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Conventional Western Treatment Associated With Chinese Herbal Medicine Ameliorates the Incidence of Head and Neck Cancer Among Patients With Esophageal Cancer

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Abstract

Background: Because of advances in medical treatment, the survival of cancer patients is prolonged. In line with the prolonged survival time of cancer the incidence of second primary cancer has increased. There is currently no effective way to prevent the occurrence of secondary primary cancer (SPC). **Objectives:** The aim of this study is to evaluate whether Chinese Herbal Medicine (CHM) is correlated with reduced occurrence of second primary cancer (SPC) of head and neck (H&N) in patients with esophageal cancer (EC). **Method:** We identified 15,546 patients who were diagnosed with esophageal cancer between Jan 1, 2000, and Dec 31, 2010. The patients with H&N cancer before receiving CHM were excluded. After the selection and matching process, both CHM and non-CHM cohorts each contained 850 individuals. We compared the cumulative incidence of SPC of H&N with or without CHM treatment in patients with EC by the Kaplan-Meier method. NodeXL is used to run a network analysis of CHM to examine the association between herbs and formulas. **Results:** Compared with non-CHM users, CHM-users showed a reduced incidence rate of SPC of H&N among the patients with EC. Reduced cumulative incidence of SPC of H&N among patients with EC was noted in the CHM cohort compared to the non-CHM cohort. The most commonly used single herbs and formulas were associated with reducing SPC occurrence. **Conclusion:** We propose that CHM as an adjuvant therapy may prevent the occurrence of SPC of H&N in patients with EC.

Keywords

secondary primary cancers, esophageal cancer, head and neck cancer, Chinese herbal medicine, cohort study

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Introduction

Esophageal cancer (EC) is one of the most commonly occurring cancers in the world. There were an estimated 483 000 new cases of EC in 2015, resulting in approximately 439 000 deaths. Globally, it is the sixth leading cause of cancer-related deaths and the seventh leading cause of years of life lost as a result of cancer.[1] There are 2 major histological subtypes: squamous cell carcinoma (SCC) and adenocarcinoma (AC), which have varying regional and ethnic distributions.[2,3] SCC currently has a higher global prevalence rate than AC, whereas approximately 79% of all

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SCC cases are found in South-Eastern and Central Asia.[3] The main geographical distribution areas of AC were in Northern and Western Europe, Northern America, and Oceania, which together accounted for 46% of AC cases globally.[3] Current treatments of EC include endoscopic therapy for early stages. Meanwhile, esophagectomy combined with neoadjuvant chemoradiotherapy with carboplatin and paclitaxel, or cisplatin and fluorouracil, is commonly used for patients with medium-grade diagnoses, whereas palliative chemotherapy with cisplatin or oxaliplatin, combined with either fluorouracil or capecitabine, is used for patients with unresectable cancers.[4] Because of the application of such advanced treatments, survival rates have seen notable increases.[4-6] As reported, the 5-year survival rate increased from 5% from 1975 to 1977, to 20.5% from 2006 to 2012.[7] Tragically, however, increased survival times lead to EC patients' increased risk of developing secondary primary cancers (SPCs). Previous reports have indicated that the standardized incidence ratio (SIR) of overall SPCs in EC patients compared with the general population are significantly increased in Taiwan,[8] whereas Zhu et al[9] reported that SIR (1.34) was enhanced by 26% according to the SEER database of the US population. Furthermore, Chuang et al[10] reported that SIR (1.15) also increased in 13 population-based cancer registries in Europe, Australia, Canada, and Singapore. All the patients with EC were at increased risk of suffering from head and neck (H&N), lung, stomach, small intestine, and kidney cancer as well as leukemia.[8-11] Among these SPCs, H&N cancer was often noted to be of the highest risk.[8-10] However, current studies on the issue of SPC only suggest close monitoring as a preferred method of early detection, so that SPCs can undergo earlier treatment.[6,11-13] There are currently no more aggressive or effective methods of SPC prevention.

Complementary and alternative medicine (CAM) therapies are commonly applied in many countries. CAM can be classified into various categories, including biological-based therapies, manipulative and body-based therapies, mind-body therapies, alternative medical systems, energy healing therapy, and special diets. Herbal medicine is defined as a category of CAMs.[14] Wu et al[15] have reported that there were about 40.6 million adults who used herbs and supplements, such as ginkgo and ginseng, in 2012, in the United States. It was observed that cancer survivors used more nonvitamin/mineral natural products than cancer-free adults (23.7% vs 18.5%) among the American population in 2012, in total spending approximately $1.2 billion annually on nonvitamin/mineral natural products, with a mean of $285 per cancer survivor.[14] However, only 3.9% reported the primary reason for their CAM use as specifically to treat cancer. This number was notably less than that for other health-related reasons, such as back pain (14.4%), joint pain/stiffness (9.8%), cardiovascular diseases (9.5%), and neck pain (6.6%).[14]

Taiwan has been under the current National Health Insurance (NHI) system since 1995. In 1997, the NHI Research Database (NHIRD) was established by the National Health Research Institute to promote research and offer informative insights for the development of national health policies. The NHIRD covers approximately 23 million insurers and is one of the largest nationwide population databases in the world.[16] As of 2015, the NHI covered 99.6% of the population in Taiwan.[17] Chinese herbal medicine (CHM) constitutes a significant category of traditional Chinese medicine (TCM) for CAM therapies. CHM treatments reimbursed by NHI since 1996 were either single-herb or multiherb products, extracted to powder form after water decoction, concentration, and excipient, by Good Manufacturing Practice–certified pharmaceutical companies.[18] In Taiwan, patients often use CHM to treat or relieve the symptoms and signs of endocrine disorders, nutritional and metabolic diseases, immunity disorders (23.2%), and genitourinary system diseases (16.6%).[17] CHM treatment may help relieve symptoms of discomfort associated with cancer or those induced by chemotherapy and/or radiotherapy.[19-21] Moreover, some studies have demonstrated that CHM has anticancer effects.[22,23]

The aim of the present study is to clarify whether CHM is associated with reduced risk of SPC of the H&N in patients with EC, which could provide an additional treatment option for patients to not only ameliorate the side effects, but also to decrease the secondary cancer recurrence rate.

