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Sex Disparities in Global Burden of Gallbladder and Biliary Tract Cancer: Analysis of Global Burden of Disease Study from 2010 to 2019

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DECLARATIONS

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Data Availability

Global Burden of Disease (GBD) study in 2019 can be accessed using the GlobalHealth Data Exchange (GHDx) query tool (http://ghdx.healthdata.org/gbd-results-tool).

RStudio software (Version 4.3.1) was utilized to obtain the figures.

Author contributions

Conceptualization, Result analysis – Priyata Dutta

Material preparation, data collection, and analysis – Priyata Dutta

The first draft of writing – Priyata Dutta

Validation- Krittameth Rakwong

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Abstract

Background: The global burden of gallbladder and biliary tract cancer (GBTC) has been on the rise, making it a major public health concern. We aim to comprehensively analyse sex disparities in the temporal trends of GBTC incidence, mortality, and disability-adjusted life years (DALYs) regionally and globally from 2010 to 2019.

Methods: Age-standardized rates of GBTC incidence, death, and DALYs were analysed utilizing the Global Burden of Disease study 2019.

Results: From 2010 to 2019, the estimated annual percent change (APC) of the Age-Standardized Incidence Rates (ASIRs) and Age-Standardized Disability-Adjusted Life Years (ASDALYs) due to GBTC globally decreased in both sexes (Males, APC: -0.80%; APC: -1.00%) and (Females, APC: -0.89 %; APC: -0.96%). At the same time, Age-Standardized Death Rates (ASDRs) decreased only in males (APC: - 0.82%) and remained stable in females. By regions, ASIRs and ASDR increased in both sexes only in Southeast Asia (SEA) but decreased in the other regions. All regions had decreased ASDALYs except for an increase in ASDALYs for females only in the SEA region (APC: 0.41%), and males have a stable trend.

Conclusion: Our study reveals substantial geographic variance in the burden of GBTC, specifically in the SEA region. Therefore, localized interventional methodologies must be undertaken to effectively address this global burden from GBTC.

Keywords: biliary tract cancer; gallbladder; sex disparity; Global Burden of Disease; Southeast Asia; incidence, prevalence, death, estimated annual percentage rates, disability adjusted life years.

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INTRODUCTION

Gallbladder cancer is the most common biliary tract neoplasm and ranks as the sixth most prevalent cancer in the gastrointestinal tract[1]. According to the GLOBOCAN 2020 estimates, gallbladder cancer is positioned as the 25th most incident cancer worldwide with more than 115,949 new cases and accounting for 0.9% of cancer-related deaths globally[2]. Despite its relatively low incidence, gallbladder cancer is responsible for 80 to 95% of all Gall bladder and biliary tract cancer (GBTC) and carries a dismal prognosis[3,4]. Due to its insidious onset, aggressive nature, delayed presentation, and advanced metastasis at diagnosis, gallbladder cancer yields poor prognosis with survival rates of less than 5%[1,4].

Ultimately, its rarity, coupled with its highly malignant biology, renders gallbladder cancer a significant disease burden. Dissimilar to other gastrointestinal malignancies, gallbladder cancer has a higher incidence in women compared to men[2-4]. The GLOBOCAN 2020 reported that the incidence rate for gallbladder cancer was 1.4 and 0.9 in females and males, respectively, underscoring a sex-specific difference in the global burden of gallbladder cancer[2]. Of note, the regional heterogeneity of this cancer was significantly evident, with Latin America, North Africa, and certain countries in Asia, Eastern, and Central Europe exhibiting higher incidence rates compared to the United States and some Western regions, including the United Kingdom, France, and Norway[2,3,5]. Genetic predisposition, different environmental exposures, and diverse intrinsic risk factors concurrently contribute to this issue[2,4,6]

Given that current epidemiological studies have primarily focused on regional analysis of gallbladder and biliary tract cancer burden[4,7-9] , few examined its global burden[3,10]. With the progression of disease over the years, understanding the global patterns will become imperative to inform policymaking aimed at mitigating the burden of gallbladder cancer. Therefore, this study aims to utilize a large population database to provide an updated and comprehensive understanding of the epidemiology and trends of the burden of gallbladder and biliary tract cancers (GBTC) across countries, time periods, and sex groups from 2010 to 2019.

