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Gallbladder cancer incidence and mortality rate trends in China: analysis of data from the population-based cancer registry

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Abstract

Background Gallbladder cancer is a major health concern in China, and awareness of the associated incidence and mortality rates is particularly important given the aging population.

Objective To determine trends in gallbladder cancer incidence and mortality rates over 12 years and quantitatively analyze the influence of demographic factors on these rates in China.

Methods We performed a retrospective study of 98,860 Chinese citizens using the Chinese Cancer Registry, a national database. Gallbladder cancer incidence and mortality data pertaining to patients treated between 2005 and 2017 were collected. Joinpoint regression models were used to estimate the annual percentage change (APC) and average APC (AAPC). We used age-period-cohort analyses and decomposition methods to investigate differing trends in incidence and mortality.

Results The age-standardized gallbladder cancer incidence and mortality rates in China trended downward between 2005 and 2017, with AAPCs of -2.023% and -1.603%, respectively. Coefficients of age effect for incidence rate increased with age up to 70 years and peaked at 70–79 years, while coefficients of age effect for the mortality rate showed a consistent increase with age. Both coefficients of period for incidence and mortality rates increased in more recent periods; in terms of the cohort effect, coefficients of cohort for rates generally decreased in later birth years but showed a partial rise between 1982 and 1996. The crude incidence rates of gallbladder cancer according to demographic and non-demographic factors were 626.09% and -526.09% respectively (366.23% and -266.23% among men, and 6068.93% and -5968.93% among women, respectively). The rates were 543.01% and -443.01%, respectively, in urban areas and were 68.22% and 31.78%, respectively, in rural areas. The mortality rates according to demographic and non-demographic factors were -495.93% and 595.93%, respectively (-1763.10% and -1863.10% for men and -270.56% and -370.56% for women, respectively). These rates were -930.33% and 1030.33%, respectively, in urban areas and were 101.48% and -1.48%, respectively, in rural areas.

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Conclusions The overall standardized gallbladder cancer incidence and mortality rates in China are trending downward, but not sufficiently so. Proper living and eating habits should be encouraged while exploring the establishment of long-term, standardized gallbladder cancer screening programs.

Keywords Gallbladder cancer, China, Age-period-cohort analysis, Incidence rate, Mortality rate

Introduction

Gallbladder cancer (GBC) is the most common malignancy of the biliary tract and, with a five-year survival rate of 5–15%, is highly lethal [1–3]. According to the International Agency for Research on Cancer-Global Cancer Observatory (GLOBOCAN), there were 115,900 new diagnoses of GBC in 2020 (ranking 24th on the global cancer incidence spectrum), while the number of deaths was 84,700 (ranking 24th on the global cancer mortality death spectrum) [4]. According to the China Cancer Registry annual report of 2020, the number of new GBC diagnoses in 2017 was 17,400 (ranking 18th on the cancer incidence spectrum in China) while the number of deaths was 13,200 (ranking 14th on the cancer mortality spectrum) [5]. As such, Chinese patients with GBC account for nearly one-quarter of all global cases [6]. Previous studies have found a significantly increasing mortality rate in rural areas from 2013 to 2019, with an average annual percent change (AAPC) of 2.64% in males and 3.85% in females [7]. In Shanghai, the largest and most modern city in China, from 1973 to 2009, the GBC incidence has risen from 1.1/105 to 2.9/100,000 in men and from 1.7/100,000 to 3.9/100,000 in women. The mortality trends increased with an estimated annual percent change (APC) of 2.8% in men and 2.5% in women [8]. GBC is a serious health concern in China and entails a heavy disease burden. Given the increasingly aging population combined with the greater risk posed by changing lifestyle habits, GBC will continue to be a notable public health hazard for the foreseeable future. Epidemiological data on China derived from the Global Burden of Disease (GBD) 2019 are estimated using previous information and models. However, there is a lack of accurate population-based data on the actual incidence and mortality rates of GBC in the country [9, 10]. Certain studies investigated only the changing trends of GBC mortality and the possible impact of aging [7, 11]. To address this gap in knowledge, we analyzed changes in GBC incidence and mortality rates in China between 2005 and 2017 using actual data obtained from the national cancer registry, and performed both age-period-cohort and population aging analyses to determine the influences of these factors on the rates. We aimed to provide scientific bases for formulating GBC prevention and treatment strategies in China.

Methods

Data source

The incidence and mortality data of registered permanent residents with GBC during 2005–2017 were derived from the China Cancer Registry Annual Report, 2008–2020 published by the National Central Cancer Registry of China, cancer registration data are usually delayed by three years [5, 12–23]. The registry encompasses 31 provinces (autonomous regions and municipalities) across the country as well as the Xinjiang Production and Construction Corps (excluding Hong Kong, Macao Special Administrative Regions, and Taiwan Province). There is a balanced sex ratio between urban and rural areas covered by Cancer Registries.The sex ratio between urban and rural is shown in Supplementary Table A.The data were reviewed, evaluated, collated and analyzed according to the requirements of the Chinese guideline cancer registration and the standards of International Agency for Research on Cancer/International Association of Cancer Registries. The classification of urban and rural areas in this study was based on the classification criteria of the China Cancer Registry Annual Report: urban areas were classified as cities above prefecture level, and rural areas were classified as counties and county-level cities. The data collection and quality control workflow is shown in Supplementary Figure A.

Statistical analysis

Joinpoint regression analysis

Data on GBC-associated incidence and mortality in the Annual Report of the China Cancer Registry from 2005 to 2017 were collected and entered into Excel 2016 (Microsoft Corp., Redmond, WA, USA) to establish a database [24]. Data were stratified according to sex, locale (urban versus rural), and age group (0 to < 1, 1–4, 5–9, 10–14, …, and 80–84 years). Segi's world population standard was used to calculate the age-standardized incidence and mortality rates (ASIRs and ASMRs, respectively). The Joinpoint Regression Program (version 4.9.0.1, IMS Inc., Calverton, MD, USA) uses regression models that search for statistically significant ($P < 0.05$) turning points by means of the Monte Carlo permutation test, and the results are used to analyze incidence and mortality trends associated with various cancers. We used this software to calculate the annual percent change (APC) and average APC (AAPC) of the ASIRs and ASMRs of GBC in China from 2005 to 2017 [25]. When joinpoints were detected, annual percentage changes were calculated for each linear segment. An APC/AAPC > 0 indicated an increasing trend in the ASIR or ASMR for the time period, whereas an APC equal to the AAPC indicated a monotonically increasing or decreasing trend in the ASIR or ASMR for the time period [26]. Using the intergroup comparative analysis in Joinpoint's advanced options, the male/female and urban/rural ASIRs and ASMRs were tested for parallelism or overlap to determine whether the trend curves of their standardized rates were consistent or parallel over time.

