# RESEARCH ARTICLE

# Colorectal Cancer Mortality Characteristics and Predictions in China, 1991-2011

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## Abstract

<u>Background</u>: To identify the epidemiological characteristics of colorectal cancer mortality in China during the period of 1991-2011, and forecast the future five-year trend. <u>Materials and Methods</u>: Mortality data for colorectal cancer in China from 1991 to 2011 was used to describe epidemiological characteristics in terms of age group, gender, and rural/urban residence. Trend surface analysis was performed to analyze the geographical distribution of colorectal cancer. Four models including curve estimation, time series modeling, gray modeling and joinpoint regression were applied to forecast the trends for the future five years. <u>Results</u>: Since 1991 the colorectal cancer mortality rate increased yearly, and our results showed that the trend would continue to increase in the ensuing 5 years. The mortality rate in males was higher than that of females and the rate in urban areas was higher than in rural areas. The mortality rate was relatively low for individuals less than 60 years of age, but increased dramatically afterwards. People living in the northeastern China provinces or in eastern China had a higher mortality rate for colorectal cancer than those living in middle or western China provinces. <u>Conclusions</u>: The steadily increasing mortality of colorectal cancer in China will become a substantial public health burden in the foreseeable future. For this increasing trend to be controlled, further efforts should concentrate on educating the general public to increase prevention and early detection by screening. More effective prevention and management strategies are needed in higher mortality areas (Eastern parts of China) and high-risk populations (60+ years old).

**Keywords:** Colorectal cancer - mortality - epidemiological characteristics - geographic distribution - prediction

## Introduction

Colorectal cancer is the second most common cancer in women (614,000 cases, 9.2% of the total) and the third most common cancer in men (746,000 cases, 10.0% of the total) worldwide (World Health Organization, 2012). Nowadays, colorectal cancer mortality has declined in the developed countries because of improved early detection and a lack of increase in morbidity (Jemal et al., 2011). However, recent reports from the World Health Organization show that the incidence of colorectal cancer is rapidly rising in many countries in Asia, such as China, Japan, Korea and Singapore. Due to the changing lifestyles and food habits, colorectal cancer is one of the three cancers with the most rapidly increasing incidence in China in the past two decades (Lu et al., 2003).

The national cancer registration system makes it possible to study many aspects of colorectal cancer. An accurate knowledge of colorectal cancer patterns is essential in the planning of national cancer control programs. However, there are no studies that present nation-wide data on colorectal cancer mortality in the past 20 years in China. Predictions of the trends and identification of geographic patterns of colorectal cancer mortality may provide important clues regarding the cause and effect of relevant factors. In this paper, we use trend surface analysis, one of the most widely used methods to reflect distributions and trends of disease, to analyze data on cancer mortality in China from 1991 to 2011 in order to describe the dynamics of death, sex, age, urban–rural location, and geographic distribution of colorectal cancer.

## Materials and Methods

*Data source*

All mortality data in 1991-2011 was obtained from the Cancer Registry of the Disease Prevention and Control Bureau, Ministry of Public Health (Zhao et al., 2008; Zhao et al., 2009; Zhao et al., 2010; He et al., 2011; He et al., 2012; Chen et al., 2013; Chen et al., 2014; Chen et al., 2015). Corresponding population data, by age, sex and year, was collected from the Chinese National Statistics Department. The National Central Cancer Registry of China collected cancer mortality data from population-based cancer registries in China which included 72 monitoring sites.

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*Evaluation of data quality*

To ensure reliability and completeness, the National Central Cancer Registration has developed a series of quality control and evaluation systems. Three aspects were used to evaluate the quality of the data including diagnosis reliability, data integrity and coding quality. In order to assure that the data over the period of 1911-2011 are reliable for estimating mortality, the quality of data was assessed based on the "Guideline of Chinese Cancer Registration" and referred to the criteria for "Cancer Incidence in Five Continents Volume IX" by the IACR and IARC. Database software, including MS-FxPro, MS-Excel, SAS and IARC issued by the IARC/IACR, were used for data collection sorting, checking and evaluation (Chen et al., 2013).

