Disease Burden of Gallbladder Cancer in China, 1990-2019, and Future Trend Analysis: Postprint

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Abstract

Background: Gallbladder cancer is difficult to detect at an early stage, is associated with poor treatment outcomes, and has a high mortality rate. Further epidemiological research on gallbladder cancer can provide valuable data to inform the formulation of prevention and treatment strategies.

Objective: To analyze the epidemiological trends of gallbladder cancer disease burden in China from 1990 to 2019, and to estimate its age, period, and cohort effects and future trends.

Methods: From March to June 2023, the Global Burden of Disease Study 2019 (GBD 2019) database was searched to extract disease burden-related data on gallbladder cancer in China from 1990 to 2019, including incidence rate, prevalence rate, mortality rate, disability-adjusted life years (DALYs) rate, and corresponding standardized rates. Joinpoint software was used to calculate the annual percent change (APC) and average annual percent change (AAPC) to analyze the trends of gallbladder cancer disease burden in China from 1990 to 2019. A Bayesian age-period-cohort (BAPC) model was constructed to predict the incidence of gallbladder cancer in China from 2020 to 2030.

Results: From 1990 to 2019, the standardized incidence rate of gallbladder cancer in China increased from 1.58/100,000 in 1990 to 2.01/100,000 in 2019, with an AAPC of 0.82% (95%CI=0.65%~1.00%); the standardized prevalence rate increased from 1.64/100,000 in 1990 to 2.40/100,000 in 2019, with an AAPC of 1.34% (95%CI=1.14%~1.54%); the standardized mortality rate increased from 1.61/100,000 in 1990 to 1.82/100,000 in 2019, with an AAPC of 0.40% (95%CI=0.24%~0.56%); the standardized DALYs rate increased from 35.18/100,000 in 1990 to 37.71/100,000 in 2019, with an AAPC of 0.25% (95%CI=0.12%~0.38%); all trend changes were statistically significant (P<0.001). BAPC model analysis showed that the net drift values for gallbladder cancer incidence and mortality rates in China from 1990 to 2019 were

0.99 (95%CI=0.81~1.18) and 0.42 (95%CI=0.21~0.63), respectively. Both gallbladder cancer incidence and mortality rates demonstrated an increasing trend with age, with peak incidence observed in the population aged 80 years and above. The risks of incidence and mortality exhibited a pattern of first decreasing, then increasing, and then decreasing again over time, peaking during 2005-2009. Both showed a trend of first increasing and then decreasing with birth cohort. BAPC model projections indicated that the standardized incidence rate, prevalence rate, mortality rate, and DALYs rate attributable to gallbladder cancer in China would demonstrate a slight upward trend from 2020 to 2030.

Conclusion: From 1990 to 2019, the standardized incidence rate, prevalence rate, mortality rate, and DALYs rate of gallbladder cancer in China demonstrated an increasing trend, indicating that the disease burden remains severe. Prevention and treatment of gallbladder cancer should be strengthened among male and elderly populations, with vigorous promotion of cancer prevention knowledge, control of biliary tract diseases, and advocacy of healthy lifestyles to reduce the disease burden of gallbladder cancer.

Full Text

Disease Burden of Gallbladder Cancer in China from 1990 to 2019 and Analysis of Future Trends

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Abstract

Background: Gallbladder cancer is characterized by difficult early detection, poor treatment efficacy, and high mortality. Further epidemiological research on gallbladder cancer can provide valuable data for formulating prevention and treatment strategies.

Objective: To analyze the epidemic trends of gallbladder cancer disease burden in China from 1990 to 2019, and to estimate its age, period, and cohort effects and future trends.

Methods: From March to June 2023, data on gallbladder cancer incidence, prevalence, mortality, disability-adjusted life years (DALYs) rate, and corresponding standardized rates in China from 1990 to 2019 were extracted from the Global Burden of Disease Study 2019 (GBD 2019) database. Joinpoint software was used to calculate the annual percent change (APC) and average annual percent change (AAPC) to analyze the trend of disease burden from 1990 to 2019. A Bayesian age-period-cohort (BAPC) model was constructed to predict the incidence of gallbladder cancer in China from 2020 to 2030.

