Complementary Chinese Herbal Medicine Therapy Improves Survival of Patients With Pancreatic Cancer in Taiwan: A Nationwide Population-Based Cohort Study

Yi-Ting Kuo, MD¹,², Hou-Hsun Liao, MD¹,², Jen-Huai Chiang, MS³, Mei-Yao Wu, MD, PhD⁴,⁵, Bor-Chyuan Chen, MD², Ching-Mao Chang, MD, PhD⁶, Ming-Hsien Yeh, MD¹,²,⁷, Tung-Ti Chang, MD, PhD¹,⁸, Mao-Feng Sun, MD, PhD¹,⁴, Chia-Chou Yeh, MD, PhD²,⁷, and Hung-Rong Yen, MD, PhD¹,⁴,⁵,⁹,¹⁰

Abstract

Background: Pancreatic cancer is a difficult-to-treat cancer with a late presentation and poor prognosis. Some patients seek traditional Chinese medicine (TCM) consultation. We aimed to investigate the benefits of complementary Chinese herbal medicine (CHM) among patients with pancreatic cancer in Taiwan. Methods: We included all patients with pancreatic cancer who were registered in the Taiwanese Registry for Catastrophic Illness Patients Database between 1997 and 2010. We used 1:1 frequency matching by age, sex, the initial diagnostic year of pancreatic cancer, and index year to enroll 386 CHM users and 386 non-CHM users. A Cox regression model was used to compare the hazard ratios (HRs) of the risk of mortality. The Kaplan-Meier curve was used to compare the difference in survival time. Results: According to the Cox hazard ratio model mutually adjusted for CHM use, age, sex, urbanization level, comorbidity, and treatments, we found that CHM users had a lower hazard ratio of mortality risk (adjusted HR = 0.67, 95% CI = 0.56-0.79). Those who received CHM therapy for more than 90 days had significantly lower hazard ratios of mortality risk than non-CHM users (90- to 180-day group: adjusted HR = 0.56, 95% CI = 0.42-0.75; >180-day group: HR = 0.33, 95% CI = 0.24-0.45). The survival probability was higher for patients in the CHM group. Bai-hua-she-she-cao (Herba Oldenlandiae; Hedyotis diffusa Spreng) and Xiang-sha-liu-jun-zi-tang (Costus and Chinese Amomum Combination) were the most commonly used single herb and Chinese herbal formula, respectively. Conclusions: Complementary Chinese herbal therapy might be associated with reduced mortality among patients with pancreatic cancer. Further prospective clinical trial is warranted.

Keywords

Chinese herbal medicine, complementary and alternative medicine, National Health Insurance Research Database, pancreatic cancer, traditional Chinese medicine

Submitted December 7, 2016; revised April 16, 2017; accepted June 15, 2017

¹Graduate Institute of Chinese Medicine, School of Chinese Medicine, College of Chinese Medicine, China Medical University, Taichung, Taiwan
²Department of Chinese Medicine, Dalin Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation, Chia-Yi, Taiwan
³Management Office for Health Data, China Medical University Hospital, Taichung, Taiwan
⁴Department of Chinese Medicine, China Medical University Hospital, Taichung, Taiwan
⁵Research Center for Traditional Chinese Medicine, China Medical University Hospital, Taichung, Taiwan
⁶Center for Traditional Medicine, Taipei Veterans General Hospital, Taipei, Taiwan
⁷School of Post-Baccalaureate Chinese Medicine, Tzu Chi University, Hualien, Taiwan
⁸School of Post-Baccalaureate Chinese Medicine, China Medical University, Taichung, Taiwan
⁹Research Center for Chinese Herbal Medicine, China Medical University, Taichung, Taiwan
¹⁰Department of Biotechnology, Asia University, Taichung, Taiwan

Corresponding Author:
Hung-Rong Yen, Research Center for Traditional Chinese Medicine, Department of Medical Research, and Department of Chinese Medicine, China Medical University Hospital, 2 Yude Road, North District, Taichung 404, Taiwan.
Email: hungrongyen@gmail.com

Creative Commons Non Commercial CC BY-NC: This article is distributed under the terms of the Creative Commons Attribution-NonCommercial 4.0 License (http://www.creativecommons.org/licenses/by-nc/4.0/) which permits non-commercial use, reproduction and distribution of the work without further permission provided the original work is attributed as specified on the SAGE and Open Access pages (https://us.sagepub.com/en-us/nam/open-access-at-sage).
Introduction

Pancreatic cancer is a type of gastrointestinal tumor that often has a poor prognosis. The incidence of pancreatic cancer has risen in recent years. Pancreatic cancer is the fourth leading cause of cancer-related death in the United States among both men and women. According to national statistical data, pancreatic cancer was the eighth leading cause of cancer-related death in Taiwan in 2013.

Pancreatic cancer occurs in men more often than in women. The causes of pancreatic cancer include smoking, alcohol consumption, chronic pancreatitis, and age. Pancreatic cancer can lead to nonspecific epigastric pain, back pain, weight loss, progressive jaundice, unexplained pancreatitis or diabetes, and chronic diarrhea. The treatments include surgery, chemotherapy, and radiotherapy. Surgery is possibly the only method known to cure the disease, but pancreatic cancer patients are often diagnosed in the late stages of the disease, resulting in a poor prognosis. The median survival is only 5 to 6 months, indicating the importance of finding other treatments to address this unmet need.

One earlier study showed the improved prognosis of pancreatic cancer patients who take traditional Chinese medicine (TCM). In that study, the authors also found that heat-clearing, diuresis-promoting, and detoxification herbs had a better efficacy. A phase II study demonstrated that a Chinese herbal formula, PHY906, has synergistic antitumor activity with capecitabine in patients with advanced pancreatic cancer who were previously treated with gemcitabine-based regimens. However, current information about the clinical treatment for patients with pancreatic cancer is very limited.

In Taiwan, the National Health Insurance (NHI) program was launched in 1995, and the health insured rate of the whole population is 99.6% as of 2015. The National Health Insurance Administration deidentified all of the registration files and claims data, and sent the datasets to the National Health Research Institutes to construct a National Health Insurance Research Database (NHIRD) for scientific research. It provides data on the insured population’s TCM and Western medical treatment use. As a result, this database can provide nationwide population-based information.

The database has been used to survey the utilization of Western medical doctors for cancer-related treatment. As it is a population-based database, an analysis of its data may lead to a better understanding of the utilization of CHM treatment in pancreatic cancer from a nationwide perspective.

Materials and Methods

Data Sources

Our study was approved by the Research Ethics Committee of China Medical University and Hospital (CMUH104-REC2-115). It was designed as a matched-cohort study. All data were acquired from the database maintained by the National Health Research Institutes. We used ambulatory and inpatient medical records for cancer care linked with the Registry for Catastrophic Illness Patients Database (RCIPD) for the period from 1997 to 2010 to identify study subjects for follow-up until the end of 2011.

