

# World Journal of *Gastroenterology*

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### EDITORIAL

- 2453 Noninvasive molecular analysis of *Helicobacter pylori*: Is it time for tailored first-line therapy?  
*Ierardi E, Giorgio F, Iannone A, Losurdo G, Principi M, Barone M, Pisani A, Di Leo A*

### REVIEW

- 2459 Pathogenesis and clinical spectrum of primary sclerosing cholangitis  
*Gidwaney NG, Pawa S, Das KM*
- 2470 Biliary tract cancer stem cells - translational options and challenges  
*Mayr C, Ocker M, Ritter M, Pichler M, Neureiter D, Kiesslich T*

### MINIREVIEWS

- 2483 Potential role of nutraceutical compounds in inflammatory bowel disease  
*Larussa T, Imeneo M, Luzzza F*
- 2493 Unusual gastric tumors and tumor-like lesions: Radiological with pathological correlation and literature review  
*Lin YM, Chiu NC, Li AFY, Liu CA, Chou YH, Chiou YY*
- 2505 New progress in roles of nitric oxide during hepatic ischemia reperfusion injury  
*Zhang YQ, Ding N, Zeng YF, Xiang YY, Yang MW, Hong FF, Yang SL*

### ORIGINAL ARTICLE

#### Basic Study

- 2511 Berberine displays antitumor activity in esophageal cancer cells *in vitro*  
*Jiang SX, Qi B, Yao WJ, Gu CW, Wei XF, Zhao Y, Liu YZ, Zhao BS*

#### Case Control Study

- 2519 Clinical utility of the platelet-lymphocyte ratio as a predictor of postoperative complications after radical gastrectomy for clinical T2-4 gastric cancer  
*Inaoka K, Kanda M, Uda H, Tanaka Y, Tanaka C, Kobayashi D, Takami H, Iwata N, Hayashi M, Niwa Y, Yamada S, Fujii T, Sugimoto H, Murotani K, Fujiwara M, Kodera Y*
- 2527 Colors of vegetables and fruits and the risks of colorectal cancer  
*Lee J, Shin A, Oh JH, Kim J*

**Retrospective Cohort Study**

- 2539 Impact of vitamin D on the hospitalization rate of Crohn's disease patients seen at a tertiary care center  
*Venkata KVR, Arora SS, Xie FL, Malik TA*

- 2545 Barcelona clinic liver cancer nomogram and others staging/scoring systems in a French hepatocellular carcinoma cohort

*Adhoute X, Pénaranda G, Raoul JL, Edeline J, Blanc JF, Pol B, Campanile M, Perrier H, Bayle O, Monnet O, Beaurain P, Muller C, Castellani P, Le Treut YP, Bronowicki JP, Bourlière M*

**Retrospective Study**

- 2556 Laparoscopic approach to suspected T1 and T2 gallbladder carcinoma

*Ome Y, Hashida K, Yokota M, Nagahisa Y, Okabe M, Kawamoto K*

- 2566 Clinical characteristics of peptic ulcer perforation in Korea

*Yang YJ, Bang CS, Shin SP, Park TY, Suk KT, Baik GH, Kim DJ*

- 2575 Effects of omeprazole in improving concurrent chemoradiotherapy efficacy in rectal cancer

*Zhang JL, Liu M, Yang Q, Lin SY, Shan HB, Wang HY, Xu GL*

**Clinical Trials Study**

- 2585 *PIK3CA* gene mutations in Northwest Chinese esophageal squamous cell carcinoma

*Liu SY, Chen W, Chughtai EA, Qiao Z, Jiang JT, Li SM, Zhang W, Zhang J*

- 2592 Endothelial progenitor cells in peripheral blood may serve as a biological marker to predict severe acute pancreatitis

*Ha XQ, Song YJ, Zhao HB, Ta WW, Gao HW, Feng QS, Dong JZ, Deng ZY, Fan HY, Peng JH, Yang ZH, Zhao Y*

- 2601 Comparative study of ROR2 and WNT5a expression in squamous/adenosquamous carcinoma and adenocarcinoma of the gallbladder

*Wu ZC, Xiong L, Wang LX, Miao XY, Liu ZR, Li DQ, Zou Q, Liu KJ, Zhao H, Yang ZL*

**Observational Study**

- 2613 Serum omentin and vaspin levels in cirrhotic patients with and without portal vein thrombosis

*Kukla M, Waluga M, Żorniak M, Berdowska A, Wosiewicz P, Sawczyn T, Buldak RJ, Ochman M, Ziara K, Krzemiński T, Hartleb M*

- 2625 Upper gastrointestinal cancer burden in Hebei Province, China: A population-based study

*Li DJ, Liang D, Song GH, Li YW, Wen DG, Jin J, He YT*

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## Observational Study

**Upper gastrointestinal cancer burden in Hebei Province, China: A population-based study**

Dao-Juan Li, Di Liang, Guo-Hui Song, Yong-Wei Li, Deng-Gui Wen, Jing Jin, Yu-Tong He

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**Author contributions:** He YT contributed to the study conception and design; Li DJ, Liang D, Song GH, Li YW and Wen DG contributed to the acquisition of data; Li DJ, Liang D, Jin J and He YT contributed to the data analysis and interpretation; Li DJ contributed to the drafting of the manuscript; Li DJ, Jin J and He YT contributed to critical revision of the manuscript.

**Institutional review board statement:** All procedures involving human participants were performed in accordance with the ethical standards and with the 2013 Helsinki declaration and its later amendments. The study was reviewed and approved by the Cancer Institute, the Fourth Hospital of Hebei Medical University, Shijiazhuang, China

**Informed consent statement:** All study participants or their legal guardian provided informed written consent prior to study enrolment.