Age-period-cohort analysis

The age-period-cohort model is commonly used in the fields of epidemiology, sociology, and demography [27, 28]. We used this model to analyze the effects of age, period, and cohort on GBC incidence and mortality utilizing the endogenous factor algorithm in the Stata 16.0 software (StataCorp LLC, College Station, TX, USA). Owing to low GBC incidence and mortality rates in individuals < 20 years of age, the cohort was classified into 13 groups wherein individuals aged 20–85 years were divided by five-year intervals. The model was expressed as $Y = \log(M) = \mu + \alpha_{agei} + \beta_{periodj} + \gamma_{cohortk} + \varepsilon$. M denotes the incidence/mortality rate of GBC in China; α, β, and γ refer to the coefficients of the three dimensions, of which α refers to the age effect (i.e., the risk of incidence/mortality for a specific age group), β is the period effect (i.e., the risk of incidence/mortality of the population within a specific period), γ is the cohort effect (i.e., the risk of incidence/mortality in the population of the same birth cohort), and μ and ε are the intercept and random error, respectively. In our study, APC model with an IE method was used to solve the multicollinearity problem that has been used in various other epidemiological studies [29, 30].To prevent data overlap between adjacent cohorts, we substituted the years 2007, 2012, and 2017 for the three period groups in the age-period-cohort model.

Decomposition method

The decomposition method is widely used to quantitatively assess the impact of population aging and other risk factor changes on shifts in crude incidence rates (CIRs) or crude mortality rates (CMRs) [31–33]. It incorporates demographic changes (e.g., population aging) that influence incidence/mortality rates as well as non-demographic factors (e.g., genetic, environmental, behavioral, and others). When evaluating deaths from different diseases, non-demographic factors contain varying elements; hence, the influences of demographic and non-demographic factors on changes in incidence and mortality rates may not be the same: the contribution rate of demographic factors = the difference owing to demographic factors / the difference in incidence/mortality rates, while the contribution rate of non-demographic factors = the difference owing to non-demographic factors / the difference in incidence/mortality rates. The contribution of demographic factors to the difference = Σ ([age-specific demographic ratio at the end of the year-age-specific demographic ratio at the beginning of the year] × [age-specific incidence/mortality rates at the end of the year + age-specific incidence/mortality rates at the beginning of the year] /2). The difference due to non-demographic factors = Σ ([incidence/mortality rate by age at the end of the year − incidence/mortality rate by age at the beginning of the year] × [population composition ratio by age at the end of the year + population composition ratio by age at the beginning of the year]/2). The difference in incidence/mortality rate = the total incidence/mortality rate at the end of the year − the total incidence/mortality rate at the beginning of the year.

Results

Descriptive analyses of changes in incidence rates

Between 2005 and 2017, 98,860 individuals were diagnosed with GBC in China with a CIR of 4.04/100,000 and an ASIR of 2.43/100,000. These included 46,090 men (46.62%) with a CIR of 3.72/100,000 and an ASIR of 2.37/100,000 as well as 52,700 women (53.38%), with a CIR of 4.37/100,000 and ASIR of 2.48/100,000; the CIR and ASIR for women were higher than those for men. In terms of locale, there were 62,659 urban patients (63.38%) with a CIR of 4.73/100,000 and ASIR of 2.69/100,000 as well as 36,201 rural patients (46.62%) with a CIR of 3.22/100,000 and ASIR of 2.07/100,000 (Table 1).

Descriptive analyses of changes in mortality rates

There were 75,224 deaths from GBC in China between 2005 and 2017, with a CMR of 3.07/100,000 and an ASMR of 1.79/100,000; these included 34,886 men (46.36%) with a CMR of 2.81/100,000 and ASMR of 1.76/100,000 as well as 40,358 women (53.64%) with a CMR of 3.34/100,000 and ASMR of 1.82/100,000; both the CMR and ASMR were higher in women than in men. In terms of locale, 48,774 deaths (64.82%) occurred in urban areas with a CMR of 3.62/100,000 and ASMR of 2.02/100,000, while 26,470 deaths (35.18%) occurred in rural areas with a CMR of 2.36/100,000 and ASMR of 1.48/100,000; the rates were higher in the former (Table 2).

Joinpoint regression analysis of incidence rates

Between 2005 and 2017, the countrywide ASIR for GBC in China showed a notable downward trend (AAPC = -2.023%, $P < 0.001$) (Fig. 1A). Upon sex

Table 1 Incidence of gallbladder cancer in China between 2005 and 2017 (per 100,000)

Year	Total			Male			Female			Urban			Rural		
	Cases (n)	Crude incidence	ASIR[a]	Cases (n)	Crude incidence	ASIR[a]	Cases (n)	Crude incidence	ASIR[a]	Cases (n)	Crude incidence	ASIR[a]	Cases (n)	Crude incidence	ASIR[a]
2005	2,139	3.89	2.59	979	3.52	2.54	1,160	4.28	2.64	1,809	4.45	2.81	330	2.32	1.82
2006	2,770	4.65	3.04	1,168	3.89	2.72	1,602	5.42	3.33	2,410	5.18	3.23	360	2.77	2.19
2007	2,618	4.38	2.78	1,202	3.98	2.72	1,416	4.79	2.85	2,276	5.10	3.06	342	2.25	1.73
2008	3,284	4.97	2.96	1,428	4.28	2.76	1,856	5.66	3.15	2,936	5.63	3.23	348	2.49	1.74
2009	3,688	4.31	2.70	1,661	3.84	2.57	2,027	4.80	2.85	2,959	5.15	3.06	729	2.61	1.86
2010	5,010	4.02	2.55	2,251	3.57	2.42	2,759	4.48	2.67	3,823	4.78	2.90	1,187	2.66	1.85
2011	5,928	4.07	2.55	2,761	3.75	2.52	3,167	4.39	2.59	4,176	4.77	2.80	1,752	3.01	2.11
2012	7,610	3.84	2.39	3,490	3.48	2.30	4,120	4.22	2.48	4,791	4.77	2.74	2,819	2.89	1.97
2013	8,881	3.92	2.40	4,110	3.58	2.32	4,771	4.27	2.47	5,182	4.64	2.62	3,699	3.22	2.14
2014	11,238	3.90	2.34	5,394	3.69	2.35	5,844	4.11	2.34	6,668	4.63	2.59	4,570	3.17	2.06
2015	12,910	4.02	2.35	6,180	3.80	2.35	6,730	4.26	2.35	7,096	4.60	2.53	5,814	3.49	2.15
2016	15,342	4.02	2.33	7,260	3.75	2.29	8,082	4.30	2.36	8,773	4.55	2.51	6,569	3.48	2.13
2017	17,442	4.00	2.30	8,206	3.71	2.26	9,236	4.29	2.34	9,760	4.58	2.51	7,682	3.44	2.08
Total	98,860	4.04	2.43	46,090	3.72	2.37	52,770	4.37	2.48	62,659	4.73	2.69	36,201	3.22	2.07

