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Nonalcoholic Cirrhosis Increased Risk of Digestive Tract Malignancies

A Population-Based Cohort Study

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Abstract: Alcoholic cirrhosis is generally accepted as a risk factor for hepatocellular carcinoma (HCC) development; however, little research has examined the relationship between nonalcoholic cirrhosis (NAC) and HCC. Thus, the aim of this study was to investigate whether NAC is associated with the risk of HCC and extrahepatic malignancies in Taiwan.

We conducted a populated-based retrospective cohort study by using data from the Taiwan National Health Insurance (NHI) program. A total of 2109 patients with NAC were identified from the NHI database between 2000 and 2011. For a control group, 4 patients without NAC were frequency-matched with each NAC patient according to sex, age, and index year. We used Cox proportional hazards regression analysis to calculate adjusted hazard ratios (aHRs) and 95% confidence intervals (CIs) and determine the effects of NAC on cancer risk.

The overall cancer risk was significantly higher in patients with NAC compared with those without NAC, and this association was consistent among age, sex, and comorbidity groups. The risk of developing HCC was remarkably high in the NAC group compared with in the control cohort (aHR = 122.7, 95% CI = 68.4–220.1); significantly higher risks of extrahepatic malignancies were observed in patients with digestive tract cancers and hematological malignancies. Further analyses stratified according sex, age, and follow-up duration revealed various patterns among the cancer types.

The results indicate that patients with NAC in Taiwan have higher risks of HCC, digestive tract cancers, and hematological malignancies.

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Abbreviations: aHR = Adjusted hazard ratio, BNHI = Bureau of National Health Insurance, CI = Confidence interval, HCC = Hepatocellular carcinoma, HR = Hazard ratio, ICD-9-CM = International Classification of Diseases, 9th Revision, Clinical Modification, IRB = Institutional Review Board, LHID 2000 = Longitudinal Health Insurance Database 2000, NAC = Nonalcoholic cirrhosis, NHI = Taiwan National Health Insurance, NHIRD = National Health Insurance Research Database.

INTRODUCTION

Liver cirrhosis is an end-stage liver disease and common consequence of the long clinical course of all chronic liver diseases. Cirrhosis causes the loss of liver cells and irreversible fibrosis of the liver. The disease is most commonly caused by excessive alcohol consumption, hepatitis B and C, fatty liver disease, primary biliary cirrhosis, autoimmune hepatitis, and other rare causes.[1] Taiwan has a high prevalence of hepatitis B, with an overall prevalence of chronic hepatitis B viral infection of 13.7% (95% confidence interval [CI] = 12.9–14.5) in 2002.[2] Liver cirrhosis and hepatocellular carcinoma (HCC), which are both closely correlated with hepatitis B, are among the 10 leading causes of death in Taiwan.[3,4]

Cancer constitutes an enormous global burden; according to GLOBOCAN estimates, approximately 14.1 million new cancer cases and 8.2 million cancer-related deaths occurred worldwide in 2012.[5] Cancer has been the leading cause of mortality among the general population in Taiwan since 1982 (6). HCC is the fifth most common malignancy worldwide and

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the third most common cause of cancer mortality.[7] In Taiwan, HCC was the third most common cancer site and second leading cause of cancer death in 2012.[6] Liver cirrhosis can evolve into HCC, and the presence of comorbidities, hepatitis B or C, alcohol consumption, and age can influence the terminal event;[8] thus, liver cirrhosis is considered a step in the progression of HCC.[9–11] In addition, cirrhosis, particularly alcoholic cirrhosis, is generally accepted as a risk factor for HCC development.[12–15]

The relationship between extrahepatic malignancies and cirrhosis has also been explored.[16–18] A population-based cohort study conducted in Denmark found an increased risk of liver and several extrahepatic cancers in patients with cirrhosis.[16] A study conducted in Sweden revealed that the overall risk of non-HCC malignancies (mostly biliary and gastrointestinal malignancies) was more than 2-fold greater for patients with cirrhosis than for the general population.[18] Regarding extrahepatic malignancies, some studies have focused on specific cancer sites and revealed higher risks of digestive tract cancers[19,20] and lymphoproliferative disorders[21] among patients with cirrhosis compared with control populations.

To the best of our knowledge, no study has examined the possible association between nonalcoholic cirrhosis (NAC) and cancer risk. Thus, we conducted a population-based retrospective cohort study to determine whether patients with NAC have an increased risk of overall or site-specific cancer. The database used was derived from the Taiwan National Health Insurance (NHI) program.