Results: From 1990 to 2019, the standardized incidence rate of gallbladder cancer in China increased from 1.58/100,000 in 1990 to 2.01/100,000 in 2019, with an AAPC of 0.82% (95%CI=0.65%~1.00%). The standardized prevalence rate increased from 1.64/100,000 in 1990 to 2.40/100,000 in 2019, with an AAPC of 1.34% (95%CI=1.14%~1.54%). The standardized mortality rate increased from 1.61/100,000 in 1990 to 1.82/100,000 in 2019, with an AAPC of 0.40% (95%CI=0.24%~0.56%). The standardized DALYs rate increased from 35.18/100,000 in 1990 to 37.71/100,000 in 2019, with an AAPC of 0.25% (95%CI=0.12%~0.38%). All trends were statistically significant (P<0.001). BAPC model analysis showed that the net drift values for incidence and mortality rates in China from 1990 to 2019 were 0.99 (95%CI=0.81~1.18) and 0.42 (95%CI=0.21~0.63), respectively. Both incidence and mortality increased with age, peaking in the 80+ age group. The risk of onset and death showed a pattern of initial decline, followed by increase, then decline again over time, peaking during 2005-2009. Both risks showed an initial increase followed by a decreasing trend across birth cohorts. BAPC model predictions indicated that standardized incidence, prevalence, mortality, and DALYs rates in China will show a slight upward trend from 2020 to 2030.

Conclusion: From 1990 to 2019, the standardized incidence, prevalence, mortality, and DALYs rates of gallbladder cancer in China showed an upward trend, indicating a serious disease burden. Prevention and treatment efforts should be strengthened for male and elderly populations, with vigorous promotion of cancer prevention knowledge, control of biliary diseases, and advocacy for healthy lifestyles to reduce the disease burden of gallbladder cancer.

Keywords: Gallbladder neoplasms; Gallbladder cancer; Global burden of disease; Incidence; Prevalence; Mortality; Disability-adjusted life years; Trend analysis

1. Introduction

Gallbladder cancer, a common malignant tumor of the biliary system, accounts for 80%-95% of bile duct cancers. Due to its subtle early symptoms, most cases are diagnosed at advanced stages with extremely poor prognosis, and the 5-year survival rate is only 5%-15% [1-3]. According to the International Agency for Research on Cancer (IARC), there were 115,900 new cases and 84,700 deaths

from gallbladder cancer globally in 2020, representing 0.6% and 0.9% of all malignant tumors, respectively [4]. As the world's most populous country, China has the highest number of gallbladder cancer cases and deaths globally, accounting for 24.9% and 27.5% of the worldwide totals. Chinese cancer registry data show that in 2016, there were 55,700 new cases and 41,400 deaths from gallbladder cancer in China, representing 1.37% and 1.72% of all malignant tumors [5]. Currently, research on the changing trends of gallbladder cancer disease burden in China remains limited. The Global Burden of Disease Study 2019 (GBD 2019) database provides comprehensive global data on the prevalence of specific diseases and risk factors, as well as their relative harm [6-7]. Therefore, this study extracted data on gallbladder cancer in China from GBD 2019 to analyze the changing disease burden, employed a Bayesian age-period-cohort (BAPC) model to explore age, period, and cohort effects and future trends, and provide references for developing gallbladder cancer prevention and control strategies.

1.1 Data Sources and Indicators

From March to June 2023, disease burden data on gallbladder cancer in China from 1990 to 2019 were extracted from the GBD 2019 database. Considering that both incidence and mortality were zero in populations under 20 years old, and that the population aged 80+ had limited representation and minimal intervention effect, this study included data for populations aged $ $20 years, with 5-year age groups. Incidence, prevalence, mortality, and DALYs rates, along with their corresponding standardized rates (all using 95% uncertainty intervals), were presented by sex and age group to describe the changing disease burden of gallbladder cancer in China from 1990 to 2019.

1.2 Statistical Methods

1.2.1 Joinpoint Regression Model: A log-linear regression model established by Joinpoint software based on data characteristics was used to calculate the annual percent change (APC), average annual percent change (AAPC), and their 95% confidence intervals, primarily for analyzing temporal trends in rates and standardized rates [8-9].

