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# The Use of San-Huang-Xie-Xin-Tang Reduces the Mortality Rate among Breast Cancer Patients

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**Simple Summary:** Since San-Huang-Xie-Xin-Tang (SHXXT) is a potent anti-tumor therapy and breast cancer is the most common cause of cancer deaths worldwide, in the present retrospective cohort study, we explore the influence of SHXXT and its constituents on the mortality rate by analyzing 5387 breast cancer patients taking SHXXT and its constituents and 5387 breast cancer patients not using SHXXT and its constituents. Our study confirms SHXXT and its constituents are a useful alternative therapy to decrease the breast cancer mortality rate. In particular, the use of SHXXT is more effective than the use of only one constituent. With the increasing cumulative days of use and the annual average dose, the anti-tumor effect is more pronounced.

**Abstract:** Globally, breast cancer is the most common cause of cancer deaths. In Taiwan, it is the most prevalent cancer among females. Since San-Huang-Xie-Xin-Tang (SHXXT) exerts not only an anti-inflammatory but an immunomodulatory effect, it may act as a potent anti-tumor agent. Herein, the study aimed to explore the influence of SHXXT and its constituents on the mortality rate among breast cancer patients in Taiwan regarding the component effect and the dose–relationship effect. By using the Taiwan National Health Insurance (NHI) Research Database (NHIRD), the study analyzed 5387 breast cancer patients taking Chinese herbal medicine (CHM) and 5387 breast cancer patients not using CHM. CHM means SHXXT and its constituents in the study. The Kaplan–Meier method was utilized to determine the mortality probabilities among patients. Whether the CHM influences the mortality rate among patients was estimated by Cox proportional hazard regression analysis. The use of CHM could lower the cancer mortality rate by 59% in breast cancer patients. The protective effect was parallel to the cumulative days of CHM use and the annual average CHM dose. In addition, the mortality rate was lower in patients who used SHXXT compared to those who only used one of its constituents. SHXXT and its constituents were all promising therapeutic weapons against breast cancer.

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## 1. Introduction

Around the world, cancer is the top reason of death. During the past two decades, the annual incidence of breast cancer has doubled or tripled in Asia [1]. In Taiwan, breast cancer is also the most common cancer among females with increasing prevalence and incidence [2–4]. The etiology of breast cancer remains unsettled, which is attributable to genetic, hormonal, or reproductive factors [5]. Although the standard treatments for breast cancer patients include radiotherapy, chemotherapy, and target therapy [6], many patients still seek for help with complementary and alternative medicine. In Taiwan, adult cancer patients who used traditional Chinese medicine (TCM) had a lower cancer mortality rate than those without using TCM (adjusted hazard ratio (HR) = 0.69). Chinese herbal medicine (CHM) and acupuncture are the most common alternative choices [7–10]. TCM elicits a protective effect against breast cancer; accordingly, consumption of Chinese herbs can reduce the incidence of invasive breast cancer [11]. In Taiwan, a large proportion of patients receive CHM and Western medicine concurrently against breast cancer [12].

Since the inflammatory signals can trigger the formation of a tumor microenvironment, several cancers arise from chronic inflammation [13]. Being a CHM, San-Huang-Xie-Xin-Tang (SHXXT) is composed of three herbal medicines, *Rhizoma Rhei*, *Radix Scutellaria*, and *Rhizoma Coptidis* at a ratio of 2:1:1 or 1:1:1 [14]. It serves as a possible therapeutic choice for hepatitis C virus (HCV) infection [15], hypertension [16–18], septic shock [19], neuronal damage [20], gastrointestinal (GI) disorders [21,22], acute lung injury [23], and cardiomyocyte injury [24]. SHXXT can decrease COX2 and NF-κB induction to suppress the replication of HCV [15]. Through the expression of COX2, ROCK-II, and PDE5, SHXXT ameliorated U46619-induced systemic and pulmonary arterial blood hypertension [18]. Mediating by the formation of iNOs, COX2, and PGE2, SHXXT can prevent hypotension in LPS-treated rats [19]. In the neuroblastoma SH-SY5Y cells, SHXXT can prevent the formation of ROS and inflammatory response against neurotoxicity [20]. In experimentally induced GI motility dysfunction mice, SHXXT is a novel prokinetic agent to alleviate GI motility dysfunction in a dose-dependent manner [21]. In *Helicobacter pylori* infection, SHXXT can induce the anti-inflammatory effect through inhibiting the activation of NF-κB, the production of iNOS, COX-2, and IL-8 in human gastric epithelial AGS cells [22]. In addition, SHXXT attenuates inflammatory responses by decreasing the expression of IL-1β, iNOS, and TNF-α in lipopolysaccharide-induced rat lung injury [23]. It can protect rats' cardiomyocyte against apoptosis through eNOs and MAPK pathways after ischemia-reperfusion injury [24]. Besides, series studies have demonstrated that SHXXT has immunomodulatory, neuroprotective, and a potent anti-cancer effect [25–28]. Since, up till now, no studies have elucidated the relevance of SHXXT for breast cancers in detail, this population-based study aimed to investigate the effect of SHXXT and its constituents on breast cancer patients by analyzing the Taiwan National Health Insurance Research Database (NHIRD). Beside the impact of single constituent or compounds on cancer mortality rate, the study also clarified the dose–relationship effect based on the stratification of cumulative days of CHM use and the annual average CHM dose.

