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ORIGINAL ARTICLE

Reproductive health considerations in cervical cancer management: A nationwide analysis of epidemiological trends and histological shifts (1993-2017)

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ABSTRACT

Background: Comprehensive evidence regarding the longitudinal trends of cervical cancer (CC) incidence and its histological subtypes in China is limited, particularly concerning the growing clinical demand for reproductive health preservation. This study analyzed incidence patterns (2013-2017) and long-term trends (1993-2017) of CC and its subtypes across China. **Methods:** Data were extracted from the Cancer Incidence in Five Continents (CI5 XII) and CI5plus databases. Trends in age-standardized incidence rates (ASIRs) were analyzed using Joinpoint regression. A novel estimation model was developed to quantify the national and regional prevalence of patients potentially eligible for fertility-sparing surgery. **Results:** Between 2013 and 2017, approximately 67,053 new CC cases were diagnosed in China. From 1993 to 2017, the incidence of CC showed a pronounced upward trend (annual percent change [APC]: 7.06). While the incidence peaked in the 50-54 age group, the rising burden in younger cohorts highlights an urgent need for reproductive health considerations. Utilizing our novel fertility-sparing potential estimation model, we identified approximately 7544 patients theoretically eligible for fertility-sparing surgery during 2013-2017. Significant regional clustering of these candidates was observed in high-burden provinces such as Jiangsu and Zhejiang, emphasizing the substantial challenge of infertility risk among young patients. **Conclusion:** China faces a significant and increasing burden of CC with notable regional variations. There is an urgent need to implement a national, integrated prevention strategy that combines standardized Human Papillomavirus (HPV) vaccination and screening with tailored fertility preservation services. Addressing these reproductive health needs is critical to mitigating the long-term impact of CC, particularly for young women in high-prevalence regions.

Keywords: cervical cancer, reproductive health, histological subtype, incidence, fertility preservation

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INTRODUCTION

Cervical cancer (CC) remains a paramount global public health challenge, ranking as one of the most common gynecological malignancies and a leading cause of cancer-related mortality among women worldwide, particularly in developing regions.[1] Furthermore, it is the second most frequent cause of cancer-related mortality in women of reproductive age.[1] In 2022, the World Health Organization reported approximately 150,000 new cases of CC in China, accounting for roughly 22.7% of the global incident cases.[2] Moreover, CC was responsible for approximately 56,000 deaths during the same period.[2] In recent years, despite a downward trend in the ASIRs of CC globally, the incidence rate of CC in China has been continuously rising and notably shifting towards younger age groups.[3] The trend toward a younger age at diagnosis implies that an increasing number of patients retain reproductive desires at the time of clinical presentation. Consequently, balancing oncological outcomes with the preservation of fertility has become a critical challenge in clinical practice. Integrating fertility-sparing strategies is essential not only for treatment efficacy but also for the long-term quality of life of these patients. China, as the nation with the highest number of CC cases worldwide,[1] presents a substantial health challenge for its female population.

CC is histologically classified into two primary subtypes: squamous cell carcinoma (SCC) and adenocarcinoma. SCC is the most prevalent subtype, representing approximately 75% to 80% of all cases, while adenocarcinoma accounts for roughly 20%.[4] CC also includes less common subtypes, such as sarcomas and other rare tumors. These subtypes exhibit distinct characteristics in terms of etiology, screening effectiveness, and prognosis.[5,6] For instance, cigarette smoking has been identified as a significant risk factor for SCC, whereas its association with adenocarcinoma remains unclear, with some studies even suggesting a potential inverse relationship.[7] Additionally, the response to screening varies across histological subtypes of CC. While traditional Papanicolaou screening is effective in detecting precancerous lesions and early-stage SCC, lesions associated with adenocarcinoma, particularly those located in the endocervical canal, are more likely to be missed.[5] Prognostic outcomes also differ significantly between SCC and adenocarcinoma. Patients with adenocarcinoma who underwent definitive radiotherapy or concurrent chemoradiotherapy exhibited worse disease-free survival and overall survival compared to those with SCC receiving similar treatments.[8] Therefore, gaining insights into the various histological subtypes of CC facilitates the formulation of tailored treatment plans and the provision of more personalized prognostic guidance to patients, ultimately improving overall treatment outcomes and enhancing their quality of life.

In recent years, numerous scholars both domestically and internationally have utilized cancer registry reporting systems to obtain incidence and mortality data for CC research.[5,9,10] For instance, Gu and colleagues estimated the incidence and mortality rates of CC in China of 2015, utilizing the data from the National Central Cancer Registry. They revealed significant geographic disparities in CC incidence, with notably high rates observed in the Central and West regions, as well as in rural areas.[11] In addition, a study investigated the global incidence of CC according to histological subtypes, employing the Cancer Incidence in Five Continents (CI5) database covering the period 2008-2012.[5] The research indicated that SCC remained the primary subtype globally, while the incidence of adenocarcinoma exhibited significant regional variation. Despite the potential existence of regional variations in CC and its subtypes, there has been a notable lack of studies that have comprehensively investigated the incidence of CC and its subtypes across various provinces and administrative regions in China. Given the heterogeneity in histological subtypes and the limitations posed by the temporal distance of previous research, there is an urgent need for updated and comprehensive epidemiological data to gain a deeper understanding of the patterns and trends of CC overall and by histological subtypes in China.

This study aimed to conduct a comprehensive assessment of CC incidence overall and by histological subtypes, across various provinces and regions in China. Utilizing the latest CI5 dataset, we have elucidated the incidence patterns of CC and its histological subtypes across China, as well as within specific regions and provinces. Additionally, incidence trends for CC and its histological subtypes over a period from 1993 to 2017 were also analyzed. These findings may provide a deep understanding of the epidemiology of CC and offer critical insights to inform public health strategies aimed at mitigating the burden of this disease in China.

MATERIAL AND METHODS

Data sources

All data utilized in this analysis were extracted from the most recent CI5 database (Volume XII)[12] and the CI5plus database.[13] The CI5 series, published every five years since the 1960s by regional and national cancer registries worldwide, contained high-quality information on new cancer cases by registry, site, sex, 5-year age group, and histology (if available), together with age-specific populations. In this analysis, we obtained historical data (1993-2012) from the CI5plus database and the most recent data (2013-2017) from the CI5 database (Volume XII).

