Burden of gynecological malignancies in China, 1990-2019: findings from the Global Burden of Disease Study 2019

Yuan Zhang[1], Xiaolei Zhang[1], Ruijie Wu[2], Tongchao Zhang[1], Xiaoyan Liu[1], Hao Chen[1], Zhen Li[2], Yuan Fang[2], Xiaorong Yang[1], and Ming Lu[1]

[1]Qilu Hospital of Shandong University
[2]Shandong University

November 11, 2022

Abstract

Objective To evaluate the epidemiological trends and patterns of cervical cancer, uterine cancer and ovarian cancer in China in 1990 and 2019. Design Systematical and updated worldwide epidemiological study. Setting Global Burden of Disease (GBD) Study 2019. Population or Sample. Chinese population was obtained from World Health Organization (WHO) World Standard Population Distribution (2000-2025) and the United Nations World Population Prospects 2019 Revision. Methods Data were extracted from the Global Burden of Diseases, Injuries, and Risk Factors Study 2019. GBD methodology was used to estimate the burden of gynecological malignancies in China, including cervical cancer, uterine cancer and ovarian cancer. Main Outcome Measures The incidence, mortality, disability-adjusted life-years (DALYs), and estimated annual percentage change (EAPC) were systematically analyzed. We additionally predicted the incidence and mortality of gynecological malignancies from 2020 to 2030. Results From 1990 to 2019, the numbers of incidence cases, deaths and DALYs of cervical cancer, uterine cancer and ovarian cancer all significantly increased. The EAPCs in age-standardized incidence rate (ASIR) of three cancers were 1.61 (95% CI: 1.35, 1.88), 1.26 (95% CI: 0.58, 1.94) and 1.88 (95% CI: 1.79, 1.98). From 2020 to 2030, the predicted numbers of incident cases and deaths of gynecological malignancies should continue to increase, and the incidences of uterine cancer would expect to exceed cervical cancer in 2030. Conclusions In China, the numbers of new cases and deaths of gynecological malignancies will continue to increase in the next ten years. Reducing the prevalence of gynecological malignancies should be prioritized in future work.

Burden of gynecological malignancies in China, 1990-2019: findings from the Global Burden of Disease Study 2019

Yuan Zhang,[a,b,c,*] Xiaolei Zhang,[d,*] Ruijie Wu,[b,*] Tongchao Zhang,[a,c] Xiaoyan Liu,[d] Hao Chen,[a,c] Zhen Li,[b] Yuan Fang,[b] Xiaorong Yang,[a,c] Ming Lu[a,b,c]

[a] Clinical Epidemiology Unit, Qilu Hospital of Shandong University, Jinan, Shandong 250012, P. R. China[b] School of Public Health, Cheeloo College of Medicine, Shandong University, Jinan, Shandong 250012, P. R. China[c] Clinical Research Center, Shandong University, Jinan, Shandong 250012, P. R. China [d] Department of Gynecology and Obstetrics, Qilu Hospital of Shandong University, Jinan, Shandong 250012, P. R. China

Correspondence

Xiaorong Yang, Clinical Epidemiology Unit, Qilu Hospital of Shandong University, No. 107, Wenhua West Road, Jinan, Shandong 250012, P. R. China.

E-mail: yangxiaorong@sdu.edu.cn

Ming Lu, Clinical Epidemiology Unit, Qilu Hospital of Shandong University, No. 107, Wenhua West Road, 250012, Jinan, Shandong 250012, P. R. China.

E-mail: *lvming@sdu.edu.cn*

Short Title:

Gynecological malignancies burden in China.

* Joint first authors and contributed equally to this paper.

Abstract

Objective To evaluate the epidemiological trends and patterns of cervical cancer, uterine cancer and ovarian cancer in China in 1990 and 2019.

Design Systematical and updated worldwide epidemiological study.

Setting Global Burden of Disease (GBD) Study 2019.

Population or Sample . Chinese population was obtained from World Health Organization (WHO) World Standard Population Distribution (2000-2025) and the United Nations World Population Prospects 2019 Revision.

Methods Data were extracted from the Global Burden of Diseases, Injuries, and Risk Factors Study 2019. GBD methodology was used to estimate the burden of gynecological malignancies in China, including cervical cancer, uterine cancer and ovarian cancer.

Main Outcome Measures The incidence, mortality, disability-adjusted life-years (DALYs), and estimated annual percentage change (EAPC) were systematically analyzed. We additionally predicted the incidence and mortality of gynecological malignancies from 2020 to 2030.

Results From 1990 to 2019, the numbers of incidence cases, deaths and DALYs of cervical cancer, uterine cancer and ovarian cancer all significantly increased. The EAPCs in age-standardized incidence rate (ASIR) of three cancers were 1.61 (95% CI: 1.35, 1.88), 1.26 (95% CI: 0.58, 1.94) and 1.88 (95% CI: 1.79, 1.98). From 2020 to 2030, the predicted numbers of incident cases and deaths of gynecological malignancies should continue to increase, and the incidences of uterine cancer would expect to exceed cervical cancer in 2030.

Conclusions In China, the numbers of new cases and deaths of gynecological malignancies will continue to increase in the next ten years. Reducing the prevalence of gynecological malignancies should be prioritized in future work.

