

Association between Traditional Chinese Medicine Use and Liver Cancer in Patients with Liver Cirrhosis: A Population-based Study

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Abstract

Background

The global incidence and mortality of liver diseases is increasing. One of the major risk factors for liver cancer is the presence of liver cirrhosis. Traditional Chinese medicines (TCM) are being sought as alternative medicines for liver diseases. This study evaluated the association between traditional Chinese herbal medicine and liver cancer in patients with liver cirrhosis.

Methods

The analytical data were collected from the Longitudinal Health Insurance Databases (LHID2005). Samples included patients with liver cirrhosis who sought Traditional Chinese medicine from 2001-2004. Diagnosis of liver cancer was from 2004-2010 using the ICD 9 codes 155 and A code A095. The Chi-square (χ^2) test was used to test for associations while multivariate logistic regression was used to investigate the association between CM and liver cancer in cirrhotic patients. All statistics were analyzed using the SAS 9.2 software (Cary, NC, USA). Differences were considered significant at p -value < 0.05.

Results

From 2001-2004, a total of 8 145 individuals were identified with liver cirrhosis; 5 469 were men and 2 676 were women. Among the cirrhotic patients who sought TCM, 25.3% of men and 20.41% of women were identified with liver cancer. Multivariate logistic regression analysis showed a significant odds ratio (OR) of 0.880 (95% CI 0.787-0.984) for liver cancer. However, when analyzed by gender, significant odds existed only in men (OR: 0.872, 95% CI 0.764-0.955).

Conclusion

There was a significant association between traditional Chinese medicine and liver cancer in men with cirrhosis.

Keywords: Cirrhosis; Liver cancer; Chinese herbal medicine

Introduction

Hepatocellular carcinoma (HCC) is the seventh most frequent cancer and the third leading cause of cancer-related death worldwide [1]. Cirrhosis is the strongest predisposing factor for HCC. Approximately 80% of cases with HCC develop in cirrhotic liver [2]. The annual incidence of HCC in patients with and without cirrhosis is 2.0-6.6 and 0.4%, respectively [2]. Variceal bleeding is one of the commonest and most severe complications of liver cirrhosis. When cirrhosis is diagnosed, varices are present in about 30-40% of compensated patients and in 60% of those who present with ascites [3]. There is no effective medication to prevent the development of varices [4]. Liver transplantation (LT) may serve as the best treatment choice for varices [5,6]. However, shortage of donor organs is a serious well known limitation [7].

Because of the complexity and difficulty involved in the treatment of liver cirrhosis, many patients seek traditional Chinese Herbal medicine (an alternative treatment). A previous study has reported the therapeutic and beneficial effects of Chinese medicine on hepatic fibrosis [8]. Chinese Medicine has also been linked to hepatoprotective effect in cirrhotic patients [9]. However, studies to investigate the links between TCM and liver cancer among patients with liver cirrhosis using a large-scale database are limited. Therefore, this study was conducted to assess the relationship between traditional Chinese herbal medicine and liver cancer in patients with liver cirrhosis.

Methods

The study data were collected from the National Health Insurance Research Database (NHIRD) which contains detailed clinical records of every patient on each visit. It also includes primary and secondary diagnostic codes as well as prescription orders. A randomized sample of 1,000,000 individuals were retrieved from the LHID2005. The database contained de-identified data hence, ethics approval was not required. Cirrhotic patients were either identified from the CD (ambulatory care expenditures by visit) or DD (inpatient expenditures by admission) datasets using the codes 571.2, 571.5, 571.6 and A code A347. The study samples included a total of 8145 cirrhotic patients: 4,509 who sought and 3,636 who did not seek TCM from 2001-2004). Excluded were individuals who were diagnosed with liver cancer from 2001 to 2004 and those who sought TCM during 2005-2010. Liver cancer diagnosis was from 2004-2010 using the ICD 9 code 155 and Acode A095.

Information about the demographic variables, insurance cost and geographical region is contained in the NHIRD.

Household income was categorized into four groups: family dependent, <\$20,000, \$20,000 to less than \$40,000, and \geq \$40,000. Insurance has been categorized into mainly six regions according to geographic and administrative districts: Taipei (Taipei City, Taipei County, Keelung City, Yilan County, Kinmen County, Lianjiang County), Northern (Taoyuan County, Hsinchu City, Hsinchu County, Miaoli County), Central (Taichung City, Taichung County, Changhua County, Nantou County), Southern (Tainan City, Tainan County, Chiayi City, Chiayi County, Yunlin County), Kao-Ping (Kaohsiung City, Kaohsiung County, Pingtung County, Penghu County), and Eastern region (Hualien County, Taitung County). Adjustments were made for socio-demographic characteristics (**Table 1**) as well as other potential confounders (hepatitis B virus, hepatitis C virus, chronic hepatitis, alcoholic hepatitis).

Table 1 Demographic characteristics of patients who sought TCM (age \geq 30), age was mean \pm S.E.