The incidence patterns of CC and its histological subtypes in China were analyzed at the national, regional, and provincial levels for the period 2013-2017, using registry data from Volume XII of the CI5 database. Trends in CC incidence and its subtypes were assessed across consecutive 5-year intervals from 1993-1997 to 2013-2017 for both China as a whole and individual provinces. Provinces included in the trend analysis were required to have at least 15 consecutive years of data (spanning 3 volumes) and include the most recent five-year period. Ultimately, data from 25 provinces were utilized for the pattern description, while 7 provinces met the criteria for inclusion in the trend analysis. The included registries in the CI5-XII and CI5plus databases represent a well-defined sample of the Chinese population, covering approximately 2.05% of the national population during the recent period. Although these datasets provide rigorous, quality-assured data, their coverage is predominantly concentrated in specific urban and developed regions.

Specifically, the pattern description encompasses 25 provinces and municipalities across 7 regions, including North (Beijing city, Hebei province, Shanxi province, Inner Mongolia Autonomous Region), Northeast (Heilongjiang province, Jilin province, Liaoning province), East (Anhui province, Fujian province, Jiangsu province, Jiangxi province, Shandong province, Shanghai city, Zhejiang province), Central (Henan province, Hubei province, Hunan province), South (Guangdong province, Guangxi Zhuang Autonomous Region), Southwest (Chongqing city, Sichuan province, Yunnan province), and Northwest (Gansu province, Qinghai province, Ningxia Hui Autonomous Region).[14] Trend analyses were conducted for the following provinces over the specified time periods: Beijing city (from 2003-2007 to 2013-2017), Guangdong province (from 1998-2002 to 2013-2017), Heilongjiang province (from 2006-2007 to 2013-2017), Hunan province (from 2003-2007 to 2013-2017), Sichuan province (from 2003-2007 to 2013-2017), Shanghai city (from 1998-2002 to 2013-2017), and Zhejiang province (from 1993-1997 to 2013-2017). It is worth noting that due to the subtype data of Heilongjiang province from 1998 to 2005 not being separated, the trend analysis for this province commenced in 2006. Similarly, data from Hubei province were excluded for the trend analysis due to the identical reason.[15] Concerning histology, CC were categorized as SCC, adenocarcinoma, sarcoma, and other tumors.[5]

Statistical analysis

The incidence rates (per 100,000 person-years) of CC and its various histological subtypes were calculated, stratified by both province and age group. Then the rates were adjusted using the Chinese population in 2000, namely the age-standardized incidence rate by the Chinese standard population (ASIRC) and Segi's world population, namely the age-standardized incidence rate by the world standard population (ASIRW).[16] To evaluate the changes in ASIRCs over time, the annual percent change (APC) or average annual percent change (AAPC) was calculated using Joinpoint Regression Program Version 5.3.0 (Statistical Methodology and Applications Branch, Surveillance Research Program, National Cancer Institute). APC assesses the internal trends, while AAPC estimates the overall average change trend across multiple intervals. When no joinpoint is observed, AAPC equals APC. Typically, detecting a single joinpoint requires 7-11 consecutive data observations.[17] However, this analysis included 5 consecutive observations from 1993-1997 to 2013-2017, thus, APC and 95% confidence intervals (CIs) were employed to characterize trends in ASIRCs over the 25-year period. Trends in ASIRCs of CC and its histological subtypes were plotted on a semi-log scale to facilitate the comparison of temporal trends across different provinces.[18] Additionally, the proportions of the ASIRC for each histological subtype relative to the overall ASIRC of CC were displayed graphically in bars across China, regions, and provinces. To further investigate the age distribution of CC by histological subtypes, age-specific incidence rates were calculated for 5-year age groups and plotted by subtypes on a semi-log scale.

Fertility-sparing potential estimation model

To evaluate the potential demand for fertility-sparing surgery (FSS) among young patients with cervical cancer, we developed a stratified estimation model based on clinical indications. This model aims to isolate the specific population theoretically eligible for fertility preservation from the overall epidemiological data.

The calculation formula is defined as follows:

$$N_{FSS\_i} = N_{\text{Total\_}{-i}} \times P_{\text{early}} \times P_{\text{eligible}}$$

In this formula, N_{FSS_i} represents the estimated number of patients in province i who are theoretically eligible for FSS; $N_{\text{Total\_i}}$ denotes the total number of new cervical cancer cases recorded in province i during 2013-2017 in our study. The parameters for the two core conversion factors are established as follows: Proportion of early-stage cases (P_{early}): Set at 25%. This parameter is based on statistical findings regarding the distribution of clinical stages of cervical cancer in China from recent multi-center retrospective studies, encompassing early-stage lesions from stage IA1 to IB1 according to the International Federation of Gynecology and Obstetrics (FIGO) staging system.[19] Proportion of patients meeting surgical indications ($P_{eligible}$): Set at 45%. This parameter is derived from the Guidelines for the Diagnosis and Treatment of Cervical Cancer in China (2022 Edition) and relevant international consensus, strictly selecting cases from the early-stage group that meet the criteria for Radical Trachelectomy (RT), such as tumor diameter ⩽ 2 cm, absence of lymphovascular space invasion (LVSI), and absence of pelvic lymph node metastasis.[20]

Based on these parameters, we utilized a composite coefficient of 11.25% ($P_{early} \times P_{eligible}$) to quantify the theoretical potential population in need of fertility protection across different provinces. This model aims to provide a reference for resource allocation and the construction of multidisciplinary team (MDT) consultations for gynecologic oncology centers through the clinical translation of epidemiological data.

It is critical to note that this formula evaluates the structural and clinical eligibility for FSS based strictly on staging and guidelines. It functions as a theoretical upper-bound estimate of potential candidates rather than an absolute indicator of real-world clinical demand, as individual reproductive intentions are not factored into this mathematical model.

RESULTS

Incidence of CC, 2013-2017

Table 1 presents the estimated nationwide numbers of new CC cases and the corresponding ASIRs of CC, along with these data in various geographical regions and provinces. We estimated that about 67,053 new cases of CC were diagnosed during 2013-2017 in China. The ASIRC and ASIRW of CC in China amounted to 11.91/100,000 and 10.92/100,000, respectively. Among the seven administrative regions, Central China showed the highest incidence rate (14.31/100,000 in ASIRC and 13.24/100,000 in ASIRW), followed by Northwest China (13.07/100,000 in ASIRC and 12.29/100,000 in ASIRW). North China exhibited the lowest incidence rates (7.95/100,000 in ASIRC and 7.30/100,000 in ASIRW).

Regarding specific provinces, Jiangxi province exhibited the highest ASIRs of CC, with 16.96/100,000 and 15.54/100,000 in the ASIRC and ASIRW, respectively, closely followed by the Guangxi Zhuang Autonomous Region (16.31/100,000 in ASIRC and 15.45/100,000 in ASIRW). Conversely, Beijing city recorded the lowest incidence for CC, standing at 6.84/100,000 in ASIRC and 6.15/100,000 in ASIRW (Table 1).