## 2. Materials and Methods

### 2.1. Data Source

From March 1995 till now, the Taiwan national health insurance (NHI) program has covered 99.6% of residents. All medical records reimbursed by the NHI were included in the NHIRD, in which the registry of beneficiaries, ambulatory and inpatient care claims data, and the registry of catastrophic illness were the source of the database. In the study, study subjects were recruited from the ambulatory and inpatient claims data liked with the registry of Catastrophic Illness during 2000 to 2010 and followed to the end of 2011.

### 2.2. Study Design and Cohort

This study aimed to evaluate the association between breast cancer mortality rate and the use of CHM, including SHXXT or one of its constituents (*Rhizoma Coptidis*, *Rhizoma Rhei*, or *Radix Scutellaria*). From the Registry for Catastrophic Illness database, 79,510 female patients who were newly diagnosed with breast cancer (International Classification of Disease, Ninth Revision, Clinical Modification (ICD-9-CM) = 174) during 2000–2010 were enrolled. The ICD-9-CM codes were identified by Chinese medicine physicians. The index date was the date of new diagnosis with breast cancer. They were followed up until the end of December 2011, death, or withdrawn from the insurance within a year of the follow-up period. Subjects younger than 18 years old or incomplete data were excluded from the analysis (n = 273). Subjects who withdraw from the insurance within a year of the follow-up period were also excluded (n = 51). A patient who took SHXXT or one of the constituents for more than 30 days was set as a CHM user (n = 5505). A patient without using CHM, acupuncture, or manipulative records was identified as a non-CHM user (n = 10,153). Subsequently, in order to match the two populations equally, the CHM user and the non-CHM user identified 5387 breast cancer patients in each group randomly frequency matched with distributions of age, and index year at 1 to 1 ratio. Age was set into three categories (18 to 39 years, 40 to 59 years, and more than 60 years). Gender was categorized as male and female. Urbanization was set into four levels (1, highest, 2, 3 and 4, lowest). The Charlson Comorbidity Index (CCI) score was divided into three groups (0, 1, and 2 or higher). Besides, treatment (radiotherapy, chemotherapy, breast cancer surgery) and drugs which patients received within half a year after the new diagnosis of breast cancer were included and followed up to the end of the study.

### 2.3. Study Outcome

All-cause mortality was set as the study outcome, in which date of death was obtained from the major illness certificate. The follow-up time was estimated in person-years, continued until the end of December 2011 or the death of the patient, whichever occurred first.

### 2.4. Statistical Analysis

The CHM user and the non-CHM user were compared in terms of demographic characteristics, CCI score, treatment, and drugs. To exam the categorical variables of the baseline characteristics, chi-square test was used. Otherwise, to exam continuous variables, t test was used. The survival probability between CHM group and non-CHM group were plotted by the Kaplan–Meier method and estimated by the Log-rank test, respectively. To calculate the HRs and 95% confidence intervals (CI) for the breast cancer mortality rate, the Cox proportional hazard model was utilized. SAS statistical software (version 9.4) was used to analyze all the database in the study with a two-tailed significance level of 0.05.

## 3. Results

### 3.1. Baseline Characteristics of Breast Cancer Patients

The baseline characteristics of the CHM user and non-CHM user were displayed in Table 1. In total, 5387 CHM users and 5387 non-CHM users with respective mean ages of 49.35 $\pm$ 10.08 and 49.41 $\pm$ 10.12 years were recruited in the analysis. In total, 67.94% of patients were 40–59 years old, and almost all patients (94.45%) had a CCI score of 0. A significantly higher percentages of patients had received previous breast surgery (94.8% vs. 85.74%, $p < 0.0001$), Cyclophosphamide (70.54% vs. 67.27%, $p = 0.0002$), Tamoxifen (69.96% vs. 65.23%, $p < 0.0001$), and Anastrozole (16.3% vs. 12.31%, $p < 0.0001$) in the CHM users. Otherwise, a significantly lower percentages of patients had received Docetaxel (16.87% vs. 21.55%, $p < 0.0001$), Paclitaxel (11.62 vs. 14.52, $p < 0.0001$) and Trastuzumab (6.61% vs. 7.82%, $p = 0.0155$) in the CHM users.