The RCIPD is part of the NHIRD, which enrolled all of the patients with catastrophic illness proven by pathological, laboratory, and clinical diagnoses by specialists and reviewed by the National Health Insurance Administration regularly. All registered cancer patients are issued catastrophic illness certificates and are free of copayments to visit TCM or Western medical doctors for cancer-related treatment. Therefore, it is a comprehensive database to survey all pancreatic cancer patients in Taiwan.

The demographic information in the database includes International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes, age, sex, clinical data, hospitalization records, outpatient records, and prescribed drugs and dosages. Our study acquired the data on pancreatic cancer patients from the RCIPD according to ICD-9-CM code 157. There were 18,487 patients with pancreatic cancer in the database. We excluded patients who were less than 20 years old, diagnosed as having acute myocardial infarction, or withdrew from the NHI program during the follow-up period. Among them, 13,943 patients were newly diagnosed from January 1, 1997 to December 31, 2010 with complete information and followed until the end of 2011 (Figure 1). We defined CHM users as those who used CHM for more than 30 days. Additionally, the main reason for them to visit the TCM doctors should be pancreatic cancer. The index date was defined as the first time that patients received CHM treatment. The immortal time was defined as the period from the initial diagnosis of pancreatic cancer to the index date. Finally, to evaluate the benefits of the adjunctive use of CHM, we used 1:1 frequency matching by age (per 5 years), sex, initial diagnostic year of pancreatic cancer, and index year to compare the 2 groups. Patients who died within 30 days of the index date were excluded. We followed the
included patients until the event of death or the end of the study period (December 31, 2011).

**Study Variables**

We classified the patients into 6 groups by age: 20-29, 30-39, 40-49, 50-59, 60-69, and more than 70 years. Urbanized residence areas were divided into 4 levels as in a previous study. We defined level 1 as the highest urbanization level and level 4 as the lowest urbanization level. The comorbidity of these patients were determined by ICD-9-CM codes: diabetes mellitus (DM, 290), prior myocardial infarction (412), angina pectoris (413.9), arrhythmia (427), chronic heart failure (CHF, 428), chronic kidney disease (CKD, 581-586), upper gastrointestinal bleeding (578.9), acute pancreatitis (577.0), chronic pancreatitis (577.1), intestinal obstruction (560.9), sepsis (038.x, 054.5, 003.1, 022.3), cachexia (799.4), peritonitis (567.9), hematemia (578.0), hemoptysis (786.3), edema (782.3), jaundice (782.4), nausea and vomiting (787.0), hypertension (401-405), hyperlipidemia (272), stroke (430-438), chronic obstructive pulmonary disease (COPD, 491, 492, 494, 496), liver diseases (570, 571, 573.3, 573.8, 573.9, 070), renal dialysis (V45.1, V56), alcoholism (291, 303, 305.00-305.03, 790.3, and V11.3), tobacco
use (305.1), and obesity (278 and A183). We also identified the patients who received total pancreatectomy (treatment code: 75410B and 75411B), partial pancreatectomy (treatment code: 75404B, 75405B, 75412B, and 75415B-75417B), or other pancreatectomy (treatment code: 75406B-75409B, 75413B, and 75414B).

**Statistical Analysis**

We used the chi-square test or Fisher’s exact test to identify the differences between CHM and non-CHM groups for categorical variables. We also used *t* tests to differentiate the mean age between the two groups. Cox proportional hazard regression analysis was performed to estimate crude and adjusted hazard ratios (HRs) of CHM use, age, sex, urbanization level, comorbidity, conventional treatment, and specific drugs used. We also evaluated the differences in survival time using Kaplan-Meier curves. All statistical analyses were performed with SAS version 9.4 (SAS Institute Inc, Cary, NC, USA), and we considered a *P* < .05 as statistically significant.

**Complementary Chinese Herbal Medicine**

We tried to identify the most common herbal formulas and single herbs prescribed to the CHM group patients. Next, we calculated the adjusted hazard ratios (mutually adjusted for age, sex, urbanization level, comorbidity, and Western medical treatment) of the CHM mentioned above. Full botanical names comply with the International Plant Names List (IPNI; http://www.ipni.org) and The Plant List (http://www.theplantlist.org/).16

**Results**

Overall, there were 451 patients with pancreatic cancer who received CHM treatment for more than 30 days after being diagnosed with pancreatic cancer (Figure 1). We performed 1:1 frequency matching by age, sex, initial diagnostic year of pancreatic cancer, and index year. There were 386 patients in both CHM and non-CHM user groups. The percentages of patients with comorbidities in the 2 groups were similar (Table 1). The percentages of patients receiving different types of pancreatectomy in the 2 groups were also similar. However, CHM users had a higher percentage of receiving radiotherapy (39.9% vs 31.35%) or chemotherapy (70.21% vs 59.59%) than non-CHM users.

According to the Cox hazard ratio model mutually adjusted for CHM use, age, sex, urbanization level, comorbidity, treatment, and drug used, we found that CHM users had a lower hazard ratio of mortality risk (adjusted *HR* = 0.67, 95% CI = 0.56-0.79) (Table 2). The mortality risk in the 50- to 59-year-old group was lower than that of the patients more than 70 years old (adjusted *HR* = 0.73, 95% CI = 0.57-0.93). Patients receiving radiotherapy also had a lower hazard ratio (adjusted *HR* = 0.78, 95% CI = 0.64-0.94).

Based on the Kaplan-Meier curves, we found that the survival probability was higher for patients in the CHM group than for those in the non-CHM group (Figure 2). Both female and male CHM users had lower mortality risks (women: adjusted *HR* = 0.66, 95% CI = 0.5-0.86; men: adjusted *HR* = 0.63, 95% CI = 0.5-0.79) (Table 3). Of the patients aged from 40 to 69 years, the mortality risk of CHM users is also lower than non-CHM users.

We classified CHM users into 3 subgroups according to the number of days they used CHM, namely, a 30- to 90-day group, 90- to 180-day group, and >180-day group. On the basis of the Cox hazard ratio model, we found that the mortality risk in CHM users who received CHM treatment for more than 90 days was significantly lower than non-CHM users (90- to 180-day group: adjusted *HR* = 0.56, 95% CI = 0.42-0.75; >180-day group: *HR* = 0.33, 95% CI = 0.24-0.45). This indicated that adjunctively taking CHM for more than 90 days had benefits on the survival of pancreatic cancer patients (Table 4).

Our study showed that there were 386 patients with pancreatic cancer who used CHMs after being diagnosed with pancreatic cancer. We identified the most commonly used single herb as Bai-hua-she-she-cao (Herba Oldenlandiae, *Hedyotis diffusa* Spreng) (Table 5). In addition, the most commonly used Chinese herbal formula was Xiang-sha-liu-jun-zi-tang (Costus and Chinese Amomum Combination).

