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Research Article

Earlier Onset of Hepatocellular Carcinoma in Chronic Hepatitis C Patients with Multiple Poor Lifestyle Habits

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Keywords
- Hepatocellular carcinoma
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Abstract

Background: Some studies have reported poor lifestyle habits (consumption of alcohol, smoking, and obesity) is the risk of Hepato Cellular Carcinoma (HCC). However, the effect of lifestyle habits on the age of HCC onset remains unknown.

Aim: The purpose of this study was to clarify whether multiple poor lifestyle habits lower the age of HCC onset in chronic hepatitis C patients.

Methods: Subjects were 441 consecutive patients at Saga Medical School Hospital who tested positive for hepatitis C virus antibody and were diagnosed as having HCC between 2000 and 2010. Electronic medical records were extracted from the data warehouse, and the relationships between lifestyle habits and the age of HCC onset were analyzed.

Results: After excluding116 patients who were hepatitis B surface antigen positive or negative for hepatitis C virus-RNA, had a history of interferon treatment, had ascites, or had missing information for the survey items relating to lifestyle factors, data were analyzed for the remaining 325 patients. Patients who consumed ≥60 g/day of alcohol, smoked ≥1 pack/day, or had BMI of ≥25 had earlier onset of cancer than the other patients. Multivariate analysis revealed these three factors as independent contributors to the earlier onset of HCC. The presence of these three factors further contributed to lowering the age at onset.

Conclusion: Multiple poor lifestyle habits lead to an earlier onset of HCC in chronic hepatitis C patients.

ABBREVIATIONS

HCV: Hepatitis C Virus; HCC: Hepatocellular Carcinoma; CH-C: Chronic Hepatitis C; COI: Cut-Off Index; Hbs-Ag: Hepatitis B Surface Antigen; BMI: Body Mass Index; HR: Hazards Ratio; IGF-1: Insulin-like Growth Factor-1

INTRODUCTION

Around 1.5–2 million people in Japan and 1.7 billion people globally have been infected by the Hepatitis C Virus (HCV). Chronic hepatitis due to HCV infection is a progressive chronic hepatic disease leading to hepatic cirrhosis and Hepato Cellular Carcinoma (HCC) [1,2]. Hepatic cancer is ranked as the third leading cause of cancer death, and most hepatic cancer is HCC [3]. The main risk factor for HCC is chronic HCV infection, which increases the risk by approximately 17-fold [4]. Some studies have reported relationships between lifestyle habits,

such as consumption of alcohol, smoking, and obesity, and HCC [5-7]. In our research investigating risk factors for HCC in Chronic Hepatitis C (CH-C) patients, we have found that BMI >25 kg/m^{2}was independently associated with HCC onset in HCV antibody-positive patients younger than 60 years of age and that post-challenge hyperglycemia was an independent risk factor for HCC in patients with HCV infection [8,9]. However, the effect of lifestyle habits on the age of HCC onset remains unknown. The purpose of this study was to clarify whether multiple poor lifestyle habits (consumption of alcohol, smoking and obesity) lower the age of HCC onset in CH-C patients.

MATERIALS AND METHODS

Patients

Subjects were 441 consecutive patients from the Division of Hepatology, Diabetes, Metabolism and Endocrinology at Saga Medical School Hospital, Japan who tested positive for HCV antibody and were diagnosed with HCC between 2000 and 2010. HCV antibody determined by chemiluminescence enzyme immunoassay (Abbott Japan, Tokyo, Japan) was considered positive if the Cut-Off Index (COI) was ≥1. HCV-RNA was measured for patients with a COI ≥1 and <10 by real-time polymerase chain reaction (Roche Diagnostics, Tokyo, Japan) to confirm the presence or absence of the virus. Hepatitis B surface antigen (HBs-Ag) determined by chemiluminescence immunoassay (Abbott Japan) was considered positive at >0.05 IU/ml. The conditions present when HCC was first diagnosed served as the factors for analysis.

The study protocol was approved by the Ethics Committee of Saga Medical School and conformed to the provisions of the Declaration of Helsinki (as revised in Tokyo 2004). All subjects provided written informed consent to the use of their data for an epidemiological study under anonymity.