Methods

Data Source

Participants of this retrospective cohort study consist entirely of Taiwan residents. We used the Registry for Catastrophic Illness Patient Database (RCIPD), a sub–data set of NHIRD, which records the medical care information of Taiwan's catastrophic illness patients. Those patients enrolled in RCIPD correspond to various pathological categories. The catchment population for the NHIRD is estimated to be more than 99% of the total population of Taiwan. Specific disease identification in the NHIRD was recorded according to the *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) code. The medical care information recorded in the NHIRD includes, among others, medical category, drug use, and surgery undergone.

Study Population and Covariates

Patients newly diagnosed with EC in the RCIPD during the years 2000 to 2010 were qualified for inclusion in this study. The patients with EC were divided into 2 groups,

classified as CHM and non-CHM cohorts. The definition of CHM users included patients having TCM clinical visits with EC ICD-9-CM code after diagnosis of EC. The non-CHM users were the population without any record of TCM clinical visit after diagnosis of EC. The index date was defined as the TCM-received date. Only individuals whose index date occurred between the years 2000 and 2010 were enrolled in this study. Those patients with H&N cancer (ICD-9-CM: 140, 141, 143-418, and 161) before the index date were excluded.

The occurrence of H&N cancer as SPC was identified among EC patients during the years 2000 to 2011. History of alcohol-related illness (ICD-9-CM: 291, 303, 305, 571.0, 571.1, 571.2, 571.3, 790.3, and V11.3), cirrhosis (ICD-9-CM: 571), anemia (ICD-9-CM: 280-285), asthma (ICD-9-CM: 493), chronic obstructive pulmonary disease (COPD; ICD-9-CM: 491, 492, 493 and 496), diabetes mellitus (ICD-9-CM: 250), hypertension (ICD-9-CM: 401-405), coronary artery disease (CAD; ICD-9-CM: 410-414), rheumatoid arthritis (ICD-9-CM: 714), systemic lupus erythematosus (ICD-9-CM: 710.0), stroke (ICD-9-CM: 430-438), esophagus ulcer (ICD-9-CM: 530.2), and esophagitis (ICD-9-CM: 530.1) before the index date were the baseline comorbidities. Surgery, chemotherapy, and radiotherapy were also considered to be variables. The job types of participants were included in the categories of office workers, manual workers, and others. In this study, we also investigated the specific usage patterns of CHMs among patients with EC.

Statistical Analysis

The final study population was recruited after propensity score match.[24] Sex, age, index year, and diagnosis year of EC were the criteria for the propensity score matching. Each CHM user was matched with a non-CHM user at a 1:1 ratio, according to the propensity score calculated. We tested the association of baseline demographics in patients with and without CHMs using χ^2 tests. χ^2 Tests were also used to compare comorbidity and treatment modality. We used the Fisher exact test instead of the χ^2 test when the cell was insufficient. The difference of mean age between CHM users and non-CHM users was evaluated using the Student *t*-test. Our study used the Kaplan-Meier method to estimate the cumulative incidence of H&N cancer during the study period. The log-rank test was conducted to compare the difference in cumulative incidence of H&N cancer between CHM and non-CHM cohorts. The effect of variables was examined in Cox proportional hazards models. This study utilized mortality to adjust Cox proportional hazards models to calculate subhazard ratio (SHR) and 95% CI. We classified the CHM receiving duration group by median CHM treatment days. NodeXL is an open-source freeware used to run a network analysis of CHM, which can be found at http://nodexl.codeplex.com/. *P* values less than .05 indicated statistical significance in this study. We performed analyses (except network analysis) with the statistical software package, SAS, version 9.4 (SAS Institute, Inc, Cary, NC).

Results

Demographic Characteristics

We identified 15 546 patients who were diagnosed with EC between January 1, 2000, and Decemeber 31, 2010 (Figure 1). There were 1261 and 12 173 participants in the CHM group and non-CHM groups, respectively. After selection by the exclusion criteria and matching process, both CHM and non-CHM cohorts each contained 850 individuals.

In terms of the demographic characteristics of the patients with EC, both the CHM and non-CHM cohorts consisted mainly of male participants (Table 1). There were 516 (60.7%) and 493 (58%) CHM and non-CHM users, aged 40 to 59 years, respectively, whereas the average ages of the CHM and non-CHM cohorts were 57.2 and 58.0 years, respectively. Although the job-type distribution of patients differed between the CHM cohort and non-CHM cohort ($P = .001$), manual workers made up approximately half of both groups; cirrhosis, hypertension, COPD, and esophagitis were the primary baseline comorbidities in the 2 cohorts. Moreover, the study found a significant difference between patients receiving chemotherapy and/or radiotherapy between the CHM and non-CHM cohorts ($P = .01$ for chemotherapy; $P < .001$ for radiotherapy). The mean induction times between CHM users and non-CHM users were 2.41 (2.02) and 2.15 (1.20) years, respectively (*t*-test $P = .61$). This indicates that there was no statistically significant difference in the mean induction time of subsequent H&N cancer after the diagnosis of EC between groups.