1.2.2 BAPC Model: The BAPC model can estimate the effects of age, period, and cohort on diseases [10-12]. This study used the BAPC model to estimate net drift, local drift, age effects, period effects, and cohort effects.

1.2.3 BAPC Model Prediction: Based on the disease burden results for gallbladder cancer in China from 1990 to 2019, the BAPC package in R software was used to predict disease burden changes from 2020 to 2030. Data from 2010-2019 were used as the test set to evaluate the accuracy of the BAPC prediction model. Evaluation metrics included mean square error (MSE), mean absolute error (MAE), mean absolute percentage error (MAPE), and fitting accuracy, with higher fitting accuracy indicating better prediction performance.

1.3 Statistical Analysis

Excel 2010 was used to collect and organize disease burden data for gallbladder cancer in China from 1990 to 2019. Joinpoint software was used to analyze trends in disease burden, the IARC website's web-based analysis tool was used to fit the BAPC model, and the BAPC package in R software was used to predict future disease burden.

2. Results

2.1 Overall Disease Burden of Gallbladder Cancer

From 1990 to 2019, the standardized incidence rate of gallbladder cancer in China increased from 1.58/100,000 in 1990 to 2.01/100,000 in 2019, with an AAPC of 0.82% (95%CI=0.65%~1.00%, P<0.001). The standardized prevalence rate increased from 1.64/100,000 in 1990 to 2.40/100,000 in 2019, with an AAPC of 1.34% (95%CI=1.14%~1.54%, P<0.001). The standardized mortality rate increased from 1.61/100,000 in 1990 to 1.82/100,000 in 2019, with an AAPC of 0.40% (95%CI=0.24%~0.56%, P<0.001). The standardized DALYs rate increased from 35.18/100,000 in 1990 to 37.71/100,000 in 2019, with an AAPC of 0.25% (95%CI=0.12%~0.38%, P<0.001). See Tables 1 and 2.

2.2 Disease Burden by Sex

From 1990 to 2019, the standardized incidence rate among Chinese males increased from 1.56/100,000 to 2.25/100,000 (a 44.23% increase), with an AAPC of 1.23% (95%CI=0.99%~1.48%, P<0.001). Among females, it increased from 1.64/100,000 to 1.84/100,000 (a 12.20% increase), with an AAPC of 0.39% (95%CI=0.08%~0.70%, P<0.001). The standardized prevalence rate in males increased from 1.60/100,000 to 2.63/100,000 (a 64.38% increase), with an AAPC of 1.70% (95%CI=1.45%~1.96%, P<0.001). In females, it increased from 1.70/100,000 to 2.23/100,000 (a 31.18% increase), with an AAPC of 0.94% (95%CI=0.64%~1.24%, P<0.001). Male standardized mortality increased from 1.62/100,000 to 2.09/100,000 (a 29.01% increase), with an AAPC of 0.86% (95%CI=0.63%~1.08%, P<0.001). Female standardized mortality decreased from 1.66/100,000 to 1.64/100,000 (a 1.20% decrease), with an AAPC of -0.06% (95%CI=-0.37%~0.25%, P<0.001). Male standardized DALYs rate increased from 34.26/100,000 to 42.60/100,000 (a 24.34% increase), with an AAPC of 0.72% (95%CI=0.47%~0.97%, P<0.001). Female standardized DALYs rate decreased from 36.46/100,000 to 33.57/100,000 (a 7.93% decrease), with an AAPC of -0.28% (95%CI=-0.52%~-0.05%, P<0.05). See Tables 1 and 2.

2.3 Disease Burden by Age Group

From 1990 to 2019, age-specific incidence, prevalence, mortality, and DALYs rates for gallbladder cancer in China remained low in the 20-39 age group, increased slowly after age 40, and rose significantly after age 60. With increasing

age, all rates increased, and the 80+ age group had the highest incidence, prevalence, mortality, and DALYs rates over the 30-year period [Figure 1: see original paper].

