RESEARCH ARTICLE

Liver Cancer Mortality Characteristics and Trends in China from 1991 to 2012

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Abstract

Purpose: To investigate the distribution of liver cancer mortality as well as its developing trend from l991 to 2012, forecast the future five-year trend, and provide a basis for the comprehensive prevention and management. Materials and Methods: Mortality data for liver cancer in China from 1991 to 2012 were used to describe characteristics and distribution of liver cancer mortality. Trend surface analysis was used to study the geographical distribution of liver cancer mortality. Curve estimation, time series modeling, gray modeling (GM) and joinpoint regression were used to predict and forecast future trends. Results: The mortality rate of liver cancer has constantly increased in China since 1991. Rates in rural areas are higher than in urban areas, and in males are higher than in females. In addition, our data predicted that the trend will continue to increase in the next 5 years. The age-specific mortality of liver cancer increases with age and peaks in the group of 80-84 years old. Geographical analysis showed the liver mortality rate was higher in the southeast provinces, such as Jiangsu, Zhejiang and Guangdong, and southwest regions like Guangxi Province. Conclusions: The standardized mortality rate of liver cancer in China has consistently increased from 1991 to 2012, and the upward trend is predicted to continue in the future. Much better prevention and management of liver cancer is needed in high mortality areas (the southwestern and southeastern parts of China) and high mortality age groups (80- to 84-year-olds), especially in rural areas.

Keywords: Liver cancer - standardized mortality - epidemiological characteristics - geographic distribution - prediction

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Introduction

According to the International Agency for Research on Cancer, cancer of the liver is the fifth most common cancer in the world, with 523, 000 cases per year for males, accounting for 7.9% of all male cancers, and 226, 000 cases per year for females, accounting for 6.5% of all female cancers. Liver cancer has high mortality and the geographic distribution of mortality is similar to that of incidence. The geographical distribution of liver cancer varies greatly worldwide, especially between developed and developing countries (Ferlay et al., 1998). More specifically, the disease is higher in developing countries, where almost 85% of the cases occur. China is a country with a high incidence of liver cancer, accounting for 55% of the world's cases (men, 35.2/100, 000; women, 13.30/100, 000) (Ferlay et al., 2001; Stewart et al., 2003). Since over 80% of deaths are in developing countries, liver cancer has been a major public health problem in these parts of the world, including China.

Liver cancer has a wide distribution and seriously threatens human health. Much is known that variations in age, sex and geographic region are likely to be related to the differences of liver cancer mortality. Research and analysis of liver cancer mortality data have important guiding significance for epidemiological studies of liver cancer. In this study, the related data of liver cancer in China from 1991-2012 was used to understand the dynamics of death, sex, age, urban or rural location, and geographic distribution of liver cancer. Prediction of the trends and identification of geographic patterns of liver cancer mortality, based on population and location, may provide information for both prevention measures and management policies. Therefore, we used trend surface analysis, one of the most widely used global surface-fitting procedures, to not only show the overall geographical distribution and the trend of liver cancer, but also to reflect disease variation in local areas, as well as the regional distribution and trend of disease (He et al., 2008; Shi et al., 2014)

Materials and Methods

Data source

Data was obtained from the nation-wide cancer mortality survey of the Disease Prevention and Control Bureau, Ministry of Public Health, for the period 1991-2012. Demographic data were collected from the Chinese

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National Statistics Department. Cancer registration data was obtained from 32 monitoring sites established by the National Cancer Center (14 sites in the urban area and 18 sites in the rural area). Data collection followed the rules and standards of the International Agency for Research on Cancer (IARC) and the International Association for Cancer Registration (China Health Statistics Yearbook, 2005; 2006; 2007; 2008; Chen et al., 2008; Zhao et al., 2008; 2009; 2010; 2011; 2012).