[a] ASIR Age-adjusted incidence rate of the world population

Table 2 Mortality from gallbladder cancer in China between 2005 and 2017 (per 100,000)

Year	Total			Male			Female			Urban			Rural		
	Cases (n)	Crude mortality	ASMR[a]	Cases (n)	Crude mortality	ASMR[a]	Cases (n)	Crude mortality	ASMR[a]	Cases (n)	Crude mortality	ASMR[a]	Cases (n)	Crude mortality	ASMR[a]
2005	1,717	3.13	2.03	783	2.81	2.00	934	3.45	2.07	1,435	3.53	2.17	282	1.98	1.54
2006	2,007	3.37	2.15	879	2.93	2.03	1,128	3.82	2.25	1,778	3.82	2.33	229	1.76	1.36
2007	2,133	3.57	2.21	964	3.19	2.15	1,169	3.95	2.28	1,816	4.07	2.37	317	2.09	1.61
2008	2,484	3.76	2.17	1,132	3.40	2.13	1,352	4.12	2.22	2,208	4.23	2.36	276	1.97	1.37
2009	2,930	3.43	2.09	1,329	3.07	2.03	1,601	3.79	2.15	2,402	4.18	2.41	528	1.89	1.32
2010	3,861	3.10	1.90	1,735	2.75	1.84	2,126	3.45	1.96	3,028	3.79	2.21	833	1.86	1.29
2011	4,803	3.30	2.00	2,224	3.02	1.98	2,579	3.58	2.02	3,434	3.92	2.21	1,369	2.35	1.62
2012	5,903	2.98	1.82	2,676	2.67	1.75	3,227	3.30	1.88	3,847	3.83	2.15	2,056	2.11	1.42
2013	6,763	2.99	1.77	3,203	2.79	1.78	3,560	3.19	1.76	4,141	3.71	2.01	2,622	2.28	1.49
2014	8,370	2.90	1.69	3,872	2.65	1.65	4,498	3.17	1.72	5,166	3.59	1.93	3,204	2.22	1.41
2015	9,674	3.01	1.70	4,567	2.81	1.69	5,107	3.23	1.71	5,439	3.53	1.86	4,235	2.54	1.53
2016	11,421	2.99	1.68	5,373	2.77	1.66	6,048	3.22	1.69	6,694	3.48	1.85	4,727	2.50	1.48
2017	13,178	3.02	1.68	6,149	2.78	1.65	7,029	3.27	1.70	7,386	3.46	1.82	5,792	2.60	1.52
Total	75,244	3.07	1.79	34,886	2.81	1.76	40,358	3.34	1.82	48,774	3.68	2.02	26,470	2.36	1.48

[a] ASMR Age-adjusted mortality rate of the world population

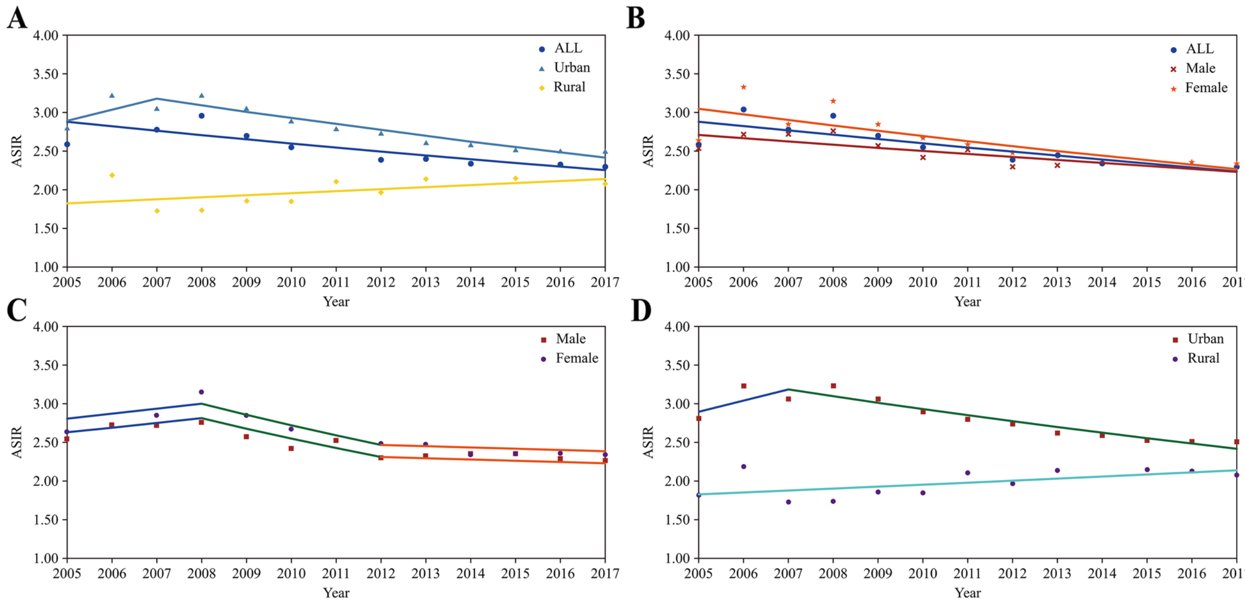

Fig. 1 Joinpoint analyses of gallbladder cancer incidence. **A** All: 2005–2017: APC = 2.02*; Urban: 2005–2007: APC = 4.79; 2007–2017: APC = 2.71*; Rural: 2005–2017: APC = 1.32*; **B** Male: 2005–2017: APC = 1.57*; Female: 2005–2017: APC = 2.43*. **C** Comparative analyses of Male and Female:2005–2008: APC = 2.28; 2008–2012: APC = 4.80; 2012–2017: APC = 0.66. **D** Comparative analyses of Urban and Rural: Urban:2005–2007: APC = 4.79; 2007–2017: APC = 2.71*; Rural: 2005–2017: APC = 1.32*. ASIR: age-standardized incidence rate; APC: annual percentage change. *Indicates that the APC is significantly different from zero at the alpha = 0.05 level

stratification, the ASIR of GBC in men decreased (AAPC = -1.572%, $P < 0.001$) and exhibited a swift decline in women (AAPC = -2.425%, $P < 0.001$) (Table 3, Fig. 1B). Comparative analyses demonstrated that both trends were parallel ($P = 0.176$) even though women had a higher ASIR than men; however, this difference gradually lessened over time (Fig. 1C). Additionally, the APC for women indicated a faster overall decrease in ASIRs.