2.4 BAPC Model Analysis Results

2.4.1 BAPC Model Analysis of Gallbladder Cancer Incidence in China (1990-2019): The net drift values for overall, male, and female gallbladder cancer incidence were 0.99 (95%CI=0.81~1.18), 0.05 (95%CI=-0.21~0.30), and 0.09 (95%CI=-0.18~0.36), respectively. Local drift values for overall, male, and female incidence increased with age, peaking in the $ $80 age group at 2.18 (95%CI=1.89~2.47), 1.55 (95%CI=1.08~2.03), and 1.84 (95%CI=1.48~2.21), respectively.

Age Effect: After controlling for period and cohort effects, gallbladder cancer incidence in the overall, male, and female populations showed an upward trend with age, increasing more gradually before age 60 and rising rapidly thereafter, most notably in the overall population, with the highest incidence in the $ $80 age group [Figure 2: see original paper]B.

Period Effect: After controlling for age and cohort effects, with 2000-2004 as the reference (RR=1.00), the RR values for overall, male, and female gallbladder cancer incidence began to decline in 1990-1994, then increased after 2000-2004, peaking in 2005-2009 (overall RR=1.16, 95%CI=1.13~1.20; male RR=1.18, 95%CI=1.13~1.24; female RR=1.11, 95%CI=1.07~1.16) before falling [Figure 2: see original paper]C.

Cohort Effect: After controlling for age and period effects, with the 1950-1954 birth cohort as the reference, the overall incidence RR showed an initial increase followed by a decrease. Risk increased among those born between 1910-1984, then decreased among those born between 1985-1999. Similar patterns were observed for males and females, with peak risk in the 1955-1959 cohort (male RR=1.01, 95%CI=0.95~1.07; female RR=1.01, 95%CI=0.95~1.07) [Figure 2: see original paper]D.

2.4.2 BAPC Model Analysis of Gallbladder Cancer Mortality in China (1990-2019): The net drift values for overall, male, and female gallbladder cancer mortality were 0.42 (95%CI=0.21~0.63), -0.46 (95%CI=-0.76~-0.17), and -0.59 (95%CI=-0.88~-0.29), respectively. Local drift values for overall, male, and female mortality increased with age, peaking in the $ $80 age group at 1.66 (95%CI=1.40~1.92), 1.11 (95%CI=0.68~1.54), and 1.26 (95%CI=0.95~1.57), respectively.

Age Effect: After controlling for period and cohort effects, gallbladder cancer mortality in the overall, male, and female populations increased with age, rising more gradually before age 60 and rapidly thereafter, most notably in the overall population, with the highest mortality in the $ $80 age group [Figure 3: see original paper]B.

Period Effect: After controlling for age and cohort effects, with 2000-2004 as the reference (RR=1.00), overall, male, and female mortality RR values began to decline in 1990-1994, then increased after 1995-1999, peaking in 2005-2009 (overall RR=1.13, 95%CI=1.09~1.16; male RR=1.15, 95%CI=1.10~1.21; female RR=1.07, 95%CI=1.03~1.11) before falling [Figure 3: see original paper]C.

Cohort Effect: After controlling for age and period effects, with the 1950-1954 birth cohort as reference, overall, male, and female mortality RR values showed an initial increase followed by a decrease. Risk increased among those born between 1910-1959, then decreased among those born between 1960-1999, peaking in the 1955-1959 cohort (overall RR=1.03, 95%CI=0.99~1.08; male RR=1.00, 95%CI=0.94~1.06; female RR=0.99, 95%CI=0.93~1.05) [Figure 3: see original paper]D.

2.5 Disease Burden Predictions

The prediction model achieved fitting accuracy above 99% for all indicators, indicating good predictive performance. The BAPC model predicted that standardized incidence, prevalence, mortality, and DALYs rates for gallbladder cancer in China will show a slight upward trend from 2020 to 2030, potentially reaching 2.07/100,000, 2.57/100,000, 1.86/100,000, and 37.81/100,000, respectively, by 2030 .

3. Discussion

Gallbladder cancer originates from glandular epithelium, most commonly in the gallbladder fundus, and is a malignant tumor that seriously threatens human health. The disease burden varies considerably by geographic region, with Chile having the highest incidence (27/100,000), followed by northern India (21.5/100,000). Other high-risk areas include Poland (14/100,000), southern Pakistan (11.3/100,000), Japan (7/100,000), and Israel (5/100,000) [13]. Gallbladder cancer prevention and control are challenging due to subtle early symptoms, late-stage diagnosis, high fatality rates, and limited understanding of risk factors and etiology [14]. Research on gallbladder cancer disease burden in China is scarce. This study analyzed GBD 2019 data to examine trends from 1990-2019 and provide clues for etiological research.