METHODS

Data Source

The NHI program, from 1996 to 2011, covered over 99% of the entire population and more than 97% of the health care institutions in Taiwan[22].We used the Longitudinal Health Insurance Database 2000 (LHID2000) as the data source for our study. The LHID2000, administered by the National Health Research Institutes (NHRI), contains the data from 1996 to 2011 of 1 million randomly sampled beneficiaries enrolled in the NHI. To protect patient privacy, all personal identification numbers were encrypted by the NHRI before the LHID 2000 was released. All diagnoses were made using the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM). Our study was approved by the Ethics Review Board of China Medical University (CMU-REC-101–012).

Sampled Participants

We identified patients aged 20 years and older who had received an NAC diagnosis (ICD-9-CM codes 571.5 and 571.6) as the NAC cohort and set the diagnosis date as the index date. The exclusion criteria were an age less than 20 years, history of cancer (ICD-9-CM codes 140–208) before the index date, and history of alcoholic cirrhosis or chronic hepatitis (ICD-9-CM codes 571.0–571.6, 571.8, and 571.9) during follow-up. For each NAC case, 4 patients without a history of cirrhosis (ICD-9-CM code 571) were identified as the non-NAC cohort and frequency-matched according to age, sex, and index year by using the same exclusion criteria.

Outcomes and Comorbidities

Cancer (ICD-9-CM codes 140–195 and 200–208) diagnoses were identified from the Registry for Catastrophic Illness Patient Database. Cancer is categorized as a catastrophic illness in the NHI program. All the patients in this study were followed from the index date until cancer diagnosis, withdrawal from the NHI, or the end of 2011. The pre-existing comorbidities and cancer-related examinations were defined as long as they existed prior to the endpoint. The comorbidities in this study included hypertension (ICD-9-CM codes 401–405), diabetes (ICD-9-CM code 250), hyperlipidemia (ICD-9-CM code 272), obesity (ICD-9-CM code 278), hepatitis B (ICD-9-CM codes V02.61, 070.20, 070.22, 070.30, and 070.32), hepatitis C (ICD-9-CM codes V02.62, 070.41, 070.44, 070.51, and 070.54), and colon polyp (ICD-9-CM codes 211.3). In addition, we considered cancer-related examinations, including esophagogastroduodenoscopy (ICD-9-OP procedure code 45.13 and 45.16), colonoscopy (ICD-9-OP procedure code 45.23), abdomen CT (ICD-9-OP procedure code 88.01 and 88.02), and abdomen ultrasonography (ICD-9-OP procedure code 45.13 and 88.76). Ascites (ICD-9-CM codes 789.5) was considered a severity of liver cirrhosis.

Statistical Analysis

The distribution of age, sex, and comorbidities was expressed as a frequency or mean ± standard deviation (SD). The categorical variables were analyzed using a chi-square test and the continuous variables were analyzed using a Student *t* test. The incidence densities were calculated according to age, sex, comorbidity, and cancer type for each cohort. Univariate and multivariate Cox proportional hazards regression models were used to estimate the hazard ratios (HRs) and 95% CIs for cancer in patients with NAC compared with those without NAC. The multivariate models were simultaneously adjusted for age, sex, and the comorbidities of hypertension, diabetes, hyperlipidemia, obesity, hepatitis B and C, and colon polyp, and diagnostic procedures of esophagogastroduodenoscopy, colonoscopy, abdomen CT, and abdomen ultrasonography. All data processing and statistical analyses were performed using SAS Version 9.4 (SAS Institute, Inc., Cary, NC, USA). A 2-tailed *P* value of <0.05 was considered statistically significant.

RESULTS

This study comprised 2109 patients with NAC and 8436 patients without cirrhosis for data analysis (Table 1). As expected, both cohorts exhibited similar distributions of age and sex; most patients were aged 65 years or older (44.8%) and were male (62.3%). The mean ages of the NAC and non-NAC cohorts were 61.3 ± 16.2 and 60.6 ± 16.4 years, respectively. The NAC cohort showed a higher prevalence of comorbidity than did the non-NAC cohort, except of hyperlipidemia. Patients in the NAC cohort were likely to have esophagogastroduodenoscopy, colonoscopy, abdomen CT, and abdomen ultrasonography.

