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Bladder Cancer

Global Trends of Bladder Cancer Incidence and Mortality, and Their Associations with Tobacco Use and Gross Domestic Product Per Capita

Jeremy Yuen-Chun Teoh[a], *Junjie Huang*[b], *Wendy Yuet-Kiu Ko*[b], *Veeleah Lok*[b], *Peter Choi*[b], *Chi-Fai Ng*[a], *Shomik Sengupta*[c], *Hugh Mostafid*[d], *Ashish M. Kamat*[e], *Peter C. Black*[f], *Shahrokh Shariat*[g,h,i,j,k,l], *Marek Babjuk*[g,j], *Martin Chi-Sang Wong*[b,*]

[a] *S.H. Ho Urology Centre, Department of Surgery, The Chinese University of Hong Kong, Hong Kong SAR, China;* [b] *JC School of Public Health and Primary Care, Faculty of Medicine, The Chinese University of Hong Kong, Hong Kong SAR, China;* [c] *Eastern Health and Monash University Eastern Health Clinical School, Box Hill, VIC, Australia;* [d] *Department of Urology, Royal Surrey County Hospital, Guildford, Surrey, UK;* [e] *The University of Texas MD Anderson Cancer Center, Houston, TX, USA;* [f] *Department of Urologic Sciences, University of British Columbia, Vancouver, BC, Canada;* [g] *Department of Urology, Comprehensive Cancer Center, Medical University of Vienna, Vienna, Austria;* [h] *Departments of Urology, Weill Cornell Medical College, New York, NY, USA;* [i] *Department of Urology, University of Texas Southwestern, Dallas, TX, USA;* [j] *Department of Urology, Second Faculty of Medicine and Hospital Motol, Charles University, Prague, Czech Republic;* [k] *Institute for Urology and Reproductive Health, I.M. Sechenov First Moscow State Medical University, Moscow, Russia;* [l] *Division of Urology, Department of Special Surgery, Jordan University Hospital, The University of Jordan, Amman, Jordan*

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Abstract

Background: Bladder cancer is a major urological disease, with approximately 550 000 new cases diagnosed in 2018.
Objective: We examined gender-specific incidence and mortality patterns, and trends of bladder cancer from a global perspective. We further investigated their associations with tobacco use and gross domestic product (GDP) per capita.
Design, setting, and participants: We retrieved data on the incidence and mortality of bladder cancer from the GLOBOCAN database, Cancer Incidence in Five Continents, and the WHO mortality database. Data on the rate of tobacco use were retrieved from the WHO Global Health Observatory. Data on GDP per capita was retrieved from the United Nations Human Development Report.
Outcome measurements and statistical analysis: We performed two sets of analyses. The first set of analysis is based on bladder cancer incidence and mortality data in 2018. The gender-specific age-standardised rates (ASRs) of incidence and mortality, and their correlations with the rate of tobacco use and GDP per capita were investigated. A multivariable linear regression analysis was also performed. In the second set of analysis, we examined the 10-yr temporal trends of bladder cancer incidence and mortality by average annual percent change using joinpoint regression analysis. A further exploratory analysis on GDP per capita in countries with decreasing trends of tobacco use was also performed.
Results and limitations: Wide variations in bladder cancer incidence and mortality were observed globally. There were positive correlations between the rate of tobacco use and the ASRs of bladder cancer incidence ($r = 0.20$) and mortality ($r = 0.38$) in men, and between the rate of tobacco use and the ASRs of bladder cancer incidence ($r = 0.67$) and mortality ($r = 0.22$) in women. There were positive correlations between GDP per capita,

* Corresponding author. 4/F, School of Public Health and Primary Care, Prince of Wales Hospital, Shatin, Hong Kong SAR, China. Tel. +852 2252 8782; Fax: +852 2606 3500.
E-mail address: wong_martin@cuhk.edu.hk (M.-S. Wong).

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and the ASRs of bladder cancer incidence in men ($r = 0.48$) and women ($r = 0.44$). There was a weak positive correlation between GDP per capita and bladder cancer mortality in men ($r = 0.19$), but no correlation with bladder cancer mortality in women ($r = 0.06$). Upon multivariable linear regression analysis, tobacco use was significantly associated with bladder cancer incidence and mortality in men, and bladder cancer incidence in women. Regarding the 10-yr temporal trends of bladder cancer, Europe has an increasing incidence but decreasing mortality, and Asia has a decreasing incidence but increasing male mortality. Among countries with decreasing trends of tobacco use, the mean GDP per capita was higher in countries with decreasing trends of bladder cancer mortality than in those with increasing trends of bladder cancer mortality. A major limitation of the study is that cancer incidence might be underdetected and under-reported in less developed nations.

Conclusions: There were observable trends of bladder cancer incidence and mortality globally. Tobacco use was significantly associated with both bladder cancer incidence and mortality. A certain level of economic capacity might be needed to further reduce bladder cancer mortality in countries with a decreasing trend of tobacco use.

Patient summary: There are different trends of bladder cancer incidence and mortality globally. Smoking is significantly associated with the incidence and mortality of bladder cancer. A higher financial capacity may be needed to further improve the disease outcomes.

1. Introduction

Bladder cancer is the 11th most common cancer worldwide, with approximately 550 000 new cases being diagnosed every year [1]. Tobacco contains a rich source of carcinogenic compounds, and it is the most important risk factor for bladder cancer, with an attributable risk of about 50% [2]. Tobacco use may also affect the progression of bladder cancer and has important implications on bladder cancer mortality [2,3]. Early access and adequate provision of health care services are crucial for early bladder cancer detection and better oncological control in the long run. To a large extent, this depends on the financial capacity of the affected individual and the nature of health care system of the country in which he/she resides.

Previously, Antoni et al. [4] conducted a review on the incidence and mortality trend of bladder cancer using figures from the GLOBOCAN database (2012), Cancer Incidence in Five Continents (up to 2007), and the WHO mortality database (up to 2012). Cumberbatch et al. [5] further published a comprehensive systematic review on the epidemiology and risk factors of bladder cancer. In recent years, the gender-specific figures on the global incidence and mortality of bladder cancer have been updated [1,6,7].

In this article, we investigated the associations of tobacco use and gross domestic product (GDP) per capita, with bladder cancer incidence and mortality. Tobacco use is a major risk factor of bladder cancer, and GDP per capita is an index reflecting a country's economic capacity to manage bladder cancer. Bladder cancer incidence and mortality data in 2018, as well as the temporal trends in the last available 10 yr were used as the outcomes of interest. We believe that the results may provide valuable insight into how we can manage bladder cancer from a public health and global perspective.

2. Patients and methods

We performed two sets of analyses in this study. The first set of analysis was based on bladder cancer incidence and mortality data in 2018. The second set of analysis was based on the 10-yr temporal trends of bladder cancer incidence and mortality.

2.1. Source of data

2.1.1. Analysis based on bladder cancer incidence and mortality data in 2018

Data on bladder cancer incidence and mortality pattern were retrieved from the GLOBOCAN database (2018) [1]. Gender-specific age-standardised rate (ASR) per 100 000 was used for both incidence and mortality figures. We also used the GLOBOCAN data to examine the correlations with tobacco use and GDP per capita. Data on the rates of tobacco use in 2010 in each country were retrieved from the WHO Global Health Observatory [8]. Data on GDP per capita in 2018 for each country was retrieved from the United Nations Human Development Report [9].

