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Prescription of Chinese herbal products is associated with a decreased risk of invasive breast cancer

Yueh-Ting Tsai, MD, PhD[a], Jung-Nien Lai, MD, PhD[b,c,*], Pei-Chia Lo, MD[a], Chin-Nu Chen, MD[d], Jaung-Geng Lin, MD, PhD[b]

Abstract

The finding of a decrease in endometrial cancer incidence among breast cancer survivors following the use of Chinese herbal products (CHPs) has led to speculation that CHPs might play a role in breast cancer prevention.

This study provides an overview of breast cancer incidence, comparing CHP users with those who do not use traditional Chinese medicine (TCM), referred to as non-TCM users. The results can provide information to clinicians for counseling women about the preventive use of TCM.

A total of 184,386 women (20–79 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 1999 to 2012. A total of 1853 incidents of invasive breast cancer were diagnosed. The person-year approach with the Poisson assumption was used to estimate the incidence density rate. The age-specific hazard ratios of breast cancer in relation to either CHP or *siwutang* (SWT) use were calculated with multivariate Cox proportional hazard regression.

More than 78% of patients had used a CHP at some point previously. The overall incidence density rate of breast cancer for non-TCM users was estimated at 1.73 per 10,000 patient-years. The corresponding values for CHP and SWT users were lower than those of the non-TCM group (CHP group = 0.85; SWT group = 0.63 per 10,000 patient-years). The covariate adjusted HRs for breast cancer were 0.57 (95% confidence interval [CI] 0.50–0.65) and 0.36 (95% CI 0.28–0.46) in women using CHPs and SWT, respectively. The findings were confirmed using propensity score matching.

Consumption of CHPs reduces the incidence of invasive breast cancer. Although the mechanism of action of these products is unclear, their use as a preventive agent for breast cancer is appropriate for many women at an increased risk of breast cancer.

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, SQDBT = *shiquandabutao*, SWT = *siwutang*, TCM = traditional Chinese medicine.

Keywords: breast cancer, Chinese herbal product, cohort study, National Health Insurance Research Database, *siwutang*, traditional Chinese medicine

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Authorship: The study concept and design were contributed by YTT, JNL, and JGL. YTT, EC, and PCL were responsible for data acquisition. PCL and JNL analyzed and interpreted the data, and the manuscript was drafted by YTT and JNL. Critical revisions were handled by YTT and JNL, and JGL contributed statistical expertise. JNL obtained the funding for the study. Administrative, technical, and material support were provided by YTT and JNL. JNL and JGL were responsible for supervising the study.

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[a] Institute of Traditional Medicine, School of Medicine, National Yang-Ming University, Taipei, [b] School of Chinese Medicine, College of Chinese Medicine, China Medical University, [c] Departments of Chinese Medicine, China Medical University Hospital, [d] Graduate Institute of Integrated Medicine, China Medical University, Taichung, Taiwan.

[*] Correspondence: Jung-Nien Lai, School of Chinese Medicine, China Medical University, Taichung, Taiwan (e-mail: ericlai111@gmail.com).

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1. Introduction

Breast cancer is the most common cancer and the fourth leading cause of cancer death among women in Taiwan.[1,2] Although some gynecological disorders may affect the risk of breast cancer, the cause of individual cases of breast cancer is typically unknowable.[3] In Taiwan, nationwide regular mammographic screening[4] and many randomized controlled trials have demonstrated that gynecological treatment is effective in treating gynecological disorders,[5–7] but the increasing breast cancer incidence in the past 10 years has generated controversy.[8] On the basis of evidence that breast cancer risk is higher among women receiving hormone therapy (HT),[9] we suggest a reduction in the prescribed dose or duration of hormone drugs for Asian women, based on previous dose-seeking trials on Caucasian women.[10]