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**Abstract****AIM**

To investigate the incidence and mortality rates of upper gastrointestinal cancer (UGIC) in Hebei Province, China, and to identify high-risk populations to improve UGIC prevention and control.

**METHODS**

Data for UGIC patients were collected from 21 population-based cancer registries covering 15.25% of the population in Hebei Province. Mortality data were extracted from three national retrospective death surveys (1973-1975, 1990-1992 and 2004-2005). The data were stratified by 5-year age groups, gender and area (high-risk/non-high-risk areas) for analysis. The age-period-cohort and grey system model were used.

**RESULTS**

The crude incidence rate of UGIC was 55.47/100000, and the adjusted rate (Segi's population) was 44.90/100000. Males in rural areas had the highest incidence rate (world age-standardized rate = 87.89/100000). The

crude mortality rate of UGIC displayed a decreasing trend in Hebei Province from the 1970s to 2013, and the adjusted rate decreased by 43.81% from the 1970s (58.07/100000) to 2013 (32.63/100000). The mortality rate declined more significantly in the high-risk areas (57.26%) than in the non-high-risk areas (55.02%) from the 1970s to 2013. The median age at diagnosis of UGIC was 65.06 years in 2013. There was a notable delay in the median age at death from the 1970s (66.15 years) to 2013 (70.39 years), especially in the high-risk areas. In Cixian, the total trend of the cohort effect declined, and people aged 65-69 years were a population at relatively high risk for UGIC. We predicted that the crude mortality rates of UGIC in Cixian and Shexian would decrease to 98.80 and 133.99 per 100000 in 2018, respectively.

### CONCLUSION

UGIC was the major cause of cancer death in Hebei Province, and males in rural areas were a high-risk population. We should strengthen early detection and treatment of UGIC in this population.

**Key words:** Upper gastrointestinal cancer; Incidence; Mortality; Age-period-cohort; Grey system model

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**Core tip:** This study is the first to examine the incidence and mortality trends of UGIC in Hebei Province. Data were collected from 21 population-based cancer registries covering 15.25% of the total population of Hebei Province in 2013. An age-period-cohort model was established to analyse the incidence rate of UGIC in a high-risk area of Hebei Province (Cixian). Additionally, we established the grey system model to predict the mortality rates of UGIC in high-risk areas of Hebei Province (Cixian and Shexian). The aim of the study was to provide epidemiological evidence for developing strategies for UGIC prevention and control.

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## INTRODUCTION

According to GLOBOCAN 2012, upper gastrointestinal cancer (UGIC) is the third most common cancer worldwide and the second leading cause of death among all cancer types. Approximately 45% of all cases occur in China<sup>[1]</sup>. The incidence and mortality proportions of UGIC are approximately 19.8% and 23.3% of all malignancies in China, respectively<sup>[2]</sup>.

Thus, monitoring and studying the incidence and mortality of UGIC can provide important information, enable effective assessment and potentially generate a strategy for UGIC prevention and control based on its distribution pattern.

Hebei Province is located in northern China along the Taihang Mountain chain and has a relatively less developed economy. This province was recognized as a high-risk area for UGIC in the 1970s. In 2015, Hebei Province had 21 population-based cancer registries that covered 11185626 registered individuals (approximately 15.25% of the total population of Hebei Province). Additionally, Hebei Province participated in three national death surveys that were conducted during the periods from 1973-1975<sup>[3]</sup>, 1990-1992<sup>[4]</sup> and 2004-2005<sup>[5]</sup>. Cixian and Shexian in Hebei Province exhibit a high frequency of UGIC; their cancer registries were established in 1974 and 2000, respectively. Several investigations<sup>[6-8]</sup> have been conducted to assess the potential risk factors and the corresponding aetiological intervention methods and screening measures for UGIC.

This study combined the data for esophageal cancer and stomach cancer to investigate the real burden of UGIC in Hebei Province and to provide information on its prevention and treatment.

## MATERIALS AND METHODS

### Cancer registry data

The Hebei Provincial Cancer Registry was established in 2009 and is responsible for cancer data collection, evaluation and publication. Data were collected from 21 local population-based registries in 2013, including 16 counties (Cixian, Shexian, Qianxi County, Wuan County, Zhanhuang County, Fengning County, Xinji County, Xingtai County, Zhangbei County, Anguo County, Haixing County, Yanshan County, Neiqiu County, Renxian, Xuanhua County and Shenze County) and 5 cities (Baoding City, Qinhuangdao City, Cangzhou City, Shijiazhuang City and Shuangqiao District of Chengde City). These counties and cities represented urban areas and rural areas, respectively. The reported cases were from multiple sources, including local hospitals, community health centres, the Urban Resident Basic Medical Insurance Program and the New Rural Cooperative Medical Scheme. All data on cancer in Hebei Province were obtained from the Hebei Provincial Cancer Registry Database. Population information was collected from the local statistical bureau or household register department in the local public security bureau. We also extracted data on UGIC in Cixian from 1989 to 2013 and Shexian from 2004 to 2013. According to the International Classification of Diseases, 10th revision (ICD-10), C15 (esophageal cancer) and C16 (gastric cancer), which are UGIC, were extracted for the analysis.

**Quality control**

The inclusion criteria for the data were based on the Guidelines of the Chinese Cancer Registration<sup>[9]</sup> and the International Agency for Research on Cancer/International Association of Cancer Registries (IARC/IACR). The analysed data had a morphological verification percentage (MV%) higher than 66%, a percentage of cancer cases identified with death certification only (DCO%) less than 15% and a mortality to incidence ratio (M/I) between 0.6 and 0.8. All of the data were checked and evaluated based on the data quality criteria.

