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Global distribution, risk factors, and recent trends for cervical cancer: A worldwide country-level analysis

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HIGHLIGHTS

- The burden of cervical cancer was highest in regions with low and medium HDI and higher alcohol consumption.
- The incidence and mortality of cervical cancer have been declining globally for the recent past decade.
- However, an increasing incidence trend was observed in North European countries and among younger females.
- Further studies are needed to explore the reasons underlying these epidemiological transitions.

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ABSTRACT

Objectives. This study aimed to evaluate the most updated worldwide distribution, risk factors, and temporal trends of cervical cancer for different countries and age groups.

Methods. The *Global Cancer Observatory* database was retrieved for the age-standardized rates (ASRs, per 100,000 persons) for incidence and mortality of cervical cancer in 2018. The associations with risk factors were examined by multivariable regression analysis, adjusting for human development index (HDI) and gross domestic products (GDP) per capita. Joinpoint regression analysis was used to calculate the 10-year annual average percent change (AAPC) for incidence and mortality.

Results. A total of 568,847 new cases (ASR, 13.1) and 311,365 deaths (ASR, 6.9) of cervical cancer were reported globally in 2018. The highest incidence and mortality were observed in Southern Africa (ASRs, 43.1 and 20.0) and countries with low HDI (ASRs, 29.8 and 23.0). Countries with higher incidence and mortality had lower HDI ($\beta = -8.19$, 95% CI -11.32 to -5.06, $p < 0.001$; $\beta = -7.66$, CI -9.82 to -5.50; $p < 0.001$) but higher alcohol consumption ($\beta = 1.89$, 95% CI 0.59 to 3.19, $p = 0.005$; $\beta = 0.98$, CI 0.08 to 1.88; $p = 0.033$). An increasing trend of incidence was also observed in younger populations, with Cyprus (AAPC, 6.96), Sweden (AAPC, 4.88), and Norway (AAPC, 3.80) showing the most prominent.

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Conclusions. The burden of cervical cancer was highest in regions with low and medium HDI and was associated with higher prevalence of alcohol consumption. There was an overall decreasing burden of cervical cancer; however, an increase in incidence and mortality was observed in some populations. More intensive preventive strategies are recommended for these populations.

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1. Introduction

Globally, cervical cancer is one of the leading causes of cancer morbidity and mortality. In 2018, cervical cancer was the fourth most common cancer, accounting for around 6% of all female cancers [1]. It ranked as the fourth most common cause of cancer deaths, attributable to 8% of all female cancer deaths globally [1]. It is associated with a loss of approximately 9.0 million Disability Adjusted Life Years (DALYs), inducing a substantial public health burden [2–4]. The burden of cervical cancer is significantly higher in developing regions. Its age-standardized incidence has been estimated at 23.8 per 100,000 female population in low-income regions as compared to 8.3 in high-income countries [1]. A similar pattern has also been observed for mortality. The age-standardized mortality was 17.4 per 100,000 female population in low-income countries as compared to 2.5 in high-income countries [1].

The main preventable risk factors for cervical cancer include human papillomavirus (HPV) infection, multiple sex partners, smoking, immunocompromised status (e.g., AIDS), chlamydia infection, long-term use of oral contraceptives, having multiple full-term pregnancies, young age at first full-term pregnancy, low economic status, and low consumption of fruits and vegetables [5]. The risk of cervical cancer is modifiable with public health preventive strategies, especially by HPV vaccination and cervical cancer screening programs [6]. Investigating the updated global disease burden, attributable risk factors, and epidemiological trend of cervical cancer is imperative, as such data would inform resource allocation for disease prevention and treatment in various countries.

However, few studies have reported the most updated global disease burden of cervical cancer and they focused on specific countries, including the United States and the United Kingdom [7,8]. Even though the Global Burden of Disease Study estimated the trend of incidence and mortality by modelling [9], there remains a research gap on its temporal pattern using data from real-world cancer registries. In addition, recent studies have indicated an increasing trend of incidence in early-onset cancers [10,11], but it is unclear whether this finding also applies to cervical cancer and for all countries. Given these research gaps, this study aimed to investigate the updated disease burden, related risk factors, and epidemiologic trends of cervical cancer. We also explored the temporal incidence and mortality trends of cervical cancer among different age groups in various countries.

2. Methods

2.1. Sources of data

The GLOBOCAN database, one of the largest cancer research databases developed by the International Agency for Research on Cancer (IARC, WHO), was accessed to retrieve the incidence and mortality of cervical cancer globally in 2018 [1,12]. The methodology applied to estimate the incidence and mortality of cervical cancer in GLOBOCAN included calculation by incidence-to-mortality ratios, predictions using trend analysis, and approximation from neighboring regions at the same period. The 2018 Human Development Index (HDI) was extracted from the United Nations. Data on the gross domestic products (GDP) per capita were derived from the World Bank. The prevalence of alcohol drinking, smoking, obesity, and hypertension were retrieved from the WHO *Global Health Observatory* (*GHO*) database. For trend analysis, *Cancer Incidence in Five Continents* I-X plus (CI5plus), Nordic Cancer Registries (NORDCAN), and the Surveillance, Epidemiology, and End Results Program (SEER) were used [13–15]. When obtaining the data on mortality rate, besides the NORDCAN and SEER database for regional-specific mortality rate, the World Health Organization Cancer Mortality Database was also used to extract the global mortality estimates [16].

