Adjunctive Chinese Herbal Medicine Treatment is Associated With an Improved Survival Rate in Patients With Cervical Cancer in Taiwan: A Matched Cohort Study

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Abstract

Background: Cervical cancer is one of the most common cancers in Taiwan. Some patients take Chinese herbal medicine (CHM). However, very few current studies have ascertained the usage and efficacy of CHM in patients with cervical cancer. The aim of this study was to investigate the benefits of complementary CHM among patients with cervical cancer in Taiwan. **Methods:** We included the newly diagnosed cervical cancer patients who were registered in the Taiwanese Registry for Catastrophic Illness Patients Database between 2000 and 2010. The end of follow-up period was December 31, 2011. Patients who were less than 20 years old, had missing information for age, withdrew from the National Health Insurance (NHI) program during the follow-up period, or only received other TCM interventions such as acupuncture or tuina massage were excluded from our study. After performing 1:1 frequency matching by age and index date, we enrolled 7521 patients in both CHM and non-CHM user groups. A Cox regression model was used to compare the hazard ratios (HRs) of the risk of mortality. The Kaplan-Meier curve was used to compare the difference in survival time. **Results:** According to the Cox hazard ratio model mutually adjusted for CHM use, age, comorbidity, treatment, and chemotherapeutic agents used, we found that CHM users had a lower hazard ratio of mortality risk (adjusted HR = 0.29, 95%CI = 0.27-0.31). The survival probability was higher for patients in the CHM group. Bai-Hua-She-She-Cao (*Herba Oldenlandiae*, synonym *Herba* Hedyotis diffusae) and Jia-Wei-Xiao-Yao-San were the most commonly prescribed single herb and Chinese herbal formula, respectively. **Conclusions:** Adjunctive CHM may have positive effects of reducing mortality rate and improving the survival probability for cervical cancer patients. Further evidence-based pharmacological investigations and clinical trials are warranted to confirm the findings in our study.

Keywords

cervical cancer, Chinese herbal medicine, integrative medicine, real-world evidence, traditional Chinese medicine, survival rate

Introduction

Cervical cancer is the third most commonly occurring cancer in women worldwide according to the latest global report. It accounted for 569 847 new cases and 311 365 cases of cancer-related mortality globally in 2018.[1] In Taiwan, the incidence of cervical cancer used to be fairly high, even exceeding the worldwide average.[2,3] Owing to Pap smear screening program implemented by Health Promotion Administration (HPA) since 1995, the early diagnosis rate and mortality rate of invasive cervical cancer have improved.[4,5] Based on the recent Taiwan's official data, the incidence (excluding carcinoma in situ) and mortality rate of cervical cancer in 2016 were 12.11 and 5.36 per 100 000 population respectively.[6] Despite current multidisciplinary treatment strategies for cervical cancer including surgery, radiation therapy and chemotherapy,[7] disease stage is still regarded as the most important prognostic

factor affecting survival for women with cervical cancer.[8] The 5-year survival rate sharply declined with stage on the basis of statistics from the American Cancer Society.[9]

Cervical cancer undoubtedly is a significant health burden not only on cancer survivors but also on all of society.[10] For patients accepting conventional treatments, they often have to endure treatment-induced side effects, complications, and cumulative organ toxicities, which have negative impacts on the quality of life (QOL).[11] For worldwide societies, cervical cancer leads to considerable disability, premature death and enormous financial cost, thus exacerbating the cycle of poverty.[10] Interestingly, previous study revealed that the lower household income, the worse the QOL of cervical cancer survivors.[12] Therefore, combinations of conventional treatments with effective and economic therapies are urgently being investigated to improve clinical response and survival rate.

Chinese herbal medicine (CHM), a key treatment modality of traditional Chinese medicine (TCM), has been practiced for thousands of years among Chinese communities. It has also been widely applied for adjuvant cancer treatment in Asian countries due to its anticancer effects proven by clinical response and evidence.[13,14] Recently, more and more literature indicated that CHM could enhance immunomodulatory activities,[15,16] inhibit carcinogenic properties,[17] prolong survival time,[18-22] alleviate side effects of chemotherapy and radiotherapy,[13] and improve the quality of life[12] in cancer patients.

