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Retrospective Study

Pancreatic cancer incidence and mortality patterns in 2006-2015 and prediction of the epidemiological trend to 2025 in China

Yin MY *et al*. Epidemiological trends of pancreatic cancer

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Abstract

BACKGROUND

Due to dietary patterns, the aging population, and other high-risk factors, the occurrence of pancreatic cancer (PC) has been rapidly increasing in China.

AIM

To present the epidemiological trends of PC in China over the past decade and the estimated trend in 2025 and to compare the international differences in PC morbidity and mortality.

METHODS

This study used a series of nationally representative data from the National Central Cancer Registry of China (NCCR), the International Agency for Research on Cancer and the Institute for Health Metrics and Evaluation databases. Age-standardized data of the PC incidence and mortality from 2006 to 2015 in China were extracted from the NCCR database. Linear regression models were used to estimate the incidence and mortality rates of PC in 2025.

RESULTS

The age-standardized rates of PC in China increased from 3.65 per 100000 in 2006 to 4.31 per 100000 in 2015 and were estimated to reach up to 5.52 per 100000 in 2025. The mortality went from 3.35 per 100000 in 2006 to 3.78 per 100000 in 2015, estimated to reach up to 4.6 per 100000 in 2025. The number of new cases and deaths was low before 45 years and the peak age of onset was 85-89 years. The incidence and mortality rates in men were higher than those in women regardless of the region in China. In addition, the incidence and mortality rates in China were higher than the average level around the world. Likewise, disability-adjusted life years attributed to PC in China were 197.22 years per 100000, above the average level around the world.

CONCLUSION

This study presented an increasing trend of PC in China and differences in morbidity, mortality and disability-adjusted life years between Chinese and global populations. Efforts need to be made to decrease the PC incidence and improve patient outcomes.

Key Words: Pancreatic cancer; China; Epidemiology; Incidence; Mortality

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Core Tip: The past decades witnessed a remarkable increase in pancreatic cancer (PC) incidence and mortality globally. We present the epidemiological status of PC in China from 2006 to 2015 by a series of nationally representative data. We describe the differences in PC distributions by age and regions. We analyzed comparisons between China and other countries to inspire the prevention and control of PC in China.

INTRODUCTION

Pancreatic cancer (PC) has one of the worst prognoses, with the age-standardized rate (ASR) of 5-year overall survival in 2014 hovering at 14.30% in Australia, followed by 11.40% in Canada and 9.88% in Norway according to CANCER SURVIVAL. The past decades have witnessed a remarkable increase in PC incidence and mortality globally. According to GLOBOCAN 2020, PC is the 13th most frequent cancer, with approximately 495773 new cases, and the 7th most fatal cancer, with approximately 466003 deaths in 2020[1].

The causes of PC remain unclear despite several known risk factors, such as tobacco smoking and a positive family history. A previous study showed three recognized risk factors for PC: smoking, elevated fasting plasma glucose and a high body-mass index

(BMI)[2]. Moreover, a systematic review demonstrated that dietary patterns with better quality, such as the Mediterranean diet, with less inflammation or better antioxidant capacity, could reduce the risk of PC[3]. Due to a dietary pattern comprised of little fresh fruit and large amounts of red meat, PC has become one of the tumors with a rapidly increasing incidence in China[4]. Furthermore, along with the aging issue, environmental pollution and its huge population, China contributes significantly to the global burden of PC, *i.e.,* one-fourth of incident global cases and deaths in 2020[1].

In this study, we present the epidemiological status of PC in China from 2006 to 2015 from a series of nationally representative data, based on which we estimated the incidence and mortality rates of PC in 2025. In addition, we described the differences in PC distributions by age and region according to the global statistics in 2019. Furthermore, comparisons of PC epidemiological characteristics between China and other countries have also been made to inspire the prevention and control of PC in China.