Funding The National Key Research and Development Program of China (No.2021YFF1201101)

Keywords Burden, gynecological malignancies, China, global burden of disease study

Introduction

Gynaecological malignancies are the leading causes of premature death and disability for women worldwide, mainly including cervical cancer, uterine cancer and ovarian cancer. There were approximately 1,309,165 new cases and 609,377 deaths of gynaecological malignancies worldwide in 2018. Cervical cancer is the fourth most frequently diagnosed cancer and the fourth leading cause of cancer death in women, with an estimated 604,000 new cases and 342,000 deaths worldwide in 2020[1]. Cervical cancer represents a major global health challenge. Uterine cancer is the sixth most commonly diagnosed cancer in women, with 417,000 new cases and 97,000 deaths in 2020.[1] Uterine cancer mostly affects post-menopausal women. For patients with advanced disease, with lymph node invasion or metastasis, the 5-year overall survival is only 50% and 20%, respectively.[2] Ovarian cancer is the most lethal of the gynecologic malignancies with highest mortality rate among all gynecological malignant tumors. Although progress has been made in the diagnosis, prevention, screening and treatment of these malignancies over the past decades, many issues remain to be unsolved, such as chemoresistance, metastasis, recurrence, and family financial burden.[3,4]

Gynecological malignancies are the serious public health problem for women in China. These malignancies put the heavy burden on women, family and society in China, so there is an urgent need for comprehensive

understanding of the epidemic trends and patterns of gynecological cancer in China. We conducted this study to investigate and characterize the temporal trends and patterns in China over 30 years based on Global Burden of Disease (GBD) 2019, and predict incidence and mortality of gynecological malignancies from 2020 to 2030. Findings of this study will provide certain enlightenment for the etiological research of these cancers in China, measure the progress of specific treatments, help policymakers allocate resources and formulate relevant medical policies and opinions in the future.

Methods

Overview

October 2020, GBD 2019 estimates incidence, prevalence, mortality, years of life lost (YLLs), years lived with disability (YLDs), and disability-adjusted life-years (DALYs) due to 369 diseases and injuries for 204 countries and territories from 1990 to 2019.[2]In this study, we describe the burden and risk factors of gynecological malignancies, including cervical cancer, uterine cancer and ovarian cancer in China.

The ethics committee of Qilu Hospital of Shandong University reviewed and approved this study. Informed consent was waived because no identifiable information was included in the analyses. This study complied with the Guidelines for Accurate and Transparent Health Estimates Reporting statement.[5]

Data sources

The detail methods of GBD study (2019) have been reported in several studies.[2,6,7] The data on incidence, mortality and DALYs were downloaded from the Institute for Health Metrics and Evaluation (IHME, http://ghdx.healthdata.org/gbd-results-tool). The codes used for GBD study analysis can be accessed through the following address: http://ghdx.healthdata.org/gbd-2019-code. In GBD study, all estimates were generated with 95% uncertainty intervals (95% UIs), which were determined based on the 2.5th and 9.75th percentiles of 1000 draw of the uncertainty distribution. The inclusion criteria were as follows: (1) the cause was "cervical cancer", "uterine cancer", and "ovarian cancer"; (2) the year was selected from 1990 to 2019 and the location was "China"; (3) "incidence", "death" and "DALYs" were selected for measures.

The age-standardized rates for the incidence, mortality, and DALYs of gynecological malignancies were estimated using the World Health Organization (WHO) World Standard Population Distribution (2000-2025). For the prediction of burden, the predicted Chinese population was obtained from the United Nations World Population Prospects 2019 Revision, by year, sex and age (https://population.un.org/wpp/Download/Standard/Population/).

Evaluation of burden of gynecological malignancies

The incidence and mortality of gynecological malignancies in the GBD dataset were evaluated in the following ways: (1) based on all the data sources that reported incidence and mortality of cervical cancer, uterine cancer and ovarian cancer (with international disease classification codes), the mortality-to-incidence ratio (MIR) was computed; (2) we calculated mortality estimates by multiplying cancer register incidence data by the MIR; (3) all these data were used as input to follow the Cause of Death Ensemble model process to determine the cancer-specific mortality of cervical cancer, uterine cancer and ovarian cancer; and (4) we divided the cancer-specific mortality of cervical cancer, uterine cancer and ovarian cancer estimates by the MIR to generate incidence. DALYs were computed by adding years of life lost (YLLs) and years lived with disability (YLDs).

Statistical analysis

Estimated annual percentage change (EAPC) was used to quantify the trends of age-standardized incidence rate (ASIR), age-standardized mortality rate (ASMR) and age-standardized DALYs rate (ASDR). The logarithmic age-standardized indicators could be fitted to a regression line, i.e., $\ln(y) = \alpha+\beta x+\varepsilon$, where y stands for the respective age-standardized indicators, x the calendar year. EAPC was calculated as $100 \times (\exp(\beta)-1)$, and its 95% confidence interval (CI) could also be calculated from the model 21. The age-standardized indicator was recognized to be in an increasing trend if the 95% CI of corresponding EAPC estimation >

0, to be decreasing trend if the 95% CI < 0, and to be stable if the 95% CI including 0. Furthermore, we predicted the numbers of new cases and deaths of gynecological malignancies from 2020 to 2030 by conducting a Bayesian age-period-cohort (BAPC) analysis using integrated nested Laplace approximation (INLA) packages in R. All analyses were conducted using R program (Version 4.0.2, R core team, Vienna, Austria). AP <0.05 was considered statistically significant.

Results

Incidence, mortality and DALYs of gynecological malignancies in 2019

In 2019, the number of incidence cases and ASIR of cervical cancer were 109.76 thousand (95% UI: 58.19, 141.54) and 11.01 per 100,000 (95% UI: 5.87, 14.22), respectively. Cervical cancer contributed to 53.44 thousand (95% UI: 30.40, 68.86) deaths, and ASMR was 5.13 per 100,000 (95% UI: 2.92, 6.60). Cervical cancer caused 1622.24 thousand (95% UI: 892.58, 2090.86) DALYs, and ASDR was 157.50 per 100,000 (95% UI: 86.90, 202.91) (Table 1).