All the cervical cancer incidence and mortality data used in the current study follow the International Classification of Disease and Related Health Problems, 10th Revision codes of cervical cancer: "Malignant neoplasm of cervix uteri" (ICD-10, C53) to ensure the data are correctly identified [17]. To allow meaningful comparison of rates between different countries in terms of incidence, mortality, and prevalence of different risk factors, age-standardization was adopted using the Segi-Doll standard population as reference [18]. Countries were categorized into low HDI (≤0.534), medium HDI >0.534 and ≤ 0.710), high HDI >0.710 and ≤ 0.796), and very high HDI (>0.796) for comparison across groups [19]. Supplementary Table 1 describes the data sources and the corresponding time frame for each country in more detail.

2.2. Statistical analysis procedures

The associations of HDI, GDP, and risk factors with incidence and mortality of cervical cancer were assessed using beta coefficients (β) with corresponding 95% confidence intervals (CI) by multivariable regression analysis. In the study, the β measured the degree of change in the outcome variable (incidence or mortality of cervical cancer) per unit increase in a predictor variable (HDI, GDP, alcohol drinking, smoking, obesity, and hypertension). Joinpoint regression [20] was employed in the current study to obtain the temporal trends of cervical cancer incidence and mortality rates in the past decade, with the ASRs gathered from the previously listed databases. To facilitate the joinpoint regression analysis, the ASRs were transformed with natural logarithm, and the corresponding standard errors (SEs) were calculated with binomial approximation. The transformed ASRs and the associated SEs were then used to calculate the Annual Percentage Change (APC) from the joinpoint regression analysis software that assumes the percentage change rate is a constant rate throughout the time interval (i.e., ten years) [21]. After obtaining the APC, the software divided the entire time interval into a maximum of three segments that were determined by the changepoint value, and attributed a weighting of each segment corresponding to their length in the proportion of the entire time interval. This allowed computation of the Average Annual Percentage Change (AAPC), which is a summary measure of the trend over a prespecified fixed interval and allows using a single number to describe the average APCs over a period of multiple years. As the AAPC takes the weighting and the slope of each segment into consideration, the AAPC was used to determine the extent and direction of the trend, which allows this study to estimate the temporal patterns of incidence and mortality rate of cervical cancer in the past decade. The positivity of AAPC represents the trend is upward sloping, and the associated 95% CI represents whether the trend is statistically significant (the overlapping of 95% CI with zero indicates a nonsignificant trend) [21]. This study analyzed and estimated the epidemiological trends of females aged 0–85, and further analysis on different age groups was also conducted (<50 years and ≥ 50 years). All *p* values ≤0.05 were considered statistically significant.

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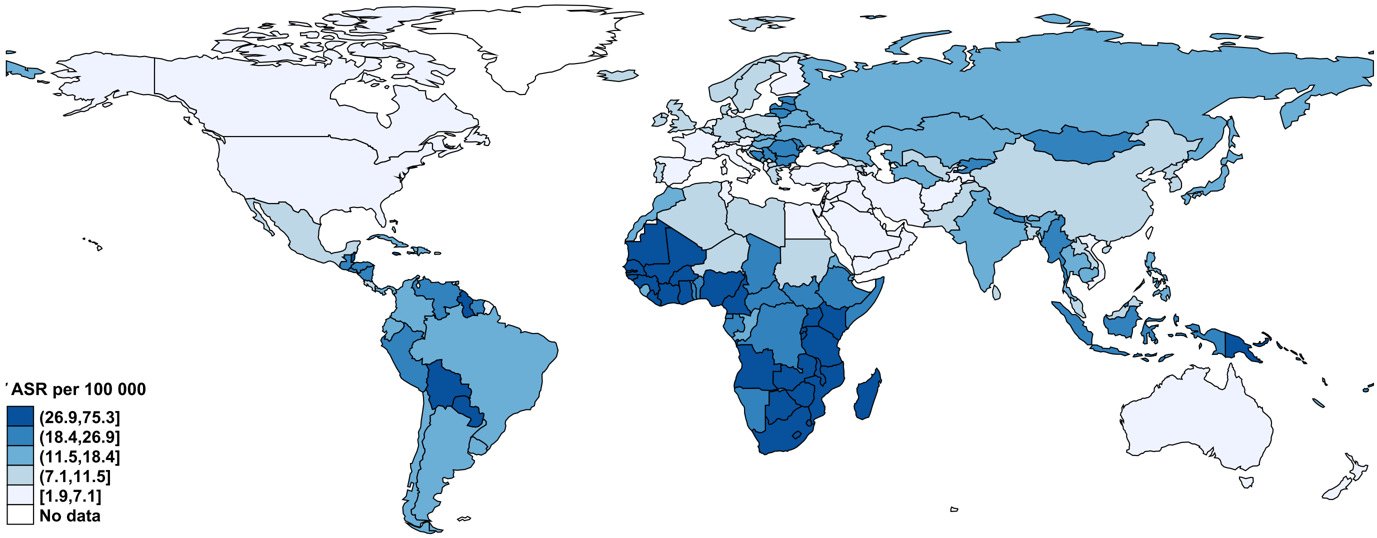

Fig. 1. Global incidence of cervical cancer in females, all ages, in 2018.

3. Results

3.1. Incidence and mortality rate of cervical cancer in 2018

There were 569, 847 newly recorded cases of cervical cancer globally in 2018 (Fig. 1) [22]. The ASR of incidence in the world was 13.1 per 100,000, with Southern Africa having the highest incidence of 43.1, followed by Eastern Africa (ASR = 40.1), Western Africa (ASR = 29.6), Melanesia (ASR = 27.7), and Middle Africa (ASR = 26.8). Considering the geographical distribution, Asia had the greatest number of new cases (315,346 new cases, accounting for 55.3% new cases in 2018), while Africa had the most number of countries with high incidence. The incidence was higher in countries with low HDI (ASR = 29.8) and medium HDI (ASR = 15.6) as compared to countries with very high HDI (ASR = 8.3).

