RESEARCH ARTICLE

Cervical Cancer Mortality Trends in China, 1991-2013, and Predictions for the Future

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Abstract

Background: To analyze cervical cancer mortality trends in China from 1991-2013 and forecast the mortality distribution in future five years (2014-2018), and provide clues for prevention and treatment. Materials and Methods: Mortality data for cervical cancer in China from 1991 to 2013 were used to describe the epidemiological characteristics and distribution, including the trend of the standardized mortality rate, urban-rural differences, and age variation. Trend-surface analysis was used to analyze the geographical distribution of mortality. Curve estimation, time series, gray modeling, and joinpoint regression were performed to predict and forecast mortality trends. Results: In recent years, the mortality rate of cervical cancer has increased, and there is also a steady increase in the incidence from 2003 to 2013 in China. Mortality rates in rural areas are higher than in urban areas. The mortality dramatically increases in the 40+ yr age group, reaching a peak in the >85 yr age group. In addition, geographical analysis showed that the cervical cancer mortality increased from the southwest to west-central and from the southeast to northeast of the country. Conclusions: The incidence rate and the mortality rate are increasing from 1991 to 2013, and the predictions show this will continue in the future. Thus, implementation of prevention and management programs for cervical cancer are necessary in China, especially for rural areas, young women in urban areas, and high risk regions (the west-central).

Keywords: Cervical cancer - epidemiological characteristics - geographic distribution - standardized mortality

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Introduction

Worldwide, cervical cancer is the second most frequently diagnosed cancer in female, and it is the third leading cause of death for women in less developed country (Torre et al., 2015). Among the estimated numbers of almost 500,000 incident cases and 270,000 deaths due to cervical cancer annually, more than 90% of cases occur in developing countries (Ferlay et al., 2010; Torre et al., 2015). According to the China's health statistic database, the mortality of cervical cancer ranks the eighth among malignant tumors in China. In last decade, the mortality of cervical cancer had significantly decreased compared with the 1970s, however, the incidence of cervical cancer among younger woman is increasing, and the mortality rates of rural China still keep high, such as Shanxi (Yang, 2003; Shi et al., 2012). It is still a serious public health issue in China.

Many epidemiological studies had revealed the tendency of incidence and mortality for cervical cancer by describing population, age, gender, areas, etc. The epidemiological characteristics of cervical cancer are continually changing. According to these investigations, cervical cancer was associated with relevant risk factors include human papillomavirus virus (HPV), socio-economic context, health behavior, and smoking (Gonzaga et al., 2013); these risk factors also have an impact on the prevalence of cervical cancer in China. Focused on this major public health problem in China, the present study aimed to explore the incidence and mortality trends of cervical cancer for woman in China, and to provide useful information for mapping our strategies for cervical cancer prevention, epidemiological research of cervical cancer, and cervical cancer control implementation and evaluation.

Trend surface analysis as a prospective method developed in recent years has been used in epidemiological studies. Trends composed of trend values represent the systematic variation of the surface area, generally considered to be due to systematic changes in the environment caused by changes in the distribution or population (Luo et al., 2008). Trend surface reflect the area variation of disease, which is the geographic distribution characteristics of the disease and causes and influencing factors, will provide important clues for epidemiologic study of cervical cancer (Zheng and Chen, 2001). We obtained available data from the National Central Cancer Registry (NCCR) of China, and used the trend surface analysis to describe the geographical distribution and epidemiological characteristics of cervical cancer.

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Materials and Methods

Data source

Data was obtained from the nation-wide cancer mortality survey during the period 1991-2013 by the National Cancer Control Office, Ministry of Public Health. The data were checked and evaluated by NCCR based on "Guideline for Chinese Cancer Registration" and referring to relevant data quality criterion of "Cancer Incidence in Five Continents Volume IX" by IARC/IACR.