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METHODS

Data source

In our study, the Global Burden of Disease Study 2019 (GBD 2019), was used to measure the disease burden due to 369 diseases and a total of 87 risk factors in 204 countries/territories[11]. An online data source, the GlobalHealth Data Exchange (GHDx) query tool (http://ghdx.healthdata.org/gbd-results-tool) created and designed by the Institute for Health Metrics and Evaluation, was used to obtain the age-standardized rates (ASRs) of gallbladder cancer-related incidence, deaths, and disability-adjusted life-years (DALYS), stratified by sex, World Health Organization (WHO) regions, and sociodemographic index (SDI), and country/regions from 2010 to 2019 for analysis.

Estimation methods in the GBD 2019 study

The estimation methods of the disease burden of GBTC in the 2019 GBD study has been described in previous studies[12-14]. The International Classification of Diseases Ninth Revision (ICD-9) and ICD Tenth Revision (ICD-10) codes have been utilized to identify GBTC[11]. Data extraction for GBTC-related mortality was carried out by utilizing population-based cancer registries, vital registration systems or verbal autopsy studies from each country/territory[11].

Multiple statistical methods were adopted to reduce data heterogeneity, including garbage code redistribution, misclassification correction, and noise reduction algorithms. A Cause of Death Ensemble model- a form of Bayesian geospatial regression analysis was used to obtain GBTC related mortality by age, sex, country/ territory and year. The incidence of GBTC was derived by dividing mortality estimates by the mortality-to-incidence ratios. DALYs were calculated as the sum of years of life lost and years lived with disability[11]. Mortality estimates for GBTC were extracted from a systematic literature search and population-based studies, performed by the GBD collaborators were also included. Analysis was further stratified by location, sex, and year. SDI was used to categorize countries/territories by development status, a metric that incorporates - total fertility rate, average highest level of education over the age of 15 and estimates of per capita income.

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Data and Statistical Analysis

ASRs were obtained by utilizing the direct method to the GBD 2019 population estimate with 5-year age groups[11]. All epidemiological measures were reported with 95% uncertainty intervals (UIs), defined as the 2.5th and 97.5th ranked values across a total of 1000 draws from a posterior distribution. Dividing the difference in values between 2010 and 2019 by the original value in 2010 we calculated the percentage change in any category from 2010 to 2019. We used the Join point Regression Program, version 4.6.0.0 (Statistical Research and Applications Branch, National Cancer Institute), to calculate the annual percent change (APC) and corresponding 95% CI to estimate the temporal change in ASRs from 2010 to 2019. It is considered as an increasing trend if the APC and the lower boundary of the 95% CI were both positive. Whereas, if the APC and the upper boundary of the 95% CI were both negative, this was reflected as a decreasing trend. A neutral trend was noted when the 95% CI crossed zero. The ratio of male-to-female ASRs for GBTC–related incidence, deaths, and DALYs were analysed by WHO regions and SDI groups. RStudio (Version 4.1.1) was used to conduct statistical analyses.

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RESULTS

Sex Differences in the Global Burden of Gallbladder and Biliary Tract Cancers

ASIR, ASDRs, and ASDALYs of GBTC in 2010 globally were 2.56 per 100,000 (95%UI 2.07-2.71), 2.21 per 100,000 (95%UI 1.77-2.34), and 44.69 per 100,000 (95%UI 35.94-47.26) in males, and 2.78 per 100,000 (95%UI 2.27-3.03), 2.46 per 100,000 (95%UI 2.01-2.69) and 50.89 per 100,000 (95%UI 42.71-56.50) in females respectively **(Figure 1)**. Globally in 2019, the outcomes in ASIRs, ASDRs and ASDALYs were 2.39 in 100,000 (95%UI 1.92-2.65), 2.05 per 100,000 (95%UI 1.66-2.26), and 41.01 in 100,000 (95%UI 33.68-45.28) in males, and 2.57 per 100,000 (95%UI 2.09-2.96), 2.26 per 100,000 (95%UI 1.86-2.60) and 46.83 per 100,000 (95%UI 38.70-53.97) in females, respectively (**Figure 1**).

From 2010 to 2019, the APC of the ASIRs due to GBTC decreased both in males (APC: -0.80%; 95%CI -0.74 to -0.86) and females (APC: -0.89%; 95%CI -1.02 to -0.77) (**Table 1**). Although over the same period, ASDRs has down trended in males (APC: -0.83%; 95%CI -0.73 to -0.92), it had a stable trend in females (APC: -0.95%; 95%CI -1.05 to 0.84) (**Table 2**). During this study period, ASDALYs decreased in both males (APC: -1.00%; 95%CI -1.09 to -0.90) and females (APC: -0.96%; 95%CI -1.04 to -0.86) (**Table 3**).