The mean follow-up durations were 3.62 years (SD = 3.75) and 6.13 years (SD = 3.43) for the NAC and non-NAC cohorts, respectively (data not shown). In total, 534 patients in the NAC cohort received cancer diagnoses, an incidence of 69.9 per 1000 person-years; 439 patients in the non-NAC cohort received cancer diagnoses, an incidence of 8.49 per 1000 person-years, yielding a crude HR of 7.03 (95% CI = 6.19–7.98) (Table 2). After adjustment for age, sex, and the comorbidities of hypertension, diabetes, hyperlipidemia, obesity, hepatitis B and C, and colon polyp, and diagnostic procedures of esophagogastroduodenoscopy, colonoscopy, abdomen CT, and abdomen ultrasonography, the risk of developing cancer

TABLE 1. Comparison of Demographics and Comorbidity Between Cirrhosis Patients and Controls

	Cirrhosis ($N = 2109$)		Control ($N = 8436$)		
	n	%	*n*	%	*P*
Age, year					0.99
≤49	556	26.4	2224	26.4	
50–64	609	28.9	2436	28.9	
≥65	944	44.8	3776	44.8	
Mean (SD)*	61.3	16.2	60.6	16.4	0.01
Gender					0.99
Women	796	37.7	3184	37.7	
Men	1313	62.3	5252	62.3	
Comorbidity					
Hypertension	1065	50.5	4024	47.7	0.02
Diabetes	461	21.9	1238	14.7	<0.001
Hyperlipidemia	450	21.3	1935	22.9	0.11
Obesity	40	1.90	109	1.29	0.04
HBV infection	451	21.4	119	1.41	<0.001
HCV infection	313	14.8	40	0.47	<0.001
Colon polyp	91	4.31	275	3.26	0.02
Diagnostic procedures					
Esophagogastroduodenoscopy	543	25.8	540	6.40	<0.001
Colonoscopy	106	5.03	115	1.36	<0.001
Abdomen CT	346	16.4	244	2.89	<0.001
Abdomen ultrasonography	374	17.8	361	4.28	<0.001

Chi-square test compared with total fatty liver disease.
HBV = hepatitis B virus; HCV = hepatitis C virus.
* *t* test.

was significantly higher for patients with NAC than for those without NAC (adjusted HR [aHR] = 6.21; 95% CI = 5.36–7.18). The incidence and risk of cancer, as stratified according to age, sex, and comorbidity, were higher in patients with NAC than in those without NAC.

Table 3 presents the results of analyses of the cancer type differences between the NAC and non-NAC cohorts. The NAC cohort exhibited a significantly higher risk of hematologic malignancy (aHR = 3.12, 95% CI = 1.34–7.25), esophagus cancer (aHR = 7.25, 95% CI = 2.44–21.6), stomach cancer (aHR = 5.50, 95% CI = 2.78–10.9), colorectal cancer (aHR = 2.58, 95% CI = 1.59–4.18), HCC (aHR = 122.7, 95% CI = 68.4–220.1), and cholangiocarcinoma (aHR = 5.10, 95% CI = 1.52–17.1), compared with the non-NAC cohort.

The men with NAC exhibited a significantly higher risk of hematologic malignancies, digestive tract cancers, HCC, cholangiocarcinoma, and nondigestive tract cancers compared with the men without NAC (Table 4). The women with NAC had significantly 3.54- and 86.0-fold higher risks of digestive tract cancers and HCC, respectively, compared with the women without NAC. Among the patients aged ≤59 years, those with NAC were at higher risk of digestive tract cancers, HCC, and nondigestive tract cancers compared with those without NAC (Table 5). Among the patients aged ≥60 years, those with NAC were at higher risk of hematologic malignancies, digestive tract cancers, HCC, cholangiocarcinoma, and nondigestive tract cancers compared with those without NAC. Furthermore, the aHRs for cancer types was stratified according to follow-up duration (Table 6). Among the patients with a follow-up duration ≤1 year, those with NAC exhibited a significantly higher risk of digestive tract cancer and HCC compared with those without NAC. However, among the patients with a follow-up duration >1 year, patients with NAC had a 21.0-fold significantly higher risk of HCC and a 1.89-fold marginally significantly higher risk of nondigestive tract cancers compared with those without NAC.

Stratified analysis by ascites status among NAC patients shows that NAC patients with ascites typically had higher aHRs of cancer when compared with NAC patients without ascites, except for cholangiocarcinoma and nondigestive tract cancers. When compared with control group, NAC with ascites exhibited a higher risk of all cancer (aHR = 7.93, 95% CI = 6.08–10.4), hematologic malignancies (aHR = 5.84, 95% CI = 1.18–29.0), digestive tract cancers (aHR = 4.92, 95% CI = 2.30–10.5), and HCC (aHR = 148.3, 95% CI = 78.8–279.0) compared with those without NAC (Table 7).

DISCUSSION

This nationwide population-based cohort study highlighted that the overall cancer risk was significantly higher in the NAC group compared with the non-NAC group, and cancer site-specific analysis revealed that the NAC cohort had a markedly higher risk of HCC development than did the control cohort. Significantly higher risks of most digestive tract cancers and hematological malignancies were observed in the NAC group. Further analysis stratified according to sex, age, and follow-up duration demonstrated different patterns among the cancer types.