Variable	TCM from 2001-2004		No TCM from 2001-2004		P -value
	(n=4 509)		(n=3 636)		
	Number	%	Number	%	
Age (2005)	55.62 \pm 15.47		56.53 \pm 16.11		0.0095
Sex					<0.0001
Men	2 749	60.97	2 720	74.81	
Women	1 760	39.03	916	25.19	
Household income					<0.0001
Dependent	1 107	24.55	800	22.00	
<20 000	2 303	51.08	2 107	57.95	
20 000-39 999	691	15.32	449	12.35	
\geq 40 000	408	9.05	280	7.70	
Geographic area					<0.0001
Taipei City	1 284	28.48	965	26.54	
North	544	12.06	504	13.86	
Central	932	20.67	527	14.49	
South	775	17.19	753	20.71	
Kaohsiung-Pingtung	785	17.41	696	19.14	
East	189	4.19	191	5.25	
Liver cancer					0.0267
Yes	1 042	23.11	917	25.55	
No	3 467	76.89	2 719	74.78	
Chronic hepatitis					<0.0001

Yes	2 864	63.52	1 973	54.26	
No	1 645	36.48	1 663	45.74	
Hepatitis B					0.0012
Yes	1 116	24.75	789	21.70	
No	3 393	75.25	2 847	78.30	
Hepatitis C					<0.0001
Yes	954	21.16	624	17.16	
No	3 555	78.84	3 012	82.84	
Alcoholic hepatitis					0.9446
Yes	286	6.34	232	6.38	
No	4 223	93.66	3 404	93.62	

Statistical analysis

The study participants were categorized into ≥ 18 , 18-40, and ≥ 40 age groups. T-test was used to analyze the age differences between individuals who received TCM and those who did not. Chi square test was used to assess the links between TCM and categorical variables while multivariate logistic regression was used to evaluate the relationship between TCM and liver cancer. All analyses were made using the SAS software (version 9.2, Cary, NC, USA). Differences were considered significant at p -value <0.05 .

Results

A total of 8,145 cirrhotic individuals aged 30 years and older were enrolled in this study. The mean age of cirrhotic men who sought TCM treatment was significantly less than that of those who never sought any treatment ($p<0.0001$) as shown in **Table 2**.

About 25.03% of cirrhotic men who sought TCM and 26.78% of those who never sought TCM were diagnosed with liver cancer. As shown in **Table 3**, the mean age of cirrhotic women who sought TCM treatment was significantly lower than that of those who did not ($p<0.0001$).

About 20.11% of cirrhotic men who sought TCM and 20.41% of those who never sought TCM were diagnosed with liver cancer. Results of multivariate logistic regression models stratified by gender and adjusted for insurance cost, geographical region and related confounders (hepatitis B virus, hepatitis C virus, chronic hepatitis, alcoholic hepatitis) are shown in **Table 4**. In the first model, the odds ratio of developing liver cancer in cirrhotic patients who sought TCM was (OR 0.880, 95% CI 0.787-0.984). Further analysis showed significant odds ratio only in men (0.872, 95% CI 0.764-0.955).

Table 2 Demographic characteristics of cirrhotic men who sought TCM (age ≥ 30), age was mean \pm S.E.

Variable	TCM from 2001-2004		No TCM from 2001-2004		P-value
	(n=2 749)		(n=2 720)		
	Number	%	Number	%	
Age (2005)	52.61 \pm 15.06		54.55 \pm 15.54		<0.0001
Household income					
Dependent	473	17.21	452	16.62	<0.0001
<20,000	1 477	53.73	1 656	60.88	
20,000-39,999	450	16.37	368	13.53	
$\geq 40,000$	349	12.70	244	8.97	
Geographic area					<0.0001
Taipei City	789	28.70	715	26.29	
North	333	12.11	395	14.52	
Central	570	20.73	416	15.29	

South	428	15.57	533	19.60	
Kaohsiung-Pingtung	505	18.37	525	19.30	
East	124	4.51	136	5.00	
Liver cancer					0.1265
Yes	688	25.03	730	26.84	
No	2 061	74.97	1 990	73.16	
Chronic hepatitis					<0.0001
Yes	1 745	63.48	1 469	54.01	
No	1 004	36.52	1 251	45.99	
Hepatitis B					0.0069
Yes	736	26.77	642	23.60	
No	2 013	73.23	2 078	76.40	
Hepatitis C					0.0694
Yes	467	16.99	413	15.18	
No	2 282	83.01	2 307	84.82	
Alcoholic hepatitis					0.1311
Yes	255	9.28	221	8.13	
No	2 494	90.72	2 499	91.88	

Table 3 Demographic characteristics of cirrhotic women who sought TCM (age>30), age was mean \pm S.E.