MATERIALS AND METHODS

Data sources

The National Central Cancer Registry of China: Since 2002, the National Central Cancer Registry of China (NCCR), a department of the National Cancer Center, has collected, evaluated and released annual cancer data from local cancer registries in mainland China[5]. In August 2018, the NCCR released the cancer data of 2015 from 501 cancer registries of 31 provinces in China, among which 368 registries were eligible according to the following standards, and it provided an approximate 22.52% coverage of the national population[6]. First, the cancer registry data submitted to the NCCR were checked based on the data-quality criteria of the International Agency for Research on Cancer (IARC)/International Association of Cancer Registries[7] and the Guidelines for Chinese Cancer Registration[8]. Moreover, the quality assessment was evaluated based on the mortality to incidence (M/I, 0.61) ratio, the proportion of cases morphologically verified (MV%,69.34%), and the proportion of death certification only (DCO%,

2.09%)[6,9]. The PC incidence and mortality data before 2009 were age-standardized to the Chinese population census in 1982, and the data from 2010 to 2015 were age-standardized to the Chinese population census in 2000. All data for the PC incidence and mortality could be extracted from published articles from the National Cancer Center[5,9-17].

The IARC: The IARC project, was established by the World Health Organization in May 1965, whose mission was to coordinate cancer research across countries globally (www.iarc.who.int). The Global Cancer Observatory (GLOBOCAN_GCO) is a featured research project website of IARC that consists of several parts, including CANCER TODAY and CANCER SURVIVAL (gco.iarc.fr). CANCER TODAY provides data on the incidence, mortality, and 1-, 3-, and 5-year prevalence for 2020 in 185 countries or territories for 36 cancer types based on codes from the International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10) (gco.iarc.fr/today). CANCER SURVIVAL provides a comprehensive view of cancer survival statistics from 12 cancer registries in 7 countries and covers the period 1995-2014 (gco.iacr.fr/survival/survmar*k*). The age-standardized data of PC incidence and mortality in each country in GLOBOCAN_GCO were released based on the world Segi's population, expressed per 100 000 personyears.

The Institute for Health Metrics and Evaluation and the Global Burden of Disease: The Institute for Health Metrics and Evaluation (IHME) is an independent research center at the University of Washington, providing the world's highest-quality information on population health and evaluating strategies to address health problems (www.healthdata.org). The Global Burden of Disease (GBD), coordinated by the IHME, analyzes updated estimates of 369 diseases and injuries and 87 risk factors from 1990 to 2019 globally. It used the global age-standardized population to measure disability-adjusted life years (DALYs) to evaluate the burden of disease on communities (www.healthdata.org/gbd).

Statistical analysis

We extracted age-standardized data on PC incidence and mortality from 2006 to 2015 from the NCCR database to examine the epidemiological trends of PC by sex and urban-rural residence in China. We also estimated the incidence and mortality rates of PC in 2025 by fitting linear regression models, in which incidence and mortality rates were used as outcome variables and the year was used as an independent variable. Statistical analysis was performed with SPSS version 24.0 (SPSS, Inc., Chicago, IL, United States).

Ethic statements

The study was reviewed and approved by the first affiliated hospital of Soochow University Institutional Review Board.

RESULTS

Age-standardized PC rates in China from 2006 to 2015 (data source: NCCR)

Figure 1 displays an upward trend in the ASRs of PC in China, from 3.65 per 100000 in 2006 to 4.31 per 100000 in 2015. We estimated that the rate would reach 5.52 per 100000 in 2025 based on the hypothesis that the future trends would be similar to the previous trends. Moreover, the rate in men in urban areas was obviously higher than the rate in men in rural areas, from 4.47 per 100000 in 2006 to 5.44 per 100000 in 2015, and we projected that the former would reach 7.49 per 100000 in 2025. On the whole, the ASR of incidence for PC was higher in urban areas than in the entire nation and higher in men than in the total population.