However, very few studies have put emphasis on the mortality rate of complementary utilization of CHM in patients with cervical cancer. One recently published meta-analysis included only 1 CHM clinical trial on patients diagnosed with cervical cancer. It is observed that the additional use of CHM significantly improved 1-year survival rate in cervical cancer patients.[23] Overall, for cervical cancer patients, at present there is insufficient evidence to conclude the effectiveness of CHM in prolonging long-term survival. Thus, we conducted this nationwide population-based retrospective cohort study in order to investigate the outcomes of CHM users with cervical cancer in Taiwan.

Materials and Methods

Data Sources

We used the Registry for Catastrophic Illness Patients Database (RCIPD), a part of the National Health Insurance Research Database (NHIRD) from the National Health Research Institutes in Taiwan, to perform this nationwide population-based cohort study. In Taiwan, the National Health Insurance (NHI) program was established in 1995. It covered more than 99% of the total population[24] and reimbursed western medical services as well as TCM services. All claims data, including de-identified (eg, sex and age) and clinical information (eg, diagnostic codes based on the International Classification of Disease, 9th Revision, Clinical Modification [ICD-9-CM], health management and treatment), has been collected in the large computerized NHI database (NHIRD). RCIPD was then established by NHIRD, which enrolled all of the patients with catastrophic illness including 30 disease categories such as cancer, systemic autoimmune disease, and cerebral palsy. Registered cancer patients with catastrophic illness certificates are able to receive TCM or Western medical care without co-payment.

Our study acquired the data on cervical cancer patients from the RCIPD according to ICD-9-CM code 180. We included patients who were newly diagnosed with cervical cancer between January 2000 and December 2010 in Taiwan. The end of follow-up period was defined as December 31, 2011. Patients who were less than 20 years old, had missing information for age, withdrew from the NHI program during the follow-up period, or only received other TCM modalities such acupuncture or tuina massage were excluded from our study.

We defined CHM users as those had received CHM treatment after a confirmed diagnosis of cervical cancer. The index date was defined as the first time that patients received CHM treatment. We randomly assigned a date between the date of the diagnosis and the endpoint as the index date for the control group. The immortal time was referred to the period from the initial diagnosis of cervical cancer to the index date. We also used 1:1 frequency

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matching by age and index date to compare CHM users and non-CHM users.

Study Variables

We classified the patients into 3 groups by age: 20 to 39, 40 to 64, and more than 65 years old in order to investigate the differences among the various age groups. The comorbidities of these patients were determined by the following ICD-9-CM codes: diabetes mellitus (DM, ICD-9-CM 250), hypertension (ICD-9-CM 401–405), chronic kidney disease (CKD, ICD-9-CM 580–589), coronary artery disease (CAD, ICD-9-CM 414), chronic obstructive pulmonary disease (COPD, ICD-9-CM 490–496), cirrhosis (ICD-9-CM 571), and hyperlipidemia (ICD-9-CM 272). We also identified the patients who received hysterectomy for cervical cancer by treatment code.

Ethical Considerations

All of the datasets were de-identified and encrypted to protect enrollees' privacy before being released for research. There was no possibility to identify individual patients from them. This study was approved by the Research Ethics Committee of China Medical University and Hospital, Taichung, Taiwan (CMUH104-REC2-115).

Statistical Analysis

In this study, SAS 9.4 (SAS Institute Inc., Cary, NC) was used for statistical analysis. For categorical variables, chi-square was used to identify the differences between CHM and non-CHM groups. For continuous variables, the independent t test was applied. Cox proportional hazard regression analysis with 95% confidence interval (CI) was performed to estimate crude and adjusted hazard ratios (HRs) of CHM use, age, comorbidity, conventional treatment, and specific chemotherapeutic agents used. We also used the Kaplan-Meier method to estimate the survival curves and the log rank test to evaluate the differences in survival time between 2 groups. A *P* value <.05 was considered statistically significant.

Results

Overall, between 2000 and 2011, there were 14 672 newly diagnosed patients with cervical cancer who have ever received CHM treatment after being confirmed diagnosis of cervical cancer. After performing 1:1 frequency matching by age and index date, which referred to the initial time of CHM use in CHM group, we included 7521 patients in both CHM and non-CHM user group (Figure 1). Clinical characteristics of the patients are listed in Table 1. The mean age of CHM and non-CHM user group were 57.6 and 57.9 respectively.

CHM user group had higher percentage of comorbidities with coronary artery disease, chronic obstructive pulmonary disease and cirrhosis than non-CHM user group (*P* < .05). No significant difference was found in other comorbidities and treatments between 2 groups. The mean and median follow-up time of CHM user group were significantly longer than non-CHM user group (CHM user group: 4.15 and 3.15 years, non-CHM user group: 2.10 and 2.33 years).