**Table 1.** Baseline characteristics of breast cancer patients.

| Characteristics | Non-CHM User (n = 5387) | CHM User (n = 5387) | *p*-Value |
|---|---|---|---|
| **Age, mean ± SD (years)** | 49.41 (10.12) | 49.35 (10.08) | 0.7591 |
| **Age group, n (%)** | | | 0.99 |
| 18–39 | 911 (16.91) | 911 (16.91) | |
| 40–59 | 3660 (67.94) | 3660 (67.94) | |
| ≥60 | 816 (15.15) | 816 (15.15) | |
| **Urbanization level, n (%)** | | | <0.0001 |
| 1 | 2002 (37.16) | 1790 (33.23) | |
| 2 | 1724 (32) | 1784 (33.12) | |
| 3 | 725 (13.46) | 879 (16.32) | |
| 4 | 936 (17.38) | 934 (17.34) | |
| **CCI score, n (%)** | | | 0.0006 |
| 0 | 5044 (96.63) | 5088 (94.45) | |
| 1 | 201 (3.73) | 214 (3.97) | |
| More than 2 | 142 (2.64) | 85 (1.58) | |
| **Treatment, n (%)** | | | |
| Breast cancer surgery | 4619 (85.74) | 5107 (94.8) | <.0001 |
| Radiotherapy | 2666 (49.49) | 2770 (51.42) | 0.0451 |
| Chemotherapy | 3936(73.06) | 3958 (73.47) | 0.632 |
| **Drugs, n (%)** | | | |
| Epirubicin | 2179 (40.45) | 2207 (40.97) | 0.583 |
| Fluorouracil | 3082 (57.21) | 3126 (58.03) | 0.391 |
| Cyclophosphamide | 3624 (67.27) | 3800 (70.54) | 0.0002 |
| Docetaxel | 1161 (21.55) | 909 (16.87) | <0.0001 |
| Paclitaxel | 782 (14.52) | 626 (11.62) | <0.0001 |
| Goserelin acetate | 67 (1.24) | 61 (1.13) | 0.5937 |
| Tamoxifen | 3514 (65.23) | 3769 (69.96) | <0.0001 |
| Anastrozole | 663 (12.31) | 878 (16.3) | <0.0001 |
| Letrozole | 771 (14.31) | 824 (15.3) | 0.1505 |
| Exemestane | 413 (7.67) | 405 (7.52) | 0.7711 |
| Toremifene | 52 (0.97) | 64 (1.19) | 0.2626 |
| Trastuzumab | 421 (7.82) | 356 (6.61) | 0.0155 |

Abbreviations: CHM, Chinese herbal medicine; CCI, Charlson Comorbidity Index.

### *3.2. Effect of CHM on Mortality Rate of Breast Cancer Patients*

At the end of the follow up, 1597 of all enrolled patients had died (456 CHM-users and 1141 non-CHM users) (Figure 1). To elucidate the effect of CHM on breast cancer mortality rate, the cancer mortality rate among CHM user and non-CHM user was stratified according to baseline characteristics of breast cancer patients using the Cox proportional hazard regression model (Table 2). Mortality incidence densities were 13.62 per 1000 person-years and 41.38 per 1000 person-years in the CHM users and non-CHM users, respectively. The mortality rate was significantly ($p < 0.001$) lower in the CHM users (decrease by 59% after adjusting for age group, urbanization level, CCI score, treatment, and drugs). In age-specific analyses, the CHM users also had a significantly lower mortality rate than

non-CHM users in all age groups. In urbanization level or CCI score-specific analyses, the CHM users also had a significantly lower mortality rate than non-CHM users in all groups. Regardless of comorbidities, treatment, and drugs, CHM users had a relatively lower mortality rate. Treatment-stratified analysis revealed that mortality was higher in the treatment group compared to the group without receiving treatment. In sub-analyses of the drug, mortality was higher in the drug group compared to the group not receiving a drug except Toremifene.

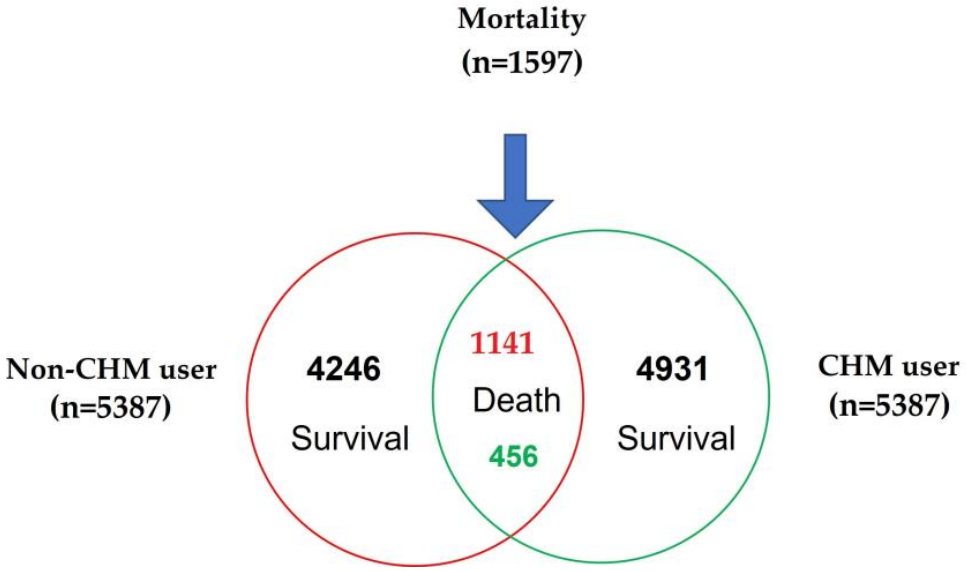


**Figure 1.** Mortality number in breast cancer patients with and without taking CHM.

**Table 2.** Breast cancer mortality rate among CHM user and non-CHM user stratified by age group, urbanization level, CCI score, treatment, and drugs.