ASRs of PC mortality in China from 2006 to 2015 (data source: NCCR)

As shown in Figure 2A, the calculated age-standardized mortality rates of PC went from 3.35 per 100000 in 2006 to 3.78 per 100000 in 2015 and were expected to reach 4.65 per 100000 in 2025. Men and women experienced a similar and relatively smooth

increase, from 3.99 per 100000 in 2006 to 4.50 per 100000 in 2015 and from 2.74 per 100000 in 2006 to 3.62 per 100000 in 2015, respectively. In terms of urban-rural residence, both men and women in urban areas presented a higher rate of PC mortality than men and women in rural areas (Figure 2B and C). In urban areas, there was an increase in mortality of men from 4.22 per 100000 in 2006 to 4.99 per 100000 in 2015 and women from 2.84 per 100000 in 2006 to 3.43 per 100000 in 2015 (Figure 2B). In rural areas, the mortality rates of men in rural areas went from 2.91 per 100000 in 2006 to 3.82 per 100000 in 2015, which exceeded that of women, and it was estimated to reach 4.92 per 100000 in 2025 (Figure 2C).

Distributions of new cases and deaths by age (per 100000) (data source: IHME)
For both sexes, ASRs of incidence and mortality were low before 45 years (all lower than 5.00 per 100000) and increased rapidly afterward, reaching a peak in the 85-89 years (64.01 *vs* 79.58 per 100000 in incidence and mortality) and then declining slightly (Figure 3). Overall, the incidence and mortality rates due to PC in men were consistently higher than those in women in the rapid growth groups.

Comparisons with other countries (data source: GLOBOCAN_GCO and GBD)
According to the CANCER TODAY database, the ASRs of PC were 5.3 *vs* 4.9 per 100,000 in China and the world and were similar with those in other developing countries, *e.g.,* Brazil and Russia (4.6-7.4 per 100000) (Supplementary Tables 1-3). The ASRs of mortality were 5.1 *vs* 4.5 per 100000 in China and the world, and were obviously lower than those in some developed countries, such as Japan and the United States ($\geq$ 6.6 per 100000) (Supplementary Tables 4-6). Furthermore, men presented a higher rate of PC than women globally (Supplementary Tables 2 and 3). For both men and women, the ASRs of mortality in China (6.0 and 4.2 per 100000) were lower than those in primary developed countries such as Japan (9.4 and 6.2 per 100000) but higher than the average level of the global rate (5.3 and 3.8 per 100,000) (Supplementary Tables 4 and 6).

There was an increasing trend in DALYs due to PC worldwide from 2000 to 2019. It was 197.22 years per 100000 in China in 2019, which was obviously higher than the global average (149.26 years per 100000) (Figure 4).

DISCUSSION

Our study presents the upward trends of the PC incidence and mortality in China from 2006 to 2015 stratified by sex and urban-rural residence. In general, the morbidity in both rural and urban regions was obviously increasing despite missing data, as was the mortality rate.

With regard to sex, men had a higher mortality rate than women. The reason for this might be less exposure to the main high-risk factors for PC, such as smoking, in the female population. As a systematic analysis showed, men in China are five times more likely than women to smoke[18].

The trends of the PC mortality and incidence were almost identical because its atypical symptoms and signs cause difficulty in making an early diagnosis, and it has a very low survival rate. Regarding regions, our study found higher mortality rate in urban relative to rural areas. More tobacco use, a high-sugar/salt/fat diet, excessive alcohol consumption and a lack of exercise in urban areas might play a significant role in this difference. Furthermore, the ease of access to health education and promotion, early detection, more efficient diagnostic tools and good medical resources are also important factors in survival[19].

The peak age of onset and death for PC was between 85-89 years, which was later than the peak age in previous studies[20]. According to the GBD database, men developed PC at around the same age as women, but at almost a twofold higher rate than women (www.healthdata.org/gbd). Given the aging population and prolonged life expectancy, the number of new PC cases is expected to increase steadily. Due to the lack of validated screening tests, it would be practical to avoid relevant high-risk factors such as tobacco use, alcohol consumption, obesity, *etc*.[21].