According to the Cox hazard ratio model mutually adjusted for CHM use, age, comorbidity, treatment, and chemotherapeutic agents used, we found that CHM users had a lower hazard ratio of mortality risk (adjusted HR = 0.29, 95% CI = 0.27-0.31) (Table 2). The mortality risk in ≥65-year-old group (adjusted HR = 2.40, 95% CI = 2.10-2.73) was significantly increased at more than twice that in the 20- to 39-year-old group. Patients with comorbidities including DM (adjusted HR = 1.34, 95% CI = 1.23-1.45) and CKD (adjusted HR = 1.77, 95% CI = 1.64-1.91) had higher mortality risk. We also found that patients receiving not only chemotherapy (adjusted HR = 1.74, 95% CI = 1.49-2.04) but also radiotherapy (adjusted HR = 1.31, 95% CI = 1.16-1.48) had higher hazard ratio.

Based on the Kaplan-Meier curves, we found that the survival probability was higher for patients in the CHM group than for those in the non-CHM group (Figure 2). In Table 3, CHM users regardless of age, comorbidity and conventional treatment options had lower mortality risk than non-CHM users.

Among the patients included, 7521 of them used CHMs after a confirmed diagnosis of cervical cancer. We identified the most commonly prescribed CHMs, which are shown in detail in Table 4. For single herbs, Bai-Hua-She-She-Cao (*Herba Oldenlandiae*, synonym *Herba* Hedyotis diffusae) was the most commonly used, followed by Da-Huang (*Radix et Rhizoma Rhei*) and Ban-Zhi-Lian (*Herba Scutellriae Barbatae*). For herbal formula, Jia-Wei-Xiao-Yao-San was the most commonly used, followed by Ma-Zi-Ren-Wan and Bu-Zhong-Yi-Qi-Tang. In addition, the highest dose of prescribed single herb and herbal formula were Dan-Shen (*Radix Salviae Miltiorrhizae*) and Xiang-Sha-Liu-Jun-Zi-Tang, respectively.