| Characteristics | Non-CHM User | | | CHM User | | | Crude HR | Adjusted HR ‡ |
|---|---|---|---|---|---|---|---|---|
| | Event | Person Years | IR † | Event | Person Years | IR † | | |
| **Total** | 1141 | 27,576 | 41.38 | 456 | 33,488 | 13.62 | 0.33 (0.3–0.37) *** | 0.41 (0.37–0.46) *** |
| **Age group** | | | | | | | | |
| 18–39 | 171 | 4879 | 34.92 | 75 | 6083 | 12.33 | 0.35 (0.27–0.46) *** | 0.4 (0.3–0.54) *** |
| 40–59 | 741 | 18,929 | 39.15 | 288 | 22,641 | 12.72 | 0.33 (0.29–0.38) *** | 0.41 (0.35–0.47) *** |
| ≥60 | 229 | 3750 | 61.07 | 93 | 4765 | 19.52 | 0.33 (0.26–0.42) *** | 0.35 (0.27–0.45) *** |
| Urbanization level | | | | | | | | |
| 1 | 348 | 10,701 | 32.52 | 138 | 11,097 | 12.44 | 0.39 (0.32–0.47) *** | 0.49 (0.4–0.6) *** |
| 2 | 368 | 8786 | 41.88 | 158 | 11,069 | 14.27 | 0.34 (0.28–0.41) *** | 0.38 (0.31–0.46) *** |
| 3 | 185 | 3512 | 52.68 | 71 | 5438 | 13.06 | 0.25 (0.19–0.33) *** | 0.33 (0.25–0.43) *** |
| 4 | 240 | 4577 | 52.43 | 89 | 5884 | 15.13 | 0.3 (0.23–0.38) *** | 0.39 (0.3–0.5) *** |
| **CCI score** | | | | | | | | |
| 0 | 1012 | 26,100 | 38.77 | 416 | 31,838 | 13.07 | 0.34 (0.3–0.38) *** | 0.41 (0.37–0.46) *** |
| 1 | 70 | 937 | 74.73 | 21 | 1240 | 16.93 | 0.23 (0.14–0.37) *** | 0.29 (0.17–0.49) *** |
| More than 2 | 59 | 539 | 109.42 | 19 | 410 | 46.30 | 0.43 (0.26–0.73) ** | 0.42 (0.24–0.73) ** |

**Table 2.** *Cont.*

| Characteristics | Non-CHM User | | | CHM User | | | Crude HR | Adjusted HR ‡ |
|---|---|---|---|---|---|---|---|---|
| | Event | Person Years | IR † | Event | Person Years | IR † | | |
| **Treatment** | | | | | | | | |
| Breast cancer surgery | | | | | | | | |
| No | 367 | 2704 | 135.74 | 48 | 1903 | 25.22 | 0.23 (0.17–0.32) *** | 0.25 (0.18–0.34) *** |
| Yes | 774 | 24,872 | 31.12 | 408 | 31,585 | 12.92 | 0.41 (0.37–0.46) *** | 0.43 (0.38–0.49) *** |
| Radiotherapy | | | | | | | | |
| No | 426 | 14,848 | 28.69 | 116 | 17,493 | 6.63 | 0.24 (0.2–0.3) *** | 0.29 (0.24–0.36) *** |
| Yes | 715 | 12,728 | 56.18 | 340 | 15,996 | 21.26 | 0.37 (0.33–0.43) *** | 0.46 (0.41–0.53) *** |
| Chemotherapy | | | | | | | | |
| No | 177 | 7689 | 23.02 | 37 | 9584 | 3.86 | 0.18 (0.13–0.26) *** | 0.2 (0.14–0.28) *** |
| Yes | 964 | 19,887 | 48.87 | 419 | 23,904 | 17.53 | 0.36 (0.32–0.41) *** | 0.45 (0.4–0.5) *** |
| **Drugs** | | | | | | | | |
| Epirubicin | | | | | | | | |
| No | 567 | 17.185 | 32.99 | 182 | 20.655 | 8.81 | 0.27 (0.23–0.32) *** | 0.35 (0.3–0.42) *** |
| Yes | 574 | 10.391 | 55.24 | 274 | 12.834 | 21.35 | 0.38 (0.33–0.44) *** | 0.44 (0.38–0.51) *** |
| Fluorouracil | | | | | | | | |
| No | 383 | 11.574 | 33.09 | 124 | 13.796 | 8.99 | 0.28 (0.23–0.34) *** | 0.35 (0.28–0.43) *** |
| Yes | 758 | 16.002 | 47.37 | 332 | 19.692 | 16.86 | 0.36 (0.31–0.4) *** | 0.42 (0.37–0.48) *** |
| Cyclophosphamide | | | | | | | | |
| No | 332 | 8825 | 37.62 | 83 | 10.396 | 7.98 | 0.23 (0.18–0.29) *** | 0.29 (0.22–0.37) *** |
| Yes | 809 | 18.751 | 43.14 | 373 | 22.093 | 16.15 | 0.37 (0.33–0.42) *** | 0.44 (0.38–0.49) *** |
| Docetaxel | | | | | | | | |
| No | 610 | 23.279 | 26.20 | 196 | 29.218 | 6.71 | 0.26 (0.22–0.31) *** | 0.31 (0.26–0.36) *** |
| Yes | 531 | 4297 | 123.57 | 260 | 4270 | 60.89 | 0.46 (0.39–0.53) *** | 0.52 (0.45–0.61) *** |
| Paclitaxel | | | | | | | | |
| No | 722 | 24.227 | 29.80 | 228 | 30.102 | 7.57 | 0.26 (0.23–0.3) *** | 0.31 (0.27–0.36) *** |
| Yes | 419 | 3349 | 125.12 | 228 | 3387 | 67.32 | 0.5 (0.43–0.59) *** | 0.55 (0.47–0.65) *** |
| Goserelin acetate | | | | | | | | |
| No | 1133 | 27.222 | 40.89 | 440 | 33.156 | 13.27 | 0.33 (0.29–0.37) *** | 0.4 (0.36–0.45) *** |
| Yes | 28 | 354 | 79.19 | 16 | 332 | 48.14 | 0.59 (0.32–1.09) | 0.49 (0.22–1.07) |
| Tamoxifen | | | | | | | | |
| No | 526 | 8274 | 63.57 | 147 | 9402 | 15.64 | 0.26 (0.22–0.31) *** | 0.34 (0.28–0.41) *** |
| Yes | 615 | 19.302 | 31.86 | 309 | 24.087 | 12.83 | 0.4 (0.35–0.46) *** | 0.45 (0.39–0.52) *** |
| Anastrozole | | | | | | | | |
| No | 895 | 23.944 | 37.38 | 299 | 27.694 | 10.80 | 0.3 (0.26–0.34) *** | 0.37 (0.32–0.42) *** |
| Yes | 246 | 3632 | 67.74 | 157 | 5795 | 27.09 | 0.39 (0.32–0.47) *** | 0.5 (0.4–0.61) *** |
| Letrozole | | | | | | | | |
| No | 898 | 23.522 | 38.18 | 295 | 28.283 | 10.43 | 0.28 (0.25–0.32) *** | 0.35 (0.3–0.39) *** |
| Yes | 243 | 4054 | 59.94 | 161 | 5206 | 30.93 | 0.49 (0.4–0.6) *** | 0.6 (0.49–0.74) *** |

