



Incidence and mortality of colorectal cancer in 2017 and the time-trend from 2010 to 2017 in Henan province, China: a population-based registry study

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Background: Henan province is an area with a serious disease burden of colorectal cancer (CRC) in China. Understanding the current incidence and mortality and the time-trend is critical to formulate and optimize prevention and control strategies for CRC. However, the current incidence and mortality and time-trend of CRC in Henan province, China have not been reported.

Methods: CRC data was got from the Henan Provincial Central Cancer Registry of China in which the data was submitted from local cancer registries. Combined with the census data, the incidence, mortality, proportion, age-standardized rate by Chinese population (ASRC), age-standardized rate by world population (ASRW), and cumulative incidence and mortality (0–74 years old) of CRC by urban and rural population, gender, and age groups were estimated. The average annual percentage change (AAPC) and its 95% confidence interval (CI) of ASRC from 2010 to 2017 were analyzed.

Results: In 2017, it was estimated that there were 20,275 new cases and 10,046 deaths of CRC in Henan province. The crude incidence was 18.73/100,000, with an age-standardized incidence rate by Chinese population (ASIRC) of 13.97/100,000 and age-standardized mortality rate by world population (ASIRW) of 13.78/100,000. The cumulative incidence was 1.66%. The mortality rate was 9.28/100,000, with an age-standardized mortality rate by Chinese population (ASMRC) of 6.49/100,000 and an age-standardized mortality rate by world population (ASMRW) of 6.45/100,000. The cumulative mortality rate was 0.69%. The ASIRC and ASMRC were higher in urban areas (15.89/100,000, 7.19/100,000) than in rural areas (13.13/100,000, 6.20/100,000), and higher in males (15.53/100,000, 7.44/100,000) than in females (12.48/100,000, 5.66/100,000). The age-specific incidence reached the peak at age of 80–84, and the age-specific mortality reached the peak at age 85. From 2010 to 2017, the overall ASIRC and ASMRC showed a steady trend ($P>0.05$), while an upward trend was observed in the mortality rate in urban males (AAPC = 3.4, 95% CI: 0.2–6.7, $P=0.040$).

Conclusions: The incidence and mortality of CRC were high in Henan province, and higher in urban areas and males. It is critical to strengthen the prevention and control of CRC, carry out targeted intervention, and promote screening and early diagnosis and treatment, particularly among urban areas and males.

Keywords: Colorectal cancer (CRC); incidence; mortality; trend; China

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Introduction

According to the latest global cancer statistics of the International Agency for Research on Cancer (IARC) under the World Health Organization (WHO), in 2020, there were about 1,931,590 new cases of colorectal cancer (CRC) and 935,173 deaths worldwide, ranking third and second in terms of global cancer incidence and death, respectively (1). Therefore, CRC has become the most common gastrointestinal tract malignancy and is a serious threat to human health.

Understanding the current incidence and mortality and the time-trend of CRC is out of the utmost importance to formulate and optimize cancer prevention and control strategies. Cancer registries are used for continuous and dynamic monitoring of annual incidence and mortality worldwide. China has established a nationwide cancer registration system. Recent reports suggested that in 2016, there were still about 408,000 new cases and 195,600 deaths of CRC in China, ranking third and fourth in incidence and death spectrum, respectively (2), even though incidence and mortality rate of CRC in China showed a decreasing trend during 2005–2015 (3). Thus, the prevention and control of CRC should be strengthened in China. The burden of CRC varies greatly in different regions due to different diet structures and lifestyles (4,5). Therefore, it is necessary to understand its epidemic characteristics in different regions, in order to provide evidence for formulating targeted intervention measures.

Henan province is an area with a serious disease burden of CRC in China. It was estimated that 20,700 new cases and 10,500 deaths occurred in 2016. The incidence and mortality of CRC ranked sixth and fifth province wide, respectively (6). The data of CRC incidence and mortality is extracted from the Henan Provincial Central Cancer Registry of China (HNCCR), and updated annually. It is important to report the latest data and the time-trends of incidence and mortality, in order to timely adjust cancer prevention and control strategies. Therefore, this study aimed to evaluate the incidence and mortality of CRC in Henan province in 2017 and the time-trends from 2010 to 2017, and provide a scientific basis for the formulation and optimization of CRC prevention and control strategies. We present the following article in accordance with the STROBE reporting checklist (available at <https://atm.amegroups.com/article/view/10.21037/atm-22-3788/rc>).