2.1.2. Ten-year time trend analysis on bladder cancer incidence and mortality

A time trend analysis on bladder cancer incidence and mortality was performed using the incidence/mortality figures of the past 10 yr from the Cancer Incidence in Five Continents (up to 2012) and the WHO mortality database (up to 2016). These databases captured the incidence and mortality data in approximately 65 and 140 countries or regions, respectively.

We also performed an exploratory analysis on GDP per capita in countries with decreasing trends of tobacco use. The trends of tobacco use in each country were determined using data from the WHO Global Health Observatory (2000 and 2010) [8]. GDP per capita in 2018 for each country was retrieved from the United Nations Human Development Report [9].

2.2. Data synthesis and statistical analysis

2.2.1. Analysis based on bladder cancer incidence and mortality data in 2018

We first generated the heat maps on age-standardised incidence and mortality rates from the WHO website to provide our readers an overall

picture of bladder cancer incidence and mortality globally [10]. The overall correlations between the ASRs of bladder cancer incidence and mortality, and tobacco use and the GDP per capita, stratified by sex, were examined using Pearson correlation coefficients (*r*). A multivariable linear regression analysis was performed to investigate whether tobacco use and GDP per capita were significant factors associated with bladder cancer incidence and mortality. Interactions between tobacco use and GDP per capita were also tested in the regression analysis.

2.2.2. Ten-year time trend analysis on bladder cancer incidence and mortality

Temporal trends of bladder cancer incidence and mortality were plotted. A joinpoint regression analysis was used to analyse the incidence and mortality trends and to identify the time point at which the trend significantly changes [11]. Logarithmic transformation of age-standardised incidence and mortality rates was performed, and standard errors were computed using binomial approximation. A maximum of three joinpoints were used as analysis options, and the average annual percent

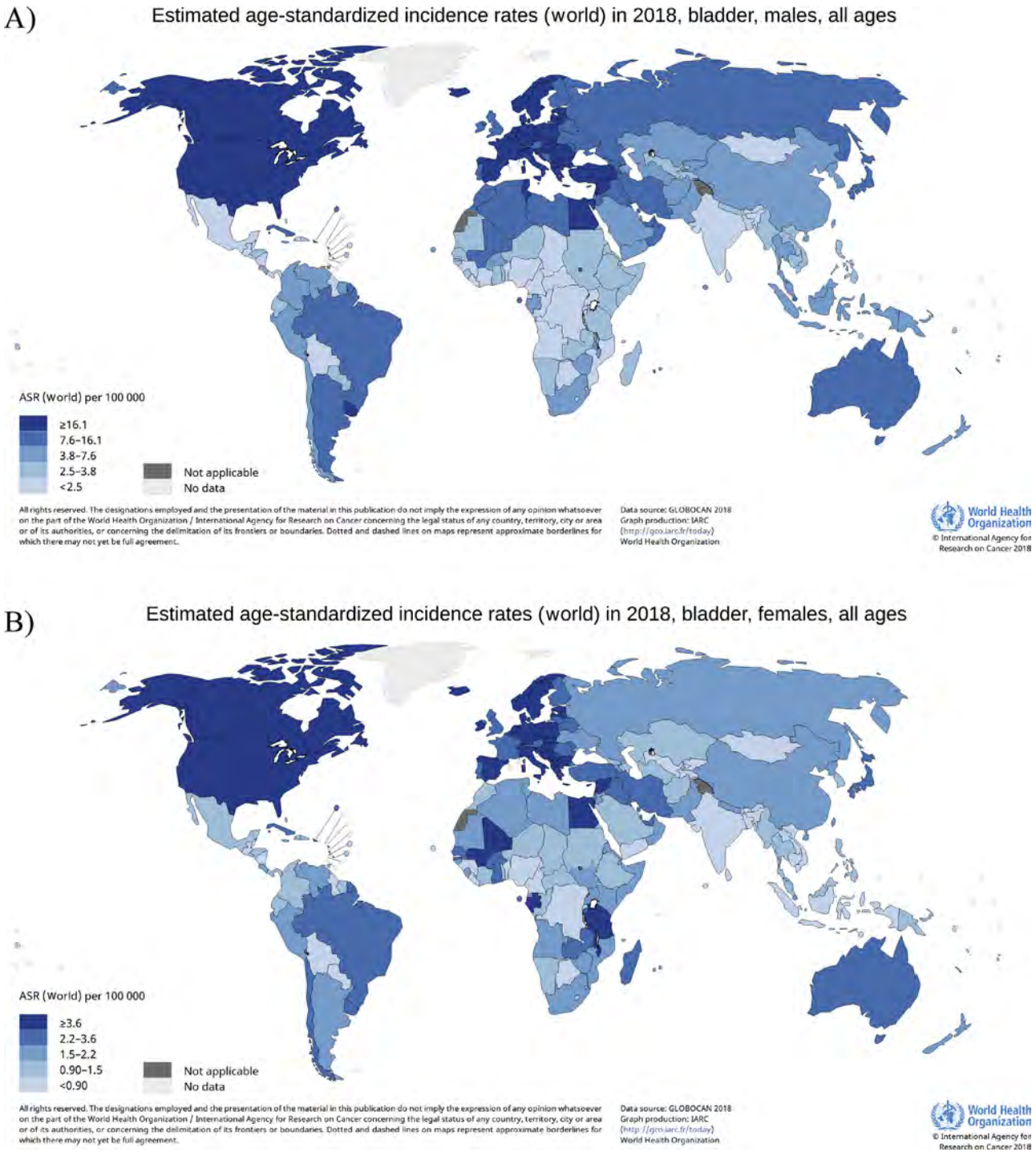

Fig. 1 – Estimated age-standardised incidence rates for (A) men and (B) women in 2018. ASR = age-standardised rate.

change (AAPC) was estimated. The AAPC was computed as a geometrically weighted average, with the weights being equivalent to the length of each segment within the specified time interval [12]. AAPCs with a 95% confidence interval (CI) of > 0 was considered a significantly increasing trend. Likewise, AAPCs with a 95% CI of < 0 was considered a significant decreasing trend [13–15]. This methodology has widely been used to examine the incidence and mortality trends of various types of cancers [4,5,13,16–20].