**Table 2.** *Cont.*

| Characteristics | Non-CHM User | | | CHM User | | | Crude HR | Adjusted HR ‡ |
|---|---|---|---|---|---|---|---|---|
| | Event | Person Years | IR † | Event | Person Years | IR † | | |
| Exemestane | | | | | | | | |
| No | 962 | 25.296 | 38.03 | 337 | 30.880 | 10.91 | 0.29 (0.26–0.33) *** | 0.37 (0.32–0.42) *** |
| Yes | 179 | 2280 | 78.49 | 119 | 2609 | 45.62 | 0.55 (0.44–0.7) *** | 0.58 (0.46–0.74) *** |
| Toremifene | | | | | | | | |
| No | 1123 | 27.243 | 41.22 | 447 | 33.027 | 13.53 | 0.33 (0.3–0.37) *** | 0.41 (0.36–0.45) *** |
| Yes | 18 | 333 | 54.05 | 9 | 461 | 19.50 | 0.35 (0.16–0.78) ** | 0.11 (0.02–0.48) ** |
| Trastuzumab | | | | | | | | |
| No | 934 | 26.041 | 35.87 | 347 | 31.897 | 10.88 | 0.31 (0.27–0.35) *** | 0.39 (0.34–0.44) *** |
| Yes | 207 | 1535 | 134.90 | 109 | 1591 | 68.50 | 0.46 (0.37–0.58) *** | 0.48 (0.38–0.61) *** |

Abbreviations: CHM, Chinese herbal medicine; CCI, Charlson Comorbidity Index; HR, hazard ratio; CI, confidence interval. † IR, incidence rates, per 1000 person-years. ‡: represented adjusted hazard ratio: mutually adjusted for CHM use, age group, urbanization level, CCI score, treatment, and drugs by Cox proportional hazard regression. ** $p < 0.01$, *** $p < 0.001$.

The survival probability between CHM user and non-CHM user among breast cancer patients was plotted in Figure 2. Kaplan–Meier survival analysis with a log rank test revealed that CHM users had significantly higher survival rate compared to non-CHM users ($p < 0.001$).

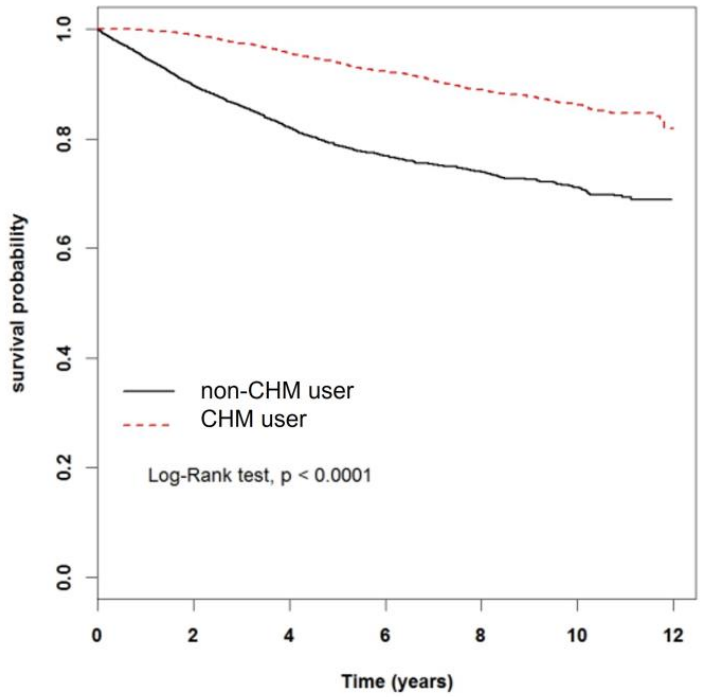


**Figure 2.** Kaplan–Meier curves for the survival analysis in breast cancer patients with and without taking CHM.

### *3.3. The Cumulative Days and Annual Average Dose of CHM Use Influence the Breast Cancer Mortality Rate*

Next, subgroup analyses were further arranged to clarify the influence of the cumulative days and annual average dose of CHM use among breast cancer patients. The results shows that the risk of cancer mortality rate significantly decreased with the increasing