The Cause-Specific Hazard Ratio and 5-Year Cumulative Incidence of H&N Cancer

The study reveals that compared with non-CHM users, CHM users presented a reduced incidence risk of H&N cancer among patients with EC (adjusted SHR = 0.58, 95% CI = 0.34-0.98, $P = .04$; Table 2). Of note, during the study period, the cumulative incidence of H&N cancer was significantly higher among non-CHM users as compared with CHM users (Figure 2). We initially defined EC patients who took CHM for ≤7 days as the low-dose CHM cohort, in contrast to CHM >7 days as the high-dose CHM cohort. The crude SHRs between

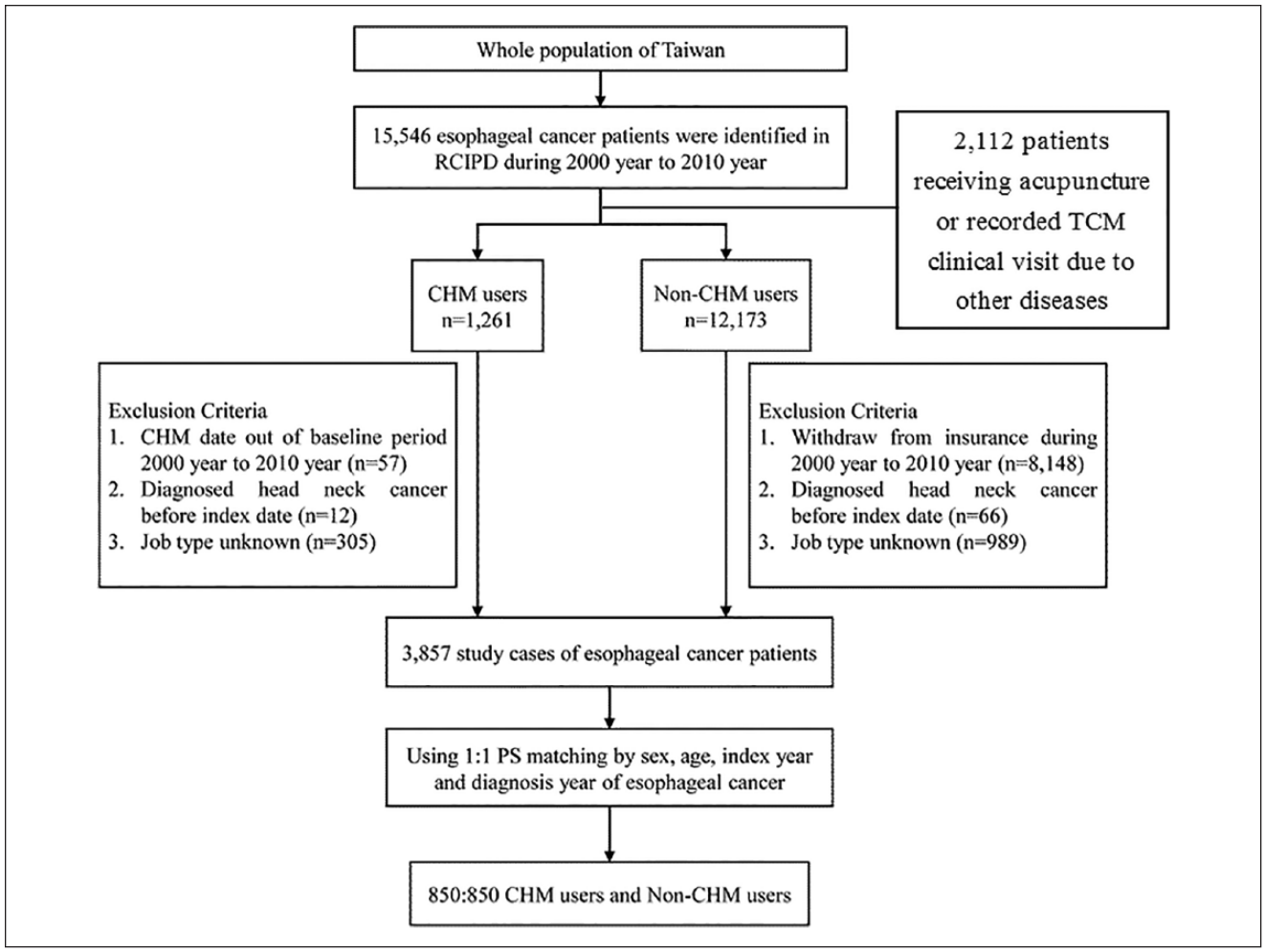

Figure 1. Flow chart of CHM and non-CHM cases from Registry for Catastrophic Illness Patient Database (RCIPD) in Taiwan during 2000-2010.
Abbreviations: CHM, Chinese herbal medicine; TCM, traditional Chinese medicine; PS, propensity score.

low- and high-dose cohorts were 0.39 (95% CI = −0.17 to 0.88; $P = .02$) and showed statistical significance. Our results demonstrated that there was no statistical significance in the dose response of CHM after adjustment (SHR = 0.48; 95% CI = −0.2 to 1.12; $P = .09$), as shown in Supplementary Table 1. We believed that the high-dose CHM cohort might show a trend to decreased incidence of SPC of H&N cancer compared with the low-dose CHM cohort with a larger number of patients. After dividing the population into 4 subgroups, on the other hand (Table 2), we found that the risk of H&N cancer among the CHM cohort that received CHM for a period of more than 28 days was significantly lower than that among the non-CHM cohort (adjusted SHR = 0.45; 95% CI = 0.21-0.97; $P = .04$).