The number of incidence cases and ASIR of uterine cancer were 66.74 thousand (95% UI: 51.38, 92.05) and 6.39 per 100,000 (95% UI: 4.89, 8.74), respectively in 2019. Uterine cancer contributed to 12.22 thousand (95% UI: 9.43,17.34) deaths, and ASMR was 1.17 per 100,000 (95% UI: 0.9, 1.66). Uterine cancer caused 364.28 thousand (95% UI: 286.56, 503.57) DALYs, and ASDR was 34.93 per 100,000 (95% UI: 27.27, 47.77) (Table 1).

The number of incidence cases and ASIR of ovarian cancer were 45.48 thousand (95% UI: 33.11, 57.38) and 4.54 per 100,000 (95% UI: 3.33, 5.71), respectively. Ovarian cancer contributed to 29.10 thousand (95% UI: 20.96, 36.86) deaths, and ASMR was 2.77 per 100,000 (95% UI: 2.01,3.50). Ovarian cancer caused 835.06 thousand (95% UI: 612.56, 1063.25) DALYs, and ASDR was 80.52 per 100,000 (95% UI: 59.44, 102.57) (Table 1).

In 2019, the numbers of incident cases and DALYs of cervical cancer, uterine cancer and ovarian cancer reached the peak among the female population aged 50-54 years (Figure 1A and 1C, Table S1 and S3). The peak numbers of deaths of cervical cancer, uterine cancer and ovarian cancer appeared at aged 50-54, 65-69 and 65-69 years, respectively. (Figure 1B, Table S2). Meanwhile, the numbers of incident cases, deaths and DALYs of ovarian cancer covered all age groups over 5 years old (Figure 1).

The incidence rate reached the peak among cervical cancer and uterine cancer aged 55-59 years, and 70-74 years for ovarian cancer. The mortality rate reached the peak among cervical cancer and uterine cancer aged over 95 years, and 90-94 years for ovarian cancer. The peak of DALY rate of cervical cancer, uterine cancer and ovarian cancer appeared at aged 55-59, 60-64 and 65-69 years, respectively (Figure 1, Table S1-S3).

Trends of incidence, mortality and DALYs of gynecological malignancies from 1990 2019

From 1990 to 2019, the numbers of incidence cases, deaths and DALYs of cervical cancer, uterine cancer and ovarian cancer all significantly increased. The EAPCs in ASIR of three cancers from 1990 to 2019 were 1.61 (95% CI: 1.35, 1.88), 1.26 (95% CI: 0.58, 1.94) and 1.88 (95% CI: 1.79, 1.98), respectively. The EAPC of ASMR and ASDR among patients with cervical cancer in 20 years was not much different with 0.09 (95% CI: -0.18, 0.36) and 0.16 (95%: -0.09, 0.41), respectively. Overall downward trends in ASMR and ASDR among patients with uterine cancer were observed with the EAPC of -2.27 (95% CI: -2.88, -1.66) and -2.21 (95%CI: -2.81, -1.60). The EAPC of death and DALYs of ovarian cancer still showed an upward trend with 1.51 (95% CI: 1.42, 1.61) and 1.15 (95%CI: 1.04, 1.25) (Table 1, Figure 2).

The incidence rate of cervical cancer aged 35-70 years was increasing from 1990 to 2019. In recent years, the incidence rate of uterine cancer has declined in most age-specific groups, but had shown a youth-oriented tendency. The incidence and death rate of ovarian cancer showed an upward trend in overall groups. Overall downward trends in mortality and DALYs rates were observed in cervical cancer and uterine cancer at most age-specific groups from 1999 to 2019. The DALYs rates of ovarian cancer increased in most age-specific groups (Figure 2).

DALYs rates and proportions attributable to risk factors for gynecological malignancies from 1990 to 2019

In all age-specific groups, the DALYs rates of cervical cancer attributed to unsafe sexual activity were the highest, and fortunately, the DALYs rates attributable to unsafe sexual activity showed a downward trend in recent years. The DALYs rates of cervical cancer due to smoking showed a downward trend in above 60-year-old groups. The DALYs rates of uterine cancer due to high body-mass index were higher between 50 and 69 years. The DALYs rates of ovarian cancer attributable to high body-mass index, high fasting plasma glucose and occupational asbestos exposure had an upward trend from 1990 to 2019.

The DALYs proportion of cervical cancer attributable to unsafe sexual activity was 100% continuously, and smoking's contribution descended in 2019 compared to 1990. Proportions of DALYs attributable to high body-mass index for uterine cancer and ovarian cancer were higher in 2019 than in 1990 in all age-specific groups. The high fasting plasma glucose was the most significant contribution to ovarian cancer, accounting for more than 6% in above 60-year-old women. The proportion of DALYs attributable to occupational asbestos exposure was slightly lower in 2019 than in 1990 (Figure 3).

Predictions ofincidence and mortality of gynecological malignancies from 2020 to 2030

Based on GBD data of gynecological malignancies from 1990 to 2019 in China, we predicted the incident cases and deaths in the next eleven years (Figure 4). The numbers of incident cases and deaths of cervical cancer, uterine cancer and ovarian cancer should continue to increase from 2020 to 2030. The predicted new cases of uterine cancer have the steepest rising slope, which is expected to exceed the cases of cervical cancer in 2030. Meanwhile, the growth of uterine cancer deaths also had the steepest slope, followed by ovarian cancer and cervical cancer. In 2030, the overall new cases of cervical cancer, uterine cancer and ovarian cancer should increase to 123,902, 132,118 and 72,488, respectively (Figure 4A). And the overall deaths of cervical cancer, uterine cancer and ovarian cancer should increase to 59,145, 18,571 and 45,680, respectively (Figure 4B).

