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Research article

Projections of cancer mortality by 2025 in central China: A modeling study of global burden of disease 2019

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ABSTRACT

Background: In China, there are few studies that have reported future estimations for cancer mortality. Therefore, this study aimed to assess cancer mortality in China and identify priorities for future cancer control strategies.
Methods: Based on the Global Burden of Disease 2019 study, we extracted data on cancer-related deaths from 1990 to 2019 in Hunan Province, China. Under the current trends evaluated using a joinpoint regression model, we fitted a linear regression model for cancer mortality projections by 2025.
Results: The age-standardized mortality rate of total cancer in Hunan, China, declined slowly and is projected to be 140.80 (95% confidence interval [CI]: 140.12–141.48) by 2025, with the mortality rate in men approximately twice that in women. In 2025, the top five causes of cancer-related deaths in males are projected to be lung, liver, colorectal, stomach, and esophageal cancers, with the corresponding causes in females being lung, breast, colorectal, liver, and cervical cancers. Between 2019 and 2025, male mortality rates due to liver and pancreatic cancer are expected to increase, while those due to the six leading female cancers will increase. Excess male deaths were associated with liver and esophageal cancers, while all main cancers in females will have excess mortality, except for colorectal cancer.
Conclusion: A comprehensive cancer spectrum characteristic of both developing and developed countries will remain in Hunan, China. Lung cancer remains the most common cause of cancer-related deaths, and tobacco control efforts are urgently required. Additional efforts should be made to promote universal screening, improve access to cancer healthcare services, optimize medical payment models, and enhance access to valuable anticancer drugs.

1. Introduction

Cancer is the second leading cause of death globally, claiming the lives of 9.6 million people annually [1]. Each year, nearly 2.3 million cancer deaths are reported nationwide [2], making cancer responsible for approximately one-fifth of all-cause deaths in the country. Moreover, a quarter of all cancer-related deaths worldwide occur in China [3]. Cancer control and prevention have become a primary health strategy in China. Especially since 2015, the Chinese government has made "Health for all, health first" as the top priority of development for the next 15 years. A series of national policies released by the Chinese government in the subsequent years,

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such as "Healthy China 2030" in 2016 [4], "China Medium-and-Long Term Plan for Prevention and Control of Chronic Diseases (2017–2025)" in 2017 [5], and "Healthy China Act (2019–2030)" in 2019 [6], promoted cancer prevention and control, reduction in cancer mortality rate, and improvement of 5-year cancer survival rates as important goals for different periods. After 2020, 2025 will be a critical year for relevant evaluation of the plans.

Although some previous studies have reported cancer mortality in China, they focused on a specific type of cancer, single-year statistics, or short-term trends [7,8]. To the best of our knowledge, few studies that have reported future estimations for all cancers in China. Mi et al. projected the cancer death rate for an industrial district in Shanghai, China [9]. There is a substantial gap in healthcare services in China due to its vast geography, large population, and socioeconomic disparity. Such a projection in Shanghai may not represent the nationwide cancer burden in China. In addition, the data in these studies were mainly collected from China's National Central Cancer Registry (NCCR), which covers only 22.5% of the Chinese population [10], far lower than the 96% and approximately 100% coverage in the United States and United Kingdom, respectively [11]. Furthermore, many Chinese cancer registries are located in urban areas, which is also problematic for the representativeness of the NCCR for the general Chinese population. Regarding the timeliness of reports, NCCR reports typically lag by 3 years; for instance, the "National Cancer Report 2019" represents the cancer situation in 2015. Another limitation is that redistribution to address a high proportion of ill-defined cancer cases in the cancer registry can lead to artificial bias. In addition, the misclassification of metastatic sites as primary cancers can lead to an overestimation of cancer sites [12].

Hunan is a centrally located and moderately economically developed province in China with a population of 69.18 million. Like many other provinces in mainland China, Hunan is undergoing rapid population aging, industrialization, and urbanization. As a result, the burden of cancer is at the medium level nationwide, with an age-standardized disability-adjusted life year of approximately 3387 to 3354 person-years per 100,000 [13]. Accordingly, we chose 2025 as the predicted year to analyze cancer mortality in Hunan. The aim of the study was to estimate cancer mortality in China in a timely and representative manner and identify priority efforts to minimize the rising trend of crude cancer death rates. In addition, as the benefits of reducing cancer mortality take effect gradually, we believe that our research to optimize future cancer control strategies will also be helpful for the next review year, 2030.