The GBD 2017 found a 2.3-fold increase in PC incidence and mortality from 1990 to 2017 and a 3-fold increase in high-sociodemographic index countries (measured by fertility rates, education and income)[22]. A systematic analysis for the GBD 2017 showed that the high rate of mortality was attributed to smoking, high fasting plasma glucose and a high BMI[2]. Another review revealed that *Helicobacter pylori* infection also demonstrated a strong positive association with PC[23]. Additionally, a study found an increased risk of PC in patients with chronic pancreatitis relative to the control group (RR = 13.3, 95%CI: 6.1-28.9)[4]. There are some other risk factors, including a lagging economy, male sex, older age, high alcohol consumption and red meat consumption, which are commonly seen lifestyle patterns in China[21,24]. Additionally, environmental pollution and food contamination, which are considered to be risk factors for PC, have become serious issues damaging public health in China in recent years[21]. Therefore, it is crucial to raise awareness of healthy lifestyles, such as a healthy balanced diet and regular exercise. Similarly, it is also necessary to carry out preventive measures such as smoking cessation, and increasing fresh fruit and vegetable intake to decrease the risk of PC during economic development and population growth and aging[19,23].

On a global scale, the ASR incidence and mortality of PC in the major developed countries, such as the United States, Canada, Japan and Australia, were higher than those in China, according to the GLOBOCAN database[1]. However, the ASR DALYs attributed to PC in China gradually increased since 2004 and were higher than the average level around the world, according to the GBD database. As mentioned above, the differences between countries might attributed to lifestyle, environment, smoking, hereditary and genetic factors. However, poor diagnostic capacity and no workable modality of effective treatment might result in international disparities. Additionally, it needs to be noted that the quality of the registries, including coverage, accuracy and integrality, might affect the differences among countries[25].

Currently, there is no recommendation for regular screening for PC in asymptomatic populations due to the low diagnostic and survival rates and lack of any effective treatment[22,23]. However, the 2019 International Cancer of the Pancreas Surveillance

Consortium recommends that individuals who carry a high-risk germline mutation or have at least one first-degree relative with PC should initiate pancreatic surveillance[26]. Two studies have shown that pancreatic surveillance among high-risk individuals resulted in downstaging PC, which resulted in higher survival rates, especially in stage I cancers[27]. These studies suggested that magnetic resonance imaging/magnetic resonance cholangiopancreatography and endoscopic ultrasound should be selected as the first-line tests for PC surveillance based on the current evidence, avoiding exposure to ionizing radiation by computed tomography. A recent review summarized the characteristics of individuals at high risk for PC in China, and in addition to a family history and gene mutation, patients at risk included those who were older than 40 years old with nonspecific abdominal symptoms; those who were diagnosed with diabetes mellitus after 60 years old; those who had chronic pancreatitis, intraductal papillary mucinous neoplasms or distal subtotal gastrectomy; and those who were addicted to smoking and alcohol[21]. Therefore, it might be necessary to carry out early surveillance among the relevant individuals mentioned above.

This study has some limitations. First, it extracted data from different sources, which covered populations from different countries. Thus, the differences in the statistical methods, quality of the registries, and the level of diagnosis and treatment might lead to incompatibility issues. Second, limited numbers of cancer registries might give rise to error factors, such as ignoring data from some underdeveloped areas. Third, the mortality rate referred only to the diagnosis of PC, not taking into account the effects of surgery or chemotherapy.

CONCLUSION

In conclusion, a significant increase in morbidity and mortality from PC in China over the past decade demonstrates that great efforts are required to reverse this trend. It is practical to modify environmental factors to prevent PC onset, such as smoking, obesity, dietary patterns, and diabetes mellitus. In addition, further basic research and multidisciplinary advances in imaging, surgery and radiochemotherapy might improve

patient outcomes to a significant extent. Moreover, it is necessary to strengthen international collaborations to create research conditions for long-term evaluations of pancreatic surveillance since trade-offs exist in the benefits and side effects of PC surveillance.

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