Methods

Data source

This is a population-based registry study. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The incidence and mortality data of CRC from 2010 to 2017 were obtained from the HNCCR (<http://www.anti-cancer.com.cn/Sites/ereport/2020/Index.html>). In Henan province, cancer data is first submitted to local cancer registries and then submitted to HNCCR by the local cancer registries. The main sources of cancer data for each local cancer registry included hospitals, community healthcare center, and village doctors. The supplementary data sources included the health insurance system, new rural cooperative medical system, and vital statistical system. Data that transferred from other provinces was also a source of cancer cases.

HNCCR takes responsibility for compiling, evaluating, and reporting long-term, high-quality incidence, mortality, and survival data submitted by local population-based cancer registries. In 2017, a total of 41 local cancer registries submitted cancer data to the HNCCR, of these, data from 3 cancer registries including Zhengzhou, Anyang, and Gushi was excluded due to the poor quality.

Population data

The provincial registered residence population data from 2010 to 2017 was estimated based on the Statistical Bulletin on National Economic and Social Development of Henan Province, taking into consideration different areas (urban/rural), gender (male/female), and age groups (0–, 1–4, 5–9, 10–14, 75–79, 80–84, 85+).

Quality control

The HNCCR assessed the quality and comparability of data, according to the requirements of the “Chinese Guideline for Cancer Registration” and “Cancer Incidence in Five Continents Volume IX” by the IARC (7–9). The mortality-to-incidence ratio (M/I), the percentage of death-certificate-only cases (DCO%), and the percentage of morphological verification (MV%) were used to evaluate the comparability, validity, and completeness of the data. In 2017, a total of 38 registries (9 urban registries and 29 rural

Table 1 Main quality control indicators of colorectal cancer registration data of the Henan cancer registry in 2017

Region	Gender	M/I	DCO%	MV%
All	Total	0.49	0.86	81.39
	Male	0.49	0.82	81.50
	Female	0.48	0.92	81.25
Urban	Total	0.48	0.83	80.00
	Male	0.50	0.79	80.41
	Female	0.46	0.89	79.47
Rural	Total	0.49	0.88	81.91
	Male	0.49	0.83	81.95
	Female	0.49	0.93	81.87

M/I, ratio of death to morbidity; DCO%, the proportion with only a death medical certificate; MV%, the proportion of pathological diagnosis.

registries) met the quality control standards and were included in the analysis database, covering a total population of 31,221,970 (male: 16,041,783; female: 15,180,187), accounting for 28.84% of the total registered residence population in the same period. The urban population was 7,060,349, accounting for 22.61%, and the rural population was 24,161,621, accounting for 77.39%. In 2017, the total M/I, DCO%, and MV% of the Henan CRC analysis database were 0.49%, 0.86%, and 81.39%, respectively. The M/I, DCO%, and MV% in urban areas were 0.48%, 0.83%, and 80.00%, respectively. The M/I, DCO%, and MV% in rural areas were 0.49%, 0.88%, and 81.91%, respectively (*Table 1*).

Outcomes and measurement

Main outcomes reported in this study included:

- (I) Incidence and mortality rates: incidence and mortality rates are usually expressed as per 100,000 of the population. The formula as follows:

$$\text{Crude incidence (mortality) rate per 100,000} = \frac{\text{New case (cancer deaths) occurring during a given time period}}{\text{Population at risk during the same time period}} \times 100,000 (1/10^5) \quad [1]$$

- (II) Proportion

Proportional distribution is the site-specific percentage level of incident cases (deaths) compared with total cases (deaths) recorded, indicating the hazards of various cancer types to human health. The formula as follows:

$$\text{Proportion of CRC} = \frac{\text{Cases of CRC}}{\text{Cases of all cancers}} \times 100\% \quad [2]$$

- (III) Cumulative rate

The cumulative rate indicates the probability of cancer onset between birth and a specific age. The rate can be compared without age standardization because it is not affected by age structures. Generally, cumulative rate at 0–74 years of age is calculated for cancer:

$$\text{Cumulative incidence (mortality) rate} = \left[\sum (\text{Age-specific incidence (mortality) rate} \times \text{Width of the age group}) \right] \times 100\% \quad [3]$$

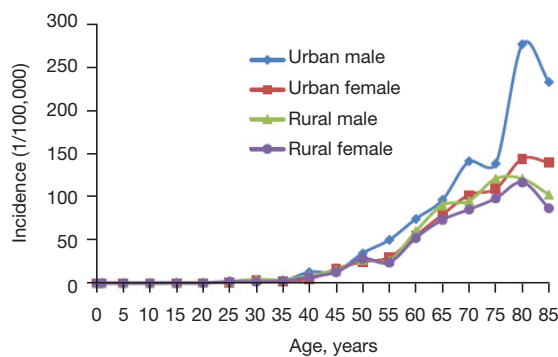
Statistical analysis

The pooled data were stratified by areas (urban/rural), gender (male/female), and age groups (0–, 1–4, 5–9, 10–14, 75–79, 80–84, 85+).

