

Prescription of Chinese herbal products is associated with a decreased risk of uterine fibroids

A population-based cohort study

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Abstract

The finding of a decrease in subsequent fibroid-related operation following the use of Chinese herbal products (CHPs) has led to speculation that CHPs might play a role in uterine fibroids prevention.

This study provides an overview of uterine fibroids incidence, comparing CHP users with those who do not use CHPs, referred to as non-CHP users. The results can provide information to clinicians for counseling women about the preventive use of CHPs.

A total of 52,151 women (20–45 years of age) were recruited from a nationwide 1-million-person representative sample of those covered by National Health Insurance in Taiwan and were followed from 2000 to 2013. Exact matching was performed for comparative analysis. The age-specific hazard ratios (HRs) of uterine fibroids in relation to either CHP or the phytoestrogen use were calculated with multivariate Cox proportional hazard regression.

More than 71% of patients had used a CHP at some point previously. The overall incidence density rate of uterine fibroids for non-CHP users was estimated at 27.5 per 1000 patient-years. The corresponding values for CHP and the phytoestrogen users were lower than those of the non-CHP group (CHP group = 15.5; the phytoestrogen group = 12.5 per 1000 patient-years). The covariate adjusted HRs for uterine fibroid were 0.73 (95% confidence interval [CI] 0.63–0.85) and 0.65 (95% CI 0.52–0.82) in women using CHPs and the phytoestrogen, respectively.

CHPs seem to contribute to a decreased risk in developing uterine fibroids. Although the mechanism of action of these products is unclear, their use as a preventive agent for uterine fibroids might be taken into consideration.

Abbreviations: CHP = Chinese herbal product, CI = confidence intervals, DCMP = Department of Chinese Medicine and Pharmacy, HR = hazard ratio, HT = hormone therapy, ICD-9-CM = International Classification of Diseases, Ninth Revision, Clinical Modification, IRB = institutional review board, NHI = National Health Insurance, NHRI = National Health Research Institutes, NT\$ = New Taiwan dollars, TCM = traditional Chinese medicine.

Keywords: Chinese herbal product, National Health Insurance Research Database, phytoestrogen, traditional Chinese medicine, uterine fibroids

1. Introduction

Most women suffer from ≥ 1 uterine fibroids (leiomyoma), which are the leading cause of hysterectomy (removal of the uterus)

during their reproductive lifespan.^[1] In the United States, more than half of women aged 15 to 50 years experience fibroid-related symptoms or health concerns.^[2,3] Fibroid-related symptoms

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include prolonged menstrual period, profound bleeding, pelvic pressure or pain, abnormal bowel function, urinary frequency, and pain with intercourse.^[4] As recommended by the United States' Agency for Healthcare Research and Quality, most studies have adopted research questions aimed at assessing the disease burden and identifying and selecting strategies for fibroid management. Although a variety of risk factors, including age at menarche, parity, and race/ethnicity, have been reported, the etiology of uterine fibroids is not well understood. Therefore, no effective therapy for uterine fibroids has been developed yet.^[5] This study was designed to bridge this research gap by applying a retrospective survey to a nationwide cohort of women before a diagnosis of uterine fibroids. The only previous survey of women before a diagnosis of uterine fibroids did not include information on asymptomatic fibroids^[6]; this oversight is a common and critical problem in fibroid research, given the underestimation of the prevalence of this disease.

The traditional Chinese medicine (TCM) holistic concept of treating a patient's system as a whole as opposed to the reductionist model of Western medicine began considerable migration to Taiwan from the Chinese mainland as early as 1664.^[7] TCM is now firmly established in Taiwanese society. When women seek TCM advice for gynecological disorders, TCM doctors consider potential uterine fibroid risk factors, such as menstruation irregularities, the amount of menstrual blood flow, period blood color, period clots, menstrual cramps, premenstrual syndrome, obesity, and unhealthy lifestyles, and then prescribe appropriate Chinese herbal products (CHPs). However, for more than a century, Western medicine has become a dominant force in women's health care. The fees for both Western medicine and TCM diagnosis and treatment are covered by the National Health Insurance system in Taiwan. Women with gynecological discomfort are free to select their own healthcare. For centuries, harmony with nature is the core value of TCM, and TCM has been used in Taiwan for hundreds of years; therefore, TCM is growing in popularity in Taiwan not merely because of such value, but gynecological drug therapies in regulating the menstrual cycle, enhancing fertility as either abortifacients cause discomfort and severe side effects that female population tend to prefer such value nowadays.

According to TCM, the formation and growth of uterine fibroids are due to an accumulation of stagnated Qi and blood at a certain time in the pelvic area. TCM practitioners are well trained to detect the severity of Qi stagnation and blood stasis in women (referred to as "suboptimal health status") before the point at which uterine fibroids form and/or are large enough to be recognized or diagnosed. TCM practitioners also are instructed women are constantly throwing off a storm of signals through their menstruation before or during the formation of a uterine fibroid, such as irregular menstruation, heavy menstrual bleeding, some brown discharge or dark brown blood, menstrual cramps, and premenstrual syndrome. Therefore, TCM practitioners believe that ensuring proper blood movement and smooth flow of Qi will relieve gynecological disorders and prevent stagnated Qi and blood from accumulating in the uterus, thereby preventing fibroid formation. On the basis of this unique TCM concept, our recent study supported the hypothesis of an inhibitory effect of TCM formulae (containing estrogenic herbs) on carcinogenesis in breast carcinoma.^[8,9] The aim of the present study was to investigate the benefit of TCM formulae or estrogenic herbs (ginseng, angelica) on estrogen-dependent fibroid prevention.