cumulative days of CHM use (HR = 0.44, 0.41 and 0.31 in 30–90 days, 90–180 days, and >180 days, respectively, $p$ for trend <0.001) (Table 3). In total, 25, 50, and 75 percentiles of the annual average CHM dose were 35.1, 67.2, and 147 (g), respectively. The risk of cancer mortality rate significantly decreased with the increasing annual average CHM dose (HR = 0.50, 0.43, 0.39, and 0.30 at <35.1 g, 35.1–67.2 g, 67.2–147 g, and >147 g, respectively, $p$ for trend <0.001) (Table 4). Relative to non-CHM users, the cancer mortality rate in CHM users was the lowest during follow-up periods <2 years and then increased with an increasing follow-up period. However, the mortality rate did not significantly differ between CHM users and non-CHM users after a follow-up of more than 5 years (Table 5). Taken together, the protective effect of CHM was parallel to the cumulative days of CHM use and the annual average CHM dose, which is most dominant during the initial usage.

**Table 3.** The risk of mortality rate stratified by the cumulative days of CHM use among breast cancer patients.

| Characteristics | N | Mortality | HR (95% CI) | |
|---|---|---|---|---|
| | | No. of Event | Crude | Adjusted † |
| **Non-CHM users** | 5387 | 1141 | 1 (reference) | 1 (reference) |
| **CHM users** | | | | |
| **30–90 days** | 3209 | 288 | 0.36 (0.31–0.40) *** | 0.44 (0.38–0.50) *** |
| **90–180 days** | 1233 | 106 | 0.33 (0.27–0.41) *** | 0.41 (0.33–0.50) *** |
| **>180 days** | 945 | 62 | 0.26 (0.20–0.33) *** | 0.31 (0.24–0.40) *** |
| ***p* for trend** | | | **<0.0001** | **<0.0001** |

Abbreviations: CHM, Chinese herbal medicine; HR, hazard ratio; CI, confidence interval. Crude HR represented relative hazard ratio. † Adjusted HR represented adjusted hazard ratio: mutually adjusted for age group, urbanization level, CCI score, treatment, and drugs by Cox proportional hazard regression. *** $p < 0.001$.

**Table 4.** The risk of mortality rate stratified by the annual average CHM dose among breast cancer patients.

| Annual Average CHM Dose (g) | N | Mortality | HR (95% CI) | |
|---|---|---|---|---|
| | | No. of Event | Crude | Adjusted † |
| **Non-CHM users** | 5387 | 1141 | 1 (reference) | 1 (reference) |
| **CHM users** | | | | |
| **<35.1 (g)/year** | 1346 | 140 | 0.42 (0.35–0.50) *** | 0.50 (0.42–0.60) *** |
| **35.1–67.2 (g)/year** | 1346 | 123 | 0.36 (0.30–0.44) *** | 0.43 (0.35–0.51) *** |
| **67.2–147 (g)/year** | 1340 | 113 | 0.33 (0.27–0.40) *** | 0.39 (0.32–0.48) *** |
| **>147 (g)/year** | 1355 | 80 | 0.23 (0.18–0.29) *** | 0.30 (0.24–0.38) *** |
| ***p* for trend** | | | <0.0001 | <0.0001 |

Abbreviations: CHM, Chinese herbal medicine; HR, hazard ratio; CI, confidence interval. Crude HR represented relative hazard ratio. † Adjusted HR represented adjusted hazard ratio: mutually adjusted for age group, urbanization level, CCI score, treatment, and drugs by Cox proportional hazard regression. *** $p < 0.001$.

### *3.4. The Impact of SHXXT and Its Constituents on the Breast Cancer Mortality Rate*

At last, to clarify the effect of SHXXT and its constituents among breast cancer patients, stratified analyses were performed further. The results reveals that the mortality rate was lower in patients who used SHXXT compound compared to patients who only used one of its constituents (HR = 0.42, 0.40, 0.39 and 0.32 for *Rhizoma Rhei*, *Radix Scutellaria*, *Rhizoma Coptidis*, and SHXXT, respectively) (Table 6). Above all, SHXXT compound elicited the more significant impact on the deceasing cancer mortality rate compared to the use of one individual constituents.

