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Trend and survival outcome in Taiwan cervical cancer patients

A population-based study

Yi-Chuan Kau, MD, PhD[a,b], Fu-Chao Liu, MD, PhD[a,b], Chang-Fu Kuo, MD, PhD[b,c,d], Huei-Jean Huang, MD[b,e,f], Allen H. Li, MD, PhD[a,b], Mei-Yun Hsieh, BS[d], Huang-Ping Yu, MD, PhD[a,b,g,*]

Abstract

Cervical cancer is one of the most common cancers in Taiwan. The aim of this study was to estimate the incidence of cervical cancer in Taiwan, the relationship between cervical cancer and previous co-morbidities, and the long-term trend of cervical cancer mortality differences in the rest of the world.

This study was based on the data of cervical cancer in the National Health Insurance Research Database from 1997 to 2013, and estimated the annual prevalence and incidence of cervical cancer. Joinpoint regression analysis was used to obtain the percentage of annual incidence of cervical cancer, morbidity and survival of patients with cervical cancer by statistical regression analysis.

The average annual percentage change (APC) was −7.2, indicating a decrease in the incidence of cervical cancer during the study period. The 1-year, 2-year, and 5-year mortality rates of cervical cancer are relatively stable. The average APC of mortality was higher in high Charlson comorbidity index (CCI) group.

This study found that both of prevalence and incidence of cervical cancer descend in Taiwan. The incidence of cervical cancer in Taiwan is increasing with age. The sample survival rate was stable in cervical cancer patients during the study period.

Abbreviations: APC = annual percentage change, CCI = Charlson comorbidity index, HPV = human papilloma virus, ICD-9-CM = International Classification of Disease, Revision 9, NHIRD = National Health Insurance Research Database, NHRI = National Health Research Institutes.

Keywords: cervical cancer, epidemiology, population-based study, survival outcome

1. Introduction

Cervical cancer is the fifth most common cancer and the third common women's cancer in the world.[1] The incidence of cervical cancer is reduced by economic development.[2] Sub-Saharan Africa, South-east Asia, Latin America and the Caribbean, and Central and Eastern Europe have the highest rates of morbidity and mortality.[3] In the past, lots of Taiwan women suffered from cervical cancer. According to Taiwan's official data, both incidence (excluding carcinoma in situ) and mortality rate of cervical cancer are the seventh highest of all female cancer in Taiwan.[4]

Between 1980 and 2010, the cumulative probability of cervical cancer incidence for individuals aged 15 to 79 years in Taiwan (3.4 in 1980 and 1.8 in 2010) is much higher than worldwide average (2.3 in 1980 and 1.4 in 2010), even than the average in developing countries (2.6 in 1980 and 1.6 in 2010). The cumulative probability of cervical cancer death in Taiwan is reached to it in global average (0.7) in 2010.[5] The aim of this study was to use the National Health Insurance Research Database (NHIRD) to estimate the incidence of cervical cancer in Taiwan, the relationship between cervical cancer and previous co-morbidities, and the long-term trend in mortality from cervical cancer in the rest of the world.

2. Materials and methods

2.1. Data sources and research samples

Since March 1, 1995, all citizens in Taiwan have been required to join the National Health Insurance (NHI) system. The database of this system regularly collects health data for all NHI-compliant individuals, and our research data database, registered between 1997 and 2013, includes approximately 28 million samples. The NHI diagnostic coding system follows the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM). We identified patients with cervical cancer using the ICD-9-CM code of 179 and 180 in the registry. The denominator

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YCK and FCL contributed equally in this study.

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[a] Department of Anesthesiology, Chang Gung Memorial Hospital, Taoyuan, Taiwan, [b] College of Medicine, Chang Gung University, Taoyuan, Taiwan, [c] Division of Rheumatology, Allergy and Immunology, Chang Gung Memorial Hospital, Taoyuan, Taiwan, [d] Office for Big Data Research, Chang Gung Memorial Hospital, Taoyuan, Taiwan, [e] Department of Obstetrics and Gynecology, Chang Gung Memorial Hospital, Taoyuan, Taiwan, [f] Gynecologic Cancer Research Center, Chang Gung Memorial Hospital, Taoyuan, Taiwan, [g] Department of Anesthesiology, Xiamen Chang Gung Hospital, Xiamen, China.

[*] Correspondence: Huang-Ping Yu, Department of Anesthesiology, Chang Gung Memorial Hospital, 5 Fu-Shin Street, Kwei-Shan, Taoyuan, Taiwan 333 (e-mail: yuhp2001@adm.cgmh.org.tw).

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data is based on all women, with such characteristics as demographics, residency, income levels, and occupations included. This epidemiologic study was approved by the institutional review board of Chang Gung Memorial Hospital. The data used in this study were anonymized so the need for patient consent was waived.

2.2. Prevalence and incidence

The cases of cervical cancer are defined as individuals who had initially been diagnosed with cervical cancer within 10 years prior to each calendar year. The prevalence rate is the number of cases divided by the total number of women in the specified calendar year. Incidence refers to the number of new cases of cervical cancer during a calendar year divided by the number of people who are likely to suffer from cervical cancer in the same year.

2.3. Trend of incidence

In order to determine the trend of incidence, we calculated the age-standardized incidence of cervical cancer in each calendar year from 1997 to 2013. Joinpoint regression analysis was used to compare the mean annual percentage change (APC) of the incidence of cervical cancer during the study period.