2. Methods

2.1. Ethics statement

The National Health Insurance (NHI) system, established in Taiwan in 1995, covers 99% of the Taiwanese population. With strict confidentiality guidelines that are closely followed in accordance with the Electronic Data Protection Act, the National Health Research Institutes (NHRI) anonymize and maintain NHI reimbursement data as files suitable for institutional research. The identification numbers of all individuals with reimbursement data in the NHI database are encrypted to protect their privacy. Our study was approved by the Institutional Review Board (IRB) of Taoyuan General Hospital, which is certified by the Ministry of Health and Welfare, Taiwan (IRB Approval Number: TYGH106-6).

2.2. Study design and population

This population-based cohort study explored the association between CHP prescriptions and the occurrence of uterine fibroids in Taiwan between January 1, 1997 and December 31, 2013. All data were obtained from the National Health Insurance Research Database (NHIRD). Each file contained medical information including data on inpatient and outpatient care facilities, drug and CHP prescriptions, and dates of each prescription, as well as patient sex, date of birth, dates of visits or hospitalizations, and diagnoses coded in the format of the *International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM)*. To facilitate research, the NHRI created a simple random sample of 1 million individuals from the 22 million insured people in Taiwan (NHIRD), a cohort that was further validated to be representative of the entire insured population of Taiwan.

The selection of study patients from the random sample was performed as follows (Fig. 1). First, all male patients (n = 485,509) or those with missing information concerning sex (n = 18,727) were excluded. Age was computed by subtracting the each patient's date of birth from the 1st day of July for each year. Patients under 20 (n = 163,902) or over 45 (n = 217,795) years of age were excluded to limit the study sample to women of reproductive age in Taiwan. A patient was defined as having uterine fibroids if she had been diagnosed as having uterine fibroids (*ICD-9-CM*: 218 or A-code: A152) between 2000 and 2013. Patients diagnosed within a 3-year range (1997–1999) were then excluded to avoid the inclusion of 199 cases with a previous history of uterine fibroids. To control for potential confounding factors, 37 patients with a history of hysterectomy were excluded. Additionally, a total of 930 patients with missing demographic data, 58,162 patients with a history of hospitalizations or emergency room visit for gynecological reasons and 2588 patients being prescribed CHP 3 months before a diagnosis of uterine fibroids were excluded. Finally, 52,151 patients qualified for inclusion in our study cohort. They were further divided into non-CHP users (n = 15,029) and CHP users (n = 37,122). Non-CHP users were defined as those who had never been prescribed CHP. CHP users were defined as those who had ever been prescribed CHP. Among the remaining 52,151 women, 2069 CHP users were matched to 4138 non-CHP users based on age, demographic factors, frequency of gynecological outpatient visit, gynecological disease (polycystic ovary syndrome, irregular menstrual cycle, premenstrual tension syndrome), HT usage (types and prescription patterns of HT and time since last known HT use) and number of physician visits for gynecological disease