Discussion

Our study mainly found that integrative CHM treatment may be beneficial for patients with cervical cancer. Regardless of age, comorbidity, and conventional treatment options, CHM users had much lower mortality risk than non-CHM users. The survival probability was higher for patients in the CHM group. Our findings were partially in accordance with a previous systematic review which reported that additional CHM treatment improved patients' 1-year survival rate significantly when compared
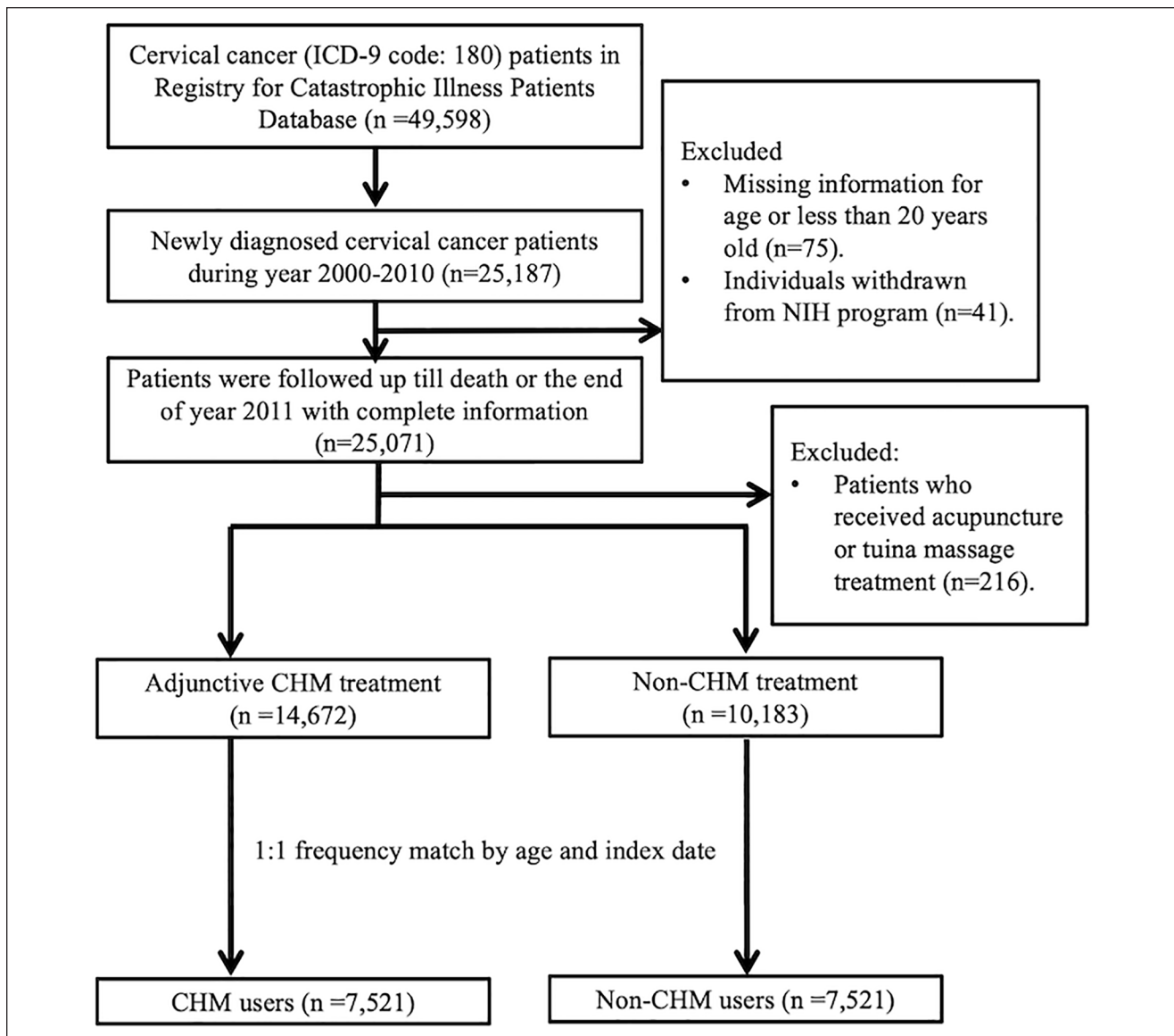
Figure 1. Recruitment flowchart of subjects from the Registry for Catastrophic Illness Patients Database (RCIPD) of the National Health Insurance Research Database (NHIRD) during the period 2000 to 2010 in Taiwan.
Abbreviations: CHM, Chinese herbal medicine.

to radiotherapy or chemotherapy alone (pooled OR = 4.16, 95% CI = 1.97-8.78).[23] Based on the positive effects proved by former literature and our study, adjuvant CHM therapy could be considered as an available and useful strategy for the treatment of cervical cancer.

With the strength of big data analytics, this study is a large-scale retrospective cohort study to investigate the outcomes of CHM users with cervical cancer in Taiwan. We used RCIPD as our dataset, which provided the nationwide population-based information in Taiwan. Therefore, the potential for selection bias could be minimized due to the real-world data assessed from the NHI program. Moreover, most previous studies of the utilization of CHM in cervical

cancer focused on either the effects of the specific herbs[25-27] or formulas[28] in vitro and in vivo. The comprehensive benefits of complementary Chinese herbal medicine use among patients with cervical cancer have rarely been reported. Our study appears to be the initial investigation of this issue. In our study, we also performed 1:1 frequency matching by age and index date, which referred to the initial time of CHM use instead of the time of newly diagnosed with cervical cancer. The immortal time bias could be partially avoided in this manner.

Cancer is regarded as a life-threatening issue for our and future generations.[29] According to the previous population-based study reported in Lancet Oncology, the predicted

Table 1. Characteristics of Cervical Cancer Patients According to the Utilization of Chinese Herbal Medicine.