In terms of regional variations, the ASIR for GBC in urban regions showed a decreasing pattern (AAPC = -1.494%, $P = 0.020$). Between 2005 and 2007, however, there was an increasing trend in the ASIR of GBC (APC = 4.795%, $P = 0.23$), which later shifted to a declining trend during 2007–2017 (APC = -2.705%, $P < 0.001$). In contrast, an upward trend (AAPC = 1.317%, $P < 0.001$) was observed in the ASIR of GBC in rural areas (Table 3, Fig. 1A). Comparative analyses revealed that, despite urban areas having a higher ASIR than rural areas, this gap narrowed over time (Fig. 1D). Moreover, the changes in the trends of both locales was statistically significant ($P = 0.003$).

Joinpoint analysis of mortality rates

Between 2005 and 2017, there was an overall decrease in the ASMR of GBC in China (AAPC = -1.603%, $P < 0.001$) (Fig. 2A).However, during the initial period of 2005–2007, there was a marked increase in this rate (APC = 4.715%, $P = 0.32$), followed by a significant and rapid drop between 2007 and 2014 (APC = -3.825%, $P = 0.003$), finally, a gradual decline from 2014 to

Table 3 Joinpoint regression analysis: APC and AAPC of age-adjusted incidence rates for gallbladder cancer in China between 2005 and 2017

Areas	Segment	APC (95% CI)	t	*P*	AAPC (95% CI)	t	*P*
All	2005–2017	-2.023* (-2.837,-1.202)	-5.392	< 0.001	-2.023* (-2.837,-1.202)	-5.392	< 0.001
Male	2005–2017	-1.572* (-2.181,-0.959)	-5.619	< 0.001	-1.572* (-2.181,-0.959)	-5.619	< 0.001
Female	2005–2017	-2.425* (-3.503,-1.335)	-4.865	< 0.001	-2.425* (-3.503,-1.335)	-4.865	< 0.001
Urban	2005–2007	4.795 (-3.607,13.922)	1.293	0.230	-1.494* (-2.736,-0.235)	-2.323	0.020
	2007–2017	-2.705* (-3.336,-2.071)	-9.727	< 0.001			
Rural	2005–2017	1.317* (0.147,2.501)	2.479	0.031	1.317* (0.147,2.501)	2.479	0.031

APC Annual percent change, *AAPC* Average annual percent change presented for the full period, *CI* Confidence interval, *$P < 0.05$

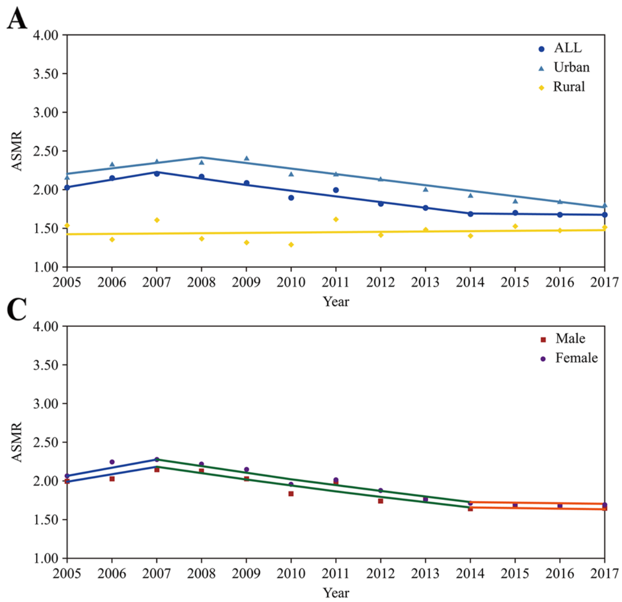

Fig. 2 Joinpoint analyses of gallbladder cancer mortality. **A** All: 2005–2017: APC = 4.72;2007–2014: APC = 3.82*;2014–2017: APC = 0.44; Urban: 2005–2008: APC = 3.06; 2008–2017: APC = 3.37*; Rural: 2005–2017: APC = 0.31*; **B** Male: 2007–2017: APC = 2.28*; Female: 2005–2007: APC = 5.13; 2007–2014: APC = 4.19*; 2014–2017: APC = 0.41. **C** Comparative analyses of Male and Female:2005–2007: APC = 4.77; 2007–2014: APC = 3.85*; 2014–2017: APC = 0.47. **D** Comparative analyses of Urban and Rural: Urban:2005–2008: APC = 3.06; 2008–2017: APC = 3.37*; Rural: 2005–2017: APC = 0.31. ASMR: age-standardized mortality rate; APC: annual percentage change. *Indicates that the APC is significantly different from zero at the alpha = 0.05 level

2017 (APC = -0.436%, P = 0.840) (Table 4). When categorized by sex, the ASMR of GBC in men showed an overall downward trend between 2005 and 2017 (AAPC = -2.283%, P < 0.001). Similarly, there was a declining trend among women (AAPC = -1.749%, P = 0.032); there was initially a rise during 2005–2007 (APC = 5.128%, P = 0.22) then a swift decrease during 2007–2014 (APC = -4.187%, P = 0.22) followed by a gradual decline during 2014–2017 (APC = -0.413%, P = 0.83) (Table 4, Fig. 2B). Comparative analyses suggested that the ASMR for women was higher than that for men despite this discrepancy decreasing gradually over time (Fig. 2C); however, the differences in overall trends for both sexes were not statistically significant (P = 0.110).

With respect to regional differences, the ASMR due to GBC in urban areas tended to decrease overall (AAPC = -1.798%, P < 0.001) (Fig. 2A). Between the years 2005 and 2008, there was a notable upward trend (APC = 3.062%, P = 0.096) followed by a rapid decrease from 2008 to 2017 (APC = -3.367%, P < 0.001). In contrast, the ASMR due to GBC in rural areas showed a slow upward trend (AAPC = 0.311%, P = 0.59) (Table 4,

Table 4 Joinpoint regression analysis: APC and AAPC of age-adjusted mortality rates for gallbladder cancer in China between 2005 and 2017

Areas	Segment	APC (95% CI)	t	*P*	AAPC (95% CI)	t	*P*
All	2005–2007	4.715 (-5.985,16.634)	1.099	0.320	-1.603* (-3.450,0.278)	-1.672	< 0.001
	2007–2014	-3.825* (-5.561,-2.056)	-5.502	0.003			
	2014–2017	-0.436 (-5.661,5.077)	-0.209	0.840			
Male	2005–2017	-2.283* (-3.014,-1.545)	-6.760	< 0.001	-2.283* (-3.014,-1.545)	-6.760	< 0.001
Female	2005–2007	5.128 (-4.067,15.205)	1.405	0.220	-1.749* (-3.317,-0.156)	-2.151	0.032
	2007–2014	-4.187* (-5.658,-2.693)	-7.106	0.001			
	2014–2017	-0.413 (-4.868,4.250)	-0.233	0.830			
Urban	2005–2008	3.062 (-0.667,6.931)	1.887	0.096	-1.798* (-2.671, -0.918)	-3.983	< 0.001
	2008–2017	-3.367* (-4.015,-2.714)	-11.737	< 0.001			
Rural	2005–2017	0.311 (-0.913,1.550)	0.557	0.590	0.311 (-0.913,1.550)	0.557	0.590

APC Annual percent change, *AAPC* Average annual percent change presented for the full period, *CI* Confidence interval, *P < 0.05

Fig. 2A). Comparative analyses revealed that urban areas presented a higher ASMR than rural ones, although this gap gradually narrowed over time (Fig. 2D). Moreover, the difference between the overall trends for both regions was significant ($P = 0.002$).