Trends in CC incidence, 1993-2017

During the period from 1993 to 2017, there was a notable surge in the ASIRC of CC in China, which experienced from 1.18 during the period of 1993-1997 to 11.91 in the span from 2013-2017 (APC: 7.06, 95% CI: 5.68, 8.85; Table 1; Figure 1, 2). Among the seven provinces analyzed, Heilongjiang Province emerged as the only province that recorded a decrease in ASIRC, while the other provinces demonstrated an upward trend, consistent with the national trend. The most pronounced increase was observed in Zhejiang province (APC: 12.10, 95% CI: 11.07, 18.44), followed by Hunan province (APC: 11.94, 95% CI: 11.49, 17.29). In comparison, the modest increases were observed in Shanghai (APC: 5.05, 95% CI: 2.21, 8.73), Guangdong province, (APC: 4.48, 95% CI: 1.57, 10.63), and Sichuan province (APC: 3.50, 95% CI: 3.21, 5.50; Figure 2).

Incidence of CC by histological subtypes, 2013-2017

Table 2 illustrates the incidence rates of four histological subtypes of CC in China, regions, and provinces. Additionally, Figure 3 depicts the proportion of ASIRC for each subtype relative to the overall ASIRC of CC. Among all subtypes, SCC consistently exhibited the highest ASIRC in most regions assessed. Nationally, the ASIRC for SCC was 7.55/100,000, accounting for 63.37% of all cases. Following SCC, other tumors ranked second with an ASIRC of 2.84/100,000, comprising 23.87% of the total. Additionally, adenocarcinoma and sarcomas exhibited ASIRCs of 1.50/100,000 (12.57%) and 0.02/100,000 (0.19%), respectively

From a regional perspective, Northeast China exhibited the highest incidence of SCC (9.56/100,000), accounting for 75.51% of the total ASIRCs of CC. Additionally, the ASIRCs of SCC in East China (7.89/100,000) and South China (7.81/100,000) were also notably high, accounting for 64.85% and 66.18% of their respective CC incidence rates. Intriguingly, Shanxi province had the highest ASIRC of SCC (12.57/100,000), which was situated in North China, a region that exhibited the lowest overall ASIRCs of SCC (5.22/100,000).

However, not all provinces exhibited the highest proportion of SCC cases among CC. Hubei province reported that other tumors constituted over 50% of CC ASIRCs, with the highest ASIRC of other tumors (6.87/100,000) among all provinces. Similarly, Ningxia Hui Autonomous Region (4.74/100,000) demonstrated an obvious higher proportion of other tumors, accounting for 44.76% of CC ASIRCs. Among all regions, the ASIRCs of other tumors in Central China (5.00/100,000), Northwest China (3.83/100,000), and Southwest China (3.38/100,000) were higher than the national level (2.84/100,000). The ASIRC in East China (2.75/100,000) was comparable to the national incidence, whereas North China showed the lowest ASIRC (1.53/100,000).

Table 1: Age-standardized cervical cancer incidence rates per 100,000 person-years from 1993-1997 to 2013-2017

Country/ Region/ Province	Historical period			Recent period (2013-2017)			APC (95% CI)
	Cases	ASIRC	ASIRW	Cases	ASIRC	ASIRW	
China	14 (1993-1997)	1.18	1.18	67,053	11.91	10.92	7.06 (5.68, 8.85)
North	—	—	—	5243	7.95	7.30	—
Beijing city	1217 (2003-2007)	5.48	4.51	1976	6.84	6.15	1.09 (-0.08, 2.34)
Hebei province	—	—	—	2266	9.17	8.52	—
Shanxi province	—	—	—	351	15.35	14.87	—
Inner Mongolia Autonomous Region	—	—	—	650	7.60	7.12	—
Northeast	—	—	—	4459	12.66	11.70	—
Heilongjiang province	86 (2006-2007)	3.41	3.03	481	11.93	11.24	-0.32 (-0.63, 4.22)
Jilin province	—	—	—	681	9.09	8.46	—
Liaoning province	—	—	—	3297	14.07	12.91	—
East	—	—	—	34,589	12.17	11.04	—
Anhui province	—	—	—	3513	15.37	14	—
Fujian province	—	—	—	970	15.50	14.52	—
Jiangsu province	—	—	—	14,685	12.55	11.56	—
Jiangxi province	—	—	—	654	16.96	15.54	—
Shandong province	—	—	—	3160	9.38	8.49	—
Shanghai city	200 (2002)	4.81	4.08	4998	9.88	8.73	5.05 (2.21, 8.73)
Zhejiang province	14 (1993-1997)	1.18	1.18	6609	13.77	12.42	12.10 (11.07, 18.44)
Central	—	—	—	10,925	14.31	13.24	—
Henan province	—	—	—	5154	14.62	13.53	—
Hubei province	—	—	—	4627	13.72	12.71	—
Hunan province	194 (2003-2007)	5.08	4.68	1144	15.92	14.69	11.94 (11.49, 17.29)
South	—	—	—	7741	11.80	11.05	—
Guangdong province	133 (1998-2002)	4.02	3.54	6070	11.00	10.29	4.48 (1.57, 10.63)
Guangxi Zhuang Autonomous Region	—	—	—	1671	16.31	15.45	—
Southwest	—	—	—	3436	12.53	11.54	—
Chongqing	—	—	—	1083	13.25	12.19	—
Sichuan province	128 (2003-2007)	8.12	7.84	1988	11.92	11.12	3.50 (3.21, 5.50)
Yunnan province	—	—	—	365	15.14	13.08	—
Northwest	—	—	—	660	13.07	12.29	—
Gansu province	—	—	—	212	12.78	12.32	—
Qinghai province	—	—	—	349	14.45	13.43	—
Ningxia Hui Autonomous Region	—	—	—	99	10.58	9.86	—

—, not available; APC, annual percent change; ASIRC, age-standardized incidence rate adjusted by the Chinese standard population in 2000; ASIRW, age-standardized incidence rate adjusted by world Segi's population; CI, confidence interval.

With respect to adenocarcinoma, the highest ASIRC was seen in Northwest China (1.85/100,000), with Gansu province (3.95/100,000), an integral part of this region, exhibiting the second-highest incidence among all provinces. Yunnan province ranked first in terms of ASIRC (4.78/100,000). Central China (1.82/100,000) also demonstrated a relatively high ASIRC. Conversely, the geographical area exhibiting the lowest ASIRC pertained to North China (1.17/100,000). Jilin province (0.67/100,000) specifically held the lowest ASIRC among all provinces. In addition, the ASIRC for sarcomas was remarkably low across China as well as all regions and provinces, consistently falling below 0.05 per 100,000 person-year, except for Yunnan province (0.06/100,000).