**Discussion**

Our study is the first nationwide study investigating the benefits of complementary CHM among patients with pancreatic cancer. This matched-cohort study was based on a database, RCIPD, which enrolled all the pancreatic cancer patients during the years 1997-2010 to compare the differences between CHM users and non-CHM users in Taiwan. We found that patients who used CHM for more than 90 days had lower mortality risk than those in the non-CHM group. Our study is in accordance with a previous study published by Tianjin Medical University Cancer Hospital, China. In that study, the hazard ratio of mortality risk was 0.419 and the median overall survival was 19 months for patients with TCM treatment versus 8 months for those without TCM treatment.4

The cancer statistics in the United States indicated that advances have been very slow for pancreatic cancer, for which the 5-year survival is only 8%.2 Our Kaplan-Meier survival curve suggested that the 5-year survival among non-CHM users was similar to that of the US cancer statistics. We found that the overall survival probability of CHM users was higher.
Table 1. Characteristics of Patients With Pancreatic Cancer According to Their Use of Chinese Herbal Medicine.

| Variable                        | Non-CHM User (n = 386) | CHM User (n = 386) | P     |
|---------------------------------|------------------------|--------------------|-------|
| **Sex**                         |                        |                    | .99a  |
| Female                          | 168 (43.52)            | 168 (43.52)        |       |
| Male                            | 218 (56.48)            | 218 (56.48)        |       |
| **Age, y, mean ± SD**           | 63.60 ± 12.03          | 62.79 ± 10.98      | .3911b|
| **Age-group, y**                |                        |                    | .99a  |
| 20-29                           | 1 (0.26)               | 1 (0.26)           |       |
| 30-39                           | 7 (1.81)               | 7 (1.81)           |       |
| 40-49                           | 32 (8.29)              | 32 (8.29)          |       |
| 50-59                           | 127 (32.9)             | 127 (32.9)         |       |
| 60-69                           | 105 (27.2)             | 105 (27.2)         |       |
| >70                             | 114 (29.53)            | 114 (29.53)        |       |
| **Urbanization level**          | 1 (highest)            | 99 (25.65)         | .1919a|
| 2                               | 116 (30.05)            | 114 (29.53)        |       |
| 3                               | 49 (12.69)             | 63 (16.32)         |       |
| 4 (lowest)                      | 122 (31.61)            | 99 (25.65)         |       |
| **Comorbidity**                 |                        |                    |       |
| DM                              | 159 (41.19)            | 165 (42.75)        | .6617a|
| Type I DM                       | 4 (1.04)               | 5 (1.3)            |       |
| Type II DM                      | 148 (38.34)            | 151 (39.12)        | .8246a|
| Hypertension                    | 194 (50.26)            | 209 (54.15)        | .2798a|
| Hyperlipidemia                  | 109 (28.24)            | 158 (40.93)        | .0002a|
| Prior myocardial infarction     | 1 (0.26)               | 2 (0.52)           | .99a  |
| Angina pectoris                 | 23 (5.96)              | 30 (7.77)          | .3191a|
| Arrhythmia                      | 38 (9.84)              | 55 (14.25)         | .0602a|
| CHF                             | 23 (5.96)              | 15 (3.89)          | .1832a|
| CKD                             | 46 (11.92)             | 58 (15.03)         | .2059a|
| Renal dialysis                  | 1 (0.26)               | 0 (0)              |       |
| Liver diseases                  | 153 (39.64)            | 208 (53.89)        | <.0001a|
| Upper gastrointestinal bleeding | 22 (5.7)               | 14 (3.63)          | .1721a|
| Acute pancreatitis              | 28 (7.25)              | 37 (9.59)          | .2434a|
| Chronic pancreatitis            | 20 (5.18)              | 26 (6.74)          | .3616a|
| Intestinal obstruction          | 9 (2.33)               | 2 (0.52)           | .0636a|
| Sepsis                          | 31 (8.03)              | 16 (4.15)          | .024a |
| Cachexia                        | 16 (4.15)              | 10 (2.59)          | .2313a|
| Peritonitis                      | 4 (1.04)               | 1 (0.26)           | .3734a|
| Hematemesis                     | 0 (0)                  | 1 (0.26)           | .029a |
| Hemothysis                      | 3 (0.78)               | 5 (1.3)            | .7251a|
| Edema                           | 37 (9.59)              | 30 (7.77)          | .3708a|
| Jaundice                        | 39 (10.1)              | 41 (10.62)         | .8133a|
| Nausea and vomiting             | 17 (4.4)               | 24 (6.22)          | .2612a|
| Ascites                         | 14 (3.63)              | 4 (1.04)           | .029a |
| Depression                      | 23 (5.96)              | 38 (9.84)          | .0454a|
| Anxiety                         | 56 (14.51)             | 81 (20.98)         | .0185a|
| Stroke                          | 51 (13.21)             | 50 (12.95)         | .9150a|
| COPD                            | 76 (19.69)             | 77 (19.95)         | .9281a|
| Alcoholism                      | 0 (0)                  | 1 (0.26)           | .3734a|
| Tobacco use                     | 1 (0.26)               | 4 (1.04)           | .99d  |
| Obesity                         | 4 (1.04)               | 3 (0.78)           |       |

(continued)
Table 1. (continued)

| Variable                                      | Non-CHM User (n = 386) | CHM User (n = 386) | P  |
|-----------------------------------------------|------------------------|--------------------|----|
| Treatment                                      |                        |                    |    |
| Radiotherapy                                  | 121 (31.35)            | 154 (39.9)         | .0131* |
| Chemotherapy                                  | 230 (59.59)            | 271 (70.21)        | .002*  |
| Surgery                                       |                        |                    |    |
| Total pancreatectomy                          | 1 (0.26)               | 1 (0.26)           | .99*  |
| Partial pancreatectomy                        | 9 (2.33)               | 12 (3.11)          | .5069* |
| Other pancreatectomy                          | 1 (0.26)               | 3 (0.78)           | .624*  |
| Drug used                                     |                        |                    |    |
| Statin                                        | 12 (3.11)              | 26 (6.74)          | .0199* |
| Gemcitabine                                   | 206 (53.37)            | 251 (65.03)        | .001*  |
| Paclitaxel                                    | 1 (0.26)               | 1 (0.26)           | .99*  |
| Tegafur                                       | 35 (9.07)              | 37 (9.59)          | .8045* |
| Irinotecan                                    | 3 (0.78)               | 1 (0.26)           | .624*  |
| Oxaliplatin                                   | 4 (1.04)               | 7 (1.81)           | .5459* |
| 5-Fluorouracil                                | 136 (35.23)            | 159 (41.19)        | .0885* |
| Leucovorin                                    | 125 (32.38)            | 137 (35.49)        | .3617* |
| Capcitabine                                   | 2 (0.52)               | 5 (1.3)            | .451*  |
| Cisplatin                                     | 61 (15.8)              | 87 (22.54)         | .0174* |
| Interval between the initial diagnosis of pancreatc cancer and the index date, days, mean (median) | 156 (68) | 141 (52) | .4263* |
| Follow-up time, years, mean (median)          | 0.74 (0.25)            | 1.25 (0.71)        |    |

Abbreviations: CHM, Chinese herbal medicine; DM, diabetes mellitus; CHF, congestive heart failure; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; SD, standard deviation.