*Statistical analysis*

The crude rate, age-standardized rate by the Chinese standard population (ASR-c) was used in the statistical analysis. The Chinese population census in 1982 and Segi's population were used for age-standardized mortality rates.

*Analysis methods*

The national registered data during 1991-2011 was used to evaluate the changes in colorectal cancer, identify the distribution of colorectal cancer by age group, gender, and rural/urban residence, and estimate the trend over the next 5 years.

To demonstrate the geographic distributions of colorectal cancer, trend-surface analysis was constructed. Trend-surface analysis is a mathematical model based on the theory of multiple regression analysis. In this mathematical model, the dependent variables were longitude (x) and latitude (y) of different cities/towns, and the independent variable was the standardized mortality of various cities/towns. Trend-surface analysis and distribution map drawings were conducted using SAS 9.1. Based on the results of the model selection analysis, a fourth degree polynomial least-squares function was used to characterize the geographic distribution of colorectal cancer mortality in China.

Four different methods --- curve estimation, time series modeling, gray modeling (GM) and Joinpoint regression were used to predict the colorectal cancer mortality trends in the next five years. Statistical analysis was performed by SPSS19.0, DPS 9.50 and Joinpoint 3.3.5.

To estimate the potential trend distribution of colorectal cancer, curve estimation was used to find the best fit to the data. Because the relationship between colorectal cancer mortality and the year was possibly nonlinear, different curve estimations (linear, logarithmic, inverse, quadratic, cubic, power, compound, S-curve, logistic, growth and exponential models) were used to determine the best fitting model. In this estimation, x stands for the year and y stands for ASR-c.

Time series analysis is comprised of methods for analyzing time series data in order to extract meaningful statistics from the data. As a part of a time series analysis, time series forecasting is used to predict future values based on previously observed values (Box GE et al.,

2011). The Auto-Regressive Integrated Moving Average (ARIMA) regression method of time series analysis considers both the historical values and residuals, and is widely used to estimate the potential trend distribution of colorectal cancer (Zhang et al., 2014).

Gray system theory uses a black-gray-white color spectrum to describe a complex system whose characteristics are only partially known or known with uncertainty (Hao et al., 2007). In this theory, a white color denotes a system that is completely characterized and a black color represents a system that is totally unknown. The GM (1, 1) model of the grey system was adopted to predict the future colorectal cancer mortality in China. Based on the theory of the gray model, X (i) means the standardized mortality rate of lung cancer, t means the year.

The joinpoint regression program is a statistical software package developed by the U.S. National Cancer Institute for the Surveillance, Epidemiology and End Results Program. The joinpoint regression model was performed to provide an estimated annual percentage change and to detect points in time where significant changes in trends occur. In this model, dependent variable X is the year, and independent variable y is the mortality rate, and each joinpoint indicates a statistically significant change in trend. We fitted a joinpoint model to find out the estimated mortality of colorectal cancer.

## Results

*Time-dependent changes in mortality rates of colorectal cancer*

Based on data from three national surveys on colorectal cancer during the periods of 1973–1975, 1990–1992, and 2004–2005, the crude colorectal cancer mortality rates were $4.60/10^5$, $5.30/10^5$, and $7.52/10^5$, respectively. The age-standardized rates of colorectal cancer were $4.20 /10^5$ in 1973–1975, $4.08 /10^5$ in 1990–1992 and $3.03/10^5$ in 2004–2005. The adjusted death rate remained relatively stable in 2003-2009 and increased gradually after 2009, with mortality being $6.15/10^5$ in 2009 (ASR-C in men: $7.28/10^5$, ASR-C in women: $5.09/10^5$), and further increased to $7.77/10^5$ in 2011 (ASR-C in men: $9.40/10^5$, ASR-C in women: $6.26/10^5$). The details and time trend are shown in figure 1.

