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# The disease burden of bladder cancer and its attributable risk factors in five Eastern Asian countries, 1990–2019: a population-based comparative study

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## Abstract

**Backgrounds** The study aimed to estimate bladder cancer burden and its attributable risk factors in China, Japan, South Korea, North Korea and Mongolia from 1990 to 2019, to discuss the potential causes of the disparities.

**Methods** Data were obtained from the Global Burden of Disease Study 2019. The annual percent change (APC) and average annual percent change (AAPC) were calculated by Joinpoint analysis, and the independent age, period and cohort effects were estimated by age-period-cohort analysis.

**Results** In 2019, the highest incidence (7.70 per 100,000) and prevalence (51.09 per 100,000) rates of bladder cancer were in Japan, while the highest mortality (2.31 per 100,000) and DALY rates (41.88 per 100,000) were in South Korea and China, respectively. From 1990 to 2019, the age-standardized incidence and prevalence rates increased in China, Japan and South Korea (AAPC > 0) and decreased in Mongolia (AAPC < 0), while mortality and DALY rates decreased in all five countries (AAPC < 0). Age effects showed increasing trends for incidence, mortality and DALY rates, while the prevalence rates increased first and then decreased in older groups. The cohort effects showed downward trends from 1914–1918 to 2004–2008. Smoking was the greatest contributor and males had the higher burden than females.

**Conclusion** Bladder cancer was still a major public health problem in East Asia. Male and older population suffered from higher risk, and smoking played an important role. It is recommended that more efficient preventions and interventions should be operated among high-risk populations, thereby reduce bladder cancer burden in East Asia.

**Keywords** Bladder cancer, Comparative study, Disability-adjusted life years, East Asia, Smoking

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## Introduction

Bladder cancer is one of the important urological cancers, and categorized as the tenth most frequently diagnosed cancer and the 13th most common cause of cancer-related death worldwide [1, 2]. According to the GLOBOCAN 2020 database, there were an estimated 573,278 new cases and 212,536 deaths caused by bladder cancer in 2020, accounting for 3.0% of all new cancer cases and 2.1% of all cancer deaths, respectively [3]. The global burden of disease study 2019 indicated that the global incidence and mortality rates of bladder cancer increased by 54.4% and 30.4% from 1990 to 2019, respectively, and the disability-adjusted life years (DALYs) due to bladder cancer reached to 4,392,583 person-years in 2019. Bladder cancer may develop when its cells grow abnormally or mutate, and many risk factors had been confirmed to be associated with the increasing risk to suffer from bladder cancer, including demographic factors such as age, gender, race and family history, diet high in fat and nitrates, exposure to high levels of carcinogens [4, 5]. The previous study had revealed that tobacco use was the most prevalent risk factor for bladder cancer development, which was responsible for around half of bladder cancer cases [3, 6].

The disease burden of bladder cancer showed remarkable diversity among different geographical regions, with the higher incidence and mortality rates observed in developed countries, while lower rates in less developing countries [7]. However, it is worth noting that bladder cancer incidence and mortality rates had decreased in developed countries, while increased in some developing countries during the past few years [7, 8], additionally, the survival rate of bladder cancer in developed countries was higher than that in developing countries [8]. Asia had more than 60% of population in the world and most countries in this region were developing countries, therefore, it's urgent to investigate the epidemiological patterns of bladder cancer burden in Asia. A recent study conducted by Zi et al. analyzed the bladder cancer burden in different regions in Asia, and they concluded that the East Asia had the most incident cases of bladder cancer, and the most significant increases of age-standardized incidence also occurred in East Asia, additionally, the highest DALYs caused by bladder cancer were observed in this region [9]. Therefore, it is very necessary to understand the current status and changing trends of bladder cancer burden in different countries in East Asia, and explore the potential causes leading to its high disease burden, so as to curb the rapid growth of bladder cancer burden in East Asia. However, comprehensive and up-to-date epidemiological study on bladder cancer burden and its risk factors remained limited.

In this study, we aimed to estimate the temporal trends of bladder cancer burden and its risk factors in five Eastern Asian countries using data from global burden of disease study 2019 (GBD 2019), the time trends of bladder cancer burden were estimated by joinpoint regression analysis, and the age, period and cohort effects were explored independently using the age-period-cohort analysis, to throw light on prevention and control of bladder cancer.

## Methods

### Data sources

The anonymized data in this study were extracted from the global burden of disease study 2019 (GBD 2019), which provided the most up-to-date estimates for epidemiological measures such as incidence, prevalence, deaths and DALYs by age, sex for 369 diseases and injuries, and 87 risk factors in 204 countries and territories from 1990 to 2019 [10]. DALY was a summary measure of population health calculated as the sum of years of life lost (YLL) and years lived with disability (YLD), which was the representative for burden of disease to simultaneously consider the life lost due to death and the reduced heath state due to disability [11]. In our study, we obtained the incidence, prevalence, mortality and DALYs and their corresponding age-standardized rates (ASRs) for bladder cancer by age, sex and year in China, Japan, South Korea, North Korea and Mongolia, and the ASRs of mortality and DALYs attributable to risk factors in these countries. In GBD 2019, the original data sources about bladder cancer included vital registration system, cancer registry, verbal autopsy data, hospital and clinical data, published literature and other types of data [12]. The GBD study has been a popular data source for researchers from all over the world to study the burden on diseases, injuries and risk factors in different areas, and the University of Washington Institutional Review Board examined and approved a waiver of informed consent.