Combined with the actual situation of cancer registration work in China, evaluation of the quality of cancer registry data was based on its integrity, reliability and validity. Data were collected by doctors with specialist knowledge. Through a goodness of fit test, it shows that there is not statistically significant difference between the regional samples and the overall. Population composition and age, sex ratios are reasonable enough to represent the national situation. To ensure reliability, estimates of the resident population on the basis of official censuses, were also derived from the same database as available to the electronic support, and available to the general public as part of registration system. All cancer cases were coded according to the International Classification of Diseases, 10th Revision (ICD-10) (code C53, for deaths because of cervical cancer) (Chen et al., 2015). The quality of these national sample surveys is credible. (China Health Statistics Yearbook, 2006; 2007; 2008; Chen, 2008; Zhao and Chen, 2008; China Health Statistics Yearbook, 2009; Zhao and Chen, 2009; 2010; 2010; China Health Statistics Yearbook, 2011; Han et al., 2011; Hao and Chen, 2012; China Health Statistics Yearbook, 2012; 2013; 2014)

Statistical models

Trend surface analysis. It was used to describe the geographic distribution of cervical cancer in China. On the basic of 40 registered cities/towns from 2007-2009 in China, we established a two-dimensional space coordinates. The space coordinates were longitude (x) and latitude (y), and the variable (z) was the mean of the cervical cancer mortality of the monitoring point, so that the mortality rates of these monitoring points have only a matching point coordinates. The method of polynomial regression was used to fit a trend surface, and the regression equation was tested for significance, according to the fitting function, and drawing contour map. Trend surface analysis and contour map drawing were performed by SAS 9.0 (SAS Institute Inc., Cary, USA).

Four models (curve estimation, time series, gray modeling (GM) and joinpoint regression) were used to estimate the trend of the cervical cancer mortality from 1991 to 2013 and to predict the following 5-year trends. These four models can predict information to establish an early warning system for the prevention of cervical cancer and provide effective scientific basis for prevention and control of cervical cancer. Statistical analysis was conducted using SPSS 19.0, DPS 7.05 and Joinpoint 4.01.

Curve estimation. There are 11 different models of curve estimation in SPSS, including linear, logarithmic, inverse, quadratic, cubic, power, compound, S-curve, logistic, growth and exponential models. The curve estimation was used to quickly complete the 11 models parameter estimation by SPSS and display the corresponding statistic for choosing the best regression model. In this regression analysis, x stands for the time (year) and y stands for standardized mortality rates (SMR).

Time-series analysis. Recently, the Box-Jenkins approach, specifically the autoregressive integrated moving average (ARIMA) model, is typically applied to predict the mortality of diseases; it can take into account changing trends, periodic changes, and random disturbances in time series (Zheng et al., 2015). Thus in this study, ARIMA time-series analysis was used to estimate the relation between time intervals and the observed value. ARIMA includes three steps: model identification, parameter estimation and diagnostic checking. The autocorrelation function (ACF), partial autocorrelation function (PACF), mean squared error (MSE) and mean absolute deviation (MAD) were selected to be the forecasting accuracy measures. In this study, based on the data of the cervical cancer mortality from 1991 to 2013 in China, we established the ARIMA (0, 1, 0) model, which can be used to predict the cervical cancer mortality successfully.

Grey model. Grey system contains not only the known information, but also information of unknown or non-known systems. Base on the gray forecast theory, GM (1, 1) model is pointed out to forecast the trend of cervical cancer in China. Even without large data, GM can effectively describe the characteristics of the few outputs using fewer (at least four number) information. The time dependent variable of the model was the number 1-23, and the independent one was the SMR, and the model was conducted by DPS software.

Joinpoint regression. It also known as piecewise linear regression is to model the time series using a few continuous linear segments. These segments are joined at points called joinpoints, which represent the timing (i.e. year) for a statistically significant change in rate trend (Goovaerts, 2013). To describe linear trends by period, the estimated annual percent change (APC) and average annual percent change (AAPC) were computed for each trends of cervical cancer in China by fitting a regression line.

Statistical analysis

All rates of cervical cancer, expressed per 100 000 population, were directly age-adjusted to the Chinese standard population in 1982 and World Segi's population standard.

Results

Cervical cancer incidence and mortality trends from 2003 to 2013

According to the third national mortality retrospective sampling survey report, compared with the second survey results in China, cervical cancer mortality was significantly decline, the crude mortality rate was $1.89/10^5$ in 1990s, $1.40/10^5$ in 2000s, which is a 25.9% reduction; the SMR was $1.64/10^5$ in 1990s, $0.94/10^5$ in 2000s, which is a 42.7% reduction. And it ranks the sixth dropped to the ninth in malignant tumors in China (Chen, 2008). Although the cervical cancer mortality was declined when compared to the 1990s and 1970s, but in recent years, it shows an increase from $1.22/10^5$ in 2003 to $2.59/10^5$ in 2011. And there is still a steady increase in the standardized incidence of cervical cancer from 2003 to 2013, with the cervical cancer incidence being $13.4/10^5$ in 2011, the standardized incidence rate $10.4/10^5$, and the incidence of urban ($10.6/10^5$) was higher than rural rate ($10.1/10^5$) by 5.57%.