Trends in CC incidence by histological subtypes, 1993-2017

Over time, the ASIRCs of almost all subtypes in China have increased, with significant raise in SCC (APC: 6.75, 95% CI: 6.17, 7.62) and adenocarcinoma (APC: 6.00, 95% CI: 4.91, 12.15) (Supplementary Figure 1, 2). Regarding different provinces, the variations observed in SCC, adenocarcinoma, and other tumors aligned with the overall trends in China. Specifically, the most significant increase in the ASIRC for SCC was observed in Hunan province (APC: 18.44, 95% CI: 18.03, 25.02), followed by Zhejiang province (APC: 10.81, 95% CI:

Table 2: Age-standardized cervical cancer incidence rates per 100,000 person-years by histological subtypes, 2013-2017

Country/ Region/ Province	Squamous cell carcinoma			Adenocarcinoma			Sarcoma			Other tumors		
	Cases	ASIRC	ASIRW	Cases	ASIRC	ASIRW	Cases	ASIRC	ASIRW	Cases	ASIRC	ASIRW
China	42,293	7.55	6.93	8326	1.50	1.37	115	0.02	0.02	16,319	2.84	2.6
North	3390	5.22	4.78	769	1.17	1.08	16	0.02	0.02	1068	1.53	1.42
Beijing city	1266	4.56	4.06	294	1.05	0.95	3	0.01	0.01	413	1.21	1.13
Hebei province	1409	5.75	5.32	383	1.54	1.44	11	0.05	0.04	463	1.84	1.72
Shanxi province	289	12.57	12.22	22	0.95	0.87	0	0	0	40	1.83	1.78
Inner Mongolia Autonomous Region	426	4.93	4.64	70	0.83	0.81	2	0.02	0.02	152	1.83	1.66
Northeast	3374	9.56	8.86	407	1.20	1.09	6	0.02	0.02	672	1.89	1.74
Heilongjiang province	349	8.78	8.25	44	1.11	1.02	1	0.03	0.02	87	2.01	1.95
Jilin province	506	6.74	6.28	50	0.67	0.61	2	0.02	0.02	123	1.66	1.55
Liaoning province	2519	10.67	9.83	313	1.40	1.26	3	0.01	0.01	462	1.99	1.8
East	22,313	7.89	7.17	4258	1.51	1.36	43	0.02	0.02	7975	2.75	2.49
Anhui province	2254	9.77	8.98	254	1.14	1.02	6	0.04	0.03	999	4.43	3.98
Fujian province	485	7.74	7.31	104	1.66	1.54	0	0	0	381	6.10	5.67
Jiangsu province	8946	7.73	7.11	1866	1.56	1.45	11	0.01	0.01	3862	3.25	2.98
Jiangxi province	485	12.54	11.48	87	2.30	2.15	0	0	0	82	2.11	1.91
Shandong province	2181	6.57	5.91	415	1.23	1.11	7	0.03	0.02	557	1.56	1.44
Shanghai city	3385	6.85	6.06	660	1.30	1.14	10	0.02	0.02	943	1.70	1.51
Zhejiang province	4577	9.41	8.55	872	1.92	1.69	9	0.02	0.02	1151	2.42	2.16
Central	5650	7.46	6.89	1397	1.82	1.69	23	0.03	0.03	3855	5.00	4.63
Henan province	3085	8.81	8.13	805	2.27	2.12	13	0.04	0.03	1251	3.50	3.24
Hubei province	1820	5.41	5.02	484	1.42	1.32	9	0.03	0.03	2314	6.87	6.34
Hunan province	745	10.57	9.7	108	1.46	1.36	1	0.01	0.01	290	3.88	3.63
South	5117	7.81	7.36	984	1.54	1.41	17	0.03	0.02	1623	2.43	2.27
Guangdong province	4182	7.57	7.12	847	1.58	1.44	14	0.03	0.02	1027	1.83	1.7
Guangxi Zhuang Autonomous Region	935	9.24	8.79	137	1.34	1.23	3	0.03	0.03	596	5.70	5.41
Southwest	2071	7.53	6.97	416	1.59	1.43	10	0.03	0.03	939	3.38	3.11
Chongqing city	645	7.95	7.3	103	1.28	1.17	2	0.02	0.02	333	4.00	3.7
Sichuan province	1239	7.44	6.97	209	1.26	1.17	7	0.04	0.04	533	3.18	2.95
Yunnan province	187	7.41	6.48	104	4.78	4.05	1	0.06	0.04	73	2.89	2.51
Northwest	378	7.39	7.00	95	1.85	1.79	0	0	0	187	3.83	3.49
Gansu province	108	6.50	6.27	62	3.95	3.78	0	0	0	42	2.32	2.26
Qinghai province	220	9.06	8.47	23	0.90	0.87	0	0	0	106	4.50	4.09
Ningxia Hui Autonomous Region	50	4.89	4.83	10	0.96	0.95	0	0	0	39	4.74	4.08

ASIRC, age-standardized incidence rate adjusted by the Chinese standard population in 2000; ASIRW, age-standardized incidence rate adjusted by world Segi's population.

4.64, 48.90). For adenocarcinoma, the most notable surge in ASIRC was recorded in Zhejiang province (APC: 27.97, 95% CI: 8.58, 176.81), following Hunan province (APC: 9.44, 95% CI: 7.79, 25.56). Regarding other tumors, Sichuan province demonstrated the highest increase in ASIRC (APC: 27.08, 95% CI: 26.15, 55.40), and Guangdong province ranked second (APC: 10.57, 95% CI: 6.99, 23.27).

However, distinct from other subtypes, sarcomas demonstrated a declining trend across various provinces. Specifically, the ASIRCs of sarcoma exhibited significant decreases in Beijing city (APC: -11.41, 95% CI: -17.34, -6.48), Hunan province (APC: -8.02, 95% CI: -10.59, -0.21), and Guangdong province (APC: -6.68, 95% CI: -8.48, -4.85). Notably, certain histological subtypes in specific provinces exhibited exceptionally wide 95% confidence intervals. These wide intervals reflect the small absolute case numbers and limited statistical stability in earlier historical time points; therefore, these specific trend estimates should be interpreted with caution.