| | Chinese herb medicine (CHM) | | | | |
| | No (N=7521) | | Yes (N=7521) | | |
Variable	n	%	n	%	*P*-value
Age mean ± SD (years)	57.9 (13.8)		57.6 (13.8)		.28[a]
Age group					
20-39	733	9.75	760	10.1	.74[b]
40-64	4226	56.2	4224	56.2	
≥65	2562	34.1	2537	33.7	
Comorbidity					
Diabetes mellitus	1062	14.1	1103	14.7	.34[a]
Hypertension	3208	42.7	3268	43.5	.32[a]
Chronic kidney disease	947	12.6	986	13.1	.34[a]
Coronary artery disease	1495	19.9	1631	21.7	.01[a]
Chronic obstructive pulmonary disease	1306	17.4	1436	19.1	.01[a]
Cirrhosis	1326	17.6	1440	19.2	.02[a]
Hyperlipidemia	1662	22.1	1735	23.1	.15[a]
Treatment					
Surgery	36	0.48	37	0.49	.91[a]
Chemotherapy	375	4.99	367	4.88	.76[a]
Cisplatin	268	3.56	264	3.51	.86[a]
Paclitaxel	50	0.66	48	0.64	.84[a]
Radiotherapy	322	4.28	322	4.28	.99[a]
Interval between the initial diagnosis of cervical cancer and the index date, days, mean (median)	654.3 (748.0)		641.1 (742.9)		.27[b]
Follow-up time, years, mean (median)	2.10 (2.33)		4.15 (3.15)		<.001[b]

[a]Chi-square test.
[b]*t*-test.

incidence of all cancers may increase significantly from 12.7 million new cases in 2008 to 22.2 million by 2030 all over the world.[30] Besides, cancer care is also a global health priority due to the growing number of aging populations with increasing prevalence of cancer.[31] The optimal effects of treatment involve improving life quality, prolonging survival time and alleviating side effects. In terms of cervical cancer, surgery remains the first treatment option for the majority of early stage patients while concurrent chemoradiotherapy (CCRT), palliative chemotherapy, and target therapy are used in the management of advanced stage.[7] However, a series of complications and side effects such as fatigue, pain, neurological bladder,[32] nausea and vomiting,[33] edema, and bone marrow suppression[34] may result in discomfort and inconvenience, which often restrict the application and effectiveness of cancer treatment.

CHM, which is seen to have relatively fewer side effects, has been proposed to be an effective and affordable adjuvant cancer treatment in different stages of cancer lesions in view of limitations in conventional cancer care.[14] As we shown in Table 4, Bai-Hua-She-She-Cao (*Herba Oldenlandiae*, synonym *Herba* Hedyotis diffusae) and Ban-Zhi-Lian (*Herba Scutellriae Barbatae*) were commonly used single herbs in cervical cancer in our study. Bai-Hua-She-She-Cao and its active constituents have been revealed a variety of pharmacological activities recently, including anticancer, chemopreventive, hepatoprotective, antiviral, antibacterial, antidiabetic, antioxidant, and gastroprotective properties.[35] In the past few years, it has widely applied in cancer therapy such as colorectal,[36-38] liver,[39] lung,[40] prostate,[41] and other cancers due to several potential anticancer effects. For instance, the extract of Bai-Hua-She-She-Cao and its active constituents have been reported to induce cell morphological changes, reduce cell viability, lead to DNA fragmentation, loss of plasma membrane asymmetry, activate caspase-9 and caspase-3 and so on.[42] We have also shown that its extract and active compound, rutin, can be used as an adjuvant in peptide-based vaccines to increase immunogenicity against human papillomavirus (HPV)-induced cervical cancer.[16] Ban-Zhi-Lian and its active constituents also have been used as an antitumor herb in several cancers.[43-45] The mechanism underlying its anticancer activity appears to involve DNA damage, cell cycle control, nucleic acid binding, protein phosphorylation and dephosphorylation and dendritic cell functions on the basis of cDNA microarray analysis.[46,47] Besides, Ban-Zhi-Lian and

Table 2. Cox Model With Hazard Ratios and 95% Confidence Intervals of Mortality Associated With Chinese Herbal Medicine and Covariates Among Cervical Cancer Patients.