Three methods were used to evaluate the quality of the data, including diagnosis reliability, data integrity and coding quality. To ensure reliability, completeness and reliability of submitted data were checked and evaluated based on the "Guideline for Chinese Cancer Registration" and referring to relevant data quality criterion of "Cancer Incidence in Five Continents Volume IX" by the IARC/RACR Software, such as MS-FoxPro, SAS, MS-Excel and IARC/IACR tools, and IARC-crgTools were used for data collation, sorting, checking and evaluation. The integrity of the death data was evaluated according to the mortality distribution of the survey counties (cities). The accuracy of death coding was used to determine the cause of coding quality (Zhao et al., 2012).

Statistical analysis

The crude rate, standardized mortality rate (SMR) and age-standardized rate by Chinese standard population were used in the statistical analysis. The data of the 1982 Chinese census was used for age adjusting.

Methods

The mortality data of liver cancer in China from 1991-2012 can be used to evaluate the dynamic changes in the standardized mortality rate of liver cancer, identify the change of distributions by population, time and place (three-dimension distribution), and estimate the trend over the next 5 years.

Trend surface was used to describe the spatial structure and spatial change of liver cancer, and geographical anomalies could be highlighted in this way. Polynomial regression was applied to fit a trend surface analysis based on standardized mortality of longitude (x) and latitude (y), and the standardized mortality rate of various areas. Four methods, including the R-square test, F-test, goodness of fit order by order test and a subjective judgment were applied to select the order of trend surface modeling. SAS9.1.3 software was used to complete trend surface analysis and contour maps.

The liver mortality data in China from 1991 to 2012 was used to estimate the trend of liver mortality and to predict the next 5-year trend. Four different methods, including curve estimation, time series modeling, gray modeling (GM) and Joinpoint regression, were used to predict the liver mortality trends. Statistical analysis was performed by SPSS19.0, DPS 7.50 and Joinpoint 4.1.0

Curve estimation models are types of linear and nonlinear curves which may be fitted to the data, including linear, logarithmic, inverse, quadratic, cubic, power, compound, S-curve, logistic, growth, and exponential curves. We used SPSS software to plot dependent variables, which helped us select a suitable model to fit. In this investigation, x stands for the time (year) and y stands for standardized mortality rates.

Time series forecasting is the use of a model to predict future values based on previously observed values. It is a form of regression analysis to test theories that the current values of one or more independent time series affects the current value of another time seriesb (Box et al., 2013). This model type is generally referred to as autoregressive integrated moving average (ARIMA), with the integers referring to the autoregressive, integrated and moving average parts of the data set, respectively. ARIMA modeling can take into account trends, seasonality, cycles, errors and non-stationary aspects of a data set when making forecasts.

The gray system theory is proposed on the uncertainty problem with no experience and less data. Gray model GM (1, 1) is the most widely used dynamic model of gray system theory and can be used for the prediction of the dominant factor which was complex (Huang et al., 2013). The improved GM (1, 1) model group and dynamic equal dimensional number progress complement was used in this paper to obtain more accurate forecasts.

The Joinpoint regression program is trend analysis software developed by the US National Cancer Institute for the analysis of data from the Surveillance Epidemiology and End Results Program. We use the Joinpoint regression model to analyze the long-term trends of liver mortality based on published data between 1991 and 2012, and to find out the estimated tendency and get the annual percentage rate change and average annual percent change of liver cancer in China (Qiu et al., 2009).

Results

Time-dependent changes in mortality rates of Liver cancer

For the past four decades, three national surveys based on the National Mortality Retrospective Sampling Survey during the periods of 1973-1975, 1990-1992, and 2004-2005 showed that the standardized mortality rates of liver cancer were 11.0/105 in 1973-1975, 17.8/105 in 1990-1992, and 17.9/105 in 2004-2005 (National Office for Cancer Prevention and Control, 2008; Chen et al., 2011). Based on recent mortality data from 2002 to 2012 in China, there is a steady increase in the mortality of liver cancer. Liver cancer standardized mortality was 21.9/105 in 2002 and 27.4/105 in 2012 (Zhao et al., 2012).

Difference between the urban and rural liver cancer mortality

Liver cancer mortality tended to increase in both urban and rural areas from 1991 to 2012. Comparing the mortality rates between rural and urban areas, the rate of liver cancer in rural areas was higher than that in urban areas. In 1991, the average mortality of rural areas was 3.2/105, higher than that in urban areas. The urban liver cancer standardized mortality in 2012 was 11.3/105, while in rural areas it was 17.3/105. The rate was 52.7% higher in the rural than that in urban areas (Zhao et al., 2012).