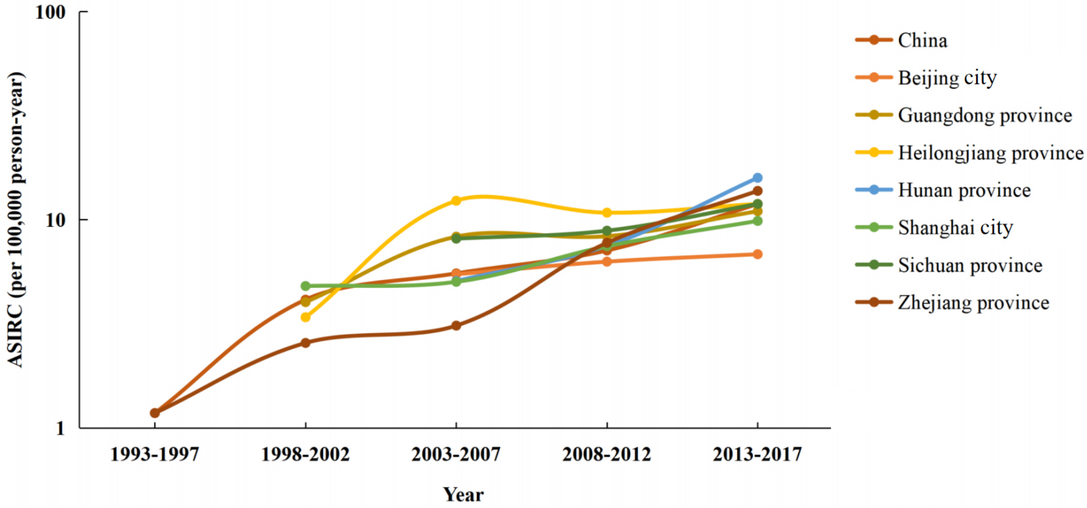

Figure 1. Trends in cervical cancer ASIRCs (per 100, 000 person-years) by China and provinces from 1993-1997 to 2013-2017. ASIRC, age-standardized incidence rate adjusted by the Chinese standard population in 2000.

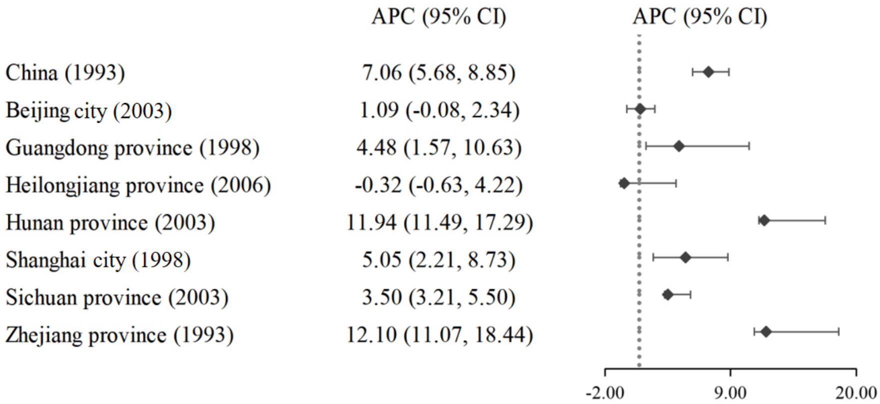

Figure 2. The annual percent change (APC) and 95% confidence interval (CI) in ASIRC of cervical cancer from 1993 to 2017. APC, annual percent change; ASIRC, age-standardized incidence rate adjusted by the Chinese standard population in 2000; CI, confidence interval.

Age-specific incidence of CC and histological subtypes, by age-groups

Figure 4 depicts the incidence rates of CC (per 100,000 person-years), stratified by age groups, across China and different regions. The incidence of CC in China and its various regions exhibited similar trends of initially rising and then declining. Within the age range of 0-24 years, the incidence was relatively low. Subsequently, it began to increase and peaked among women within the 50-54 age group. As age further increased, the incidence declined slightly.

Furthermore, SCC, adenocarcinoma, and other tumors all demonstrated a similar pattern to overall CC (Supplementary Figure 3). However, sarcoma, due to its extremely low incidence, exhibited fluctuating trends across China and seven regions.

Quantitative trends in potential candidates for fertility-sparing surgery (2013-2017)

Based on the fertility-sparing potential estimation model developed in this study, the total number of patients in China theoretically eligible for fertility-sparing surgery (Radical Trachelectomy, RT) between 2013 and 2017 was approximately 7544. As illustrated in Table 3, we quantified the scale of this specific patient population through a three-tier filtering process: starting from a total incidence of 67,053 cases, we identified early-stage