### Definition of bladder cancer

In GBD 2019, bladder cancer was diagnosed based on the Tenth and Nineth Revision of the International Classification of Diseases (ICD-10) (code as C67-C67.9, D09.0, D30.3, D41.4-D41.8, D49.4, Z12.6-Z12.79, Z80.52, Z85.51) and ICD-9 (code as 188-188.9, 223.3, 233.7, 236.7, 239.4, V10.51, V16.52, V76.3) [9, 10].

### Risk factors

In GBD 2019, smoking and high fasting plasma glucose (HFPG) were identified as the risk factors for bladder cancer [12], and with the counterfactual analysis, the estimated exposure per risk was estimated based on theoretical minimum risk exposure level (TMREL). Current smokers were defined as individuals who currently use any smoked tobacco products every day or occasionally, former smokers were defined as individuals who quit smoking for at least six months, and the TMREL of smoking was 0 [12]. High fasting plasma glucose was defined as the mean level in population, and the TMREL was 4.8–5.4 mmol/L [13]. The population attributable fraction (PAF) was then calculated by the exposure levels of risk factors, which represented if the exposure level of the risk factors was reduced to TMREL, the proportion of the cause burden that would be reduced. Finally, the attributable burden was calculated by the product of PAF and the burden for the causes. In our study, the ASRs of mortality and DALY rates of bladder cancer attributable to smoking and high fasting plasma glucose by sex and year in China, Japan, South Korea, North Korea and Mongolia were extracted to estimate the attributable burden of bladder cancer to risk factors. The age-standardized rates were adjusted by the world age-standard population [12].

#### Statistical analysis

In this study, the joinpoint regression analysis was conducted to investigate the long-term trends of age-standardized incidence, prevalence, mortality and DALY rates by sex in five Eastern Asian countries from 1990 to 2019. The primary principle of this analysis was to divide the long-term trends of rates into several segments based on "joinpoint", and to create a straight line for each segment to estimate the time trend of the rates over a certain time period [14, 15]. The Monte Carlo permutation test was used to identify the numbers and locations of the "joinpoints", and $P<0.05$ as considered statistically significant. The annual percent change (APC) and its was calculated to describe the changes in temporal trends for each segment, and the average percent change (AAPC) was estimated as the geometric weighted average of APCs of several segments, to describe the changes in temporal trends during the entire period [16, 17]. The APC/AAPC>0 indicated the rates increased during the study period, while APC/AAPC<0 indicated the rates decreased during the study period. The 95% confidence interval (CI) for each APC and AAPC value was provided for their statistical significance. The joinpoint analysis was performed by the Joinpoint Regression Program, Version 4.9.0.0 (Surveillance Research Program, National Cancer Institute).

The age-period-cohort (APC) analysis was applied to identify the relative risks of bladder cancer from age, period and cohort effects, which has been widely used for identifying the characteristics of time-varying measures in epidemiology and sociology fields [18, 19]. To fit the pattern of APC model, the age-specific rates of incidence, prevalence, mortality and DALY of bladder cancer were recoded into successive 5-year age groups from 15 to 19 to 80–84 years, consecutive 5-year periods (1990–2019) and successive 5-year cohort groups from 1914 to 1918 to 2004–2008 [15]. The APC analysis suffered from the "identification problem" induced by the exact linear dependency between age, period and cohort (cohort=period - age), and the intrinsic estimator (IE) was used to solve the un-identification in our study [20]. Besides, the central age period, and birth cohort groups were defined as the reference values in our APC analyses [21]. In case of an even number of categories, the reference value was set to the lower of the two central values. The APC analysis was performed by the Stata, version 12.0 (StataCorp, College Station, Texas, USA).

## Results

#### Long-term trends of bladder cancer burden

The time trends of ASRs of incidence, prevalence, mortality and DALY of bladder cancer in five countries from 1990 to 2019 were shown in Fig. 1, and the their AAPC values and 95%CI were provided in Table 1. The incidence and prevalence rates showed increasing trends in China, Japan and South Korea (AAPC>0), while decreasing trends in Mongolia (AAPC<0). From 1990 to 2019, the mortality and DALY rates for bladder cancer showed decreasing trends in all five countries (AAPC<0), and the largest decreases occurred in Mongolia ($AAPC_{mortality}$ =-1.74%, $AAPC_{DALY}$ =-2.09%) and South Korea ($AAPC_{mortality}$ = -0.77%, $AAPC_{DALY}$ = -1.06%). In 2019, Japan exhibited the highest incidence (7.70 per 100,000) and prevalence rates (51.09 per 100,000), South Korea recorded the highest mortality rate (2.31 per 100,000), and China had the highest DALY rate (41.88 per 100,000), while Mongolia had the lowest rates. Additionally, a significant gender difference was observed in the bladder cancer burden, with rates were much higher in males compared to females.

The APCs for different years of ASRs of incidence, prevalence, mortality and DALY were shown in Fig. 2. For age-standardized incidence, the greatest increases were observed in South Korea (APC=4.77%) during 1990–1996 and in China (APC=3.51%) during 2007–2010, while the greatest decrease occurred in Mongolia (APC=-8.05%) during 1999–2003 (Fig. 2A). The overall trends of age-standardized prevalence were similar to the incidence, with the greatest increases seen in South Korea and China and the greatest decrease in Mongolia (Fig. 2B). Age-standardized mortality and DALY rates exhibited similar general trends across the five countries between 1990 and 2019, with the largest decreases observed in Mongolia ($APC_{mortality}$ = -8.23% during 1999–2004, $APC_{DALY}$ = -9.45% during 1999–2003) (Fig. 2C and D).