Variable	Frequency of mortality (n = 4664)	Crude[a]		Adjusted[b]	
		HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Chinese herbal medicine use					
No	3171	1.00 (Reference)		1.00 (Reference)	
Yes	1493	031 (0.29-0.33)	<.001	0.29 (0.27-0.31)	<.001
Age group					
20-39	290	1.00 (Reference)		1.00 (Reference)	
40-64	2145	1.33 (1.18-1.51)	<.001	1.32 (1.17-1.50)	<.001
≥65	2229	2.40 (2.12-2.71)	<.001	2.40 (2.10-2.73)	<.001
Comorbidity					
Diabetes mellitus					
No	3810	1.00 (Reference)	<.001	1.00 (Reference)	<.001
Yes	854	1.43 (1.33-1.54)		1.34 (1.23-1.45)	
Hypertension					
No	2353	1.00 (Reference)	<.001	1.00 (Reference)	.40
Yes	2311	1.32 (1.24-1.40)		0.97 (0.90-1.04)	
Chronic kidney disease					
No	3759	1.00 (Reference)	<.001	1.00 (Reference)	<.001
Yes	905	1.83 (1.70-1.97)		1.77 (1.64-1.91)	
Coronary artery disease					
No	3451	1.00 (Reference)	<.001	1.00 (Reference)	.11
Yes	1213	1.32 (1.23-1.40)		1.06 (0.99-1.15)	
Chronic obstructive pulmonary disease					
No	3677	1.00 (Reference)	<.001	1.00 (Reference)	.57
Yes	987	1.21 (1.13-1.30)		1.02 (0.95-1.10)	
Cirrhosis					
No	3792	1.00 (Reference)	.76		
Yes	872	0.99 (0.92-1.06)			
Hyperlipidemia					
No	3663	1.00 (Reference)	.03		
Yes	1001	0.93 (0.86-0.99)			
Treatment					
Surgery					
No	4635	1.00 (Reference)	.37		
Yes	29	1.18 (0.82-1.70)			
Chemotherapy					
No	4206	1.00 (Reference)	<.001	1.00 (Reference)	<.001
Yes	458	2.08 (1.89-2.29)		1.74 (1.49-2.04)	
Cisplatin					
No	4355	1.00 (Reference)	<.001	1.00 (Reference)	.31
Yes	309	1.94 (1.73-2.18)		1.10 (0.92-1.31)	
Paclitaxel					
No	4585	1.00 (Reference)	<.001	1.00 (Reference)	<.001
Yes	79	2.69 (2.15-3.36)		2.62 (2.09-3.28)	
Radiotherapy					
No	4301	1.00 (Reference)	<.001	1.00 (Reference)	<.001
Yes	363	1.79 (1.61-1.99)		1.31 (1.16-1.48)	

[a]Crude HR represents relative hazard ratio.
[b]Adjusted HR represents adjusted hazard ratio: mutually adjusted through Cox proportional hazard regression model for CHM use, age group, comorbidities of diabetes mellitus, hypertension, chronic kidney disease, coronary artery disease, chronic obstructive pulmonary disease, hyperlipidemia, treatment (including surgery, chemotherapy, and radiotherapy), and chemotherapeutic agents used (including Cisplatin and Paclitaxel).
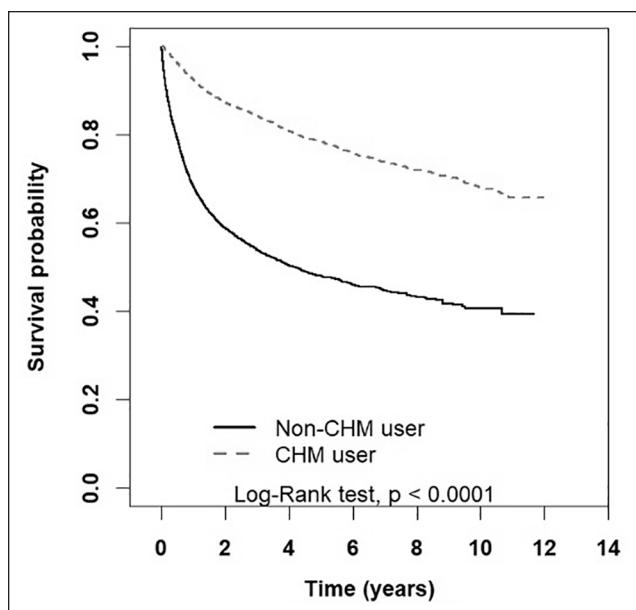
Figure 2. Kaplan-Meier curves of survival rate in cervical cancer patients of CHM and non-CHM group (log-rank test, $P < .001$).
Abbreviation: CHM, Chinese herbal medicine.

its active constituents could effectively improve the side effects of chemo- or radiotherapy such as dysfunction of liver, diarrhea, fatigue, and pain.[48] As the results revealed in our study, Jia-Wei-Xiao-Yao-San was the most commonly used herbal formula in cervical cancer. It has been frequently administered concurrently with chemotherapy, contributing to 1 of the top 3 prescribed formulations for breast, colon and gastric cancer patients in Taiwan.[49] Interestingly, according to the previous nationwide population-based study, cervical cancer is a prominent risk factor for developing depression following diagnosis in Taiwan.[5] This finding revealed by Shyu et al may account for the common prescription of Jia-Wei-Xiao-Yao-San which has been widely used to treat neuropsychological disorders based on the "liver depression and qi stagnation" of TCM syndrome. Furthermore, we found the precipitating medicine including Da-Huang (*Radix et Rhizoma Rhei*) and Ma-Zi-Ren-Wan were commonly used in our study. These findings confirmed that constipation is a common bowel symptom associated with radical pelvic surgeries and pelvic radiation for gynecologic cancer.[50,51] For survivors who were 1 year post-treatment of cervical and endometrial cancer, nearly 60% of them have suffered from constipation according to