Table 2 Estimation of the incidence of colorectal cancer in Henan province in 2017

Region	Gender	No. of cases	Crude incidence (1/100,000)	Proportion (%)	ASIRC [†] (1/100,000)	ASIRW [‡] (1/100,000)	Cumulative rate 0–74 (%)
All	Total	20,275	18.73	6.99	13.97	13.78	1.66
	Male	10,940	19.47	7.03	15.53	15.30	1.82
	Female	9,335	17.92	6.95	12.48	12.34	1.49
Urban	Total	7,145	22.10	8.22	15.89	15.76	1.87
	Male	4,048	24.43	8.66	18.59	18.48	2.16
	Female	3,097	19.66	7.70	13.41	13.26	1.60
Rural	Total	13,130	17.29	6.47	13.13	12.92	1.56
	Male	6,892	17.40	6.33	14.18	13.91	1.67
	Female	6,238	17.17	6.63	12.07	11.94	1.44

[†], age-standardized incidence rates by Chinese standard population; [‡], age-standardized incidence rates by world standard population (Segi's).

**Figure 1** Colorectal cancer incidence rate in Henan province in 2017.

The crude incidence, mortality, proportion and cumulative risk for subjects aged 0 to 74 years were calculated. The estimated numbers of new cancer cases and deaths in 2017 were calculated using the age-specific rates multiplied by the corresponding estimated provincial age-specific population. Age-standardized incidence and mortality rates were adjusted by the Chinese standard population in 2000 and World Segi's population. All statistical analyses were conducted using SAS V.9.4.

The temporal trends in age-standardized incidence rates by Chinese standard population (ASIRC) and age-standardized mortality rates by Chinese standard population (ASMRC) from 2010 to 2017 were examined using Joinpoint Regression Program, stratified by areas and gender. The average annual percentage change (AAPC) and 95% confidence interval (CI) were calculated to assess the

change of ASIRC and ASMRC, with P value less than 0.05 considered as statistically significant.

Results

Incidence of CRC in 2017

It was estimated that in 2017, there were 20,275 new CRC cases (10,940 males and 9,335 females) in Henan province, accounting for 6.99% of the total number of new cases of malignant tumors, ranking seventh in the total number of malignant tumors. The incidence was 18.73/100,000, the ASIRC was 13.97/100,000, the age-standardized incidence rate by world standard population (ASIRW) was 13.78/100,000, and the cumulative rate (0–74 years) was 1.66%. Of the total new cases, 35.24% [7,145] were in urban areas and 64.76% [13,130] were in rural areas. The ASIRW in urban areas was 1.21 folds higher than that in rural areas, and the ASIRW in males was 1.24 folds higher than that in females (*Table 2*).

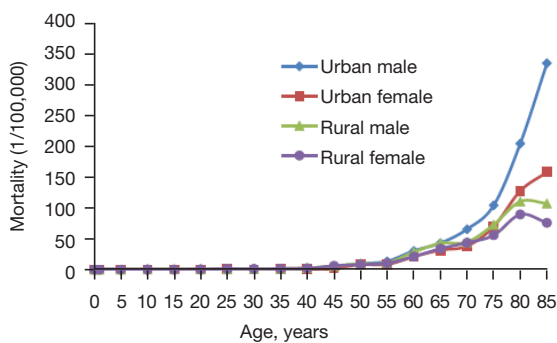
Age-specific incidence in 2017

The incidence of CRC increased with age in Henan in 2017. It was relatively lower among the population younger than 35 years old, then increased dramatically and reached its peak at 80–84 years old. The pattern was similar between urban and rural areas. In the age groups above 35, the incidences of males in urban and rural areas were higher than those in females (*Figure 1*).