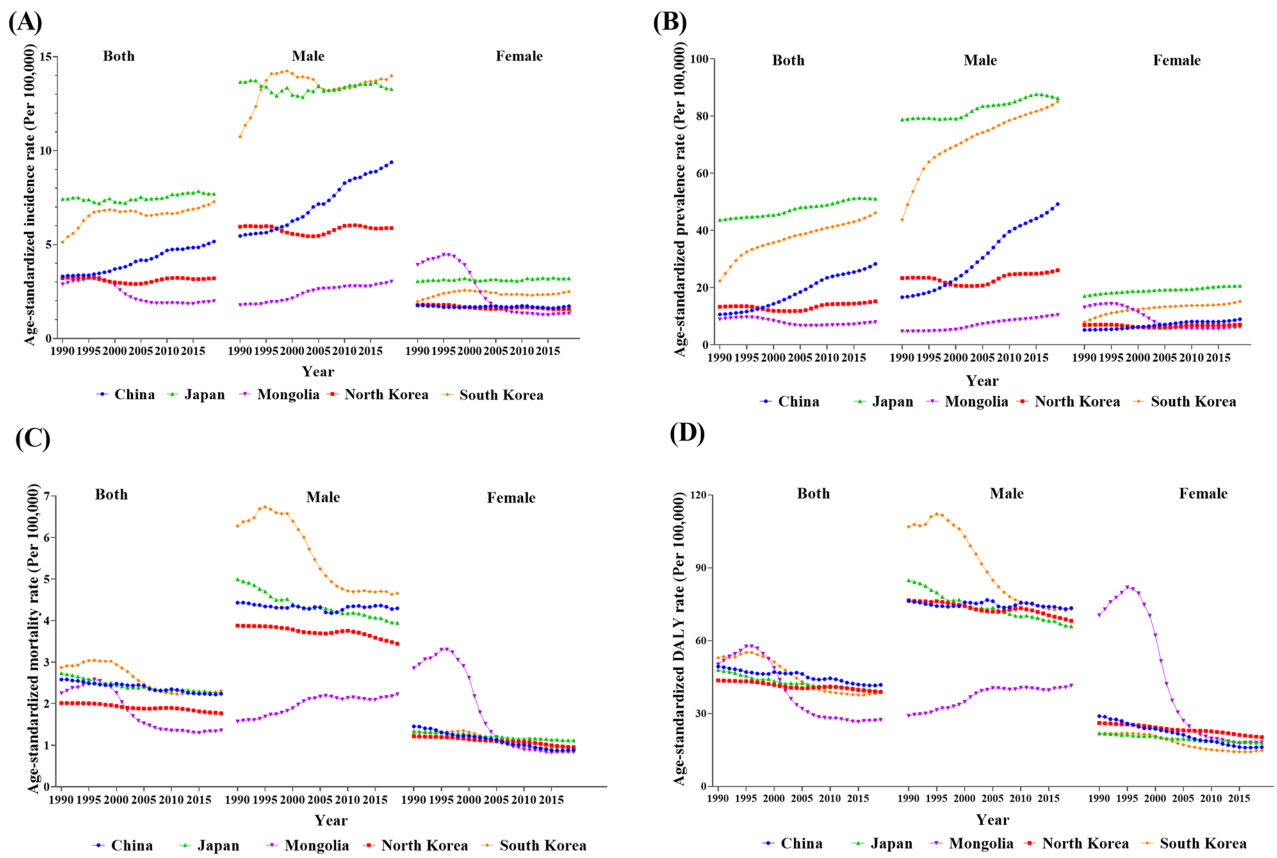


**Fig. 1** The age-standardized incidence, prevalence, mortality and DALY rates of bladder cancer by sex in five Asians countries from 1990 to 2019. (**A:** Incidence; **B:** Prevalence; **C:** Mortality; **D:** DALY)

**Age, period and cohort effects of bladder cancer burden**

Figure 3 depicted the results of age-period-cohort analysis for bladder cancer in five Eastern Asian countries. Overall, the age effect for incidence risk significantly increased from the 15–19 years age group to the 80–84 years age group (except for a slight decrease after 75–79 years of age in North Korea), and the rate of increase accelerated in the elder age groups (Fig. 3A). The age effect of mortality and DALY risks of bladder cancer were similar to those observed for the incidence (Fig. 3C and D). The prevalence risk of bladder cancer initially increased but then began to decrease in the older age groups (Fig. 3B). Generally, bladder cancer incidence risk were higher in Japan, South Korea and China than in North Korea and Mongolia in the older age stage. The RR of period effects for incidence and prevalence of bladder cancer significantly increased over time in China, Japan, South Korea and North Korea during the observation period. However, in Mongolia, the RR of period effects first decreased from 1994 to 2004 and thereafter generally increased from 2004 to 2019. The period effects of mortality and DALY rates of bladder cancer showed the slight upward trends in China, Japan, South Korea and North Korea over the study period, whereas the period RR in Mongolia decreased before 2004. The cohort effects showed downward trends from 1914–1918 to 2004–2008 in all five countries. The earlier birth cohorts had suffered from higher risk, while the more recent birth cohorts had experienced the lower risks.