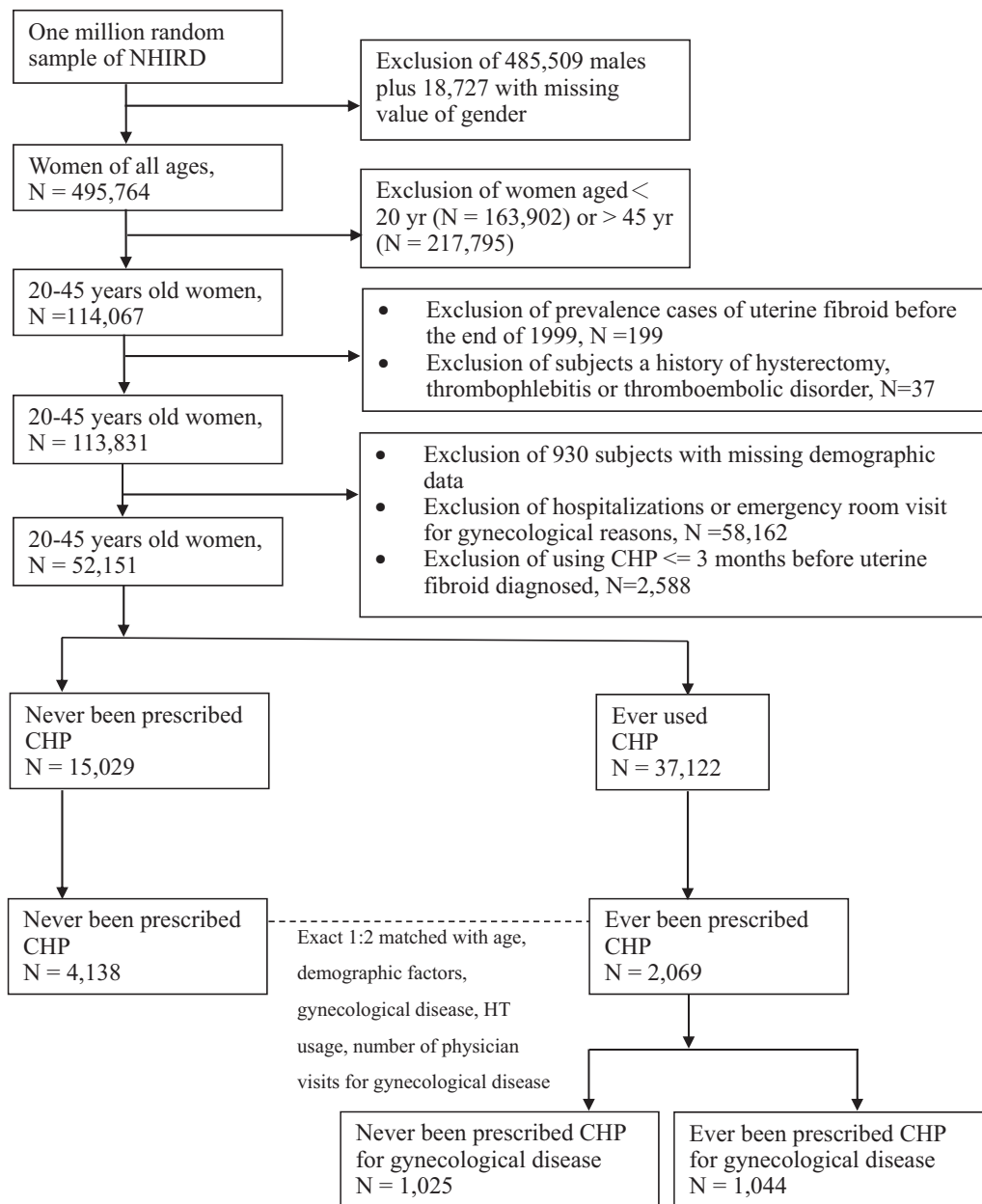


Figure 1. Algorithm of recruitment of subjects into the cohort from Taiwanese women of the National Health Insurance Research Database (NHIRD) followed from 2000 to 2013 in Taiwan. CHP=Chinese herbal product, HT=hormone therapy, NHIRD=National Health Insurance Research Database.

using the exact matching to reduce the bias from confounding variables.

2.3. Study variables

To identify the key factors associated with the development of uterine fibroids, demographic factors were selected according to previous studies.^[10-12] The first date of coding was defined as the index date. We calculated the age from the index date. Patients' monthly income in New Taiwan dollars (NT\$) was assigned to one of the following four categories: NT\$0, NT\$1 to NT\$19,999, NT\$20,000 to NT\$39,999, and ≥NT\$40,000. Furthermore, the level of urbanization of the community of residence was stratified into 3 classifications.^[13] The baseline

comorbidities included polycystic ovary syndrome, irregular menstruation, premenstrual syndrome.

2.4. Exposure assessment for hormone therapy

The reimbursement database contained details regarding the prescribed conventional medicines, which included all types of hormone therapy (HT) and the commercial names of 14 types of estrogen-containing drugs and 10 types of progesterone-containing drugs. The risk of uterine fibroids was analyzed according to when patients had been administered HT (nonuse; estrogen [E]-alone; progesterone [P]-alone; E+P; other preparations, including progesterone alone and vaginal or other local treatments.).

2.5. CHPs and exposure assessment

To prevent confounding by the indication of uterine fibroids, only medications (including herbal products) prescribed 3 months before the diagnosis of uterine fibroids were considered in the exposure dose. Corresponding information regarding the CHPs was obtained from the Department of Chinese Medicine and Pharmacy (DCMP), Ministry of Health and Welfare, Taiwan, including the name of each herb or herbal formula, effective approval date and period, DCMP manufacturer code, and name of the CHP manufacturer. In addition, each pharmaceutical company publishes and submits detailed information on the composition of every product, which can be retrieved from the DCMP website.^[14] All CHPs that have favorable manufacturing practices and meet DCMP standards receive the same classification. On the basis of the aforementioned information, the original amount of each herb or herbal formula in grams could be determined for calculating the cumulative doses prescribed to the patients.

2.6. Data analysis

The χ^2 test was used to compare the distributions of age (20–24, 25–29, 30–34, and 35–45 years), income level, urbanization status, selected underlying illnesses, CHP, and HT usage between the non-CHP and CHP groups. Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated using a multivariate Cox proportional hazard regression model to assess the risk of uterine fibroids by adjusting for age, income level, urbanization status, gynecological disease (polycystic ovary syndrome, irregular menstrual cycle, premenstrual tension syndrome), and HT usage. Multivariate Cox proportional hazard regression models were employed to determine the effect of phytoestrogen herbs, ginseng and angelica, on the risk of uterine fibroids by using HRs with 95% CIs. Further data analysis was performed to evaluate cumulative CHP dose (≤ 300 g, 301–1800 g, > 1800 g) for uterine fibroids patients in the CHP group. The age-specific incidence density rate was also evaluated when the denominator was the sum of the person-time values (person-years in the current study) of the at-risk population.

The date of censoring was either the date of a patient's withdrawal from the NHI or the study termination date (ie, December 31, 2013). Death was defined as withdrawal of the patient from the NHI program. A significance level of $\alpha = 0.01$ was selected. SAS version 9.4 (SAS Institute, Cary, NC) was used for data management and analysis.

3. Results

The database of outpatient claims from 2000 to 2013 contains information on 52,151 female patients. Among them, 37,122 (71.2%) used CHPs (Table 1). Table 1 shows the characteristics of the study population as well as the use of HT and CHPs. The overall incidence of uterine fibroids in CHP and non-CHP groups was 93.2 and 121.4 per thousand population at risk, respectively. The mean (\pm standard deviation; SD) age of the non-CHP users was 31.5 (± 5.1) years, which was close to that of the CHP users 31.2 (± 5.6) years. More non-CHP users than CHP users had income levels of NT\$0 to 19,999 and fewer were exposed to exogenous hormones not only types of HT, but also time since last known HT use. Following matching, these 2 groups were substantially more similar than the original groups.

Of the women visiting TCM doctors, 50,889 visits were treated with prescription of Chinese herbal remedies as summarized in Table 2. Symptoms, signs, and ill-defined conditions were the most frequent indications which CHPs were prescribed by TCM doctors in Taiwan. Table 3 presents the most common herbal formulae prescribed in the CHP visits.

Table 4 shows the results of the multivariate Cox model used to control for 7 potential confounders (age, monthly income, urbanization status, polycystic ovary syndrome, irregular menstruation, types and prescription patterns of HT, and time since last known HT use).