In the past 400 years, through migration to Taiwan from the Chinese mainland, traditional Chinese medicine (TCM) has become firmly established in the Taiwanese society.[11] TCM is promoted as natural and thus harmless; complementary and alternative medicines similar to TCM are also used in Western countries.[12–14] In addition, the Taiwanese government has increased efforts to raise awareness of TCM in the past 20 years. According to previous reports, evidence of the therapeutic benefit of TCM is not definitive,[15] and women are likely to cite personal beliefs to justify TCM use in Taiwan.[16,17] TCM health care is based more on the women who have diseases than on the diseases themselves. When women seek TCM treatment for gynecological disorders, TCM doctors consider potential breast cancer risk factors, such as irregular menstruation, sleep difficulty, obesity, and unhealthy lifestyles, and provide appropriate recommendations before prescribing Chinese herbal products (CHPs).[18] For more than a century, Western medicine has become a dominant force in women's health care in Taiwan. TCM doctors in Taiwan thus encourage the coadministration of Western drugs and CHPs to relieve women's residual discomfort.[19] Because of the lack of previous evidence supporting this prescription policy, debate has occurred in the medical community regarding the herb–drug interaction that may result. Recent evidence suggests that CHP use in Taiwan has reduced the risk of breast cancer among women receiving exogenous hormones.[20]

Despite the wide use of TCM for treating gynecological diseases, little is known about the role of TCM in health promotion or breast cancer prevention. Recently, the inhibitory effect of *shiquandabutao* (SQDBT) on carcinogenesis in breast carcinoma has been reported.[21] This effect was attributed to one of its main components, *siwutang* (SWT).[22] SWT, also known as *samultang* in Korean and *shimotsu-to* in Japanese, is a combination of 4 herbs, namely *baishao* (*Paeoniae alba* radix; *Paeonia lactiflora* Pall.), *dong quai* (*Angelicae sinensis* radix; *Angelica sinensis* (Oliv.) Diels), *chuanxiong* (*Ligustici chuanxiong* radix; *Ligusticum striatum* DC.), and *shudihuang* (*Rehmanniae preparata* radix; *Rehmannia glutinosa* Steud), and is a commonly prescribed TCM formula for gynecological discomfort owing to qi and blood vacuity.[23,24] A recent study showed that SWT inhibited the growth of MCF-7 and MDA-MB-231 cells,[25] but the results of this study contrasted with those of Chiu,[26] revitalizing the recurring debate in the medical and TCM community regarding the safety and potential therapeutic applications of SWT in women's health care. The central concern for clinicians is how to provide individualized suggestions regarding CHP or SWT use for women who have 1 or more breast cancer risk factors. This study investigated the benefit of CHP or SWT use among women and how this benefit varies by age.

2. Materials and methods

2.1. Ethics statement

The National Health Insurance (NHI) Program, 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 individual privacy. Our study was approved by the institutional review board (IRB) of Taipei City Hospital, which is certified by the Department of Health, Taiwan (IRB Approval Number: TCHIRB-1010722).

2.2. Study design and population

This population-based cohort study investigated the association between CHP prescriptions and the occurrence of breast cancer in Taiwan between January 1, 1999, and December 31, 2012. All data were obtained from the NHI reimbursement database. 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 has created a simple random sample of 1 million individuals from the 22 million insured people in Taiwan (NHI Research Database), 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 = 495,835) or those with missing information concerning gender (n = 3) were excluded. Age was calculated by subtracting the patient's birthday from January 1, 2002. Patients under 20 (n = 169,924) or over 79 (n = 3765) years of age were excluded to limit the study sample to the main consumers of CHPs in Taiwan. A patient was defined as having breast cancer if she had been diagnosed as having breast cancer (ICD-9-CM: 174 or A-code: 113) between 2002 and 2012. Patients diagnosed within a 3-year range (1999–2001) were then excluded to avoid the inclusion of 54,361 cases of prevalent breast and corpus cancer. To control for potential confounding factors, 11 patients who had used tamoxifen prior to any diagnosis of gynecological cancer and 81,118 patients who had been prescribed HT were excluded. Additionally, 1948 patients were excluded who had a history of hysterectomy, thrombophlebitis, or thromboembolic disorder. Also, a total of 609 patients with a follow-up period of < 3 months and 8040 patients with missing data were excluded. Finally, 184,386 patients qualified for inclusion in our study cohort. They were further divided into non-TCM users (n = 40,092) and TCM users (n = 144,294). Non-TCM users were defined as those who never been prescribed TCM. TCM users were defined as those who ever used TCM. The general definition of TCM includes Chinese herbal products, acupuncture,