The cancer burden in Taiwan has been a concern for the government, which has inspirited several prevention programs for certain major cancers, such as education of the general population to avoid high-risk factors of cancer and receive periodical cancer screening, and has aimed at decreasing cancer incidence and mortality rates.[23] Consequently, more population-based research in the field of cancer-prevention epidemiology, such as the current study of cancer risk among patients with NAC, continues to be conducted.

Sorensen et al conducted a nationwide cohort study to investigate the risks of HCC and other cancers in patients with cirrhosis in Denmark, determining that the risk of HCC was exceptionally high (standardized incidence ratio = 36, 95% CI = 32–41).[16] A similar phenomenon has been observed by other researchers,[17,18,24] and this finding is consistent with our data, which indicated a markedly higher risk of HCC among patients with NAC than among those without NAC (aHR = 122.7, 95% CI = 68.4–220.1). Liver cirrhosis has long been regarded as the most critical premalignant lesion of HCC,[25] and research has established that liver cirrhosis is a substantial determinant for HCC development,[26–28] regardless of the presence of alcohol cirrhosis or NAC.

Except for hematologic malignancy, the cancer sites with a significantly higher risk among the patients with NAC in our study were exclusively digestive tract cancers (except for pancreatic cancer) (Table 3). Our findings are consistent with earlier reports. Randi et al evaluated the possible association between cirrhosis and digestive tract neoplasms and found that cirrhotic patients had an increased risk of oral, pharyngeal, and esophageal cancers. Randi et al indicated that the excessive risk found for upper digestive tract cancers may be partially due to a residual confounding of alcohol consumption and tobacco use.[19] In the present study, we excluded patients with alcoholic

TABLE 2. Comparisons of Incidence Densities and Hazard Ratio of Cancer by Study Cohorts

	Cirrhosis			Control				
	Case	PY	Rate†	Case	PY	Rate†	Crude HR* (95% CI)	Adjusted HR‡ (95% CI)
All‡	534	7637	69.9	439	51697	8.49	7.03 (6.19–7.98)[c]	6.21 (5.36–7.18)[c]
Age§								
≤49	84	3033	27.7	35	15927	2.20	11.4 (7.68–16.9)[c]	9.64 (6.15–15.1)[c]
50–64	190	2198	86.5	119	15684	7.59	9.43 (7.49–11.9)[c]	7.55 (5.77–9.89)[c]
≥65	260	2406	108.1	285	20087	14.2	6.27 (5.29–7.44)[c]	5.67 (4.66–6.91)[c]
Gender‖								
Women	136	3317	41.0	130	20248	6.42	5.68 (4.46–7.23)[c]	5.41 (4.09–7.17)[c]
Men	398	4320	92.1	309	31449	9.83	7.81 (6.72–9.07)[c]	6.60 (5.55–7.84)[c]
Comorbidity¶								
Hypertension								
No	293	3832	76.5	181	27331	6.62	9.63 (7.99–11.6)[c]	8.50 (6.81–10.6)[c]
Yes	241	3805	63.3	258	24366	10.6	5.26 (4.41–6.28)[c]	4.86 (3.98–5.94)[c]
Diabetes								
No	442	6051	73.1	363	43932	8.26	7.58 (6.59–8.71)[c]	6.55 (5.57–7.71)[c]
Yes	92	1586	58.0	76	7765	9.79	5.10 (3.75–6.94)[c]	4.96 (3.51–7.01)[c]
Hyperlipidemia								
No	467	5408	86.4	347	39,154	8.86	7.99 (6.95–9.19)[c]	7.01 (5.96–8.25)[c]
Yes	67	2229	30.1	92	12,543	7.33	3.90 (2.84–5.34)[c]	3.66 (2.57–5.20)[c]
Obesity								
No	529	7441	71.1	437	50,988	8.57	7.07 (6.22–8.03)[c]	6.17 (5.33–7.15)[c]
Yes	5	195	25.6	2	709	2.82	7.92 (1.53–41.0)[a]	16.5 (0.30–897.0)
HBV infection								
No	379	6224	60.9	431	50,875	8.47	6.34 (5.52–7.28)[c]	6.01 (5.15–7.01)[c]
Yes	155	1413	109.7	8	821	9.74	7.37 (3.62–15.0)[c]	6.82 (3.30–14.1)[c]
HCV infection								
No	443	6764	65.5	435	51,422	8.46	6.77 (5.92–7.73)[c]	5.87 (5.05–6.84)[c]
Yes	91	873	104.3	4	275	14.6	4.43 (1.62–12.1)[b]	6.13 (2.15–17.5)[c]
Colon polyp								
No	514	7234	71.1	410	50,018	8.20	7.36 (6.46–8.38)[c]	6.47 (5.57–7.53)[c]
Yes	20	403	49.6	29	1680	17.3	2.70 (1.53–4.78)[c]	3.45 (1.80–6.63)[c]

HBV = hepatitis B virus; HCV = hepatitis C virus.