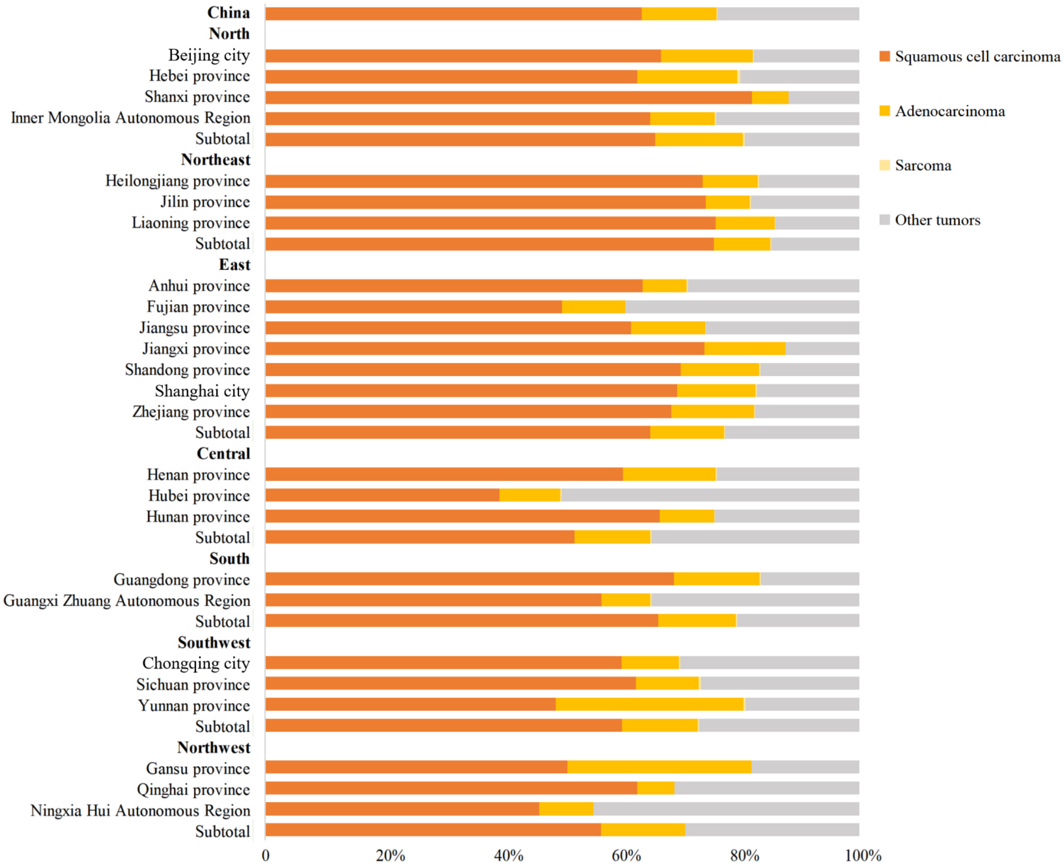

Figure 3. Proportion of the ASIRCs (per 100,000 person-years) of cervical cancer by histological subtypes across China, regions, and provinces, 2013-2017. ASIRC, age-standardized incidence rate adjusted by the Chinese standard population in 2000.

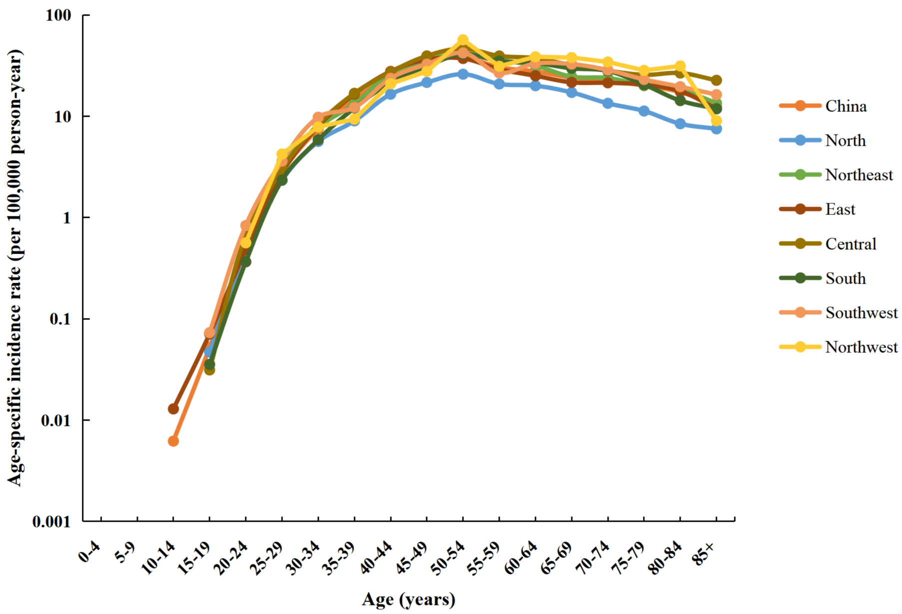

Figure 4. Age-specific incidence rate (per 100,000 person-years) of cervical cancer by 5-year age groups and regions, 2013-2017.

cases (FIGO stages IA1-IB1, approximately 25% of the total) and subsequently isolated those meeting clinical surgical indications (approximately 45% of early-stage cases). Although the overall incidence rate remained relatively stable, we observed a significant regional clustering of potential fertility-sparing needs in provinces with high cervical cancer burdens, such as Jiangsu (1652 cases) and Zhejiang (744 cases). These findings suggest that despite the partial containment of overall cervical cancer incidence in some regions, the population facing the crisis of potential infertility remains substantial due to the observed trend of early-onset disease, further highlighting the significant disparities in healthcare resource distribution across different regions.

DISCUSSION

Main findings

This population-based analysis provided the most recent estimations regarding the patterns and trends in the incidence of CC and its histological subtypes, across China, regions, and provinces. From 1993-1997 to 2013-2017, the incidence of CC experienced a significant increase. Additionally, the incidence of CC and its histological subtypes exhibited considerable variability across different regions. Notably, the incidence of CC and its subtypes, with the exception of sarcoma, predominantly peaked in the 50-54 age group.

Temporal trends of CC incidence in China

In recent years, China's rapid economic development has led to cumulative exposure to various risk factors, including younger age at sexual debut, unsafe sexual practices, and multiple sexual partners, thereby increasing the incidence of Human papillomavirus (HPV) infection.[21,22] HPV is a widespread sexually transmitted infection, with persistent infection by high-risk human papillomavirus (hrHPV) types being the primary cause of CC.[23] A population- or employee-based cervical screening study conducted across 37 Chinese cities in 2015[24] revealed that the overall positive rate for HPV among the participants was 21.07%, which exceeded the global average level of 11.7%.[25] On the other hand, convincing evidence suggests that Human Immunodeficiency Virus (HIV) infection also elevates the risk of CC.[26] As economically relatively developed provinces, Zhejiang and Hunan exhibit high population mobility,[27] which may contribute to a faster growth trend in HIV infection rates. Moreover, factors encompassing relatively liberal sexual attitudes and compromised immunity resulting from heightened work-related stress can potentially lead to a marked elevation in HPV infection rates.[28] These factors collectively contribute to a substantial increase in the incidence of CC in these regions, even exceeding the national growth rate.

Table 3: Estimated number of CC patients theoretically eligible for FSS by province in China, 2013-2017

Country/ Region/ Province	Number of new cases from 2013 to 2017	Estimated number of patients potentially requiring FSS
China	67,053	7543
North	5243	590
Beijing city	1976	222
Hebei province	2266	255
Shanxi province	351	39
Inner Mongolia Autonomous Region	650	73
Northeast	4459	502
Heilongjiang province	481	54
Jilin province	681	77
Liaoning province	3297	371
East	34,589	3891
Anhui province	3513	395
Fujian province	970	109
Jiangsu province	14,685	1652
Jiangxi province	654	74
Shandong province	3160	356
Shanghai city	4998	562
Zhejiang province	6609	744
Central	10,925	1229
Henan province	5154	580
Hubei province	4627	521
Hunan province	1144	129
South	7741	871
Guangdong province	6070	683
Guangxi Zhuang Autonomous Region	1671	188
Southwest	3436	387
Chongqing city	1083	122
Sichuan province	1,988	224
Yunnan province	365	41
Northwest	660	74
Gansu province	212	24
Qinghai province	349	39
Ningxia Hui Autonomous Region	99	11

CC, cervical cancer; FSS, fertility-sparing surgery.