**Bladder cancer burden attributable to smoking and HFPG**

Table 2 showed the age-standardized mortality and DALY rates, and the corresponding AAPCs of bladder cancer owing to risk factors by sex in difference countries. Generally, smoking was the greatest contributor to mortality and DALYs of bladder cancer. For both sexes, in 2019, the highest mortality owing to smoking were found in China (1.02 per 100,000) and South Korea (0.92 per 100,000), while the lowest in Mongolia (0.42 per 100,000). The patterns of DALY rates attributable to smoking were similar to the mortality rates, with the highest rates in China (19.71 per 100,000) while the lowest in Mongolia (9.28 per 100,000). For HFPG, the highest mortality (0.23 per 100,000) and DALY (3.63 per 100,000) rates were located in in South Korea, while the lowest rates in Mongolia. Between 1990 and 2019, the mortality and DALY rates attributable to smoking significantly decreased in China, North Korea, Japan and South

**Table 1** The age-standardized incidence, prevalence, mortality and DALY rates in 1990 and 2019 and the corresponding average annual percent change (AAPC) of bladder cancer in five eastern Asian countries

| Location | Sex | Incidence (Per 100,000) | | | Prevalence (Per 100,000) | | | Mortality (Per 100,000) | | | DALY (Per 100,000) | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | 1990 | 2019 | AAPC (%) | 1990 | 2019 | AAPC (%) | 1990 | 2019 | AAPC (%) | 1990 | 2019 | AAPC (%) |
| China | | | | | | | | | | | | | |
| | Both | 3.30 | 5.16 | 1.56(1.30, 1.82) | 10.63 | 28.32 | 3.44(3.29, 3.60) | 2.58 | 2.24 | -0.53(-0.76, -0.30) | 49.41 | 41.88 | -0.59(-0.81, -0.38) |
| | Female | 1.75 | 1.72 | -0.09(-0.40, 0.22) | 5.22 | 8.99 | 1.86(1.80, 1.93) | 1.45 | 0.88 | -1.77(-2.04, -1.50) | 28.99 | 16.22 | -2.05(-2.34, -1.76) |
| | Male | 5.46 | 9.38 | 1.85(1.62, 2.07) | 16.67 | 49.24 | 3.82(3.65, 3.99) | 4.43 | 4.30 | -0.10(-0.28, 0.07) | 76.38 | 73.49 | -0.15(-0.34, 0.03) |
| North Korea | | | | | | | | | | | | | |
| | Both | 3.21 | 3.20 | -0.02(-0.12, 0.08) | 13.32 | 15.27 | 0.46(0.40, 0.53) | 2.01 | 1.77 | -0.45(-0.52, -0.39) | 43.71 | 38.90 | -0.40(-0.45, -0.35) |
| | Female | 1.78 | 1.56 | -0.48(-0.57, -0.40) | 6.91 | 7.04 | 0.05(-0.03, 0.12) | 1.21 | 0.95 | -0.84(-0.87, -0.80) | 26.17 | 20.35 | -0.86(-0.90, -0.82) |
| | Male | 5.95 | 5.88 | -0.05(-0.13, 0.03) | 23.35 | 26.07 | 0.38(0.32, 0.43) | 3.88 | 3.44 | -0.42(-0.46, -0.38) | 76.62 | 68.22 | -0.40(-0.45, -0.34) |
| Japan | | | | | | | | | | | | | |
| | Both | 7.42 | 7.70 | 0.19(0.09, 0.29) | 43.69 | 51.09 | 0.55(0.50, 0.59) | 2.73 | 2.26 | -0.65(-0.71, -0.59) | 47.96 | 39.35 | -0.67(-0.73, -0.61) |
| | Female | 3.05 | 3.20 | 0.18(-0.09, 0.45) | 17.09 | 20.66 | 0.66(0.60, 0.71) | 1.34 | 1.12 | -0.64(-0.85, -0.43) | 21.94 | 18.06 | -0.69(-0.86, -0.51) |
| | Male | 13.65 | 13.28 | -0.02(-0.13, 0.09) | 78.82 | 86.30 | 0.32(0.27, 0.37) | 5.00 | 3.94 | -0.81(-1.03, -0.58) | 84.95 | 65.98 | -0.88(-0.95, -0.81) |
| Mongolia | | | | | | | | | | | | | |
| | Both | 2.89 | 1.99 | -1.29(-1.55, -1.03) | 8.93 | 7.92 | -0.43(-0.60, -0.25) | 2.25 | 1.36 | -1.74(-2.05, -1.42) | 50.32 | 27.47 | -2.09(-2.27, -1.90) |
| | Female | 3.92 | 1.33 | -3.70(-4.03, -3.37) | 13.12 | 6.23 | -2.60(-2.85, -2.35) | 2.86 | 0.84 | -4.17(-4.55, -3.80) | 70.52 | 18.22 | -4.55(-4.82, -4.29) |
| | Male | 1.78 | 3.03 | 1.84(1.62, 2.06) | 4.71 | 10.45 | 2.81(2.72, 2.90) | 1.57 | 2.23 | 1.19(0.73, 1.64) | 29.12 | 41.53 | 1.25(0.99, 1.51) |
| South Korea | | | | | | | | | | | | | |
| | Both | 5.13 | 7.28 | 1.12(0.95, 1.28) | 22.35 | 46.17 | 2.45(2.35, 2.55) | 2.87 | 2.31 | -0.77(-0.96 -0.59) | 53.01 | 38.91 | -1.06(-1.29, -0.82) |
| | Female | 1.97 | 2.49 | 0.77(0.56, 0.98) | 7.93 | 15.20 | 2.25(2.14, 2.35) | 1.27 | 0.96 | -1.00(-1.21, -0.79) | 21.68 | 14.83 | -1.34(-1.48, -1.19) |
| | Male | 10.74 | 13.98 | 0.88(0.74, 1.03) | 43.80 | 85.06 | 2.31(2.20, 2.41) | 6.28 | 4.66 | -1.01(-1.23, -0.79) | 106.96 | 73.04 | -1.36(-1.53, -1.19) |