* Crude HR, relative hazard ratio.

† Rate, incidence rate, per 1000 person-years.

‡ Adjusted HR was calculated by Cox proportional hazard regression and adjusted for age, gender, comorbidities of hypertension, diabetes, hyperlipidemia, obesity, HBV infection, HCV infection, and colon polyp, and diagnostic procedures of esophagogastroduodenoscopy, colonoscopy, abdomen CT, and abdomen ultrasonography.

§ Adjusted HR was calculated by Cox proportional hazard regression stratified by age, and adjusted for gender, hypertension, diabetes, hyperlipidemia, obesity, HBV infection, HCV infection, and colon polyp, and diagnostic procedures of esophagogastroduodenoscopy, colonoscopy, abdomen CT, and abdomen ultrasonography.

‖ Adjusted HR was calculated by Cox proportional hazard regression stratified by gender and adjusted for age, hypertension, diabetes, hyperlipidemia, obesity, HBV infection, HCV infection, and colon polyp, and diagnostic procedures of esophagogastroduodenoscopy, colonoscopy, abdomen CT, and abdomen ultrasonography.

¶ Adjusted HR was calculated by Cox proportional hazard regression stratified by comorbidity and adjusted for age, gender, colon polyp, and diagnostic procedures of esophagogastroduodenoscopy, colonoscopy, abdomen CT, and abdomen ultrasonography and mutually adjusted comorbidity.[a]$P < 0.05$, [b]$P < 0.01$, [c]$P < 0.001$.

cirrhosis and still found an association between risk of digestive tract cancers and NAC. Zullo et al highlighted a significant 2.6-fold ($P < 0.01$) higher prevalence of gastric cancer than that expected in patients with cirrhosis.[20] A previous study mentioned cirrhosis as an independent risk factor for colonic adenomas,[29] which may contribute to the relationship between HCC and colorectal cancer. Lombardo et al suggested that liver cirrhosis might be considered an immunological disturbance that increases the risk of developing lymphoproliferative disorders;[21] such a suggestion is in agreement with our results showing a significantly higher risk of hematologic malignancy in the NAC group than in the control group.

Because of the relatively few cases related to each cancer site investigated in this study, the risk estimates were unstable and the power was inadequate for stratified analysis. Therefore, we pooled our patients with cancers other than hematologic malignancy, HCC, or cholangiocarcinoma and categorized such patients into those with digestive tract and nondigestive tract cancers for further analyses stratified according to sex, age, and follow-up duration. We revealed that both men and patients

TABLE 3. Comparison of Incidence and Hazard Ratio of Subdivision Cancer According to Cirrhosis Status

	Cirrhosis		Control			
Cancer (ICD-9-CM)	**Case**	**Rate†**	**Case**	**Rate†**	**Crude HR* (95% CI)**	**Adjusted HR‡ (95% CI)**
Hematologic malignancy (200–208)	10	1.31	23	0.44	2.70 (1.28–5.68)[b]	3.12 (1.34–7.25)[b]
Head and neck cancer (140–149, 161)	7	0.92	35	0.68	1.32 (0.59–2.98)	1.85 (0.77–4.42)
Esophagus cancer (150)	8	1.05	8	0.15	6.42 (2.40–17.2)[c]	7.25 (2.44–21.6)[c]
Stomach cancer (151)	21	2.75	22	0.43	5.67 (3.11–10.3)[c]	5.50 (2.78–10.9)[c]
Colorectal cancer (153–154)	26	3.40	79	1.53	2.13 (1.37–3.32)[c]	2.58 (1.59–4.18)[c]
HCC (155)	401	52.5	12	0.23	165.7 (93.3–294.2)[c]	122.7 (68.4–220.1)[c]
Cholangiocarinoma (156)	6	0.79	7	0.14	4.89 (1.63–14.7)[b]	5.10 (1.52–17.1)[b]
Pancreas cancer (157)	8	1.05	11	0.21	4.18 (1.67–10.4)[b]	2.72 (0.93–7.95)
Lung cancer (162)	16	2.10	86	1.66	1.24 (0.73–2.12)	1.54 (0.85–2.80)
Female breast cancer (174)	2	0.60	18	0.89	0.68 (0.16–2.94)	1.23 (0.28–5.38)
Uterus cancer (180–184)	4	1.21	11	0.54	2.11 (0.67–6.63)	2.03 (0.60–.6.80)
Prostate cancer (185)	8	1.85	47	1.49	1.22 (0.58–2.59)	1.58 (0.73–3.44)
Urinary system cancer (188–189)	7	0.92	39	0.75	1.19 (0.53–2.66)	1.60 (0.69–3.72)
Brain cancer (191)	1	0.13	9	0.10	1.30 (0.15–11.1)	2.26 (0.25–20.2)
Thyroid cancer (193)	2	0.26	7	0.14	1.98 (0.41–9.55)	1.97 (0.34–11.5)
Others	7	0.92	29	0.56	1.63 (0.72–3.73)	1.88 (0.79–4.47)