*Difference between the urban and rural colorectal cancer*

The distribution of colorectal cancer was variable among rural and urban areas as well. The crude mortality rates in the urban areas were much higher than those in the rural areas. After being adjusted by the differential under-reporting rates, the adjusted rates in the urban areas were still higher than those in the rural areas. The death rates of colorectal cancer displayed an increasing trend for both rural and urban areas during the period of 1991-2011 (Figure 1). In 1991 the crude mortality rate of colorectal cancer was 13.47 per 100 000 populations in urban areas, and 6.89 in rural areas, and the adjusted death rates were 6.35 and 4.03, respectively. In 2011, the corresponding rates were 13.27 and 8.84, and 6.43 and 1.40, respectively. With joinpoint regression analysis, we

got a conclusion that the average annual percent change of the standardized mortality rate in urban areas was 6.52% ($P<0.05$), whereas in rural areas it was 3.28% ($P<0.05$).

*Age-specific and gender characteristics of colorectal cancer mortality*

Age-specific mortality rate of colorectal cancer increased with age. The majority of the deaths from colorectal cancer remained relatively low before 40 years old and then dramatically increased after 60 years, finally reaching a peak after 85 years old. In both urban and rural areas the mortality rates peaked with individuals 85 years old, reaching $234.50/10^5$ for urban men, $144.69/10^5$ for urban women, $166.69/10^5$ for rural men and $87.42/10^5$ for rural women. The sex-ratio of male to female deaths in urban and rural areas was 1.29:1 and 1.43:1, respectively (Figure 2).

*Geographical distribution of colorectal cancer mortality*

Trend surface analysis based on four aspects, namely the R-square test, F-test, goodness-of-fit order by order test, and subjective judgment method, was built to show the spatial distribution of colorectal cancer mortalities in China. A meaningful third-order trend surface equation for colorectal cancer mortality trends ($F=3.48$, $P<0.01$, $R^2=0.5945$) of the geographic distribution can be predicted using Equation z:

z=18949.5663-329.7961*x-469.4235*y+1.41527*x*x+8.6253*x*y-1.2025*y*y+0.00000*x*x*x-0.0375*x*x*y+0.0032*x*y*y+0.0087*y*y*y
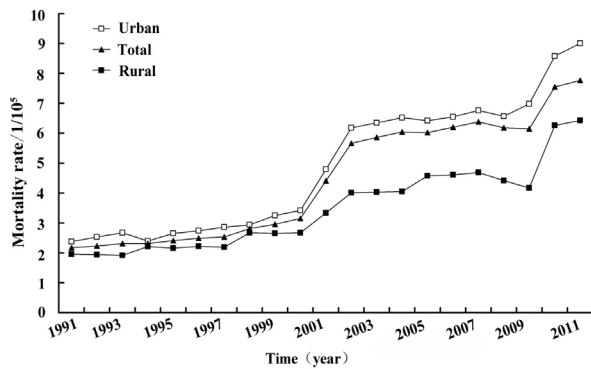


**Figure 1. Mortality Rate of Colorectal Cancer in Urban and Rural Areas During 1991-2011 in China ($1/10^5$)**
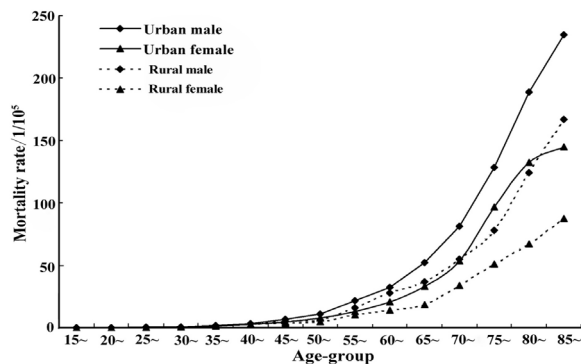


**Figure 2. Change in Age-Specific Mortality of Colorectal Cancer among Urban and Rural Areas, and Different Genders in China in 2011**

In this third-order trend surface equation, x stands for longitude of the cities/towns, y stands for latitude, and z stands for the standardized mortality ratio of colorectal cancer in various areas. These models have a goodness of fit at 59.45% for colorectal cancer mortality rates in China. Figure 3 shows that there was a tendency for the mortality rate to be higher in the eastern areas than in the central areas, and is relatively lower in the western areas of China. At the provincial level, it was highest in eastern and southeastern China (such as Shanghai, Jiangsu, Zhejiang, Fujian and Guangdong provinces), followed by northern China (such as Liaoning, Jilin and Heilongjiang provinces). At the county level, Jiashan, Yangzhong of Jiangsu province, Shanghai Municipality and Guangzhou of Guangdong province stood out with the highest rates of colorectal cancer, followed by Shenyang, Anshan of Liaoning province, and Harebinnangangqu of Heilongjiang province.