2.4. Trends of mortality

In the specified calendar year, we calculated 1-, 2- and 5-year mortality rates for cervical cancer. Then our study samples were divided into 2 groups according to their Charlson comorbidity index (CCI), CCI $\leq$ 3 or CCI $\geq$ 4, to compare the trend in those mortality rates from 1997 to 2013.

2.5. Statistical analysis

Joinpoint regression program (version 4.0.4; National Cancer Institute, Bethesda, MD) was used to estimate the trend in the incidence of cervical cancer. The Bayesian information criterion is used to generate different "junction points" when the linear trend of the prevalence or incidence of the cancer changes significantly and the best fit is determined. The average APC is calculated for each segment. The significance level is set to 0.05. All statistical analyses were performed on SAS statistical software, version 9.3 (SAS Institute, Cary, NC).

3. Results

3.1. Clinical characteristics of patients with cervical cancer

This study enrolled 22,080,199 registered National Health Insurance (NHI) samples in Taiwan between 1997 and 2013. The total case number of cervical cancer is 37,678. The average age was 57.2 ± 14.3 years. The basic characteristics of the patients are listed in Table 1. The missing data of place of residence and income levels were 489 and 238, respectively. More than half of the patients live in urban areas; 31.96% and 10.71% of the patients live in suburban and rural areas respectively. For the income levels, the middle income class (Quintile 3: US $631–661) has the highest prevalence of 35.03%, followed by the lowest and then the highest income class. Therefore, the relationship between the prevalence of cervical cancer and the level of income is not linear in Taiwan. In comorbidities, the Charlson comorbidity index (CCI) values for most cervical cancer patients were 2 in 1997 which however became zero in 2013, implying that the relationship between cervical cancer and other pre-existing medical conditions is low.

Table 1

Clinical characteristics of patients with cervical cancer from 1997 to 2013.

		By calendar year		
	Cervical cancer cases (n = 37,678)	1997 (n = 3032)	2013 (n = 1410)	*P* value
Age (years) (mean ± SD)	57.2 ± 14.3	56.0 ± 13.7	58.0 ± 15.5	<.0001
Place of residence, No. (%)				<.0001
Urban	21,111 (56.03)	1596 (52.64)	823 (58.37)	
Suburban	12043 (31.96)	979 (32.29)	440 (31.21)	
Rural	4035 (10.71)	357 (11.77)	137 (9.72)	
Unknown	489 (1.3)	100 (3.3)	10 (0.71)	
Income levels, No. (%)				<.0001
Quintile 1 (US $ 30-513)	7661 (20.33)	560 (18.47)	311 (22.06)	
Quintile 2 (US $ 521–626)	4486 (11.91)	550 (18.14)	24 (1.70)	
Quintile 3 (US $ 631–661)	10676 (28.33)	1165 (38.42)	99 (7.02)	
Quintile 4 (US $ 691–908)	7167 (19.02)	204 (6.73)	600 (42.55)	
Quintile 5 (US $ 947–5985)	7450 (19.77)	497 (16.39)	369 (26.17)	
Unknown	238 (0.63)	56 (1.85)	7 (0.50)	
Occupation, No. (%)				<.0001
Dependents of the insured individuals	11151 (29.6)	758 (25)	478 (33.9)	
Civil servants, teachers, military personnel and veterans	800 (2.12)	55 (1.81)	36 (2.55)	
Non-manual workers and professionals	7000 (18.58)	631 (20.81)	249 (17.66)	
Manual workers	15,848 (42.06)	1433 (47.26)	481 (34.11)	
Other	2879 (7.64)	155 (5.11)	166 (11.77)	
Charlson index				<.0001
0	11,015 (29.23)	977 (32.22)	1232 (87.38)	
1	1351 (3.59)	21 (0.69)	10 (0.71)	
2	16,800 (44.59)	1835 (60.52)	61 (4.33)	
3	3350 (8.89)	130 (4.29)	38 (2.7)	
≥4	5162 (13.70)	69 (2.28)	69 (4.89)	
Mean of Charlson comorbidity index (mean ± standard deviation)	2.24 ± 2.57	1.49 ± 1.30	0.54 ± 1.83	

Table 2

Crude and standardized prevalence and incidence of cervical cancer from 1997 to 2013.