**National retrospective survey of mortality**

In the mid-1970s, a nationwide retrospective survey of causes of mortality was conducted in 29 provinces, including all 153 cities and counties. This survey covered 47.725 million people in Hebei Province<sup>[3]</sup> and provided a profile of cancer mortality in Hebei Province.

The second national retrospective sampling survey of cancer mortality was conducted from 1990 to 1992. This survey used a stratified sampling method and covered approximately 10% of the population in China<sup>[4]</sup>. A total of 21 cities and counties, including 6.375 million people in Hebei Province, were enrolled in the sampling areas.

The third national retrospective stratified sampling survey of all causes of death was performed during the period from 2004–2005 in 31 provinces/municipalities/autonomous regions, which included Hebei Province. A total of 18 cities and counties were selected as sampling areas, covering 13.79 million people and 20.15% of the total population of Hebei Province<sup>[5]</sup>.

The pooled data for UGIC from the three national retrospective sampling surveys were stratified by area (high-risk/non-high-risk areas) and gender. Cixian, Shexian and Zhanhuang counties were selected as the high-risk areas; the rest counties were considered non-high-risk areas.

**Statistical analysis**

The data analyses were performed using SPSS version 19.0 (SPSS Inc., Chicago, IL, United States), SAS version 9.4 (SAS Institute Inc., Cary, NC, United States) and Microsoft Excel 2003 (Microsoft, United States). The world age-standardized rate (ASR World) and Chinese age-standardized rate (ASR China) were calculated based on Segi's population and the Chinese population in 2000, respectively. Long-term trends of UGIC in Cixian and Shexian were analysed using an age-period-cohort model and grey system (GM) (1, 1) model. We used an age-period-cohort model to estimate the relative risks by age, period, and birth cohort based on the Cixian data collected from 1989 to 2013. Additionally, we extracted thirteen 5-year age groups from 25–29 to 85+ years old and five 5-year periods ranging from 1989–1993 to 2009–2013 to

produce birth cohorts from 1904–1908 to 1984–1988. The three components (*i.e.*, cohort, period, and age) in the age-period-cohort model were linearly dependent. Thus, we adopted the common method of including an additional arbitrary reference constraint for the period effect<sup>[10,11]</sup>. Additionally, the periods from 2004–2008 and 2009–2013 and the birth cohort from 1934–1938 were chosen as reference groups for the 85+ age group.

Based on the crude mortality rates of UGIC in Cixian and Shexian from 2004–2013, an Excel table was used to establish the GM (1, 1)<sup>[12]</sup>. The posterior error ratio (C) and small error probability (P) were used to determine the prediction accuracy, the relative error between the predicted value and the actual value, and the extrapolated prediction of mortality of UGIC in Cixian and Shexian from 2014–2018.

**RESULTS****Incidence of UGIC in 2013**

In 2013, there were 6205 new UGIC cases (4328 in males and 1877 in females), accounting for 24.62% of all types of cancer in the Hebei Provincial Cancer Registry areas. The crude incidence rate of the total areas was 55.47 per 100000 people. The ASR World and the ASR China in 2000 were 44.90 and 44.16/100000 people, respectively (Table 1). The incidence rate of UGIC was higher in males than in females. The incidence rate was 2.62 times higher in rural areas (75.17/100000) than in urban areas (28.69/100000). Almost 78% of the new cases were from rural cancer registries, and more than 50% of the cases were males from rural areas. The male incidence rate was highest in rural areas (101.35/100000). The median age at diagnosis of UGIC was 65.06 years (64.73 years in males and 66.03 years in females) in Hebei Province. The median age was 4.36 years younger in rural areas (64.37 years) than in urban areas (68.74 years).

The age-specific incidence rate was relatively low for individuals younger than 40 years of age and then increased dramatically. The incidence rate reached the peak in the 85+ age group (504.44/100000), although the incidence rate reached the peak in the 80–84 age group (598.17/100000) for males. The trend in the urban and rural areas was similar to the overall trend (Figure 1).

**Age, period and cohort effects in Cixian**

Generally, the trend of the incidence rates of UGIC decreased with the year of birth. The incidence rate increased after a decrease and then decreased again for individuals age older than 55 years but remained steady for the 25-to-54-year-old age groups (Figure 2).

Age, period and cohort effects contributed to the observed changes in the UGIC incidence. The model including all three components had the best

**Table 1 Upper gastrointestinal cancer in Hebei Provincial Cancer Registry areas, 2013**

Area	Gender	Upper gastrointestinal cancer				Esophageal cancer				Stomach cancer			
		No.	Crude rate (1/10 <sup>5</sup> )	ASR China (1/10 <sup>5</sup> )	ASR World (1/10 <sup>5</sup> )	No.	Crude rate (1/10 <sup>5</sup> )	ASR China (1/10 <sup>5</sup> )	ASR World (1/10 <sup>5</sup> )	No.	Crude rate (1/10 <sup>5</sup> )	ASR China (1/10 <sup>5</sup> )	ASR World (1/10 <sup>5</sup> )
Total	Both genders	6205	55.47	44.16	44.90	2349	21.00	16.63	16.91	3856	34.47	27.54	27.99
	Male	4328	75.8	62.43	63.50	1517	26.57	21.83	22.16	2811	49.23	40.60	41.34
	Female	1877	34.28	26.43	26.75	832	15.19	11.59	11.81	1045	19.08	14.84	14.94
Urban	Both genders	1360	28.69	21.73	21.65	449	9.47	7.12	7.16	911	19.22	14.61	14.49
	Male	969	40.46	32.51	32.5	315	13.15	10.51	10.48	654	27.31	22.00	22.02
	Female	391	16.67	12.03	11.74	134	5.71	4.00	4.05	257	10.96	8.03	7.69
Rural	Both genders	4845	75.17	62.3	63.75	1900	29.48	24.45	24.97	2945	45.69	37.85	38.79
	Male	3359	101.35	85.84	87.89	1202	36.27	30.92	31.67	2157	65.08	54.91	56.22
	Female	1486	47.46	38.79	39.69	698	22.29	18.05	18.37	788	25.17	20.73	21.31