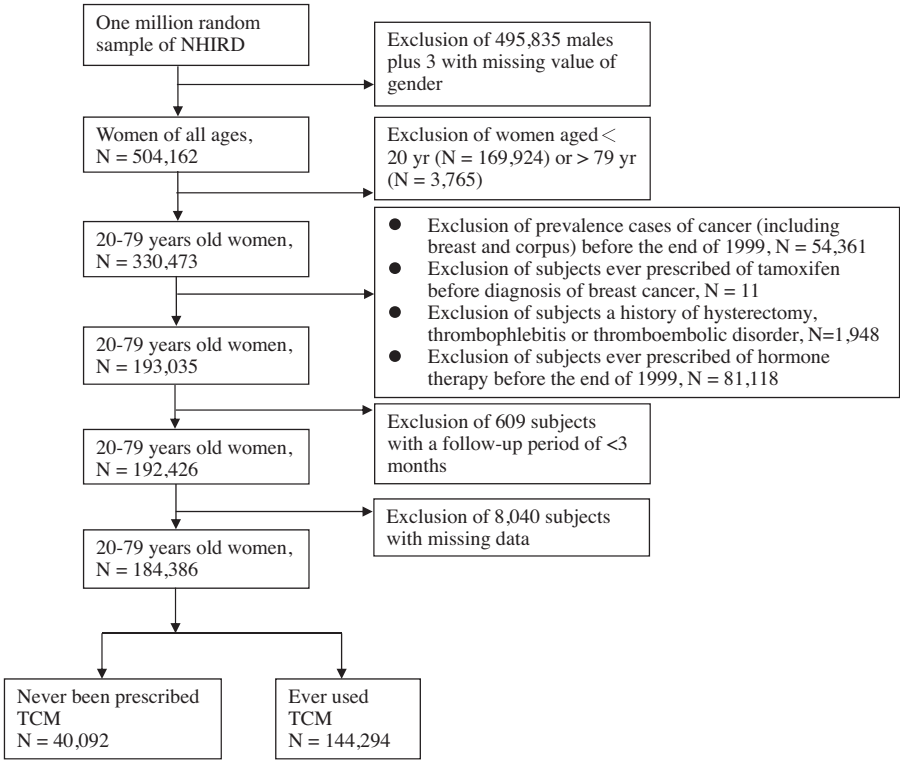

Figure 1. Algorithm of recruitment of subjects into the cohort from the breast cancer patients of the National Health Insurance Research Database followed from 1999 to 2012 in Taiwan. NHIRD = National Health Institutes Research Database, TCM = traditional Chinese medicine.

moxibustion, massage, and relocation manipulative therapy. A method of comparison included the covariates matched with propensity score at a 1:1 ratio was performed to reduce the bias due to confounding variables among study population that received the TCM treatment versus those that did not.

2.3. Study variables

To identify the key factors associated with the development of breast cancer, the demographic factors were selected according to previous studies.[9,20,27] Patients' monthly income in New Taiwan dollars (NT$) was placed in 1 of the following 4 categories: NT$0–NT$19,999, NT$20,000–NT$39,999, and ≥NT$40,000. Furthermore, the level of urbanization of their communities of residence were stratified into 7 classifications (with 1 indicating the most urbanized and 7 indicating the least urbanized).[28] The baseline comorbidities were determined according to patient medical records from 3 years before the index date. These comorbidities included diabetes mellitus, obesity, oophorectomy, endometriosis, leiomyoma of the uterus, irregular menstruation, premenstrual syndrome, and polycystic ovary syndrome.

2.4. Exposure assessment for HT

The reimbursement database contained details regarding the prescribed conventional medicines, which included all types of HT and the commercial names of 14 types of estrogen-containing drugs and 10 types of progestogen-containing drugs. The risk of breast cancer was analyzed according to when patients had been administered HT (nonuse, current use, last use 1–3 years previously, last use 4–5 years previously).

2.5. CHPs and exposure assessment

To prevent confounding by the indication of breast cancer, only medications (including herbal products) prescribed before the diagnosis of breast cancer were considered 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.[29] All CHPs that have favorable manufacturing practices and meet DCMP standards receive the same classification. According to the standard prescription data published by the DCMP, which can be acquired by matching the product number from the NHIRD, 46 other herbal formulas are derived from SWT. All people who had used SWT or formulas with the same composition could thus be identified for our study. Based on the previous information, the original amount of each herb or herbal formula in grams could be determined for calculating the cumulative doses prescribed to individuals.