Year	Prevalence (per 100,000 population)			Incidence (per 100,000 person years)	
	N	Crude	Standardized	Crude	Standardized
1997	10,295,249	113.3 (111.3–115.4)	153.2 (150.4–156.0)	30.4 (29.4–31.5)	41.9 (40.4–43.5)
1998	10,364,360	133.1 (130.9–135.3)	176.9 (173.9–179.8)	32.9 (31.8–34.0)	44.8 (43.2–46.3)
1999	10,415,250	152.0 (149.6–154.3)	198.2 (195.1–201.4)	33.3 (32.2–34.4)	44.4 (42.8–45.9)
2000	10,472,943	171.9 (169.4–174.4)	221.3 (218.1–224.6)	30.5 (29.5–31.6)	39.7 (38.3–41.2)
2001	10,569,667	185.2 (182.6–187.8)	236.9 (233.6–240.2)	27.8 (26.8–28.8)	35.8 (34.5–37.2)
2002	10,579,175	196.5 (193.9–199.2)	248.7 (245.3–252.1)	24.0 (23.1–25.0)	30.5 (29.2–31.7)
2003	10,634,872	205.4 (202.7–208.1)	255.5 (252.1–258.9)	21.8 (20.9–22.7)	27.1 (26.0–28.3)
2004	10,750,148	213.8 (211.1–216.6)	261.8 (258.4–265.2)	21.7 (20.8–22.6)	26.2 (25.1–27.3)
2005	10,839,573	221.4 (218.6–224.2)	267.5 (264.1–270.9)	19.5 (18.7–20.3)	23.2 (22.1–24.2)
2006	10,921,783	227.0 (224.2–229.8)	270.0 (266.6–273.4)	17.1 (16.3–17.9)	20.1 (19.2–21.0)
2007	10,985,626	231.1 (228.2–233.9)	269.9 (266.5–273.2)	16.1 (15.4–16.9)	18.4 (17.5–19.3)
2008	11,047,306	234.1 (231.3–237.0)	267.6 (264.3–270.8)	15.9 (15.1–16.6)	17.8 (16.9–18.6)
2009	11,071,832	238.1 (235.3–241.0)	265.4 (262.2–268.6)	15.4 (14.6–16.1)	16.8 (16.0–17.7)
2010	11,108,703	240.7 (237.9–243.7)	261.4 (258.3–264.6)	14.5 (13.8–15.3)	15.6 (14.8–16.4)
2011	11,118,128	242.3 (239.4–245.2)	255.9 (252.8–258.9)	14.4 (13.7–15.1)	15.1 (14.3–15.8)
2012	11,123,311	244.2 (241.3–247.1)	251.0 (248.0–254.0)	13.2 (12.6–13.9)	13.5 (12.8–14.2)
2013	11,041,385	245.4 (242.5–248.3)	245.4 (242.5–248.3)	13.0 (12.4–13.7)	13.0 (12.4–13.7)

3.2. Prevalence and incidence of cervical cancer

Table 2 shows the prevalence and incidence of cervical cancer in Taiwan between 1997 and 2013. The age-adjusted standardized rate is higher than the crude estimate. In 1997, the prevalence was 153.2 per 100,000 persons, reaching a peak at 270.0 per 100,000 people in 2006, which then decreased yearly to 245.4 per 100,000 populations in 2013 (Fig. 1). The standardized incidence peaked at 1998, with a rate of 44.8 per 100,000 person year and then decreased yearly to 13.0 per person year in 2013 (Fig. 2). Figures 3 and 4 show the geographic variation in the prevalence and incidence of cervical cancer in Taiwan in 2013. Taipei City has a relative lower prevalence and incidence than the rural area in southern Taiwan (Pingtung County).

3.3. Regression analysis of prevalence and incidence of cervical cancer

Table 3 shows the results of regression analysis of the prevalence and incidence of cervical cancer. The average annual percentage change (APC) in incidence of cervical cancer is −7.2 per person per year (95% confidence interval, CI: −8.1 to −6.2, $P < .05$), indicating that the incidence of cervical cancer decreased over the study period. The average APC in prevalence is still a positive value, implying that the survival rate of cervical cancer is high. The optimal analogue connection point for calculating the incidence of cervical cancer was 2, and 3 divisions were observed within the study period: 2.2 persons per 100,000 person-years between 1997 and 1999, −10.7 persons per 100,000 person-years between 1999 and 2006, and −5.0 persons per

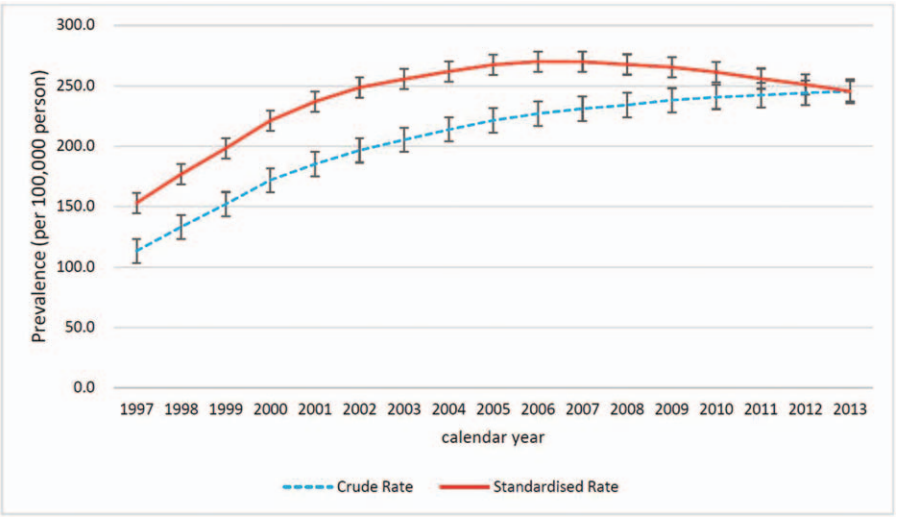

Figure 1. Trends of crude and standardized prevalence of cervical cancer in Taiwan from 1997 to 2013.