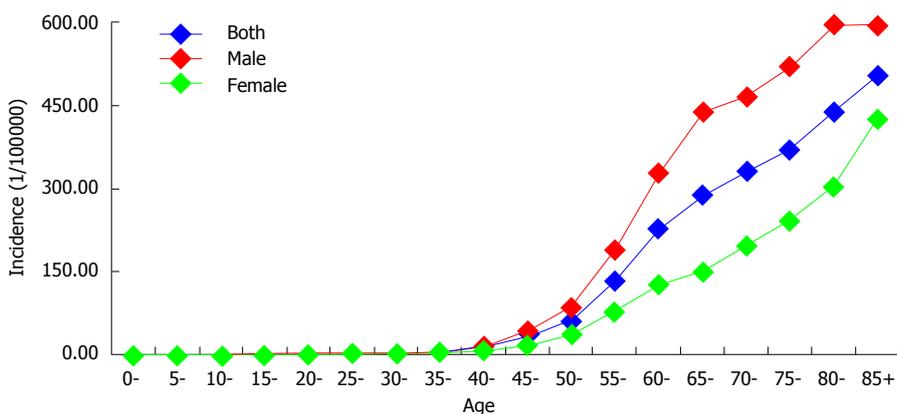


Figure 1 Age-specific incidence rates of upper gastrointestinal cancer in Hebei Province, 2013.

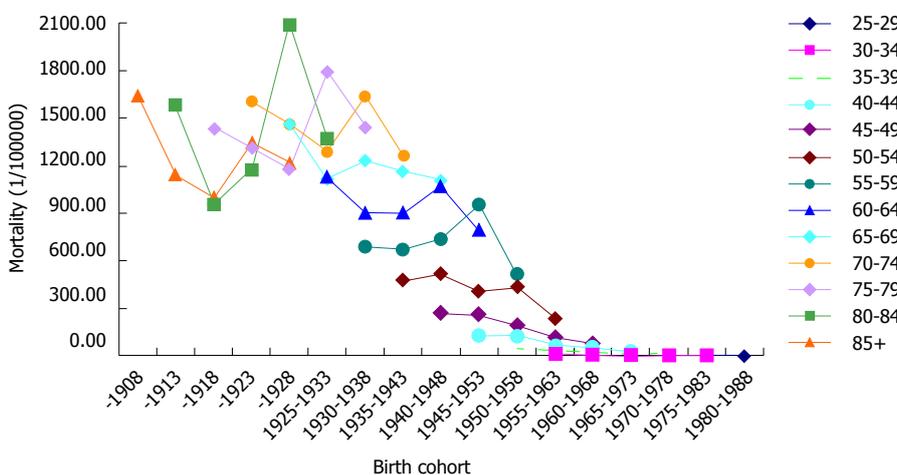


Figure 2 Trend in the age-specific incidence rate of upper gastrointestinal cancer plotted against the birth cohort.

goodness of fit, *i.e.*, the model had the lowest Akaike’s information criterion value (691.267).

The incidence rate increased with age but decreased with the cohort. Figure 3 details the age effect and shows an increasing trend for individuals aged 25-65 years. The 65-69 age group had the highest relative risk (RR = 2.38) compared with the reference group (85+ age group). The birth cohort effect showed a consistent decline in the incidence rate

in all cohorts after those born in the early 1900s. The RR of the period effects was lower from 1989-1993 compared to the reference group (Figure 3).

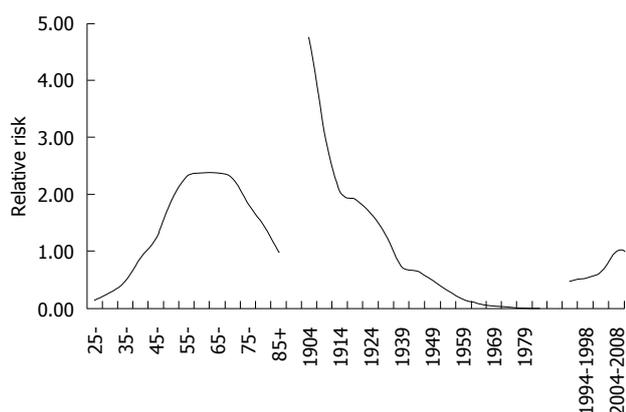
**Mortality rates of UGIC in Hebei Province, 1970s-2013**

A decreasing trend in the mortality rates of UGIC was observed in the period from 1973-1975 (50.53/100000) to 2013 (40.21/100000). The mortality rates increased slightly from the 1970s to 1990s