Patients with a comorbidity of asthma or CAD presented a lower incidence of H&N cancer (adjusted SHR = 0.09, 95% CI = 0.02-0.32, P value <.001 for asthma; adjusted SHR = 0.27, 95% CI = 0.09-0.84, P value = .02 for CAD; Table 2). Because there were only 2 events of asthma and 3 events of CAD in all EC patients associated with H&N cancer, it is difficult to conclude that CHM really had the effect of ameliorating the incidence of SPC (H&N cancer) in the EC patients with asthma and CAD. Among the study population, surgery and radiotherapy enhanced the recurrence probability of head and neck cancer (adjusted SHR = 2.32, 95% CI = 1.14-4.73, P value = .02 for surgery; adjusted SHR = 4.78, 95% CI = 1.04-21.89, P value = .04 for radiotherapy; Table 2). Furthermore, patients receiving surgery and/or radiotherapy treatment demonstrated an increased incidence rate of H&N cancer compared with those not having undergone such treatments. To further investigate the effect of CHM on the incidence rates of H&N cancer with and without CHM use in patients with EC in different treatment stratifications, we found that the CHM cohort demonstrated a decreased incidence rate of H&N cancer in patients receiving chemotherapy and/or radiotherapy

Table 1. Demographic Characteristics of the Patients Newly Diagnosed With Esophageal Cancer in Taiwan in 2000-2010.

	Non-CHM, n = 850, 50.00%		CHM, n = 850, 50.00%		
Variable	n	Percentage	n	Percentage	*P* Value
Sex					.63
Female	35	4.12	39	4.59	
Male	815	95.9	811	95.4	
Age at baseline (years)					.33
20-39	40	4.71	30	3.53	
40-59	493	58.0	516	60.7	
≥60	317	37.3	304	35.8	
Mean (SD)[a]	58.0(12.5)		57.2(11.2)		.17
Job type					.001
Office worker	161	18.9	187	22.0	
Manual worker	423	49.8	463	54.5	
Others	266	31.3	200	23.5	
Baseline comorbidity					
Alcohol-related illness	192	22.6	197	23.2	.77
Cirrhosis	313	36.8	351	41.3	.06
Anemia	140	16.5	128	15.1	.42
Asthma	81	9.53	71	8.35	.40
Chronic obstructive pulmonary disease	253	29.8	248	29.2	.79
Diabetes mellitus	121	14.2	137	16.1	.28
Hypertension	299	35.2	284	33.4	.44
Coronary artery disease	137	16.1	163	19.2	.10
Rheumatoid arthritis	1	0.12	0	0	
Systemic lupus erythematosus	0	0	0	0	
Stroke	95	11.2	88	10.4	.58
Esophagus ulcer	98	11.5	117	13.8	.17
Esophagitis	260	30.6	288	33.9	.15
Treatment					
Surgery	77	9.06	74	8.71	.80
Chemotherapy	627	73.8	671	78.9	.01
Radiotherapy	688	80.9	748	88.0	<.001
Target therapy[b]	3	0.35	1	0.12	.62
Mean follow-up period (median), year	1.38 (0.73)		1.63 (0.89)		
Mean induction time (median), year[a]	2.41 (2.02)		2.15 (1.2)		.61
Mean CHM duration[c] (median), year			0.54 (0.31)		

Abbreviation: CHM, Chinese herbal medicine.
[a]Student *t*-test.
[b]Fisher exact test.
[c]Duration is the period between esophageal cancer diagnosis date and index date.

rather than surgery, compared with the non-CHM cohort (adjusted SHR = 0.47, 95% CI = 0.26-0.85, $P < .05$ for chemotherapy; adjusted SHR = 0.56, 95% CI = 0.32-0.95, $P < .05$ for radiotherapy). This indicates that CHM reduced the risk of SPC of H&N cancer occurrence caused by chemotherapy and/or radiotherapy, as shown in Table 3. The overall incidence of SPC of H&N cancer in the CHM cohort was lower than that of the non-CHM cohort. More specifically, after stratification of the follow-up period, the adjusted SHR was 0.45 (95% CI = −0.21 to 0.94) in the CHM cohort within the follow-up period of less than 2 years, as shown in Table 3.

Single Herbs and Formulas Commonly Prescribed in TCM Clinical Practice

The most popular herbal prescription for patients with EC was Hedyotidis Diffusae Herba (Table 4). The second and third most frequently prescribed herbs were *Fritillaria thunbergii* and Scutellariae Barbatae Herba, respectively. The top 3 formulas prescribed for patients with EC were Xiang-Sha-Liu-Jun-Zi-Tang, Ban-Xia-Xie-Xin-Tang, and Shen-Ling-Bai-Zhu–San, respectively (Table 5). The composition of the 10 most common formulas is shown in Supplementary Table 2. For each treatment involving

Table 2. Cox Model–Measured Hazard Ratio and 95% CIs of Head and Neck Cancer Associated With CHM Use and Covariates Among Esophageal Cancer Patients.