*Chi-square test.

The urbanization level was categorized by the population density of the residential area into 4 levels, with level 1 as the most urbanized and level 4 as the least urbanized.

Fisher’s exact test.

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

| Variable                                      | Patients With Pancreatic Cancer (n = 790) | Crude* | Adjustedb |
|-----------------------------------------------|------------------------------------------|--------|-----------|
| CHM used (reference = non-CHM user)           |                                          |        |           |
| Non-CHM user                                  |                                          | 1.00   | Reference |
| CHM user                                     |                                          | 0.63 (0.54-0.74) | <.0001 | 0.67 (0.56-0.79) | <.0001 |
| Sex                                           |                                          |        |           |
| Female                                        |                                          | 1.00   | Reference |
| Male                                          |                                          | 1.08 (0.92-1.26) | .3527 | 1.05 (0.88-1.24) | .5882 |
| Age group, y                                  |                                          |        |           |
| 20-29                                         |                                          | 0.34 (0.05-2.44) | .2837 | 0.35 (0.05-2.56) | .2993 |
| 30-39                                         |                                          | 0.52 (0.27-0.98) | .0433 | 0.52 (0.27-1.03) | .0592 |
| 40-49                                         |                                          | 0.83 (0.62-1.13) | .2449 | 0.85 (0.6-1.23) | .3925 |
| 50-59                                         |                                          | 0.73 (0.6-0.89) | .0017 | 0.73 (0.57-0.93) | .0111 |

(continued)
Table 2. (continued)

| Variable                                | No. of Death (n = 633) | Crudea HR (95% CI) | P     | Adjustedb HR (95% CI) | P     |
|-----------------------------------------|------------------------|--------------------|-------|------------------------|-------|
| 60-69                                   | 177                    | 0.98 (0.79-1.2)    | .8092 | 0.95                   | (0.75-1.19) | .6401 |
| >70                                     | 190                    | 1.00 Reference     |       | 1.00                   | Reference |
| Urbanization level                      |                        |                    |       |                        |        |
| 1 (highest)                             | 174                    | 1.00 Reference     |       | 1.00 Reference         |        |
| 2                                       | 181                    | 0.99 (0.8-1.22)    | .9293 | 1.07                   | (0.85-1.33) | .5679 |
| 3                                       | 90                     | 0.89 (0.69-1.14)   | .3574 | 0.90                   | (0.68-1.18) | .432  |
| 4 (lowest)                              | 188                    | 1.22 (1.15-1.5)    | .0542 | 1.28                   | (1.02-1.6) | .0317 |
| Comorbidity (reference = no comorbidity)|                        |                    |       |                        |        |
| DM                                      | 265                    | 1.07 (0.92-1.26)   | .3795 | 1.04                   | (0.88-1.24) | .6256 |
| Hypertension                            | 326                    | 1.03 (0.88-1.2)    | .7112 | 0.92                   | (0.76-1.1) | .3573 |
| Hyperlipidemia                          | 215                    | 0.95 (0.8-1.12)    | .509  | 1.05                   | (0.86-1.27) | .6296 |
| Prior myocardial infarction             | 2                      | 0.65 (0.16-2.58)   | .5369 | 0.75                   | (0.18-3.12) | .6915 |
| Angina pectoris                         | 43                     | 1.06 (0.78-1.45)   | .6983 | 1.07                   | (0.76-1.5) | .7115 |
| Arrhythmia                              | 75                     | 1.05 (0.82-1.33)   | .7102 | 1.12                   | (0.85-1.47) | .4254 |
| CHF                                     | 32                     | 0.97 (0.68-1.39)   | .8872 | 0.83                   | (0.56-1.22) | .3385 |
| CKD                                     | 87                     | 0.95 (0.76-1.19)   | .6735 | 0.98                   | (0.77-1.26) | .8772 |
| Renal dialysis                          | 1                      | 0.96 (0.14-6.84)   | .9687 | 0.71                   | (0.1-5.23) | .7333 |
| Liver diseases                          | 294                    | 0.84 (0.72-0.98)   | .025  | 0.87                   | (0.73-1.03) | .0984 |
| Upper gastrointestinal bleeding         | 29                     | 0.98 (0.68-1.43)   | .9267 | 1.18                   | (0.79-1.76) | .4256 |
| Acute pancreatitis                      | 52                     | 0.82 (0.62-1.09)   | .1724 | 0.76                   | (0.54-1.05) | .0983 |
| Chronic pancreatitis                    | 38                     | 0.89 (0.64-1.23)   | .4699 | 0.92                   | (0.64-1.33) | .6649 |
| Intestinal obstruction                  | 8                      | 1.38 (0.68-2.79)   | .3763 | 1.19                   | (0.56-2.54) | .6467 |
| Sepsis                                  | 41                     | 1.39 (1.01-1.91)   | .042  | 1.41                   | (1.19-1.99) | .0488 |
| cachexia                                | 21                     | 1.74 (1.12-2.7)    | .0129 | 1.54                   | (0.97-2.46) | .0698 |
| Peritonitis                             | 4                      | 0.95 (0.35-2.54)   | .916  | 1.00                   | (0.35-2.82) | .9998 |
| Hematemesis                             | 1                      | 5.87 (0.82-41.97)  | .0776 | 8.71                   | (1.18-64.58) | .0342 |
| Hemoptysis                              | 7                      | 1.12 (0.53-2.36)   | .7661 | 1.02                   | (0.47-2.22) | .9549 |
| Edema                                   | 57                     | 1.32 (1.17)        | .0488 | 1.30                   | (0.96-1.77) | .0923 |
| Jaundice                                | 64                     | 0.89 (0.69-1.15)   | .3645 | 0.87                   | (0.66-1.14) | .2972 |
| Nausea and vomiting                     | 34                     | 1.10 (0.78-1.56)   | .5737 | 1.12                   | (0.78-1.6) | .5495 |
| Asites                                  | 16                     | 2.22 (1.35-3.66)   | .0017 | 1.76                   | (1.03-3) | .039  |
| Depression                              | 51                     | 0.96 (0.72-1.27)   | .7656 | 1.01                   | (0.73-1.4) | .9394 |
| Anxiety                                 | 111                    | 0.93 (0.76-1.14)   | .4865 | 0.91                   | (0.72-1.16) | .441  |
| Stroke                                  | 86                     | 1.13 (0.9-1.42)    | .2918 | 0.95                   | (0.73-1.23) | .7032 |
| COPD                                    | 131                    | 1.18 (0.98-1.43)   | .0861 | 1.15                   | (0.93-1.43) | .2035 |
| Alcoholism                              | 1                      | 1.34 (0.19-9.53)   | .7699 | 3.43                   | (0.44-26.83) | .2401 |
| Tobacco use                             | 3                      | 1.09 (0.35-3.4)    | .8764 | 1.60                   | (0.49-5.19) | .4339 |
| Obesity                                 | 6                      | 1.18 (0.53-2.63)   | .6943 | 1.68                   | (0.6-4.68) | .322  |
| Treatment                               |                        |                    |       |                        |        |
| Radiotherapy                            | 231                    | 0.82 (0.7-0.97)    | .0192 | 0.78                   | (0.64-0.94) | .0078 |
| Chemotherapy                            | 433                    | 1.21 (1.02-1.44)   | .0261 | 1.25                   | (0.82-1.9) | .3042 |
| Surgery                                 |                        |                    |       |                        |        |
| Total pancreatectomy                    | 1                      | 0.54 (0.08-3.82)   | .5346 | 1.08                   | (0.14-8.22) | .9378 |
| Partial pancreatectomy                  | 15                     | 0.54 (0.32-0.9)    | .0184 | 0.59                   | (0.35-1) | .0491 |
| Other pancreatectomy                    | 2                      | 0.34 (0.08-1.35)   | .1257 | 0.41                   | (0.1-1.67) | .2133 |
| Drug used                               |                        |                    |       |                        |        |
| Statin                                  | 22                     | 0.45 (0.3-0.69)    | .0003 | 0.45                   | (0.28-0.71) | .0005 |
| Gemcitabine                             | 400                    | 1.22 (1.04-1.44)   | .0178 | 1.26                   | (0.86-1.83) | .2372 |