2. Materials and methods

2.1. Data

Based on the Global Burden of Disease (GBD) 2019 study, we extracted the data on cancer-related deaths in Hunan, China, from 1990 to 2019, stratified by the underlying cause of death, age, and sex. The GBD comprises multiple sources of mortality data. As for the causes of death database, the input data were extracted from vital registration, verbal autopsy, cancer registries, police records, surveillance, survey/census, and other sources [12,14]. Using the cause of death ensemble model, Bayesian meta-regression, spatiotemporal Gaussian process regression, and life table model, the GBD study estimates and fills in mortality rates by year, sex, and age [12,15]. Compared with cancer registry data, GBD data has a much higher data-source coverage and is much less subject to time-lag reports. In addition, the GBD study can also adjust for bias from ill-defined cancer cases in the cancer registry by mapping the different coding systems to the GBD causes [12].

Using the Tenth International Classification of Diseases (ICD-10), we identified cancer codes C00–C97 for the analysis. Although the spectrum of cancer-related deaths is unlikely to change significantly in a few years, the ranking of neighboring cancers is likely to change, and the 10 leading causes of cancer deaths often account for no less than 80% of all cancers combined [16,17]. Therefore, we chose the leading 15 cancers based on the order of cancer-related deaths in 2019 to estimate the top 10 cancers in the study. The 15 selected cancers were coded as follows: lip and oral cavity; nasopharynx (C00–C14); esophagus (C15); stomach (C16); colorectum (C18–C21); liver (C22); pancreas (C25); trachea, bronchus, and lung (C33–C34); breast (C50); cervix (C53); uterine (C54–C55); prostate (C61); brain and central nervous system (CNS) (C70–C72); non-Hodgkin lymphoma (C82–C85); and leukemia (C91–C95).

2.2. Study design

We considered the age-standardized rate (ASR) of cancer mortality as the primary indicator of the projection. It was calculated using age-specific death rates standardized to the sixth Chinese population census (2010). We constructed a joinpoint regression model to identify changes in the temporal trends of cancer mortality, with a maximum of four joinpoints. The joinpoint regression model was developed by the National Cancer Institute. Temporal trends were estimated by fitting a series of linear segments based on the Monte Carlo Permutation Test and Bayesian Information Criterion method [18,19]. We illustrated the changes over time with the overall percent change, annual percent change (APC), and average APC. Based on a single-year change resulting from the average APC, the overall percent change was estimated by exponentiating the number of studied years minus one [20].

We fitted a linear regression model to the current trend, which was evaluated using the joinpoint regression model to project the cancer mortality rate and 95% confidence intervals (CIs) in 2025. The joinpoint model has been used by the American Cancer Society since 2012 to project cancer deaths and is now popularly used elsewhere in the world [21–23]. We also projected excess ASRs attributed to adverse changes over time. Adverse changes were defined as any decelerated, stalled, or reversed changes in status over time [24]. The excess ASRs were estimated in three steps. First, we chose the most significant APC as the estimation point to calculate expected cancer mortality, assuming the cancer mortality rates will maintain the same annual change as the chosen APC till 2025. We then calculated the difference between the observed or projected cancer-related mortality rates and expected results to obtain absolute excess mortality. Finally, we divided the difference values by the expected results to obtain a relative change in excess mortality.