We further performed an exploratory analysis in countries with decreasing trends of tobacco use. Countries with a lower rate of tobacco use in 2010 than those in 2000 were considered to have a decreasing trend of tobacco use. We divided the countries with a decreasing trend of tobacco use into two groups: group 1 included countries with decreasing bladder cancer incidence/mortality and group 2 included countries with increasing bladder cancer incidence/mortality. The mean GDP per capita between the two groups

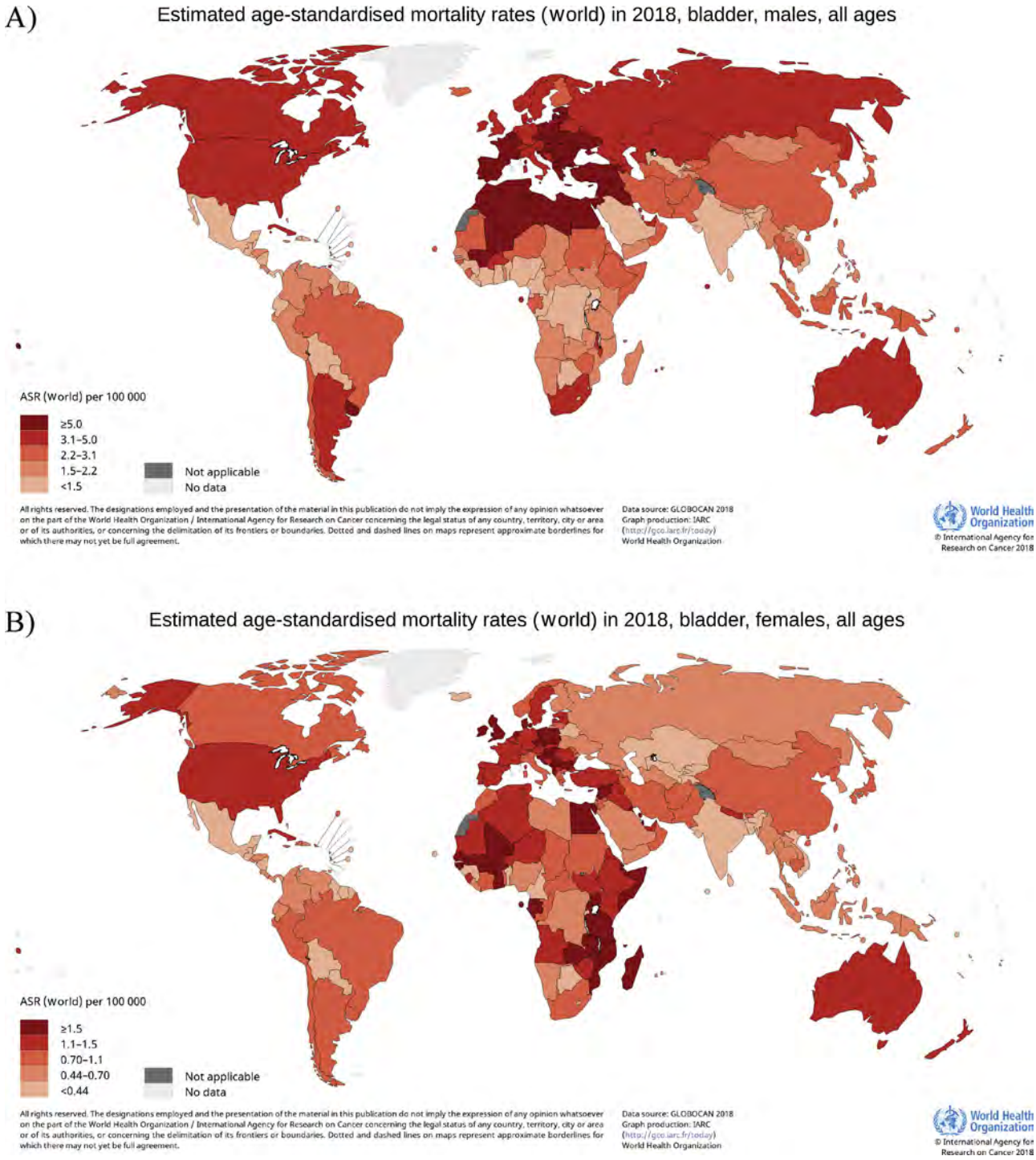

Fig. 2 – Estimated age-standardised mortality rates for (A) men and (B) women in 2018. ASR = age-standardised rate.

was compared using the Mann-Whitney *U* test. A *p* value of <0.05 was considered statistically significant.

3. Results

3.1. Analysis based on bladder cancer incidence and mortality data in 2018

3.1.1. Age-standardised incidence and mortality rates of bladder cancer in 2018

There were a total of 549 393 new cases of bladder cancer and 199 922 cases of bladder cancer–related deaths in 2018. For the male population, a wide variation was observed in the ASRs of bladder cancer incidence, ranging from 1.3 per 100 000 in middle Africa to 26.5 per 100 000 in Southern Europe; for the female population, the variation of ASRs in bladder cancer incidence was less prominent, ranging from 0.8 per 100 000 in South Central Asia to 5.5 per 100 000 in Southern Europe. The ASRs of bladder cancer mortality were 3.2 per 100 000 for the male population and 0.9 per 100 000 for the female population.

The heat maps for the ASRs of bladder cancer incidence and mortality are shown in Figures 1 and 2, respectively. The detailed figures are summarised in the Supplementary material.

3.1.2. Correlations between the incidence/mortality of bladder cancer and tobacco use in men and women

For men, there were positive correlations between tobacco use and bladder cancer incidence ($r = 0.20$) and between tobacco use and mortality ($r = 0.38$). For women, there was a strong positive correlation between tobacco use and bladder cancer incidence ($r = 0.67$), and a weak positive correlation between tobacco use and bladder cancer mortality ($r = 0.22$; Fig. 3).

3.1.3. Correlations between the incidence/mortality of bladder cancer and GDP per capita in men and women

There were moderate positive correlations between GDP per capita and bladder cancer incidence in men ($r = 0.48$) and women ($r = 0.44$). There was a weak positive correlation between GDP per capita and bladder cancer