*Estimation and forecasting*

Using small sample data might be risky to assume the derived distribution, so we attempted to build four independent, but complementary predictive models with different statistical methods, and compared the results to find a suitable trend for mortality of colorectal cancer in future years. We assumed that the society, the economy, the environment and the lifestyle had no dynamic and changeable characteristics, and the mortality data from 1991-2011 was suitable for building a predictive model. The error value (ERR) and the 95% confidence interval (95%CI) were used to be the forecasting accuracy measures.

Curve estimation: we found the cubic model fitted the trend best, and the cubic curve model gave acceptable and stable predictive estimates of mortality. The equation is: y=2.41-0.24*x+0.05* x*x-0.001* x*x*x, where x stands for the year, and y stands for mortality rate ($R^2=0.95$, $F=106.62$, $P<0.001$) (Tables 1 and 2).

Time series model: the ARIMA (0, 1, 0) model was the most suitable and adopted for prediction ($R^2=0.95$, $P=0.86$) (Tables 1 and 2).
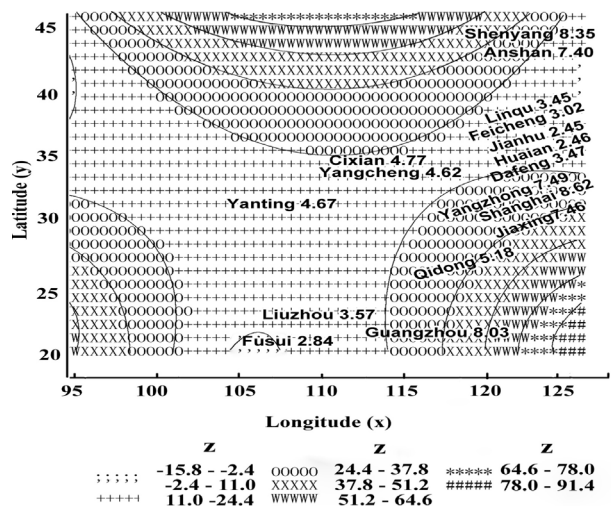
Gray model (GM): the GM (1, 1) model was used