**Table 2** Mortality rates of upper gastrointestinal cancer in Hebei Province from the 1970s to 2013

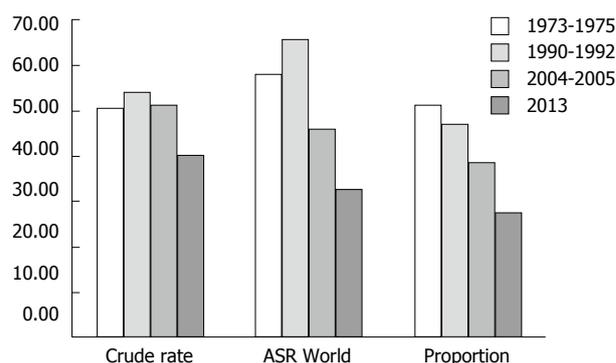
	1973-1975			1990-1992			2004-2005			2013		
	Both	Male	Female	Both	Male	Female	Both	Male	Female	Both	Male	Female
Deaths	72347	49516	22831	10429	7049	3380	7103	4927	2176	4498	3000	1498
Crude rate (1/10 <sup>5</sup> )	50.53	67.68	32.61	53.72	70.82	35.72	51.24	69.16	32.29	40.21	52.54	27.35
ASR China (1/10 <sup>5</sup> )	57.61	79.19	36.29	65.24	90.35	41.46	45.84	64.49	27.71	32.76	44.86	21.28
ASR World (1/10 <sup>5</sup> )	58.07	80.04	36.30	65.62	91.02	41.45	46.01	64.75	27.70	32.63	44.77	21.03
Ratio (%)	51.29	58.14	40.86	47.00	49.75	42.13	38.55	41.94	32.59	27.64	29.55	24.49
Median age (yr)	66.15	65.78	67.04	66.22	65.81	67.11	68.09	67.64	69.23	70.39	69.21	72.95

ASR China: Age-standardized rate based on China's standard population (2000); ASR World: Age-standardized rate based on the world standard population.



**Figure 3** Estimation of age, period and birth cohort effects on the upper gastrointestinal cancer incidence in Cixian, 1989-2013.

and then dropped sharply. In Hebei Province, the data from the four periods of the death survey indicated that the mortality rate in 2013 had decreased by 20.42%, 25.15% and 21.53% compared with the three periods from the national sampling surveys of causes of death (1973-1975, 1990-1992, and 2004-2005, respectively). Age standardization decreased the rates by 43.81%, 50.27% and 29.08%, respectively. For males, the ASR World in 1973-1975 (80.04/100000) was 1.79 times higher than that in 2013 (44.77/100000). In females, the rate decreased from 36.30/100000 in 1973-1975 to 21.03/100000 in 2013 (Table 2, Figure 4). The proportions of UGIC among all types of cancers were 51.29%, 47.00%, 38.55% and 27.64% during the periods from 1973-1975, 1990-1992, 2004-2005, and 2013, respectively, and showed a stepwise decrease, especially for males. The mortality rates of UGIC dropped in both the high-risk and non-high-risk areas from the 1970s to 2013. The mortality rates in 2013 decreased by 57.26%, 54.17% and 29.44% in the high-risk areas compared with the three periods from the sampling surveys of national causes of death (1973-1975, 1990-1992, and 2004-2005) and by 55.02%, 39.67% and 21.65% in the non-high-risk areas, respectively. The mortality rates in the high-risk areas were 3.76 times higher than those in the non-high-risk areas in 2013. Additionally, the ASR



**Figure 4** Mortality of upper gastrointestinal cancer in Hebei Province from the 1970s to 2013.

World ratio between the high-risk areas and non-high-risk areas was lower than those from the three death survey periods (3.95, 4.94 and 4.17, respectively) (Table 3).

According to the graph depicting the age-specific rates in different periods, the periods from 1973-1975, 2004-2005 and 2013 had similar trends. Beginning with the 45-49 age group, the mortality rate of UGIC increased. The mortality rate reached the peak in the 80-84 age group. In contrast, the mortality rate of the 70-74 age group was highest from 1990-1992. The age-specific mortality rates were lower in 2013 than in 1973-1975, 1990-1992 and 2004-2005 for those younger than 75 years of age but dramatically increased thereafter, with reports of mortality rates higher than the rates in the three sampling surveys of national causes of death (Figure 5).

#### **Median age at death of UGIC patients in Hebei Province, 1970s-2013**

The median age at death caused by UGIC gradually increased. The median was 66.15 years in 1973-1975 and 66.22 years in 1990-1992. The median age at death increased from 68.09 years in 2004-2005 to 70.39 years in 2013. The median age at death for females increased to 72.95 years in 2013.

There was a notable delay in the median age at death caused by UGIC from the 1970s to 2013 in the high-risk areas. The median age of death was delayed

**Table 3 Mortality rates of upper gastrointestinal cancer in high-risk areas and non-high-risk areas of Hebei Province from the 1970s to 2013**

	1973-1975				1990-1992				2004-2005				2013			
	Deaths	Crude rate (1/10 <sup>5</sup> )	ASR World (1/10 <sup>5</sup> )	Median age (yr)	Deaths	Crude rate (1/10 <sup>5</sup> )	ASR World (1/10 <sup>5</sup> )	Median age (yr)	Deaths	Crude rate (1/10 <sup>5</sup> )	ASR World (1/10 <sup>5</sup> )	Median age (yr)	Deaths	Crude rate (1/10 <sup>5</sup> )	ASR World (1/10 <sup>5</sup> )	Median age (yr)
High-risk areas																
Male	2975	214.94	286.44	62.99	3182	189.69	300.62	62.91	2005	158.63	188.08	65.46	969	143.19	131.41	69.22
Female	1536	118.93	150.76	64.70	1645	98.63	133.82	64.55	910	76.25	80.50	67.21	489	75.68	59.43	73.04
Both genders	4511	168.60	218.69	63.54	4827	140.79	203.94	63.48	2915	118.62	132.47	66.01	1458	110.22	93.46	70.37
Non-high-risk areas																
Male	46541	64.85	76.49	65.95	3867	46.73	58.14	66.10	2922	49.87	45.00	67.12	2031	40.36	34.22	69.21
Female	21295	30.99	34.39	67.22	1735	22.26	24.85	66.36	1266	22.83	18.91	68.11	1009	20.89	15.91	72.91
Both genders	67836	48.28	55.34	66.32	5602	35.04	41.26	66.18	4188	36.72	31.77	67.41	3040	30.82	24.89	70.40

ASR World: Age-standardized rate based on the world standard population.

