Master of Medicine

The Clinical Behavior and Survival of

Patients with Hepatocellular Carcinoma and

a Family History of the Disease

The Graduate School
of the University of Ulsan

Department of Medicine
Chang, Se-Heon

The Clinical Behavior and Survival of

Patients with Hepatocellular Carcinoma and

a Family History of the Disease

Supervisor : Shim, Ju-Hyun

A Dissertation

Submitted to

The Graduate School of the University of Ulsan

In partial Fulfillment of the Requirements

For the Degree of

Doctor of medicine

By

Chang, Se-Heon

Department of Medicine
Ulsan, Korea
August, 2018

The Clinical Behavior and Survival of Patients with Hepatocellular Carcinoma and a Family History of the Disease

This certifies that the [dissertation/master thesis]
Of Chang, Se-Heon is approved.

Lee, Han-Chu

Committee Chiar Dr.

Song, Gi-Won

Committee Member Dr.

Shim, Ju-Hyun

Committee Member Dr.

Department of Medicine

Ulsan, Korea

August, 2018

Abstract

Background & Aims: Familial clustering is a common feature of hepatocellular carcinoma (HCC) as well as a risk factor for the disease. We aimed to assess whether such a family history affected prognostic outcomes in patients with HCC diagnosed at different stages of the disease.

Methods: This hospital registry-based cohort study included 5,484 patients initially diagnosed with HCC. Individual family histories of cancer were obtained by interview and reported by trained nurses who constructed three-generation pedigrees. Overall survival data were compared between cases with and without first-degree relatives affected by HCC, with adjustment for other potential predictors.

Results: Of 5,484 patients, 845 (15.4%) had first-degree relatives with a history of HCC. A family history was associated with longer survival in the entire cohort (adjusted hazard ratio [HR] 0.89, 95% confidence interval [CI] 0.80-0.98, P=0.025). A significant trend for reduced risk of death with increasing number of affected family members was also observed (P for trend=0.018). Stage-stratified analysis showed that the presence of a family history was especially associated with a reduced risk of death in the subset of patients with HCC at a (very) early stage (adjusted HR 0.83, 95% CI 0.69-0.99; P=0.042). The proportion of cases receiving curative treatment was also higher in early-stage patients with a family history (72.6% vs. 63.3%; P<0.001).

Conclusion: A first-degree family history of the disease is a prognostic factor for improved survival in patients with HCC, especially in those whose tumors can be cured by radical treatments.

Lay Summary

Although hepatocellular carcinoma (HCC) has been observed to cluster within families after adjusting for proven risk factors including hepatitis infections, the prognostic impact of family history on the treatment and subsequent survival of patients with HCC remains unclear. In this large, well-characterized, hospital-based cohort study, the incidence of a family history in a new HCC series was about 16%, and familial clustering of HCC was associated with a reduced risk of overall mortality in patients with the disease. The benefit of a family history was more prominent in patients with very early or early stage HCC. A first-degree family history was closely associated with initial treatment by radical surgery with curative intent rather than by non-surgical options. The association between family history and patient survival suggests that HCC patients with affected relatives seek medical attention more actively and have a higher probability of choosing more effective treatments, irrespective of their invasiveness.

Keywords: Liver Cancer; Family; Prognosis; Treatment; Clustering

List of Abbreviations

Hepatocellular carcinoma, HCC; hepatitis B virus, HBV; Asan BiomedicaL research Environment, ABLE; Barcelona Clinic Liver Cancer, BCLC; Transarterial chemoembolization, TACE; hazard ratio, HR; body mass index, BMI; alpha-fetoprotein, AFP; interquartile range, IQR; hepatitis C virus, HCV; Model for end-stage liver disease, MELD; confidence interval, CI.

Index

Figure and Table index

INTRODUCTION

Evidence has accumulated over many years of a relationship between the risk of developing a specific cancer and a family history of the disease [1-4]. In addition, numerous studies have reported positive or negative effects of a family history on the prognostic outcomes of patients with different types of cancer [5-9]. Most attention in this matter has been given to malignancies of the digestive and reproductive systems, which are the most common cancers in both men and women [5,6,9-11].

Interestingly, hepatocellular carcinoma (HCC), which is the third leading cause of cancer deaths globally despite its lower ranking for incidence, has been observed to cluster within families sharing genes and environments [12-14]. The familial clustering of the disease was found to be unrelated to a viral etiology of hepatitis B in both Asians and Europeans, but understandably increased in subjects with HCC due to vertically transmitted hepatitis B virus (HBV) [13,15-17]. Because of this strong familial association of HCC risk, the former American guidelines recommend routine surveillance of hepatitis B carriers of all ages with family histories of HCC, like for high-risk cirrhotic patients [18]. An international study of the prognostic role of family history in HCC patients concluded that the familial cancer group had better survival than its sporadic counterpart, and suggested that this was due to the cancers being detected at an earlier stage of tumor growth and liver damage [19]. However, that (Hong Kong) study gave only unadjusted estimates without detailed information on family membership and generations.

Our aim in this study was to examine the incidence of a family history of cancer at the time of HCC diagnosis, and to investigate the association between familial cancer clustering and survival outcomes over time in a large clinical set of patients first diagnosed with HCC; since the patients were ethnically homogeneous Koreans the data should not be skewed by racial and environmental biases. We also wanted to see whether the presence of affected blood relatives influenced treatment decision-making in clinical practice.