(continued)
Previous studies usually showed a preference of using TCM in women. However, in the current study in pancreatic cancer, there was no obvious tendency of more female CHM users. This is probably because of the fact that the incidence rate of pancreatic cancer is higher in males.

Our study not only showed that adjunctive Chinese herbal therapy had the potential to improve survival but also identified some candidate herbs and formulas deserving further investigation. The most commonly used Chinese herb was Bai-hua-she-she-cao (Herba Oldenlandiae; Hedyotis diffusa Spreng). In recent studies, one indicated that Bai-hua-she-she-cao could suppress tumor angiogenesis in vivo via inhibition of Sonic hedgehog signaling in colorectal cancer. Another found that the novel cyclotides in Bai-hua-she-she-cao had anticancer activity. Ban-zhi-lian (Herba Scutellariae Barbatae; Scutellaria barbata D Don) could promote the tumor inhibition rate of 5-fluorouracil, which is often prescribed to pancreatic cancer patients. It could also extend the survival time and elevate immune function in H22 tumor-bearing mice. Cryptotanshinone, one of the constituents of Dan-shen (Radix Salviae Miltiorrhizae; Salvia miltiorrhiza Bunge) could exert anticancer effects by inducing apoptosis and cell cycle arrest via inhibition of the STAT3 signaling pathway in human pancreatic cell line. Shen-qu (Medicated Leaven; Massa Medicata Fermentata) could help with digestion by its diverse bacterial and fungal communities. Recent studies on the human microbiome have highlighted how perturbations of commensal bacterial populations can influence the interplay between inflammation and microbiome in the context of pancreatic carcinogenesis. Shen-qu appeared to be a commonly prescribed herb for pancreatic cancer patients implying that further studies toward this direction are needed. It is noteworthy that the common herb, Huang-qin (Radix Scutellariae; Scutellaria baicalensis Georgi), is one of the major herbs of a Chinese herbal formula PHY906, which has been shown to be a safe and feasible salvage therapy for advanced pancreatic cancer in a phase II clinical trial.

The most common Chinese herbal formula was Xiang-sha-liu-jun-zi-tang (Costus and Chinese Amomum Combination). In a meta-analysis of randomized controlled trials, Xiang-sha-liu-jun-zi-tang was found to improve the symptom of dyspepsia. Pancreatic cancer patients often

---

**Table 2. (continued)**

| Variable          | No. of Death (n = 633) | Crudea HR (95% CI) | P  | Adjustedb HR (95% CI) | P  |
|-------------------|-------------------------|-------------------|----|-----------------------|----|
| Paclitaxel        | 2                       | 0.56 (0.14-2.23)  | 4081 | 0.59 (0.14-2.46)     | 4663 |
| Tegafur           | 58                      | 0.83 (0.63-1.08)  | 1645 | 0.74 (0.55-0.99)     | 0448 |
| Irinotecan        | 3                       | 0.93 (0.3-2.9)    | 903  | 0.63 (0.18-2.24)     | 4795 |
| Oxaliplatin       | 10                      | 0.88 (0.47-1.64)  | 6762 | 0.77 (0.35-1.67)     | 5067 |
| 5-Fluorouracil    | 258                     | 1.08 (0.92-1.27)  | 3426 | 0.98 (0.67-1.45)     | 9301 |
| Leucovorin        | 231                     | 1.06 (0.9-1.24)   | 4986 | 1.10 (0.75-1.63)     | 6216 |
| Capecitabine      | 6                       | 1.02 (0.46-2.29)  | 9528 | 1.13 (0.42-3.07)     | 807  |
| Cisplatin         | 127                     | 0.89 (0.73-1.08)  | 2392 | 0.84 (0.67-1.06)     | 1384 |

Abbreviations: CHM, Chinese herbal medicine; DM, diabetes mellitus; CHF, congestive heart failure; CKD, chronic kidney disease; HR, hazard ratio; CI, confidence interval; COPD, chronic obstructive pulmonary disease.

aCrude HR represents relative hazard ratio.

bAdjusted HR represents adjusted hazard ratio: mutually adjusted for CHM use, age, sex, urbanization level, comorbidity (as in the list of Table 2), treatment (as in the list of Table 2) and drug used (as in the list of Table 2) in Cox proportional hazard regression.

---

**Figure 2.** Kaplan-Meier curves of survival rate in pancreatic cancer patients of CHM and non-CHM group. CHM, Chinese herbal medicine.
suffer from gastrointestinal symptoms, which might explain why the formula was prescribed the most often. The other formulas, such as Shen-ling-bai-zhu-san (Ginseng and Bai-zhu Atractylodes Formula) and Ping-wei-san (Cang-zhu Atractylodes and Magnolia Formula) are also often used for gastrointestinal discomforts in TCM. Jia-wei-xia-yao-san was also the commonly used formula. It can relieve anxiety and improve insomnia, which are often symptoms that cancer patients experience. Liao et al. also indicated that Jia-wei-xia-yao-san and chai-hu-shu-gan-tang improved survival in patients with liver cancer. In another study, Jia-wei-xia-yao-san was found to be effective in reducing mortality in patients with advanced breast cancer.