Within this population, we identified 857 patients who had been newly diagnosed with myoma (CHP users, $n = 230$; non-CHP users, $n = 627$) during the 14-year study period (2000–2013) and who were aged between 20 and 45 years. The overall incidence densities of the non-CHP and CHP users were 27.5 and 15.5 per 1000 person-years, respectively. The highest incidence density rate was noted in patients aged 30 to 34 and 35 to 45 years (32.7 and 21.8 per 1000 person-years for the non-CHP and CHP groups, respectively). After controlling for potential covariates, women using CHPs were found to have a lower risk of developing myoma, with an overall HR of 0.73 (95% CI, 0.63–0.85). We observed a significant association between myoma status and age ($P < .01$) and thus conducted further age-stratified analysis. The adjusted HR decreased most in patients using CHPs who were aged 30 to 34 years (HR, 0.67; 95% CI, 0.53–0.85), followed by patients using CHPs who were aged 20 to 24 years (HR, 0.67; 95% CI, 0.42–1.05; Table 4). There were about 50% of CHP users adopted phytoestrogen and it is worthy to note that the adjusted HR decreased in phytoestrogen users who were aged 25 to 29 years (HR, 0.58; 95% CI, 0.36–0.91) and aged 30 to 34 years (HR, 0.57; 95% CI, 0.40–0.83) compared with non-CHP users as shown in Table 5. Table 6 shows the incidence densities and HRs of myoma in non-CHP users and ginseng users. We observed 423 patients with myoma in the non-CHP group and 120 patients with myoma in the ginseng group between 2000 and 2013; for both groups, the highest incidence density rate was noted in patients aged 35 to 45 years (32.0 and 19.3 per 1000 person-years for the non-CHP and ginseng groups, respectively). The overall incidence density rates calculated for the non-CHP and ginseng groups were 27.4 and 11.7 per 1000 person-years, respectively, representing a covariate-adjusted HR of 0.57 (95% CI, 0.46–0.70). Under similar circumstances, as shown in Table 7, the adjusted HR decreased significantly among the angelica users (HR, 0.64; 95% CI, 0.53–0.77). Table 8 shows the incidence densities and HRs of myoma in non-CHP and CHP users for gynecological disease. We observed 332 patients with myoma in non-CHP group and 89 patients with myoma in CHP group between 2000 and 2013; the adjusted HR decreased most in patients using CHPs who were aged 20 to 24 years (HR, 0.27; 95% CI, 0.12–0.64), followed by patients using CHPs who were aged 30 to 34 years (HR, 0.56; 95% CI, 0.39–0.80). The overall incidence density rates calculated for the non-CHP and CHP groups were 28.3 and 12.1 per 1000 person-years, respectively, representing a covariate-adjusted HR of 0.54 (95% CI, 0.42–0.68). For different amount of cumulative CHP dose, the overall adjusted HR were 0.60 (95% CI, 0.45–0.80) and 0.42 (95% CI, 0.26–0.68), respectively, decreasing along with the increasing cumulative CHP dose (Table 9).

Table 1
Demographic characteristics of Taiwanese women aged 20 to 45 from 2000 to 2013 in Taiwan.

Characteristic	Before matched				Exact matched		
	Overall	Prescribed Chinese herbal medicine		P	Prescribed Chinese herbal medicine		P
		Nonuse	Use		Nonuse	Use	
Patient no. (%)	52,151	15,029 (28.8)	37,122 (71.2)		4138 (66.7)	2069 (33.3)	
newly diagnosed uterine fibroid	5283	1824	3459				
Incidence of uterine fibroid [†]	101.3	121.4	93.2				
Outpatient visit for gynecological disease, mean \pm SD)	5.5 (\pm 8.5)	4.3 (\pm 6.5)	5.8 (\pm 8.8)	<.001	2.7 (\pm 2.3)	2.7 (\pm 2.3)	1.00
Age, y				<.001			1.00
Mean (\pm SD)	31.3 (\pm 5.4)	31.5 (\pm 5.1)	31.2 (\pm 5.6)		31.3 (\pm 5.3)	31.3 (\pm 5.4)	
20~24	5851	1106 (7.4)	4745 (12.8)		432 (10.4)	216 (10.4)	
25~29	13,997	4361 (29.0)	9636 (25.9)		1146 (27.7)	573 (27.7)	
30~34	18,346	5505 (36.6)	12,841 (34.6)		1456 (35.2)	728 (35.2)	
35~45,	13,957	4057 (27.0)	9900 (26.7)		1104 (26.7)	552 (26.7)	
\$NT/month (Premiums)				<.001			1.00
0	3599	1482 (9.8)	2117 (5.7)		564 (13.6)	282 (13.6)	
1–19,999	18,712	7493 (49.9)	11,219 (30.2)		1540 (37.2)	770 (37.2)	
20,000–39,999	21,214	4402 (29.3)	16,812 (45.3)		1456 (35.2)	728 (35.2)	
\geq 40,000	8626	1652 (11.0)	6974 (18.8)		578 (14.0)	289 (14.0)	
Urban level (%)				.32			1.00
1 (highest)	42,077	12,115 (80.6)	29,962 (80.7)		3102 (75.0)	1551 (75.0)	
2	4126	1279 (8.5)	2847 (7.7)		456 (11.0)	228 (11.0)	
3 (lowest)	5948	1635 (10.9)	4313 (11.6)		580 (14.0)	290 (14.0)	
Co-morbidity							
Polycystic ovary syndrome				<.001			1.00
No	50,881	14,903 (99.2)	35,978 (96.9)		4116 (99.5)	2058 (99.5)	
Yes	1322	126 (0.8)	1144 (3.1)		22 (0.5)	11 (0.5)	
Irregular menstrual cycle				<.001			1.00
No	34,905	12,191 (81.1)	22,714 (61.2)		2574 (62.2)	1287 (62.2)	
Yes	17,246	2838 (18.9)	14,408 (38.8)		1564 (37.8)	782 (37.8)	
Premenstrual tension syndrome				<.001			1.00
No	51,870	15,000 (99.8)	36,870 (99.3)		4136 (99.9)	2068 (99.9)	
Yes	281	29 (0.2)	252 (0.7)		2 (0.1)	1 (0.1)	
CHP use				<.001			<0.001
Nonusers	15,029	15,029 (100.0)	0 (0.0)		4138 (100.0)	0 (0.0)	
CHP users							
For gynecological disease	19,429	0 (0.0)	19,429 (52.3)		0 (0.0)	1044 (50.5)	
Others	17,693	0 (0.0)	17,693 (47.7)		0 (0.0)	1025 (49.5)	
Cumulative CHP dose				<.001			<0.001
Never use	15,029	15,029 (100.0)	0 (0.0)		4138 (100.0)	0 (0.0)	
\leq 300 g	17,143	0 (0.0)	17,143 (46.2)		0 (0.0)	989 (47.8)	
301–1800 g	13,716	0 (0.0)	13,716 (36.9)		0 (0.0)	769 (37.2)	
>1800 g	6263	0 (0.0)	6263 (16.9)		0 (0.0)	311 (15.0)	
Types and prescription patterns of HT				<.001			1.00
Never use [‡]	37,943	12,287 (81.8)	25,656 (69.1)		2828 (68.3)	1414 (68.3)	
Estrogen-alone	648	186 (1.2)	462 (1.2)		44 (1.1)	22 (1.1)	
Progesterone-alone	4994	1238 (8.2)	3756 (10.1)		700 (16.9)	350 (16.9)	
Estrogen and progesterone combination	1571	257 (1.7)	1314 (3.6)		52 (1.3)	26 (1.3)	
Mixed type [‡]	6995	1061 (7.1)	5934 (16.0)		514 (12.4)	257 (12.4)	
Time since last known HT use				<.001			1.00
Never use [‡]	37,943	12,287 (81.8)	25,656 (69.1)		2828 (68.3)	1414 (68.3)	
Current use	3373	846 (5.6)	2527 (6.8)		368 (8.9)	184 (8.9)	
Last use 1–3 y previously	7566	1401 (9.3)	6165 (16.6)		760 (18.4)	380 (18.4)	
Last use 4–5 y previously	3269	495 (3.3)	2774 (7.5)		182 (4.4)	91 (4.4)	