Age-specific and gender characteristics of liver cancer mortality

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Figure 2 shows that mortality rates of liver cancer increase with age. Age-specific mortality rates of liver cancer remained at a low level in the 0 to 35 years age group, and started to rise significantly at age ~35 years, reaching a peak at the age of 80~84 years, and then falling. In the 35~ to 40-year-old age group, the mortality rose to 6.68/105 in city, while it rose to 18.4/105 in rural areas. Mortality peaked at 166.10/105 in rural areas and 142.0 /105 in urban areas in the 80~ to 84-year-old age group. The trend of age-specific liver mortality in urban areas was similar as that in rural areas.

Since the nineties, liver cancer has shown significant gender-dependent differences, with males having higher mortality than females in each age group. The sex-ratio of male to female deaths was 2.60:1 according to the survey of death causes for the periods of 2004-2005, which is the third survey in China. The ratio of male and female is 2.5:1 in 35~ to 64-year olds while the ratio is more than 4~5:1 in 30~ to 49-year olds. Liver cancer was the second cause of death for all cancers in males, and the third cause of death reason in females in 2009. The liver cancer standardized mortality for men was 36.8/105 in 2012, while the mortality of women was 13.4/105 (Zhao et al., 2008; 2009; 2010; 2011; 2012).

Geographical distribution of liver cancer mortality

A binary polynomial regression equation was built for trend surface analysis though four methods, including the R-square test, F-test, goodness-of-fit order by order test, and subjective judgment method based on the geographical epidemiology of liver cancer. A meaningful second-order trend surface equation (F=4.3, $p<0.01$, $R^2=0.46$) for liver cancer mortality trends of the geographic distribution can be predicted through:

z=-1405.9-19.3*x-13.8*y+0.06*x*x+0.17*x*y-0.11*y*y

In this equation, z stands for the standardized mortality rate of liver cancer for various areas, x stands for longitude and y stands for latitude. The model can fit goodness as 45.5% of the death variation of liver cancer in China, suggesting several geographic distribution characteristics. The contour maps of liver cancer mortality rates drawn by the mathematical models showed a unique liver cancer geographic distribution pattern in China. Liver cancer mortality was significantly related to geographic location, being higher in the southeast coastal areas (Jiangsu, Fujian and Zhejiang province) and southwest (Guangxi province) areas than inland. Nationally, at the county level, Fusui of the Guangxi autonomous region, Sihui of Guangdong province, and Qidong of Jiangsu province stood out with the highest rates of liver cancer mortality (Figure 3), suggesting that environmental factors play an important role in the development of liver cancer.

Estimation and forecasting

When the sample of the latest data is small, the sample information may not be fully used and it is risky to assume the derived distribution. Consequently, we applied four independent, but complementary predictive models (curve estimation, time series modeling, Gray modeling, Joinpoint regression) for data analysis to find a suitable trend for mortality of liver cancer in the next five years. Assuming that factors, such as social, economic, environmental and lifestyle, had no dynamic change, data for liver cancer mortality from 1991-2012 is suitable for building a predictive model. The error value (ERR) and the 95% confidence interval (95%CI) were selected to be the forecasting accuracy measures.

Curve estimation: the cubic curve model fitted the predictive trend best ($R^2=0.97$, F=320.8, $p<0.01$) (Tables 1 and 2). The equation is: y= 15.7+0.18*x +2.27* x*x-1.53* x*x*x, where x stands for the year, and y stands for mortality rate.

Time series model: according to liver cancer mortality data, the built autoregressive integrated moving average (ARIMA) model was suitable for prediction ($R^2=0.96$, $p=0.06$) (Tables 1 and 2).