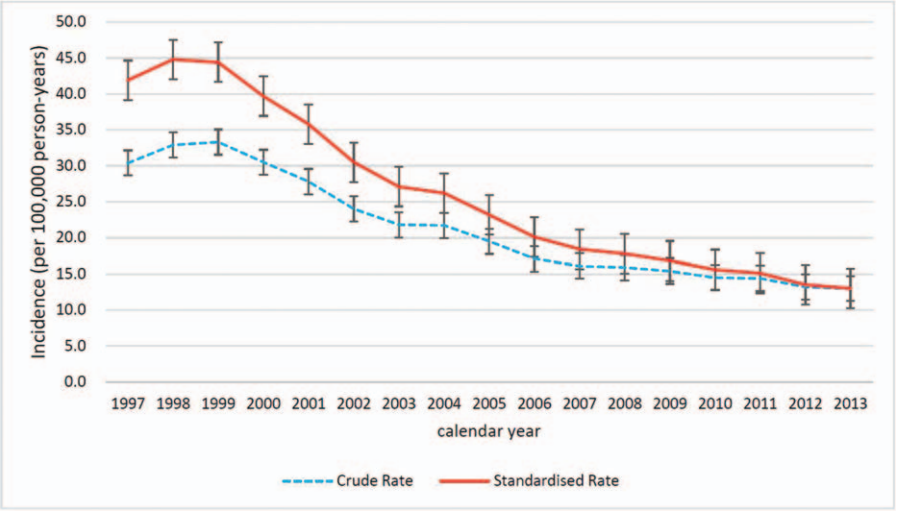

Figure 2. Trends of crude and standardized incidence of cervical cancer in Taiwan from 1997 to 2013.

100,000 person-years between 2006 and 2013. This suggests that the rate of decline slowed down after 2006. The age-specific prevalence and incidence of cervical cancer in 2013 are shown in Figure 5. Both of them increased with age.

3.4. Cervical cancer mortality

In Taiwan, the 1-year, 2-year, and 5-year survival rates of cervical cancer are relatively stable (Table 4), with an average APC rate of 0.3. The 1- and 5-year survival rates have improved in CCI $\geq$ 4 group following age-adjusted CCI. However, the trends of survival rates slightly decreased after 1999 for all the 1-, 2-, or 5-year intervals (Fig. 6). In view of the potentially significant impact of disease severity and patient complications on survival outcomes, we allocated our study samples into 2 groups according to their CCI. There was statistically significant difference between the CCI $\leq$ 3 group and the CCI $\geq$ 4 group. In the CCI $\geq$ 4 group, the survival rates increased from 1997 to 2000 and then declined slightly. However, there were no significant changes over time in the CCI $\leq$ 3 group (Fig. 7).

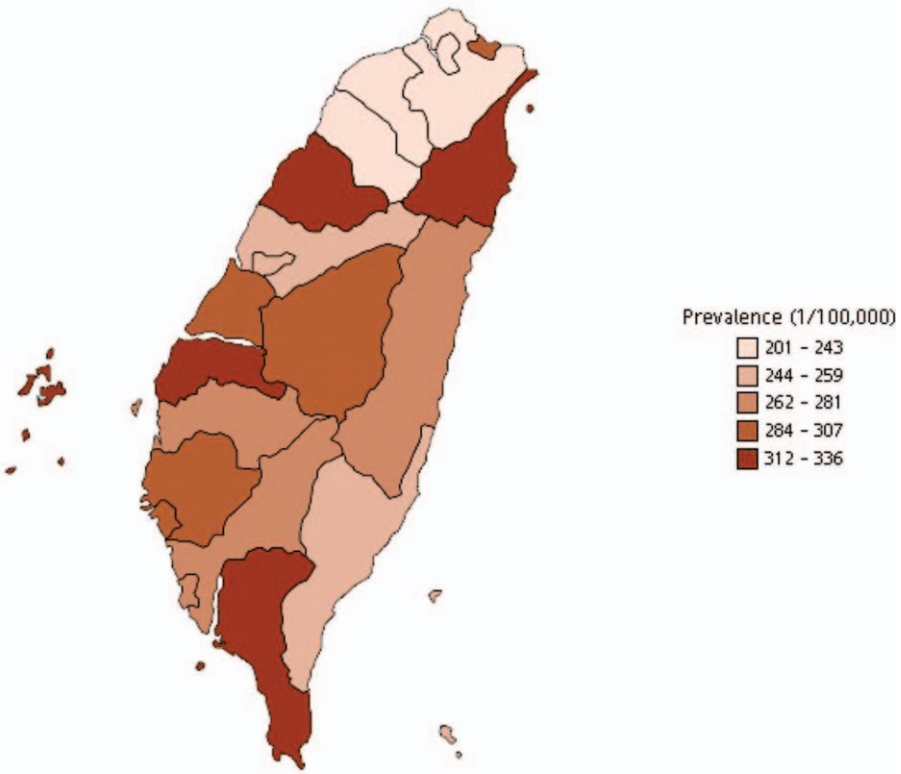

Figure 3. Geographic variation in the prevalence of cervical cancer in Taiwan in 2013.