A total of 311,365 deaths were reported to be due to cervical cancer globally in 2018 (Fig. 2). The ASR of mortality in the world was 6.9 per 100,000, with Eastern Africa having the highest mortality of 30.0, followed by Western Africa (ASR = 23.0), Middle Africa (ASR = 21.1), Southern Africa (ASR = 20.0), and Melanesia (ASR = 19.0). Similar to the incidence rate, Asia had the highest number of deaths (168,411 cases, accounting for 54.1% of deaths in 2018), while Africa had the most countries with high mortality. The mortality rate was also higher in countries with low HDI (ASR = 23.0) and medium HDI (ASR = 9.5) as compared to countries with very high HDI (ASR = 2.7).

3.2. Associations of risk factors with incidence and mortality

Countries with higher incidence and mortality of cervical cancer had lower HDI ($\beta = -8.19$, 95% CI -11.32 to −5.06, $p < 0.001$; $\beta = -7.66$, 95% CI -9.82 to −5.50, $p < 0.001$) but higher alcohol consumption ($\beta = 1.89$, 95% CI 0.59 to 3.19, $p = 0.005$; $\beta = 0.98$, 95% CI 0.08 to 1.88, $p = 0.033$) after adjusting for GDP, smoking, obesity, and hypertension (Figs. 3, 4).

3.3. Temporal trends of cervical cancer

The incidence and mortality trends of cervical for each country between 1980 and 2018 are shown in Supplementary Fig. 1**.** The results of joinpoint regression analysis are presented in Supplementary Fig. 2.

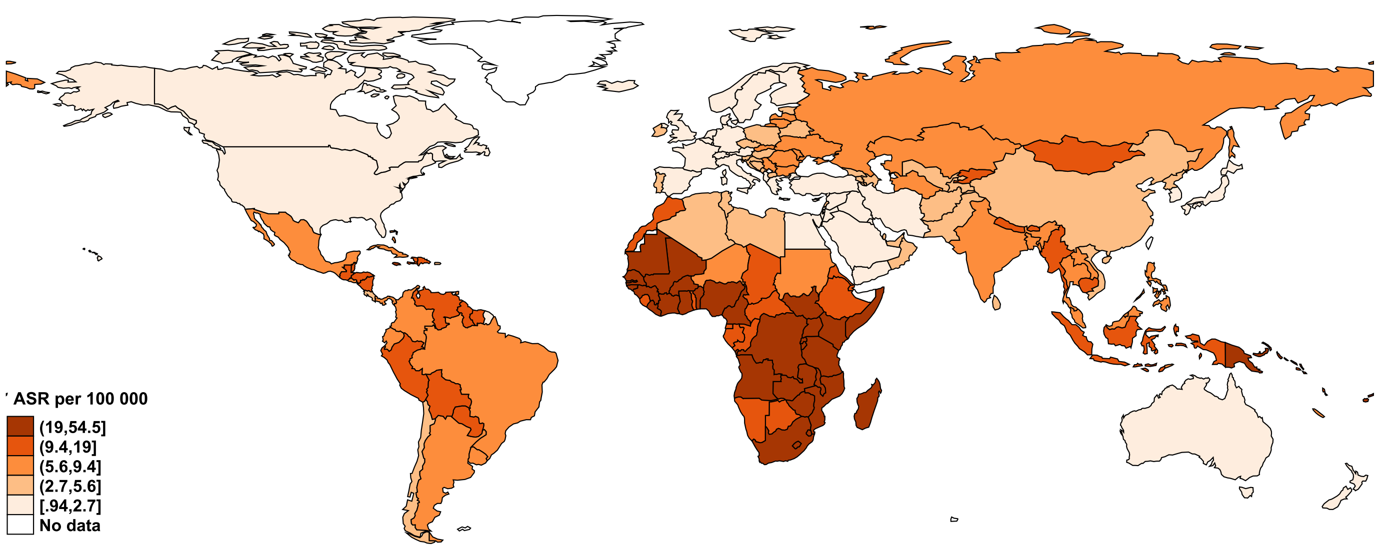

Fig. 2. Global mortality of cervical cancer in females, all ages, in 2018.