		Crude			Adjusted[a]		
Characteristics	Event Number (n = 58)	HR	(95% CI)	*P* Value	HR	(95% CI)	*P* Value
CHM							
No	35	1	Reference		1	Reference	
Yes	23	0.62	(0.37-1.04)	.07	0.58	(0.34-0.98)	.04
CHM duration							
Nonuser	35	1	Reference		1	Reference	
<14 Days	11	1	(0.51-1.96)	.99	0.86	(0.44-1.67)	.66
14-27	3	0.38	(0.12-1.22)	.10	0.4	(0.13-1.27)	.12
≥28 Days	9	0.49	(0.24-1.02)	.06	0.45	(0.21-0.97)	.04
Sex							
Women	0	1	Reference		1	Reference	
Men	58						
Age, years							
20-39	2	1	Reference		1	Reference	
40-59	45	1.61	(0.39-6.59)	.51	1.82	(0.42-7.89)	.42
≥60	11	0.63	(0.14-2.82)	.55	0.98	(0.2-4.82)	.98
Job type							
Office worker	17	1	Reference		1	Reference	
Manual worker	31	0.7	(0.39-1.26)	.24	0.77	(0.42-1.41)	.40
Others	10	0.41	(0.19-0.9)	.03	0.63	(0.28-1.4)	.26
Baseline comorbidity (yes vs no)							
Alcohol-related illness	20	1.86	(1.09-3.19)	.02	1.19	(0.63-2.22)	.60
Cirrhosis	31	1.83	(1.1-3.06)	.02	1.57	(0.88-2.79)	.13
Anemia	7	0.71	(0.33-1.57)	.40	0.8	(0.37-1.76)	.59
Asthma	2	0.35	(0.09-1.43)	.14	0.09	(0.02-0.32)	<.001
Chronic obstructive pulmonary disease	15	0.86	(0.48-1.54)	.60	1.46	(0.79-2.71)	.23
Diabetes mellitus	7	0.78	(0.35-1.71)	.53	1.03	(0.42-2.53)	.94
Hypertension	18	0.87	(0.5-1.51)	.62	1.52	(0.81-2.88)	.20
Coronary artery disease	3	0.25	(0.08-0.79)	.02	0.27	(0.09-0.84)	.02
Rheumatoid arthritis	0						
Systemic lupus erythematosus	0						
Stroke	1	0.15	(0.02-1.06)	.06	0.2	(0.03-1.66)	.14
Esophagus ulcer	9	1.25	(0.61-2.53)	.54	1.25	(0.6-2.62)	.55
Esophagitis	18	0.97	(0.56-1.69)	.91	0.93	(0.53-1.65)	.81
Treatment (yes vs no)							
Surgery	10	2.53	(1.28-4.99)	.01	2.32	(1.14-4.73)	.02
Chemotherapy	49	1.71	(0.85-3.47)	.14	0.84	(0.4-1.79)	.66
Radiotherapy	56	5.08	(1.25-20.67)	.02	4.78	(1.04-21.89)	.04

Abbreviations: CHM, Chinese herbal medicine; HR, hazard ratio.
[a]Adjusted HR: adjusted for sex, age, job type, all comorbidities, and all treatments in Cox proportional hazards regression.

patients with EC, 32.22% of the CHM prescriptions consisted of 5 or 6 individual combinations of single herbs and/or formulas (Supplementary Figure 1), whereas prescriptions with 7 or 8 CHM combinations made up 27.26%. The prescriptions of Hedyotidis Diffusae Herba along with Scutellariae Barbatae Herba and *F thunbergii* were the most frequent CHM combinations prescribed by TCM practitioners (Figure 3).

Discussion

This is the first report using the NHIRD to compare the risk of SPC of the H&N among patients diagnosed with EC with and without CHM treatment. In a recent study, Chen et al[8] reported that the cumulative incidence of H&N cancer remained significantly high within a follow-up time of more than 10 years among patients with EC. Notably, this study

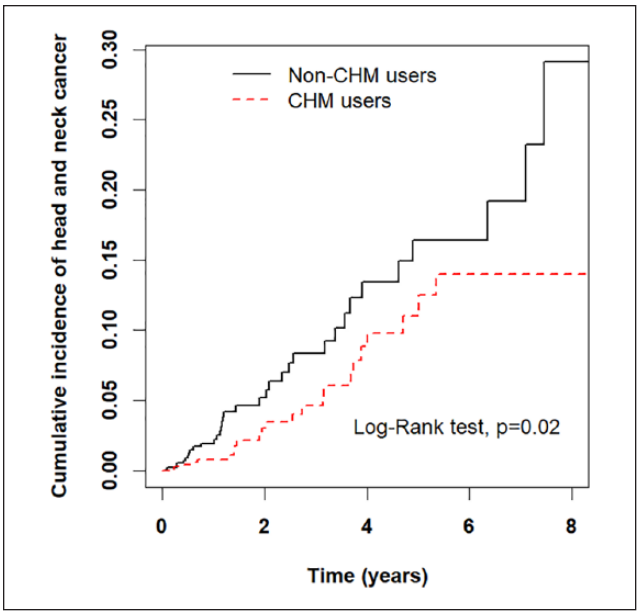

Figure 2. Kaplan-Meier analysis of cumulative incidence of head and neck cancer between esophageal cancer patients with and without Chinese herbal medicine (CHM) use. The cumulative incidence of head and neck cancer was significantly higher among non-CHM users as compared with CHM users in the patients with esophageal cancer (log-rank test, $P = .02$).

reveals that the cumulative incidence of H&N cancer in EC patients with CHM treatment is 15% of the total cumulative incidence rate, within a follow-up time of 8 years. In contrast, the incidence in patients without CHM use rose to approximately 30% of the cumulative incidence rate during the 8-year follow-up period. These findings indicate that patients with EC using CHM demonstrate a decreased risk of developing H&N cancer over a longer-term follow-up period. The decreased incidence rate in the CHM cohort within the follow-up period of less than 2 years suggests that CHM treatment as early as possible may have a protective effect against incidence of SPCs.