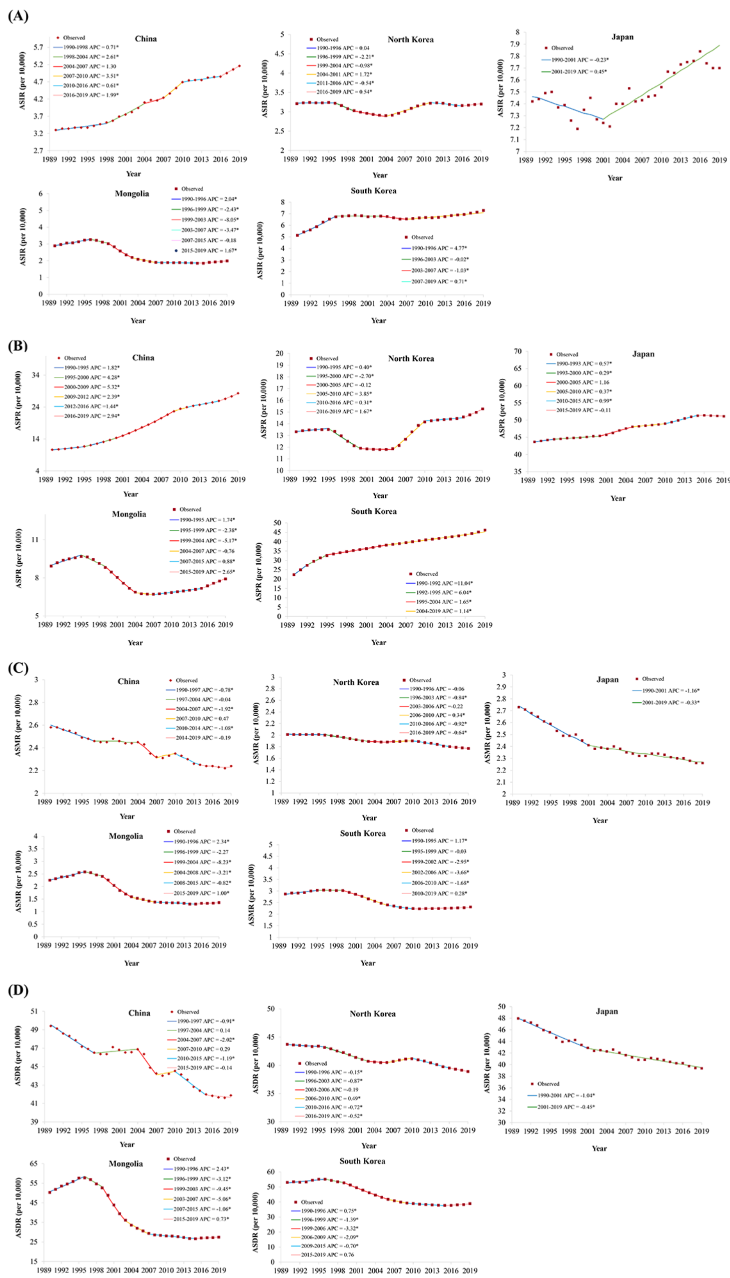


**Fig. 2** The results of Joinpoint analysis of age-standardized incidence, prevalence, mortality and DALY rates of bladder cancer in five Asians countries from 1990 to 2019. (**A:** Incidence; **B:** Prevalence; **C:** Mortality; **D:** DALY rates)

Korea (AAPC<0), while they significantly increased in Mongolia (AAPC>0). In terms of HFPG, the attributable mortality and DALY rates showed significant downward trends in Japan (AAPC<0), while significant upward trends in North Korea from 1990 to 2019 (AAPC>0).

It was worth noting that the mortality and DALY rates of bladder cancer attributable to these two risk factors varied between sex groups. Specifically, males were more susceptible to the effect of for smoking and HFPG, exhibiting substantially greater attributable mortality and DALY rates compared to females in all five countries in 2019. From 1990 to 2019, males in Mongolia constituted the primary population affected by smoking and HFPG, with significantly increasing trends in attributable mortality and DALY rates compared with females.

## Discussion

Bladder cancer had been recognized as a global health challenge with higher incidence cases and mortality, and a large proportion of the global burden were located in