95% CI, 95% confidence interval.
* Crude HR, relative hazard ratio.
† Rate, incidence rate, per 1000 person-years.
‡ Adjusted HR: multivariable analysis including age, sex, comorbidities of hypertension, diabetes, hyperlipidemia, obesity, HBV infection, HCV infection and colon polyp, and diagnostic procedures of esophagogastroduodenoscopy, colonoscopy, abdomen CT, and abdomen ultrasonography.[a]$P < 0.05$, [b]$P < 0.01$, [c]$P < 0.001$.

aged ≥60 years who had cirrhosis exhibited consistently higher risks among all cancer types. It is difficult to figure out the reasons to explain the differences that emerge from these stratified analyses. One possible explanation is that these 2 groups comprised more patients than did their counterparts, increasing the likelihood of yielding a significantly different risk estimate. Men patients with NAC had higher risks for all cancer types; on the other hand, women patients with NAC only had significantly higher risks for HCC and digestive tract cancers. Although less women cases of NAC, we assume that women patients tend to be amenable for further gastrointestinal tract examinations after diagnosis of NAC, which may increase the opportunity to detect digestive tract cancers. In general, older people are more prone to developing cancer, and we assume that any risk factor (eg, NAC) may trigger the cancer development process. The risk of HCC was most pronounced during early follow-up (≤1 year; aHR = 206.6; 95% CI = 28.9–1477.3) compared with late follow-up, a finding that is in accordance with that of Sorensen et al.[16] In addition, the risk of digestive tract cancers among the patients with NAC was more prominent during early follow-up. We assume that patients with NAC might have received clinical checkups at gastrointestinal departments more frequently after NAC diagnosis, increasing the likelihood of digestive tract malignancies

TABLE 4. Cox Model with Hazard Ratios and 95% Confidence Intervals of Subdivision Cancer Associated with Cirrhosis Stratified by Sex

	Male with Cirrhosis		Female with Cirrhosis	
	No ($N = 5252$)	**Yes ($N = 1313$)**	**No ($N = 3184$)**	**Yes ($N = 796$)**
Variable (ICD-9-CM)	**Adjusted HR* (95% CI)**		**Adjusted HR* (95% CI)**	
Hematologic malignancy (200–208)	1 (Reference)	4.14 (1.53–11.2)[b]	1 (Reference)	1.53 (0.25–9.18)
Digestive tract cancer (150, 151, 153–154, 157)	1 (Reference)	3.54 (2.35–5.33)[b]	1 (Reference)	3.54 (1.90–6.60)[b]
HCC (155)	1 (Reference)	141.9 (69.5–289.5)[b]	1 (Reference)	86.0 (30.9–239.5)[b]
Cholangiocarinoma (156)	1 (Reference)	6.31 (1.40–28.4)[a]	1 (Reference)	3.14 (0.46–21.4)
Nondigestive tract cancer	1 (Reference)	1.96 (0.99–3.87)[a]	1 (Reference)	2.35 (0.89–6.18)

95% CI, 95% confidence interval HR, hazard ratio.
* Adjusted HR: multivariable analysis including age, comorbidities of hypertension, diabetes, hyperlipidemia, obesity, HBV infection, HCV infection and colon polyp, and diagnostic procedures of esophagogastroduodenoscopy, colonoscopy, abdomen CT, and abdomen ultrasonography.[a]$P < 0.05$, [b]$P < 0.001$.