The association of EC with SPC, especially for H&N cancers, was first identified by the connection to the field cancerization effect in 1953 by Slaughter et al.[25] It has been reported that smoking, drinking, and heat damage are high-risk factors for developing SCC.[3,26-28] The carcinogenic effects of tobacco and alcohol may concurrently influence other parts of the aerodigestive tract. The affected epithelium of the aerodigestive tract may be activated in more than one location within the body, leading to a process of irreversible change, eventually resulting in carcinogenesis. Finally, these carcinogens, exposed in sufficient intensity for a period of time, will trigger the development of multiple independent primary cancers.[9,10,25] In addition to smoking and drinking, betel nut is also an addictive substance commonly used in the Asian region.[29] As reported, betel nut has been found to cause cancers in the upper aerodigestive tract, including oral SCC and SCC of the pharynx, esophagus, and larynx.[30] Betel nut and betel nut extract exert carcinogenicity, mutagenicity, and genotoxicity to result in tumor production by many mechanisms.[31] Chewing betel nut causes mucosal exposure to 4 *N*-nitrosamines formed by areca alkaloids, 2 of which are carcinogenic,[32] through reactive oxygen species activation. Because of reactive oxygen species attacking salivary glands and the oral mucosa, the structural change of oral mucosa facilitates penetration by the betel nut ingredients and environmental toxicants. We consider that the mucosa change induced by a variety of carcinogens such as cigarettes and betel nut will increase the risk of H&N cancer among patients with EC. In Taiwan, it has been reported that SCC accounts for about 95.5% of all ECs.[33] Chen et al[8] have reported that major surgery (HR = 1.24; 95% CI = 1.06-1.44; $P = .006$) is an independent risk factor of subsequent development of SPC. In this study, we found a similar result, specifically that surgery increased the risk of SPC H&N cancer. Based on the observations of this study, we can propose that CHM can interrupt the process of field cancerization via adjusting the constitution of patients with EC. Clinical CHM prescriptions are composed of several natural products, each containing numerous chemical compounds and each exerting its specific therapeutic functions on multiple targets within the human body. As tumorigenesis and metastasis involve multiple signaling pathways, inhibitors that affect a single pathway may not fully counter the disease progression and may even cause resistance.[34] CHM prescriptions, causing relatively fewer side effects and offering a multitargeted approach, may play an important role in the treatment of both original cancers and SPCs.

According to TCM theory, the formation of individual constitutions results from congenital inheritance and lifestyle influences, including environmental conditions and dietary habits. The specific constitution causes the body's susceptibility to particular pathogenic factors and determines the trend of syndrome changes.[35] It has been shown that the frequent use of tobacco and alcohol leads to the development of phlegm-dampness and dampness-heat constitutions.[36] Patients with such a phlegm-dampness constitution are known to be particularly susceptible to metabolic syndromes, such as hyperlipidemia, diabetes, obesity, and hypertension,[37] which are also associated with H&N cancer.[38,39] As reported, the risk for oral cancers in male individuals increased 15%, in parallel with the standard deviation metabolic risk score increment.[39] In addition, the heat effect of dampness-heat constitution contributes to chronic inflammation resulting from increased oxidative stress and has been suggested as the mechanism responsible for increased susceptibility to cancer.[40,41] This study reveals the 10 most commonly prescribed formulas for patients with EC. Among them, Xiang-Sha-Liu-Jun-Zi-Tang is clinically applied to those with the phlegm-dampness constitution to

Table 3. Incidence Rates, Hazard Ratio, and CIs of Head and Neck Cancer With and Without CHM Among Esophageal Cancer Patients in Different Treatment and Follow-up Period Stratifications.

	CHM						CHM vs Non-CHM	
	No (n = 850)			Yes (n = 850)			Crude SHR (95% CI)	Adjusted SHR (95% CI)
	Event	Person-years	IR	Event	Person-years	IR		
Treatment								
Surgery	5	117	42.7	5	140	35.7	0.83 (0.24-2.82)	0.69 (0.13-3.53)
Chemotherapy	31	812	38.2	18	1038	17.4	0.51 (0.29-0.9)*	0.47 (0.26-0.85)*
Radiotherapy	34	874	38.9	22	1127	19.5	0.56 (0.33-0.96)*	0.56 (0.32-0.95)*
Follow-up period (years)								
<2	20	779	25.7	11	879	12.5	0.53 (0.25-1.1)	0.45 (0.21-0.94)*
2-3	10	228	43.9	8	289	27.7	0.63 (0.25-1.6)	0.66 (0.24-1.77)
≥4	5	165	30.3	4	222	18.1	0.64 (0.17-2.47)	1.07 (0.2-5.66)

Abbreviations: CHM, Chinese herbal medicine; SHR, subhazard ratio; IR, incidence rate.

Table 4. The 10 Most Common Single Herbs Prescribed for Patients With Esophageal Cancer.