Difference between the urban and rural cervical cancer mortality

Compared to the second national mortality retrospective sampling survey report, the cervical cancer mortality of urban areas was falling by 13.5%, the SMR was falling by 31.8%, and the proportion fell to 1.40%. As well as the urban, the mortality of rural areas was falling by 29.9%, the SMR was falling by 44.2%, and the proportion fell to 2.14%. The decline degree of rural mortality is larger than those from the urban areas. But the cervical cancer mortality of rural is still higher than the urban from 1991 to 2013 (Figure 1). It shows the mortality in the rural areas keep growing from 1991 to 2013, and those in urban areas declined from 1991 to 2001, and rose again from 2002. With the joinpoint analysis, the AAPC of the SMR in rural areas was 7.5% more than that in urban areas from 2004-2013 ($P<0.05$)

Age characteristics of female cervical cancer mortality

The cancer mortality was relatively low before age 35 and then dramatically increased in 40- year age group, reaching peak at ≥85 year group. The mortality in urban areas was the highest in the age group of 80-85 years ($15.6/10^5$), and the rural mortality was the highest in the 75-80 years ($12.4/10^5$). Before age group of 45 years, the mortality in urban rose faster and higher than that in rural, especially in the 25-45 year group, and the age-specific mortality in urban was lowered than that in rural in all of age-groups between the 50-80 years. (Figure 2)

Geographical distribution of cervical cancer mortality

Trend surface analysis can build a binary polynomial regression equation according to the relationship between the cervical cancer mortality rate and their corresponding geographical locations, and use the hypothesis-test theory to check and select the order of trend surface modeling. A meaningful third-order trend surface equation was used to show the geographic distribution of cervical cancer mortality (R^2=0.49, F=3.41, P=0.005). The third-order trend surface equation is:

$$Z=-28403.992+738.104\ x^2+27.205\ y-6.384\ x^2-0.586\ xy+0.434\ y^2+0.019\ x^3+0.001\ x^2+0.003\ xy^2-0.009\ y^3.$$

Where z stands for the SMR of cervical cancer for various cities/towns, x stands for longitude of the cities/towns, and y stands for latitude. This model indicates that the cervical cancer mortality in China explained by geographic factors of variation is 48.9%.

The contour map was draw by SAS software, which showed the unique distribution of cervical cancer mortality in China. There are two trends shown in the contour plot. One starts from a minimum in southwest (such as Fusui, Chongqing), which gradual increase surround the highest level in the west-central (such as Yangcheng, Shexian) in China. It shows the surround low and the highest in the central. The other tendency is mortality rates increased gradually from the southeast (Guangzhou, Changle) to the elevated levels in northeast areas (Dandong, Haerbin). (Figure 3)

Estimation and forecasting

The latest data usually appears a small set to inadequately assume the derived distribution. Under the assumption that society, economy, environment and

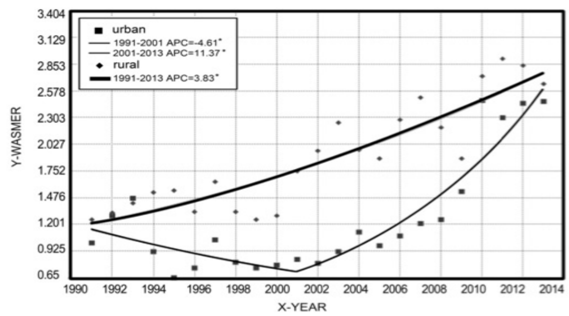

Figure 1. Urban-rural Differences of Standardized Mortality Rateof Cervical Cancer in China from 1991 to 2013