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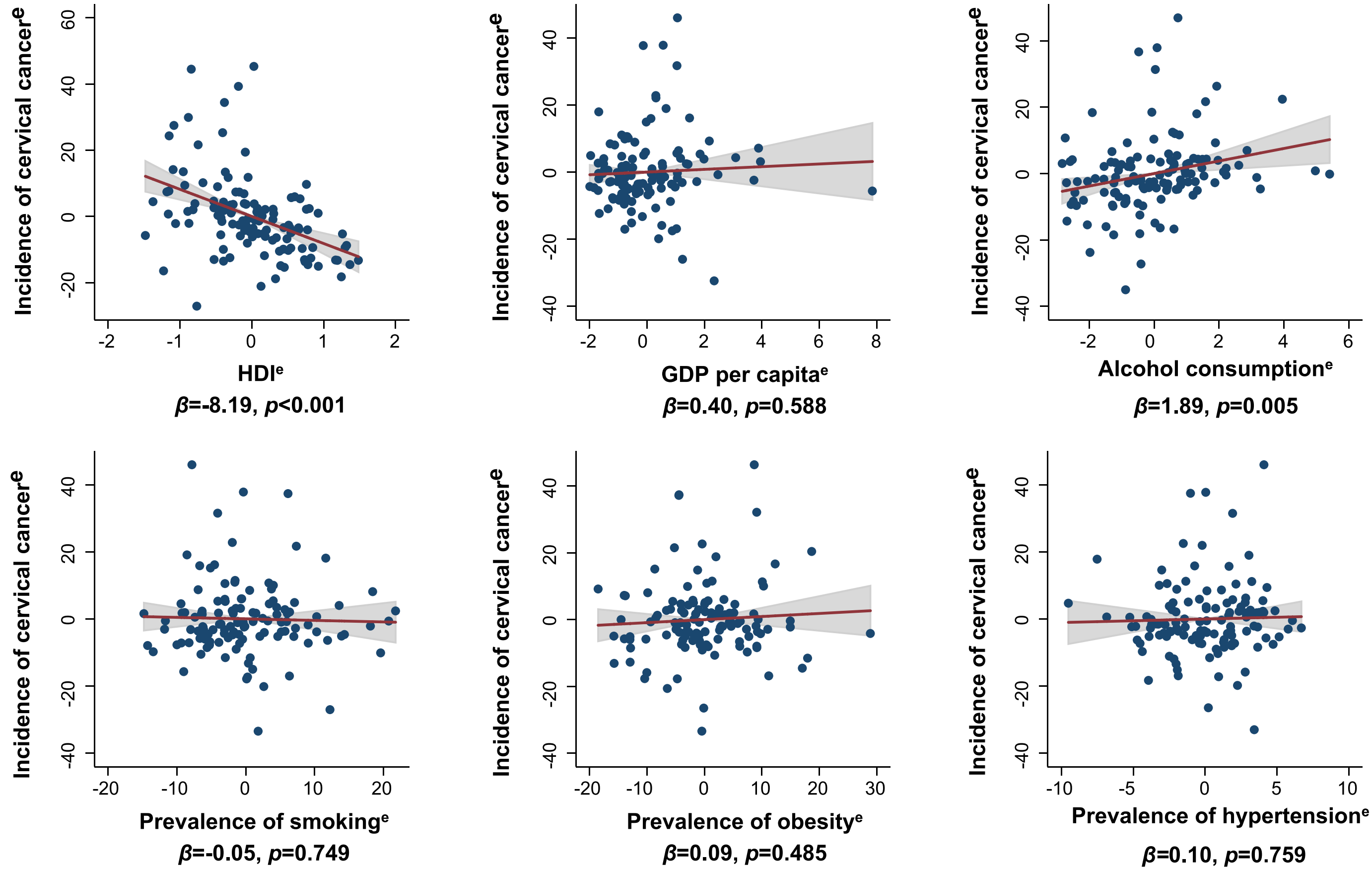

Fig. 3. Associations between risk factors and incidence of cervical cancer.