Table 3. Incidence rates, Hazard Ratios, and Confidence Intervals of Mortality for Patients Stratified by Age Group, Comorbidity, Treatment, and Chemotherapeutic Agents Used.

| | Chinese herb medicine used | | | | | | Compared with Non-CHM user | |
| | Non-CHM | | | CHM | | | | |
Variable	Event	Person years	IR	Event	Person years	IR	Crude HR (95% CI)	Adjusted HR† (95% CI)
Age group								
20-39	220	1697	129.6	70	3274	21.4	0.22 (0.17-0.29)***	0.23 (0.17-0.30)***
40-64	1517	9343	162.4	628	17250	36.4	0.29 (0.27-0.32)***	0.28 (0.26-0.31)***
≥65	1434	4815	297.8	795	10691	74.4	0.31(0.29-0.34)***	0.31(0.28-0.33)***
Comorbidity								
No	1169	7220	161.9	475	12575	37.8	0.31(0.27-0.34)***	0.30 (0.27-0.34)***
Yes	2002	8635	231.8	1018	18640	54.6	0.30(0.28-0.32)***	0.29 (0.27-0.32)***
Treatment								
Surgery								
No	3151	15785	199.6	1484	31038	47.8	0.31 (0.29-0.33)***	0.30 (0.28-0.31)***
Yes	20	71	281.6	9	177	51.0	0.26 (0.11-0.58)**	0.13 (0.05-0.37)**
Chemotherapy								
No	2920	15100	193.4	1286	29878	43.0	0.29 (0.27-0.31)***	0.28 (0.26-0.30)***
Yes	251	756	332.2	207	1336	154.9	0.47 (0.39-0.57)***	0.47 (0.39-0.47)***
Cisplatin								
No	3004	15333	195.9	1351	30283	44.6	0.30 (0.28-0.32)***	0.28 (0.26-0.30)***
Yes	167	523	319.2	142	932	152.4	0.48 (0.38-0.60)***	0.49 (0.38-0.62)***
Paclitaxel								
No	3127	15770	198.3	1458	31063	46.9	0.30 (0.29-0 .32)***	0.29 (0.27-0.31)***
Yes	44	86	514.1	35	152	230.7	0.34 (0.21-0.57)***	0.39 (0.23-0.67)**
Radiotherapy								
No	2954	15170	194.7	1347	29829	45.2	0.30 (0.28-0.32)***	0.29 (0.27-0.31)***
Yes	217	685	316.6	146	1386	105.4	0.37 (0.30-0.46)***	0.36 (0.29-0.45)***

Abbreviations: CHM, Chinese herbal medicine; IR, incidence rates per 1000 person-years; HR, hazard ratio; CI, confidence interval.
†Adjusted HR represents adjusted hazard ratio: mutually adjusted through Cox proportional hazard regression model for CHM use, age group, comorbidities (including diabetes mellitus, hypertension, chronic kidney disease, coronary artery disease, chronic obstructive pulmonary disease, hyperlipidemia), treatment (including surgery, chemotherapy and radiotherapy) and chemotherapeutic agents used (including Cisplatin and Paclitaxel).
**$P < .01$. ***$P < .001$.

Table 4. The Top 10 Most Common Usage of Chinese Herbal Medicine (CHM) for Patients With Cervical Cancer.