Data selection

Items in the electronic medical records were stored in a data warehouse in extensible markup language format and were retrievable via simple object access protocol using open database connectivity. Match conditions were set to partial match because the medical records had been entered as free text using a keyboard and because keywords had not been stored as separate items.

Definition of lifestyle factors and the onset age

Poor lifestyle habits were defined as consuming ≥60 g/day alcohol, smoking ≥1 pack/day, or having a body mass index (BMI) ≥25 at the time of HCC detection. The type of alcohol and the amount of nicotine and tar were not considered in this study. The Japan Society for the Study of Obesity criterion of a BMI ≥25 was used to indicate obesity, and BMI was calculated as weight (kg)/[height (m) x height (m)]. The duration of exposure to these lifestyle factors and previous exposure history were unknown.

Nobody can detect carcinogenesis within the liver at a cellular level. Therefore, the age of HCC diagnosis with clinical imaging was defined as the onset of HCC.

HCC diagnosis and staging

HCC was diagnosed by at least two imaging tests including ultrasonography, dynamic computed tomography, dynamic magnetic imaging, and/or angiographic computed tomography. Tumor stage was classified according to the article published by the Liver Cancer Study Group of Japan [10]: i) tumor diameter ≤ 20 mm; ii) single tumor; and iii) no vascular invasion. Tumors conforming to three, two, one, and none of the conditions were classified as stage I, II, III, and IV tumors, respectively.

Statistical analysis

The cumulative incidence of cancer was estimated by the Kaplan–Meier method and the incidence curves were compared using the log-rank test. The Mann-Whitney U test, Kruskal-Wallis test, or Steel-Dwass test was used for comparison of average age at HCC onset. Chi-squared test was used for comparison of the rate of patients with or without poor lifestyle habits. Multivariate analysis of the factors relating to the age of HCC onset was performed using Cox's proportional hazards model. Two-tailed *P* values less than 0.05 were considered significant. Statistical analysis was performed using SPSS Statistics ver. 21 (SPSS Japan, Tokyo, Japan).

RESULTS

Patient characteristics

A total of 116 patients were excluded because they were either HBs-Ag positive or negative for HCV-RNA, had a history of interferon treatment, had ascites, or had missing information for the survey items relating to lifestyle factors (Figure 1). Table 1 shows the patient characteristics of the remaining 325 patients subject to analysis. All factors are data at the onset of HCC.

Sex was male for 214 patients, and female for 111 patients. The average age at cancer onset was 70.7±8.7 years (range, 42-91 years). The average BMI was 22.4±3.2 (14.7-35.0). The average FIB-4 index, which correlates with liver fibrosis, was 7.3±5.1 (1.0-46.4). Two hundred and sixty eight patients had FIB-4 index ≥3.25 which was used to indicate cirrhosis, and FIB-4 index was

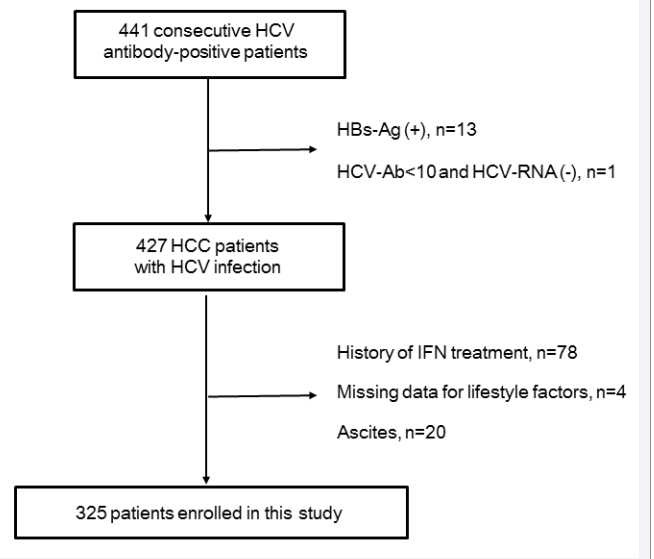

Figure 1 Recruitment and participant flow: 325 patients were subject to analysis.

calculated as age (years) xAST (U/L) / [platelets (10^9/L) xALT (U/L)$^{1/2}$] [11]. Child-Pugh classification was A for 245 patients, B for 73 patients, and C for 7 patients, and hepatic cancer staging was I for 78 patients, II for 111 patients, III for 106 patients, and IV for 30 patients. Of the 325 patients, 84 (26%) consumed ≥60 g/day alcohol, 165 (51%) smoked ≥1 pack/day, and 66 (20%) had a BMI ≥25.