We further predicted the age-standardized incidence rate and death rate of gynecological malignancies from 2020 to 2030 (Figure 5). Age-standardized rates of incidence and mortality of cervical cancer should show a downward trend (Figure 5A and 5B). The age-standardized incidence rate of uterine cancer should show a slow upward trend and the death rate of uterine cancer remain stabilized trend (Figure 5C and 5D). Seriously, the age-standardized rates of incidence and mortality of ovarian cancer should show an upward trend (Figure 5E and 5F).

Discussion

Cancer is a leading cause of death and disability worldwide, especially in women.[8,9]Gynecologic cancers which have negative effects on the physical and psychological health of patients, seriously threaten women's life and health. According to GLOBOCAN 2020 Project data, cervical cancer, uterine cancer, and ovarian cancer are among the top 10 common cancers in females worldwide.[1]China is the world's most populous country with around 685 million women. Approximately 214,400 new cases of gynecologic cancer occurred in 2015, and there were about 74,800 deaths from gynecologic cancer in China.[10] Therefore, it is of great social significance to comprehensively understand the epidemic trends and patterns of gynecological cancers in China. In this study, we not only assessed the prevalence of gynecologic cancers in China, but also systematically analyzed trends of incidence, mortality, DALYs and proportions attributable to risk factors for gynecological malignancies from 1990 to 2019. In addition, we predicted incidence and mortality rates for gynecologic malignancies from 2020 to 2030. This is one substantial study to investigate the long-term trends of morbidity and mortality for gynecologic malignancies in China and to assess DALYs rates and proportions attributable to risk factors for gynecological malignancies from 1990 to 2019.

The global costs associated with cancer are significant and are estimated to comprise 2-4% of the annual gross domestic product (GDP). The majority of the world's cancer burden occurs in low- and middle- income countries (LMICs).[11]In addition to social and economic burden on women and their family, gynecologic ma-

lignancies play negative effects on women's self-concept, body image, sense of femininity and sex life.[12-16]Most of the people in China have medical insurance, however cancer costs are only partly covered by insurance. Medical costs are still problem for patients with gynecologic malignancies. Due to women's increasingly important roles in the family and society in China, gynecologic cancer patients are more likely to suffer from anxiety and depression. China is the most populous country in the world, so cancer patterns in China is an important focus of public health. China is undergoing a transition period from being a developing country to a developed country, with a large number of female residents, it is of great social significance to summarize and analyze the epidemiological patterns of gynecologic malignancies in China.

The incidence, mortality, disability-adjusted life-years (DALYs) could be used to measure disease and economic burdens.[7,17-20] The burden of cancer incidence and mortality is growing rapidly worldwide. Around the world, the total incidence and mortality of gynecologic cancers increased sharply from 1990 to 2019. From 1990 to 2019, the numbers of incidence cases, deaths and DALYs of cervical cancer, uterine cancer and ovarian cancer all significantly increased, which is consistent with the reports in another paper.[7] As shown in Table 1, the ASIRs and ASDRs of these three types of cancers exhibited different epidemiological patterns. We analyzed numbers and rates of incidence, death and DALYs of cervical cancer, uterine cancer and ovarian cancer by age in 2019 in China. Data showed that the numbers of incident cases and DALYs of cervical cancer, uterine cancer and ovarian cancer reached the peak among the female population aged 50-54 years. Meanwhile, the peak numbers of deaths of cervical cancer, uterine cancer and ovarian cancer appeared at aged 50-54, 65-69 and 65-69 years, respectively. More screenings and attention should be paid to Chinese women aged 50-69 years. The results showed that the high-risk group of gynecologic cancer was middle-aged and elderly women in China; The middle-aged and elderly population is the key population to carry out comprehensive prevention and control of malignant tumors. It is necessary to strengthen the health examination, health knowledge education, tumor screening, early diagnosis, early treatment, tumor registration and follow-up of the middle-aged and elderly population. The prevention and treatment of gynecologic cancer is a long-term and arduous task. On the basis of improving the monitoring of cancer incidence and death, we should fully analyze the types of high-incidence cancers and high-risk factors in different age groups, and adopt targeted prevention and treatment strategies with overall consideration, so as to obtain a good effect of tumor prevention and treatment.

We explored DALYs rates and proportions attributable to risk factors for gynecological malignancies from 1990 to 2019, in order to provide scientific basis for effective prevention and intervention of cervical cancer, uterine cancer and ovarian cancer. Cervical cancer is one of the leading causes of cancer-related deaths in women worldwide,[21] meanwhile, it is the most common gynecologic cancer in China. High-risk subtypes of the human papillomavirus (HPV) cause almost all cervix cancers.[22] Persistent infection of the lower genital tract by one of the high-risk HPV (hrHPV) types is the "necessary" cause of cervical cancer. HPV16 and 18 are associated with approximately 71% of cervical cancer cases, while 31, 33, 45, 52 and 58 are associated with another 19% of cases.[23-25] High proportion of sexually active women become infected with some human papillomavirus type by age 25 years, but most infections resolve spontaneously.[26] It suggests that the infection is predominantly transmitted through the sexual activity. Our results showed that, the DALYs rates of cervical cancer attributed to unsafe sexual activity were the highest in all age-specific groups, and the DALYs rates attributable to unsafe sexual activity showed a downward trend in recent years. However, the DALYs proportion of cervical cancer attributable to unsafe sexual activity was 100% continuously. Studies show that cervical cancer is positively correlated with premature sexual life, excessive sexual life, multiple sexual partners and unclean sexual life. The risk of cervical cancer in women with initial sexual behavior [?] 21 years old is lower than that in women with initial sexual behavior aged 15˜16 years old.[27] It is an effective measure to improve people's awareness of cervical cancer related knowledge, HPV vaccine and cervical cancer screening and improve their awareness of prevention and control in China. Cervical cancer screening has become one of the most common gynecological screening programs in China.[28] This is of great significance in the early diagnosis of cervical cancer. Studies have shown that smoking and passive smoking are also related to the occurrence of cervical cancer and precancerous lesions. The mechanism may be that the concentration of nicotine in cervical mucus of smoking women increases significantly, consumes a large number of Langham