CHP = Chinese herbal product, \$NT = New Taiwan dollars, HT = hormone therapy.

* Per 1000 people.

[†] Including last use \geq 6 years previously.

[‡] Mixed type refers to the estrogen-alone (E-alone); estrogen together with progesterone (E+P); other preparations, which included progesterone only and vaginal and other local treatments and combinations of the above preparation types.

Table 2

Frequency distribution of Chinese herbal products visits by major disease categories (according to 9th ICD codes) for Taiwanese women aged 20 to 45 from 2000 to 2013 in Taiwan.

Major disease category	ICD-9-CM code range	Number of visits (%) Chinese herbal remedies
Symptom, signs, and ill-defined conditions	780–799	11,912 (23.4%)
Disease of genitourinary system	580–629	8984 (17.7%)
Disease of respiratory system	460–519	8132 (16.0%)
Disease of digestive system	520–579	7624 (15.0%)
Others*		3629 (7.1%)
Disease of the skin and subcutaneous tissues	680–709	3178 (6.2%)
Disease of musculoskeletal system and connective tissue	710–739	2904 (5.7%)
Injury and poisoning	800–999	1538 (3.0%)
Disease of nervous system and sense organs	320–389	1364 (2.7%)
Disease of circulation system	390–459	659 (1.3%)
Endocrine, nutritional and metabolic diseases, and immunity disorders	240–279	441 (0.9%)
Psychotic Disease	290–319	269 (0.5%)
Infectious and parasitic disease	001–139	138 (0.3%)
Neoplasms	140–239	117 (0.2%)
Supplementary classification	V01–V82, E800–E999	0 (0.0%) 0 (0.0%)
Total		50,889 (100%)

ICD-9-CM = International Classification of Diseases, Ninth Revision, Clinical Modification.

*Include ranges of 280–289, 630–677, 740–759, 760–779 ICD-9-CM code and missing data.

4. Discussion

The present study is, to our knowledge, the first population-based analytical epidemiological study of uterine fibroids based on a nationwide database of representative incident cases with matched controls. Furthermore, this is the first study to report negative relationship between the use of CHPs and the subsequent risk of developing uterine fibroids in a female population. Further analysis indicated that the risk for the development of uterine fibroids among phytoestrogen, ginseng, angelica consumers was decreased compared to those who never used CHP. Our findings on the protective effects of CHPs against uterine fibroids are similar to those of an *in vitro* study that demonstrated growth inhibitory activity on the human lei-

Table 3

Top 10 herbal formulae prescribed by traditional Chinese medicine doctors for Taiwanese women aged 20 to 45 from 2000 to 2013 in Taiwan (frequency of prescriptions, n=49,783).

Herbal formulae	Frequency of prescriptions, n (%)	Average daily dose, g	Average duration for prescriptions, days
Jia-Wei-Xiao-Yao-San	4944 (9.9)	11.6	37.7
Chuan-Xiong-Cha-Tiao-San	2655 (5.3)	9.1	26.9
Ma-Zi-Ren-Wan	2609 (5.2)	1.5	48.2
Ge-Gen-Tang	2305 (4.6)	13.0	21.2
Ban-Xia-Xie-Xin-Tang	2303 (4.6)	7.9	33.6
Dang-Gui-Shao-Yao-San	2094 (4.2)	11.5	26.5
Xin-Yi-Qing-Fei-Tang	1993 (4.0)	8.9	26.6
Ping-Wei-San	1938 (3.9)	4.6	25.8
Yin-Qiao-San	1911 (3.8)	8.4	18.7
Shao-Yao-Gan-Cao-Tang	1719 (3.5)	12.1	15.9

omyoma cell line.^[15,16] Major risk factors for uterine fibroids, such as age and HT, were controlled through multivariate modeling and thus could not have acted as confounders in the present study.