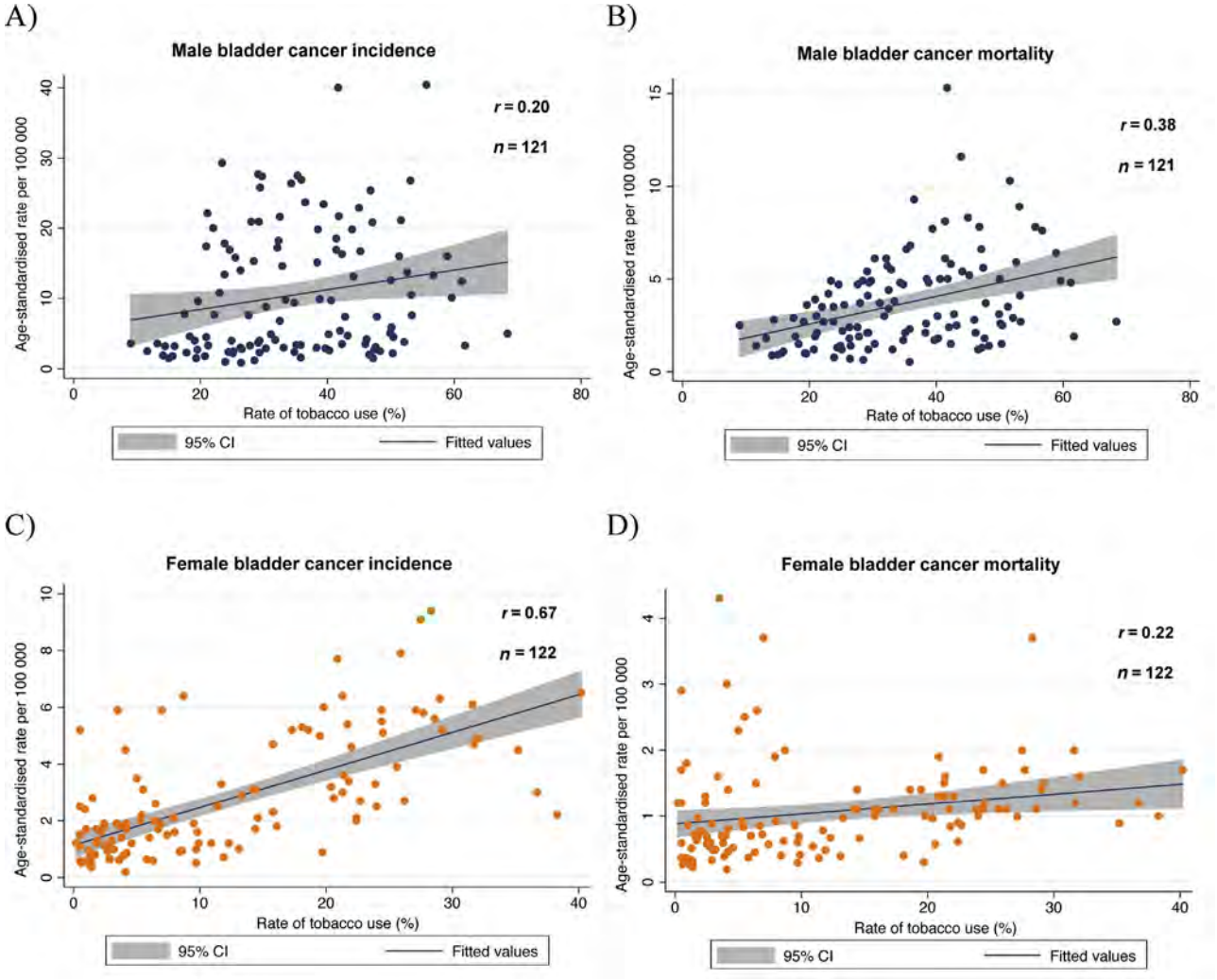

Fig. 3 – Correlations between the rate of tobacco use and (A) bladder cancer incidence in men, (B) bladder cancer mortality in men, (C) bladder cancer incidence in women, and (D) bladder cancer mortality in women. 95% CI = 95% confidence interval.

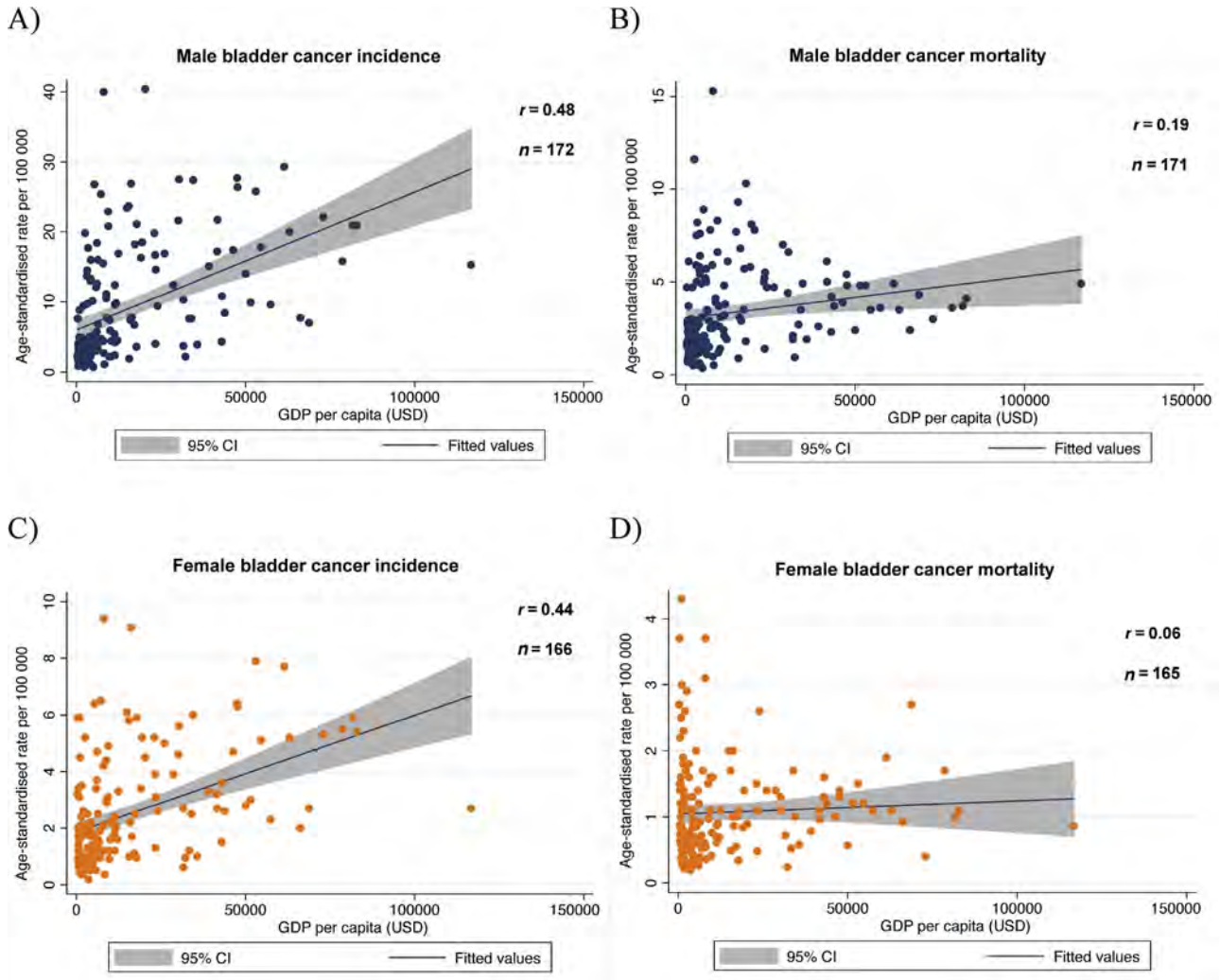

Fig. 4 – Correlations between GDP per capita and (A) bladder cancer incidence in men, (B) bladder cancer mortality in men, (C) bladder cancer incidence in women, and (D) bladder cancer mortality in women. 95% CI = 95% confidence interval; GDP = gross domestic product.

mortality in men ($r = 0.19$), but no correlation between GDP per capita and bladder cancer mortality in women ($r = 0.06$; Fig. 4).

3.1.4. *Multivariable linear regression analysis on bladder cancer incidence and mortality*

Upon multivariable linear regression analysis (Table 1), tobacco use was a significant factor associated with bladder cancer incidence in men (coefficient 0.152, 95% CI 0.017–0.286, $p = 0.027$) and women (coefficient 0.116, 95% CI 0.078–0.154, $p < 0.001$). Tobacco use was associated with bladder cancer mortality in men (coefficient 0.067, 95% CI 0.025–0.108, $p = 0.002$), but not associated with bladder cancer mortality in women (coefficient 0.015, 95% CI–0.003 to 0.033, $p = 0.095$). GDP per capita was not associated with bladder cancer incidence and mortality in both men and women. No significant interactions between tobacco use and GDP per capita were noted in all regression analyses.