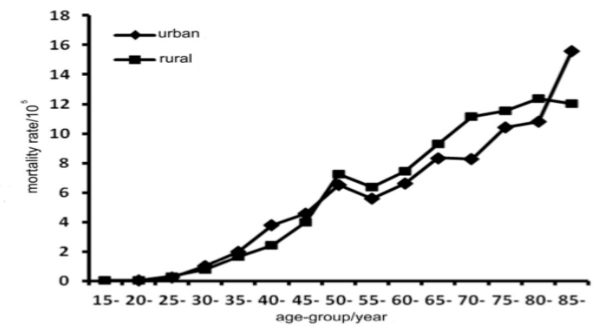

Figure 2. Change in Age-specific Mortality of Cervical Cancer between Urban and Rural Area in China from in 2013

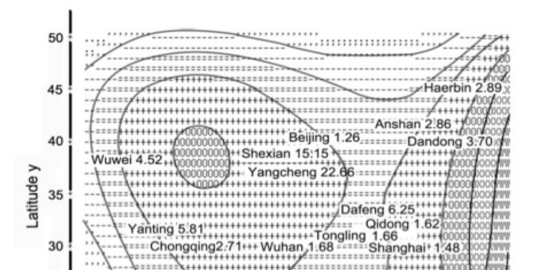

Figure 3. Geographical Distribution of the Standardized Mortality Rate of Cervical Cancer in China from 2007 to 2009

Table 1. Predicted Mortality for Cervical Cancer, by 4 Models, in China from 1991 to 2013(1/10^5)

Year	Observed	Cubic		ARIMA (0,1,0)		GM (1,1)		Joinpoint	
(X)	SMR(Y)	Modeled SMR	Fitted Error	Modeled SMR	Fitted Error	Modeled SMR	Fitted Error	Modeled SMR	Fitted Error
1991	1.08	1.21	-0.13	1.20	-0.12	0.80	0.28	1.17	-0.09
1992	1.18	1.21	-0.03	1.07	0.11	0.84	0.34	1.17	0.01
1993	1.30	1.20	0.10	1.17	0.13	0.88	0.42	1.17	0.13
1994	1.25	1.18	0.07	1.29	-0.04	0.92	0.33	1.17	0.08
1995	1.19	1.16	0.03	1.25	-0.06	0.97	0.22	1.17	0.02
1996	1.07	1.13	-0.06	1.19	-0.12	1.02	0.05	1.17	-0.10
1997	1.35	1.11	0.24	1.34	0.01	1.07	0.28	1.17	0.18
1998	1.09	1.09	0.00	1.08	0.01	1.12	-0.03	1.17	-0.08
1999	1.02	1.08	-0.06	1.10	-0.08	1.18	-0.16	1.17	-0.15
2000	1.06	1.08	-0.02	1.03	0.03	1.24	-0.18	1.17	-0.11
2001	1.12	1.08	0.04	1.08	0.04	1.30	-0.18	1.17	-0.05
2002	1.15	1.10	-0.34	1.14	0.01	1.36	-0.21	1.17	-0.02
2003	1.22	1.14	0.08	1.17	0.05	1.43	-0.21	1.17	0.05
2004	1.32	1.20	0.12	1.24	0.08	1.50	-0.18	1.17	0.15
2005	1.19	1.27	-0.08	1.35	-0.16	1.58	-0.39	1.17	0.02
2006	1.31	1.37	-0.06	1.22	0.09	1.65	-0.34	1.31	0.00
2007	1.49	1.50	-0.01	1.34	0.15	1.74	-0.25	1.47	0.02
2008	1.43	1.65	-0.22	1.53	-0.10	1.82	-0.39	1.65	-0.22
2009	1.64	1.83	-0.19	1.47	0.17	1.91	-0.27	1.85	-0.21
2010	2.60	2.05	0.55	2.60	0.00	2.01	0.59	2.07	0.53
2011	2.59	2.30	0.29	2.65	-0.06	2.11	0.48	2.32	0.27
2012	2.65	2.60	0.06	2.64	0.01	2.22	0.43	2.60	0.05
2013	2.56	2.93	-0.37	2.70	-0.14	2.33	0.23	2.92	-0.36
Overall models		Cubic		ARIMA (0,1,0)		GM (1,1)		Joinpoint	
Fitted	Median	1.20		1.24		0.86		1.17	
Error	Interquartile Range	0.54		0.33		0.10		0.48	
%	95%CI	(1.23,1.68)		(1.23,1.72)		(0.78,0.94)		(1.24,1.69)	