The strength of the present study was in using a nationwide representative population (NHIRD) of female patients seeking medical care who had comprehensive 14-year medical records. The diagnosis of uterine fibroids in Taiwan is based on ultrasonographic evidence, and therefore the present study was able to avoid the false-positive and -negative results of questionnaire studies.^[3,17,18] A previous study posited that focusing primarily on symptomatic women underestimates the true prevalence of uterine fibroids because of the unknown distribution of subclinical tumors.^[2] However, the NHIRD covers >99.5% of the Taiwanese population who have sought medical help in actual practices and researchers have used this database to prove that the incidence of breast cancer^[19] and preterm birth^[20] is significantly higher in patients with uterine fibroids than in those without uterine fibroids.

Previous clinical and experimental studies have confirmed that estrogen and progesterone are critical factors in the onset and growth of uterine fibroids.^[21,22] In addition, our previous study revealed that, unexpectedly, female patients who sought medical advice from TCM health care were most likely to consume

Table 4

Overall and age-specific incidence densities and relative hazards of myoma (ICD-9:218) in the non-CHP and CHP groups.

	Non-CHP users			CHP users			Univariable HR (95% CI) in association with CHP users	Adjusted HR [‡] (95% CI) in association with CHP users
	No. of subjects	No. of events	ID [†] (per 1000 patient-years) (95% CI)	No. of subjects	No. of events	ID [†] (per 1000 patient-years) (95% CI)		
Age, y								
20~24	432	75	19.8 (15.8–24.8)	216	25	10.5 (7.1–15.6)	0.67 (0.42–1.05)	0.67 (0.42–1.05)
25~29	1146	176	25.5 (22.0–29.5)	573	65	13.8 (10.8–17.6)	0.74 (0.56–0.98)	0.74 (0.56–0.98)
30~34	1456	272	32.7 (29.1–36.9)	728	91	16.7 (13.6–20.5)	0.67 (0.53–0.85)*	0.67 (0.53–0.85)*
35~45	1104	104	27.7 (22.9–33.6)	552	49	21.8 (16.5–28.8)	0.94 (0.67–1.32)	0.94 (0.67–1.32)
Total	4138	627	27.5 (25.5–29.8)	2069	230	15.5 (13.7–17.7)	0.73 (0.63–0.85)*	0.73 (0.63–0.85)*

AHR = adjusted hazard ratio, CHP = Chinese herbal product, CI = confidence interval, HR = hazard ratio, ICD-9 = International Classification of Diseases, Ninth Revision, ID = incidence density, IR = incidence rate.

* $P < .01$.

† Based on Poisson assumption.

‡ Based on Cox proportional hazard regression with adjustment for age, income level, urbanization status, history of polycystic ovary syndrome, irregular menstruation, premenstrual syndrome, and HT usage.

Table 5
Overall and age-specific incidence densities and relative hazards of myoma (ICD-9:218) in the Non-CHP and PHYTO groups.

	Non-CHP users			PHYTO users [†]			Univariable HR (95% CI) in association with PHYTO users	Adjusted HR [‡] (95% CI) in association with PHYTO users
	No. of subjects	No. of events	ID [‡] (per 1000 patient-years) (95% CI)	No. of subjects	No. of events	ID [‡] (per 1000 patient-years) (95% CI)		
Age, y								
20~24	208	37	20.3 (14.8–28.1)	104	16	13.9 (8.5–22.8)	0.87 (0.48–1.56)	0.87 (0.48–1.56)
25~29	570	80	21.4 (17.2–26.7)	285	23	9.0 (6.0–13.5)	0.58 (0.36–0.91)	0.58 (0.36–0.91)
30~34	734	126	30.0 (24.3–34.5)	367	36	12.2 (8.8–16.9)	0.57 (0.40–0.83)*	0.57 (0.40–0.83)*
35~45	554	58	30.7 (23.7–39.7)	277	23	20.0 (13.3–30.1)	0.79 (0.49–1.29)	0.79 (0.49–1.29)
Total	2066	301	25.5 (22.8–28.6)	1033	98	12.5 (10.3–15.3)	0.65 (0.52–0.82)*	0.65 (0.52–0.82)*

ICD-9 = International Classification of Diseases, Ninth Revision, CHP = Chinese herbal product, ID = incidence density; CI = confidence interval; IR = incidence rate; HR = hazard ratio; AHR = adjusted hazard ratio; PHYTO = phyto-estrogens.

* P < .01.

[†] PHYTO CHPs users included CHP containing phytoestrogen herbs.

[‡] Based on Poisson assumption.

[§] Based on Cox proportional hazard regression with adjustment for age, income level, urbanization status, history of polycystic ovary syndrome, irregular menstruation, premenstrual syndrome, and HT usage.

Table 6
Overall and age-specific incidence densities and relative hazards of myoma (ICD-9:218) in the Non-CHP and GINSENG groups.