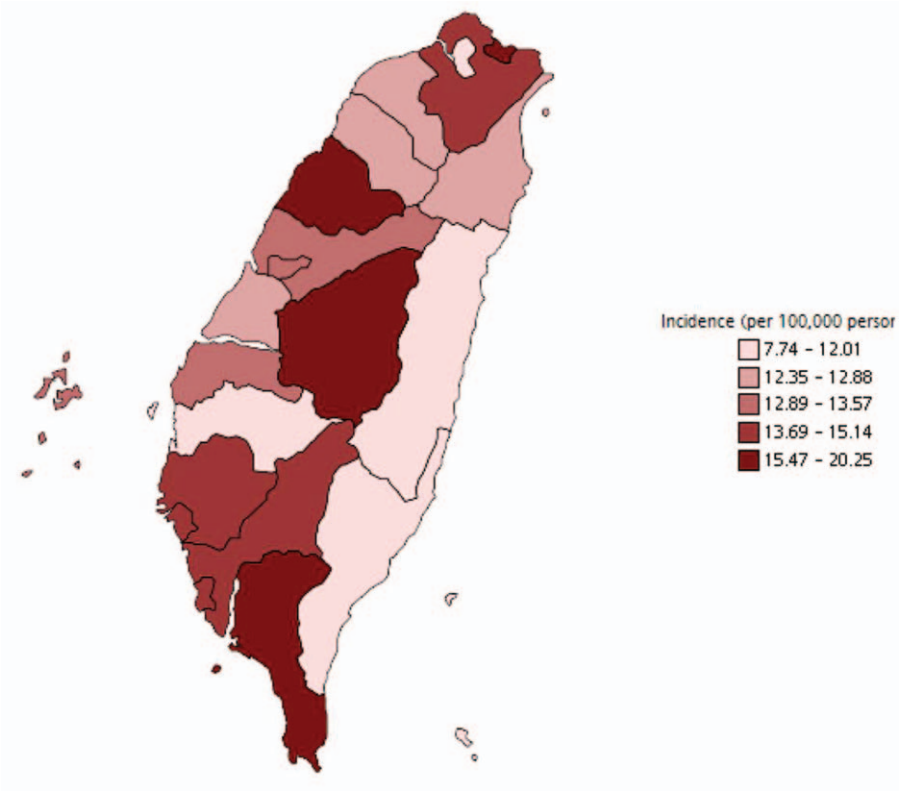

Figure 4. Geographic variation in the incidence of cervical cancer in Taiwan in 2013.

4. Discussion

Cervical cancer is the most common neoplasm for women of childbearing age in developing countries.[6] The reduction in the incidence of cervical cancer can be achieved by cervical smear screening.[7,8] Papanicolaou test (Pap smear) is the most scientifically proven screening tool in the world. Pap smear can be used to detect precancerous lesions or early asymptomatic cervical cancer, and studies have shown that large-scale Pap smear screening can reduce the incidence of 60% to 90% of cervical cancer and associated mortality.[9] The 5-years survival rate of early stage cervical cancer detected by Pap smear is close to 90%.[10]

In Taiwan, the NHI has paid for the Pap smear screening for women over 30 years old since 1995, which could explain the yearly decrease in morbidity after 1998.[11] The main reason of difference of prevalence and incidence of cervical cancer between Taiwan and developed countries is the lower Pap smear rate. The Pap smear rate is 69% 75% in developed countries.[12,13] Whereas the 3-year cumulative Pap smear rate in Taiwan was only around 54% from 2003 to 2015.[14] One study revealed that reasons for Taiwanese women avoiding Pap smear included fear of discomfort or pain, shyness, lack of medical knowledge, not feeling urgent, busyness, loss of confidence in Pap smear screening, feeling not possible to get cervical cancer, and not being able to face a bad result of Pap smear.[15] In many countries, cervical cancer is often diagnosed at 30 to 59 years old.[16–18] In our study, the incidence of cervical cancer in Taiwan increases with age. It might be caused by the lower percentage of elderly women receiving the Pap tests.[19] Taiwan will achieve a similar result of prevalence and incidence as in developing countries if a comparable Pap smear rate can be obtained. The promotion of the Pap smear thus increasing the Pap smear rate remains an important task for the government of Taiwan.

Table 3

Joinpoint analysis of cervical cancer prevalence and incidence in Taiwan, 1997–2013.

	1997	2013	Average APC	Segment 1 APC	Segment 2 APC	Segment 3 APC	Segment 4 APC
Cervical cancer prevalence (per 100,000 population)	153.2 (150.4–156.0)	245.4 (242.5–248.3)	3.0 (2.5 to 3.5)*	1997–2000 13.2 (11.6 to 14.8)*	2000–2003 4.9 (2.5 to 7.3)*	2003–2007 1.4 (0.3 to 2.4)*	2007–2013 −1.7 (−2.0 to −1.3)*
Cervical cancer incidence (per 100,000 person years)	41.9 (40.4–43.5)	13.0 (12.4–13.7)	−7.2 (−8.1 to −6.2)*	1997–1999 2.2 (−5.0 to 9.9)	1999–2006 −10.7 (−11.9 to −9.5)*	2006–2013 −6.0 (−7.2 to −4.8)*	

APC = annual percent change.
* $P < .05$.