Age-period-cohort analysis

In terms of the age effect, coefficients of age for GBC incidence exhibited a significant increase overall and peaked at 70–79 years, following which it gradually declined. Notably, women and rural residents showed a decreasing trend before 25–29 years. In contrast, men had the highest age effect in the 70–74-year group; women, urban residents, and rural residents all had their highest age effect at 75–79 years. The age effect of GBC mortality was consistent across sexes and locales; coefficients of age mortality continued to increase with age and peaked at 75–79 years, then slowly declined (Figs. 3A,D and 4A,D; Supplementary Table B; Supplementary Table C).

In terms of period, coefficients of period for GBC incidence rates among men, women, and individuals residing in urban and rural areas increased over time. Prior to

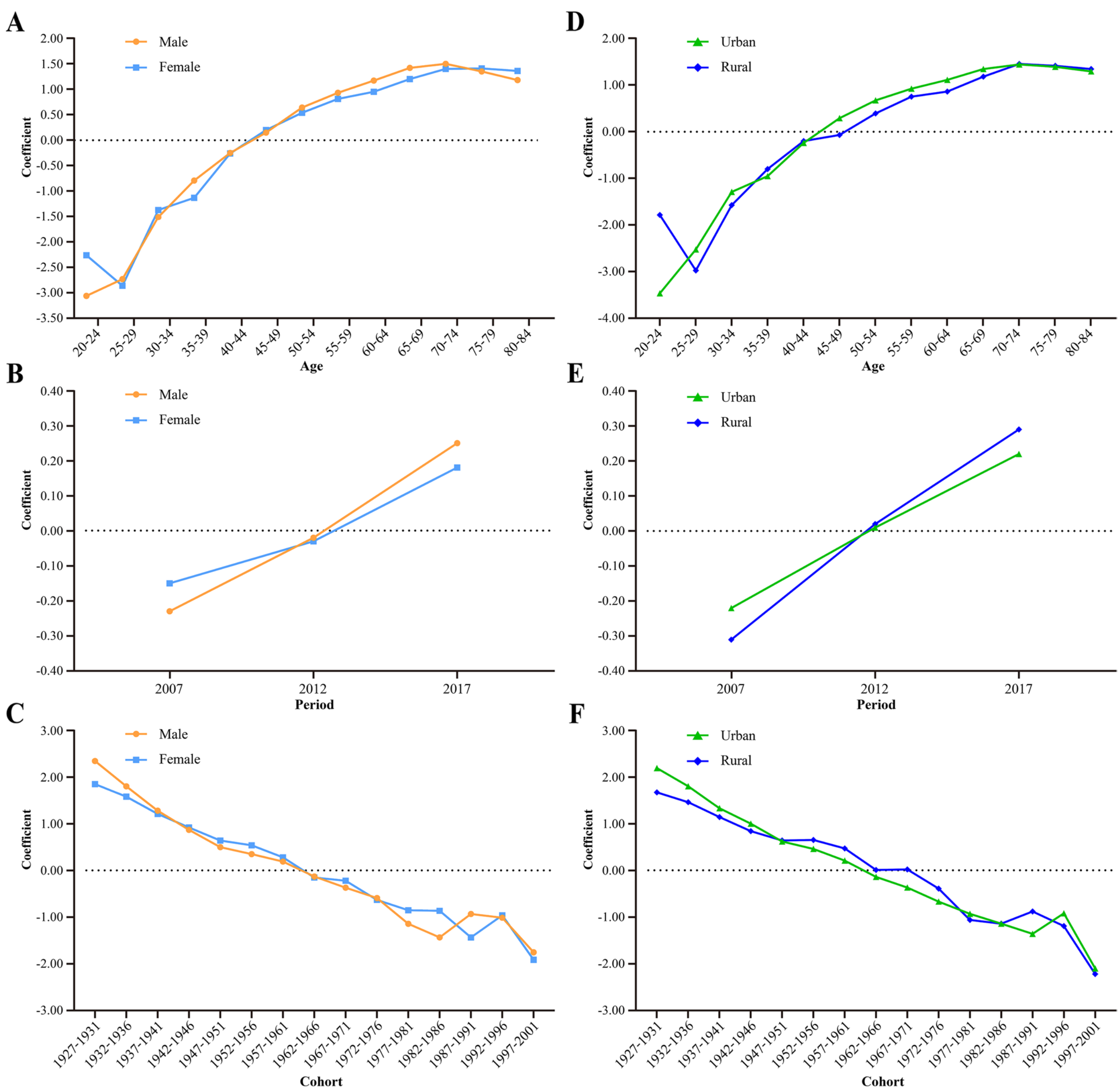

Fig. 3 Age-period-cohort analyses of gallbladder cancer incidence. Age analyses (**A**, **D**), period analyses (**B**, **E**), and birth cohort analyses (**C**, **F**)