	Non-CHP users			Ginseng users			Univariable HR (95% CI) in association with Ginseng users	Adjusted HR [‡] (95% CI) in association with Ginseng users
	No. of subjects	No. of events	ID [‡] (per 1000 patient-years) (95% CI)	No. of subjects	No. of events	ID [‡] (per 1000 patient-years) (95% CI)		
Age, y								
20~24	284	45	17.1 (12.8–22.9)	142	14	8.6 (5.1–14.6)	0.62 (0.34–1.13)	0.62 (0.34–1.13)
25~29	730	119	26.4 (22.1–31.6)	365	32	9.9 (7.0–14.0)	0.54 (0.36–0.80)*	0.54 (0.36–0.80)*
30~34	950	178	30.8 (26.6–35.6)	475	44	11.4 (8.5–15.4)	0.49 (0.36–0.69)*	0.49 (0.36–0.69)*
35~45	754	81	32.0 (25.7–39.7)	377	30	19.3 (13.5–27.7)	0.74 (0.49–1.13)	0.74 (0.49–1.13)
Total	2718	423	27.4 (24.9–30.1)	1359	120	11.7 (9.8–14.0)	0.57 (0.46–0.70)*	0.57 (0.46–0.70)*

ICD-9 = International Classification of Diseases, Ninth Revision, ID = incidence density; CI = confidence interval; IR = incidence rate; HR = hazard ratio; AHR = adjusted hazard ratio; CHP = Chinese herbal product.

* P < .01.

[†] Based on Poisson assumption.

[‡] Based on Cox proportional hazard regression with adjustment for age, income level, urbanization status, history of polycystic ovary syndrome, irregular menstruation, premenstrual syndrome, and HT usage.

phytoestrogens, which are weak estrogens.^[23] Additionally, estrogen-like herbs, such as ginseng and angelica, were frequently prescribed for treating primary dysmenorrhea in Taiwan, 2 contain ginseng and 8 contain angelica.^[24] However, no studies have investigated whether female consumers of CHP have an increased subsequent risk of developing uterine fibroids. The present findings show a negative relationship between consump-

tion of CHPs and subsequent risk of uterine fibroids in female patients (Table 4). As shown in Tables 5–8, the analysis was limited to women who consumed CHPs containing phytoestrogen and estrogen-like herbs (ginseng and angelica) because these Chinese herbs could be a confounding factor in the development of uterine fibroids. The present study found that the age distribution independently contributes to negative results among

Table 7
Overall and age-specific incidence densities and relative hazards of myoma (ICD-9:218) in the Non-CHP and ANGELICA groups.

	Non-CHP users			Angelica users			Univariable HR (95% CI) in association with Angelica users	Adjusted HR [‡] (95% CI) in association with Angelica users
	No. of subjects	No. of events	ID [‡] (per 1000 patient-years) (95% CI)	No. of subjects	No. of events	ID [‡] (per 1000 patient-years) (95% CI)		
Age, y								
20~24	328	48	15.9 (12.0–21.1)	164	16	8.5 (5.2–13.9)	0.67 (0.38–1.17)	0.67 (0.38–1.17)
25~29	814	133	25.7 (21.7–30.4)	407	42	11.9 (8.8–16.1)	0.63 (0.45–0.89)*	0.63 (0.45–0.89)*
30~34	1110	211	32.9 (28.8–37.7)	555	60	13.8 (10.7–17.8)	0.57 (0.43–0.76)*	0.57 (0.43–0.76)*
35~45	814	76	27.6 (22.0–34.5)	407	31	17.7 (12.4–25.2)	0.82 (0.54–1.24)	0.82 (0.54–1.24)
Total	3066	468	27.0 (24.6–29.5)	1533	149	13.0 (11.0–15.2)	0.67 (0.56–0.79)*	0.64 (0.53–0.77)*

AHR = adjusted hazard ratio, CI = confidence interval, HR = hazard ratio, ICD-9 = International Classification of Diseases, Ninth Revision, ID = incidence density, IR = incidence rate; CHP = Chinese herbal product.

* P < .01.

[†] Based on Poisson assumption.

[‡] Based on Cox proportional hazard regression with adjustment for age, income level, urbanization status, history of polycystic ovary syndrome, irregular menstruation, premenstrual syndrome, and HT usage.

Table 8
Overall and age-specific incidence densities and relative hazards of myoma (ICD-9:218) in the Non-CHP and CHP users for gynecological disease.

	Non-CHP users			CHP users			Univariable HR (95% CI) in association with CHP users	Adjusted HR [‡] (95% CI) in association with CHP users
	No. of subjects	No. of events	ID [†] (per 1000 patient-years) (95% CI)	No. of subjects	No. of events	ID [†] (per 1000 patient-years) (95% CI)		
Age, y								
20~24	226	62	19.8 (15.5–25.5)	113	6	4.6 (2.1–10.2)	0.27 (0.12–0.64)*	0.27 (0.12–0.64)*
25~29	540	164	25.8 (22.1–30.1)	270	28	12.1 (8.3–17.5)	0.60 (0.39–0.91)	0.60 (0.39–0.91)
30~34	704	255	32.8 (29.0–37.1)	352	38	13.9 (10.1–19.1)	0.56 (0.39–0.80)*	0.56 (0.39–0.80)*
35~45	506	96	28.1 (23.0–34.3)	253	17	17.0 (10.5–27.3)	0.59 (0.34–1.01)	0.59 (0.34–1.01)
Total	1976	332	28.3 (25.4–31.5)	988	89	12.1 (9.8–14.9)	0.54 (0.42–0.68)*	0.54 (0.42–0.68)*

AHR = adjusted hazard ratio, CHP = Chinese herbal product, CI = confidence interval, HR = hazard ratio, ICD-9 = International Classification of Diseases, Ninth Revision, ID = incidence density, IR = incidence rate. * $P < .01$.

[†] Based on Poisson assumption.

[‡] Based on Cox proportional hazard regression with adjustment for age, income level, urbanization status, history of polycystic ovary syndrome, irregular menstruation, premenstrual syndrome, and HT usage.