3.2. *Ten-year time trend analysis on bladder cancer incidence and mortality*

3.2.1. *Incidence and mortality trends of bladder cancer from a global perspective*

Among men, there were decreasing trends of bladder cancer incidence in countries from Asia, Oceania, North America, and South America (Fig. 5). On the contrary, there was an increasing trend of bladder cancer incidence in European countries. Of note, among the five countries with significant increases in bladder cancer incidence worldwide, four were European countries. Among females, there were also decreasing trends of bladder cancer incidence in countries from Asia, Oceania, North America, and South America (Fig. 6). In contrast, there were increasing trends of bladder cancer incidence in women in European countries. There were a total of 10 countries with significant increases in bladder cancer in women worldwide, and nine of them were from Europe.

Table 1 – Multivariable linear regression analysis on bladder cancer incidence and mortality in men and women

	Coefficient	95% CI		*p* value
		Lower	Upper	
Male bladder cancer incidence				
Tobacco use	0.152	0.017	0.286	0.027
GDP per capita	−0.001	−0.001	0.001	1.0
Tobacco use × GDP per capita	0.001	−0.001	0.001	0.064
Male bladder cancer mortality				
Tobacco use	0.067	0.025	0.108	0.002
GDP per capita	−0.001	−0.001	0.001	0.5
Tobacco use × GDP per capita	0.001	−0.001	0.001	0.14
Female bladder cancer incidence				
Tobacco use	0.116	0.078	0.154	<0.001
GDP per capita	0.001	−0.001	0.001	0.5
Tobacco use × GDP per capita	0.001	−0.001	0.001	0.9
Female bladder cancer mortality				
Tobacco use	0.015	−0.003	0.033	0.095
GDP per capita	−0.001	−0.001	0.001	0.3
Tobacco use × GDP per capita	0.001	−0.001	0.001	0.5

CI = confidence interval; GDP = gross domestic product.

In the male population, there were decreasing trends of bladder cancer mortality in countries from Oceania, North America, and Europe (Fig. 7). Among the 18 countries with significant decreases in bladder cancer mortality, 12 were from Europe. On the contrary, there were three countries with significant increases in bladder cancer mortality, and two of them were from Asia. In the female population, there were decreasing trends of bladder cancer mortality in countries from North America and Europe (Fig. 8). There were a total of nine countries with significant decreases in bladder cancer mortality, and six of them were from Europe. Among the four countries with significant increases in bladder cancer mortality, two were from Asia and two were from Europe.

Temporal trends and joinpoint regression graphs of incidence and mortality for each individual country are presented in the Supplementary material. For the joinpoint regression analysis, the time point at which there was a change in the incidence/mortality trend for each individual country was also illustrated.

3.2.2. GDP per capita in countries with decreasing trends of tobacco use

In this analysis, we focused on countries with decreasing trends of tobacco use and determined whether the GDP per capita differed between countries with decreasing trends of bladder cancer incidence/mortality (group 1) and countries with increasing trends of bladder cancer incidence/mortality (group 2; Table 2). In terms of male and female bladder cancer incidence, there were no significant differences in GDP per capita between the two groups. For male bladder cancer mortality, group 1 had a significantly higher GDP capita than group 2 (USD: 42 184 ± 4133 vs 22 112 ± 5317, $p = 0.003$). For female bladder cancer mortality, group 1 also had a significantly higher GDP capita than group 2 (USD: 48 000 ± 4176 vs 23 197 ± 4859, $p < 0.001$).

4. Discussion

In this study, we provided a comprehensive update on the patterns and temporal trends of bladder cancer incidence and mortality, and we also explored their associations with tobacco use and GDP per capita. The results provided valuable insight into understanding the epidemiology of bladder cancer and how we can improve the situation from a wider perspective.

4.1. Tobacco use, gender, and bladder cancer incidence/mortality

Tobacco is a rich source of carcinogenic compounds including polycyclic aromatic hydrocarbons, aromatic amines, heterocyclic amines, and N-nitroso compounds [21]. Smoking is a significant factor associated with bladder cancer, and its harm tends to increase with smoking intensity and smoking duration [3]. Smoking might also affect the progression of bladder cancer, as reflected by the highest disease-specific mortality among current smokers [2].

According to the GLOBOCAN data in 2018 [1], the ASRs of bladder cancer incidence were 9.6 per 100 000 for males and 2.4 per 100 000 for females, corresponding to a male to female ratio of 4:1. Similarly, the risk of bladder cancer mortality was also 3.6 times higher in the male population (ASRs of 3.2 per 100 000 for males and 0.9 per 100 000 for females). It is important to take note that these results were global figures without adjustment of tumour stage, tumour grading, and treatment modality. Gender disparity in the development and progression of bladder cancer is possible due to potential biological and hormonal differences [22–26]. To complicate it further, delays in presentation and diagnostic workup in female patients have been reported previously [27–29]; this may