Variations in patterns of CC incidence across different regions

The study revealed that incidence rates in Central and West regions were notably higher compared with those in East and North regions. Such notable geographical disparities may reflect differences in risk factors across regions, as well as significant inequalities in accessibility to adequate screening programs and effective cancer diagnostic facilities.[29]

Regions or provinces with higher HPV infection rates generally demonstrate correspondingly elevated CC incidence rates. For instance, regions encompassing Shanxi, Hubei, Hunan, and extending to Jiangxi province constitute a high-incidence belt for CC, where the prevalence of HPV infection, particularly hrHPV types, is also notably elevated.[30] Furthermore, the incidence of HPV infection in Southwest China surpasses that of East China, aligning with the observed patterns in CC incidence.[31,32] Interestingly, despite the fact that the HPV detection rate in Northeast China is among the highest nationwide, approximately 19.85%, the incidence of CC remains relatively low.[33] This may be attributed to the region's more comprehensive screening system, which facilitates timely detection and subsequent appropriate therapeutic interventions.[33] Furthermore, insufficient availability of medical resources and a lack of health awareness frequently pose obstacles to the universal implementation of CC screening programs in West regions, such as cervical cytology examination, HPV genotyping assays, and visual inspection with acetic acid, among others.[34] A population-based study investigated the knowledge of HPV among women in West China. Among the 1109 participants who completed the questionnaire, only 28.85% had heard of HPV. Within this subgroup, half of them knew that HPV could lead to CC, and only 26 individuals answered all questions related to HPV correctly.[34] Therefore, efforts should be dedicated to health education to enhance health awareness, thereby facilitating the promotion and popularization of screening programs.

In economically advanced regions such as Beijing and Shanghai cities, a significant number of women opt to receive HPV vaccine, owing to the abundance of medical resources and a robust health awareness.[35] Study indicated that during the period from 2018 to 2020, Beijing city and Shanghai city exhibited the highest full-course HPV vaccination rates, standing at 8.28% and 7.37%, respectively.[36] However, in economically less developed or remote areas, exemplified by Guangxi Zhuang Autonomous Region and Qinghai province, low vaccination rates, inadequate sexual education, and high HPV infection rates result in a higher incidence of CC.[35]

Although China has approved the HPV vaccination, yet to date, the vaccination coverage remains relatively low.[37] According to data spanning from 2017 to 2022, the first-dose vaccination rate among female individuals aged 9 to 45 years in China stands at a mere 0% to 10%, with the proportion completing the full three-dose regimen dropping significantly to a range of 0.01% to 6.21%. These figures fall far below the World Health Organization's target of achieving a 90% vaccination rate among eligible adolescent and young female populations.[38] A multi-center survey encompassing women aged 15-59 years from 21 urban and rural areas revealed that the level of knowledge regarding HPV among Chinese women was significantly limited, with only 34% of urban and 16% of rural women in the general population being aware of HPV vaccine.[39] Furthermore, a survey conducted across 14 schools in mainland China, involving over 4, 000 students, found that only 17.1% of the respondents had heard of the HPV vaccine.[40] Compelling evidence has unequivocally confirmed that vaccination programs targeting the most prevalent hrHPV strains have the potential to prevent approximately 87% of CC cases globally.[41] Therefore, in high-incidence areas, especially Central and West China, there is an urgent need to intensify health education efforts and enhance vaccination rates in order to decrease HPV infection rates, thereby effectively lowering the incidence of CC.

Variations in other risk factors, including socioeconomic status, educational attainment, smoking habits, sexual behaviors, and personal hygiene practices, are partly attributed to elevate the incidence of CC by increasing the risk of HPV infection indirectly.[7,42,43] Furthermore, in China, the phenomena of early marriage, early fertility, and high parity are notably prevalent, particularly in the Southwest and Northwest border areas.[44] These factors, can potentially cause trauma to the cervix, thereby elevating the risk of CC.[45,46] Typically, early marriage is often accompanied by a higher number of childbirths and a greater frequency of induced abortions.[45] Consequently, provinces with higher rates of early marriage, such as Guangxi Zhuang Autonomous Region, Qinghai province, and Yunnan province, exhibit relatively high incidence rates of CC, which may be partially attributable to these reproductive health factors.[47]

Variations in patterns of CC incidence by histological subtypes across different regions

The current study also uncovered regional variations in the distribution of histological subtypes of CC. This disparity may stem from the intricate interplay between CC carcinogenesis and implemented prevention strategies. The present analysis demonstrated that SCC remained the predominant subtype. A nationwide study conducted in the United States revealed that the incidence of SCC exceeded that of adenocarcinoma across all age groups, aligning with the findings observed in our study.[48]

Research has demonstrated that nicotine intake among chronic smokers impairs the body's immune system, hindering the clearance of HPV infections, thereby elevating the incidence of CC, especially SCC.[7,49] Specifically, regions such as Yunnan and Hunan provinces exhibit relatively high smoking rates, which may correlate with high SCC incidence.[50] Conversely, areas like Beijing and Shanghai cities, where smoking rates are comparatively lower, demonstrate correspondingly low SCC rates.[50] Additionally, the Pap smear test exhibits greater sensitivity in detecting precursor lesions of SCC.[5] Therefore, targeted interventions aimed at reducing smoking rates in these high-risk areas, along with promoting regular Pap smear screenings, could be pivotal in mitigating the burden of SCC.

In terms of adenocarcinoma, the relatively high incidence rates observed in Gansu and Yunnan provinces might be associated with prolonged use of oral contraceptives, leading to endocrine disruptions.[51] Studies have indicated that individuals who have taken oral contraceptives for over eight years faced nearly a twofold increased risk of CC, particularly the adenocarcinoma subtype.[51,52] Currently, DNA testing has been found to be of higher effectiveness in preventing adenocarcinoma than cytology-based testing.[53] A pooled analysis of four European randomized trials confirmed a larger gain for adenocarcinoma than for SCC with HPV testing as the primary screening strategy.[53] Consequently, the selection of technologies and methods for CC screening should be tailored in response to the subtype-specific incidence, serving as a vital public health investment. Additionally, the high incidence of other tumors in Fujian and Hubei provinces might be partly attributed to unfavorable lifestyle habits prevalent in these regions, such as irregular sleep patterns, imbalanced dietary intake, and insufficient physical activity.[54]

Age distribution of CC incidence in China

Numerous studies have demonstrated a trend towards a decreasing age demographic among individuals affected by CC in China, suggesting a shift towards younger populations.[55] This aligns with the findings of our research, which identified the peak age group as 50-54 years old. A global study examining trends in CC incidence has identified a disproportionate rise in incidence rates among younger women in various countries, including China.[56] This may be associated with various factors such as their early initiation of sexual activity, inadequate contraceptive practices, limited health knowledge, and unhealthy lifestyles, including insufficient sleep and imbalanced diets.[57,58]