Finally, we verified the accuracy of the joinpoint model. We used mortality data from 1990 to 2010 to predict the mortality rate from all cancers combined in 2015 and compared the difference between the projected and observed values in the same year, predicting and comparing values in 2016 using data from 1990 to 2011, predicting and comparing values in 2017 using data from 1990 to 2012, predicting and comparing values in 2018 using data from 1990 to 2013 and values in 2019 using data from 1990 to 2014. We illustrated the verification results with three features: percentage error (PE, %), mean absolute percentage error (MAPE, %), and mean square error (MSE) [25]. The formulas used for these were $SE = \frac{1}{n}\sum_{i=1}^{n}(\widehat{y} - y_i)^2$, $PE = \frac{|\widehat{y} - y_i|}{y_i} \times 100\%$, and $MAPE = \frac{1}{n}\sum_{i=1}^{n}\frac{|\widehat{y} - y_i|}{y_i} \times 100\%$, where $\widehat{y}$ represents the projected value, and y_i represents the observed value. A MAPE less than 10% was considered accurate [26].

2.3. Statistical analysis

We used joinpoint regression program 4.8.0.1 (Statistical Research and Applications Branch, National Cancer Institute, MD, USA), with a *P*-value less than 0.05, which was considered significantly different. Line graphs were created in R version 4.0.0 (R Foundation for Statistical Computing, Vienna, Austria).

3. Results

The crude death rate and ASR of mortality (in deaths per 100,000 people) for all cancers combined showed opposite temporal trends (Fig. 1A). Compared with the significant increase in the crude cancer death rate, the ASR for cancer mortality showed a non-significant decrease of 8.47% from 1990 to 2019, with an average APC of −0.32%, and is projected to be 140.80 (95% CI: 140.12–141.48) by 2025. For most of the study period, opposite temporal trends were observed between the sexes (Fig. 1B). In females, the total cancer ASR decreased by 36.70% from 1990 to 2019, with an average APC of −1.66%, and is projected to be 93.70 (95% CI: 91.49–96.00) by 2025. Annual reductions in mortality due to all cancers varied over time in females, with larger APCs prior to 2007. In males, the total cancer ASR increased rapidly until 2012 and then gradually declined, with a projected ASR of 181.77 (95% CI: 179.48–184.09) by 2025.

Fig. 2 (A,B) shows the top 10 projected causes of cancer-related deaths. By 2025, the top 10 cancers causing death in men are expected to be the same as those in 2019. The top five causes of cancer-related deaths in men were also evaluated, including lung, liver, colorectal, stomach, and esophageal cancers. Among women, 9 of the top 10 causes of cancer-related deaths are projected to be the same as those in 2019, and the five leading causes will be lung, breast, colorectal, liver, and cervical cancer. Regarding the proportion changes in mortality rates between 2019 and 2025, the mortality rate of liver cancer in males is projected to change the most, increasing by 3.65%, while the mortality rate of lung cancer in females will have the greatest proportion change, increasing by 3.38%.

Compared with the mortality rates in 2019, 8 of the 10 leading causes of cancer deaths in males will decline by 2025 (Fig. 3A and B). The projected mortality rates of the top five cancers among men in 2025 are 62.56 (95% CI: 61.84–63.27) for lung cancer, 29.12 (95% CI: 27.35–31.01) for liver cancer, 19.08 (95% CI: 18.61–19.57) for colorectal cancer, 15.84 (95% CI: 15.52–16.15) for stomach cancer, and 8.41 (95% CI: 7.98–8.86) for esophageal cancer. In women, mortality due to 4 of the 10 leading cancers will decline. The