cells, and leads to the reduction of cervical immunity. According to relevant statistics, the risk of cervical cancer increased 11.8 times in patients with passive smoking time [?]5 h/d.[29] The results of our study show that the DALYs rates of cervical cancer due to smoking showed a downward trend in above 60-year-old groups, and smoking's contribution descended in 2019 compared to 1990 (shown in Figure 3). This indicates that health education, lifestyle improvement and anti-smoking laws must be carried out throughout the comprehensive prevention and control of cancer. This has important implications for improving women's reproductive health.

Studies have found that obesity may be an important factor affecting the occurrence and development of uterine cancer.[30-32]Body-mass index (BMI) was positively correlated with the risk of endometrial cancer, and the risk of endometrial cancer in overweight and obese people was 2.45 times and 3.5 times higher than that in normal people, respectively.[33] In a prospective study of 36 755 women, there was a strongly positive and linear association of BMI with the risk of uterine cancer.[32] Our results indicated that the DALYs rates of uterine cancer due to high body-mass index were higher between 50 and 69 years. In addition, proportions of DALYs attributable to high body-mass index for uterine cancer were higher in 2019 than in 1990 in all age-specific groups. Previous data also showed that compared with normal BMI, 181 genes involved in lipid metabolism, fatty acid metabolism and metabolic signal transduction pathway were up-regulated or down-regulated in obese patients with uterine cancer.[34] In recent decades, the implementation of comprehensive staging surgery for uterine cancer, the application of minimally invasive technology, reasonable adjuvant chemotherapy and radiotherapy, and comprehensive treatment for advanced patients have greatly improved the prognosis of patients. However, the pharmacokinetic changes and metabolic abnormalities caused by obesity will reduce the chemotherapy effect of uterine cancer and cause poor prognosis.[35] Improving the risk awareness of high-risk groups for uterine cancer, carrying out active and effective screening, changing adverse lifestyle, and early intervention for metabolic diseases can reduce the risk of uterine lesions, and effectively reduce the incidence and mortality of uterine cancer.

The result showed that the incidence and death rate of ovarian cancer showed an upward trend in overall groups in China from 1990 to 2019. As one of the deadliest cancers, the early diagnosis of ovarian cancer is very difficult. When patients are diagnosed, they are often in the middle and advanced stage, which is not conducive to the treatment and prognosis of patients. The 5-year survival rate will not exceed 30%.[36] Previous studies suggested that the risk factors for ovarian cancer mainly included family genetic history, fertility factors, menstrual history, body mass index, obesity, lifestyle, diet, hormone replacement therapy and so on.[37-41] Other studies have shown that organic dust, asbestos, and talcum powder are also risk factors for ovarian cancer.[42,43] We analyzed the DALYs rates and proportions attributable to risk factors for ovarian cancer in China from 1990 to 2019. As shown in Figure 3, the DALYs rates of ovarian cancer attributable to high body-mass index, high fasting plasma glucose and occupational asbestos exposure had an upward trend from 1990 to 2019. In addition, proportions of DALYs attributable to high body-mass index for ovarian cancer were higher in 2019 than in 1990 in all age-specific groups. This seems to suggest that with the increase of China's GDP and the improvement of people's quality of life, the malignant tumors caused by metabolic diseases are on the rise. It is necessary to formulate relevant strategies, including promoting exercise, healthy diet, regular screening, controlling metabolic diseases and so on. The proportion of DALYs attributable to occupational asbestos exposure was slightly lower in 2019 than in 1990. Although most countries prohibit the use of asbestos, millions of people still work in factories exposed to asbestos, and at least 90000 people die each year from asbestos related diseases or cancer diseases.[44]Governments should increase efforts to limit the production and use of asbestos, and find alternatives to reduce asbestos exposure. Regular occupational disease screening and physical examination for women at risk of asbestos exposure also contribute to the prevention of ovarian cancer.