Table 9
Overall and age-specific incidence densities and relative hazards of myoma (ICD-9:218) among CHP users in the different cumulative dose groups.

	≤300 g			301–1800 g			>1800 g			Adjusted HR (95% CI) in association with 301–1800 g group	Adjusted HR [‡] (95% CI) in association with >1800 g group
	No. of subjects	No. of events	ID [†] (per 1000 patient-years) (95% CI)	No. of subjects	No. of events	ID [†] (per 1000 patient-years) (95% CI)	No. of subjects	No. of events	ID [†] (per 1000 patient-years) (95% CI)		
Age, y											
20~24	106	17	15.4 (9.6–24.8)	78	6	6.7 (3.0–14.8)	32	2	5.4 (1.4–21.8)	0.60 (0.23–1.57)	0.46 (0.10–2.18)
25~29	282	42	20.7 (15.3–28.0)	213	19	9.8 (6.3–15.4)	78	4	5.3 (2.0–14.2)	0.64 (0.36–1.12)	0.33 (0.12–0.95)
30~34	345	56	24.1 (18.6–31.3)	275	28	12.6 (8.7–18.2)	108	7	7.7 (3.7–16.1)	0.62 (0.39–0.99)	0.38 (0.17–0.84)
35~45	256	29	28.4 (19.7–40.8)	203	14	17.2 (10.2–29.1)	93	6	14.5 (6.5–16.1)	0.55 (0.29–1.06)	0.55 (0.22–1.36)
Total	989	144	22.2 (18.9–26.1)	769	67	11.4 (9.0–14.5)	311	19	7.8 (5.0–12.2)	0.60 (0.45–0.80)*	0.42 (0.26–0.68)*

ICD-9 = International Classification of Diseases, Ninth Revision, CHP = Chinese herbal product, ID = incidence density; CI = confidence interval; IR = incidence rate; HR = hazard ratio; AHR = adjusted hazard ratio. * $P < .01$.

[†] Based on Poisson assumption.

[‡] Based on Cox proportional hazard regression with adjustment for age, income level, urbanization status, history of polycystic ovary syndrome, irregular menstruation, premenstrual syndrome, and HT usage.

relative elders resulting in reducing the protective effect of CHP against developing uterine fibroids. Nevertheless, a decreased risk of developing uterine fibroids was still observed in most of the subgroups in the CHP group. Our previous study supported the assumption that the antiestrogenic effect of CHPs may inhibit the proliferation and growth of estrogen-dependent breast cancer cells.^[23,25,26] Similarly, we were unable to rule out the possibility that consumption of CHPs, particularly those containing estrogen-like Chinese herbs, inhibits the proliferation and growth of estrogen-dependent uterine fibroids. Despite these potentially promising results, further research is warranted to clarify the potential molecular mechanisms of phytoestrogens involved in uterine fibroid development and growth.

Our previous clinical trial revealed that Chinese herbs are effective in reducing heavy menstrual bleeding and relieving period cramps before or during menstruation,^[2] which might be the most common symptoms of uterine fibroids.^[27] The present study demonstrated that the three most frequently prescribed formulas for relieving discomfort among the female population were Jia-Wei-Xiao-Yao-San, Chuan-Xiong-Cha-Tiao-San, and Ge-Gen-Tang, which, according to the classical literature, are said to calm the liver, resolve depression, and alleviate musculoskeletal pain and fatigue, respectively. Chinese herbs clearly mediate the

fluctuations in women’s hormonal milieu, resulting in the delayed onset or slowed growth of uterine fibroids. TCM doctors treat symptom, signs, and ill-defined conditions on the basis of holistic considerations for women who suffer from multiple symptoms in many organ systems, rather than by making a successful clinical diagnosis, which is among the most critical tasks for physicians. From the viewpoint of TCM, uterine fibroids occur because dampness and pathogenic phlegm prevent the free flow of blood and Qi in the uterus. Therefore, when a deficiency of blood or Qi is diagnosed, TCM doctors frequently prescribe CHPs containing angelica or ginseng, respectively, to alleviate symptoms related to gynecological disorders (a pathological summary of the body’s health condition at a particular stage in the disease process). This unique treatment philosophy of TCM, which can possibly be used to adjust the potential determinants of uterine fibroid risk, is likely to achieve a lower risk of developing subsequent uterine fibroids. According to our research, this is the first study to indicate that Chinese herbs, particularly ginseng, angelica, and phytoestrogens, might be effective as a prophylactic treatment for uterine fibroids in Asian women after taking potential risk factors into consideration.

The present study had some limitations. First, our study identified patients with uterine fibroids on the basis of ICD-9-CM codes in the NHIRD. We could not distinguish whether uterine

fibroids had been diagnosed using ultrasound, histologically, or on the basis of symptoms. Therefore, we may not have included asymptomatic patients. Second, only the prescription duration could be ascertained, and the compliance was unknown; we were therefore unable to assess the efficacy. Accurate assessment of efficacy requires further study. Third, the NHIRD does not contain information on menopausal status; however, we attempted to control for this factor by performing age matching. Fourth, numerous studies of TCM have been conducted in recent years. The results of several studies implied that TCM was only a powerful placebo; we could not rule out this potential possibility. Finally, according to a previous study, other risk factors exist for the development of uterine fibroids, such as body mass index, family, pregnancy, and menopausal status. These risk factors were unavailable because of the encryption of the database.

5. Conclusions

In conclusion, CHPs seems to contribute to a decreased risk in developing uterine fibroids. However, additional double-blind, randomized, placebo-control studies are needed for evaluating the efficacy of ginseng, angelica, and phytoestrogen as a method for preventing uterine fibroids. Our findings suggest that TCM care might be beneficial to prevent women from developing uterine fibroids.

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