Sex Differences in the Burden of Gallbladder and Biliary Tract Cancers by Regions

The estimated rates (ASIRs, ASDRs, and ASDALYs) by regions are summarized in **Tables 1-3**. From 2010 to 2019, the ASIRs in both males and females increased only in the South-East Asia (SEA) region (APC: 0.39%; 95%CI 0.30 to 0.48 and APC: 0.74%; 95%CI 0.51 to 0.98) and decreased in all regions with a biggest drop in the Western Pacific (WP) Region (APC: -1.37%; 95%CI -1.48 to -1.27 and APC: -1.85%; 95%CI -2.17 to -1.53) (**Figure 1**). During this same period, the ASIRs in males remained stable in the Eastern Mediterranean (EM) Region (APC: 0.03%, 95%CI -0.001 to 0.07). Similarly, the WP Region has the greatest decrease in APC for ASDRs of gallbladder cancer for both males and females (APC: -1.45%; 95%CI -1.57 to -1.33 and APC: -2.07%; 95%CI -2.34 to -1.81) and an increase in ASDRs for both males and females only in SEA (APC: 0.21%; 95%CI 0.08 to 0.34 and APC: 0.59%; 95%CI 0.34 to 0.84). Although all regions had showed the downward trend of ASDALYs, WP had the largest decrease in both sex (APC: -1.59%; 95%CI -1.80 to -1.30 and APC: -2.14%; 95%CI -2.37 to -1.90, respectively) except an increase in ASDALYs for females only in the South-East Asia region (APC: 0.41%; 95%CI 0.16 to 0.65) and a stable trend in males (APC: -0.06%; 95%CI -0.16 to 0.04). The ratio of male to female ASIRs due to gallbladder cancer in 2019 was 0.93 globally and ranged from 0.51 in the EM region to 1.26 in the WP (**Table 4**). In

addition, the ratio of male to female ASDRs in 2019 was 0.91 globally and ranged from 0.50 in the EM to 1.31 in the WP Region (**Table 5**). Similarly, the ratio of male to female ASDALYs in 2019 was 0.88 globally and ranged from 0.48 in the EM to 1.32 in the WP Region (**Table 6**).

Sex Differences in the Burden of Gallbladder and Biliary Tract Cancers by SDIs

Our study reveals an increase in ASIR in males only in the low-middle SDI countries (APC: 0.17%; 95%CI 0.06 to 0.29) alongside a decrease in all other SDI countries with the highest decrease in high SDI countries (APC: -1.14%; 95%CI -1.23 to -1.05) **(Tables 1-3)**. Among females, the high-middle SDI countries have the greatest decrease in ASIR (APC: -1.49%; 95%CI -1.64 to -1.35), while low-middle SDI countries have the greatest increase in ASIR (APC: 0.66%; 95% CI 0.37 to 0.95) (**Figure 2**). Similarly, in the female population, the high-middle SDI countries have the greatest decrease in both ASDRs (APC: -1.70%; 95%CI -1.82 to -0.57) and ASDALYs (APC: -1.74%; 95%CI -1.83 to -1.64) with the low-middle SDI countries showing the greatest increase in ASDRs (APC: 0.57%; 95%CI 0.35 to 0.78) and ASDALYs (APC: 0.47%; 95%CI 0.11 to 0.84) as well **(Figure 2)**. However, in the male population, the ASDRs of all SDI groups decreased from 2010 to 2019 except for the stable low-middle SDI countries. Similarly, the ASDALYs of the males in all SDI groups showed a decreasing trend, with the largest decrease seen in the high-SDI countries (APC: -1.43; 95%CI -1.51 to -1.33). In 2019, the ratio of male to female ASIRs was 0.93 globally and ranged from 0.58 in low-SDI countries to 1.18 in high-SDI countries. A similar observation was found for both ASDRs and ASDALYs in 2019, with a ratio of 0.91 and 0.88 globally and ranged from 0.59 and 0.56 in low-SDI countries to 1.15 and 1.16 in high-SDI countries respectively.

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DISCUSSION

Limited studies comprehensively exploring the sex differences in the global burden of GBTC currently exist. Our study further provides the analysis of updated global data, examining this issue in GBTC burden across temporal trends, regions, and SDIs. Building upon prior studies of GBD 2017 on the global burden of GBTC, our study validated and expanded upon the understanding of global increasing trends in the number of incidences of GBTC from 1990 to 2017[15,16]. Consistent with previous findings, both our study and GBD 2019 data highlight a persistent rising burden of GBTC in females compared to males.