CHM prescription		Frequency	Number of person (days)	Average daily dose (g)	Average duration for prescription (days)
Single herbs					
Pin-yin name	*Scientific name*				
Bai-Hua-She-She-Cao	Herba Oldenlandiae (synonym Herba Hedyotidis Diffusae)	2186	30282	1.6	13.9
Da-Huang	Radix et Rhizoma Rhei	1674	18874	0.7	11.3
Ban-Zhi-Lian	Herba Scutellriae Barbatae	1441	20275	1.7	14.1
Dan-Shen	Radix Salviae Miltiorrhizae	1057	12299	2.6	11.6
Bai-Zhu	Rhizoma Atractylodis macrocephalae	1033	10966	1.5	10.6
Gan-Cao	Radix Glycyrrhizae Uralensis	1010	11400	2.2	11.3
Hou-Po	Cortex Magnoliae officinalis	966	9883	1.1	10.2
Bei-Mu	Bulbus Fritillariae	881	8307	2.1	9.4
Hai-Piao-Xiao	Os Sepiae seu Sepiellae	875	9076	2.0	10.4
Zhi-Shi	Fructus Immaturus Citri Aurantii	839	8128	1.1	9.7
Chinese herbal formulas					
Jia-Wei-Xiao-Yao-San		1625	22029	4.7	13.6
Ma-Zi-Ren-Wan		1087	12185	2.9	11.2
Bu-Zhong-Yi-Qi-Tang		922	11631	4.3	12.6
Xiang-Sha-Liu-Jun-Zi-Tang		833	9600	7.0	11.5
Gui-Pi-Tang		720	8202	6.2	11.4
Sheng-Mai-San		629	6696	4.2	10.6
San-Zhong-Kui-Jian-Tang		580	6663	4.2	11.5
Dang-Gui-Shao-Yao-San		559	5574	4.2	10.0
Suan-Zao-Ren-Tang		543	6086	4.2	11.2
Qi-Ju-Di-Huang-Wan		536	8660	3.9	16.2

a previous US study.[52] In brief, although several CHMs mentioned above have implied effectiveness in cancer therapy, their precise mechanism still remains to be clarified.

In our study, we also found that the mortality risk in ≥65-year-old group was much higher than the other 2 groups. The finding was consistent with the previous studies due to the 2 main reasons. On one hand, Kau et al[3] disclosed that the incidence of cervical cancer in Taiwan is increasing with age, which might be attributable to the lower percentage of elderly women receiving the Pap tests[53] which leads to more advanced disease at diagnosis.[54] On the other hand, for older patients with cancer, the existence of comorbidities is common, which may influence prognosis, treatment choice, and overall survival.[55,56] Although an earlier study showed that comorbidity was an independent predictor of survival in women with either early or late stage cervical cancer,[57] our findings indicated cervical cancer patients with comorbidity of DM and CKD had higher mortality risk. Because of the fact that Taiwan has the relatively higher prevalence of DM[58] and CKD[59] than the global average, cervical cancer patients with these 2 comorbidities are required to struggle with not only cancer therapies but also the multiple complications of DM and CKD. Certainly,

DM and CKD contributed to the higher risk of all-cause mortality compared with patients without these 2 comorbidities.[60,61] Comorbidity may also limit treatment options of cervical cancer and increase the risk of treatment complications.[62] In addition, we also found that cervical cancer patients receiving not only chemotherapy but also radiotherapy had higher mortality hazard ratio. The result implied that advanced stage cervical cancer compared with early stage had poor prognosis. Due to the treatment options depending on the stage of cervical cancer, patients with advanced stage disease were prone to undergo the chemo- or radiotherapy while patients with early stage disease generally received surgery.

Our study had several limitations. First of all, we were unable to access the complete and detailed information noted in the electronic medical records of hospitals and clinics. Although we tried to match the 2 groups, FIGO staging, histological types and performance status were not provided in our datasets. Second, other factors affecting mortality of cervical cancer such as socioeconomic status, lifestyle, exercise habits and motivation could not be estimated in our study. Third, as only the herbal concentrate-granules are covered by NHI payment in Taiwan,

patients who used natural product supplements or self-paid herbal decoctions without clinic visits were excluded from our study due to the lack of records of NHIRD. Lastly, despite the reduction in the hazard ratio of CHM use revealed in our study, we were not capable of proving how long the CHM use might conduce to those benefits for cervical cancer patients. Future studies aimed to provide detailed information of CHM use, including the cumulative dose effects, are warranted.

Conclusion

In summary, adjunctive Chinese herbal medicine may have positive effect of reducing mortality rate in cervical cancer patients regardless of age, comorbidity and treatment. For long-term survival, the utilization of Chinese herbal medicine could improve the survival probability. Integrative treatment with Chinese herbal medicine might be recommended as an effective strategy for cervical cancer patients. Further evidence-based pharmacological investigations and clinical trials are needed to confirm the findings in our study.

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