Gray model (GM): based on the theory of the gray model, $X_{(i)}$ indicates the standardized mortality rate of

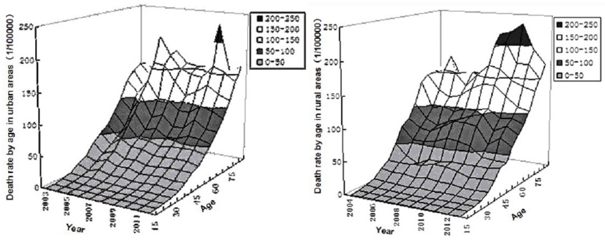

Figure 1. Trends in Age-Specific Mortality of Liver Cancer by Area in China from 2002-2012

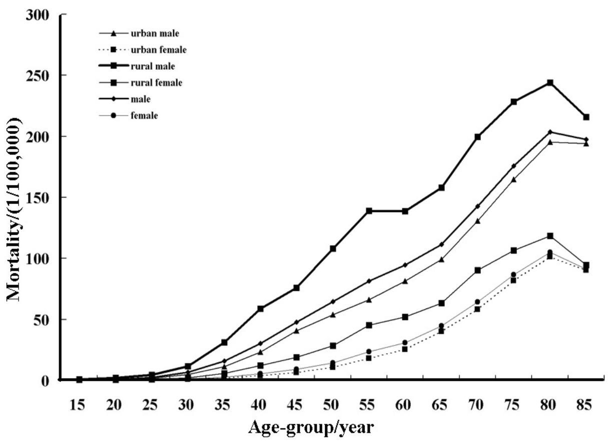

Figure 2. Change in Age-Specific Mortality of Cacer among Urban and Rural Areas, and Different Genders in China in 2012

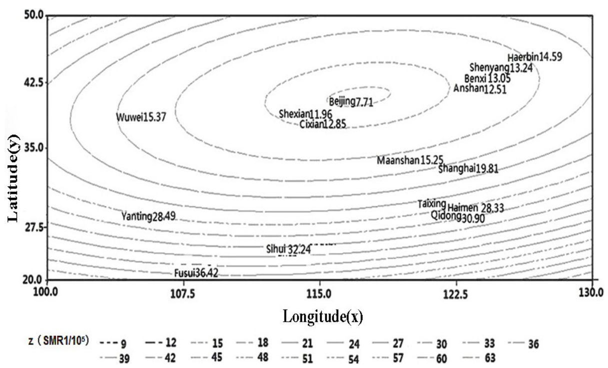

Figure 3. Geographical Distribution of the Standardized Mortality Rate of Liver Cancer from 2003 to 2007 in China

Table 1. Mortality for Liver Cancer, by 4 Models, in China from 1991 to 2012 (1/10^5)

Year (X)	Observed SMR(Y)	Cubic Modeled SMR	Cubic Fitted error	ARIMA (0,1,0) Modeled SMR	ARIMA (0,1,0) Fitted error	GM (1,1) Modeled SMR	GM (1,1) Fitted error	Joinpoint Modeled SMR	Joinpoint Fitted error
1991	15.1	15.9	-0.81	16.4	-0.17	16.2	-1.09	15.4	-0.63
1992	16.4	16.2	0.23	15.6	0.10	16.6	-0.22	16.1	-0.06
1993	17.3	16.5	0.76	16.9	0.05	17.1	0.22	16.7	0.14
1994	16.6	17.0	-0.39	17.9	-0.15	17.6	-0.95	17.3	-0.55
1995	18.2	17.6	0.58	17.1	0.12	18.1	0.08	17.9	0.10
1996	19.3	18.2	1.11	18.7	0.07	18.6	0.70	18.6	0.39
1997	18.3	18.8	-0.59	19.8	-0.18	19.1	-0.86	19.2	-0.52
1998	19.4	19.5	-0.15	18.8	0.07	19.7	-0.26	19.8	-0.12
1999	20.0	20.3	-0.26	19.9	0.01	20.2	-0.19	20.4	-0.09
2000	20.7	21.0	-0.39	20.6	0.01	20.8	-0.13	21.1	-0.06
2001	21.0	21.8	-0.82	21.2	-0.02	21.4	-0.39	21.7	-0.21
2002	21.9	22.6	-0.70	21.5	0.04	22.0	-0.12	22.3	-0.04
2003	23.9	23.3	0.53	22.4	0.15	22.6	1.24	22.9	0.69
2004	24.3	24.0	0.21	24.4	-0.01	23.2	1.00	23.6	0.49
2005	25.0	24.7	0.32	24.8	0.03	23.9	1.13	24.2	0.58
2006	25.8	25.4	0.47	25.6	0.03	24.6	1.24	24.8	0.63
2007	26.2	25.9	0.28	26.4	-0.02	25.3	0.92	25.4	0.45
2008	26.9	26.4	0.51	26.8	0.02	26.0	0.93	26.1	0.48
2009	26.0	26.8	-0.79	27.5	-0.14	26.7	-0.69	26.7	-0.42
2010	27.0	27.2	-0.14	26.6	0.04	27.5	-0.48	27.3	-0.22
2011	27.5	27.4	0.10	27.5	0.00	28.3	-0.79	27.9	-0.39
2012	27.4	27.5	-0.06	28.0	-0.06	29.1	-1.67	28.6	-0.87
Overall Models									
		Cubic		ARIMA (0,1,0)		GM (1,1)		Joinpoint	
Fitted	Median	0.02		0.15		-0.16		-0.06	
Error	Interquartile Range	9.2		0.09		1.65		0.84	
(%)	95%CI	(-0.21, 0.23)		(-0.04, 0.35)		(-0.36, 0.32)		(-0.19, 0.17)	