Lifestyle factors in relation to the tumor stage and the age of cancer onset

The rate of patients with or without poor life style factors was not significant differences between tumor stages of cancer onset (Table 2). In a group of early stage at cancer diagnosis, there were in a group of cancer onset at a young age, the rate of patients with poor life style factors was high. The rate of patients without poor life style factors was high in a group of cancer onset at an old age (Table 3). Average age at cancer onset was significantly lower for those patients who consumed alcohol (71.9±8.2 vs. 67.4±9.3, p<0.001), smoked (73.3±7.0 vs. 68.2±9.4, p<0.001), were obese (71.2±8.8 vs. 68.9±8.0, p=0.022) (Figure 2).

Factors contributing to earlier onset of cancer

Sex, Fib4-index, Child-Pugh class, Tumor stage and three life style factors were employed as dependent variable, and the age was used as a time-variable factor. Multivariate analysis using Cox's proportional hazards model revealed consumption of alcohol ≥60 g/day (hazards ratio (HR), 1.43; p=0.014), smoking ≥1 pack/day (HR, 1.50; p=0.003), and BMI ≥25 (HR, 1.40; p=0.023) as independent contributors to the earlier onset of HCC (Table 4).

Prevalence of factors in relation to the age of cancer onset in patients with multiple poor lifestyle habits

The number of poor lifestyle factors per patient was 0 in 114 patients, 1 in 125 patients, 2 in 68 patients, and 3 in 18 patients. In total, 86 patients had 2 or 3 poor lifestyle factors concurrently. Average age (range) in years in patients with 0 factors was 73.9±6.8 (54-91), with 1 factor was 70.9±8.7 (48-89), with 2 factors were 65.8±9.1 (42-80), and with 3 factors was 67.5±8.4 (55-82) (Figure 3). The cumulative incidence in 70 years old patients with 0 factors was 24.6%, with 1 factor was 37.6%, and

Table 1: Clinical characteristics of patients at HCC onset.

Factors	Male (n=214)	Female (n=111)	Total (n=325)
Age (years)	69.7 ± 9.3 (42-91)	72.7 ± 7.1 (48-88)	70.7 ± 8.7 (42-91)
Height (cm)	162.1 ± 6.1 (143-178)	147.6 ± 5.8 (128-170) 159.1)	157.2 ± 9.1 (128-178)
Body weight (kg)	58.4 ± 8.4 (37.6-93.8)	49.8 ± 8.4 (34.1-74.4)	55.5 ± 9.3 (34.1-93.8)
PLT (×10^4/μL)	11.8 ± 5.2 (2.3-28.3)	9.7 ± 4.4 (3-26.2)	11.0 ± 5.0 (2.3-28.3)
PT (%)	78.9 ± 15.6 (25-119)	76 1± 3.9 (41-111)	77.9 ± 15.1 (25-119)
T-Bil (mg/dL)	1.2 ± 1.5 (2-20.2)	1.1 ± 0.6 (0.4-5.3)	1.1 ± 1.3 (0.2-20.2)
AST (IU/L)	73.2 ± 56.4 (11-481)	69.3 ± 37 (20-260)	71.5 ± 50.6 (11-481)
ALT (IU/L)	66.9 ± 54.6 (8-421)	51.4 ± 30.3 (13-189)	61.6 ± 48.2 (8-421)
Alb (g/dL)	3.6 ± 0.5 (2-4.9)	3.5 ± 0.5 (2-4.8)	3.6 ± 0.5 (2-4.9)
FIB-4 index	6.7 ± 5.4 (1.0-46.4)	8.5 ± 4.2 (1.7-24.1)	7.3 ± 5.1 (1.0-46.4)
<3.25 / ≥3.25	48 / 162	9 / 106	57 / 268
Child-Pugh class			
A / B / C	161 / 47 / 6	84 / 26 / 1	245 / 73 / 7
Tumor diameter (cm)	3.2 ± 2.5 (0.5-20)	3.0 ± 2.1 (0.7-12)	3.1 ± 2.4 (0.5-20)
Number of tumors			
Single / Multiple	84 / 130	53 / 58	137 / 188
Tumor stage			
I / II / III / IV	46 / 73 / 74 / 21	32 / 38 / 32 / 9	78 / 111 / 106 / 30
Alcohol (g/day)			
<60 / ≥60	133 / 81	108 / 3	241 / 84
Smoking (pack/day)			
<1 / ≥1	63 / 151	97 / 14	160 / 165
BMI (kg/m^2)	22.2 ± 3 (14.9-35.0)	22.9 ± 3.5 (14.7-33.4)	22.4 ± 3.2 (14.7-35.0)
<25 / ≥25	178 / 36	81 / 30	259 / 66
No. of poor lifestyle habits			
0 / 1 / 2 / 3	39 / 97 / 63 / 15	75 / 28 / 5 / 3	114 / 125 / 68 / 18