According to the data forecast, there will be 28.4 million new cancer cases worldwide by 2040, an increase of 47% compared with 19.3 million cases in 2020.[1] The global economic burden on cancer will be heavy. Based on GBD data of gynecological malignancies from 1990 to 2019 in China, we predicted the incident cases and deaths in the next eleven years. Results showed that the numbers of incident cases and deaths of cervical cancer, uterine cancer and ovarian cancer should continue to increase from 2020 to 2030. This

indicates that the economic burden on gynecological malignancies in China will further increase in the next decade. We further analyzed the trends of three major gynecological malignancies, in order to facilitate government departments to adjust their budgets, better allocate prevention and research funds, and adjust the total prevention expenditure. The predicted new cases of uterine cancer have the steepest rising slope, which is expected to exceed the cases of cervical cancer in 2030. Meanwhile, the growth of uterine cancer deaths also had the steepest slope, followed by ovarian cancer and cervical cancer. In recent years, with the rapid development of China's economy, people's living habits and diet structure have changed greatly. With the increase of metabolic diseases, uterine cancer also has an increasing incidence rate and younger onset trend. Uterine cancer has become a serious problem endangering the health of Chinese women. It is urgent to establish effective screening methods to realize the early diagnosis and treatment of uterine cancer. Screening guidelines for uterine cancer have been developed in the United States,[45] the United Kingdom,[46] Germany,[47] and other countries. In addition to carrying out primary prevention, changing lifestyle and reducing risk factors, it is also important to carry out secondary prevention with periodic screening among high-risk groups in China. According to China's Expert Consensus on Screening and Early Diagnosis of Endometrial Cancer, screening is recommended for women over 45 years old, especially those with metabolic syndrome such as diabetes and obesity, history of estrogen use, tamoxifen treatment, and family history of cancer. Molecular classification was applied to uterine cancer when the results of the Cancer Genome Atlas (TCGA) project were published.[48] This molecular classification is important for diagnosis, prognosis and treatment of uterine cancer.

There are several limitations of the current study. First, the predictions were based on the GBD Study, in some cases, primary data was lacking. The quality of original individual registration data greatly affects the accuracy and stability of database estimation, and the missing or false data may lead to bias. This bias was also kept low due to the GBD study's many measures to reduce this bias, such as correcting incompleteness, underreporting and misclassification, as well as reassigning garbage code, and so on. Second, due to the limited information in the GBD database, the burden of gynecological malignancies caused by other risk factors cannot be fully evaluated.

Conclusion

From 1990 to 2019, the numbers of incidence cases, deaths and DALYs of cervical cancer, uterine cancer and ovarian cancer all significantly increased. Unsafe sex, smoking, high body-mass index, high fasting plasma glucose, and occupational exposure to asbestos are the leading risk factors of gynecological malignancies in China From 2020 to 2030, the predicted numbers of incident cases and deaths of these three major gynecologic cancers will continue to increase, and the incidences of uterine cancer would expect to exceed cervical cancer in 2030. Our results will provide suggestions for the government to take tailored actions for the future management of gynecological malignancies. Measures to improve the early diagnosis and new effective treatment methods should be formulated to reduce the burden of gynecological malignancies.

Acknowledgement

This work was supported by the National Key Research and Development Program of China (No.2021YFF1201101).

Contribution to authorship

YZ, XY, and ML contributed to the concept of the manuscript. YZ, XZ, RW and TZ completed the first draft of the manuscript. YF, ZL, and RW contributed to the data collection. HC and XY provided critical feedback on data analysis and results interpretation. YZ, XZ, and XL contributed to the discussion part of the manuscript. ML revised the manuscript critically for important intellectual content. All authors contributed to the framework construction, results interpretation, manuscript revision, and approved the final version of the manuscript. The corresponding authors attest that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

Data Availability Statement

All data can be extracted from the online GBD repository, http:// ghdx.healthdata.org/gbd-results-tool.

Conflict of interest

The authors have no conflict of interest to declare.

References

1 Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. *CA Cancer J Clin* 2021;71:209-249.

2 Diseases GBD & Injuries C. Global burden of 369 diseases and injuries in 204 countries and territories, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019. *Lancet*2020;396:1204-1222.

3 Lheureux S, Gourley C, Vergote I & Oza AM. Epithelial ovarian cancer.*Lancet* 2019;393:1240-1253.

4 Lu KH & Broaddus RR. Endometrial Cancer. *N Engl J Med*2020;383:2053-2064.

5 Stevens GA, Alkema L, Black RE, Boerma JT, Collins GS, Ezzati M, et al. Guidelines for Accurate and Transparent Health Estimates Reporting: the GATHER statement. *PLoS Med* 2016;13:e1002056.

6 Collaborators GBDD. Global age-sex-specific fertility, mortality, healthy life expectancy (HALE), and population estimates in 204 countries and territories, 1950-2019: a comprehensive demographic analysis for the Global Burden of Disease Study 2019. *Lancet*2020;396:1160-1203.

7 Wang Z, Guo E, Yang B, Xiao R, Lu F, You L, et al. Trends and age-period-cohort effects on mortality of the three major gynecologic cancers in China from 1990 to 2019: Cervical, ovarian and uterine cancer. *Gynecol Oncol* 2021;163:358-363.

8 Global Burden of Disease Study C. Global, regional, and national incidence, prevalence, and years lived with disability for 301 acute and chronic diseases and injuries in 188 countries, 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013. *Lancet*2015;386:743-800.

9 Soerjomataram I, Lortet-Tieulent J, Parkin DM, Ferlay J, Mathers C, Forman D, et al. Global burden of cancer in 2008: a systematic analysis of disability-adjusted life-years in 12 world regions. *Lancet*2012;380:1840-1850.

10 Chen W, Zheng R, Baade PD, Zhang S, Zeng H, Bray F, et al. Cancer statistics in China, 2015. *CA Cancer J Clin* 2016;66:115-132.

11 Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. *Int J Cancer* 2015;136:E359-386.

12 Hu Y, Ma Z, Zhang H, Gao T, Gao J, Kong Y, et al. Prevalence of and factors related to anxiety and depression symptoms among married patients with gynecological malignancies in China. *Asian J Psychiatr* 2018;37:90-95.