*SMR-standardized mortality rates

Table 2. Predicted Mortalities for Liver Cancer, by 4 Models, in China During 2013-2017(1/10^5)

Year	Cubic	ARIMA (0, 1, 0)	GM (1, 1)	Joinpoint	Overall `x ±SD	Overall 95%CI
2013	27.4	27.9	29.9	27.5	28.4±1.06	(0.24,1.43)
2014	27.3	28.4	30.8	27.4	28.5±1.62	(0.05,2.01)
2015	26.9	28.9	31.6	26.9	28.8±2.02	(0.47,2.70)
2016	26.5	29.4	32.5	26.6	28.8±2.85	(0.10,3.50)
2017	25.8	29.9	33.5	26.6	28.8±3.61	(0.16,4.42)
X±SD	26.8±0.66	28.9±0.79	31.7±1.40	27.2±0.93	-	-
95%CI	(0.18, 0.84)	(0.27, 1.00)	(0.46, 1.78)	(0.28, 1.17)	-	-

Table 3. APC[a] and AAPC[b] of Age-standardized Rates for Liver Cancer in China from 1991-2012

Trend	APC[a]/AAPC[b]	Urban	Rural	Overall
Segment 1	Years	1991-1993	1991-1998	1991-1993
	APC (95%CI)	4.3 (-13.9, 26.3)	0.3 (-2.8, 3.4)	5.8 (-2.5, 14.8)
Segment 2	Years	1993-1996	1998-2008	1993-2001
	APC (95%CI)	-0.8 (-18.1, 20.1)	12.5[c] (0.1, 26.4)	2.7[c] (1.6, 3.8)
Segment 3	Years	1996-1999	2008-2012	2001-2005
	APC (95%CI)	6.3 (-12.2, 28.1)	0.9 (-0.9, 2.8)	4.9[c] (0.7, 9, 2)
Segment 4	Years	1999-2012	ND[d]	2005-2012
	APC (95%CI)	0.3 (-0.7, 1.3)	ND[d]	1.1[c] (0, 2.2)
Full Range	Years	1991-2012	1991-2012	1991-2012
	AAPC (95%CI)	1.4c (0.9, 1.8)	3.7[c] (2.7, 4.7)	3.0[c] (2.7, 3.2)

*APC[a]-annual percent change; AAPC[b]-annual percent change; [c]-significantly different from zero at alpha=0.05 (p<0.05); ND[d]-no data

liver cancer, and t is the year. We chose the GM (1, 1) model to perform the forecast, with fitting parameters: a=-0.03, b=15.5. The equation is: $X_{(t+1)}=569.2^{0.03t}-553.3$ (C=0.20, p=1.00, Q_{min}=-3.22) (Tables 1 and 2).