**Figure 3. Geographical Distribution of the Mortality Rates of Colorectal Cancer in China ($1/10^5$)**

**Table 1. Mortality for Colorectal Cancer, by 4 Models, in China from 1991 to 2011 (1/10⁵)**

| Year (X) | ASR-c (1/105) | Cubic | | ARIMA(0,1,0) | | GM(1,1) | | Joinpoint | |
|---|---|---|---|---|---|---|---|---|---|
| | | Modeled SMR | Fitted error | Modeled SMR | Fitted error | Modeled SMR | Fitted error | Modeled SMR | Fitted error |
| 1991 | 2.17 | 2.22 | -0.05 | 2.22 | 0.05 | 2.17 | 0.00 | 1.39 | -0.78 |
| 1992 | 2.41 | 2.13 | 0.10 | 2.31 | -0.08 | 2.32 | -0.09 | 1.70 | -0.71 |
| 1993 | 2.36 | 2.13 | 0.18 | 2.39 | -0.08 | 2.48 | -0.17 | 2.00 | -0.36 |
| 1994 | 2.31 | 2.20 | 0.11 | 2.48 | -0.17 | 2.64 | -0.33 | 2.31 | 0.00 |
| 1995 | 2.31 | 2.35 | 0.06 | 2.49 | -0.08 | 2.82 | -0.41 | 2.62 | 0.31 |
| 1996 | 2.49 | 2.56 | -0.07 | 2.61 | -0.12 | 3.01 | -0.52 | 2.92 | 0.43 |
| 1997 | 2.53 | 2.82 | -0.29 | 2.70 | -0.17 | 3.22 | -0.69 | 3.23 | 0.70 |
| 1998 | 2.81 | 3.13 | -0.32 | 2.75 | 0.06 | 3.43 | -0.62 | 3.54 | 0.73 |
| 1999 | 2.96 | 3.48 | -0.52 | 3.05 | -0.09 | 3.66 | -0.70 | 3.84 | 0.88 |
| 2000 | 3.15 | 3.85 | -0.70 | 3.21 | -0.06 | 3.91 | -0.76 | 4.15 | 1.00 |
| 2001 | 4.41 | 4.25 | 0.16 | 3.41 | 1.00 | 4.18 | 0.23 | 4.42 | 0.05 |
| 2002 | 5.66 | 4.66 | 1.00 | 4.69 | 0.97 | 4.46 | 1.20 | 4.76 | -0.90 |
| 2003 | 5.86 | 5.07 | 0.79 | 5.95 | -0.09 | 4.76 | 1.10 | 5.07 | -0.79 |
| 2004 | 6.04 | 5.48 | 0.56 | 6.16 | -0.12 | 5.08 | 0.96 | 5.38 | -0.66 |
| 2005 | 6.02 | 5.87 | 0.15 | 6.36 | -0.34 | 5.42 | 0.60 | 5.68 | -0.34 |
| 2006 | 6.20 | 6.25 | -0.05 | 6.35 | -0.15 | 5.79 | 0.41 | 5.99 | -0.21 |
| 2007 | 6.38 | 6.59 | -0.21 | 6.54 | -0.16 | 6.18 | 0.20 | 6.30 | -0.08 |
| 2008 | 6.18 | 6.90 | -0.72 | 6.74 | -0.56 | 6.60 | -0.42 | 6.60 | 0.42 |
| 2009 | 6.15 | 7.16 | -1.01 | 6.55 | -0.40 | 7.05 | -0.90 | 6.91 | 0.76 |
| 2010 | 7.55 | 7.37 | 0.18 | 6.53 | 1.02 | 7.52 | 0.03 | 7.23 | -0.33 |
| 2011 | 7.77 | 7.52 | 0.25 | 7.95 | -0.18 | 8.03 | -0.26 | 7.52 | -0.25 |

ASR-c: age-standardized mortality for China; ARIMA: Autoregressive Integrated Moving Average; GM (1, 1): Gray Modeling (1, 1)

**Table 2. Predicted Mortalities for Colorectal Cancer, by 4 Models, in China During 2012-2016(1/10⁵)**

| Year | Cubic | ARIMA (0,1,0) | GM (1,1) | Joinpoint | Overall x̄ ±SD | 95%CI |
|---|---|---|---|---|---|---|
| 2012 | 7.59 | 8.18 | 8.57 | 7.82 | 8.04±0.43 | (7.70,8.38) |
| 2013 | 7.59 | 8.41 | 9.15 | 8.12 | 8.32±0.65 | (7.79,8.89) |
| 2014 | 7.5 | 8.85 | 9.77 | 8.42 | 8.64±0.94 | (7.83,9.43) |
| 2015 | 7.32 | 9.3 | 10.43 | 8.72 | 8.94±1.29 | (7.81,10.00) |
| 2016 | 7.03 | 9.76 | 11.14 | 9.02 | 9.24±1.71 | (7.71,10.61) |
| x̄ ±SD | 7.41±0.24 | 8.90±0.64 | 9.81±1.02 | 8.42±0.47 | | |
| 95%CI | (7.20,7.57) | (8.41,9.40) | (9.04,10.59) | (8.06,8.78) | | |

*SD-standard deviation; CI-confidence interval

to perform the forecast, with fitting parameters: a=-0.07 b=1.96. The equation is: $X(t+1) = 32.15^{0.07t} - 30.04$ (C=0.29, P =1.0) (Tables 1 and 2).