2.6. Data analysis

A chi-squared test was used to compare the distributions of age (20–29, 30–39, 40–49, 50–59, 60–69, and 70–79 years), income level, urbanization status, and comorbidities between the non-TCM and CHP groups. Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated using a multivariable Cox proportional hazard regression model to assess the risk of breast cancer by adjusting for age, income level, urbanization

status, and selected underlying illnesses. 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 patients with in-hospital mortality attributable to causes other than breast cancer were censored from the survival analysis, with the date of their deaths as the date of censoring. If a study patient had no in-hospital mortality, the date of censoring was either the date of her withdrawal from the NHI or the study termination date (i.e., December 31, 2012). A significance level of $\alpha = 0.05$ was selected. SAS version 9.3 (SAS Institute, Cary, NC) was used for data management and analysis.

3. Results

The database of outpatient claims from 1999 to 2012 contains information on 184,386 female patients. Among them, 144,294 (78.3%) used CHPs (Table 1). Table 1 shows the characteristics

Table 1

Demographic characteristics of Taiwanese women aged 20 to 79 from 2002 to 2012 in Taiwan.

	Before matched			Propensity score matched		
	Prescribed Chinese herbal medicine			Prescribed Chinese herbal medicine		
Variable	Nonuse	Use	*P*	Nonuse	Use	*P*
Characteristics						
Median follow-up time, y	9.8	10.1		9.8	10.5	
Age, y			<.001		0.99	
Mean, ±SD	45.8 (±16.4)	40.9 (±15.1)		45.8 (±16.4)	45.6 (±16.4)	
20–29	7345	39,859		7345	7369	
30–39	9041	35,143		9041	9043	
40–49	8876	32,324		8876	8877	
50–59	5000	15,055		5000	4995	
60–69	5124	13,805		5124	5120	
70–79	4706	8108		4706	4688	
$NT/month, premiums			<.001			.91
0–19,999	31,671	108,235		31,671	31,670	
20,000–39,999	6196	28,293		6196	6221	
≥40,000	2225	7766		2225	2201	
Urban level			<.001			1.00
1, highest	13,059	47,119		13,059	13,058	
2	11,157	41,610		11,157	11,161	
3	6326	24,765		6326	6322	
4	5245	18,427		5245	5255	
5	1045	2690		1045	1034	
6	1728	4987		1728	1727	
7, lowest	1532	4696		1532	1535	
Diabetes mellitus						
No	37,263	136,997	<.001	37,263	37,320	.43
Yes	2829	7297		2829	2772	
Oophorectomy						
No	39,919	143,572	.08	39,919	39,924	.79
Yes	173	722		173	168	
Endometriosis						
No	40,033	143,930	<.001	40,033	40,043	.34
Yes	59	364		59	49	
Irregular menstrual cycle						
No	38,168	133,667	<.001	38,168	38,177	.88
Yes	1924	10,627		1924	1915	
Premenstrual syndrome						
No	39,550	141,378	<.001	39,550	39,587	.25
Yes	542	2916		542	505	
TCM use						
Nonusers	40,092	0		40,092	0.0	
TCM users			<.001			<.001
≤300 g	0	51,466		0	15,220	
300–1800 g	0	50,038		0	13,761	
Above 1800 g	0	42,790		0	11,111	
Time since last known HT use			<.001			.97
Never use*	34,459	105,829		34,459	34,437	
Current use	1061	6558		1061	1080	
Last use 1–3 years previously	2873	21,103		2873	2865	
Last use 4–5 years previously	1699	10,804		1699	1710	
Total	40,092	144,294		40,092	40,092	

$NT = New Taiwan dollars, HT = hormone therapy, TCM = traditional Chinese medicine.

* Including last use ≥6 years previously.

Table 2

Overall and age-specific incidence densities and relative hazards of breast cancer (ICD-9:174) in the non-TCM and TCM groups.