Table 3 Estimation of colorectal cancer mortality in Henan province in 2017

Region	Gender	No. of cases	Crude mortality (1/100,000)	Proportion (%)	ASMRC [†] (1/100,000)	ASMRW [‡] (1/100,000)	Cumulative rate 0–74 (%)
All	Total	10,046	9.28	5.45	6.49	6.45	0.69
	Male	5,456	9.71	4.85	7.44	7.45	0.77
	Female	4,590	8.81	6.39	5.66	5.60	0.61
Urban	Total	3,526	10.91	6.66	7.19	7.25	0.70
	Male	2,042	12.32	6.20	8.98	9.14	0.85
	Female	1,484	9.42	7.40	5.66	5.69	0.55
Rural	Total	6,520	8.59	4.96	6.20	6.12	0.69
	Male	3,414	8.62	4.30	6.77	6.71	0.73
	Female	3,106	8.55	5.99	5.68	5.59	0.64

[†], age-standardized mortality rates by Chinese standard population; [‡], age-standardized mortality rates by world standard population (Segi's).

**Figure 2** Colorectal cancer mortality rate in Henan province in 2017.

Mortality of CRC in 2017

It was estimated that there were 10,046 CRC deaths (5,456 males and 4,590 females) in Henan province in 2017, accounting for 5.45% of all cancer deaths, ranking sixth of all cancer deaths. The mortality rate was 9.28/100,000, the ASMRC was 6.49/100,000, the ASMRW was 6.45/100,000, and the cumulative rate (0–74 years old) was 0.69%. Of the total CRC deaths, 35.10% [3,526] were in urban areas and 64.90% [6,520] were in rural areas. The mortality rate in urban areas was 1.16 times higher than that in rural areas, and the mortality rate in males was 1.31 times higher than that in females (Table 3).

Age-specific mortality in 2017

In 2017, the age-specific mortality rate was relatively

lower than the population younger than 50 years, and then dramatically increased. The mortality rate reached the peak after 85 years old in urban areas and reached the peak in the 80–84 age group in rural areas. In the age group over 50, the mortality rate of males was higher than that of females in both urban and rural areas (Figure 2).

Trends in the incidence rate and mortality rate of CRC

Group 1: trend of incidence rate

The temporal trend in the ASIRC of CRC was shown as Table 4.

From 2010–2017, the ASIRC of CRC in Henan province showed a stable trend (AAPC =1.5%, 95% CI: –0.6% to 3.6%, P=0.138). The ASIRC of CRC in different gender groups were stable in 2010–2017 (male: AAPC =1.6%, 95% CI: –0.7% to 4.0%, P=0.135; female: AAPC =1.1%, 95% CI: –0.7% to 3.0%, P=0.186). The ASIRC of CRC in urban and rural areas showed a stable trend in 2010–2017 (urban: AAPC =2.4%, 95% CI: –0.7% to 5.6%, P=0.106; rural: AAPC =1.0%, 95% CI: –1.4% to 3.4%, P=0.368).

Taking into account the differences between urban and rural areas and different gender groups, the population was further divided into urban males, urban females, rural males, and rural females. The ASIRC of CRC in urban males from 2010 to 2017 showed a significant upward trend (AAPC =3.4%, 95% CI: 0.2% to 6.7%, P=0.040). The ASIRC showed a steady trend in urban females and rural males and females (urban females: AAPC =1.1%, 95% CI:

Table 4 Temporal trends in ASIRC and ASMRC of colorectal cancer from 2010 to 2017 in Henan province