The limitations of this study need to be mentioned. The RCPID did not provide detailed information regarding pathological types, staging, and the results of the clinical examinations. In addition, the RCPID did not provide the information about whether the tumors were resectable or not. In order to reduce the bias, we tried to identify the patients who received surgeries of different types of pancreatectomy by treatment codes. In our study, the numbers of the patients who received different types of pancreatectomy in both cohorts were similar. We also included these factors in the analysis of mortality risk to reduce the bias. The second limitation is that the RCPID did not provide the data about lifestyles, such as smoking, alcohol drinking, or food

### Table 3. Incidence Rates, Hazard Ratios, and Confidence Intervals of Mortality for Patients Stratified by Demographic Characteristics, Comorbidity, Treatment, and Drug Used.

| Variables                  | Non-CHM User (n = 386) | CHM User (n = 386) | Compared With Non-CHM User |
|----------------------------|------------------------|--------------------|---------------------------|
|                            | Event Person Years IR  | Event Person years IR | Crude HR (95% CI) | Adjusted HR (95% CI) |
| Total                      | 320 286 1119.33        | 313 483 647.46     | 0.63 (0.54-0.74)*** | 0.67 (0.56-0.79)*** |
| Sex                        |                        |                    |                           |
| Female                     | 137 118 1159.66        | 134 204 655.96     | 0.62 (0.48-0.78)*** | 0.66 (0.5-0.86)** |
| Male                       | 183 168 1090.92        | 179 279 641.25     | 0.64 (0.52-0.79)*** | 0.63 (0.5-0.79)*** |
| Age group, y               |                        |                    |                           |
| 20-29                      | 1 0 2148.53            | 0 2 0              |              |                        |
| 30-39                      | 4 14 276.44            | 6 13 478.28        | 0.96 (0.27-3.46)        |                        |
| 40-49                      | 26 22 1155.85          | 27 45 601.29       | 0.56 (0.32-0.97)*      | 0.19 (0.06-0.68)*      |
| 50-59                      | 103 107 965.33         | 99 198 500.63      | 0.62 (0.47-0.82)***     | 0.55 (0.4-0.77)***     |
| 60-69                      | 92 64 1428.76          | 85 102 830.76      | 0.57 (0.42-0.76)***     | 0.52 (0.36-0.74)***     |
| >70                        | 94 77 1215             | 96 124 777.28      | 0.71 (0.53-0.94)*       | 0.8 (0.57-1.14)        |
| Urbanization level         |                        |                    |                           |
| 1 (highest)                | 81 76 1060.37          | 93 146 636.6       | 0.67 (0.5-0.91)***      | 0.62 (0.44-0.88)**     |
| 2                          | 95 75 1259.94          | 86 153 563.12      | 0.55 (0.41-0.74)***     | 0.55 (0.39-0.77)***    |
| 3                          | 39 50 775.14           | 51 79 646.42       | 0.75 (0.49-1.14)        | 0.64 (0.32-1.28)       |
| 4 (lowest)                 | 105 84 1253.23         | 83 106 785.1       | 0.63 (0.47-0.84)**      | 0.63 (0.45-0.88)**     |
| Comorbidity b              |                        |                    |                           |
| No                         | 37 37 998.91           | 28 47 594.66       | 0.61 (0.37-1.00)        | 0.62 (0.33-1.16)       |
| Yes                        | 283 249 1137.25        | 285 436 653.16     | 0.64 (0.54-0.75)***     | 0.64 (0.54-0.76)***    |
| Treatment c                |                        |                    |                           |
| No                         | 105 126 832.24         | 69 167 412.81      | 0.58 (0.43-0.79)***     | 0.62 (0.43-0.9)*       |
| Yes                        | 215 160 1346.1         | 244 316 771.48     | 0.62 (0.51-0.74)***     | 0.61 (0.5-0.74)***     |
| Drug used d                |                        |                    |                           |
| No                         | 117 134 872.75         | 77 147 524.02      | 0.66 (0.49-0.88)**      | 0.62 (0.44-0.87)**     |
| Yes                        | 203 152 1337.04        | 236 336 701.37     | 0.59 (0.49-0.71)**      | 0.65 (0.53-0.8)**      |

Abbreviations: IR, incidence rates per 1000 person-years; CHM, Chinese herbal medicine; DM, diabetes mellitus; CHF, congestive heart failure; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; HR, hazard ratio; CI, confidence interval.

Adjusted HR represents adjusted hazard ratio: mutually adjusted for CHM use, age, sex, urbanization level, comorbidity, treatment, and drug used in Cox proportional hazard regression.

Comorbidities included the following: DM, prior myocardial infarction, angina pectoris, arrhythmia, CHF, CKD, upper gastrointestinal bleeding, acute pancreatitis, chronic pancreatitis, intestinal obstruction, sepsis, cachexia, peritonitis, hematemesis, hemoptysis, edema, jaundice, nausea and vomiting, ascites, alcoholism, tobacco use, obesity, hypertension, hyperlipidemia, depression, anxiety, stroke, COPD, liver diseases, and renal dialysis.

Treatment included the following: radiotherapy, chemotherapy, surgery (total pancreatectomy, partial pancreatectomy, and other pancreatectomy).

Drug use included the following: statin, gemcitabine, paclitaxel, tegafur, irinotecan, oxaliplatin, 5-fluorouracil, leucovorin, capecitabine and cisplatin.

*P < .05. **P < .01. ***P < .001.
### Table 4. Hazard Ratios and 95% Confidence Intervals of Mortality Risk Associated With the Cumulative Use (in Days) of Chinese Herbal Medicine Among Patients With Pancreatic Cancer.

| No. of CHM Days | Death Events (n = 661) | Hazard Ratio (95% CI) | Hazard Ratio (95% CI) |
|-----------------|------------------------|-----------------------|-----------------------|
|                 | n                      |                       | Crude<sup>a</sup>     | Adjusted<sup>b</sup> |
| Non-CHM user    | 386                    | 320                   | 1.00 (reference)      | 1.00 (reference)     |
| CHM user (CHM ≥ 30 days) |            |                       |                      |                     |
| 30-90 days      | 238                    | 204                   | 0.87 (0.73-1.04)***   | 0.89 (0.74-1.07)***   |
| 90-180 days     | 79                     | 63                    | 0.54 (0.41-0.70)***   | 0.56 (0.42-0.75)***   |
| >180 days       | 69                     | 46                    | 0.31 (0.23-0.43)***   | 0.33 (0.24-0.45)***   |
| P for trend     |                        |                       | <.0001                | <.0001                |

**Abbreviations:** CHM, Chinese herbal medicine; HR, hazard ratio; CI, confidence interval.

<sup>a</sup>Crude HR represents relative hazard ratio.