	Non-TCM users			TCM users				
	No. of subjects	No. of events	ID* (per 10,000 patient–years) (95% CI)	No. of subjects	No. of events	ID* (per 10,000 patient–years) (95% CI)	Crude HR (95% CI) in association with TCM users	Adjusted HR† (95% CI) in association with TCM users
Age, y								
20–29	7345	30	0.45 (0.32–0.65)	7369	15	0.20 (0.12–0.33)	0.50 (0.27–0.93)	0.53 (0.29–0.99)
30–39	9041	144	1.73 (1.47–2.04)	9043	88	0.95 (0.77–1.17)	0.61 (0.47–0.80)	0.65 (0.50–0.85)
40–49	8876	218	2.64 (2.32–3.02)	8877	107	1.17 (0.96–1.41)	0.49 (0.39–0.62)	0.51 (0.40–0.64)
50–59	5000	106	2.23 (1.84–2.70)	4995	62	1.20 (0.93–1.53)	0.59 (0.43–0.80)	0.58 (0.43–0.80)
60–69	5124	88	1.82 (1.47–2.24)	5120	46	0.87 (0.66–1.17)	0.52 (0.37–0.75)	0.52 (0.36–0.74)
70–79	4706	49	1.21 (0.92–1.60)	4688	31	0.68 (0.48–0.97)	0.64 (0.41–0.99)	0.65 (0.41–1.02)
Total	40,092	635	1.73 (1.60–1.86)	40,092	349	0.85 (0.76–0.94)	0.55 (0.48–0.63)	0.57 (0.50–0.65)

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

* Based on Poisson assumption.

† Based on Cox proportional hazard regression with adjustment for age, geographic area, urbanization status, history of diabetes, obesity, oophorectomy, endometriosis, myoma, irregular menstrual, premenstrual syndrome, polycystic ovary syndrome, abortion, and HT usage.

of the study population as well as the use of HT and CHPs. The median follow-up time was similar for both groups. The mean (±SD) age of the non-TCM users was 45.8 (±6.4) years, higher than that of the CHP users 40.9 (±5.1) years. More non-TCM users than CHP users had income levels of NT$0–19,999 and were not exposed to exogenous hormones. Following matching, the differences between the 2 groups are substantially more similar than the original groups.

Forest plots from multivariate Cox regression models were used to control for 12 potential confounders (age, monthly income, urbanization status, diabetes mellitus, obesity, oophorectomy, endometriosis, leiomyoma of the uterus, irregular menstruation, premenstrual syndrome, polycystic ovary syndrome, and HT). The results demonstrated a strong association between the estimated dose of prescribed CHPs and a decrease in breast cancer risk. Compared with non-HT users (including those who ceased HT for 6 years or more), current HT users had a 3.5-fold higher risk of breast cancer (adjusted HR, 3.50; 95% CI, 2.36–5.19; $P < .001$), and women who ceased HT for 1 year had a 2.7-fold higher risk of breast cancer (adjusted HR, 2.70; 95% CI, 2.10–3.48; $P < .001$). Compared with non-TCM users, those who consumed ≤300 g of CHPs had a 35% lower risk of breast cancer (adjusted HR, 0.65; 95% CI, 0.55–0.77; $P < .001$), those who consumed 300–1800 g of CHPs had a 51% lower risk of breast cancer (adjusted HR, 0.49; 95% CI, 0.40–0.59; $P < .001$), and those who consumed more than 1800 g of CHPs had a 70% lower risk of breast cancer (adjusted HR, 0.30; 95% CI, 0.23–0.39; $P < .001$; see Table, Supplemental Digital Content, which illustrates the breast cancer risk in Taiwanese women, http://links.lww.com/MD/B845).

Within this population, we identified 984 patients who had been newly diagnosed with breast cancer (CHP group, n = 349; non-TCM users, n = 635) over the 14-year study period (1999–2012) and who were aged between 20 and 79 years. The overall incidence densities of non-TCM and CHP users were respectively 1.73 and 0.85 per 10,000 person-years. The highest incidence density rate was noted in patients aged 40 to 49 and 50 to 59 years (2.64 and 1.20 per 10,000 person-years for the non-TCM and CHP groups, respectively). After controlling for potential covariates, women using CHPs were found to have a significantly lower risk of developing breast cancer, with an overall HR of 0.57 (95% CI 0.50–0.65). We observed a significant interaction between breast cancer status and age ($P < .001$) and thus further conducted an age-stratified analysis. The adjusted HR was most reduced in patients using CHPs who were aged 40 to 49 years (HR, 0.51; 95% CI, 0.40–0.64), followed by patients using CHPs who were aged 60 to 69 years (HR, 0.52; 95% CI, 0.36–0.74; Table 2). Table 3 shows the incidence densities and HRs of breast cancer in non-TCM users and SWT users. We observed 635 patients with breast cancer in

Table 3

Overall and age-specific incidence densities and relative hazards of breast cancer (ICD-9:174) in the non-TCM and SWT users.