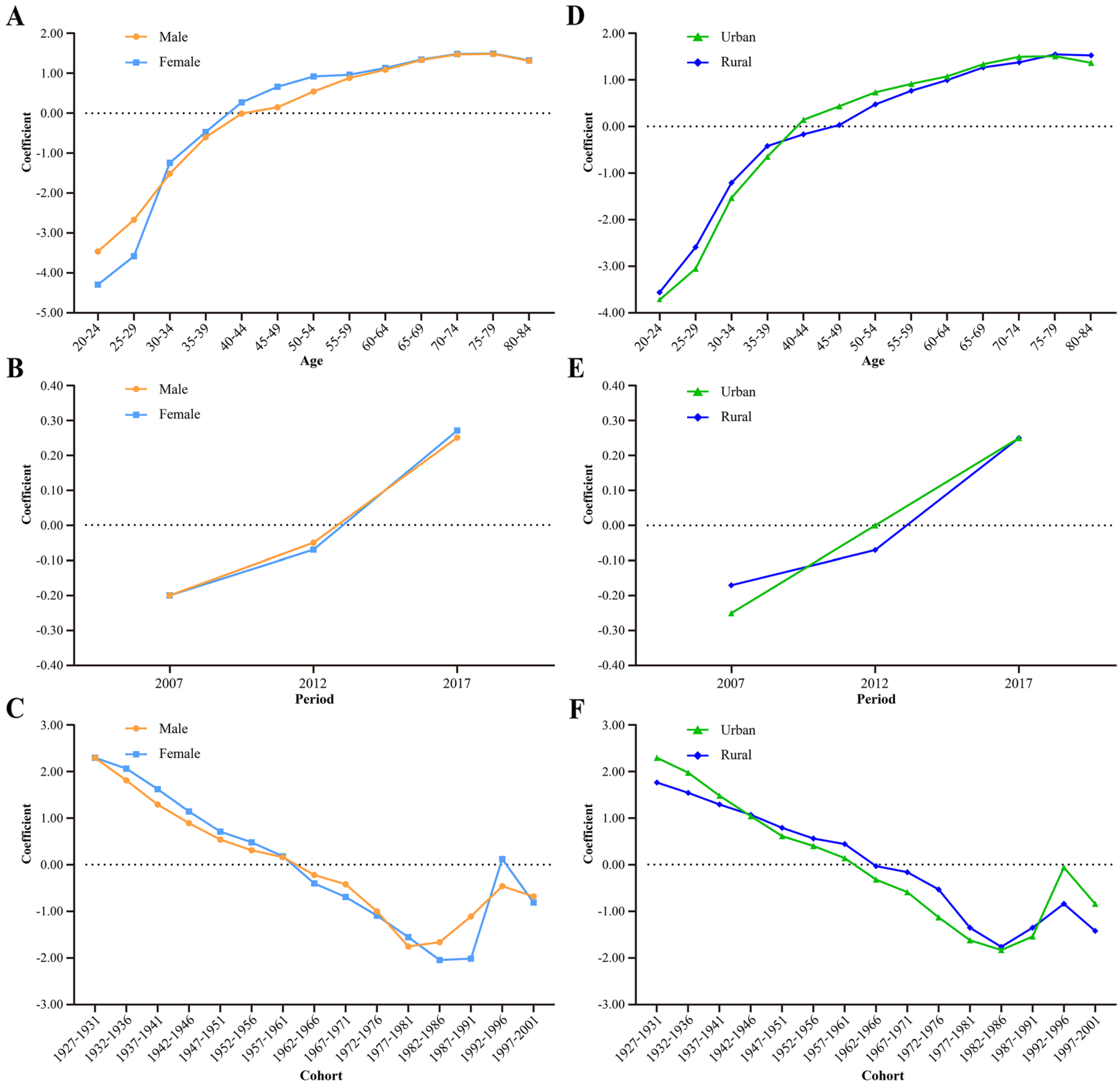

Fig. 4 Age-period-cohort analyses of gallbladder cancer mortality. Age analyses (**A**, **D**), period analyses (**B**, **E**), and birth cohort analyses (**C**, **F**)

2012, women had higher coefficients of period for GBC incidence rates sex disparity reversed after 2012. Between 2005 and 2017, coefficients of period for the GBC incidence rates accelerated at a higher rate among men than among women; coefficients of period for these rates were higher in urban areas than in rural ones before 2012, but the trend reversed thereafter. Additionally, between 2005 and 2017, coefficients of period for GBC incidence rates increased more rapidly among rural populations than among urban ones (Fig. 3B, E; Supplementary Table B; Supplementary Table C).

Period effect analysis on GBC mortality rates in all groups followed a similar increasing trend over time. Prior to 2012, coefficients of period for the GBC mortality rates were higher in men than in women, with the sex gap widening over time. However, the trend reversed after 2012, with women exhibiting higher coefficients of period for mortality rates and a more rapid increase than men. Before 2012, rural populations had higher coefficients of period for GBC mortality rates than did urban ones, but the latter experienced a faster increase with time. After 2012, urban areas witnessed higher coefficients of period for mortality rates than rural ones, although the latter had a more rapid increase (Fig. 4B, E; Supplementary Table B; Supplementary Table C).

In terms of the cohort effect, all groups showed a consistent coefficients of cohort for GBC incidence rate decline over time. Notably, women exhibited a rapid increase from 1982 and 1996 while men as well as patients in both urban and rural areas showed a declining trend between 1982 and 1996. Our model indicated that, compared to those born in 1927–1931, coefficients of period for GBC incidence rates among men, women, and residents of both urban and rural areas in China who were born between 1997 and 2001 decreased by coefficients of 4.089, 3.753, 4.290, and 3.890, respectively. The greatest reduction in incidence was in urban areas (Fig. 3C, F; Supplementary Table B; Supplementary Table C).

Cohort effects analysis of mortality among men and women in both urban and rural areas showed an overall declining trend. Notably, women and rural populations experienced a rapid increase in coefficients of period for mortality during 1981–1995 and 1976–1995, respectively. Our model revealed that, compared to those born in 1927–1931, coefficients of period for the mortality rates among men, women, and residents of urban and rural populations in China born between 1997 and 2001 decreased by coefficients of 2.971, 3.099, 3.128, and 3.178, respectively, with the greatest decline observed in urban populations (Fig. 4C, F; Supplementary Table B; Supplementary Table C).

Decomposition method analyses

The decomposition analysis of GBC incidence rates from 2005 to 2017 revealed significant variations across sexes and locales in China (Fig. 5A). Overall, the population experienced a CIR difference of 0.10 per 100,000, with demographic factors contributing to a 626.09% increase and non-demographic factors producing a 526.09% decrease. In men, the CIR difference was 0.19 per 100,000, with demographic factors accounting for a 366.23% increase and non-demographic factors causing a 266.23% decrease. Among women, the CIR difference was minimal at 0.01 per 100,000, with demographic factors contributing to a substantial 6068.93% increase and non-demographic factors leading to a 5968.93% decrease. In urban areas, the CIR difference was 0.13 per 100,000, with demographic and non-demographic factors causing a 543.01% increase and a 443.01% decrease, respectively. Conversely, in rural areas, the CIR difference was notably higher at 1.13 per 100,000, with demographic and non-demographic factors contributing to increases of 68.22% and 31.78%, respectively. The higher GBC incidence rates among men, women, and urban residents in 2017 compared to 2005 was primarily driven by changes in demographic factors, while non-demographic factors had a suppressive effect. However, both demographic and non-demographic factors contributed to increased incidences in rural areas.

Decomposition analyses of GBC mortality rate disparities from 2005 to 2017 demonstrated significant variations across the sexes and locales (Fig. 5B). For the overall population, the CMR difference was 0.11 per 100,000, with demographic factors contributing to a 495.93% decrease and non-demographic factors leading to a 595.93% increase. Among men, the CMR difference was 0.03 per 100,000, with demographic factors accounting for a 1763.10% decrease and non-demographic factors resulting in an 1863.10% increase. Among women, the CMR difference was 0.18 per 100,000, with demographic factors contributing to a 270.56% decrease and non-demographic factors leading to a 370.56% increase. In urban areas, the CMR difference was 0.06 per 100,000, with demographic factors causing a 930.33% decrease and non-demographic factors resulting in a 1030.33% increase. Conversely, in rural areas, the CMR difference was significantly higher at 0.62 per 100,000, with demographic factors contributing to a 101.48% increase and non-demographic factors leading to a 1.48% decrease. Our analysis indicated that the lower GBC mortality rates among men, women, and urban residents in 2017 compared to 2005 was primarily driven by non-demographic factors. However, the increase in mortality in rural areas was predominantly influenced by demographic factors.