**Table 5.** The effects of the cumulative days of CHM use on the mortality rate among breast cancer patients stratified by follow-up period.

| Characteristics | Mortality | HR (95% CI) | |
|---|---|---|---|
| | No. of Event | Crude | Adjusted † |
| **Follow-up period:≤2 years** | | | |
| **Non-CHM users** | 440 | 1 (reference) | 1 (reference) |
| **CHM users** | | | |
| **30–90 days** | 136 | 0.43 (0.35–0.52) *** | 0.51 (0.42–0.62) *** |
| **90–180 days** | 52 | 0.42 (0.31–0.56) *** | 0.45 (0.34–0.61) *** |
| **>180 days** | 24 | 0.25 (0.17–0.38) *** | 0.29 (0.19–0.44) *** |
| **Follow-up period: 2–5 years** | | | |
| **Non-CHM users** | 137 | 1 (reference) | 1 (reference) |
| **CHM users** | | | |
| **30–90 days** | 91 | 0.82 (0.63–1.07) | 0.88 (0.68–1.15) |
| **90–180 days** | 37 | 0.83 (0.58–1.20) | 0.82 (0.57–1.19) |
| **>180 days** | 28 | 0.87 (0.58–1.31) | 0.82 (0.55–1.24) |
| **Follow-up period: >5 years** | | | |
| **Non-CHM users** | 25 | 1 (reference) | 1 (reference) |
| **CHM users** | | | |
| **30–90 days** | 16 | 0.70 (0.37–1.31) | 0.60 (0.31–1.51) |
| **90–180 days** | 6 | 0.69 (0.28–1.67) | 0.58 (0.22–1.57) |
| **>180 days** | 8 | 1.28 (0.58–2.83) | 0.75 (0.32–1.78) |

Abbreviations: CHM, Chinese herbal medicine; HR, hazard ratio; CI, confidence interval. Crude HR represented relative hazard ratio. † Adjusted HR represented adjusted hazard ratio: mutually adjusted for age group, urbanization level, CCI score, treatment, and drugs by Cox proportional hazard regression. *** $p < 0.001$.

**Table 6.** The effects of CHM formulation on mortality rate among breast cancer patients.

| CHM Prescription | Mortality | | HR (95% CI) | |
|---|---|---|---|---|
| | N | No. of Event | Crude | Adjusted † |
| **Non-CHM user** | 5387 | 1141 | 1 (reference) | 1 (reference) |
| **Single constituent** | | | | |
| ***Rhizoma Rhei*** | 3049 | 278 | 0.36 (0.31–0.41) *** | 0.42 (0.37–0.48) *** |
| ***Radix Scutellaria*** | 3958 | 327 | 0.32 (0.28–0.36) *** | 0.40 (0.36–0.46) *** |
| ***Rhizoma Coptidis*** | 2644 | 215 | 0.31 (0.27–0.36) *** | 0.39 (0.34–0.45) *** |
| **Compounds** | | | | |
| **SHXXT** | 489 | 33 | 0.25 (0.18–0.36) *** | 0.32 (0.22–0.45) *** |

Abbreviations: CHM, Chinese herbal medicine; HR, hazard ratio; CI, confidence interval. Crude HR represented relative hazard ratio. † Adjusted HR represented adjusted hazard ratio: mutually adjusted for age group, urbanization level, CCI score, treatment, and drugs by Cox proportional hazard regression. *** $p < 0.001$.

## 4. Discussion

This retrospective, large-scale, population-based cohort study is not only the first Taiwanese study to investigate the cancer mortality rate among breast cancer patients who received SHXXT or its constituents but also the first study in the Asian population. The use of SHXXT or its constituents reduced the breast cancer mortality rate by 59%. Notably, the protective effect of SHXXT and its constituents on breast cancer increased with the cumulative days and annual average dose. Moreover, the mortality rate was lower in

breast cancer patients who used the SHXXT compound than those who only used one of its constituents.

Series studies have reported that extracts of SHXXT constituents have anti-cancer effects. According to the gene set enrichment analysis by Cheng et al., SHXXT can exert anti-proliferative effects on breast cancer HepG2 cells through regulating p53 signaling [26]. The decoction SHXXT typically contains *Rhizoma Rhei*, *Radix Scutellaria*, and *Rhizoma Coptidis* at ratios of 2:1:1 or 1:1:1. Notably, the anti-proliferative effects of SHXXT are mainly conferred by *Rhizoma Coptidis*. The major component of *Rhizoma Coptidis* is berberine; it can induce human breast cancer cell apoptosis by upregulating TNF-α and interferon-β in a time- or dose-dependent manner [29,30]. Chou and their colleagues reported that berberine induces cytotoxicity in breast cancer cells through reactive oxygen species, dysregulation of redox regulation, centrosomal structure, electron transport, cell signaling, protein folding, proteolysis, and protein trafficking [31]. Berberine decreases cell viability by inhibiting the Ras/MAPK and PI3K pathways, by suppressing activation of growth factor receptors (Her2/neu, EGF receptor, and VEGF receptor), by increasing apoptosis-related molecules (Smac/DIABLO, caspases, and Bax), tumor suppressor genes (p53, Clip/p21, Klip/p27, and Rb) [32], and over-expression of HDAC1 [33], prohibitin [34], serine/threonine protein phosphatase 2A [35,36], and by blockade of Bcl-2 expression. In addition, berberine can increase the amount of E-cadherin and suppress activation of the Wnt/ β-catenin pathway to modulate tumor cell migration and metastasis [37]. Apart from berberine, coptisine is an isoquinoline alkaloid extract of *Rhizoma Coptidis*, from which can emerge the anti-metastasis effect. Through down-regulating MMP-9 and increasing TIMP-1, coptisine can suppress adhesion, migration, and invasion of MDA-MB-231 breast cancer cells [38]. Hence, *Rhizoma Coptidis* inhibits the breast cancer cell proliferation and metastasis based on these two important components.