Region	Gender	2010	2011	2012	2013	2014	2015	2016	2017	AAPC (%)	95% CI (%)	P value
ASIRC [†] (1/100,000)												
All	Total	12.07	13.5	13.46	14.53	13.04	13.36	14.68	13.77	1.5	-0.6 to 3.6	0.138
	Male	13.31	14.88	15.01	16.29	14.27	15.18	16.56	15.21	1.6	-0.7 to 4.0	0.135
	Female	10.97	12.22	12.07	12.88	11.88	11.7	12.9	12.39	1.1	-0.7 to 3.0	0.186
Urban	Total	15.06	13.19	15.36	17.09	17.03	15.84	17.97	15.89	2.4	-0.7 to 5.6	0.106
	Male	17.02	15.35	17.27	19.58	19.58	19.42	22.19	18.58	3.4	0.2 to 6.7	0.040
	Female	13.35	11.34	13.7	14.87	14.84	12.85	14.1	13.41	1.1	-2.3 to 4.6	0.456
Rural	Total	11.57	13.61	13.09	14.04	12.39	12.94	13.82	13.12	1.0	-1.4 to 3.4	0.368
	Male	12.68	14.81	14.57	15.63	13.41	14.48	15.09	14.18	0.8	-1.7 to 3.5	0.458
	Female	10.59	12.43	11.74	12.54	11.38	11.5	12.6	12.07	1.1	-2.3 to 4.6	0.456
ASMRC [‡] (1/100,000)												
All	Total	5.71	7.28	6.89	6.80	6.42	6.91	6.91	6.43	0.6	-2.3 to 3.6	0.626
	Male	6.70	8.46	8.04	7.84	7.66	8.09	8.27	7.29	0.6	-2.4 to 3.7	0.667
	Female	4.77	6.21	5.86	5.95	5.29	5.87	5.67	5.66	0.8	-2.5 to 4.1	0.595
Urban	Total	7.40	7.97	8.13	7.38	9.95	8.71	8.70	7.21	0.9	-3.4 to 5.4	0.628
	Male	8.81	9.55	10.14	8.70	12.36	10.77	10.96	8.97	1.6	-3.2 to 6.6	0.446
	Female	6.26	6.52	6.39	6.15	7.90	7.13	6.67	5.66	0.0	-4.0 to 4.2	0.993
Rural	Total	5.41	7.18	6.65	6.72	5.84	6.61	6.47	6.20	0.3	-3.2 to 4.0	0.832
	Male	6.35	8.26	7.62	7.67	6.89	7.66	7.59	6.77	-0.1	-3.5 to 3.5	0.958
	Female	4.50	6.19	5.76	5.98	4.85	5.65	5.43	5.67	0.8	-3.4 to 45.3	0.654

[†], age-standardized incidence rates by Chinese standard population; [‡], age-standardized mortality rates by Chinese standard population. AAPC, average annual percentage change.

-2.3% to 4.6%, P=0.456; rural males: AAPC =0.8%, 95% CI: -1.7% to 3.5%, P=0.458; rural females: AAPC =1.0%, 95% CI: -1.2% to 3.3%, P=0.321).

Group 2: trend of mortality rate

The temporal trend in the ASMRC of CRC was shown as *Table 4*.

From 2010 to 2017, the ASMRC of CRC in Henan province showed a stable trend (AAPC =0.6%, 95% CI: -2.3% to 3.6%, P=0.626). The ASMRC of CRC among different genders from 2010 to 2017 also showed a stable trend (male: AAPC =0.6%, 95% CI: -2.4% to 3.7%, P=0.667; female: AAPC =0.8%, 95% CI: -2.5% to 4.1%, P=0.595). The ASMRC of CRC in urban and rural areas from 2010 to 2017 showed a stable trend (urban: AAPC =0.9%, 95% CI: -3.4% to 5.4%, P=0.628; rural: AAPC =0.3%, 95% CI: -3.2% to 4.0%, P=0.832).

The ASMRC of CRC in urban males and females and rural males and females from 2010 to 2017 showed a stable trend (urban males: AAPC =1.6%, 95% CI: -3.2% to 6.6%, P=0.446; urban females: AAPC =0.0%, 95% CI: -4.0% to 4.2%, P=0.993; rural males: AAPC =-0.1%, 95% CI: -3.5% to 3.5%, P=0.958; rural females: AAPC =0.8%, 95% CI: -3.4% to 5.3%, P=0.654).

Discussion

CRC is one of the most common malignant tumors in China. Based on cancer registration data of Henan province, this study analyzed the incidence and mortality rates of CRC in Henan province in 2017 and the changing trend between 2010–2017, finding that the CRC incidence rate and mortality rate ranked seventh and sixth of all malignant tumors, respectively. The disease burden of CRC was high

in Henan province, suggesting that prevention and control measures should be further strengthened.

CRC can be regarded as a symbol of socio-economic development. In regions or countries experiencing major development and transformation, the incidence increases along with the increase of the Human Development Index (HDI) (10,11). This study showed that the ASIRC and ASMRC of CRC in Henan province in 2017 were 13.97/100,000 and 6.49/100,000, respectively, which were slightly lower than the latest data published by the National Cancer Center (ASIRC in 2016: 17.65/100,000, ASMRC: 7.99/100,000) (12). This result was consistent with the HDI level of Henan province in China (13). Nevertheless, with the development of the social economy, HDI is rising in Henan province (13). It is speculated that the incidence of CRC will increase in Henan province without intervention.