Discussion

Our results showed that the ASIR of GBC among Chinese residents showed a decreasing trend from 2005 to 2017, more so in women than in men and among urban residents than in rural ones. However, the gaps between the sexes and locales continued to narrow. The trend of change in the ASMRs of GBC among Chinese residents was basically the same as that of ASIRs, which was consistent with previously published data [7, 10]. In terms of sex distribution, both the ASIR and ASMR of women were higher than those of men. This may be related to higher estrogen levels in women, which up regulates cholesterol synthesis and thus increases the risk of gallstones; this in turn slows bile secretion and leads to pancreatic fluid reflux into the gallbladder and subsequent inflammation that is a precursor to GBC [34, 35]. Additionally, studies have shown that for every 5 kg/m^2 increase in body mass index, the risk of GBC in women increases 0.59-fold compared to that in men [36]. The higher incidence and mortality rates in urban areas than in rural ones could be attributed to the westernized lifestyle and dietary habits within the former [37].

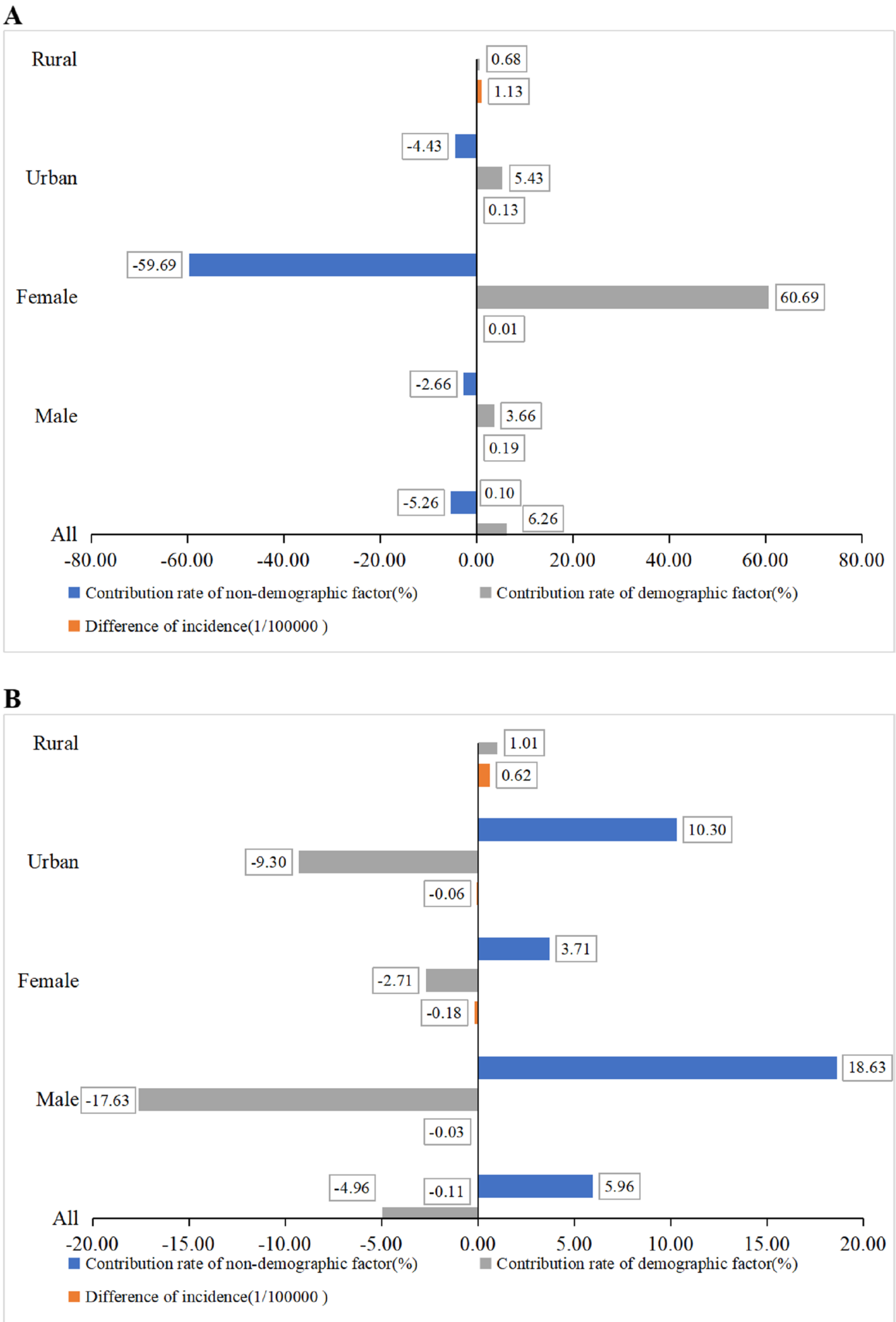

Fig. 5 Decomposition method analysis of crude incidence of gallbladder cancer (**A**) and mortality from gallbladder cancer (**B**) in China between 2005 and 2017

In 2017, the ASIR of GBC in China was 2.30/100,000 while the ASMR was 1.79/100,000. The most recent the GLOBOCAN 2020 report indicated that the global standardized GBC incidence and mortality rates were 1.2/100,000 and 0.84/100,000, respectively; those in Asia were 1.40/100,000 and 1.10/100,000, respectively, while those in the United States were 0.68/100,000 and 0.31/100,000, respectively [4]. Moreover, the 2019 GBD data shows that global GBC standardized incidence and mortality rates were 2.01/100,000 and 1.82/100,000, respectively, while those in the United States were 0.68/100,000 and 0.31/100,000, respectively [9]. Hence, both databases indicated higher GBC incidence and mortality rates in China and the Asian region than in the United States and globally. The incidence and mortality rates of GBC in China are higher than in other countries [8], potentially owing to differences in risk factor exposure across various regions. These factors include female sex, congenital developmental abnormalities, obesity, personal or family history of gallstones, chronic infection and inflammation of the gallbladder, and older age [38, 39]. Geographic, racial, and cultural variations influence these factors to a greater extent than environmental and genetic ones [40]. The differences in GBC incidence and mortality rates between the GLOBOCAN 2020 and GBD 2019 databases may be attributed to differences in GBC International Classification of Diseases coding, the quality of cancer registration and healthcare management systems, one-year time lag between the two databases, and methodological differences. In our study, the GBC incidence and mortality data were based on the more accurate national cancer registries [41].