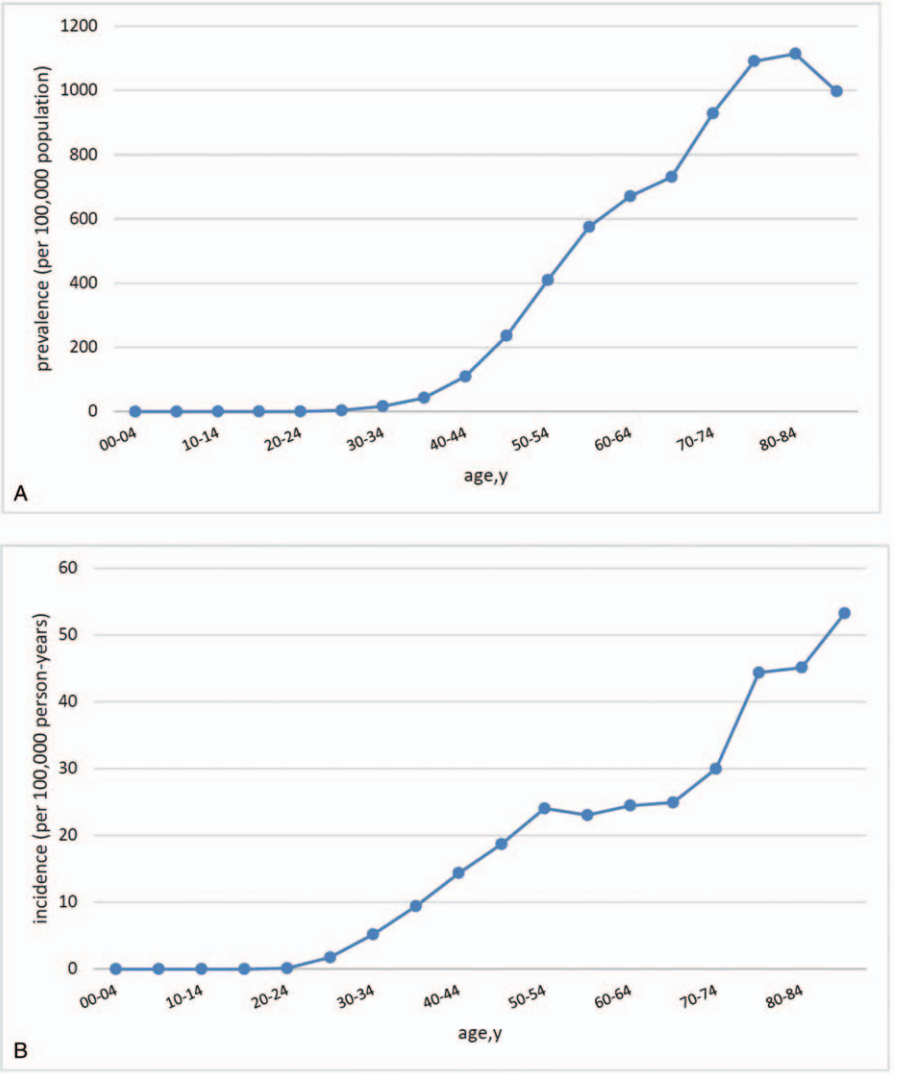

Figure 5. Age-specific prevalence (A) and incidence (B) of cervical cancer in Taiwan in 2013.

Human papilloma virus (HPV) infection can result in precancerous lesions, such as high grade dysplasia, which then increases the risk of cervical cancer.[20] HPV vaccination has been confirmed as the most pragmatic strategy for primary prevention of cervical cancer in the world.[21] Therefore, HPV vaccine is recommended especially for girls between the ages of 9 to 13 to prevent cervical cancer via reducing HPV infection.[22–24] In Taiwan, the quadrivalent and bivalent HPV vaccines have been available since 2006 and 2008. However, since there is a latency period of 10 to 15 years between HPV exposure and cervical cancer, a significant reduction of cervical cancer incidence cannot be found in our study.[25] Due to government support to give free HPV vaccination to young girls (9–15 years old), the decline in the prevalence and incidence of cervical cancer in Taiwan will be expected in the future.

Since the early detection and treatment of cervical cancer improves the survival rate, the prevalence rate was not reduced simultaneously in our study. The standard treatment for early stage and advanced stage of cervical cancer is radical hysterectomy with pelvic lymph nodes dissection and radiotherapy (or concurrent chemoradiotherapy), respectively.[26,27] There has been no promising improvement in treatment for cervical cancer over the past decade. On the analysis of cervical cancer mortality, a previous study showed that comorbid conditions were independent predictors of survival in women with either early or late stage cervical cancer.[28] However, comorbidities may serve as a barrier to participation in cervical cancer screening in the population with a high CCI.[29]

There are several limitations of our research. The NHIRD is a secondary database, and clinical information of staging or treatment of cancer can only be obtained from the Taiwan Cancer Registry Database (CRD). However, we have validated the National Cancer Registry as a highly accurate source for the diagnosis of cervical cancer and the correlation between NHIRD and CRD is high for the diagnosis of this cancer.[30] In addition, NHIRD includes 99.9% of Taiwan's population, while CRD has population coverage of 98.4% in 2012, indicating that these 2 databases complement each other. The epidemiological statistics showed the results of this study are consistent with the conclusions of previous studies. Third, NHIRD could not record the complete personal hobbies of the insured. The information of risk factors, likely for smoking habit, alcohol drinking, self-report

Table 4

Joinpoint analysis of cervical cancer survival rate in Taiwan, 1997–2013.

