. Although the current effect of HPV vaccination on preventing cervical cancer development is relatively limited because most of the target vaccination population has not entered the high-risk age groups and the vaccine uptake was very low in many countries,[47] it will be the most important way to decrease the long-term cervical cancer burden with reasonable uptake.[29]

On the basis of the description of the temporal trends of cervical cancer incidence and mortality in the most recent 10 years, the current study also projected future trends in the next 15 years. Although the predictions were restricted to those countries with a high or very high HDI that had qualified data, the differences in trends may be able to reflect differences in the availability, coverage, and quality of prevention strategies and the prevalence of risk factors.[48] The United States, France, and Switzerland began to implement HPV vaccinations as early as in 2006[49] and thus might benefit from decreases in the prevalence of HPV and the incidence of precancerous lesions among young women.[50] Denmark (1967), Costa Rica (1995), and Norway (1995)[40,51] have carried out nationally organized screening programs for decades. The stable and even decreasing trends in cervical cancer incidence in these countries suggest the effectiveness of their control strategies. However, because of the low coverage (40%) of screening program and the low uptake (<1%) of HPV vaccination,[42,43,46] Japan still showed evidently increasing trends. Estonia also presented an increasing trend in incidence, possibly resulting from the inadequate coverage (35%) and insufficient quality of their screening program.[52] In addition, 10 and 16 of the 27 included countries showed decreasing and stable trends, respectively, which were attributed mainly to decreased incidence and increased survival.[14] The long-term organized screening programs in Denmark and Norway have been proven to have a major impact on reducing mortality by decreasing incidence and increasing the capacity to detect early stage cervical cancer.[53] The improvements in clinical treatments (eg, the use of radiotherapy in combination with hyperthermia) in the Netherlands reportedly have reduced mortality by improving survival.[54] The current projections might also provide a necessary reference for the possible cervical cancer burden in the near future and provides a caution for those countries that still have increasing trends. Future prevention and control strategy planning could take these issues into consideration.

The main strength of the current study is the use of high-quality incidence and mortality data from official databases released by the IARC. However, several

limitations should also be mentioned. First, our future trends were projected using the NORDPRED age-period-cohort method and could not consider differences in advances of prevention and control strategies and changes in risk factor prevalence between countries. However, this modelling is the most widely used method. Second, underdiagnosis and underreporting might happen during cancer registration, particularly in less developed countries. Third, age-specific data on hysterectomy were unavailable for each population over the study period, which might have uncertain biases on our findings.[55] Finally, because of the limits of data availability and quality, in the current study, we were unable to analyze the incidence and mortality trends in African countries, although they reportedly had the heaviest cervical cancer burden.

Globally, cervical cancer incidence and mortality rates were negatively correlated with socioeconomic development. Both temporal and predicted trends remained stable or even decreased in most of the analyzed countries, especially in those with effective cervical cancer screening programs and HPV vaccination. Further studies are required to clarify the factors contributing to increase, and strategies that work to decrease, the incidence and mortality of cervical cancers

FUNDING SUPPORT

This study was funded by the National Key Research and Development Project (no. 2016YFC1302503).

CONFLICT OF INTEREST DISCLOSURES

The authors made no disclosures.

AUTHOR CONTRIBUTIONS

Shujuan Lin: Conception and design, collection and assembly of the data, data analysis and interpretation, writing, and editing. **Kai Gao:** Collection and assembly of the data, data analysis and interpretation, writing, and editing. **Simeng Gu:** Data curation and analysis and review. **Liuqing You:** Data curation and analysis and review. **Sangni Qian:** Methodology, supervision, and review. **Mengling Tang:** Supervision and review. **Jianbing Wang:** Supervision and review. **Kun Chen:** Conceptualization, methodology, validation, formal analysis, investigation, resources, data curation, writing–original draft, and visualization. **Mingjuan Jin:** Conceptualization, methodology, validation, formal analysis, investigation, resources, data curation, writing–original draft, and visualization.

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