Joinpoint regression: the joinpoint regression model was applied to detect the best points in time where a statistically significant change over time in the linear slope of the trend occurred (Tables 1 and 2).

## Discussion

This study presents nation-wide data on colorectal cancer mortality in China over the last two decades. Our data analysis was performed based on data for demography and death, collected through the National Cancer Center over the period from 1991 to 2011. Due to probability sampling and rigorous management, the data had good representativeness.

Colorectal cancer may be one of the diseases that correlate with industrialization. WHO reported that the age-standardized mortality rates of colorectal cancer in Western developed countries, such as Europe, United States, the United Kingdom and Australia, were about 1-2 times higher than that in China in the same period (World Health Organization, 2012). But in these countries, the mortality rate of colorectal cancer has declined. In some Asian countries, such as Japan, South Korea and Singapore, the age-standardized rates of colorectal cancer are also higher than those in China. This is, to some extent, probably attributed to the increased risk factors associated with industrialization, such as changing lifestyles and food habits, as well as smoking related factors. At present, little is known about the etiology of colorectal cancer. The known factors for colorectal cancer include family history, smoking, physical inactivity, BMI, and nutritional habits (Boyle et al., 2012; Hansen et al., 2013).

Our data show that colorectal cancer mortality appears to be largely different between urban and rural areas. The mortality rates in urban areas are higher than that in rural areas. Life-style and dietary factors might play an important role in the higher mortality rates observed in urban areas. Moreover, the higher rates in the urban areas also could be partly attributed to improved diagnoses. A previous study shows that education predicted greater screening frequency, as the colorectal cancer screening rate is higher in college graduates than in those with less than a high school education (Ma et al., 2012). People living in rural areas have a lower education level and were less likely to have ever received any type of screening

for colorectal cancer. Thus, there is an urgent need for education of the general public in China and improvement of screening in rural areas. Similar to the other studies (Wang et al., 2003), colorectal cancer mortality is strongly related to age. Our study indicates that colorectal cancer mortality rate increases rapidly in people over the age of 60, and peaks in the 85 age group. People over 60 years old require regular screening every year. Our data also finds colorectal cancer mortality in males to be higher than in females, but the male to female mortality rate ratio showed a decreasing trend.

A trend-surface analysis procedure was used to identify the geographical distribution of colorectal cancer. Due to higher level of industrialization and urbanization, the mortality rate is considerably higher in northeastern and eastern China than that in centtral or western China, Jiashan, Yangzhong of Jiangsu province, Shanghai municipality, Guangzhou of Guangdong province Shenyang, Anshan of Liaoning province, and Harebinnangangqu of Heilongjiang province. Colorectal cancer has regional features similar to pancreatic cancers (Wang et al., 2003). Dietary and smoking factors are common risk factors to both cancers and may be relevant to the similarly increased trends of colorectal and pancreatic cancers (Jin et al., 1993; Sung et al., 2008).

Our study indicates that the mortality rate of colorectal cancer is increasing and will continue to rise in the ensuing five years. With the steadily increasing mortality of colorectal cancer in China, it will become a substantial public health burden in the foreseeable future. The peak mortality of colorectal cancer will arrive soon in the next few decades. Despite the increase in colorectal cancer mortality, public awareness is low in many countries. A survey showed that men above 50 years old were particularly unaware of the symptoms of colorectal cancer and the benefits of screening (Kahi et al., 2009). Studies from the West have shown that screening reduces colorectal cancer by up to 53 % (Stephens, 1999; Atkin et al., 2010; Schoen et al., 2012). Therefore, it is crucial to set up screening indicators earlier to reduce the number of deaths from colorectal cancer. Short- and long-term colorectal cancer prevention strategies should be focused on reducing colorectal cancer mortality. Reducing modifiable risk factors, combined with personalized risk communication, can improve public awareness and participation in screening participants, especially for those at higher risk. With regard to cancer care, broad efforts aimed at both improving cancer prevention and early detection with screening are no doubt essential. The main objective of the screening program is to screen as many residents as possible, as well as to educate the population about the importance of early prevention and early diagnosis.

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