	1997	Last year	Average APC	Segment 1 APC	Segment 2	Segment 3	Segment 4
Total							
1-year survival rate	88.2 (87.0–89.3)	84.8 (82.0–87.2)	−0.3 (−0.6 to 0.1)	**1997–2000** 0.7 (0.001–1.4)*	**2000–2003** −0.8 (−2.3 to 0.7)	**2003–2006** 0.6 (−1.0 to 2.2)	**2006–2013** −0.9 (−1.2 to −0.6)*
2-year survival rate	79.8 (78.4–81.2)	76.8 (74.1–79.3)	−0.3 (−0.7 to 0.2)	**1997–1999** 2.2 (−1.1 to 5.6)	**1999–2012** −0.6 (−0.9 to −0.4)*		
5-year survival rate	68.8 (67.1–70.4)	66.4 (64.0–68.7)	−0.3 (−1.0 to 0.4)	**1997–1999** 3.1 (−1.2 to 7.5)	**1999–2009** −1.0 (−1.4 to −0.6)*		
CCI							
CCI ≤ 3							
1-year survival rate	89.0 (87.8–90.1)	85.3 (82.6–87.7)	−0.2 (−0.5 to 0.1)	**1997–1999** 1.3 (−0.7 to 3.2)	**1999–2006** 0.1 (−0.3 to 0.4)	**2006–2013** −0.8 (−1.3 to −0.4)*	
2-year survival rate	80.8 (79.3–82.1)	77.8 (75.0–80.3)	−0.1 (−0.4 to 0.3)	**1997–2000** 2.0 (0.3 to 3.6)*	**2000–2012** −0.6 (−0.9 to −0.3)*		
5-year survival rate	69.9 (68.2–71.5)	70.9 (68.2–73.3)	0.2 (−0.4 to 0.7)	**1997–1999** 4.2 (0.6 to 7.9)*	**1999–2009** −0.6 (−0.9 to −0.3)*		
CCI ≥ 4							
1-year survival rate	55.1 (42.6–65.9)	74.7 (58.1–85.5)	1.4 (−0.2 to 3.0)	**1997–2000** 11.0 (1.4 to 21.6)*	**2000–2013** −0.7 (−1.2 to −0.2)*		
2-year survival rate	40.6 (29.0–51.8)	61.8 (49.0–72.3)	1.2 (−1.0 to 3.6)	**1997–2000** 12.8 (−0.3 to 27.6)	**2000–2012** −1.5 (−2.1 to −0.8)*		
5-year survival rate	18.8 (10.7–28.8)	46.6 (40.8–52.2)	−1.0 (−3.0 to 1.1)				
Age-adjusted CCI							
CCI ≤ 3							
1-year survival rate	85.0 (81.7–88.3)	90.0 (85.1–95.0)	0.2 (−0.3 to 0.7)	**1997–2005** 0.2 (−0.2 to 0.6)	**2005–2011** −0.9 (−1.7 to −0.2)*	**2011–2013** 3.7 (0.1 to 7.5)*	
2-year survival rate	79.4 (76.2–82.6)	81.4 (76.7–86.0)	0.1 (−0.5 to 0.7)	**1997–2000** 1.7 (−0.4 to 3.8)	**2000–2010** −0.8 (−1.2 to −0.4)*	**2010–2012** 2.2 (−1.9 to 6.5)	
5-year survival rate	70.0 (67.0–72.9)	71.5 (67.5–75.6)	−0.01 (−0.7 to 0.7)	**1997–1999** 3.2 (−1.6 to 8.3)	**1999–2009** −0.7 (−1.0 to −0.3)*		
CCI ≥ 4							
1-year survival rate	61.9 (59.1–64.7)	87.9 (83.0–92.8)	2.0 (0.6 to 3.5)*	**1997–1999** 12.7 (4.2 to 21.9)*	**1999–2007** 0.01 (−1.0 to 1.1)	**2007–2011** −2.4 (−6.1 to 1.5)	**2011–2013** 9.1 (0.9 to 18.0)*
2-year survival rate	51.2 (48.7–53.7)	74.4 (70.0–78.9)	1.8 (−0.01 to 3.6)	**1997–1999** 19.0 (3.2 to 37.3)*	**1999–2012** −0.6 (−1.4 to 0.1)		
5-year survival rate	36.3 (34.1–38.4)	56.9 (53.2–60.5)	3.6 (1.2 to 6.1)*	**1997–1999** 28.7 (10.23 to 50.2)*	**1999–2009** −0.8 (−1.9 to 0.5)		

APC, annual percent change.
* $P < .05$.

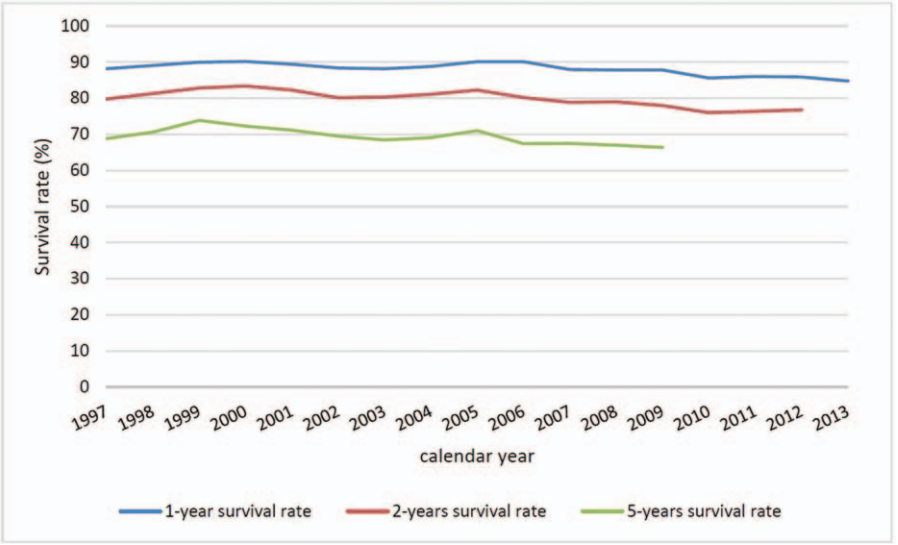

Figure 6. Trends of one, 2, and 5-year survival rates of cervical cancer in Taiwan from 1997 to 2013.