We observed a global decline in ASIR and ASDALYs due to GBTC from 2010 to 2019 in both males and females consistent with the previous studies[16]. This observed decline is mostly attributed to improved healthcare accessibility and health literacy, allowing early detection and timely intervention[16]. However, our study demonstrated a steady decline in ASDRs among males while remaining stable among females. This data highlights a higher burden of GBTC in females, emphasizing sex disparity and a significant female predominance in GBTC cases.

Risk factors that have been most implicated in developing GBTC include obesity, sex, age, and metabolic diseases[17]. This sex disparity is largely attributed to genetic factors, particularly sex hormones[3], wherein females exhibit a higher susceptibility to gallbladder pathologies than their male counterparts. Increased parity and pregnancies have been proven to be strongly associated with gallstone-related gallbladder diseases[18-20]. The main pathophysiology involved estrogen-mediated increased biliary cholesterol secretion and decreased gallbladder contraction, resulting in increased cholesterol saturation in bile and subsequent gallstone formation. Additionally, females carry a higher level of estrogen throughout their reproductive years compared to males, and this elevates the risk of developing gallbladder and biliary tract diseases[15,18,21]. Moreover, lifestyle factors such as obesity, a sedentary lifestyle, and a cholesterol-rich diet are also more commonly observed in females compared to males[22-24]. Hence, addressing this sex disparity requires increased attention and targeted interventions such as promoting physical activity, advocating for healthy diets, and raising awareness, especially in females.

Our study, in line with prior research, highlights significant geographical disparities in GBTC burden. Hundal et al. reported that Asia exhibited significantly gallbladder cancer incidence rate compared to European, United States, Western and Mediterranean countries with particularly affecting Northern Indian and Pakistani females[25]. Regarding regional perspective, our study revealed increased ASIRs and ASDRs in both males and females solely in Southeast

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Asia, while both indices decreased in the other regions, Western Pacific region had the biggest decline. However, ASDALYs exhibited a decline in all the regions with the largest appearing in the WP region in both males and females, except the Southeast Asia region, that showed stable ASDALYs for males APC: -0.06%) and increase in females (APC: 0.41%). These variations in ASIRs, ASDRs, and ASDALYs across different regions stem from variations in socioeconomic, genetic, and environmental factors, as well as differences in disease prevalence, healthcare awareness, and access to healthcare[15,16]. This current study indicated increased ASIR, ASDR, and ASDALY rates observed in the Southeast Asia region, which were likely linked to poverty, widened care gaps, socioeconomic conditions, low health literacy and lack of access to healthcare. In addition to common risk factors, consuming raw fish can cause liver fluke and *Opisthorchis viverrini* infection, one of the leading risk factors for the development of cholangiocarcinoma in Southeast Asia regions[26]. Notably, *Salmonella* infection poses higher risks of biliary tract cancer[27-30]. Moreover, this bacterial infection is endemic to Asian countries, potentially contributing to a higher risk of GBTC development in the region[30]. Studies have shown a temporal relationship between chronic bacterial infections and the development of gallbladder cancer particularly in areas with high endemicity of infections[28]. Individuals with chronic *Salmonella* infection or being carriers of typhoid were also shown to have higher susceptibility to GBTC compared to non-carriers[27,28], underscoring the need for improved sanitation and vaccination policies to curb the spread in endemic Asian countries.

Furthermore, our analysis revealed an upward trend of ASIRs among both males and females in low-middle SDI countries, coupled with an increase in ASDRs and ASDALYs in females from 2010 to 2019. However, the other SDI countries showed decreasing trends for both groups, with the largest drop observed in high SDI countries. The correlation between ASIR and the high development index (HDI) of each country was first analyzed by Li et al.[15], showing that countries with a high HDI in 2019 had a lower GBTC burden, which is consistent with the SDI findings of our study. As obesity, diet, and physical activity levels are potential risk factors underlying these trends, the improvements in health literacy, increased consumption of healthy diet, engagement in physical activity, and enhanced accessibility to healthcare services support our findings. Conversely, sedentary lifestyles and increased high-calorie diet consumption in low SDI regions may have contributed to the upward trend observed in lower SDI countries[15].