13 Perez-Tejada J, Labaka A, Pascual-Sagastizabal E, Garmendia L, Iruretagoyena A & Arregi A. Predictors of psychological distress in breast cancer survivors: A biopsychosocial approach. *Eur J Cancer Care (Engl)* 2019;28:e13166.

14 Li WJ, Miao M, Gan YQ, Zhang ZJ & Cheng G. The relationship between meaning discrepancy and emotional distress among patients with cancer: the role of posttraumatic growth in a collectivistic culture. *Eur J Cancer Care (Engl)* 2016;25:491-501.

15 Hsu HC, Tsai SY, Wu SL, Jeang SR, Ho MY, Liou WS, et al. Longitudinal perceptions of the side effects of chemotherapy in patients with gynecological cancer. *Support Care Cancer* 2017;25:3457-3464.

16 Lee JT, Kuo HY, Huang KG, Lin JR & Chen ML. Diversity of sexual activity and correlates among women with gynecological cancer.*Gynecol Oncol* 2020;159:503-508.

17 Yi M, Li A, Zhou L, Chu Q, Song Y & Wu K. The global burden and attributable risk factor analysis of acute myeloid leukemia in 195 countries and territories from 1990 to 2017: estimates based on the global burden of disease study 2017. *J Hematol Oncol* 2020;13:72.

18 Deng Y, Li H, Wang M, Li N, Tian T, Wu Y, et al. Global Burden of Thyroid Cancer From 1990 to 2017. *JAMA Netw Open* 2020;3:e208759.

19 Bai X, Yi M, Dong B, Zheng X & Wu K. The global, regional, and national burden of kidney cancer and attributable risk factor analysis from 1990 to 2017. *Exp Hematol Oncol* 2020;9:27.

20 Global Burden of Disease Cancer C, Kocarnik JM, Compton K, Dean FE, Fu W, Gaw BL, et al. Cancer Incidence, Mortality, Years of Life Lost, Years Lived With Disability, and Disability-Adjusted Life Years for 29 Cancer Groups From 2010 to 2019: A Systematic Analysis for the Global Burden of Disease Study 2019. *JAMA Oncol* 2021;

21 Arbyn M, Weiderpass E, Bruni L, de Sanjosé S, Saraiya M, Ferlay J, et al. Estimates of incidence and mortality of cervical cancer in 2018: a worldwide analysis. *Lancet Glob Health* 2020;8:e191-e203.

22 Crosbie EJ, Einstein MH, Franceschi S & Kitchener HC. Human papillomavirus and cervical cancer. *Lancet* 2013;382:889-899.

23 Bosch FX, Lorincz A, Muñoz N, Meijer CJ & Shah KV. The causal relation between human papillomavirus and cervical cancer. *J Clin Pathol* 2002;55:244-265.

24 Forman D, de Martel C, Lacey CJ, Soerjomataram I, Lortet-Tieulent J, Bruni L, et al. Global burden of human papillomavirus and related diseases. *Vaccine* 2012;30 Suppl 5:F12-23.

25 Small W, Jr., Bacon MA, Bajaj A, Chuang LT, Fisher BJ, Harkenrider MM, et al. Cervical cancer: A global health crisis. *Cancer*2017;123:2404-2412.

26 Dunne EF, Unger ER, Sternberg M, McQuillan G, Swan DC, Patel SS, et al. Prevalence of HPV infection among females in the United States.*Jama* 2007;297:813-819.

27 Vinodhini K, Shanmughapriya S, Das BC & Natarajaseenivasan K. Prevalence and risk factors of HPV infection among women from various provinces of the world. *Arch Gynecol Obstet* 2012;285:771-777.

28 Cao M, Li H, Sun D, He S, Yu Y, Li J, et al. Cancer screening in China: The current status, challenges, and suggestions. *Cancer Lett* 2021;506:120-127.

29 Natphopsuk S, Settheetham-Ishida W, Sinawat S, Pientong C, Yuenyao P & Ishida T. Risk factors for cervical cancer in northeastern Thailand: detailed analyses of sexual and smoking behavior. *Asian Pac J Cancer Prev* 2012;13:5489-5495.

30 Sung H, Siegel RL, Torre LA, Pearson-Stuttard J, Islami F, Fedewa SA, et al. Global patterns in excess body weight and the associated cancer burden. *CA Cancer J Clin* 2019;69:88-112.

31 Aubrey C, Black K, Campbell S & Pin S. Endometrial cancer and bariatric surgery: A scoping review. *Surg Obes Relat Dis*2019;15:497-501.

32 Lindemann K, Vatten LJ, Ellstrøm-Engh M & Eskild A. The impact of BMI on subgroups of uterine cancer. *Br J Cancer* 2009;101:534-536.

33 Scherübl H. [Excess Body Weight and Cancer Risk]. *Dtsch Med Wochenschr* 2020;145:1006-1014.

34 Roque DR, Makowski L, Chen TH, Rashid N, Hayes DN & Bae-Jump V. Association between differential gene expression and body mass index among endometrial cancers from The Cancer Genome Atlas Project.*Gynecol Oncol* 2016;142:317-322.

35 Bouleftour W, Mery B, Chanal E, Rowinski E, Viard A, Forges F, et al. Obesity and chemotherapy administration: between empiric and mathematic method review. *Acta Oncol* 2019;58:880-887.

36 Lynch HT, Casey MJ, Snyder CL, Bewtra C, Lynch JF, Butts M, et al. Hereditary ovarian carcinoma: heterogeneity, molecular genetics, pathology, and management. *Mol Oncol* 2009;3:97-137.

37 Zhang Y, Luo G, Li M, Guo P, Xiao Y, Ji H, et al. Global patterns and trends in ovarian cancer incidence: age, period and birth cohort analysis. *BMC Cancer* 2019;19:984.