Data are expressed as means ± standard deviation or as number of patients. Figures in parentheses indicate range.
Abbreviations: PLT: Platelet Count; PT: Prothrombin Time; T-Bil: Total Bilirubin; Alb: Serum Albumin; AST: Aspartate Aminotransferase; ALT: Alanines Aminotransferase; BMI: Body Mass Index

Table 2: Lifestyle factors of patients classified with the tumor stage at HCC onset.

	Tumor Stage of HCC onset				
Variables	**I (n=78)**	**II (n=111)**	**III (n=106)**	**IV (n=30)**	***P* value**
Alcohol (g/day)					
<60 / ≥60	63 / 15	80 / 31	79 / 27	19 / 11	0.276
Smoking (pack/day) (pack/day)					
<1 / ≥1	41 / 37	60 / 51	49 / 57	10 / 20	0.187
BMI (kg/m^2)	22.5 ± 3.0	22.6 ± 3.3	22.1 ± 3.0	22.6 ± 3.8	0.820
<25 /≥25	61 / 17	87 / 24	90 / 16	21 / 9	0.290
No. of poor					
lifestyle habits					
0 / 1 / 2 / 3	31 / 31 /10 / 6	40 / 40 /27 / 4	38 / 40 /24 / 4	5 / 14 / 7 / 4	0.174

Data are expressed as means ± standard deviation or as number of patients.
Abbreviations: BMI: Body Mass Index

Table 3: Lifestyle factors of patients classified with the age of HCC onset.

	Age of HCC onset (years)				
Variables	**60 (n=39)**	**60-69 (n=83)**	**70-79 (n=155)**	**≥ 80 (n=48)**	***P* value**
Alcohol (g/day)					
<60 / ≥60	19 / 20	59 / 24	120 / 35	43 / 5	<0.001
Smoking (pack/day) ()()(pack/day)					
<1 / ≥1	7 / 32	35 / 48	87 / 68	31 / 17	<0.001
BMI (kg/m^2)	23.3 ± 3.5	23.0 ± 3.2	22.2 ± 3.0	21.5 ± 3.2	0.022
<25 / ≥25	29 / 10	61 / 22	127 / 28	42 / 6	0.176
No. of poor					
lifestyle habits					
0 / 1 / 2 / 3	3 / 15 /16 / 5	23 / 30 / 26 / 4	63 / 61 / 23 / 8	25 / 19 / 3 / 1	<0.001

Data are expressed as means ± standard deviation or as number of patients.
Abbreviations: BMI: body mass index