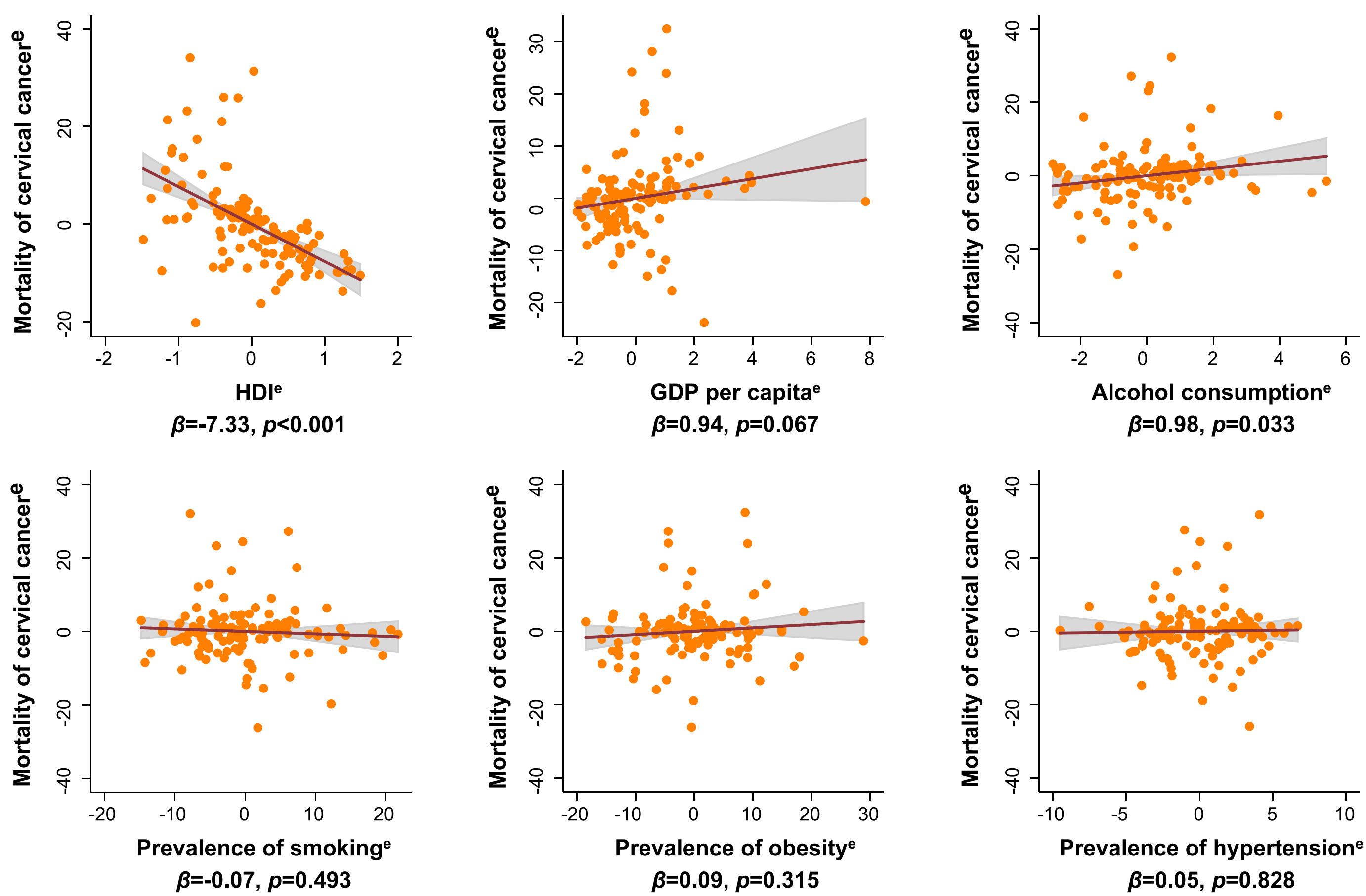

Fig. 4. Associations between risk factors and mortality of cervical cancer.

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3.4. Incidence trends of cervical cancer in females, all ages

Ten countries showed a significant increase in the incidence of AAPC (Fig. 5). Among these countries, Japan had the highest AAPC (AAPC = 3.35, 95% CI 1.43 to 5.30, $p = 0.001$) followed by Ireland (AAPC = 3.18, 95% CI 0.20 to 6.24, $p = 0.039$), and Sweden (AAPC = 2.88, 95% CI 0.97 to 4.83, $p = 0.008$). China, Australia, Finland, Norway, the United Kingdom (UK), Belarus, and the Netherlands also had significantly positive AAPC of incidence. In contrast, there were 15 countries with a negative AAPC of incidence: Bahrain (AAPC = -8.65, 95% CI -14.16 to −2.79, $p = 0.010$), Brazil (AAPC = -8.55, 95% CI -13.06 to −3.80, p = 0.001) and Kuwait (AAPC = -8.15, 95% CI 14.81 to −0.97, $p = 0.031$) had the greatest reductions in cervical cancer incidence.

3.5. Mortality trends of cervical cancer in females, all ages

Four countries demonstrated a significant increase in mortality rates, namely the Philippines (AAPC = 5.44, 95% CI 3.93, 6.97, $p < 0.001$), Italy (AAPC = 1.47, 95% CI 0.03, 2.93, $p = 0.046$), Japan (AAPC = 1.23, 95% CI 0.34, 2.13, $p = 0.013$), and the Russia Federation (AAPC = 0.73, 95% CI 0.35, 1.10, $p = 0.002$) (Fig. 5). On the other hand, 12 countries showed a significant decrease in mortality rates, with Kuwait having the largest reduction (AAPC = -9.25, 95% CI -16.23, −1.69, $p = 0.023$), followed by Korea (AAPC = -3.91, 95% CI -5.16, −2.65, $p < 0.001$), Chile (AAPC = -3.84, 95% CI -5.25, −2.41, p < 0.001), Switzerland (AAPC = -3.77, 95% CI -6.48, −0.98, $p = 0.015$), and Singapore (AAPC = -3.69, 95% CI -5.95, −1.38, $p = 0.006$). Poland, Colombia, Austria, the UK, Australia, Brazil, and the United States had declining mortality trends as well.

3.6. Incidence trends of cervical cancer in females aged ≥50

Most of the countries had a decreasing incidence trend and only a few countries had an increasing trend (Fig. 6). Among those with increasing trend, only four countries had a statistically significant increase and included Estonia (AAPC = 4.71, 95% CI 2.74, 6.71, $p = 0.001$), Slovakia (AAPC = 2.63, 95% CI 0.56, 4.74, $p = 0.019$), Japan (AAPC = 2.57, 95% CI 1.21, 3.94, $p = 0.002$), and Bulgaria (AAPC = 1.60, 95% CI 0.31, 2.90, $p = 0.021$). For the countries with decreasing incidence rates, Brazil (AAPC -11.08, 95% CI -17.62, −4.01, $p = 0.003$), Chile (AAPC = -9.13, 95% CI -17.02, −0.50, $p = 0.041$) and Colombia (AAPC = -6.48, 95% CI -8.59, −4.33, $p < 0.001$) demonstrated the greatest incidence reductions.

3.7. Incidence trends of cervical cancer in females aged < 50

Ten countries had significantly positive AAPC, with Cyprus (AAPC = 6.96, 95% CI 2.06, 12.11, $p = 0.011$), Sweden (AAPC = 4.88, 95% CI 2.43, 7.38, p = 0.002), and Norway (AAPC = 3.80, 95% CI 1.22, 6.46, $p = 0.009$) having the highest increase in incidence rates (Fig. 6). Other countries that shared a similar increasing trend were Japan, China, Ireland, the UK, the Netherlands, Belarus, and Australia. On the contrary, ten countries had a decreasing trend. Slovenia (AAPC = -8.78, 95% CI -10.95, −6.55, p < 0.001), Poland (AAPC = -6.42, 95% CI -10.32, −2.36, $p = 0.007$), and Thailand (AAPC = -6.21, 95% CI -9.15, −3.18, p = 0.002) were the three countries with the greatest decline in incidence, followed by India, Colombia, the Philippines, France, Austria, Korea, and Israel.