	Non-TCM users			SWT users				
	No. of subjects	No. of events	ID* (per 10,000 patient-years) (95% CI)	No. of subjects	No. of events	ID* (per 10,000 patient-years) (95% CI)	Crude HR (95% CI) in association with SWT users	Adjusted HR† (95% CI) in association with SWT users
Age, y								
20–29	7345	30	0.45 (0.32–0.65)	3444	7	0.19 (0.09–0.41)	0.50 (0.22–1.13)	0.58 (0.26–1.33)
30–39	9041	144	1.73 (1.47–2.04)	3603	19	0.50 (0.32–0.79)	0.33 (0.21–0.53)	0.36 (0.23–0.59)
40–49	8876	218	2.64 (2.32–3.02)	2951	26	0.84 (0.57–1.23)	0.36 (0.24–0.54)	0.37 (0.25–0.56)
50–59	5000	106	2.23 (1.84–2.70)	1338	7	0.50 (0.24–1.04)	0.25 (0.12–0.53)	0.24 (0.11–0.51)
60–69	5124	88	1.82 (1.47–2.24)	1222	7	0.55 (0.26–1.16)	0.33 (0.16–0.72)	0.32 (0.15–0.69)
70–79	4706	49	1.21 (0.92–1.60)	1020	7	0.69 (0.33–1.44)	0.66 (0.30–1.46)	0.67 (0.30–1.48)
Total	40,092	635	1.73 (1.60–1.86)	13,578	73	0.63 (0.57–0.69)	0.34 (0.27–0.43)	0.36 (0.28–0.46)

AHR = adjusted hazard ratio, CI = confidence interval, ICD-9 = International Classification of Diseases, Ninth Revision, ID = incidence density, IR = incidence rate, HR = hazard ratio, TCM = traditional Chinese medicine, SWT = *siwutang*.

* Based on Poisson assumption.

† Based on Cox proportional hazard regression with adjustment for age, geographic area, urbanization status, history of diabetes, obesity, oophorectomy, endometriosis, myoma, irregular menstrual, premenstrual syndrome, and polycystic ovary syndrome, abortion, and HT usage.