Although this study provides an updated global analysis of sex disparities in the burden and trends of GBTC from 2010 to 2019, several limitations are evident. Firstly, the quality and

quantity of modelling data pose challenges. Due to the paucity of data in various regions, trend analysis heavily relies on modelling data derived from previous trends, resulting in potential inaccuracies. Moreover, regions with low socioeconomic status, such as South-East Asia and Africa, may be underrepresented mostly due to factors like low health literacy and limited access to healthcare, limiting generalizability. Future studies, thus, should incorporate large-scale population-based health surveys for more representative data. Secondly, analysis and discussion between subtypes of GBTC were not conducted in this study. Different subtypes could potentially demonstrate significant differences in epidemiology, pathophysiology, prognosis, and trends, warranting further analysis. Thirdly, risk factors for GBTC were not evaluated, which could provide valuable insights into the disease etiology and inform preventive measures. Lastly, significant differences in variable preventive steps and management policies among countries with different SDIs were not explored. More comprehensive data on these factors are necessary for a deeper understanding of their impacts on disease burden and the development of effective interventions.

In conclusion, our study presents an updated and comprehensive global overview of the comparative burden of GBTC between males and females across different regions and SDIs from 2010 to 2019. While ASIRs, ASDRs, and ASDALYs exhibited a global decline in both males and females, females still had a higher burden than males. Interestingly, an increased burden of GBTC was also observed in low-middle SDI regions, particularly affecting females. Ultimately, our results offer valuable insights into the global burden of GBTC, assisting policymakers in inventing and implementing cost-effective strategies ranging from prevention and early diagnosis to various management strategies. By effectively addressing and reversing the increasing trend of GBTC cases, these strategies can significantly impact public healthcare outcomes and alleviate the burden of GBTC on affected populations.

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FIGURES AND TABLES

Figure 1: Sex differences in estimated rates by Global and Regions

Figure 2: Sex differences in estimated rates by Global and SDIs

Table 1: Age-standardized incidence rates of gallbladder and biliary tract cancer in 2010 and 2019, and the temporal trend of age-standardized incidence rates from 2010 to 2019, stratified by sex.

Table 2: Age-standardized death rates of gallbladder and biliary tract Cancer 2010 and 2019, and the temporal trend of age-standardized death rates from 2010 to 2019, stratified by sex.

Table 3: Age-standardized disability adjusted life-year rate of gallbladder and biliary tract cancer in 2010 and 2019, and the temporal trend of age-standardized disability-adjusted life-years rates from 2010 to 2019, stratified by sex.

Table 4: Ratio of male and female age-standardized incidence rates of gallbladder and biliary tract cancer in 2010 and 2019

Table 5: Ratio of male and female age-standardized death rate of gallbladder and biliary tract cancer in 2010 and 2019

Table 6: Ratio of male and female age-standardized disability life-years rates of gallbladder and biliary tract cancer in 2010 and 2019

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Table 1: Age-standardized incidence rates (ASIRs) of gallbladder and biliary tract cancer in 2010 and 2019, and the temporal trend of age-standardized incidence rates from 2010 to 2019, stratified by sex

	MALE			FEMALE		
	2010 ASIR, per 100,000 (95%UI)	2019 ASIR per 100,000 (95%UI)	APC in ASIR (95%CI)	2010 ASIR, per 100,000 (95%UI)	2019 ASIR, per 100,000 (95%UI)	APC in ASIR (95%CI)
Global	2.56 (2.07-2.71)	2.39 (1.92-2.65)	-0.80 (-0.86 to -0.74) *	2.78 (2.27-3.03)	2.57 (2.09-2.96)	-0.89 (-1.02 to -0.77) *
SDI						
High SDI	3.78 (2.92-4.00)	3.42 (2.67-3.89)	-1.14 (-1.23 to -1.05) *	3.20 (2.54-3.63)	2.90 (2.28-3.46)	-1.15 (-1.41 to -0.89) *
High-middle SDI	2.72 (1.96-2.95)	2.51 (1.72-2.93)	-0.91 (-1.02 to -0.81) *	2.84 (2.18-3.09)	2.49 (1.86-2.91)	-1.49 (-1.64 to -1.35) *
Low SDI	1.38 (1.11-1.58)	1.36 (1.11-1.57)	-0.23 (-0.42 to -0.04) *	2.26 (1.69-2.77)	2.33 (1.80-2.80)	0.37 (0.02 to 0.73) *
Low-middle SDI	1.68 (1.45-1.98)	1.70 (1.44-2.01)	0.17 (0.06 to 0.29) *	2.56 (2.16-3.14)	2.71 (2.28-3.26)	0.66 (0.37 to 0.95)
Middle SDI	1.86 (1.60-2.09)	1.81 (1.49-2.13)	-0.37 (-0.44 to -0.30) *	2.16 (1.85-2.52)	2.01 (1.66-2.54)	-0.85 (-0.99 to -0.71) *
Region						
African Region	1.07 (0.93-1.39)	1.05 (0.91-1.34)	-0.22 (-0.32 to -0.13) *	1.48 (1.23-1.87)	1.44 (1.18-1.86)	-0.31 (-0.35 to -0.26) *
Eastern Mediterranean Region	1.35 (1.14-1.56)	1.36 (1.11-1.59)	0.03 (-0.001 to 0.08)	2.79 (2.31-3.36)	2.68 (2.20-3.31)	-0.41 (-0.46 to -0.37) *
European Region	2.44 (1.94-2.56)	2.23 (1.76-2.53)	-0.93 (-1.11 to -0.75) *	2.49 (2.03-2.94)	2.19 (1.82-2.70)	-1.40 (-1.67 to -1.13) *
Region of the Americas	2.11 (1.89-2.38)	2.00 (1.73-2.35)	-0.82 (-0.66 to -0.51) *	2.98 (2.63-3.77)	2.76 (2.36-3.61)	-0.83 (-0.97 to -0.68) *
South-East Asia Region	1.99 (1.51-2.21)	2.06 (1.50-2.43)	0.39 (0.30 to 0.48) *	2.69 (2.12 -3.17)	2.87 (2.13-3.42)	0.74 (0.51 to 0.98) *
Western Pacific Region	3.71 (2.68-4.05)	3.31 (2.32-3.88)	-1.37 (-1.48 to -1.27) *	3.08 (2.16-3.45)	2.63 (1.77-3.17)	-1.85 (-2.17 to -1.53) *