4. Discussion

4.1. Summary of study findings

This study reported the most up-to-date global incidence and mortality rates for cervical cancer, their associated risk factors, and temporal trends by age and countries/regions. We found that the burden of cervical cancer was highest in regions with low HDI and was associated with a higher prevalence of alcohol consumption. Although there was an

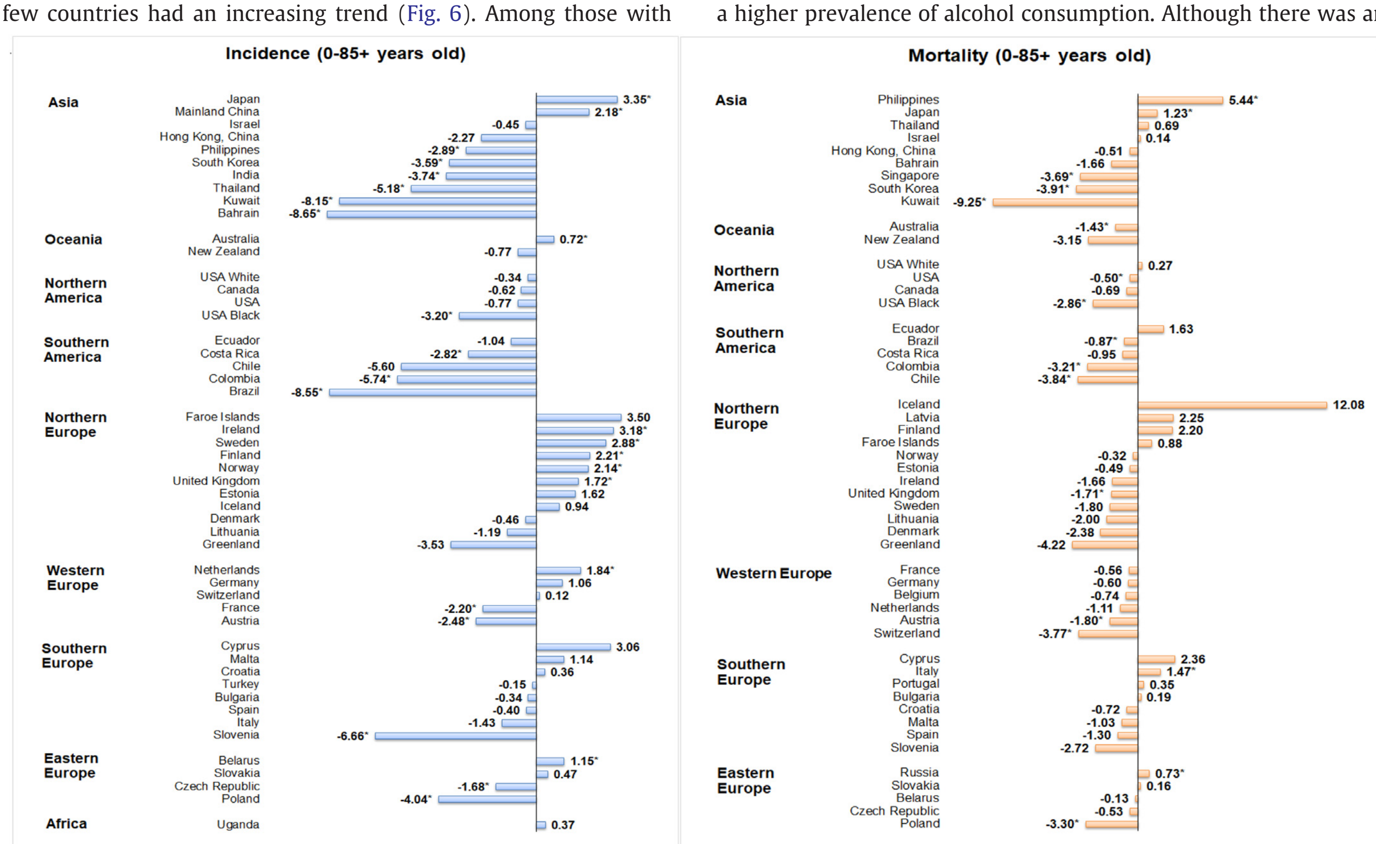

Fig. 5. Incidence and mortality AAPCs of cervical cancer in females, all ages.