*SMR-standardized mortality rate

Table 2. Predicted Mortality for Cervical Cancer, by 4 Models, in China from 2014 to 2018(1/10^5)

Year	Cubic	ARIMA (0,1,0)	GM (1,1)	Joinpoint	Overall x̄±SD	Overall 95%CI
2014	3.30	2.62	2.44	3.17	2.88±0.42	(2.22,3.55)
2015	3.72	2.68	2.57	3.43	3.10±0.56	(2.20,4.00)
2016	4.19	2.74	2.69	3.68	3.33±0.73	(2.16,4.50)
2017	4.71	2.81	2.83	3.93	3.57±0.92	(2.10,5.04)
2018	5.29	2.88	2.97	4.18	3.83±1.14	(2.02,5.64)
x̄±SD	4.24±0.79	2.74±0.10	2.63±0.17	3.55±0.33	—	—
95%CI	(3.27,5.22)	(2.62,2.88)	(2.37,2.90)	(3.03,4.07)	—	—

*SD-standard deviation; 95%CI-95% confidence interval

lifestyle factors had no dynamic changing, we build 4 predictive models (curve estimation, time series modeling, gray modeling, joinpoint regression) with different statistical methods and compared the results with each other to estimate the cervical cancer mortality from 1991-2013 and found a suitable trend of cervical cancer in future five years (2014-2018).The fitted error value and the 95% Confidence Interval (CI) are selected to describe the forecasting accuracy.

Curve estimation: Among the 11 models, the cubic curve model fitted the trend best (R^2=0.88, F=45.6, P<0.001). The equation is: $y=1.2+0.016x-0.007x^2$, where x stands for the year, and y stands for mortality rate (Tables 1 and 2).

Time series model: Depending on the above mortality data, we establish the autoregressive integrated moving average ARIMA model for prediction (R^2=0.97, P=0.087) (Tables 1 and 2).

Gray model: According to the gray model theory, X (i) stands for the SMR of cervical cancer, t stands for the year. And the GM (1, 1) model was used to the forecast, with fitting parameters: a=-0.049, b=0.72. The equation is:

$X_{(t+1)}=15.95e^{-0.049t}-14.73$ (C=0.58, P=0.78, Q_{min}=-0.85) (Tables 1 and 2).

Joinpoint regression: To fit the model, the variable X stands for the year, and the independent variable y is the mortality rate, which used for a statistically significant change in rate trend to describe linear trends by period, and the APC and AAPC of the SMR in China during 1991-2013 were established (Tables 1, 2 and 3).

Discussion

Cervical cancer is the common cause of cancer-related deaths in the world. Although the incidence of cervical cancer in China is low in comparison to that of western

Table 3. APC and AAPC of Age-Standardized Rates for Cervical Cancer in China from 1991-2013

Trends	APC[a]/AAPC[b]	Urban	Rural	Overall
Segment 1	Years	1991-2001	1991-2013	1991-2005
	APC (95%CI)	-4.6[c] (-8.5,-0.6)	3.8[c] (2.9,4.7)	0(-1.5,1.6)
Segment 2	Years	2001-2013	ND[d]	2005-2013
	APC (95%CI)	11.4[c] (7.9,14.9)	ND[d]	12.1[c] (8.2,16.2)
Full Range	Years	1991-2013	1991-2013	1991-2013
	AAPC (95%CI)	3.8[c] (1.4,6.3)	3.8[c] (2.9,4.7)	4.3[c] (2.7,5.9)
	Comparing the AAPC differences in urban and rural areas			
Last 5 Obs	AAPC (95%CI)	11.4[c] (7.9,14.9)	3.8[c] (2.9,4.7)	12.1[c] (8.2,16.2)
(2009-2013)	AAPC difference (95%CI)	7.5 (4.0,10.1) [c]		ND[d]
Last 10 Obs	AAPC (95%CI)	11.4[c] (7.9,14.9)	3.8[c] (2.9,4.7)	12.1[c] (8.2,16.2)
(2004-2013)	AAPC difference (95%CI)	7.5 (4.0,10.1)[c]		ND[d]

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

countries, the mortality rate remains relatively high, especially in rural areas (Jia et al., 2013). Based on our study, we found that although the mortality of cervical cancer was significantly declined compared with 1970s and 1990s, but in recent years it has been increased, and the trend is predicted to continue in the future five years.