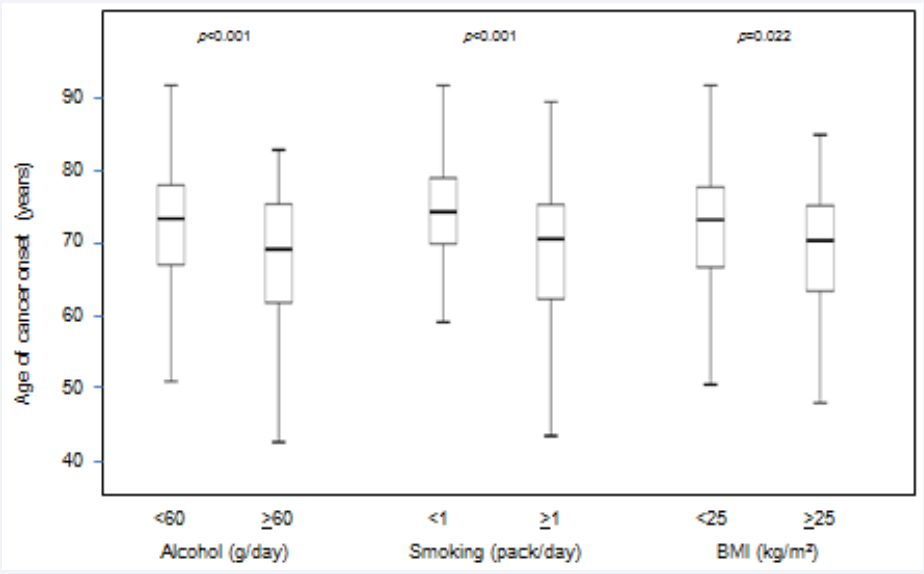

Figure 2 Recruitment and participant flow: 325 patients were subject to analysis.

Table 4: Multivariate analysis of clinical factors for younger age at HCC onset.

Variables	HR	95% CI			*P* value
Sex					
Male	1.00	Referent			
Female	1.07	0.806	-	1.423	0.635
FIB-4 index					
<3.25	1.00	Referent			
≥3.25	0.83	0.896	-	1.143	0.249
Child-Pugh class					
A	1.00	Referent			
B or C	1.39	1.058	-	1.837	0.018
Tumor stage					
I / II	1.00	Referent			
III / IV	0.84	0.667	-	1.049	0.122
Alcohol (g/day)					
<60	1.00	Referent			
≥60	1.43	1.076	-	1.896	0.014
Smoking (pack/day)					
<1	1.00	Referent			
≥1	1.50	1.142	-	1.957	0.003
BMI (kg/m^2)					
<25	1.00	Referent			
≥25	1.40	1.049	-	1.870	0.023

Abbreviations: BMI: Body Mass Index; HR: Hazard Ratio; CI: Confidence Interval

with 2-3 factors was 60.5% (Figure 4). Multivariate analysis using Cox's proportional hazards model revealed multiple poor lifestyle habits independently contributed to the earlier onset of cancer. Compared with patients without poor lifestyle habits, the hazard ratios for 1, and 2-3 factors were 1.42 times, and 2.61 times, respectively (Table 5). In 160 patients without smoking ≥1pack/day, the hazard ratios for non-obese patients with alcohol ≥60 g/day were 1.06 times, and the hazard ratios for obese patients with alcohol ≥60 g/day were 12.9 times (Table 6a). In 241 patients without alcohol ≥60 g/day, the hazard ratios for non-obese patients with smoking ≥1pack/day were 1.45 times, and the hazard ratios for obese patients with smoking ≥1pack/day were 3.05 times (Table 6b). Alcohol drinking and smoking increased earlier onset of cancer for obese patients compared with non-obese patients.

DISCUSSION

This study clarified that the accumulation of multiple poor lifestyle habits (consumption of ≥60 g/day alcohol, smoking ≥1 pack/day, and BMI ≥25) leads to earlier onset of HCC in CH-C patients. Heavy drinking enhances HCV-related Hepato carcinogenesis [12]. The risk for HCC onset has been reported to increase with alcohol consumption ≥60 g/day, and alcohol consumption has been shown to cause hepatic fibrosis and increase the incidence of cancer in general [13,14]. Fibrosis occurs through the following mechanism. When the liver is exposed to continuous inflammation as a result of regularly consuming alcohol consumption, the damaged hepatocytes release tumor necrosis factor-alpha, vascular endothelial growth factor, insulin-like growth factor-1 (IGF-1), and CXC chemokine, which activate the hepatic sinusoidal endothelial cells, hepatic stellate cells, and Kupffer cells [15]. Activated Kupffer cells produce inflammatory cytokines such as transforming growth factor beta, which activates the hepatic stellate cells and induces transformation of myofibroblasts. Activated hepatic stellate cells then promote the production of collagen in the extracellular matrix. Meanwhile, matrix metalloproteinase's in the fibrin degradation pathway are inhibited by an inhibiting factor, tissue