Our study found that coefficients of age for GBC incidence and mortality gradually increased with age and peaked at 70–79 years, which was consistent with previous studies [7]. The peak among men (70–74 years) was earlier than that for women; this may be due to the differences in dietary habits and aging as well as higher rates of obesity and other diseases among men (one-third of GBCs are caused by obesity) [42]. Moreover, men tend to smoke and consume alcohol more than women [43, 44]. Notably, 25 to 34-year-olds showed the fastest-growing coefficients of age for incidence and mortality rates; this is also attributable to obesity given existing data that these age groups are at high risk for it [45, 46]. Therefore, the role of age (particularly the 25–34- and 70–79-year groups) should be taken into account when devising policies for reducing GBC diagnoses.

The period effect means that unique medical technology, diagnostic methods, economic and cultural changes in a specific period can increase the risk of a disease [29]. Period effect analyses showed that the overall coefficients of period for incidence and mortality rates trended upward over time and were mainly divided into two eras: 2007–2012 and 2012–2017; coefficients of period for GBC incidence and mortality rates were higher in the latter. Explanations include increased detection coefficients of period for rates owing to the implementation of cancer prevention policies in 2012 [47] and of China's Cancer Prevention and Control Three-year Action Plan (2015–2017) [48]. Furthermore, advances in China's GBC detection technology between 2012 and 2017, increased awareness of this disease in China [49], and higher cholecystectomy rates may also have improved early GBC detection [50]. Notably, health care services in rural areas have vastly improved since 2012, which further explains higher detection rates [51].

The cohort effect represents the impact of early life economic level, living habits and environmental factors on the risk of a disease [29]. Early in life exposure to adverse risk factors may affect future life [52]. Cohort effect analysis showed that coefficients of cohort GBC incidence and mortality rates have been decreasing over time. These coefficients of cohort for rates rebounded between 1982 and 1996, possibly owing to increased pollution, dietary changes, migration from rural areas, and other factors associated with socioeconomic development in China. Notably, women born between 1982 and 1996 showed a rapid growth in coefficients of cohort for GBC incidence rates. Coefficients of cohort for mortality rates remained high owing to the influence of fertility [53], and it was previously found that the risk of cholecystic cancer in women with three or more children is more than three-fold higher than that in women with fewer offspring; this may be attributable to increased levels of progesterone and endogenous estrogen during pregnancy, which increases the risk of cholecystic cancer and death – these factors may also explain the increased risk of GBC [54].

The decomposition method revealed that variations in the CIRs and CMRs of GBC between 2005 and 2017 are attributable to demographic factors, other non-demographic factors, and their synergistic effects; population aging was the predominant factor. This was particularly evident in the elevated rates observed in rural regions. Over time, the GBC incidence rate increased across the entire population regardless of sex or locale. Demographic factors evidently contribute to the elevated CIRs, whereas non-demographic factors appear to mitigate this increase. Of particular concern is the marked rise in GBC incidence in rural areas between 2005 and 2017; this predominantly stemmed from the interplay of demographic and non-demographic factors, with the former playing a crucial role.

The mortality rate due to GBC in the whole population declined at varying degrees over time. Non-demographic factors contributed to this decline, while demographic factors contributed to preventing it; however, external factors such as health promotion outweighed the impact of demographic factors. This indicates improvements in health, medical care, and economic development in China as well as reduced environmental risk factors. Moreover, it suggests that the mitigation of risk factors can offset the higher mortality associated with aging. Notably, the mortality rate due to GBC in rural areas increased by 0.62/100,000 in 2017 compared to 2005, mainly owing to demographic factors. The limited health resources in rural areas are a major challenge for elderly patients with GBC, and maximizing the cost-effectiveness of limited health resources while coping with the impact of aging in rural areas still needs to be actively addressed by policymakers.

The situation of disease burden prevention and control of GBC in China is not optimistic, and the primary and secondary prevention of GBC need to be further strengthened. Healthy lifestyles such as maintaining normal body mass, regular diet and reducing alcohol consumption and smoking can effectively reduce the risk of gallbladder cancer, while high-risk groups should undergo regular GBC screening for early detection, early diagnosis and early treatment. In the future, the cancer registry should focus on strengthening the construction of the cancer prevention and treatment system in primary health care institutions, and gradually promote the standardized clinical diagnosis and treatment level and improve the prognosis of GBC according to the distribution of incidence and mortality of GBC in different regions and genders, and it is recommended to steadily implement the project of early diagnosis and early treatment of GBCin the whole country.

Strengths and limitations

This study provided nationwide GBC statistics in China using the most representative data available; i.e., from the Chinese Cancer Registry. Moreover, our study was the first to quantify the impact of population aging on GBC incidence and mortality in China. However, changes in the Registry's coverage across the years produced certain skewing in the data's representativeness. Additionally, cancer registration data are usually delayed by three years, which limits their timeliness. Lastly, this study was not individual-based; hence, it was impossible to investigate causative factors with respect to GBC incidence and mortality.

Conclusion

Our study showed that the GBC incidence and associated mortality in China decreased between 2005 and 2017, with notable differences between the sexes and also between urban versus rural areas. The coefficients of age for incidence and mortality rates were highest in the 70–79-year group and increased quickest in the 25–34-year group. As such, policies aimed at reducing GBC and increasing awareness of it ought to focus on Chinese women and residents of rural areas while working to control known risk factors, improve the primary prevention system, and adopt a comprehensive and effective prevention and treatment strategy.

Abbreviations

AAPC	Average annual percentage change
APC	Annual percentage change
ASIR	Age-standardized incidence rate
ASMR	Age-standardized mortality rate
CIR	Crude incidence rate
CMR	Crude mortality rate
GBC	Gallbladder cancer
GBD	Global Burden of Disease
GLOBOCAN	Global Cancer Observatory

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12889-024-20584-9.

Supplementary Material 1. Supplementary Figure A. Flow diagram showing data acquisition. ICD-10: International Classification of Diseases, 10th edition. Supplementary Table A. Sex radio of urban and rural population in China Cancer Registries between 2005 and 2017. Supplementary Table B. Effect coefficients of the gallbladder cancer incidence of age, period, and cohort factors. Supplementary Table C. Effect coefficients of the gallbladder cancer mortality of age, period, and cohort factors.

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Authors' contributions

Xinzhou Zhang is responsible for study design, data analysis and writing. Chenyun Xu contributed to study conception. Han Zhang, Xinxin Du, and Quanyu Zhang aided in data acquisition and checked it, Manman Lu, Yanrong Ma and Wenjun Ma contributed to revising the manuscript. All authors commented on previous versions of the manuscript read and approved the final manuscript.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

This study analyzed the existing incidence and mortality information extracted from the China Cancer Registry Annual Report, 2008–2020 published by the National Central Cancer Registry of China. Basic information of patients is not identifiable in this database, and no information regarding biological samples of the patients is provided. No administrative permissions were required to access and use the dataset in this study. Therefore, requirement of ethics approval and consent to participate is not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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