38 Wang X, Ping FF, Bakht S, Ling J & Hassan W. Immunometabolism features of metabolic deregulation and cancer. *J Cell Mol Med*2019;23:694-701.

39 Zhang S, Gong TT, Liu FH, Jiang YT, Sun H, Ma XX, et al. Global, Regional, and National Burden of Endometrial Cancer, 1990-2017: Results From the Global Burden of Disease Study, 2017. *Front Oncol*2019;9:1440.

40 Puente D, López-Jiménez T, Cos-Claramunt X, Ortega Y & Duarte-Salles T. Metabolic syndrome and risk of cancer: a study protocol of case-control study using data from the Information System for the Development of Research in Primary Care (SIDIAP) in Catalonia. *BMJ Open* 2019;9:e025365.

41 Olsen CM, Green AC, Whiteman DC, Sadeghi S, Kolahdooz F & Webb PM. Obesity and the risk of epithelial ovarian cancer: a systematic review and meta-analysis. *Eur J Cancer* 2007;43:690-709.

42 Camargo MC, Stayner LT, Straif K, Reina M, Al-Alem U, Demers PA, et al. Occupational exposure to asbestos and ovarian cancer: a meta-analysis. *Environ Health Perspect* 2011;119:1211-1217.

43 Salehi F, Dunfield L, Phillips KP, Krewski D & Vanderhyden BC. Risk factors for ovarian cancer: an overview with emphasis on hormonal factors. *J Toxicol Environ Health B Crit Rev* 2008;11:301-321.

44 Burki T. Asbestos production increases despite WHO opposition.*Lancet Oncol* 2009;10:846.

45 Bhatla N & Denny L. FIGO Cancer Report 2018. *Int J Gynaecol Obstet* 2018;143 Suppl 2:2-3.

46 Sundar S, Balega J, Crosbie E, Drake A, Edmondson R, Fotopoulou C, et al. BGCS uterine cancer guidelines: Recommendations for practice.*Eur J Obstet Gynecol Reprod Biol* 2017;213:71-97.

47 Emons G, Steiner E, Vordermark D, Uleer C, Bock N, Paradies K, et al. Interdisciplinary Diagnosis, Therapy and Follow-up of Patients with Endometrial Cancer. Guideline (S3-Level, AWMF Registry Number 032/034-OL, April 2018) - Part 2 with Recommendations on the Therapy and Follow-up of Endometrial Cancer, Palliative Care, Psycho-oncological/Psychosocial Care/Rehabilitation/Patient Information and Healthcare Facilities. *Geburtshilfe Frauenheilkd*2018;78:1089-1109.

48 Cancer Genome Atlas Research N, Kandoth C, Schultz N, Cherniack AD, Akbani R, Liu Y, et al. Integrated genomic characterization of endometrial carcinoma. *Nature* 2013;497:67-73.

TABLE 1 Overall incidence, deaths, DALYs and EAPC from 1990 to 2019 by cervical cancer, uterine cancer and ovarian cancer in China

	Cervical cancer	Uterine cancer	Ovarian cancer
Incidence			
1990: No.$\times 10^3$	40.68 (30.92, 73.18)	24.28 (18.18, 29.96)	12.68 (9.91, 17.51)
ASIR per 10^5	8.41 (6.44, 15)	5.13 (3.89, 6.29)	2.56 (2, 3.58)
2019: No.$\times 10^3$	109.76 (58.19,141.54)	66.74 (51.38,92.05)	45.48 (33.11,57.38)
ASIR per 10^5	11.01 (5.87,14.22)	6.39 (4.89,8.74)	4.54 (3.33,5.71)
1990-2019: EAPC	1.61 (1.35,1.88)	1.26 (0.58,1.94)	1.88 (1.79,1.98)
Deaths			
1990: No.$\times 10^3$	26.42 (20.52, 43.53)	10.6 (7.95, 13.04)	8.04 (6.18, 11.67)
ASMR per 10^5	5.85 (4.59, 9.57)	2.38 (1.81, 2.9)	1.76 (1.36, 2.59)
2019: No.$\times 10^3$	53.44 (30.40,68.86)	12.22 (9.43,17.34)	29.10 (20.96,36.86)
ASMR per 10^5	5.13 (2.92,6.60)	1.17 (0.9,1.66)	2.77 (2.01,3.50)
1990-2019: EAPC	0.09 (-0.18,0.36)	-2.27 (-2.88,-1.66)	1.51 (1.42,1.61)

	Cervical cancer	Uterine cancer	Ovarian cancer
DALYs			
1990: No.$\times 10^3$	855.36 (654.48, 1432.99)	332.05 (238.02, 411.58)	275.06 (212.26, 377.97)
ASDR per 10^5	176.40 (135.68, 294.69)	69.61 (50.73, 85.85)	55.57 (42.86, 77.80)
2019: No.$\times 10^3$	1622.24 (892.58, 2090.86)	364.28 (286.56, 503.57)	835.06 (612.56, 1063.25)
ASDR per 10^5	157.50 (86.90, 202.91)	34.93 (27.27, 47.77)	80.52 (59.44, 102.57)
1990-2019: EAPC	0.16 (-0.09,0.41)	-2.21 (-2.81,-1.60)	1.15 (1.04,1.25)

Data in parentheses are 95% uncertainty intervals (UI). ASIR=age-standardized incidence rate. ASMR=age-standardized mortality rate. DALYs=disability-adjusted life years. ASDR=age-standardized DALY rates. EAPC=estimated annual percentage change.