Prescription Name (in Chinese)	Frequency	Number of Person-days, Frequency	Average Daily Dose (g)	Average Duration for Prescription (days)
Bai-Hua-She-She-Cao [*Hedyotis diffusa*]	1967	23052	1.5	11.7
Bei-Mu [*Fritillaria thunbergii*]	1110	13274	1.2	12
Ban-Zhi-Lian [*Scutellaria barbata* D Don]	1030	12267	2.1	11.9
Dan-Shen [*Salvia miltiorrhiza*]	819	10991	1.4	13.4
Huang-Qi [*Astragalus membranaceus*]	854	10950	1.6	12.8
Hai-Piao-Xiao [Os Sepiae]	613	8583	1.6	14
Hou-Po [*Magnolia officinalis*]	740	8342	1.2	11.3
Mai-Men-Dong [Radix Ophiopogon japonicus]	605	6838	1.4	11.3
Bai-Zhu [*Atractylodes macrocephala*]	587	6610	1.4	11.3
Huang-Qin [*Scutellaria baicalensis*]	534	6371	1.2	11.9

relieve various symptoms associated with the digestive tract, such as chemotherapy-induced nausea and vomiting as well as anorexia-cachexia syndrome.[42] It has been demonstrated that Liu-Jun-Zi-Tang exhibited both anti-inflammatory and antioxidative protective effects on mice exposed to cigarette smoke through enhanced activities of antioxidant enzymes and by attenuating the levels of lipid oxidative production through inhibiting phosphorylation of IκB-α and NF-κB.[43] Additionally, Liu-Jun-Zi-Tang has been shown to regulate insulin secretion and ameliorate metabolic syndromes,[39] which are beneficial for the prevention of SPC initiation.[44,45]

Here, we found that radiotherapy increased the risk of SPC of the H&N in patients with EC, in line with a report by Zhu et al.[9] As we know, radiation therapy for primary cancers is highly associated with an increased risk of developing SPC in nearby organs.[9] It is biologically plausible that DNA damage resulting from radiotherapy is a potential mechanism leading to the occurrence of SPC in the irradiated H&N area.[46,47] Based on the observations of this study, we can propose that CHM could prevent the development of SPC of the H&N via protecting against radiotherapy-induced DNA damage. Ban-Xia-Xie-Xin-Tang (BXXXT) is commonly used for treatment of chemotherapy- and radiotherapy-induced mucositis in patients with EC. BXXXT simultaneously decreases DNA damage induced by radiotherapy through multiple mechanisms, including by inhibiting COX2 activity and PGE2 production and by restraining MAPK upregulation to reduce stable free radicals and prevent reactive oxygen species formation.[21,48] Furthermore, Gan-Lu-Yin (GLY) is frequently used for the treatment of oral ulcers after chemotherapy and/or radiotherapy in patients with H&N cancer. GLY decreases the level of TNF-α release via inhibiting the NF-κB–, AKT-, and ERK-dependent pathways.[49] Based on this, we propose that this protective effect may also be applied to the prevention of SPC occurrence of H&N in patients with EC. Moreover, CHM is associated with immune modulation in patients with EC to avoid the development of SPC of the

Table 5. The 10 Most Common Formulas Prescribed for Patients With Esophageal Cancer.

Prescription Name (in Chinese)	Frequency	Number of Person-days, Frequency	Average Daily Dose (g)	Average Duration for Prescription (days)
Xiang-Sha-Liu-Jun-Zi-Tang	951	12999	4.8	13.7
Ban-Xia-Xie-Xin-Tang	743	9884	5	13.3
Shen-Ling-Bai-Zhu-San	658	8601	6.1	13.1
Bu-Zhong-Yi-Qi-Tang	640	7292	6	11.4
Pao-Ho-Wan	486	6629	3.9	13.6
Gan-Lu-Yin	578	6113	6.2	10.6
Xuan-Fu-Dai-Zhe- Shi-Tang	443	5462	4.1	12.3
Ping-Wei-San	422	4844	3.8	11.5
Jia-Wei-Xiao-Yao-San	362	4641	3.9	12.8
Liu-Wei-Di-Huang-Wan	399	4510	4.7	11.3