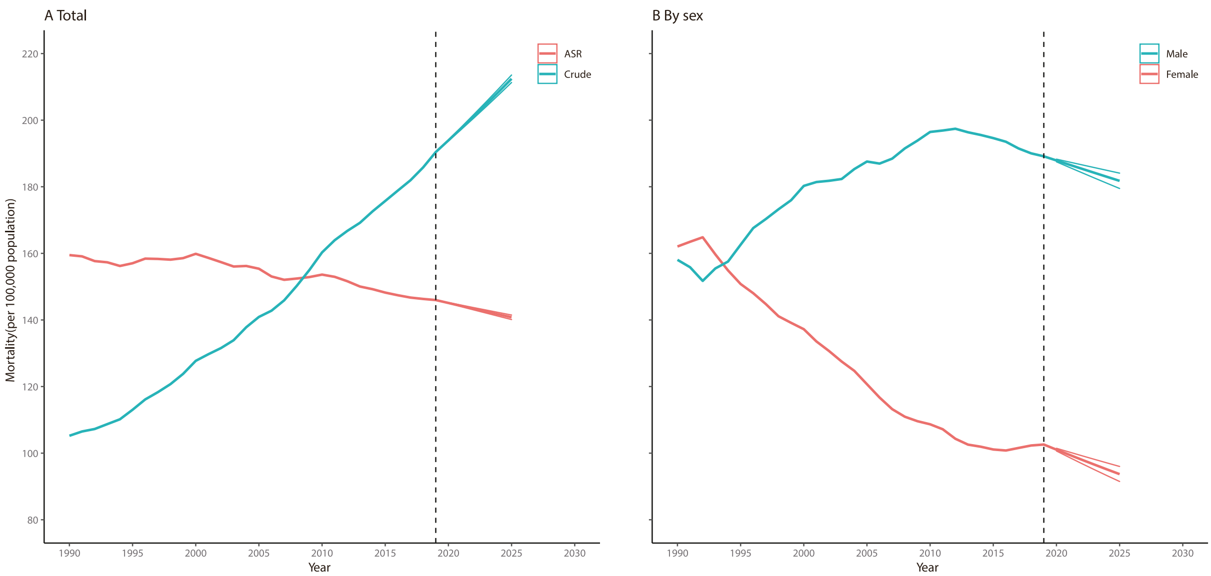

Fig. 1. Cancer mortality during from 1990 to 2019 and projections by 2025 in Central China. Dash line: distinguishing observed years from projected years.

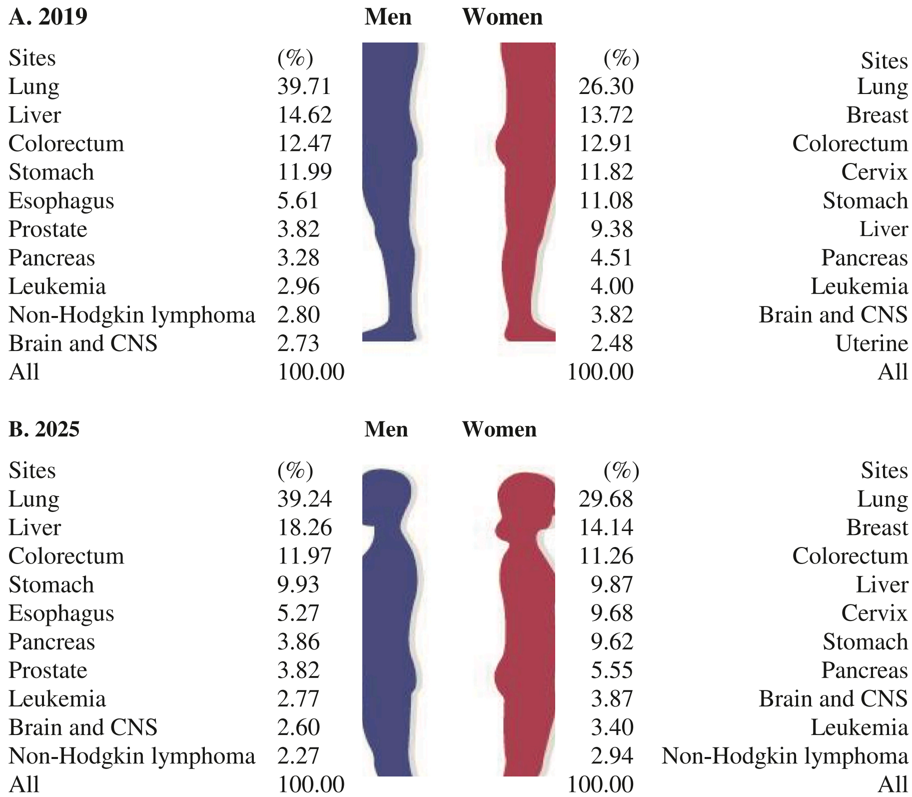

Fig. 2. In comparison with 2019 (A), the top 10 projected causes of cancer-related deaths by sex in 2025 (B) in Central China.