<sup>b</sup>Adjusted HR represents adjusted hazard ratio: mutually adjusted for CHM use, age, sex, urbanization level, comorbidity (as in list of Table 2), treatment (as in list of Table 2), and drug used (as in list of Table 2) in Cox proportional hazard regression.

<sup>*P < .05. **P < .01. ***P < .001.</sup>

### Table 5. Hazard Ratios and 95% Confidence Intervals of Mortality Risk Associated With the Use of Most Common Chinese Herbal Medicine for Patients With Pancreatic Cancer.

| CHM Prescription | n | No. of Events | Hazard Ratio (95% CI) | Hazard Ratio (95% CI) |
|------------------|---|--------------|-----------------------|-----------------------|
|                 |   |              |                      |                      |
| Non-CHM user    | 386 | 320         | 1.00 (reference)      | 1.00 (reference)     |
| CHM user        |     |             |                      |                      |
| Single herbs    |    |             |                      |                      |
| Bai-hua-she-she-cao; Herba Oldenlandiae; Hedyotis diffusa Spreng | 112 | 90 | 0.61 (0.47-0.79)**   | 0.64 (0.49-0.83)**   |
| Shen-qu; Medicated Leaven; Massa Medicata Fermentata | 91 | 73 | 0.60 (0.45-0.79)**   | 0.60 (0.45-0.79)**   |
| Huang-qin; Radix Scutellariae; Scutellaria baicalensis Georgi | 91 | 70 | 0.63 (0.48-0.81)***   | 0.72 (0.54-0.96)*    |
| Ban-zhi-lian; Herba Scutellariae Barbatae; Scutellaria barbata D Don | 89 | 75 | 0.61 (0.47-0.79)**   | 0.68 (0.51-0.90)**   |
| Dan-shan; Radix Salviae Miltiorrhizae; Salvia miltiorrhiza Bunge | 80 | 61 | 0.50 (0.38-0.66)***   | 0.55 (0.40-0.74)***   |
| Huang-qi; Radix Astragali; Astragalus membranaceus, Astragalus henryi, Astragalus hoanthcy | 80 | 62 | 0.59 (0.45-0.78)**   | 0.65 (0.48-0.88)**   |
| Chai-hu; Radix Bupleuri; Bupleurum chinense DC, Bupleurum scorzonerifolium Willd. | 76 | 57 | 0.61 (0.46-0.81)**   | 0.70 (0.52-0.96)*    |
| Da-huang; Radix et Rhizoma Rhei; Rheum palmatum L., R tanguticum Maxim et Reg, R officinale Baill. | 75 | 62 | 0.79 (0.60-1.04)***   | 0.88 (0.66-1.18)***   |
| Xiang-fu; Cyperus Rhizome; Cyperus rotundus L. | 59 | 40 | 0.46 (0.33-0.65)***   | 0.46 (0.32-0.65)***   |
| Hsi-piao-xiao; Os Sepiae seu Sepiellae; Sepia pharaonis, Sepia maindroni de Rocheburme, Sepia esculenta Hoyle | 39 | 29 | 0.57 (0.39-0.84)**   | 0.59 (0.39-0.88)*    |

**Chinese herbal formulas<sup>c</sup>**

| Xiang-sha-juan-zhi-tang; Costus and Chinese Amomum Combination | 106 | 83 | 0.63 (0.49-0.80)**   | 0.72 (0.55-0.94)*    |
| Shen-ling-bai-zhu-san; Ginseng and Bai-zhu Atractyloides Formula | 87 | 70 | 0.61 (0.47-0.79)**   | 0.65 (0.49-0.87)**   |
| Ping-wei-san; Cang-zhu Atractyloides and Magnolia Formula | 85 | 67 | 0.61 (0.47-0.80)**   | 0.66 (0.49-0.88)**   |
| Xiao-chai-hu-tang; Minor Bupleurum Decoction | 85 | 72 | 0.66 (0.51-0.86)**   | 0.71 (0.54-0.95)*    |
| Gui-pi-tang; Ginseng and Longan Combination | 76 | 66 | 0.67 (0.51-0.87)**   | 0.67 (0.50-0.90)**   |
| Jia-wei-xiao-yan-san; Bupleurum & Three Peony Formula | 71 | 56 | 0.55 (0.41-0.73)***   | 0.61 (0.44-0.85)*    |
| Ban-xia-xie-xin-tang; Pinellia Combination | 63 | 52 | 0.60 (0.45-0.81)***   | 0.65 (0.47-0.90)***   |
| Bao-he-wan; Tangerine and Chinese Hawthorn Formula | 61 | 49 | 0.66 (0.49-0.90)**   | 0.74 (0.53-1.14)***   |
| Chai-hu-shu-gan-tang; Bupleurum and Cyperus Formula | 55 | 35 | 0.42 (0.30-0.60)***   | 0.45 (0.31-0.65)***   |
| Hua-hsiang-cheng-chi-San; Patchouli Formula | 34 | 23 | 0.44 (0.29-0.68)***   | 0.50 (0.31-0.79)***   |

**Abbreviation:** CHM, Chinese herbal medicine.

<sup>cCrude HR represents relative hazard ratio.</sup>

<sup>dAdjusted HR represents adjusted hazard ratio: mutually adjusted for CHM use, age, sex, urbanization level, comorbidity (as in list of Table 2), treatment (as in list of Table 2), and drug used (as in list of Table 2) in Cox proportional hazard regression.

<sup>**P < .05. ***P < .01. ****P < .001.</sup>
and dietary factors. We have tried our best to acquire the information of illnesses resulting from these personal habits and lifestyles. Patients diagnosed as having alcoholism, tobacco use, or obesity were similar in both cohorts (Table 1). It is also important to mention that only randomized controlled clinical trials can prove definite clinical efficacy. Our nationwide matched-cohort study can provide some hints for the design of future clinical trials.

**Conclusion**

In summary, adjunctive Chinese herbal medicine may have benefits in reducing mortality rate in pancreatic cancer patients. Bai-hua-she-she-cao and Xiang-sha-liu-jun-zitang appeared to be the most commonly used single herb and Chinese herbal formula for the treatment of pancreatic cancer patients. Future pharmacological investigations or clinical trials to validate these findings are warranted.

**Authors’ Note**

This study was based in part on data from the National Health Insurance Research Database, provided by the National Health Insurance Administration, Ministry of Health and Welfare, and managed by National Health Research Institutes. The interpretation and conclusions contained herein do not represent those of National Health Insurance Administration, Ministry of Health and Welfare, or National Health Research Institutes.

**Declaration of Conflicting Interests**

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

**Funding**

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This study was supported by China Medical University under the Aim for Top University Plan of the Ministry of Education, Taiwan. This study was also supported in part by the Taiwan Ministry of Health and Welfare Clinical Trial and Research Center of Excellence (MOHW106-TDU-B-212-113004).