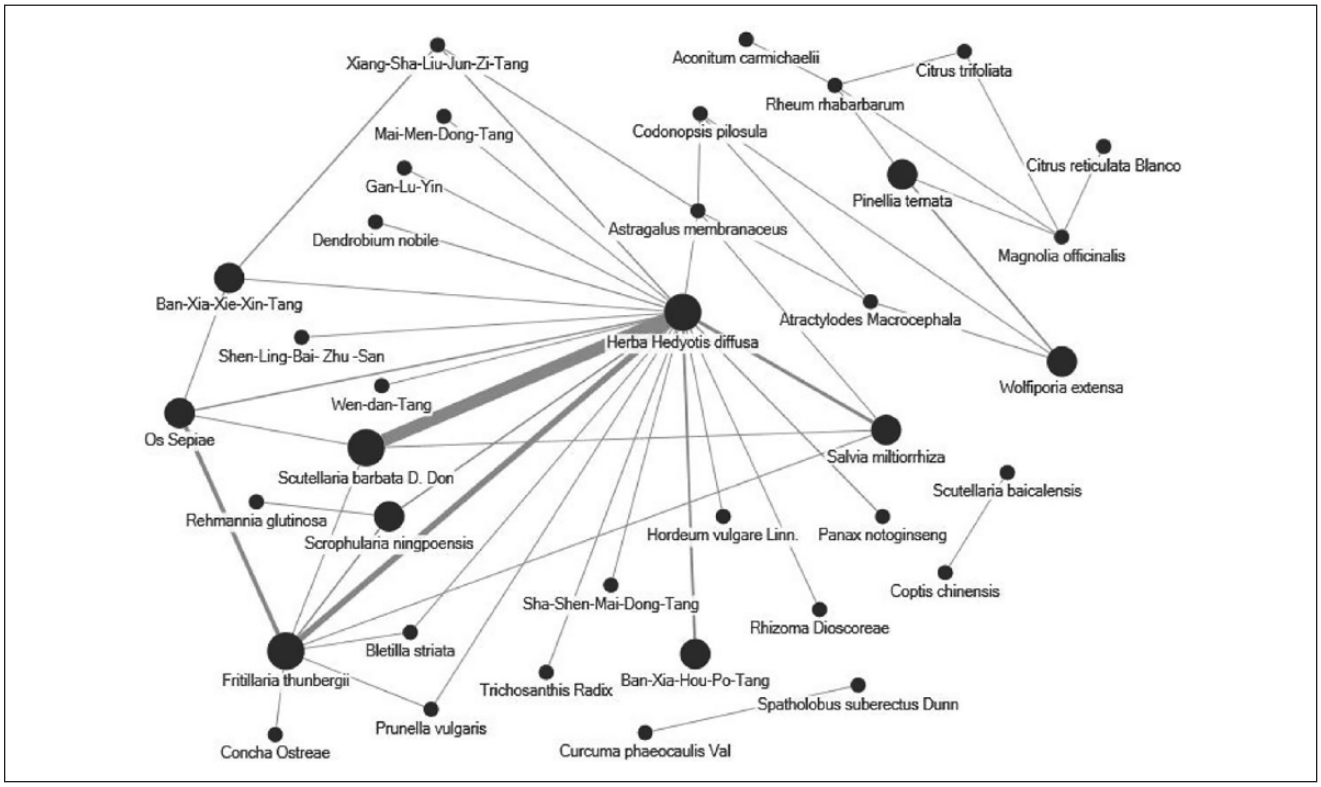

Figure 3. Network analyses of the most frequently used 50 herb and formula combinations for all patients with esophageal cancer. The size of the spot indicates the frequency of Chinese herbal product prescribed, and the width of the line indicates the frequency of association between 2 Chinese herbal products.

H&N. Notably, Bu-Zhong-Yi-Qi-Tang has been shown to relieve cancer-related fatigue[50] by enhancing interleukin-18 to induce cell-mediated immunity and improve the host's defensive capabilities.[51] In addition, Jia-Wei-Xiao-Yao-San can rehabilitate paclitaxel-induced axonal involvement and promote recovery from paclitaxel-induced neuropathy via increasing the proportion of phosphorylated ERK1/2 and phosphorylated AKT to promote neurite outgrowth with NGF.[52] As a result of Jia-Wei-Xiao-Yao-San use, quality of life can be improved, allowing patients to accept a more complete treatment of chemotherapy.

The prescription of CHM, in combination with numerous single herbs or formulas, aims to potentiate therapeutic efficacy and mitigate side effects.[53] As such, Figure 3 illustrates network analyses of the most frequent herbs and formula combinations for patients diagnosed with EC. We found that Hedyotidis Diffusae Herba, Scutellariae Barbatae Herba, and *Fritillaria thunbergii* can be

combined in clinical prescription, which may result in enhanced anticancer effects.[53,54] Significantly, *Magnolia officinalis* and *Scutellaria baicalensis* were reported to induce apoptosis both in esophageal and H&N cancers, which could contribute to clinical anticancer effects.[22,23,55,56] The biological anticancer activities and possible mechanisms of the most common single herbs are illustrated in Supplementary Table 3.[22,23,34,54-66]

The data used for the present study were extracted from the NHIRD; however, there inevitably exist some limitations and flaws. The NHI does not provide patient specifics, including laboratory data, images, pathology reports, disease stage, metastasis status, or lifestyle details. Therefore, we could not confirm preliminary histological subtypes of EC patients. Because of a lack of data, we also could not evaluate whether CHM influenced risk factors such as exposure to tobacco and/or alcohol. Moreover, some cancer patients may take supplements or medications from pharmacies instead of hospitals, the data of which were not recorded by the NHI. Additionally, the NHI only reimburses prescriptions of CHM by licensed TCM practitioners who register the data; therefore, data from those doctors who do not participate in the NHI program (fewer than 10%) will be excluded.[17]

Conclusion

In conclusion, this study demonstrates that CHM, which has been shown to relieve symptoms of discomfort associated with cancer and cancer treatment, is also associated with reduced incidence of SPC of the H&N in EC patients. This effect may result from the multicomponent compositions, multitargeted mechanisms, and presence of fewer side effects. CHM may also reduce cancer-promoting side effects of conventional treatments such as radiotherapy. However, it is necessary to further validate the relationship between CHM and the reduced incidence rate of SPC of the H&N by conducting a prospective clinical trial involving patients with EC in the near future.

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Authors' Note

C-CC and K-WB wrote the manuscript, interpreted the data, and contributed equally to this work. Y-CS collected, assembled, and analyzed the data. H-JL, W-LW, C-YL, C-FT and M-FS provided and checked the data. S-TH designed and conceived the study, and amended the manuscript. C-CC, K-WB, H-JL, Y-CS, W-LW, C-YL, C-FT, M-FS, and S-TH approved the final manuscript. The Review Board and Ethics Committee of China Medical University Hospital, Taiwan, approved the data used for this research (CMUH104-REC2-115(CR-3)). All information of patients was decoded in the database from NHIRD, and informed consent was not needed.

Declaration of Conflicting Interests

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Supplemental Material

Supplemental material for this article is available online.

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