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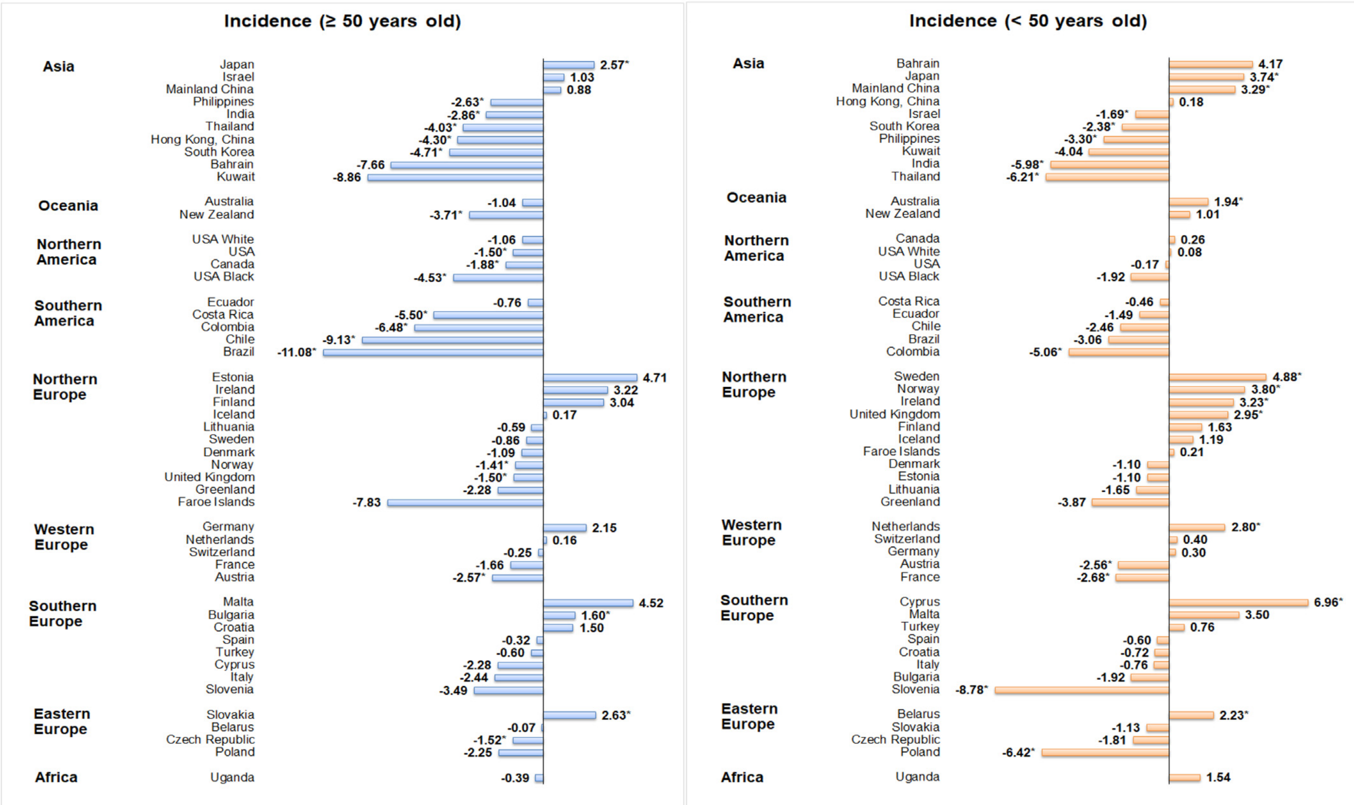

Fig. 6. Incidence AAPCs of cervical cancer in females ≥50 and < 50 years old.

overall decreasing trend of cervical cancer mortality in the recent past decade, an increase in incidence was observed in North Europe and younger females.

4.2. Explanation of findings and comparison with previous literature

We found that lower HDI was associated with higher incidence and mortality of cervical cancer, which is consistent with previous studies. A study based on the 2008 GLOBOCAN database showed that for every 0.2 unit increase in HDI, the risk of cervical cancer incidence decreased by 20%, and the risk of cervical cancer mortality also declined by 33% [23]. The higher burden of cervical cancer in lower HDI countries could be attributable to the higher prevalence of HPV infection, and the lower coverage rate of HPV vaccination and cervical cancer screening in these countries [24]. Studies have shown that the prevalence of HPV, especially for the high-risk HPV-16 and 18, were generally higher in developing regions than in developed regions [24]. The higher uptake rate of HPV vaccination may play a larger role in the lower prevalence of HPV infection in more affluent countries [25]. As for the coverage of cervical cancer screening, a global analysis of 57 countries found that 63% and 19% of females participated in cervical cancer screening in high-income and low-income countries, respectively [26]. The lower screening coverage likely resulted in higher rates of late-stage cancer diagnosis, and hence higher mortality of cervical cancer in lower-income countries, explaining in part the observed higher mortality in countries with low HDI.

The burden of cervical cancer was also found to be positively associated with the total amount of alcohol consumption. These associations could be explained by the carcinogenic effect of alcohol and the behavior of drinkers after alcohol intake. Studies have shown that heavy alcohol use was a risk factor for cervical cancer [27–29]. The primary metabolite of ethanol, acetaldehyde, and oxidative stress associated with alcohol could result in DNA methylation which could, in turn, increase the risk of cervical cancer [30]. Alcohol use is also associated with risky behaviors, decreased health awareness, and low adherence to health advice and/or utilization of preventive health services (e.g., condom use, and screening and vaccination) [29]. There is also a significant impact of social inequality on the control of alcohol consumption and cervical cancer [31]. In most countries, people who have a low socioeconomic status have a higher risk of mortality for cervical cancer than do more advantaged population groups. The alcohol consumption is often higher in groups with low socioeconomic status; the social gradient also depends on economic development, cultural factors, and social and health policies for individual countries [32]. People with low socioeconomic status also have worse access to screening, vaccination, and timely diagnosis and treatment for cervical cancer. Reduction of alcohol consumption in disadvantaged groups is necessary to achieve substantial decreases in the burden of cervical cancer.