Legend: ASIR, Age-standardized incidence rates; APC, annual percent change; SDI, sociodemographic index; 95%CI, 95% Confidence Interval; 95%UI, 95% Uncertainty Interval, * Statistical Significance $p< 0.05$

Table 2: Age-standardized death rates (ASDRs) of Gallbladder and Biliary tract Cancer in 2010 and 2019, and the temporal trend of age-standardized death rates from 2010 to 2019, stratified by sex.

	MALE			FEMALE		
	2010 ASDR, per 100,000 (95% UI)	2019 ASDR, per 100,000 (95% UI)	APC in ASDR (95% CI)	2010 ASDR, per 100,000 (95% UI)	2019 ASDR, per 100,000 (95% UI)	APC in ASDR (95% CI)
Global	2.21 (1.77-2.34)	2.05 (1.66-2.26)	-0.827 (-0.92 to -0.73) *	2.46 (2.01-2.69)	2.26 (1.86-2.60)	-0.95 (-1.05 to 0.85)
SDI						
High SDI	2.74 (2.06-2.89)	2.49 (1.87-2.71)	-1.06 (-1.17 to -0.94) *	2.41 (1.87-2.68)	2.17 (1.69-2.47)	-1.25 (-1.44 to -1.06) *
High-middle SDI	2.41 (1.71-2.61)	2.17 (1.50-2.49)	-1.15 (-1.31 to -0.99) *	2.52 (1.94-2.77)	2.17 (1.64-2.51)	-1.70 (-1.82 to -1.57) *
Low SDI	1.43 (1.16-1.65)	1.40 (1.16-1.62)	-0.35 (-0.54 to -0.14) *	2.30 (1.76-2.81)	2.37 (1.80-2.83)	0.331 (- 0.03 to 0.7)
Low-middle SDI	1.70 (1.48-1.97)	1.70 (1.47-1.99)	0.06 (-0.07 to 0.19)	2.57 (2.16-3.19)	2.69(2.19-3.28)	0.57 (0.354 to 0.782) *
Middle SDI	1.81 (1.57-2.02)	1.72 (1.46-2.01)	-0.66 (-0.71 to -0.59) *	2.09 (1.80-2.46)	1.90 (1.56-2.39)	-1.09 (-1.21 to -0.96) *
Region						
African Region	1.11 (0.97-1.44)	1.08 (0.93-1.41)	-0.35 (-0.42 to -0.27) *	1.53 (1.26-1.95)	1.48(1.20-1.89)	-0.41 (-0.43 to -0.38) *
Eastern Mediterranean Region	1.34 (1.11-1.57)	1.31 (1.08-1.55)	-0.19 (-0.23 to -0.14) *	2.78 (2.31-3.46)	2.63 (2.10-3.29)	-0.59 (-0.63 to -0.54) *
European Region	1.84 (1.47-1.92)	1.65 (1.32-1.78)	-1.19 (-1.47 to -0.89) *	2.04 (1.66-2.40)	1.77 (1.50-2.13)	-1.59 (-1.87 to -1.31) *
Region of the Americas	1.60 (1.45-1.81)	1.50 (1.35-1.72)	-0.63 (-0.71 to -0.54) *	2.50 (2.21-3.17)	2.30 (2.02-3.01)	-0.88 (-1.06 to -0.70) *
South-East Asia Region	1.98 (1.50-2.18)	2.01 (1.52-2.36)	0.21 (0.08 to 0.34) *	2.68 (2.13-3.18)	2.83 (2.08-3.39)	0.59 (0.34 to 0.84) *
Western Pacific Region	3.34 (2.39-3.64)	2.95 (2.14-3.42)	-1.45 (-1.57 to -1.33) *	2.71 (1.88-3.03)	2.26 (1.55-2.68)	-2.07 (-2.34 to -1.81) *