TABLE 5. Cox Model with Hazard Ratios and 95% Confidence Intervals of Subdivision Cancer Associated with Cirrhosis Stratified by Age

	Age ≤59 years		Age ≥60 years	
	Cirrhosis		Cirrhosis	
	No ($N = 3873$)	Yes ($N = 968$)	No ($N = 4563$)	Yes ($N = 1141$)
Variable (ICD-9-CM)	Adjusted HR* (95% CI)		Adjusted HR* (95% CI)	
Hematologic malignancy (200–208)	1 (Reference)	2.63 (0.35–19.8)	1 (Reference)	3.40 (1.32–8.74)[a]
Digestive tract cancer (150, 151, 153–154, 157)	1 (Reference)	4.43 (2.21–8.87)[c]	1 (Reference)	3.24 (2.16–4.87)[c]
HCC (155)	1 (Reference)	2.49.4 (61.1–1018.8)[c]	1 (Reference)	106.6 (55.8–203.7)[c]
Cholangiocarinoma (156)	1 (Reference)	—	1 (Reference)	6.25 (1.80–21.7)[b]
Nondigestive tract cancer	1 (Reference)	3.05 (1.05–8.86)[a]	1 (Reference)	1.99 (1.03–3.83)[a]

* Adjusted HR: multivariable analysis including sex, and comorbidities of hypertension, diabetes, hyperlipidemia, obesity, HBV infection, HCV infection and colon polyp, and diagnostic procedures of esophagogastroduodenoscopy, colonoscopy, abdomen CT, and abdomen ultrasonography. [a]$P < 0.05$, [b]$P < 0.01$, [c]$P < 0.001$.

being detected during early follow-up. Although we adjusted the relative gastrointestinal diagnostic procedures, the residual confounding may still exist.

Because other factors of Child-Pugh score are not available in the dataset, we only used ascites to assess the severity of HCC. NAC patients with ascites tend to have higher aHRs of subsequent cancer development compared with NAC patients without ascites, and it may partially contribute to the relatively poor prognosis of NAC patients with ascites. In our multivariate analyses, we eliminated possible confounding effects by adjusting for comorbidities including hypertension, diabetes, hyperlipidemia, obesity, colon polyp, and hepatitis B and C. All these factors have been suggested as possibly related to cancer or cirrhosis risk.[10,30–32]

NAC was defined as ICD-9-CM codes 571.5 (cirrhosis of liver without mention of alcohol) and 571.6 (biliary cirrhosis). The diagnosis of NAC was included heterogeneous causes of liver cirrhosis especially including biliary cirrhosis. It was known that significant differences of characteristics and outcomes between viral hepatitis-related cirrhosis and nonalcoholic steatohepatitis (NASH)-related cirrhosis, and cirrhosis due to NASH is associated with a lower rate of development of HCC compared with viral hepatitis-related cirrhosis.[33,34] Epidemiological studies supported the link between primary biliary cirrhosis and HCC.[35,36] However, this study did not specify the different causes of cirrhosis for further sophisticated analyses because we could not differentiate the diagnosis of NASH-related cirrhosis or viral hepatitis-related cirrhosis in the NHIRD.

The current study demonstrates the generalizability and high follow-up compliance strengths of population-based nationwide database sources. However, several limitations must be addressed when interpreting the current findings. First, surveillance bias may have contributed to the association observed between NAC and digestive tract cancers, although we tried to adjust some examinations. As mentioned, patients with NAC likely receive more clinical checkups than does the general population, providing them with more opportunities for detecting cancer, particularly cancers affecting the gastrointestinal tract (which NAC also affects), and hematologic

TABLE 6. Cox Model with Hazard Ratios and 95% Confidence Intervals of Subdivision Cancer Associated with Cirrhosis Stratified by Follow-up Duration

	Follow-up Duration ≤1 year		Follow-up Duration >1 year	
	Cirrhosis		Cirrhosis	
	No ($N = 354$)	Yes ($N = 787$)	No ($N = 8082$)	Yes ($N = 1322$)
Variable (ICD-9-CM)	Adjusted HR* (95% CI)		Adjusted HR* (95% CI)	
Hematologic malignancy (200–208)	1 (Reference)	2.06 (0.59–7.16)	1 (Reference)	0.92 (0.17–4.97)
Digestive tract cancer (150, 151, 153–154, 157)	1 (Reference)	2.99 (1.63–5.49)[a]	1 (Reference)	1.25 (0.73–2.16)
HCC (155)	1 (Reference)	206.6 (28.9–1477.3)[a]	1 (Reference)	21.0 (10.3–42.9)[a]
Cholangiocarinoma (156)	1 (Reference)	7.09 (0.75–67.1)	1 (Reference)	—
Non-digestive tract cancer	1 (Reference)	0.70 (0.23–2.09)	1 (Reference)	1.89 (0.99–3.64)

* Adjusted HR: multivariable analysis including age, sex, and comorbidities of hypertension, diabetes, hyperlipidemia, obesity, HBV infection, HCV infection and colon polyp, and diagnostic procedures of esophagogastroduodenoscopy, colonoscopy, abdomen CT, and abdomen ultrasonography.
[a]$P < 0.001$.