Consistent with the results of the national cancer registry and those of Guangzhou province, Jiangsu province, and other areas (14-16), there were also significant differences in the incidence and mortality of CRC between urban and rural areas and gender in Henan province. The ASIRC and the ASMRC in Henan province were 1.21 times and 1.31 times higher than those of rural areas in 2017, respectively. The ASIRC and ASMRC of males were 1.24 times and 1.31 times higher than those of females, respectively. The westernization of lifestyle in urban areas and the fact that men consume more alcohol, red meat, tobacco, and fewer vegetables than women might be the reasons for the differences in CRC incidence rates between urban and rural areas and between genders (17). We further found that the incidence rate of male CRC in urban areas increased significantly in 2010–2017, indicating that effective prevention and control of CRC, such as improving diet and exercise, should be implemented, especially in urban areas, to prevent CRC.

A previous study has demonstrated that population-based colonoscopy screening was important and effective in promoting the early diagnosis of CRC, preventing its occurrence and development, and reducing mortality (18). The general population aged above 40 years old was recommended to receive CRC risk assessment, based on the “guideline for early diagnosis and treatment of colorectal cancer in China” issued by the National Cancer Center (19). However, this study showed that the incidence of CRC in Henan province increased rapidly after 35 years old, suggesting that the general population risk assessment age in Henan should be earlier than 35 years old. Although the age-specific incidence rate of CRC reached the peak at

80–84 years of age, considering the life expectancy of these populations, a health economics assessment of screening is needed to evaluate the cost effectiveness of screening.

In this study, the age-specific mortality rate of CRC increased rapidly after age 50 and peaked after age 85. There was a 5-year interval between the peak of the incidence rate and mortality rate, indicating a good survival prognosis. According to the cancer survival data of the Chinese population collected by the National Cancer Center from 2003 to 2015, the age-standardized 5-year relative survival rate of Chinese CRC patients increased at an annual rate of 2.9%, reaching 56.9% from 2012 to 2015 (20). However, the 5-year survival rate of CRC patients in China was still lower than that in developed countries, for example, 70% in South Korea and Australia and about 65% in Canada and the United States (21). In addition to the difference in diagnosis and treatment techniques of CRC, the late implementation of screening and early diagnosis and treatment in China as well as imperfect measures were also important reasons for the low survival rate. The survival rate of CRC was related to the stage and could reach more than 90% in early-stage patients and only 14% in advanced-stage patients (22). However, due to the unobvious symptoms of early CRC, most patients have reached the advanced stage at their first visit to see a doctor (23). Therefore, screening and early diagnosis and treatment should be applied to improve the overall survival rate. In the United States, nationwide CRC screening has been launched since the 1970s, resulting in a 36.2% reduction in the age-standardized incidence of advanced CRC and a 52.4% decrease in age-standardized mortality (24,25). In 2012, China launched the “Urban Cancer Early Diagnosis and Treatment Project”, aiming to promote the implementation of colonoscopy screening among urban high-risk groups. However, so far, only about 14% of the high-risk population have received colonoscopy screening, and most positive patients have not received timely treatment due to the lack of an effective follow-up and referral system (26,27). Therefore, it is necessary to understand the barriers in colonoscopy screening and CRC treatment for high-risk groups in the future, and then expand the coverage of screening and early diagnosis and treatment.

This is the first study to explore the current incidence and mortality rates of CRC in Henan province and the changing trend from 2010–2017. The data were from the cancer registration data of Henan province and was of high quality. However, the total population covered was low, with less than 30% of the registered residents included.

In order to improve the accuracy and reliability of the study, the HNCCR should enroll more cancer registries. Furthermore, we only discussed the trends of incidence and mortality in different urban, rural, and gender groups, but did not analyze the trends in different age groups in detail. Detailed research needs to be further performed.

Conclusions

In conclusion, the disease burden of CRC in Henan province is high, and is higher in urban areas than in rural areas, and higher in males than females. The incidence rate and mortality rate of CRC in Henan province significantly increased among urban males from 2010 to 2017. Early detection and prevention of CRC are of great importance. In the future, targeted interventions should be carried out according to the characteristics of the CRC incidence rate and mortality rate, to determine the age of screening, solve the factors restricting the expansion of screening and early diagnosis and treatment, and gradually reduce the incidence and mortality of CRC.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at <https://atm.amegroups.com/article/view/10.21037/atm-22-3788/rc>

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <https://atm.amegroups.com/article/view/10.21037/atm-22-3788/coif>). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

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