**Table 4 Mortality data analysis of upper gastrointestinal cancer *via* the grey system model in Cixian and Shexian**

Year	t	Cixian			Shexian		
		Mortality rate	Predicted rate	Error	Mortality rate	Predicted rate	Error
2004	1	113.41			156.08		
2005	2	117.74	124.88	-7.13	158.66	160.24	-1.57
2006	3	126.51	129.78	-3.27	150.89	159.62	-8.73
2007	4	123.38	123.73	-0.35	145.89	164.62	-18.73
2008	5	122.51	118.66	3.85	167.40	172.49	-5.09
2009	6	123.59	112.34	11.25	168.63	156.75	11.88
2010	7	99.45	102.87	-3.42	148.73	137.70	11.02
2011	8	114.65	115.50	-0.85	147.39	136.52	10.88
2012	9	112.17	110.93	1.24	138.28	134.65	3.63
2013	10	106.87	106.87	0.00	139.88	139.90	-0.02
2014	11		106.18			141.57	
2015	12		104.29			139.64	
2016	13		102.42			137.73	
2017	14		100.59			135.85	
2018	15		98.80			133.99	

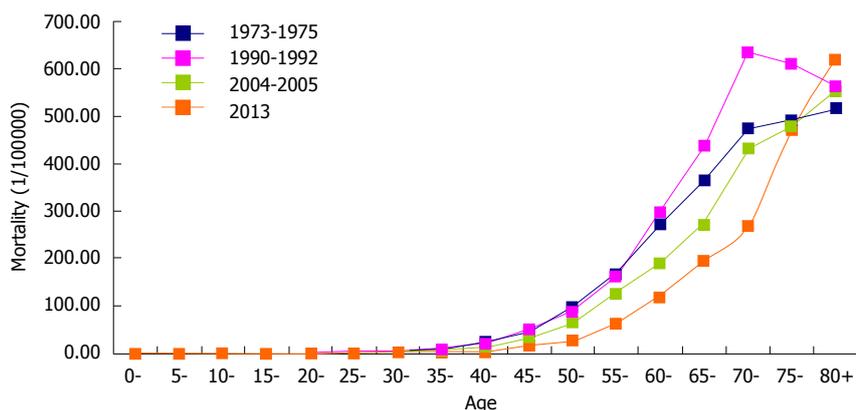


Figure 5 Age-specific mortality rates of upper gastrointestinal cancer in Hebei Province from the 1970s to 2013.

by 6.84 years in the high-risk areas compared to only 4.08 years in the non-high-risk regions. The median age at death for females was delayed by 8.34 and 5.69 years in the high-risk areas and non-high-risk areas, respectively. In 2013, the median age at death in the high-risk areas (70.37) was similar to that in the non-high-risk areas (70.40).

**Mortality rate prediction for UGIC in Cixian**

The mortality rate of UGIC in Cixian was 113.41 per 100000 in 2004. The mortality rate decreased to 106.87 per 100000 in 2013. The GM (1, 1) equation was  $Y_t = -6992.90e^{-0.01802(t-1)} + 7106.31$ , which predicted that the mortality rate of UGIC in Cixian would decrease to 98.80 per 100000 in 2018, with a

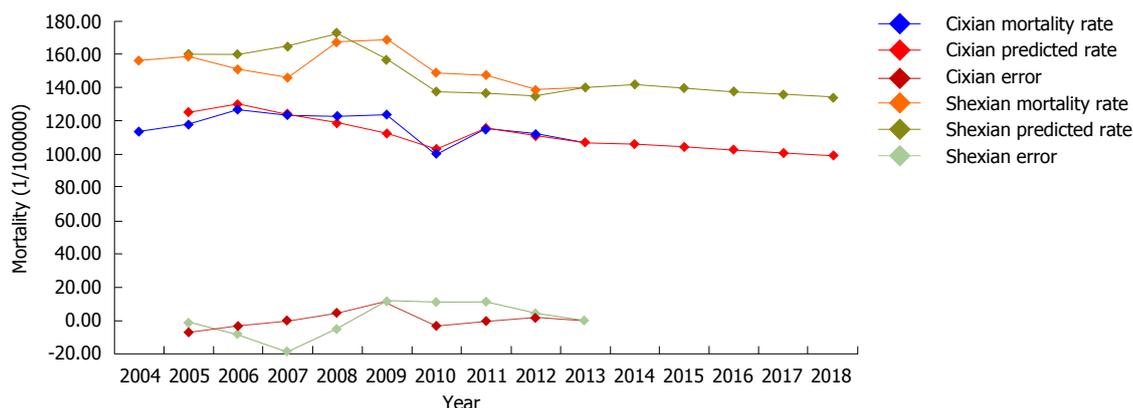


Figure 6 Mortality rate prediction of upper gastrointestinal cancer via the grey system model in Cixian and Shexian.

maximum relative error of 9.10%. The  $C$  was 0.58, and the  $P$  was 0.78, which indicated that the model was qualified (Table 4, Figure 6).