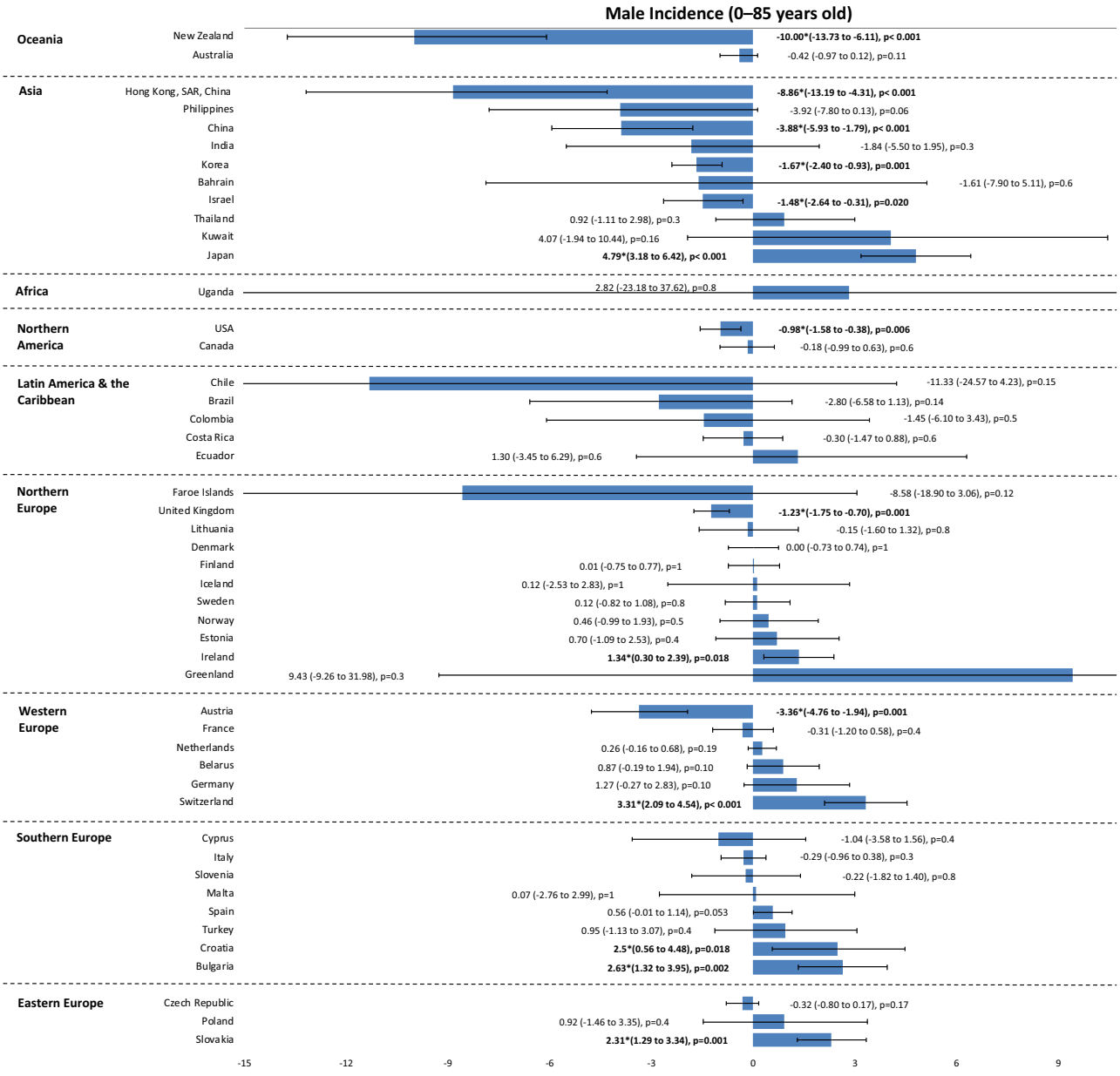

Fig. 5 – The average annual percent change in the incidence of bladder cancer in men. $^{*}p < 0.05$.

result in a more advanced disease upon presentation and poorer long-term survival.

Our results showed positive correlations between tobacco use, and bladder cancer incidence and mortality, in both men and women. Upon multivariable linear regression analysis, tobacco use was significantly associated with bladder cancer incidence and mortality in men, and bladder cancer incidence in women. Although tobacco use was not significantly associated with bladder cancer mortality in women, the potential harm of smoking may be underestimated given the generally low rates of tobacco use in women. The WHO has set a global target of a 30% relative reduction in the prevalence of tobacco use in persons aged ≥15 yr by 2025 [30]. With such an initiative, hopefully the global incidence and mortality of bladder cancer can be improved in the long run.

4.2. GDP per capita and bladder cancer incidence/mortality

GDP represents the total monetary value of all final goods and services produced within a country, and it is often used as an indicator of economic well-being. The financial capacity of an individual and the economic capacity of his/her country may have strong implications on his/her access to diagnostic and therapeutic health care services [31–33]. Our results showed that a higher GDP per capita was positively correlated with the ASR of bladder cancer incidence. This can be a result of better awareness of the

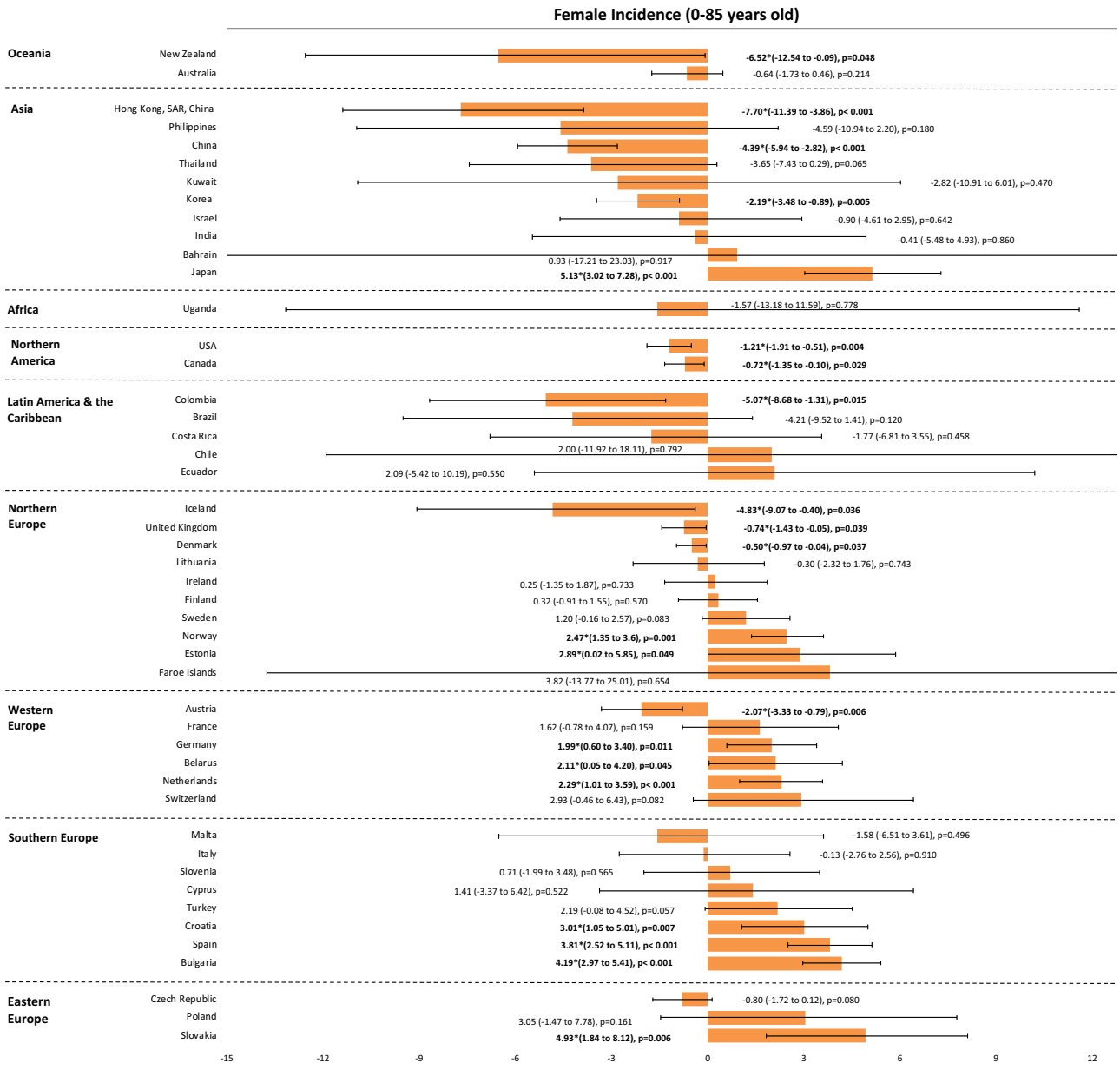

Fig. 6 – The average annual percent change in the incidence of bladder cancer in women. *$p < 0.05$.

disease and easier access to the health care system, resulting in earlier detection of bladder cancer in wealthier countries. Another postulation is that countries with higher GDP may have differences in dietary habits such as increased meat consumption [34]. Dietary factors were suspected risk factors of bladder cancer [5], but the link was not well established. While we expect a better health care delivery for advanced bladder cancer in wealthier countries, we detected only a weak positive correlation between GDP per capita and the ASR of bladder cancer mortality in men, and no correlation in women. GDP per capita was also not associated with bladder cancer mortality upon multivariable linear regression analysis. This may be a reflection of a relative lag in advancement in the treatment of advanced bladder cancer in the past two decades [35,36]. On the contrary, when we focus on countries with decreasing trends of tobacco use, countries with decreasing trends of bladder cancer mortality had a higher mean GDP per capita than those with increasing trends of bladder cancer mortality. Therefore, a certain degree of economic capacity may still be important to further reduce the mortality rates in countries with decreasing trends of tobacco use.