Variable	TCM from 2001-2004		No TCM from 2001-2004		P-value
	(n=1760)		(n=916)		
	Number	%	Number	%	
Age (2005)	60.30 \pm 14.93		62.42 \pm 16.32		0.0011
Household income					0.0034
Dependent	634	36.02	348	37.99	
<20 000	826	46.93	451	49.24	
20,000-39,999	241	13.69	81	8.84	
\geq 40 000	59	3.35	36	3.93	
Geographic area					<0.0001
Taipei City	495	28.13	250	27.29	
North	211	11.99	109	11.90	
Central	362	20.57	111	12.12	
South	347	19.75	220	24.02	
Kaohsiung-Pingtung	280	15.91	171	18.67	
East	65	3.69	55	6.00	
Liver cancer					0.8539
Yes	354	20.11	187	20.41	

No	1 406	79.89	729	79.59	
Chronic hepatitis					<0.0001
Yes	1.119	63.58	504	55.02	
No	641	36.42	412	44.98	
Hepatitis B					0.0006
Yes	380	21.59	147	16.05	
No	1.380	78.41	769	83.95	
Hepatitis C					0.0096
Yes	487	27.67	211	23.03	
No	1.273	72.33	705	76.97	
Alcoholic hepatitis					0.2684
Yes	31	1.76	11	1.20	
No	1.729	98.24	905	98.80	

Table 4 Risk of liver cancer in cirrhotic patients who sought TCM, adjusted for age, sex, household income and region.

Variable	Total		Men		Women	
	O.R	95% C.I	O.R	95% C.I	O.R	95% C.I
TCM in 2001-2004						
Yes	0.880	0.787-0.984	0.872	0.764-0.955	0.893	0.722-1.104
No	1.000	-	1.000	-	1.000	-
Age (2005)	1.027	1.022-1.031	1.028	1.023-1.033	1.022	1.013-1.031
Sex						
Male	1.000	-				
Female	1.937	1.705-2.200				
Household income						
Dependent	1.189	1.035-1.366	1.355	1.132-1.622	0.936	0.751-1.167
<20 000	1.000	-	1.000	-	1.000	-
20,000-39,999	1.184	0.999-1.403	1.308	1.077-1.589	0.839	0.585-1.203
≥ 40 000	1.089	0.884-1.343	1.187	0.949-1.484	0.607	0.301-1.222
Geographic area						
Taipei City	1.000	-	1.000	-	1.000	-
North	0.890	0.740-1.070	0.960	0.772-1.194	0.719	0.506-1.022
Central	0.903	0.764-1.068	0.918	0.750-1.124	0.880	0.653-1.186
South	0.940	0.797-1.108	1.055	0.863-1.289	0.718	0.535-0.962
Kaohsiung-Pingtung	1.004	0.852-1.183	1.150	0.947-1.396	0.710	0.519-0.970
East	0.549	0.398-0.757	0.540	0.366-0.795	0.588	0.332-1.041
Co-morbidity						
Chronic hepatitis	1.173	1.041-1.322	1.085	0.942-1.250	1.417	1.131-1.776

Hepatitis B	2.696	2.386-3.046	3.111	2.692-3.595	1.802	1.424-2.282
Hepatitis C	2.491	2.186-2.839	2.384	2.018-2.817	2.642	2.138-3.265
Alcoholic hepatitis	0.431	0.317-0.585	0.475	0.348-0.649	<0.001	-

Discussion

To our knowledge, this is the first nationwide population-based study to evaluate the relationship between liver cirrhosis, Chinese traditional medicine and liver cancer. Cirrhotic men who received TCM had a significantly lower risk of liver cancer. The risk was also lower but insignificant in their female counterparts. There may have been an interaction effect of TCM and hormones on liver cirrhosis. Future studies would help to clarify such interactions. In Taiwan, liver cancer accounts for more than 28% of total deaths [10]. The annual standardized mortality incidence increased from 22.7/100 000 in 1991 to 26.2/100 000 in 2009 [10]. The majority of patients with hepatocellular carcinoma (HCC) worldwide have underlying cirrhosis [11]. Hepatocellular carcinoma occurs at a rate of 1 to 4% per year after cirrhosis is established [12] while cirrhosis underlies HCC in approximately 80%-90% of cases worldwide [13]. Preventing the development of liver cancer in patients with liver cirrhosis is an important public health issue.

In Taiwan, chronic hepatitis B and C are the leading causes of liver cirrhosis [14-16]. About 95% of liver cirrhosis is caused by both B and C types of hepatitis viruses. Other causes include alcohol, chronic hepatitis, and persistence [14]. In this study, adjustments were made for potential confounders such as hepatitis B, C, alcohol and chronic hepatitis. HCC was significantly lower in cirrhotic patients who had received TCM. The mean age of cirrhotic men who were exposed to TCM was below that of their non-exposed counterparts. Significant association between traditional Chinese medicine and liver cancer was found only in men. More studies that take into account gender disparity are essential.

This study has some limitations. First, no specific Chinese medicine was included in the model. Second, there is a dearth of information about the stage of liver cirrhosis. Third, the NHIRD contain records of different scientifically processed Chinese herbal medications whose herbal preparations range from a single to multi-ingredient preparations. This makes it difficult to determine how frequently the patients were taking the medications. Finally, adjustments were not made for potential behavioral confounders such as smoking and drinking.

Conclusion

There was a significant association between traditional Chinese medicine and liver cancer in men with cirrhosis.

Conflict of Interest

Authors have no conflict of interest to disclose.

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