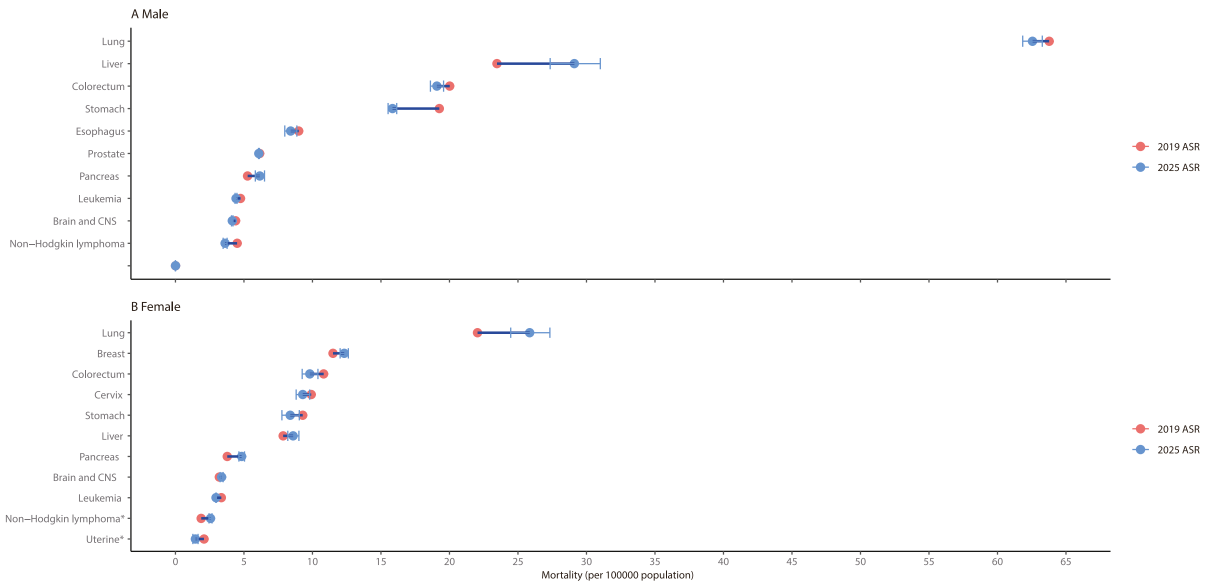

Fig. 3. Compared with the mortality rates in 2019, the 10 leading causes of cancer deaths by 2025 and by sex. *: Non-Hodgkin lymphoma will rise from the eleventh cause of cancer death to the tenth cause, while uterine cancer will decline from the tenth to the eleventh cause.

projected mortality rates of the five leading cancers in females in 2025 are 25.86 (95% CI: 24.47–27.33) for lung cancer, 12.32 (95% CI: 12.02–12.62) for breast cancer, 9.81 (95% CI: 9.25–10.40) for colorectal cancer, 8.59 (95% CI: 8.20–9.01) for liver cancer, and 9.29 (95% CI: 8.81–9.8) for cervical cancer. Among the same eight cancers in both sexes, the largest ASR difference was expected to be 3.39 for liver cancer, followed by 2.42 for lung cancer.

The top five cancers projected to cause death according to age group are presented in Table 1. By 2025, leukemia will be the most common cause of death in the 0–14 years age group. In the age group of 15–44 years, the three common causes of cancer-related deaths will differ significantly between the sexes, with liver, lung, and colorectal cancer in males and breast, lung, and cervical cancer in females as the most common causes of death. For people aged >44 years, lung cancer will be the most frequent cause of cancer-related deaths. Breast cancer will remain among the top five cancers causing deaths in women aged 15 years and older, while cervical cancer will remain among the top five causes in women aged 15–59 years. Similar to lung cancer in females, the ranking of colorectal cancer as a cause of cancer-related death in female will rise rapidly with age.

Regarding excess cancer deaths (Table 2), male excess mortality will be associated with both liver and esophageal cancers due to adverse changes in mortality rates. The relative excess mortality rates of liver and esophageal cancers in males are expected to be 115.64% and 31.09%, respectively. Nine of the top 10 causes of cancer-related deaths (excluding colorectal cancer) in women will undergo adverse changes in mortality rates. Among the five leading causes of cancer-related deaths in women, the excess ASR of liver cancer was the highest (112.85%), followed by cervical cancer (85.52%), breast cancer (56.40%), and lung cancer (41.17%).