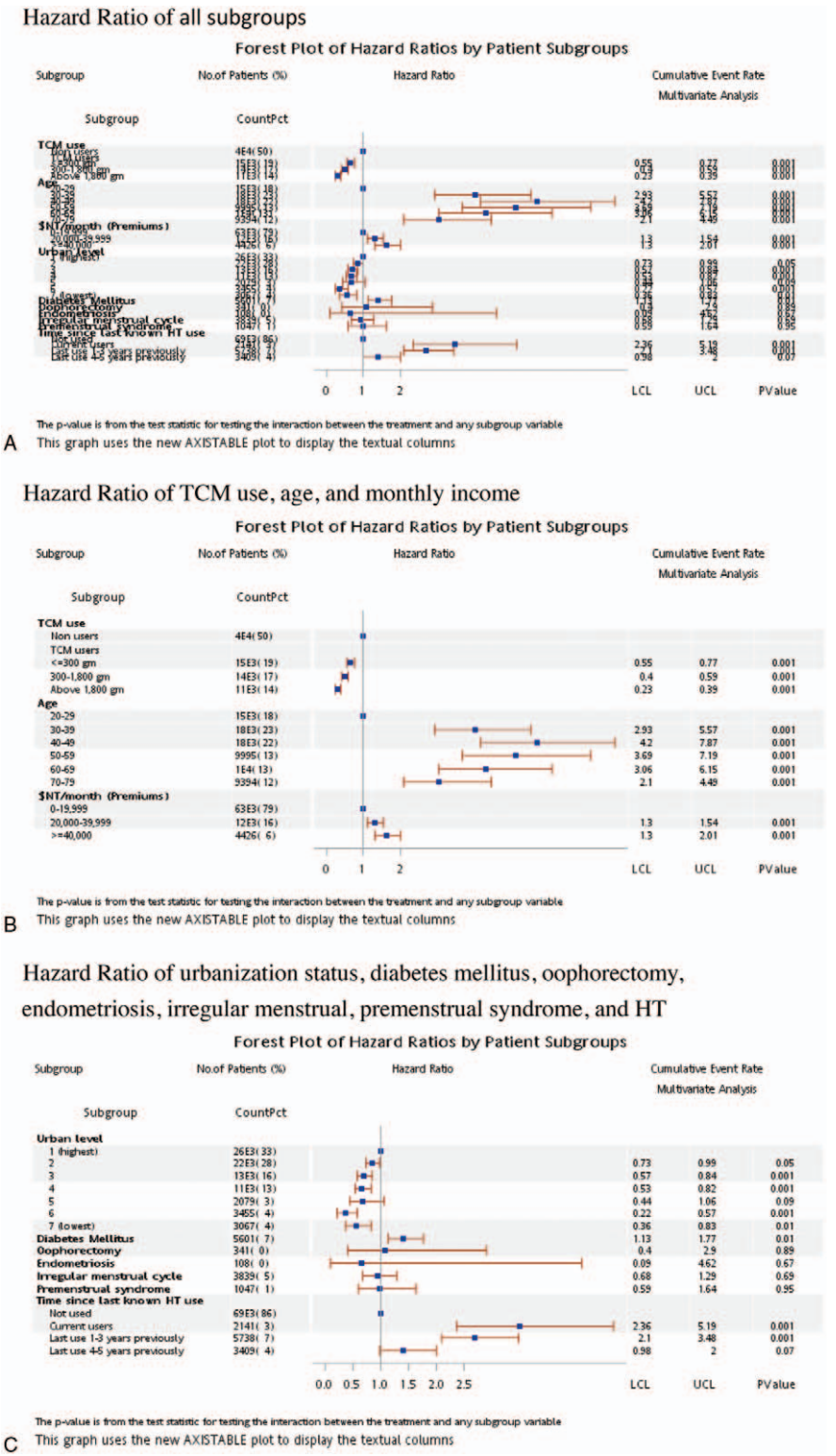

Figure 2. Forest plot for adjusted Cox Proportional Hazards Model Analysis of the breast cancer risk in Taiwanese women. Hazard ratio of (A) all subgroups, (B) TCM use, age, monthly income, and (C) urbanization status, diabetes mellitus, oophorectomy, endometriosis, irregular menstrual, premenstrual syndrome, and hormonal therapy (HT). HT = hormone therapy, TCM = traditional Chinese medicine.

the non-TCM group and 73 patients with breast cancer in the SWT group between 2002 and 2012. For both groups, the highest incidence density rate was noted in patients aged 40 to 49 years (2.64 and 0.84 per 10,000 person-years, respectively). The overall incidence density rates calculated for the non-TCM and SWT groups were respectively 1.73 and 0.63 per 10,000 person-years, representing a covariate adjusted HR of 0.36 (95% CI, 0.28–0.46).

4. Discussion

According to our research, this is the first study to use a nationwide cohort to document a dose–response relationship between the use of TCM in female patients and a decreased risk of breast cancer after controlling for confounders. Our findings on the protective effects of TCM against breast cancer are similar to those of an in vitro study that demonstrated growth inhibitory activity on human breast cancer cell lines.[30–33] Elevated risks of breast cancer were found among current users of HT compared with past users and nonusers. The risk of breast cancer associated with age, which was the strongest risk factor for breast cancer noted in our study, was comparable to that determined in previous studies.[34] In our study, the peak incidence of breast cancer was observed in women aged 40 to 49 years, which is also consistent with the findings of previous studies. These major risk factors for breast cancer were controlled through multivariate modeling and thus could not act as confounders in the present study.

Because the use of TCM is accepted in Taiwan, 71.1% of all female patients in our study sought medical advice from TCM outpatient services during the study period. Notably, all TCM treatments were prescribed by qualified TCM practitioners. This enabled us to rule out the possibility of selection or recall bias. Additionally, the power of our study was strengthened because we used a homogenous population of 184,386 female patients who had comprehensive 14-year medical records. The registration of invasive breast cancer as a catastrophic illness in Taiwan is based on pathology and cytologic evidence and allows for a full waiver of copayment; such a diagnosis is made only after serious consideration and is generally accurate. Access to specific procedural codes for breast cancer in our data makes the possibility of misclassification of breast cancer unlikely. Moreover, the findings of our study, shown in Fig. 2, corroborate the results of a previous study that demonstrated that women of higher socioeconomic status[35] or with diabetes mellitus[36] are more likely than others to develop breast cancer.