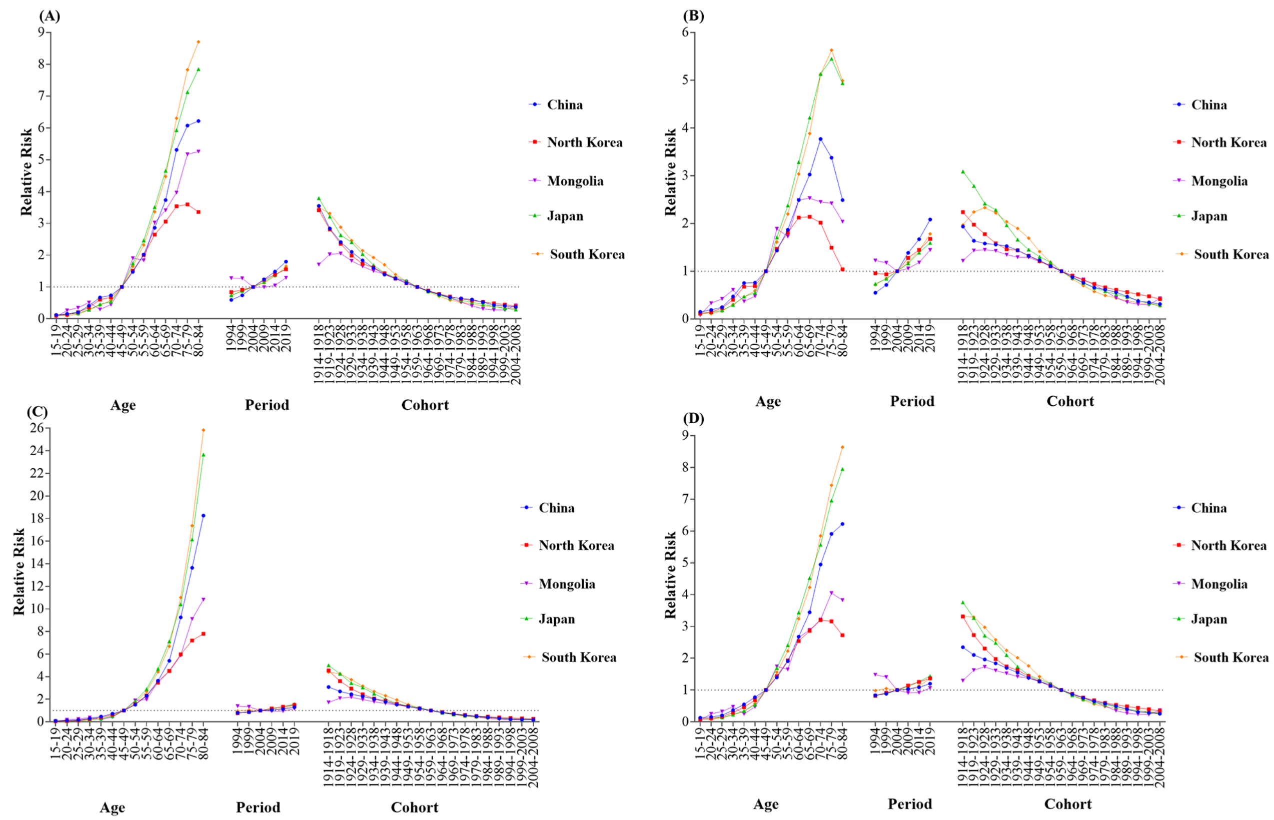


**Fig. 3** The age, period and cohort effects of bladder cancer in incidence, prevalence, mortality and DALY rates in five Asians countries (**A:** Incidence; **B:** Prevalence; **C:** Mortality; **D:** DALY)

Asia, particularly in East Asia [9, 22]. Based on the GBD 2019 study, the current study systematically estimated the current burden and temporal trends of bladder cancer in Eastern Asian countries by Joinpoint regression and age-period-cohort analysis, and also evaluated the attributable burden of bladder cancer attributable to possible risk factors. The findings can provide scientific references for policy makers to formulate effective prevention and intervention strategies in these countries.

Our results revealed that the burden of bladder cancer varied considerably among countries in East Asia. Specifically, in 2019, Japan had the highest age-standardized incidence and prevalence rates, and South Korea and China had the highest mortality and DALY rates, while Mongolia had the lowest rates for incidence, prevalence, mortality and DALY. From 1990 to 2019, the incidence and prevalence rates of bladder cancer showed significantly increasing trends in China, Japan and South Korea, while decreasing trends in Mongolia, besides, the mortality and DALY rates for bladder cancer all showed decreasing trends in five countries. The regional differences across these countries might be explained by the heterogeneity in the prevalence of risk factors, detection rate, oncology care and healthcare resource allocation [12, 23]. The previous studies had indicated the degrees of social development would have influence on genitourinary cancers, specifically, more developed countries had the higher incidence, mortality and DALYs for bladder cancers, especially in countries with advanced wealth and technological resources [9]. Eastern Asia is the most prosperous part of Asia, of which Japan and South Korea had been considered high-income countries. The higher levels of incidence rates in these countries might be contributed to widespread practice of diagnostic tests, such as cystoscopy, urine cytology and CT scan [24]. While in less developed countries like Mongolia and North Korea, the lower socioeconomic development restricted the access to screening programs for bladder cancer, thereby to contribute to the lower incidence rates.

Additionally, tobacco use, occupational exposure to chemicals, western-style diet, obesity and lack of physical activity were also contributed to the disparities of bladder cancer burden across countries [4]. The GBD 2019 study estimated the attributable burden of bladder cancer owing to smoking and HFPG, which was two important risk factors robustly associated with bladder cancer [12]. Smoking was the biggest risk factor of developing bladder cancer, which had been reported to be responsible for half of bladder cancer cases because of the high prevalence [4]. A Meta-analysis included 90 studies showed that