Table 3 showed the results from the accuracy of the Joinpoint model. A range of 0.22%–1.44% was estimated for PE of total cancer mortality rates over the verified years 2015–2019 and a MAPE of 0.59%. The MSE was estimated to be 0.721.

4. Discussion

Previous studies have demonstrated the excellent accuracy of joinpoint models. For example, Chen et al. compared five projection models (Bayesian state-space method, joinpoint regression method, Nordpred method, state-space method, and vector autoregressive analysis method) for predicting 4-year-ahead mortality and found that the joinpoint model had the smallest error [21]. In another accuracy assessment study, the authors compared their 2015 predictions with observed data and concluded that all estimates were within 5% of the subsequently certified data and most were within 2% [27]. In this study, our verification also showed good accuracy of the joinpoint model, with a MAPE of total cancer mortality at 0.59%.

During the past three decades, although the crude death rate from total cancer has increased in Hunan, China, the ASR of total cancer mortality has decreased. These opposing trends can be attributed to the rapidly aging population. An empirical study of 287 Chinese cities from 2000 to 2010 revealed that the percentage of "elderly" cities increased from 50% to 90% [28]. The total cancer mortality rate in men has been declining since 2012, which is promising for the future. In contrast, while the total cancer mortality rate among women has continuously declined, this decline slowed down from 2007. However, the cancer mortality rate in men is projected to be nearly twice that of women by 2025, indicating the need for male-focused cancer prevention strategies.

By 2025, the five leading causes of cancer-related deaths in males are projected to be lung, liver, colorectal, stomach, and esophageal cancer, corresponding to lung, breast, colorectal, liver, and cervical cancer as the leading causes in females. This means that the integrated cancer spectrum characteristics of both developing and developed countries will persist in China for at least several years. Cancers traditionally prevalent in developed countries should be considered cautiously, and lung cancer should be the first concern because it has quickly become the leading cause of cancer-related deaths in China. Despite a reduction in the mortality rate and the absence of excess mortality, colorectal cancer will still remain the third leading cause of cancer-related deaths. We should not ignore the excess mortality from leading cancers in females because almost all of them will undergo adverse changes in mortality rates.

We found that breast and cervical cancers will remain the top two causes of cancer-related deaths in females aged 15–44 years. This is strongly driven by the slow progress in widespread screening and adequate human papillomavirus (HPV) vaccination (against

Table 1
Projected mortality rates of top five cancers for 2025 by age group (years).

Rank	0–14		15–44		45–59		60–79		80+	
	site	ASR[a]	Site	ASR[a]	site	ASR[a]	site	ASR[a]	site	ASR[a]
Male										
1	Leukemia	1.50	Liver	11.08	Lung	71.08	Lung	321.93	Lung	644.77
2	Brain and NS	0.90	Lung	6.79	Liver	50.64	Liver	97.41	Colorectum	272.22
3	Non-Hodgkin lymphoma	0.27	Colorectum	4.82	Colorectum	22.34	Colorectum	82.31	Prostate	212.45
4	Liver	0.17	Leukemia	3.09	Stomach	18.92	Stomach	73.36	Liver	189.04
5	[b]		Stomach	2.57	Esophagus	9.97	Esophagus	39.58	Stomach	168.59
Female										
1	Leukemia	1.09	Breast	3.52	Lung	25.14	Lung	119.87	Lung	239.66
2	Brain and NS	0.79	Lung	2.79	Breast	21.50	Colorectum	42.21	Colorectum	112.03
3	Non-Hodgkin lymphoma	0.14	Cervix	2.63	Cervix	17.37	Breast	41.94	Stomach	83.44
4	Liver	0.14	Leukemia	1.88	Liver	10.17	Liver	39.41	Liver	66.20
5	[b]		Stomach	1.32	Colorectum	9.20	Stomach	36.81	Breast	64.21

* a. ASR: age-standardized rate (per 100000 population).