Our previous clinical trial found that Chinese herbs mediated the fluctuations in women's hormonal milieu, resulting in less frequent accompanying premenstrual syndrome, lighter menstrual flow, and fewer cramps prior to or during menstruation, which might be a predictive factor for breast cancer.[37] TCM doctors in Taiwan evaluate clinical symptoms and signs through 4 diagnostic methods (inspection, listening and smelling, inquiry, and pulse-feeling and palpation) for women with irregular menstruation, dysmenorrhea, insomnia, or menopausal symptoms. Thereafter, syndrome differentiation (a pathological summary of the body's health condition at a particular stage in the disease process) is confirmed. According to the results of studies that have determined prescriptions based on syndrome differentiation, the significantly decreased breast cancer risk in CHP users implies that this therapeutic concept in TCM might be a potential alternative for preventing the development of breast cancer through the elimination of "subhealth status." The association between decreasing breast cancer risk and increasing cumulative CHP dose was apparent in the present study and supported this hypothesis. Furthermore, subgroup analysis indicated that postmenopausal women simultaneously receiving HT and CHPs eventually attained a lower long-term risk of breast cancer than that of HT users. This indicates the apparent effect modification of CHP consumption in women exposed to exogenous estrogen. Thus, further research is necessary to confirm how each TCM remedy contributes to these suppressive modulations in the individual estrogen receptor subclass.

In general, TCM doctors treat gynecological disorders according to syndrome differentiation theory rather than by making specific diagnoses; this is based on holistic considerations for women, who suffer from a range of symptoms and complications at various anatomical sites. When a deficiency of blood is diagnosed, TCM doctors frequently prescribe SWT for alleviating various common symptoms of gynecological disorders, namely premenstrual syndrome, menstrual cramps, and irregular menstruation.[38] In accordance with a previous in vitro study,[25] the present study demonstrated that breast cancer risk was substantially lower among women receiving SWT compared with non-TCM users after potential confounders were considered. Furthermore, we conducted sensitivity analyses by stratification to assess age-specific incidence densities between CHP or SWT users and non-TCM users. Significant protective effects of TCM and SWT use against breast cancer risk were detected in most women in reproductive age groups. Hence, patients undergoing TCM health care, which uses pattern identification (*bian zheng lun zhi*) to adjust for gynecological disorders that might be potential determinants of breast cancer risk, are likely to be at a lower risk of developing subsequent breast cancer. According to our research, this is the first study to indicate that SWT might act as a prophylactic treatment for breast cancer in Asian women, after potential risk factors are considered.

The present study had some limitations. First, because the identities of patients are encrypted and thus not available through the NHI reimbursement database, any histopathology reports could not be obtained to verify the diagnoses. However, in Taiwan, National Health Insurance Company requires precertification of invasive breast cancer prior to oncologists' cancer treatment. Second, CHPs purchased directly from TCM herbal pharmacies or health foods that contain herbs used in TCM was not evaluated. Thus, the frequency of TCM use might have been underestimated. However, because the NHI system comprehensively covers TCM prescriptions, the cost of which is generally less than the cost of herbs sold on the market, most patients are not willing to pay extra for herbal products outside the National health insurance program. Third, any medical records could not be obtained to identify the reasons why patients left Taiwan or died before either the diagnosis of breast cancer or end of the study. Particularly, in our study, the differences in breast cancer risks between CHP or SWT consumers and non-TCM users in the propensity score-matching or stratified analyses were consistently observed.

5. Conclusions

In conclusion, integrating TCM health care into HT seems to contribute to a decrease in the risk of developing breast cancer. However, additional double-blind, randomized, placebo-control studies are needed for evaluating the cost-effectiveness of SWT as a method for preventing breast cancer in patients treated with HT. Our findings suggest that if conventional medical and TCM care is equally available, the integration of these health care systems is likely to be beneficial to women, particularly those with a high risk of developing breast cancer.

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