**Table 2** The age-standardized mortality and DALY rates of bladder cancer attributable to smoking and high fasting plasma glucose in 1990 and 2019 and the corresponding average annual percent change (AAPC) in five eastern Asian countries

| Location | Sex | Smoking | | | | | | High fasting plasma glucose | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Mortality (Per 100,000) | | | DALY (Per 100,000) | | | Mortality (Per 100,000) | | | DALY (Per 100,000) | | |
| | | 1990 | 2019 | AAPC (%) | 1990 | 2019 | AAPC (%) | 1990 | 2019 | AAPC (%) | 1990 | 2019 | AAPC (%) |
| China | | | | | | | | | | | | | |
| | Both | 1.13 | 1.02 | -0.41(-0.59, -0.24) | 21.82 | 19.71 | -0.40(-0.60, -0.19) | 0.17 | 0.17 | -0.10(-0.59, 0.39) | 2.85 | 2.87 | -0.06(-0.56, 0.43) |
| | Female | 0.22 | 0.11 | -2.54(-2.92, -2.15) | 3.92 | 1.87 | -2.53(-2.86, -2.21) | 0.09 | 0.06 | -1.49(-2.00, -0.97) | 1.65 | 1.04 | -1.61(-2.18, -1.03) |
| | Male | 2.50 | 2.32 | -0.25(-0.44, -0.07) | 43.93 | 41.00 | -0.26(-0.40, -0.11) | 0.29 | 0.33 | 0.28(-0.15, 0.71) | 4.54 | 5.18 | 0.37(-0.12, 0.87) |
| North Korea | | | | | | | | | | | | | |
| | Both | 0.68 | 0.62 | -0.31(-0.37, -0.25) | 15.77 | 14.79 | -0.22(-0.28, -0.17) | 0.10 | 0.12 | 0.84(0.77, 0.90) | 1.83 | 2.41 | 0.97(0.91, 1.03) |
| | Female | 0.09 | 0.08 | -0.75(-0.79, -0.72) | 2.09 | 1.74 | -0.64(-0.69, -0.59) | 0.06 | 0.07 | 0.44(0.40, 0.48) | 1.08 | 1.24 | 0.48(0.43, 0.53) |
| | Male | 1.93 | 1.64 | -0.57(-0.65, -0.49) | 39.93 | 34.16 | -0.54(-0.59, -0.48) | 0.19 | 0.25 | 0.88(0.81, 0.94) | 3.38 | 4.45 | 0.97(0.91, 1.03) |
| Japan | | | | | | | | | | | | | |
| | Both | 1.18 | 0.69 | -1.89(-1.99, -1.78) | 22.46 | 13.76 | -1.72(-1.80, -1.64) | 0.19 | 0.17 | -0.38(-0.61, -0.15) | 3.06 | 2.72 | -0.44(-0.68, -0.21) |
| | Female | 0.20 | 0.12 | -1.70(-1.77, -1.63) | 3.93 | 2.48 | -1.60(-1.71, -1.50) | 0.07 | 0.07 | -0.35(-0.50, -0.20) | 1.06 | 0.93 | -0.50(-0.69, -0.32) |
| | Male | 2.74 | 1.49 | -2.13(-2.24, -2.02) | 48.50 | 27.43 | -2.00(-2.10, -1.91) | 0.38 | 0.32 | -0.58(-0.90, -0.27) | 6.00 | 5.01 | -0.69(-0.94, -0.43) |
| Mongolia | | | | | | | | | | | | | |
| | Both | 0.38 | 0.42 | 0.41(0.19, 0.62) | 8.71 | 9.28 | 0.21(0.06, 0.35) | 0.06 | 0.06 | -0.05(-0.44, 0.33) | 1.11 | 1.02 | -0.29(-0.65, 0.07) |
| | Female | 0.23 | 0.07 | -4.24(-4.93, -3.55) | 6.15 | 1.72 | -4.29(-4.61, -3.97) | 0.07 | 0.03 | -2.65(-3.19, -2.10) | 1.45 | 0.58 | -3.07(-3.48, -2.65) |
| | Male | 0.61 | 0.99 | 1.65(1.37, 1.93) | 12.42 | 19.92 | 1.67(1.43, 1.91) | 0.04 | 0.10 | 2.79(2.46, 3.12) | 0.74 | 1.69 | 2.83(2.65, 3.02) |
| South Korea | | | | | | | | | | | | | |
| | Both | 1.34 | 0.92 | -1.30(-1.52, -1.07) | 25.81 | 16.24 | -1.58(-1.79, -1.37) | 0.20 | 0.23 | 0.37(0.16, 0.59) | 3.57 | 3.63 | 0.05(-0.11, 0.21) |
| | Female | 0.26 | 0.16 | -1.57(-1.75, -1.39) | 3.88 | 2.14 | -2.10(-2.23, -1.96) | 0.08 | 0.08 | 0.02(-0.15, 0.19) | 1.30 | 1.17 | -0.38(-0.60, -0.16) |
| | Male | 3.57 | 2.19 | -1.68(-1.84, -1.52) | 62.50 | 35.59 | -1.93(-2.17, -1.68) | 0.46 | 0.48 | 0.09(-0.18, 0.35) | 7.59 | 7.19 | -0.19(-0.42, 0.03) |

the incidence risk of bladder cancer was higher in current smokers (relative risk: 3.37, 95%CI: 3.01, 3.78) and former smokers (1.98, 95%CI: 1.76, 2.22) compared to nonsmokers [25]. Our study had also concluded that the higher mortality and DALY rates of bladder cancer were caused by smoking in South Korea, China and Japan, which was closely associated with the higher prevalence of smoking in these three countries. The WHO global report on trends in prevalence of tobacco use 2000–2025 (fourth edition) showed the age-standardized prevalence of smoking in 2000 were 27.5% in China, 37.1% in Japan and 35.7% in South Korea, which were expected to fall to 24.6%, 15.5% and 17.4% by 2025, respectively [26]. If the downward trends of smoking prevalence rates could maintain, the cancer burden caused by smoking would be improved in the future [26]. Our study also indicated that the HFPG was associated with the increases of deaths and DALYs of bladder cancer, and the previous study estimated the HFPG increased by 37.7% globally during the past three decades [13]. Therefore, targeted measures should be taken to reduce the prevalence of HFPG, such as improving the health awareness of population, changing an unhealthy lifestyle.