Joinpoint regression: in Joinpoint regression modeling, dependent variable X is the year, and independent variable y is the mortality rate. We used this model to identify points where a statistically significant change over time in linear slope of the trend occurred. In China, the estimated average annual percent change (AAPC) of the standardized mortality rate was 2.1% during 1991-2012 (Tables 1, 2 and 3).

Discussion

We showed that the SMR of liver cancer in China has been steadily rising, and the upward trend is predicted to continue in the foreseeable future through the above four analysis. This will seriously threaten human health. According to the four forecast analysis, the predicted mortality of the cubic model and ARIMA model were more accurate than the GM model and Joinpoint regression analysis.

Accumulating data has shown that liver cancer mortality is significantly different in the various regions of China. In terms of mortality rates between urban and rural areas, there appears to be a relatively large difference. The mortality rates in rural areas are higher than those in urban areas. Previous studies have indicated that the prevalence rates of risk factors mentioned above are higher in rural areas than in urban areas (Mao et al., 2007). Because of lower income, less education, absence of public awareness and lack of resources for people, poorer health services in rural areas, residents in rural areas are more vulnerable to liver cancer, which can lead to higher mortality rates that are higher in rural than in urban areas (Cheng et al., 2013). This suggests that prevention should focus more on rural populations.

Data of mortality by age show that liver cancer mortality increases rapidly in people over the age of 35, and peaks in the 80 to 84 age group. People over the age of 35 should actively prevent liver cancer. The reasons for higher rates of liver cancer in males may relate to sex-specific differences in exposure to risk factors. Men are more likely to be infected with HBV and HCV, consume alcohol, smoke cigarettes, and have increased iron stores.

Trend surface analysis, one of the most widely used global surface-fitting procedures, was used to identify the geographical distribution of liver cancer. The trend surface analyses illustrate that there is a tendency for liver mortality rates to be higher in the southeast and southwest areas, rather than the central or western areas. High risk areas are among the warm, humid, marine-climate areas, such as Qidong, Taixing of Jiangsu province, Fujian, Guangxi, and Zhejiang province. On the contrary, Bingjing, Haerbing, Gansu, Xinjiang, and Qinghai show the lowest mortality. Wang et al noted that the geographical distribution characteristics of liver cancer was linked to aflatoxin contamination, and noted that the "Toxigenic Days" distribution of aflatoxin are consistent with the distribution of liver crude death rate of eastern coastal areas (Wang et al., 1983). But this still did not explain the reasons for the Mainland of China to answer the high mortality of inland, and there may be dietary habits, potential environmental factors affecting this population (Kensler et al., 2003; Luo et al., 2005). As a gastrointestinal tumor, liver cancer has regional features similar to esophageal carcinoma. Both of the cancers are concentrated in southeast and southwest China, such as Jiangsu, Zhejiang and Guangxi province. However, liver cancer has a relatively low mortality rate in the northeast and northwest regions of China, while the mortality of esophageal cancer in northern China, such as Shaanxi, Xinjiang and Harbin, is relatively high (Tang et al., 2014), suggesting that environmental factors play an important roles in the development of liver cancer. The key regions for the prevention and control of liver cancer should be the southeast coastal areas and southwest areas.

In conclusion, liver cancer is the most common cancer and is becoming one of the most serious public health issues in China. The mortality rate of liver cancer is increasing and will continue to rise steadily in the foreseeable future. Diminishing the spread of liver cancer-associated infections, such as HBV and HCV, and avoiding dietary exposure to aflatoxins are the essence of primary prevention. Early detection, early diagnosis, and early treatment in high risk groups of liver cancer are the goals of secondary prevention for the cancer of the liver (Chen et al., 2010). Prevention and treatment of liver cancer remains to be the major task of cancer control in China. Much better prevention and management of liver cancer is needed in high mortality areas, such as the southwestern and southeastern parts of China. The prevention strategy of liver cancer also should be focused on the 80- to 84 year-olds in urban areas.

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