In addition, we found an overall decreasing trend in incidence and mortality of cervical cancer for the recent past decade. Previous studies have also identified similar decreasing trends in the burden of cervical cancer [9] [33]. The widespread implementation of HPV vaccination and increasing coverage of screening may be the major drivers for these trends. By 2020, 55% of all countries worldwide had introduced HPV vaccination, with an overall rate of vaccine uptake at around 15% [34]. The currently approved HPV vaccines provide >70% protection against all cervical cancers. However, most low- and middle-income countries have very limited access to HPV vaccination due to logistic reasons [34]. Furthermore, there has been increasing use of cervical cancer screening globally [26]. For instance, the Thailand government initiated a systematic screening program of cervical cancer for all Thai females aged 35–60 years from 2002. This may explain in part the decline in incidence of cervical cancer between 2000 and 2010, with an APC of −4.7% [35]. A study conducted in Brazil found a significant declining trend in cervical cancer mortality from 2003 to 2012 (APC = -0.17, $p < 0.001$), and the adoption of screening was believed to be one of the main reasons for the reduction [36].

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Notably, we found an increasing trend of cervical cancer in Northern European countries, especially among younger females. While the reasons for this phenomenon remain unknown, several factors may play a role. For example, the participation rate of cervical cancer screening among younger females is suboptimal in these countries. Although the overall coverage rate of cervical cancer screening was relatively high in Ireland (74.7%), Finland (66.8%), and Norway (66.5%) [37,38], the uptake rate was only 20% for females aged 25–30 years [39]. Another study also indicated that the increase in incidence among younger females in the UK may be associated with decreased screening activity [40]. Secondly, the increasing prevalence HPV infection in these countries may explain in partthe rising incidence. For example, data from the HPV Information Centre, which provides global data, suggest that the prevalence of HPV16 and/or 18 among females with cervical cancer in Ireland, Sweden, Finland, Norway, and the UK (74.2%, 70.5%, 88.5%, 78.2%, and 79.0%, respectively) were higher than the estimated global prevalence in 2019 (69.4%) [37]. In addition, the HPV prevalence in females with normal cervical cytology was significantly higher in younger females (≤44 years) than in subjects aged >44 years globally [37]. The increasing HPV prevalence may be related to advancement of age at first sexual activity, increased number of lifetime sexual partners, and more permissive sexual attitudes in the younger population [41,42]. Thirdly, the improvement in techniques of cervical cancer screening tools may have an effect. A study conducted in Norway indicated that the main reason for the increased incidence of precancerous lesions from 1992 to 2016 (particularly in females aged <50 years) was the changes in screening tools [42]. The primary screening test has gradually changed from conventional cytology to liquid-based cytology or HPV test, which were more sensitive than the traditional methods [42]. In addition, a study from Sweden suggested the increasing incidence trends may be due to the increasing number of immigrants from countries with limited cervical cancer screening and HPV vaccination [43]. From 2012 to 2015, nearly 450,000 people immigrated to Sweden. Since female immigrants were enrolled in the Swedish cervical cancer screening programme, the increased immigration could have contributed to the rise in its incidence. Although estimates indicate that the most prominent dialogue focuses on migration from low-income and middle-income countries (LMICs) to high-income countries (HICs), the majority of global migration occurs within LMICs, which may also have an impact on the incidence of cervical cancer. For instance, migrant female sex workers in Benin, Ethiopia, and Kenya are at greater risk of HIV than non-migrant sex workers and higher risk of HPV infection and cervical cancer [44].

There is an important role of social and health policies in the control of cervical cancer and its risk factors by a relatively complete public health and medical system for the primary prevention [45]. Primary prevention is a particularly effective way to fight cervical cancer as a substantial proportion of cervical cancer burden is preventable by modifying risk factors. The avoidance of exposure to alcohol and smoking is also likely to prevent other cancers and non-communicable diseases. As the preventive effort does not need to be renewed with every generation, it is especially important in low-income countries with limited resources. Therefore, primary prevention should be prioritised as an integral part of cancer control.

4.3. Strengths and limitations

The current study reported the most up-to-date global incidence and mortality of cervical cancer, their associated risk factors, and temporal trends by age and countries/regions based on cancer registries of high quality. Nevertheless, some limitations need to be acknowledged. First, data on incidence and mortality might be underreported in low-income countries/regions, as the cancer registries are less well-established. Secondly, the prevalence of HPV infection, coverage of HPV vaccination, cervical cancer screening, and health insurance coverage were not accounted for in the analysis of risk factors. Thirdly, the study could not examine the temporal trends in different subtypes of cervical cancer (squamous cell carcinomas and adenocarcinomas). As the risk factors for different subtype of cervical could be different, the results bear important implications for the prevention of cervical cancer.

5. Conclusions

In summary, findings of this study demonstrated that, incidence and mortality of cervical cancer have been declining globally, likely due to the introduction and widespread implementation of HPV vaccination and increasing coverage of screening on a global scale. However, an increasing incidence trend of cervical cancer was observed in North European countries and among younger females. More intensive preventive strategies are recommended for these populations, and further studies are needed to explore the reasons underlying these epidemiological transitions. Also, the burden of cervical cancer was highest in countries with low HDI and was associated with a higher prevalence of alcohol consumption. Efforts to reduce the prevalence of high-risk HPV infection and alcohol consumption, increase the coverage of HPV vaccination, and promote cervical cancer screening and health insurance coverage especially among populations in low and middle-income countries may be beneficial for further reducing the burden of cervical cancer.

Author contribution

MCSW and JH participated in the conception of the research ideas, study design, interpretation of the findings, and writing of the first draft of the manuscript. JH, YD, and MST, and VL retrieved information from the relevant databases and performed statistical analysis; DB, LZ, DELP, WX, ZJZ, EE, and MW made critical revisions on the manuscripts and provided expert opinions on implications of the study findings.

Declaration of Competing Interest

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ygyno.2021.11.005.

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