Legend: ASDR, Age-standardized death rates; APC, annual percent change; SDI, sociodemographic index; 95%CI, 95% Confidence Interval; 95%UI, 95% Uncertainty Interval, * Statistical Significance $p< 0.05$

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Table 3: Age-standardized DALY (ASDALYs) of Gallbladder and Biliary tract cancer in 2010 and 2019, and the temporal trend of age-standardized disability-adjusted life years rates from 2010 to 2019, stratified by sex.

	MALE			FEMALE		
	2010 ASDALY, per 100,000 (95% UI)	2019 ASDALY, per 100,000 (95% UI)	APC in ASDALY (95% CI)	2010 ASDALY, per 100,000 (95% UI)	2019 ASDALY, per 100,000 (95% UI)	APC in ASDALY (95% CI)
Global	44.69 (35.94-47.26)	41.01 (33.68-45.28)	-1.00 (-1.09 to -0.90) *	50.89 (42.71-56.50)	46.83 (38.70-53.97)	-0.96 (-1.04 to -0.86) *
SDI						
High SDI	51.62 (40.64-53.89)	45.43 (35.90-49.38)	-1.43 (-1.51 to -1.33) *	44.72 (37.14-52.68)	39.10 (33.12-47.19)	-1.53 (-1.70 to -1.36) *
High-middle SDI	50.06 (35.47-54.48)	45.02 (30.85-52.21)	-1.18 (-1.33 to -1.02) *	52.78 (40.27-57.67)	45.28 (33.72-53.00)	-1.74 (-1.83 to -1.64) *
Low SDI	31.52 (25.19-36.37)	30.29 (24.95-35.35)	-0.48 (-0.65 to -0.31) *	54.03 (41.12-65.78)	54.07 (40.96-64.86)	-0.002 (-0.27 to 0.27)
Low-middle SDI	38.01 (32.78-44.51)	37.44 (32.18-43.66)	-0.18 (-0.36 to -0.004) *	59.61 (50.18-71.69)	61.94 (50.36-73.33)	0.47 (0.11 to 0.84) *
Middle SDI	38.74 (33.12-42.81)	36.37 (30.68-42.80)	-0.75 (-0.83 to -0.67) *	44.70 (37.68-51.71)	40.31 (32.96-49.67)	-1.19 (-1.30 to -1.08) *
Region						
African Region	23.60 (20.36-30.34)	22.63 (19.37-29.64)	-0.46 (-0.51 to -0.40) *	32.85 (27.09-40.87)	31.08 (25.11-39.16)	-0.61 (-0.63 to -0.58) *
Eastern Mediterranean Region	29.89 (24.64-35.22)	29.05 (23.47-34.13)	-0.30 (-0.33 to -0.26) *	64.15 (52.67-78.31)	60.03 (46.36-74.90)	-0.68 (-0.73 to -0.64) *
European Region	37.14 (30.21-38.58)	32.94 (29.76-35.68)	-1.29 (-1.62 to -0.95) *	40.87 (34.28-48.62)	35.04 (30.28-42.64)	-1.70 (-1.95 to -1.44) *
Region of the Americas	34.22 (31.13-38.08)	32.31 (29.21-36.82)	-0.60 (-0.69 to -0.50) *	55.48 (49.35-69.82)	50.80 (45.50-65.84)	-0.96 (-1.1 to -0.82) *
South-East Asia Region	43.88 (33.13-48.54)	43.71 (32.74-51.79)	-0.06 (-0.16 to 0.04) *	61.88 (47.88-71.56)	64.36 (45.94-77.51)	0.41 (0.16 to 0.65) *
Western Pacific Region	61.18 (45.92-66.72)	53.34 (39.96-62.79)	-1.59 (-1.80 to -1.30) *	48.90 (35.59-54.50)	40.51(28.27-48.76)	-2.14 (-2.37 to -1.90) *