4.3. *Incidence and mortality trends of bladder cancer*

We observed relatively consistent patterns of bladder incidence and mortality across countries within the same continent, in particular for Europe, North America, Oceania,

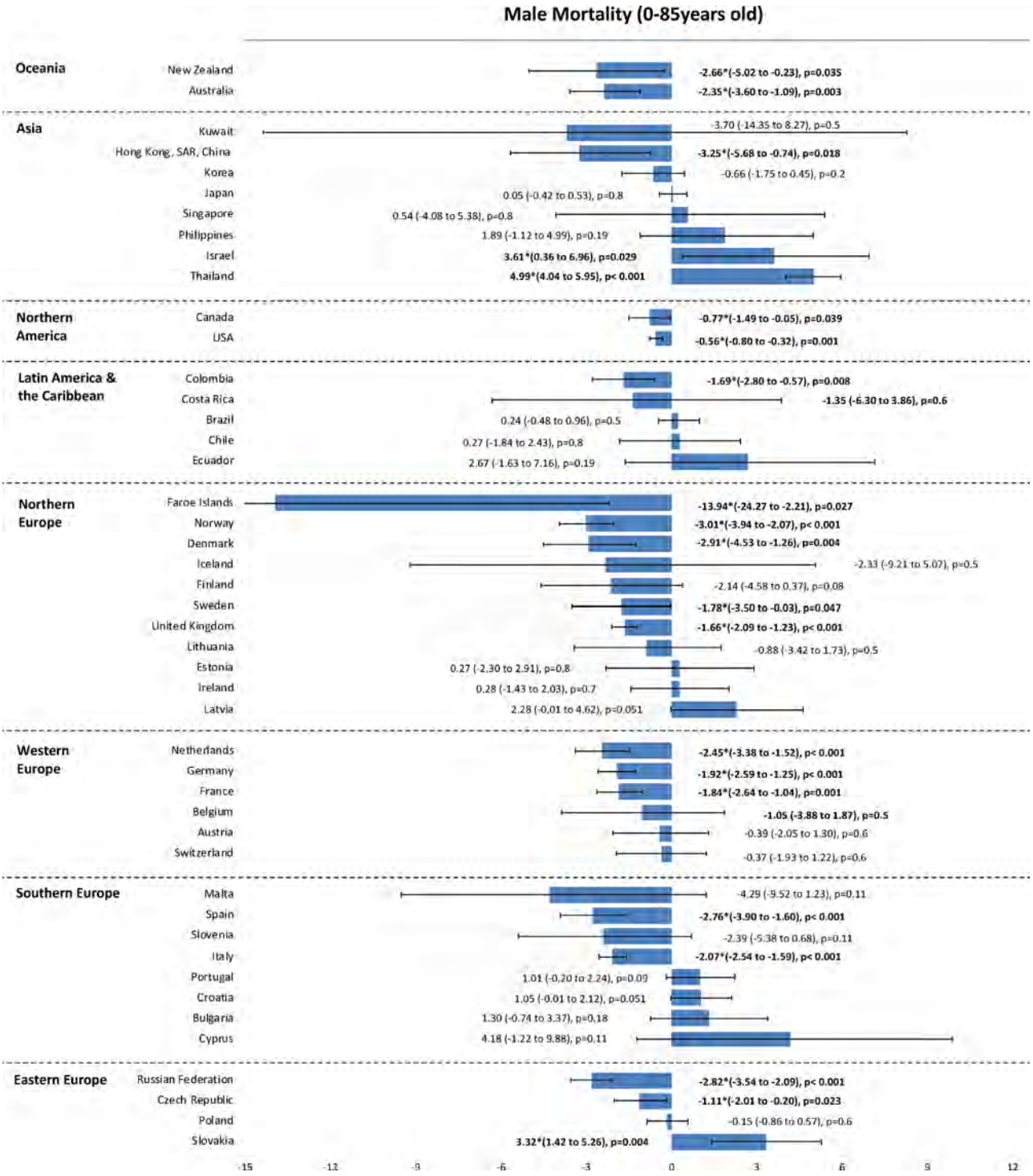

Fig. 7 – The average annual percent change in the mortality of bladder cancer in men. $^{*}p < 0.05$.

and Asia. Apart from the rates of tobacco use and GDP per capita, the existing health care policy and the mode of health care delivery may also have a significant impact on the incidence and mortality trends of bladder cancer. The establishment of bladder cancer advocacy groups may also affect the public's awareness towards this disease. Interestingly, we observed contrasting differences between Europe and Asia, in both incidence and mortality trends of bladder cancer. The possible underlying reasons for such differences are discussed in the following sections.

4.3.1. *Europe—increase in incidence but decrease in mortality*

We observed an increase in incidence but a decrease in mortality for bladder cancer in European countries. This