*b. The sites were not presented because of deaths less then 6 annually or missing at least one age group.

Table 2
The excess mortality rate of top ten cancers in Hunan, China, 1990–2025.

Male				Female			
Sites	Projected	Expected	Excess change (%)[a]	Sites	Projected	Expected	Excess change (%)
Lung	62.56	62.56	0.00	Lung	25.86	18.32	41.17
Liver	29.12	13.50	115.64	Breast	12.32	7.88	56.40
Colorectum	19.08	19.08	0.00	Colorectum	9.81	9.81	0.00
Stomach	15.84	15.84	0.00	Liver	8.59	4.04	112.85
Esophagus	8.41	6.41	31.09	Cervix	8.43	4.54	85.52
Pancreas	6.16	6.16	0.00	stomach	8.38	4.35	92.42
Prostate	6.09	6.09	0.00	Pancreas	4.83	3.32	45.36
Leukemia	4.42	4.42	0.00	Brain and CNS	3.37	2.14	57.59
Brain and CNS	4.15	4.15	0.00	Leukemia	2.96	1.34	121.53
Non-Hodgkin lymphoma	3.62	3.62	0.00	Non-Hodgkin lymphoma	2.56	0.60	327.19

[a] Excess (%): (Projected-Expected)/Expected*100.

Table 3
The results from the prediction accuracy of the Joinpoint model in the study.

Studied years	Verified Year	Projected value	Observed value	PE (%)	MAPE (%)	MSE
1990–2010	2015	148.54	148.22	0.22	0.59	1.84
1990–2011	2016	147.97	147.42	0.37		
1990–2012	2017	146.62	146.72	−0.07		
1990–2013	2018	148.40	146.31	1.43		
1990–2014	2019	143.87	145.98	−1.44		

[1] Projected value = Age-standardized rate of mortality from all cancers combined projected, in per 100,000 populations.
[2] Real value = observed age-standardized rate of mortality from all cancers combined, in per 100,000 populations..
Abbreviations: MSE = Mean Square Error, PE=Percentage Error, MAPE = Mean Absolute Percentage Error.

cervical cancer). China finally established a free screening program for cervical and breast cancers in rural county-level areas in 2009 [29]. Nine years later, the coverage of areas implementing this program remained low, at 52.7% for cervical cancer and 33.5% for breast cancer [10]. In Hunan, this program was not universally implemented until 2016 [30]. China also delayed establishing a cervical cancer immunization program because the HPV vaccine was already being administered in 71% of high-income countries when the program was established in mainland China in 2016 [31,32]. These results indicate a real need to increase screening coverage and improve access to HPV vaccination among women of target ages.

As mentioned above, China has established a series of robust targets to curb the increase in crude cancer mortality. However, it is challenging to achieve these targets owing to the current grim situation of cancer prevalence, prevention, and control in China. In particular, under the current coronavirus disease 2019 (COVID-19) pandemic, patients with cancer have twice the probability of contracting COVID-19 than the general population [33], and patients with cancer and COVID-19 are at higher risk of severe outcomes [34,35]. Therefore, urgent measures are needed to form comprehensive cancer prevention strategies. The first is to reduce and prevent modifiable risk factors for cancers, responsible for approximately 60% of cancer deaths in China [36]. Rather than reviewing the well-known risk factors [37,38], we highlighted the most urgent strategy in China—tobacco control—because approximately 25% of cancer deaths in China are attributed to smoking [39], and the top priority is to increase excise taxes (currently at 11%) on tobacco products in China [40].

However, cancer control cannot rely solely on reducing the risk factors, and additional aggressive strategies need to be developed.

First, universal and opportunistic screening and standardization of medical examinations should be promoted. China has not established a systematic and standardized screening system for common cancers [41]. In Hunan, a free screening program covering lung, breast, colorectal, upper gastrointestinal, and liver cancer in urban areas was launched in 2012 [42]. However, the coverage of this program was very low, with only two cities and counties participating. Another free screening program covering upper gastro-intestinal cancers in the rural areas of Hunan also had relatively low coverage [30]. Hence, there is an urgent need to extend these screening programs nationwide. In particular, a series of effective cancer screening procedures should be established as standard screening tools for high-risk populations. For cancers with inefficient screening protocols, such as liver cancer, the protocols should be further optimized. In addition, a standard medical examination is crucial for detecting cancer or precancerous lesions. Accordingly, with first-class comprehensive grade-A or specialized cancer hospitals as leaders, related work in screening methods, tools, programs, and personnel skills should be standardized.