#### Mortality rate prediction for UGIC in Shexian

The mortality rate of UGIC in Shexian was decreased by 10.38% from 2004 to 2013. The GM (1, 1) equation was  $Y_t = -11725.81e^{-0.01376(t-1)} + 11881.89$ , which predicted that the mortality rate of UGIC in Shexian would decrease to 133.99 per 100000 in 2018, with a maximum relative error of 12.84%. The  $C$  and  $P$  were 0.94 and 0.44, respectively, indicating that the model was up to standard (Table 4, Figure 6).

## DISCUSSION

This study is the first to examine the incidence and mortality trends of UGIC in Hebei Province, China. The study collected data from 21 population-based cancer registries covering 15.25% of the total population of Hebei Province in 2013, which had not achieved maximal coverage in this province to date. The aim was to provide epidemiological evidence for developing strategies to control UGIC. The crude incidence rate of UGIC was 55.47/100000 in Hebei Province, which was approximately 1.06 times higher than the rate in the Chinese population (52.45/100000) and far higher than the global rate (19.95/100000)<sup>[1,2]</sup>. In Hebei Province, newly diagnosed UGIC cases comprised 24.62% of all cancer types, whereas the cases accounted for only 10.0% of all cancer types worldwide. The mortality rate of UGIC in males in the rural areas of Hebei Province was approximately 5.08 times higher than the global statistics. Males in rural areas of Hebei Province were a population at high risk of developing UGIC.

Our data showed that the burden of UGIC was heavy in Hebei Province. UGIC resulted from lifestyle habits, such as an unreasonable dietary structure, tobacco smoking, alcohol drinking, smoked food consumption and poor oral health<sup>[13-17]</sup>. A significant inverse association has been reported between fruit

consumption and UGIC (esophageal cancer, RR = 0.60; gastric cancer, odds ratio (OR) = 0.43)<sup>[18,19]</sup>. An intake of cereal fibre was significantly inversely associated with the risk of cancers of the gastrointestinal tract<sup>[18]</sup>. One recent study showed that insufficient consumption of fresh fruits may be a serious risk factor in Hebei Province, and the dietary fibre intake was only 37.3% of the reference intake from 2010-2013<sup>[20]</sup>. Heavy smoking and chronic alcohol consumption were reported to be major risk factors for UGIC<sup>[21]</sup>. People who were current cigarette smokers were associated with an increased risk of esophageal cancer (RR = 1.67) and gastric cancer (RR=1.60) compared with people who had never smoked<sup>[22]</sup>. In China, the smoking rate was 52.9% for males, and the second-hand smoking rate was approximately 72.4%, which was significantly higher than the global level<sup>[23]</sup>. In Hebei Province, the cigarette smoking rate was 26.08% for both genders and 48.09% for males<sup>[24]</sup>. Additionally, the smoking prevalence is still increasing. According to an investigation on alcohol consumption in adult residents in Hebei Province<sup>[25]</sup>, the total drinking rate was 41.1% and was higher in males (71.8%) than in females (19.7%). Males were the primary population that drank alcohol. Because maintaining good life habits is necessary for health, we suggest that people, especially males in rural areas, quit smoking and limit alcohol consumption.

Economic, environmental and genetic risk factors can also lead to the high incidence and mortality rates of UGIC<sup>[26-28]</sup>. UGIC is a disease of the poor and the socially disadvantaged. A large number of epidemiological studies have confirmed that the UGIC risk is higher in populations with a lower socioeconomic status due to limited medical care, limited education and poor living conditions<sup>[29-33]</sup>. Almost 78% of the new cases occurred in rural areas of Hebei Province in 2013. The per capita annual net income of urban households (¥17278) was approximately 2.64 times higher than that of rural households (¥6539) in Hebei Province in the 2010s<sup>[34]</sup>. The low income sets constraints on the involvement of the population in health care for

the prevention or treatment of illnesses and injuries, the possibility of a good education level, which would improve their health awareness and lifestyle, the ability to live in a favourable environment where they could avoid exposure to bacteria, viruses and other infection-causing agents, and their dietary choices. One study identified risk factors for esophageal cancer in residents of Hebei Province and showed that living in rural areas (OR = 3.14) and eating mildewed food (OR = 7.44) were risk factors for esophageal cancer<sup>[35]</sup>.

A family history of cancer is an important risk factor for UGIC. A first-degree family history of esophageal or gastric cancer was significantly associated with UGIC development, with an adjusted OR of 4.7 (95%CI: 2.6-8.4)<sup>[36]</sup>. A study on residents of Hebei Province found that having a family history of esophageal cancer was a risk factor for this malignancy, with an OR of 3.23<sup>[35]</sup>. In Cixian, a family history of gastric cancer was shown to be a risk factor for this malignancy (OR = 1.84)<sup>[7]</sup>. Therefore, appropriate screening strategies, especially for relatives of patients, should be considered for the prevention and control of UGIC in Hebei Province.

Moreover, UGIC was associated with geographic factors. Liang *et al.*<sup>[8]</sup> showed that the nitrate, nitrite, nitrogen and ammonia levels in high-risk areas of Hebei Province were seven times higher than those in low-risk regions and exceeded the national standards for drinking water. Cao *et al.*<sup>[6]</sup> also found that the nitrate level in Shexian (a high-risk area), Hebei Province was five times higher than that in Chicheng County (a low-risk area) and that the nitrogen and ammonia levels in Shexian were also higher. This finding suggests that nitrate and ammonia were important risk factors for UGIC. Therefore, we should improve drinking water quality and provide safe water to the high-risk areas of Hebei Province.