TABLE 7. Comparisons of Incidence and Hazard Ratios of Cancer by Ascites Status of Liver Cirrhosis

Variables	*N*	Event	Rate‡	Crude HR* (95% CI)	Adjusted HR† (95% CI)
All cancer					
Controls	8436	439	8.49	1 (Reference)	1 (Reference)
Cirrhosis without ascites	1839	456	63.3	6.60 (5.79–7.53)[c]	6.06 (5.22–7.03)[c]
Cirrhosis with ascites	270	78	179.7	11.9 (9.30–15.2)[c]	7.93 (6.08–10.4)[c]
Hematologic malignancy (200–208)					
Controls	8436	23	0.44	1 (Reference)	1 (Reference)
Cirrhosis without ascites	1839	8	1.11	2.34 (1.05–5.25)[a]	2.87 (1.18–6.95)[a]
Cirrhosis with ascites	270	2	4.61	7.35 (1.69–32.0)[b]	5.84 (1.18–29.0)[a]
Digestive tract cancer (150, 151, 153–154, 157)					
Controls	8436	120	2.32	1 (Reference)	1 (Reference)
Cirrhosis without ascites	1839	55	7.64	3.10 (2.25–4.27)[c]	3.39 (2.39–4.83)[c]
Cirrhosis with ascites	270	8	18.4	5.73 (2.78–11.8)[c]	4.92 (2.30–10.5)[cc]
HCC (155)					
Controls	8436	12	0.23	1 (Reference)	1 (Reference)
Cirrhosis without ascites	1839	335	46.5	156.5 (88.0–278.5)[c]	120.2 (67.0–215.7)[c]
Cirrhosis with ascites	270	66	152.1	242.5 (130.9–449.2)[c]	148.3 (78.8–279.0)[c]
Cholangiocarinoma (156)					
Controls	8436	7	0.14	1 (Reference)	1 (Reference)
Cirrhosis without ascites	1839	6	0.83	5.36 (1.80–16.0)[b]	5.73 (1.73–19.0)[b]
Cirrhosis with ascites	270	0	0.00	–	–
Nondigestive tract cancer					
Controls	8436	80	1.55	1 (Reference)	1 (Reference)
Cirrhosis without ascites	1839	17	2.36	1.52 (0.90–2.56)	2.25 (1.30–3.91)[b]
Cirrhosis with ascites	270	0	0.00	—	—

95% CI, 95% confidence interval HR, hazard ratio.

* Crude HR, relative hazard ratio.

† Adjusted HR: multivariable analysis including age, sex, comorbidities of hypertension, diabetes, hyperlipidemia, obesity, HBV infection, HCV infection, and colon polyp, and diagnostic procedures of esophagogastroduodenoscopy, colonoscopy, abdomen CT, and abdomen ultrasonography.

‡ Rate, incidence rate, per 1000 person-years. [a]$P < 0.05$, [b]$P < 0.01$, [c]$P < 0.001$.

malignancy in cirrhotic patients more tended to receive blood tests as more hospital stay in cirrhotic patients is expected. Second, misclassification of cirrhosis type (alcoholic and nonalcoholic) may exist. People with cirrhosis may not declare being an alcoholist because of shame or social stigma, which would lead to their cirrhosis being erroneously classified as nonalcoholic, and it may induce an overestimated cancer risk of NAC. However, this problem cannot be fixed and it is difficult to exactly assess its effect on the risk analysis. Third, the LHID2000 does not contain information regarding patient lifestyle or behavior; thus, we could not adjust for factors such as alcohol consumption, smoking history, and diet. These unhealthy habits can increase the risk of cancer[37,38] and liver diseases such as cirrhosis.[39–41] Although we restricted our cases to NAC in our analysis, the uncontrolled lifestyle factors and the residual confounding of alcohol consumption might have distorted the results. Fourth, the diagnostic procedures retrieved from the NHIRD may not include all examinations. Some examinations are not covered by NHI and patients need to pay by themselves. Therefore, the relatively lower rate of examinations may not reflect the actual situation and we cannot accurately identify patients with regular surveillance from NHIRD to see if they have a better chance to detect digestive tract cancer. Despite the limitations of the administrative data, the information regarding NAC and cancer diagnosis was highly reliable.

In summary, the overall cancer incidence among patients with NAC in Taiwan was significantly higher than among the general population. Apart from HCC, the patients with NAC also exhibited higher risks of developing most digestive tract cancers and hematologic malignancies. The association could be partially due to surveillance bias (although we have tried to eliminate it by adjusting some diagnostic procedures) and possibly an immunological disturbance of cirrhosis; however, the underlying mechanisms require further comprehensive investigation.

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