We found that standardized incidence, prevalence, mortality, and DALYs rates for gallbladder cancer in China increased from 1990-2019, contrasting with declining trends in most countries worldwide, indicating that China's gallbladder cancer prevention situation remains severe. Major risk factors include gallstones, biliary anomalies, obesity, smoking, and alcohol consumption [15-18]. Gallstones are the primary risk factor, with larger stones conferring greater risk, though the mechanism remains unclear. Current evidence suggests gallstones slow bile release, while biliary anomalies cause pancreatic juice reflux into the gallbladder, stimulating inflammation and increasing cancer risk [19]. Obesity may increase cholesterol saturation in bile, promoting gallstone formation. Stud-

ies show that each 5 kg/m^2 increase in BMI raises gallbladder cancer risk by 0.59-fold [20].

Notably, the increases in standardized incidence, prevalence, mortality, and DALYs rates were higher among males than females from 1990-2019. By 2019, male rates exceeded female rates, reversing the 1990 pattern and contradicting findings from global studies and registry-based studies in Gansu and Shanghai that showed lower male rates [21-23]. This discrepancy may reflect that GBD data are model-based estimates whose accuracy depends heavily on the quality of original registry data. Additionally, males may have higher exposure to risk factors, particularly more prevalent smoking and alcohol consumption, whose cumulative effects may have gradually increased male disease burden [24].

We found that incidence, prevalence, mortality, and DALYs rates increased significantly after age 60, peaking in the $ $80 age group, consistent with BAPC age effects showing increasing incidence and mortality with age. This identifies middle-aged and elderly populations as key targets for prevention and control. Period effects showed decreasing risks after 2010, likely reflecting improved healthcare and diagnostic technologies that enhance early detection. Cohort effects showed initial increases then decreases in risk across birth cohorts, rising among those born 1910-1984 for incidence and 1910-1959 for mortality, then declining among those born 1985-1999 and 1960-1999, respectively. These cohort patterns reflect not only disease changes but also historical, social, and medical developments. Before the founding of the People's Republic of China, social turmoil, war, natural disasters, and scarce medical resources may have increased risks. After 1949, China's healthcare system gradually improved, reducing mortality risk. Following reform and opening-up, rapid medical development, widespread early cancer screening, and enhanced health awareness further reduced incidence and mortality risks [25].

Predictions indicate slight upward trends in standardized incidence, prevalence, mortality, and DALYs rates from 2020-2030, suggesting that gallbladder cancer prevention and control in China faces ongoing challenges requiring strengthened primary and secondary prevention. Healthy lifestyles—including maintaining normal weight, regular diet, and reducing smoking and alcohol consumption—can effectively reduce risk [26-27]. High-risk populations, such as those with chronic calculous cholecystitis, atrophic gallbladder with contents, filled gallstones, gallbladder wall thickening with long-standing stones, hilar masses, or liver masses adjacent to the gallbladder as the initial manifestation, should undergo regular screening for early detection, diagnosis, and treatment.

Limitations: (1) Due to data distribution constraints, we could not explore regional variations in gallbladder cancer burden within China. (2) Some GBD data are mathematically modeled, which may be less accurate and complete than population-based cancer registry data.

In conclusion, standardized incidence, prevalence, mortality, and DALYs rates of gallbladder cancer in China increased from 1990-2019, representing a serious

disease burden. Prevention and treatment should be strengthened for male and elderly populations, with vigorous promotion of cancer prevention education, biliary disease control, and healthy lifestyles to reduce the gallbladder cancer burden.

Author Contributions: LIU Shanshan and LI Chuyi were responsible for overall design, data analysis, and manuscript writing and revision. ZHENG Ying, LU Lixia, and LI Bin were responsible for data collection, analysis, and organization. DANG Zheng and YU Xiaohui were responsible for quality control and review and provided funding support.

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Note: Figure translations are in progress. See original paper for figures.