The mortality rate of UGIC in Hebei Province dropped from the 1970s to 2013. In Hebei Province, the data from the four periods of the death survey indicated that the mortality rate in 2013 had decreased by 20.42% compared with the mortality rate in 1973-1975 in the sampling survey of national causes of death. In both high-risk and non-high-risk areas, the mortality rates of UGIC dropped from the 1970s to 2013, although the rates declined more in the high-risk areas than in the non-high-risk areas.

The age-specific mortality rate was lower in 2013 than in 1973-1975, 1990-1992 and 2004-2005 for individuals younger than 75 years but was dramatically increased in the 75-79 age group. This latter group had an age-specific mortality rate in 2013 that was higher than the rates in 1973-1975, 1990-1992 and 2004-2005, showing the ageing population trend. At present, as economic growth drives the standards of living higher, the median age at death caused by UGIC increases. The median age at death caused by UGIC increased approximately 4 years from the 1970s to 2013. This rate is increasing faster in high-risk areas

than in non-high-risk areas; indeed, the median age at death in high-risk areas (70.37) was basically the same as that in non-high-risk areas (70.40) in 2013. This finding indicated that we had achieved a great success in the screening, early detection and treatment of UGIC in Hebei Province, especially in high-risk areas. Additionally, diagnosis and treatment have improved, which can extend people's lifespan. However, we need to continue efforts to reduce the mortality rate.

The prognosis of UGIC is poor. The main reason is that most cases are asymptomatic during early stages and thus are detected at an advanced stage when they are no longer amenable to surgical resection. Therefore, screening and treating patients with upper gastrointestinal precancerous lesions is important for preventing the development of UGIC in high-risk individuals. Cixian and Shexian have been chosen as demonstration bases for the early detection and treatment of UGIC. Endoscopy with mucosal iodine staining is a sensitive technique to identify clinically relevant UGIC. Since 2000, a national screening programme using endoscopy with mucosal iodine staining and an index biopsy combined with a pathological examination to confirm and stage the disease has become available at 17 sites in Hebei Province, including Cixian and Shexian. At present, 25000 high-risk individuals in Hebei Province are screened every year. The screening programme has reduced the total cancer mortality rates in the Cixian and Shexian populations and may be one reason for the decreasing trend of mortality.

We showed the age, period and birth cohort effects of the condition in Cixian from 1989 to 2013 via an age-period-cohort model. The age and cohort effects played an important role. People aged between 65 and 69 years were a population at relatively high risk for UGIC. The total trend of the cohort effect was a decline, and the early birth cohort had higher risk of developing UGIC. One reason could be that long-term unhealthy lifestyle behaviours, such as heavy smoking, chronic alcohol consumption, and a weakened immune system, increased the birth cohort effect of the incidence risk in rural areas during these time periods. The period effect did not show large variation. Using the grey system model, we found that the mortality rates of UGIC in Cixian and Shexian exhibited a downward trend that should be attributed to the early diagnosis and treatment in these high-risk areas of Hebei Province. The model predicted that the mortality rates of UGIC would decrease to 98.80 and 133.99 per 100000 in 2018, respectively. However, we should still enhance UGIC control and prevention measures.

In summary, the mortality rate of UGIC has been decreasing over the past 40 years. However, UGIC was the major cause of cancer death in Hebei Province. Intensifying the primary prevention by adopting a healthy lifestyle and the secondary prevention with endoscopic iodine staining are priorities for the reduction of the morbidity and mortality of UGIC in

Hebei Province.

## COMMENTS

### Background

Globally, approximately 45% of upper gastrointestinal cancer cases (including esophageal cancer and stomach cancer) occur in China. The incidence and mortality proportions of these cancers account for approximately 19.8% and 23.3% of all malignancies in China, respectively. Hebei Province is recognized as a high-risk area for upper gastrointestinal cancer.

### Research frontiers

In China, the burden of upper gastrointestinal cancer is heavy. However, few studies have investigated the epidemiological trends of upper gastrointestinal cancer. This research focused on the analysis of the real burden of upper gastrointestinal cancer in Hebei Province and the trend in the high-risk regions of Hebei Province and China to provide epidemiological evidence for developing strategies to control upper gastrointestinal cancer.

### Innovations and breakthroughs

The study collected data from 21 population-based cancer registries covering 11185626 individuals in Hebei Province in 2013. The authors applied the age-period-cohort model to analyse the incidence rate of upper gastrointestinal cancer in one high-risk area of Hebei Province (Cixian), and predicted the mortality rates of upper gastrointestinal cancer in the high-risk areas of Hebei Province (Cixian and Shexian) using a grey system model.

### Applications

This study investigated the real burden of upper gastrointestinal cancer in Hebei Province. This study analysed the reasons why the incidence and mortality rates of upper gastrointestinal cancer were higher in the high-risk areas than in the non-high-risk areas and why the mortality rates decreased. The results will provide reference values for upper gastrointestinal cancer control.

### Peer-review

The aim of this study was to provide epidemiological evidence for developing strategies to control upper gastrointestinal cancer (UGIC), which is defined as the principle cause of death in a large area of China (*i.e.*, Hebei Province, which has a risk that is 5.08 times higher than the estimated global risk). All of the epidemiological data are of enormous importance since they represent the basis for a smart health policy that should be oriented and balanced on actual risk data for different regions and populations. The manuscript is well written and organized.

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