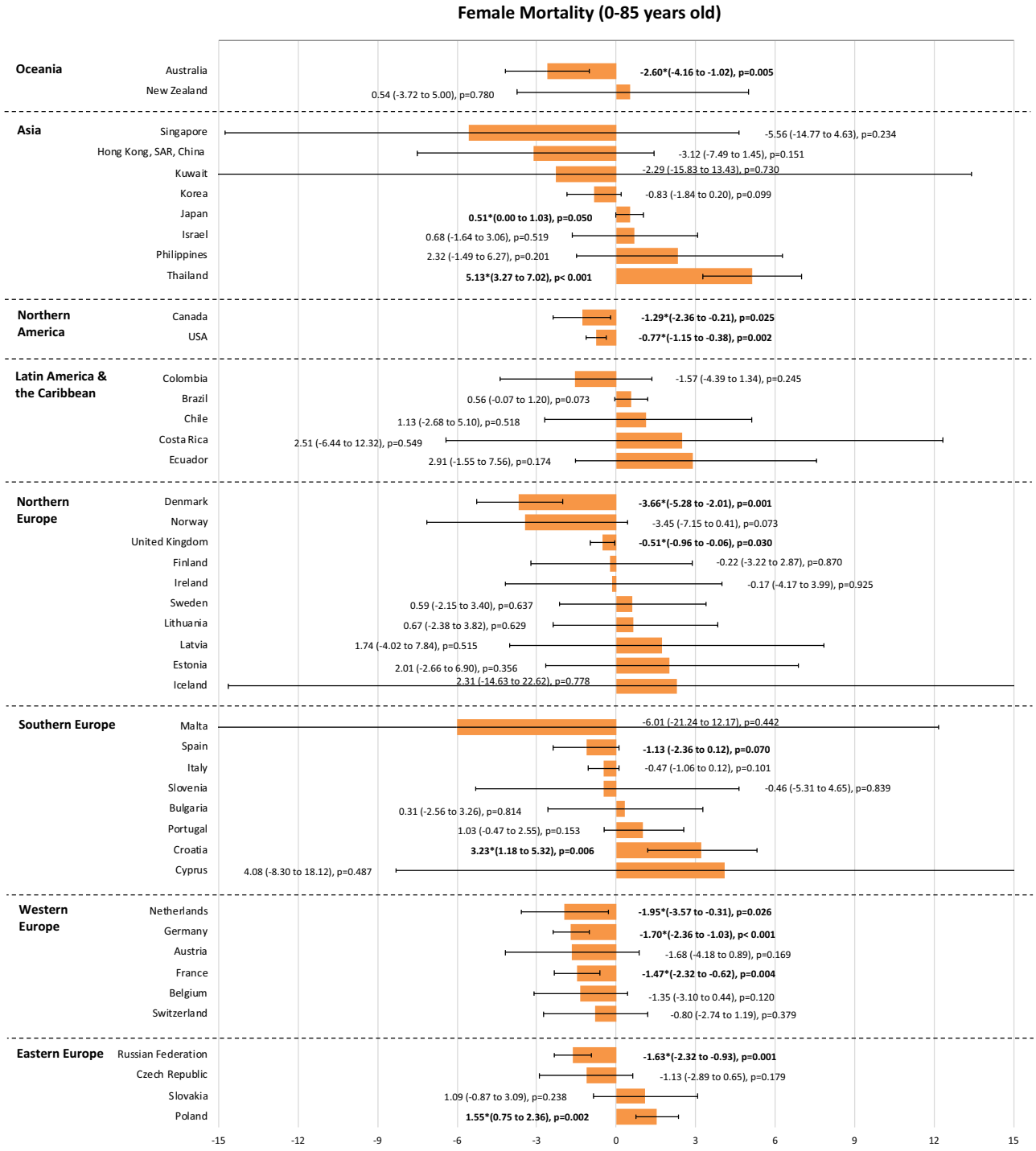

Fig. 8 – The average annual percent change in the mortality of bladder cancer in women. $^{*}p < 0.05$.

may be due to better awareness and earlier detection of the disease, resulting in better oncological control and reduction in mortality. Universal health coverage (UHC) is important to ensure access to urological care without suffering financial hardship [37]. The UHC partnership initiative has been established since 2011, and most European countries were involved in this initiative [38]. European Health Insurance Card also allows an individual access to medically necessary, state-provided health care in any of the 27 European Union countries under the same conditions and at the same cost as people insured in that country [39]. The UHC partnership initiative is still relatively young; it will be interesting to see whether the increasing incidence of bladder cancer will reach a turning point as the programme matures with time. There are also an increasing number of patient advocacy groups for the betterment of patients suffering from bladder cancer. For example, Fight Bladder Cancer is a UK-based bladder cancer

Table 2 – Mean GDP per capita among countries with a decreasing trend of tobacco use

	Group 1[a]	Group 2[b]	*p* value
Male bladder cancer incidence	*n* = 19	*n* = 21	
GDP per capita (USD)	28 403 ± 4386	34 934 ± 5983	0.6
Male bladder cancer mortality	*n* = 26	*n* = 14	
GDP per capita (USD)	42 184 ± 4133	22 112 ± 5317	0.003
Female bladder cancer incidence	*n* = 20	*n* = 19	
GDP per capita (USD)	30 476 ± 5221	36 376 ± 5844	0.5
Female bladder cancer mortality	*n* = 22	*n* = 16	
GDP per capita (USD)	48 000 ± 4176	23 197 ± 4859	<0.001

GDP = gross domestic product.
[a] Group 1: countries with a decreasing trend of bladder cancer incidence/mortality.
[b] Group 2: countries with an increasing trend of bladder cancer incidence/mortality.

charity founded and run by bladder cancer survivors and their families [40]. Better awareness of the disease certainly plays an important role in early detection and treatment of bladder cancer.

4.3.2. *Asia—decrease in incidence but increase in male mortality*

A decrease in bladder cancer incidence in Asia appears to be promising, but at the same time worrying when it is accompanied by an increase in male mortality. Most Asian countries are considered economically developing countries [41]. The public hospital sector is often underdeveloped and may not be able to meet community needs due to the lack of financial and policy support [42]. Limited access to health care services may lead to underdetection of bladder cancer, resulting in late presentation of the disease. Lack of access to more advanced oncological treatment may also affect long-term cancer control. All these factors may lead to higher bladder cancer mortality in the long run. The problem of an ageing population also appears to be much more severe in Asia than in the other continents [43]. Bladder cancer affects elderly men with a median diagnosis age of 73 yr [5], and it is likely to be an increasing problem in Asian countries where population growth continues more than in other areas of the world. There is an urgent need for additional resource allocation in the health care sector. Reform of the health care systems in Asia has also been proposed [42].

4.4. *Strengths and limitations*

This study provides an updated overview of the global incidence and mortality of bladder cancer as well as their temporal trends. The data extracted from the GLOBOCAN database, Cancer Incidence in Five Continents, and the WHO mortality database are of high quality in terms of their validity and completeness, especially when the International Agency for Research on Cancer continues to take active steps to refine the estimation methods for better data quality and availability [44]. Nevertheless, there are several limitations that should be addressed. First, although data from GLOBOCAN and Cancer Incidence in Five Continents were all derived from country-specific cancer registries, cancer incidence might be underdetected and under-reported, especially in less developed nations. Likewise, cancer registries that include reported figures from a small region of the country may limit the generalisability and representation of the findings. Second, we examined the correlations between tobacco use and bladder cancer incidence/mortality. However, correlation does not imply causation, and we must pay extra caution while interpreting the magnitude of the correlation coefficients. Country-level data were used for our regression analysis, but it does not allow more granular analysis based on individuals. The present analysis did not incorporate the tissue type, staging, and other characteristics of bladder cancer. These disease characteristics certainly have important implications on the mortality rate, but are impossible to adjust based on the available global data. Third, rates of tobacco use in 2010 were used as we expected a lead time between tobacco use and the development of bladder cancer [3]. However, they do not reflect on the exact duration and intensity of tobacco use. This may induce a bias to the analysis and interpretation of the results. It is also difficult to obtain global data on the other risk factors of bladder cancer, such as occupational carcinogenic exposure and schistosomiasis; therefore, these factors were not taken into account in our study. Fourth, different cancer registries might have different guidelines on how to document a cancer case or cancer death, and this policy could change over time. Disease coding practices may differ among the countries, and this might affect the changes in temporal trends. Nevertheless, we believe that this study provides valuable insight into the most updated global trends and patterns of bladder cancer, and have important implications on health care policy making and how we can improve bladder cancer incidence and mortality from a wider perspective.

5. Conclusions

We observed different trends of bladder cancer incidence and mortality globally. Tobacco use was significantly associated with both bladder cancer incidence and mortality. Hence, a global effort to promote smoking cessation is extremely important to reduce bladder cancer incidence and mortality in the long run. Among countries with a decreasing trend of tobacco use, a certain level of economic

capacity might be needed to reduce bladder cancer mortality further.

***Author contributions*:** Martin Chi-Sang Wong had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Teoh, Wong.
Acquisition of data: Huang, Ko, Lok, Choi.
Analysis and interpretation of data: Teoh, Huang, Choi.
Drafting of the manuscript: Teoh, Wong.
Critical revision of the manuscript for important intellectual content: Ng, Sengupta, Mostafid, Kamat, Black, Shariat, Babjuk.
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Appendix A. Supplementary data

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