As a results of APC analysis, significant increases of age effects for incidence, morality and DALY of bladder cancer were observed in five countries, and significant increases of prevalence in the middle ages and decreases of prevalence in older ages were also observed in five countries. As we known, bladder cancer had been considered as primarily a disease of the elderly population, and age was the greatest single risk factor for developing bladder cancer [27, 28], which might be associated with the cumulative environmental exposure to carcinogens for these population, such as smoking and occupational exposures [29]. Additionally, these groups had more time for development and accumulation of cellular events that can lead to neoplastic transformation, and prolonged exposures due to the decreased bladder voiding function, which would also explain the relationship between disease burden of bladder cancer and ageing process [29]. East Asia was aging faster than the rest of the world [30], hence, greater attention needed to be paid to the development of cancer in the elder groups, to reduce the huge disease burden and improve the life quality for these groups. The period effects usually indicated the impacts of a complex set of factors with immediate effects [31]. When age and cohort effects were controlled in our study, the period effect showed the increasing trends for incidence, prevalence, mortality and DALY rates in China, Japan, South Korea and North Korea, while significant decreases from 1994 to 2004 and increases from 2004 to 2019 were observed in Mongolia. The increasing effects of period might be contributed to the rapid economy transformation and urbanization during the past few decades [27]. Additionally, the higher exposures to causal factors, such as tobacco use and occupational carcinogens, might also play an important role in the risk of bladder cancer, and the previous study indicated that smoking prevalence and consumption of hazardous industrial chemicals had significantly increased in developing countries in the past few decades, which could partly explain the increasing period effects of bladder cancer in this study [8]. The cohort effects on bladder cancer burden showed downward trends from 1914–1918 to 2004–2008 in five countries, which were consistent with other studies [27, 31]. The improved living conditions, nutrition intake and healthcare services, and stronger health awareness in younger cohorts could reduce the exposure to risk factors, thereby to decrease the risk of bladder cancer. Therefore, it was necessary to develop the strategies according to the different backgrounds of birth or different age stage to reduce bladder cancer burden in different countries in East Asia.

It was worth noting that the disease burden of bladder cancer varied between sex groups, and males had much higher levels of disease burden than females, which could be explained by the disparities of anatomical structure, behavior response to health problems and exposures to risk factors. For example, there were marked differences of smoking prevalence rates between males and females in Eastern Asian countries, and it's reported by WHO that in 2020, tobacco smoking prevalence rates of males and females in 2020 were 45.3% and 1.7% in China, 30.1% and 10.0% in Japan, and 35.7% and 5.9% in South Korea [26]. The sex differences of smoking prevalence would contribute to the disparities of bladder cancer burden among males and females, so in our study, we found that the mortality and DALY rates of bladder cancer attributable to smoking for males were much higher than those for females. It was worth noting that in Mongolia, males continued to have an increasing bladder cancer burden attributable to smoking and HFPG, which should draw the attention of local governments and public health departments.

There were some limitations in our study. Firstly, data used in our study were obtained from the GBD study, and the limitations associated with the availability of primary data in the GBD study were also applicable to this study. For instance, underreporting in low-income countries or overestimation in areas with better diagnostic facilities could skew the results. Although the GBD study implemented numerous adjustments and corrections to capture uncertainty, it remains challenging to thoroughly avoid inaccuracy because some values were estimated rather than directly measured, particular in locations with sparse or absent data [10]. Secondly, the risk factors for bladder cancer in GBD 2019 were limited in smoking and HFP. Due to data unavailability, we did not analyze other risk factors, such as occupational exposures or dietary factors. Thirdly, we excluded the age groups over 84 years because of the fixed pattern of the IE algorithm of the age-period-cohort analysis. Finally, it was inevitable to be affected by ecological fallacy because the interpretations of the results were based on population level rather than individual level data. Therefore, further individual-based studies needed to be conducted to confirm the findings of this study.

## Conclusion

To sum up, bladder cancer poses a significant health risks in East Asia, with variations in disease burden and risk factors across genders, age groups and countries. The higher burden was observed in Japan, China and South Korea, while the lowest burden in Mongolia. After controlling for age and cohort effects, the burden of bladder cancer shows an increasing trend in East Asian countries. Males were more likely to suffer from bladder cancer compared to females, and the population of older age groups and earlier birth cohorts were considered at high risk for bladder cancer. Smoking and high FPG were important contributors to deaths and DALYs due to bladder cancer in the five East Asia countries, especially in China, Japan and South Korea. The findings emphasize the need for efficient preventions and interventions to address these specific risk factors and vulnerable populations in East Asia.

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**Author contributions**

LL wrote the manuscript text, and HL prepared tables and figures. HL, PZ, JJ and XZ participated in the discussion of data analysis and put forward many constructive comments on the method part of the text. JH gave guidance on the overall idea of the text, and collected the discussion part of the information. JH and YJ made many precise and insightful requirements for the details and diagrams in the text. All authors read and approved the final manuscript.

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**Data availability**

The data that support the findings of this study are available from http://ghdx.healthdata.org/gbd-results-tool.

## Declarations

**Ethics approval and consent to participate**

All anonymized data are accessible online at http://ghdx.healthdata.org/gbd-results-tool, the Institute for Health Metrics and Evaluation. The deidentified, compiled data was used in the GBD investigation. the University of Washington Institutional Review Board examined and approved a waiver of informed consent.

**Competing interests**

The authors declare no competing interests.

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