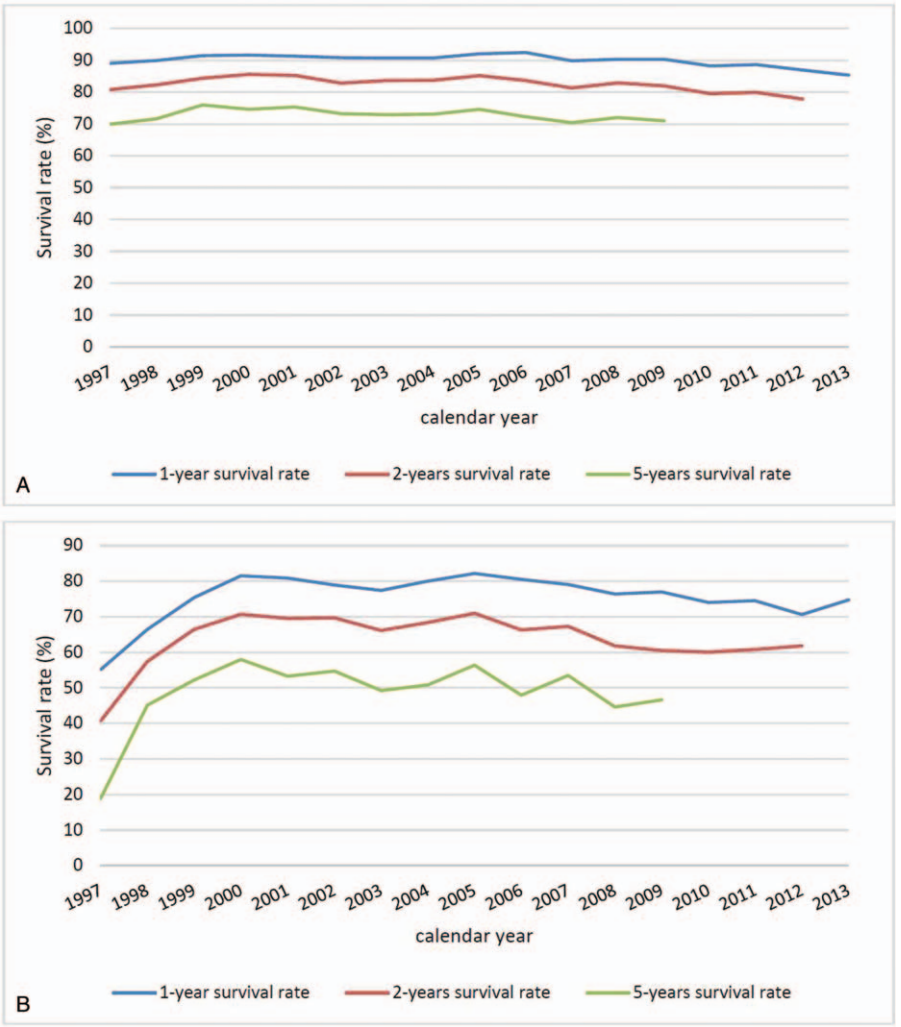

Figure 7. Trends of one, 2, and 5-year survival rates of cervical cancer according to Charlson index ((A): Charlson index ≤ 3; (B): Charlson index ≥ 4) in Taiwan from 1997 to 2013.

exposure is also a limitation of this study. Finally, this study reports prevalence over 10 years, rather than lifetime prevalence, and we may have underestimated the prevalence of cervical cancer, but overestimated its incidence.

5. Conclusion

In summary, this large-population based study found that both prevalence and incidence of cervical cancer had been declining in Taiwan. The incidence of cervical cancer in Taiwan increases with age. The survival rate was stable in our sample of cervical cancer patients during the study period. By increasing the HPV vaccination rate and providing effective screening and treatment, it is expected that, in the near future, the incidence and mortality rate of cervical cancer in Taiwan will be reduced to the global average.

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Author contributions

Contributions: Conception and design: F-CL, H-PY; Acquisition of data: F-CL, Y-CK; Data analysis and interpretation: C-FK, F-CL, Y-CK, H-PY, H-JH, M-YH; Manuscript drafting and critical revising: F-CL, Y-CK, AH-L, H-PY; Final approval of manuscript: All authors.

Conceptualization: Fu-Chao Liu, Huang-Ping Yu.
Data curation: Yi-Chuan Kau, Fu-Chao Liu, Mei-Yun Hsieh.
Formal analysis: Yi-Chuan Kau, Fu-Chao Liu, Chang-Fu Kuo, Mei-Yun Hsieh.
Funding acquisition: Huang-Ping Yu.
Methodology: Chang-Fu Kuo.
Resources: Chang-Fu Kuo.
Software: Chang-Fu Kuo.
Supervision: Huei-Jean Huang, Huang-Ping Yu.
Writing – original draft: Yi-Chuan Kau, Fu-Chao Liu, Huang-Ping Yu.

Writing – review & editing: Yi-Chuan Kau, Fu-Chao Liu, Chang-Fu Kuo, Huei-Jean Huang, Allen H Li, Huang-Ping Yu.

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