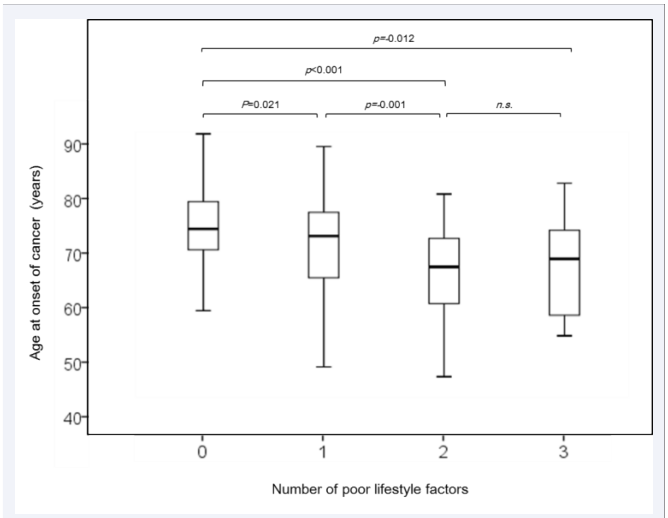

Figure 3 Average age at cancer onset in patients with multiple poor lifestyle habits: Average age at cancer onset was lower in patients with multiple factors at HCC onset.

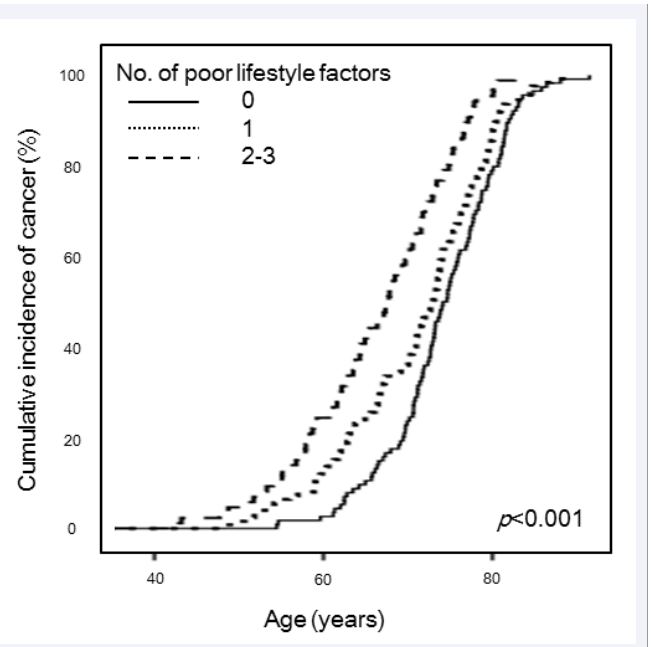

Figure 4 Cumulative incidence of cancer estimated by the Kaplan–Meier method in patients with multiple poor lifestyle habits: Multiple poor lifestyle habits lower the age of cancer onset.

Table 5: Multivariate analysis of factors for younger age at HCC onset when adopting the number of poor lifestyle factors as variables of lifestyle habits.

Variables	HR	95% CI			*P* value
Sex					
Male	1.00	Referent			
Female	1.11	0.840	-	1.468	0.462
FIB-4 index					
<3.25	1.00	Referent			
≥3.25	0.81	0.587	-	1.121	0.205
Child-Pugh class					
A	1.00	Referent			
B or C	1.37	1.041	-	1.802	0.025
Tumor stage					
I / II	1.00	Referent			
III / IV	0.83	0.658	-	1.036	0.097
No. of poor lifestyle factors					
0	1.00	Referent			
1	1.42	1.062	-	1.905	0.018
2-3	2.61	1.889	-	3.618	<0.001

Abbreviations: HR: Hazard Ratio; CI: Confidence Interval

Table 6: Multivariate analysis of factors for younger age at HCC onset by type of patients with multiple lifestyle habits after adjusting for sex: a) patients without smoking ≥1 pack/day (n=160), b) patients without alcohol ≥60 g/day (n=241).

a)								
Variables			**No.**	**HR**	**95% CI**			***P* value**
BMI≥25 (kg/m^2)	Alcohol≥600 (g/day)	Smoking≥1 (pack/day)						
No	No	No	114	1.00	Referent			
No	Yes	No	11	1.06	0.546	-	2.072	0.857
Yes	No	No	33	1.56	1.046	-	2.304	0.029
Yes	Yes	No	2	12.9	2.893	-	57.650	<0.001
b)								
Variables			**No.**	**HR**	**95% CI**			***P* value**
BMI≥25 (kg/m^2)	Alcohol≥60 (g/day)	Smoking≥1 (pack/day)						
No	No	No	114	1.00	Referent			
No	No	Yes	81	1.45	1.023	-	2.050	0.037
Yes	No	No	33	1.47	0.995	-	2.178	0.053
Yes	No	Yes	13	3.05	1.673	-	5.574	<0.001

Abbreviations: HR: Hazard Ratio; CI: Confidence Interval

inhibitor of metalloproteinase, and fibrin production becomes dominant.