HPV infection rates vary across different age groups. A multi-center cross-sectional study has demonstrated that the prevalence of hrHPV in China is particularly high among individuals aged below 25 years and those between 41 and 45 years, exhibiting two distinct peaks in infection rates.[59] Notably, young women under the age of 25 years typically possess a more robust immune system, which enables them to effectively eliminate HPV viruses, thereby preventing persistent infections that could progress to precancerous lesions or CC.[60] The second peak in HPV infection rates may be attributed to an increase in HPV exposure opportunities, alterations in the internal milieu of the female body, and modifications within the immune system.[59] Based on the natural progression of HPV-induced cervical carcinogenesis, a persistent HPV infection necessitates a natural evolution period of 10-20 years to develop into CC. Consequently, it is imperative for young women to undergo regular screening and take early prevention and control measures, encompassing the administration of HPV vaccines and sexual hygiene education.

Clinical significance and implications for fertility preservation

In this study, by constructing a quantitative estimation model, we have made a pioneering attempt to bridge the gap between national epidemiological surveillance data and individualized reproductive decision-making. Our findings indicate that thousands of young patients with cervical cancer in China are positioned at the critical intersection of oncological treatment efficacy and the desire for future fertility. Traditionally, epidemiological studies have focused primarily on incidence and mortality, often overlooking the urgent clinical demand for fertility preservation within the patient care pathway.[61]

According to our model, significant provincial variations—as illustrated in Table 3—reveal an inequitable distribution of fertility preservation resources across China. In regions characterized by a high incidence of cervical cancer and a higher proportion of young patients, standard screening and treatment protocols are insufficient. We propose that future prevention and control strategies should integrate fertility risk assessment into the routine clinical care pathway for all newly diagnosed young patients. Specifically, a MDT approach should be implemented at the time of diagnosis to comprehensively evaluate the balance between oncological safety margins and reproductive potential, thereby translating epidemiological data into precision medicine.[62] Furthermore, the establishment of a national registry for patients undergoing fertility-sparing treatment is essential. Such a platform would not only facilitate the validation of our estimation model but also provide high-quality, evidence-based data to support the formulation of reproductive health strategies tailored to young Chinese women. However, translating this theoretical model into clinical practice requires careful consideration of real-world psychosocial dynamics. In clinical reality, a patient's decision to undergo FSS is heavily multi-factorial, shaped by individual age, current parity, marital status, socio-economic flexibility, and fear of oncological recurrence. Consequently, the actual clinical demand for fertility-sparing procedures will inevitably be lower than the theoretical upper-bound generated by our epidemiological model.

Strengths and limitations

The strengths of the present study are rooted in its extensive data coverage and meticulous subtype analysis. Firstly, the study harnessed the CI5 database, which encompasses high-quality CC incidence data spanning five continents, offering a comprehensive overview of CC incidence patterns and trends on a national and regional scale. Secondly, the study not only analyzed the overall CC incidence across regions and provinces, but also conducted an in-depth exploration of the incidence patterns and temporal trends of various histological subtypes. These comprehensive analyses are pivotal for understanding the etiology and potential risk factors associated with specific subtypes and for tailoring targeted prevention and treatment strategies accordingly.

However, the study also has several limitations. A major constraint was the relatively small sample size in the trend analyses of specific subtypes for certain provinces, such as Heilongjiang, Zhejiang, and Sichuan, which may lead to instability in trend estimation and result in wide 95% CIs. Furthermore, given the instability in trend estimation for some histological subtypes due to sparse data, future efforts should consider more robust statistical alternatives, such as Bayesian models, to address this issue and enhance the reliability of trend analysis in regions characterized by low case counts.[63] Additionally, the provincial data were approximately estimated by aggregating the data from their corresponding cities, districts, and counties. However, certain provinces, such as Heilongjiang, Ningxia, and Qinghai, consisted of a limited number of cities or counties, potentially leading to underrepresentation in the dataset. Our fertility-sparing estimation model relies on fixed clinical coefficients and carries an implicit assumption that all clinically eligible patients possess the desire to preserve fertility, which oversimplifies real-world reproductive behavioral decision-making. Lastly, because the CI5 database selects high-quality, registry-specific data mostly from urban or selected areas, the population representativeness may be skewed, thereby limiting the generalizability of our nationwide extrapolations to the entire, highly diverse population of China, particularly in less-developed rural sectors.

CONCLUSION

Our research utilized the CI5 and CI5plus databases to delineate the most recent prevalent patterns and trends in CC incidence, thereby conducting a comprehensive assessment of the CC burden in China. From 1993-1997 to 2013-2017, China has undergone a pronounced upward trend in the incidence of CC. In Central and West regions of China, the ASIRs of CC were notably high. Conversely, North regions exhibited relatively low ASIRs. Among the various subtypes, SCC exhibited the highest proportion of CC. Except for sarcoma, various subtypes such as SCC and adenocarcinoma have exhibited similar trends in incidence as CC. The increased incidence rates of overall CC and subtypes in China may stem from HPV infection, vaccination practices, economic conditions, and health education initiatives. Integrating novel tools like hrHPV testing, cytology screening, and DNA methylation testing into comprehensive strategies may control CC's burden in China. In establishing national and regional prevention and control systems, it is essential to look beyond the reduction of incidence rates and incorporate "functional preservation" into a comprehensive management framework. Standardizing clinical pathways for fertility preservation in patients with cervical cancer is vital to transition from a sole focus on "curing cancer" to a more holistic model of comprehensive rehabilitation and the continuation of life.

DECLARATIONS

Supplementary information

Supplementary materials are only available at the official site of the journal (www.hksmp.com).

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None.

Author contributions

Hao L, Chen YH: Content concept development; Drafting documents. Shen Y: Article review; Edit. All authors contributed equally to this work.

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Ethical approval

This article is based on secondary analysis of publicly available aggregated data from the CI5 XII and CI5plus databases, published by the International Agency for Research on Cancer. As the data are de-identified and freely available for research purposes, no specific ethical approval was required for this study.

Informed consent

Not applicable.

Conflict of interest

The authors declare no competing interests.

Use of large language models, AI and machine learning tools

No artificial intelligence (AI) tools or large language models (LLMs) were used in the design, conduct, analysis, or writing of this study.

Data availability statement

The Cancer Incidence in Five Continents data is publicly available at: https://ci5.iarc.fr/Default.aspx.Processed datasets used in the analysis are available from the corresponding author upon reasonable request.

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