In addition to *Rhizoma Coptidis*, *Radix Scutellaria* is another constituent of SHXXT, which also has an anti-cancer effect due to its containing Oroxylin A and numerous flavonoids such as wogonin and baicalin [39]. Being a major component of *Radix Scutellaria*, Oroxylin A inhibits the binding activity of hexokinase-II (HK-II) with mitochondria in a SIRT3-dependent manner to suppress glycolysis and induce mitochondrial cytotoxicity in human breast cancer cell lines [40]. Another component of *Radix Scutellaria*, wogonin, inhibits breast cancer cells invasion by downregulating ERK1/2 and PKC-δ [41]. Through decreasing both endogenous and PMA-induced MMP-9 expression, wogonin could inhibit tumor invasion and metastasis [42]. Wogonin also could induce cell differentiation, impair cell apoptosis, and activate both antioxidant and anti-angiogenesis activity against breast cancer formation [43–46].

Moreover, the other constituent of SHXXT, *Rhizoma Rhei*, exerts a high estrogenic potency, of which chrysophanol 1-O-β-D-glucopyranoside, aloe emodin, and rhapontigenin are the main isolated compounds. Most breast cancer cells are estrogen receptor-(ER)/progesterone receptor (PR)-positive, with human epidermal growth factor receptor 2 (HER2)-negative (69%), and almost half of postmenopausal patients have ER-positive breast cancer cells [47,48]. Since estrogen can stimulate ER-positive breast cancer cell to proliferate, a selective ER modulator that blocks the binding of estrogen to ER is effective to treat ER-positive breast cancer [49,50]. Through regulating the expression of ER, *Rhizoma Rhei* can modulate the proliferation of breast cancer MCF-7 cell in a concentration-dependent manner [51]. Chrysophanol 1-O-β-D-glucopyranoside mediates mitochondria-dependent apoptosis, whereas aloe emodin and rhapontigenin activate the caspase-8 pathway to induce mitochondria-independent apoptosis. Therefore, *Rhizoma Rhei* components could help hormone replacement therapy and chemoprevention against breast cancer owing to their potent estrogenic and inhibitory activities [52].

Since three constituents of SHXXT all have an important anti-cancer effect, the cancer mortality rate influence of the SHXXT component is supposed to be superior to that of a single constituent. Around the world, the major causes of morbidity and mortality are tumor invasion and metastasis. To halt the breast cancer mortality, the main objective is

to inhibit cancer invasion and metastasis. Since extracts of three SHXXT constituents not only have anti-proliferative and anti-angiogenesis effects but also exert anti-invasive and anti-metastatic impacts on breast cancer, the multi-component nature of medicinal herbs makes them particularly suitable to treat complex disease through synergistic activity [53]. Therefore, SHXXT is more effective than its individual components in terms of reducing mortality in breast cancer patients.

The strength of the study is that the study traced a large sample size of patients for a long period by using NHIRD. NHIRD is good for assessing survival rates, herb–drug interactions, and the cost-effectiveness of drug treatments. In addition, the study analyzed the specific ascertainment of numerous outcome events, the identification of an exposure–response relationship, and the comparison of different average annual doses. Besides, the data contained in an administrative database rather than data collected in a hospital-based study helped to avoid selection bias.

However, several limitations are retained in the study. First, this retrospective observational study could only analyze the data contained in NHIRD. Since the de-identified data are released for public research and the NHIRD is a claims-based database, no additional clinical information is available, e.g., histology subtype, gene change, and cancer staging [54–56]. Second, some possible confounders such as lifestyle practices, physical activity, dietary intake, and genetic factors are unavailable. Besides, the exposure–response relationship is only expressed in terms of cumulative days of CHM use; the actual adherence could not be ascertained. In addition, patients directly purchasing CHM or herbs from herbal pharmacies or health food stores cannot be identified in the NHI program. Only CHM prescribed by licensed doctors can be reimbursed; hence, the frequency of the CHM use might have been under-estimated. However, a large portion of patients would likely prefer to purchase CHM in the NHI system because of the comprehensive coverage and lower cost of CHM prescriptions. Finally, randomized controlled trials should be arranged in the future due to the more powerful statistical significance.

## 5. Conclusions

Our study suggests that exposure to CHM and SHXXT, especially a high annual average dose, or high cumulative use days, is associated with reduced mortality in breast cancer patients. Patients receiving SHXXT for more than 30 days as a treatment apparently seem to have a better overall survival outcome than do patients who did not receive it more than 30 days. However, mortality increased with a follow-up duration at all timepoints except >5 years. Hence, SHXXT and its individual compounds can be considered promising therapeutic weapons against breast cancer. Although the detailed mechanisms are as yet elusive, SHXXT is generally considered the stronger anti-inflammatory medicine, or the so-called "clear the heat", in the Chinese Medicine system. Therefore, we are now performing ongoing clinical trials at Kaohsiung medical university hospital which were approved by the Institutional Review Board of Kaohsiung Medical University Hospital to investigate the effects of SHXXT intervention in patients who suffer from breast cancer.

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