According to our forecast analysis, the burden of cervical cancer is still result in a serious health problem in China. Most cases of cervical cancer are associated with extrinsic, environmental, and lifestyle factors (Gonzaga et al., 2013). Therefore, focusing on the prevention and treatment of cervical cancer is very necessary.

Obviously, high morbidity must cause high mortality. Thus, the decline in mortality is mainly due to the effective treatment of early cases of cervical cancer. There is strong epidemiologic evidence indicating that HPV, early sexual initiation (<16 years), multiple sex partners (more than four), oral contraceptive and dietary habits all play important roles in the etiology of cervical cancer (Yang L, 2003; Gonzaga et al., 2013). Among the principal risk factors, HPV is considered to be a cause of the disease and the most dangerous. There is survey shows that the women who positive for HPV DNA have a risk of developing cervical cancer 15–50 times higher than those without HPV DNA (Gonzaga et al., 2013). In recent years, due to the significantly decreased of cervical cancer mortality rates, the existence of risk factors for cervical cancer have commanded little attention. Thus, we should actively promote the healthy lifestyle, the healthy concept, the healthy diet, improve the living environment, and especially advance the screening program.

Cervical cancer screening has resulted in well-documented declines in cervical cancer incidence and mortality. According to the WHO, 80% to 100% coverage of the target population with Pap smear screening and an organized network for adequate diagnosis and treatment would allow a 60% to 90% reduction in cervical cancer (Boyle and Levin, 2008). In order to appropriately explore potential models for cervical cancer screening, free cervical cancer screening was available for rural women between 35 to 59 years in China since 2009 (Jing et al., 2011). However, a study showed that the knowledge about importance of cervical screening for early cancer diagnosis was lacked among rural women (Jia et al., 2013), resulting in women were less willing to undergo screenings. So the government should make a nationwide strategy to raise public awareness about cervical cancer screenings.

As shown in the investigation results, we found that the mortality rates in rural areas were higher than those in urban areas. This is mainly due to the cervical cancer screenings are uncommon or are poorly accessible in rural areas than in urban areas, as well as the economic, cultural and clinical condition still hold a poor level. In addition, the highest mortality rate is in the 80 to 85 years and the 25-40 age-specific mortality in urban was rapidly rose. For the populations over 40 years, cervical cancer prevention and early diagnosis and treatment are necessary. At the same time, we should paid more attention to the rural populations, and the increased tendency of cervical cancer mortality in young women, especially the 25-65 age group in urban, the queue effect may change the cervical cancer mortality trends in future. And this could be due to change of their sex concepts, promiscuous behavior, and increase of HPV infection and venereal disease. Therefore, effective prevention measures should be implemented to reduce cervical cancer morbidity and mortality both in urban and rural areas.

As one of the most widely used global surface-fitting procedure, trend surface analysis based on the principle of the least square method to build a polynomial function and ensure that the sum of the squared deviations from the trend surface is minimum (Shi et al., 2014; Tang et al., 2014). The trend-surface analysis shows that cervical cancer mortality rate in a geographical distribution has two tendencies on the monitoring point: the first one is it starts from southwest, increases surrounding the west-central in China; the second one is the tendency increased from the southeast to northeast areas. According to the analysis, we found cervical cancer mortality had certain geographic distribution; therefore, geographical environment factors may play an important role in the occurring of cervical cancer. Actually, the cervical cancer mortality in Yangcheng of Shanxi, Hebei, Jiangxi, Shanxi and Hubei province was higher than in other regions. And the early epidemiological investigation shows that the high incidence of cervical cancer in Shanxi province geographical areas was distributed along the TaiHang Mountains. The cause may be the less fresh vegetables intake by the populations, which leads to the lack of folic acid, resulting in the women tend to succumb to infections by HPV. The associations between Women's lifestyle, dietary factors, folate and cervical cancer need to explore most carefully.

To sum up, the data presented here may be considered indicators for cervical cancer control in China. The mortality rate of cervical cancer may continue to rise in the future years. Early detection, early diagnosis, and early treatment for cervical cancer can be implemented for preventing with half the effort. High risk group should be better planning of strengthen the personal hygiene, health lifestyle, and nutrition balance. Also, we should speed up the cervical cancer vaccine research to promote and improve the prevention model of cervical cancer screening for the women of childbearing age.

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