Second, universal access to quality cancer healthcare services should be improved. There are vast disparities in the quality of healthcare services in China, and high-quality services are generally concentrated in large hospitals in large cities. Therefore, rapid advances in access to cancer healthcare services are required. One of the top priorities is to establish a well-functioning hierarchical referral strategy based on a regional medical consortium. Although a cancer-specific consortium in Hunan was formed in 2017 [43], most of the work is in the primary stage, and additional practical details need to be determined. Specifically, a smooth dual referral mechanism must be established within the medical consortium. A routine cancer telemedicine platform integrated with a multidisciplinary team model also needs to be constructed. Large tertiary hospitals should maintain the platform and conduct joint telemedicine consultations with local secondary hospitals to provide continuous integrated medical care for patients with cancer. Additional work is needed to enhance the homogeneity of cancer healthcare services, such as establishing technology to update effective practices, guidelines for cancer control, and periodically providing global vision training.

Third, medical payment models need to be optimized and access to high-value anticancer drugs must be improved. The Chinese government has imposed zero tariffs on imported anticancer drugs since May 2018 and has been expanding the list of medical insurance covering anticancer drugs. However, patients with cancer often cannot obtain listed drugs in hospitals. This is mainly driven by administrative controls over the cost of health insurance and the proportion of drug costs in total payments [44]. Currently, most recognized targeted and innovative anticancer drugs are still not covered by medical insurance in China. An optimized medical payment model needs to be implemented urgently. Specifically, improving national drug price negotiations, dynamically adjusting the list of insured drugs, and increasing the covered proportion of high-value anticancer drugs on the medical insurance list with a higher reimbursement rate are required. In addition, the policy of administration-dominated cost control should be reformed to ensure that the listed drugs are all available from hospitals.

Our study has some limitations. First, we collected GBD data for the analysis which were subject to all the limitations of the GBD study. For example, the GBD study may not have included all available data sources because the data search is limited, and new data are not always accessible. In addition, if the data sources contain many undefined or ill-defined causes, redistribution may change the cancer estimates. Second, we projected cancer mortality under current trends, assuming no additional future efforts; however, these additional efforts are likely to be made. Nevertheless, the benefits of possible additional efforts will be gradual and will only slightly impact the results of our study. Third, we did not estimate the crude cancer death rates or the number of cancer deaths by 2025 because of possible changes in the population age structure. Finally, due to the lack of urban-rural stratified GBD data for Hunan, we did not analyze the corresponding urban-rural differences in cancer mortality. This may weaken the completeness of cancer-related mortality data in China.

5. Conclusion

The mortality rate of total cancer in Hunan, China, has slowly declined from 1990 and will continue to decline till 2025. Although the cancer mortality rate in men has been declining since 2012, efforts should target men, given that the mortality rate in men will be nearly twice that in women. A comprehensive cancer spectrum characteristic of both developing and developed countries is expected to persist in China in the coming years. Cancers traditionally prevalent in developed countries, mainly lung, breast, and colorectal, should not be overlooked. Lung cancer remains the most common cause of cancer-related death, highlighting tobacco control as the first priority to reduce this modifiable risk factor in China. Additional efforts should focus on promoting universal and opportunistic screening, standardizing medical examinations, improving access to cancer healthcare services within the medical consortium, optimizing medical payment models, and enhancing access to high-value anticancer drugs.

Author contribution statement

Qiaohua Xu, Maigeng Zhou: Conceived and designed the experiments; Performed the experiments; Analyzed and interpreted the data; Wrote the paper.

Donghui Jin: Performed the experiments.

Peng Yin: Contributed reagents, materials, analysis tools or data.

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Data availability statement

Data will be made available on request.

Declaration of interest's statement

The authors declare no competing interests.

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