According to the International Agency for Research on Cancer, smoking is a causal risk factor for HCC [16]. Smoking has been reported to increase the risk for HCC onset in HCV-positive patients [17-19]. Tobacco contains several carcinogenic substances that bind to DNA when activated by enzymes, and they subsequently cause gene mutations during DNA replication. In particular, mutations in the cancer and tumor suppressor genes induce neoplastic growth. Furthermore, smoking causes

oxidative stress and subsequent DNA damage, and thus becomes an additional factor for cancer onset [20].

Patients with a BMI ≥30 have a 4 times greater risk of HCC than patients with hepatic cirrhosis and a 48 times greater risk than patients with no history of liver disease [21]. Obesity causes insulin resistance and hyper insulinaemia, and insulin resistance accelerates the progression of hepatic fibrosis, contributing to HCC onset [22]. Hyper insulinaemia promotes IGF-1 activity through the inhibition of IGF binding protein. IGF-1 then promotes cellular proliferation and inhibits apoptosis, contributing to the onset of HCC [23]. In recent reports involving experiments with mice, enteric Gram-positive bacteria increased and the risk of HCC increased due to the conversion of cholic acid to deoxycholic acid when the mice developed obesity [24]; deoxycholic acid damages DNA, causing cell aging and HCC onset.

In this study, poor lifestyle habits were found to lead to an earlier onset of HCC not a risk of cancer. According to previous reports, consumption of alcohol, smoking, and diabetes are risk factors for hepatocarcinogenesis, but persons with a BMI ≥30 who do not drink do not have an increased risk, while those who consume alcohol only do have an increased risk [25]. Several cohort studies have investigated the consumption of alcohol, smoking, and obesity in relation to the risk of HCC onset, but none have investigated the accumulation of multiple poor lifestyle habits in relation to age of cancer onset. This study is therefore the first to clarify that multiple poor lifestyle habits lead to an earlier onset of HCC.

The limitation of this study was that we were unable to investigate the duration of exposure or exposure history to poor lifestyle habits as this study was a retrospective data review. Japan imposes a legal ban on alcohol drinking and smoking under 20 years old, so the approximate duration of exposure could be investigated. It was the limitation that FIB4-index, Child-Pugh class, and tumor stage were factors at the cancer onset. Consumption of coffee, green tea, and branched-chain amino acids, which have antioxidant properties and inhibit the advance of liver fibrosis, are associated with reduced risk of HCC [26-29]. The evaluation for the presence of these factors and liver biopsy are not investigated. These problems were cleared by using FIB4-index and tumor stage as a dependent variable of multivariate analysis in (Table 4, 5). FIB-4 index, although at HCC onset, could be used in place of liver fibrosis stage. Of the 325 patients, 268 (82%) had a FIB-4 index ≥3.25 which was a high potential of cirrhosis. FIB-4 index ≥3.25 was a specificity of 97% and a positive predictive value of 65% for advanced fibrosis [11]. The age of cancer onset was defined on the basis of age when the cancer was diagnosed, and so the delay in cancer diagnosis made the age of cancer onset older. The rate of patients with or without poor life style factors was not significant differences between tumor stages of cancer onset (Table 2). This show that time of cancer diagnosis is no differences between two groups. Age of HCV infection was unknown, but this was not that big of a problem because the duration of HCV infection had less to do with HCC development [30]. The age of cancer onset in hepatitis C patients in Japan has increased in recent years [31]. In this study, the observation period was 10 years and therefore the contribution to HCC onset due to changes in the disease structure and societal background cannot be denied.

CONCLUSION

Multiple poor lifestyle habits lower the age of cancer onset in CH-C. Therefore, preventing people with CH-C from developing poor lifestyle habits is important from the perspective of the cancer onset period.

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