Legend: ASDALY, Age-standardized disability-adjusted life years; APC, annual percent change; SDI, sociodemographic index; 95%CI, 95% Confidence Interval; 95%UI, 95% Uncertainty Interval, * Statistical Significance $p < 0.05$

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Table 4: Ratio of Male and Female Age-standardized Incidence Rates of Gallbladder and Biliary tract cancer in 2010 and 2019

	2010			2019		
	Male ASIR	**Female ASIR**	**Ratio of Male/Female ASIR**	**Male ASIR**	**Female ASIR**	**Ratio of Male/Female ASIR**
Global	2.56	2.78	0.92	2.39	2.57	0.93
SDI						
High SDI	3.78	3.20	1.18	3.42	2.90	1.18
High-middle SDI	2.72	2.84	0.96	2.51	2.49	1.01
Low SDI	1.38	2.26	0.61	1.36	2.33	0.58
Low-middle SDI	1.68	2.56	0.66	1.70	2.71	0.63
Middle SDI	1.86	2.16	0.86	1.81	2.01	0.90
Region						
African Region	1.07	1.48	0.72	1.05	1.44	0.73
Eastern Mediterranean Region	1.35	2.79	0.48	1.36	2.68	0.51
European Region	2.44	2.49	0.98	2.23	2.19	1.02
Region of the Americas	2.11	2.98	0.71	2.00	2.76	0.72
South-East Asia Region	1.99	2.69	0.74	2.06	2.87	0.72
Western Pacific Region	3.71	3.08	1.20	3.31	2.63	1.26

Legend: ASIR, Age-standardized incidence rates; SDI, sociodemographic index

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Table 5: Ratio of Male and Female Age-standardized death rates of Gallbladder and Biliary tract cancer in 2010 and 2019

	2010			2019		
	Male ASDR	**Female ASDR**	**Ratio of Male/Female ASDR**	**Male ASDR**	**Female ASDR**	**Ratio of Male/ Female ASDR**
Global	2.21	2.46	0.90	2.05	2.26	0.91
SDI						
High SDI	2.74	2.41	1.14	2.49	2.17	1.15
High-middle SDI	2.41	2.52	0.96	2.17	2.17	1.00
Low SDI	1.43	2.30	0.62	1.40	2.37	0.59
Low-middle SDI	1.70	2.57	0.66	1.70	2.69	0.63
Middle SDI	1.81	2.09	0.87	1.72	1.90	0.91
Region						
African Region	1.11	1.53	0.73	1.08	1.48	0.73
Eastern Mediterranean Region	1.34	2.78	0.48	1.31	2.63	0.50
European Region	1.84	2.04	0.90	1.65	1.77	0.93
Region of the Americas	1.60	2.50	0.64	1.50	2.30	0.65
South-East Asia Region	1.98	2.68	0.74	2.01	2.83	0.71
Western Pacific Region	3.34	2.71	1.23	2.95	2.26	1.31

Legend: ASDR, Age-standardized death rates; SDI, sociodemographic index

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Table 6: Ratio of Male and Female Age-standardized DALY rates of gallbladder and Biliary tract cancer in 2010 and 2019

	2010			2019		
	Male ASDALY	**Female ASDALY**	**Ratio of Male/Female ASDALY**	**Male ASDALY**	**Female ASDALY**	**Ratio of Male/Female ASDALY**
Global	44.69	50.89	0.88	41.01	46.83	0.88
SDI						
High SDI	51.62	44.72	1.15	45.43	39.10	1.16
High-middle SDI	50.06	52.78	0.95	45.02	45.28	0.99
Low SDI	31.52	54.03	0.58	30.29	54.07	0.56
Low-middle SDI	38.01	59.61	0.64	37.44	61.94	0.60
Middle SDI	38.74	44.70	0.87	36.37	40.31	0.90
Region						
African Region	23.60	32.85	0.72	22.63	31.08	0.73
Eastern Mediterranean Region	29.89	64.15	0.47	29.05	60.03	0.48
European Region	37.14	40.87	0.91	32.94	35.04	0.94
Region of the Americas	34.22	55.48	0.62	32.31	50.80	0.64
South-East Asia Region	43.88	61.88	0.71	43.71	64.36	0.68
Western Pacific Region	61.18	48.90	1.25	53.34	40.51	1.32

Legend: ASDALY, Age-standardized disability-adjusted life years rates; SDI, sociodemographic index

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