**References**

1. Kamisawa T, Wood LD, Itoi T, Takaori K. Pancreatic cancer. *Lancet*. 2016;388:73-85.
2. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2016. *CA Cancer J Clin*. 2016;66:7-30.
3. Torres-Rosas R, Yehia G, Peña G, et al. Dopamine mediates vagal modulation of the immune system by electroacupuncture. *Nat Med*. 2014;20:291-295.
4. Yang X, Hao J, Zhu CH, et al. Survival benefits of Western and traditional Chinese medicine treatment for patients with pancreatic cancer. *Medicine (Baltimore)*. 2015;94:e1008.
5. Saif MW, Li J, Lamb L, et al. First-in-human phase II trial of the botanical formulation PHY906 with capcitabine as second-line therapy in patients with advanced pancreatic cancer. *Cancer Chemother Pharmacol*. 2014;73:373-380.
6. National Health Insurance Administration. *National Health Insurance Annual Report 2015-2016*. Taipei, Taiwan: National Health Insurance Administration; 2015.
7. Chang CC, Lee YC, Lin CC, et al. Characteristics of traditional Chinese medicine usage in patients with stroke in Taiwan: a nationwide population-based study. *J Ethnopharmacol*. 2016;186:311-321.
8. Liao HH, Yeh CC, Lin CC, et al. Prescription patterns of Chinese herbal products for patients with fractures in Taiwan: a nationwide population-based study. *J Ethnopharmacol*. 2015;173:11-19.
9. Huang MC, Pai FT, Lin CC, et al. Characteristics of traditional Chinese medicine use in patients with rheumatoid arthritis in Taiwan: a nationwide population-based study. *J Ethnopharmacol*. 2015;176:9-16.
10. Lee AL, Chen BC, Mou CH, Sun MF, Yen HR. Association of traditional Chinese medicine therapy and the risk of vascular complications in patients with type II diabetes mellitus: a nationwide, retrospective, Taiwanese-registry, cohort study. *Medicine (Baltimore)*. 2016;95:e2536.
11. Kuo YT, Chang TT, Muo CH, et al. Use of complementary traditional Chinese medicines by adult cancer patients in Taiwan: a nationwide population-based study [published online June 1, 2017]. *Integr Cancer Ther*. doi:10.1177/1534735417716302.
12. Hung KF, Hsu CP, Chiang JH, et al. Complementary Chinese herbal medicine therapy improves survival of patients with gastric cancer in Taiwan: a nationwide retrospective matched-cohort study. *J Ethnopharmacol*. 2017;199:168-174.
13. Fleischer T, Chang TT, Chiang JH, Sun MF, Yen HR. Improved survival with integration of Chinese herbal medicine therapy in patients with acute myeloid leukemia: a nationwide population-based cohort study. *Integr Cancer Ther*. 2016;16:156-164. doi:10.1177/153473541664171.
14. Fleischer T, Chang TT, Chiang JH, Chang CM, Hsieh CY, Yen HR. Adjunctive Chinese herbal medicine therapy improves survival of patients with chronic myeloid leukemia: a nationwide population-based cohort study. *Cancer Med*. 2016;5:640-648.
15. Yen HR, Sun MF, Lin CL, Sung FC, Wang CC, Liang KL. Adjunctive traditional Chinese medicine therapy for patients with chronic rhinosinusitis: a population-based study. *Int Forum Allergy Rhinol*. 2015;5:240-246.
16. Chan K, Shaw D, Simmonds MS, et al. Good practice in reviewing and publishing studies on herbal medicine, with special emphasis on traditional Chinese medicine and Chinese materia medica. *J Ethnopharmacol*. 2012;140:469-475.
17. Shih CC, Liao CC, Su YC, Tsai CC, Lin JG. Gender differences in traditional Chinese medicine use among adults in Taiwan. *PLoS One*. 2012;7:e32540.
18. Yadav D, Lowenfels AB. The epidemiology of pancreatitis and pancreatic cancer. *Gastroenterology*. 2013;144:1252-1261.
19. Lin J, Wei L, Shen A, et al. *Hedyotis diffusa* Willd extract suppresses Sonic hedgehog signaling leading to the inhibition of colorectal cancer angiogenesis. *Int J Oncol*. 2013;42:651-656.
20. Hu E, Wang D, Chen J, et al. Novel cyclotides from *Hedyotis diffusa* induce apoptosis and inhibit proliferation and migration of prostate cancer cells. *Int J Clin Exp Med*. 2015;8:4059-4065.
21. Dai Z, Liu X, Ji Z, et al. The effect-enhancing and toxicity-reducing action of the extract of herb *Scutellariae barbatae* for chemotherapy in hepatoma H22 tumor-bearing mice. *J Tradit Chin Med*. 2008;28:205-210.

22. Ge Y, Yang B, Chen Z, Cheng R. Cryptotanshinone suppresses the proliferation and induces the apoptosis of pancreatic cancer cells via the STAT3 signaling pathway. *Mol Med Rep*. 2015;12:7782-7788.

23. Xu Y, Xie YB, Zhang XR, Chen C, Xiang H, Xie Q. Monitoring of the bacterial and fungal biodiversity and dynamics during massa medicata fermentata fermentation. *Appl Microbiol Biotechnol*. 2013;97:9647-9655.

24. Zambirinis CP, Pushalkar S, Saxena D, Miller G. Pancreatic cancer, inflammation, and microbiome. *Cancer J*. 2014;20:195-202.

25. Xiao Y, Liu YY, Yu KQ, Ouyang MZ, Luo R, Zhao XS. Chinese herbal medicine liu jun zi tang and xiang sha liu jun zi tang for functional dyspepsia: meta-analysis of randomized controlled trials. *Evid Based Complement Alternat Med*. 2012;2012:936459.

26. Huang CY, Lai WY, Sun MF, et al. Prescription patterns of traditional Chinese medicine for peptic ulcer disease in Taiwan: a nationwide population-based study. *J Ethnopharmacol*. 2015;176:311-320.

27. Riedlinger JE, Tan PW, Lu W. Ping wei san, a Chinese medicine for gastrointestinal disorders. *Ann Pharmacother*. 2001;35:228-235.

28. Lee KH, Tsai YT, Lai JN, et al. Concurrent use of hypnotic drugs and Chinese herbal medicine therapies among Taiwanese adults with insomnia symptoms: a population-based study. *Evid Based Complement Alternat Med*. 2013;2013:987862.

29. Liao YH, Lin CC, Lai HC, et al. Adjunctive traditional Chinese medicine therapy improves survival of liver cancer patients. *Liver Int*. 2015;35:2595-2602.

30. Lee YW, Chen TL, Shih YR, et al. Adjunctive traditional Chinese medicine therapy improves survival in patients with advanced breast cancer: a population-based study. *Cancer*. 2014;120:1338-1344.