PATIENTS AND METHODS

Data sources and collection

Approval of the Institutional Review Board of Asan Medical Center (IRB No.2016-0683) was obtained for this large registry-based retrospective cohort study, and treatment-naive patients initially diagnosed with HCC by a three-digit diagnostic code specified by the seventh revision of the International Classification of Diseases (ICD-7) were identified from our prospectively-constructed hospital-based cancer registry. This registry is a part of the National Cancer Registration Program and has been described in previous studies from our center [20,21]. Health-related behaviors together with relevant demographic factors and clinical information on the patients were reviewed from their inpatient and outpatient medical records using the anonymized clinical database system of our institution (Asan BiomedicaL research Environment, ABLE) [22,23]. Demographic and socioeconomic data were collected from computerized admission documents completed by trained nurses during patient interviews employing a structured questionnaire. The nursing charts included information on educational level, substance use (tobacco and alcohol), past and present medical histories, and basic anthropometric data. Medical histories of family members were recorded in detail on each patient's chart, together with pedigrees containing information including history and sites of cancers, and causes of death of close blood relatives (first- and second-degree relatives). We also examined laboratory data related to liver function and viral hepatitis, and checked radiological results to determine stage of HCC based on the size and number of tumors, vascular invasion, and extrahepatic metastasis; in addition, HCC treatment modalities and the associated survival outcomes were obtained from the ABLE system and database of the National Population Registry of the Korea National Statistical Office using the unique personal identification numbers of the patients.

Patient details

Patients over 20 years of age who were diagnosed as having HCC and underwent treatment for the disease for the first time between 2007 and 2011 were included in this study (n=8,246, Fig.1). Of these, 2,762 were initially excluded for the following reasons: 2,712 had had previous treatment for HCC prior to visiting our center; 36 had concurrent non-HCC malignancies; and 14 of whom did not have complete records of family health histories. The diagnosis of HCC was based on either

pathological or radiological findings in accord with international guidelines [18,24]. Cirrhosis of the liver was also defined either histologically or based on radiographic abnormalities (i.e. nodular changes of liver morphology, splenomegaly, gastrointestinal varices, or ascites). Stages of HCC at diagnosis were classified by the Barcelona Clinic Liver Cancer (BCLC) system [24]. The HCC treatment for each patient was principally decided according to their hierarchy of efficacy in lengthening life.

Surgical resection was based on the anatomical segments of the liver whenever possible. Radiofrequency ablation was performed percutaneously under sonographic or computed tomographic guidance. Transarterial chemoembolization (TACE) was usually carried out using a mixture of iodized oil and cisplatin or adriamycin, and absorbable gelatin sponge particles [25]. Most of transplant cases (97.4%) received grafts from living-related donors.
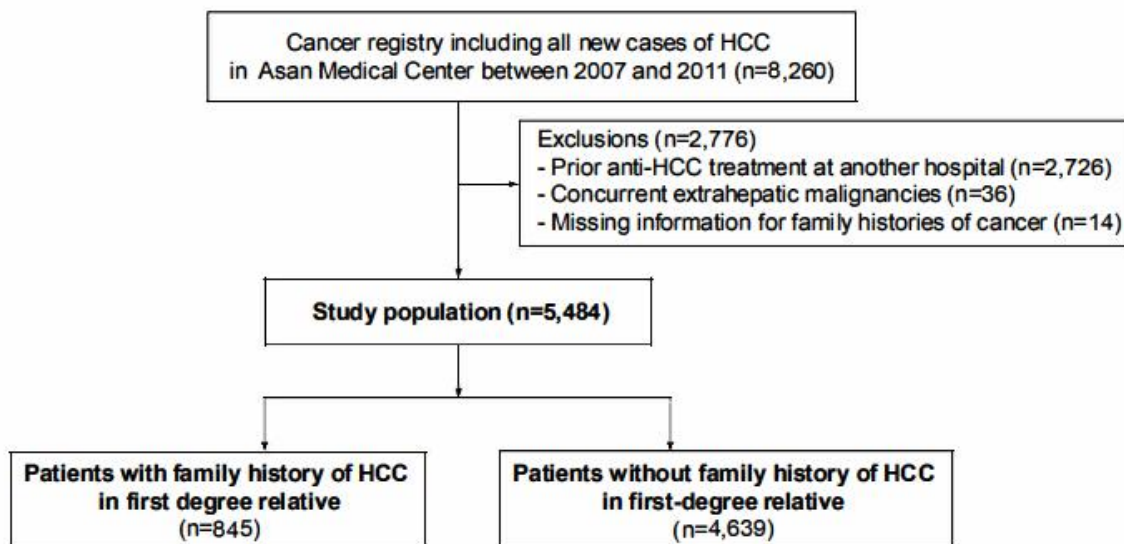
Figure 1. Patient flow diagram.

Family histories

Family histories of cancer were routinely taken by a trained nurse using a structured questionnaire based on a three-generation pedigree [1]. For each relative, the study participant was asked about any serious medical conditions and whether the relative was still alive, or, if the relative had died, the date and cause of death. Positive family histories of cancer were recorded according to type of cancer (HCC or cancer of all types other than HCC) and the generation of the affected relatives (first-degree or second-degree). First-degree relatives included parents, siblings, and offspring; and second-degree relatives included aunts, uncles, nieces, nephews, and grandparents. A patient with a family history of cancer in both first- and second-degree relatives was regarded as having a first-degree history. Only histories of cancer in one or more first-degree relatives that were reliably reported were included as established family histories in the final analysis [26].

Statistical analysis

The main aim of the statistical analysis was to compare the overall survival of patients with and without a family history of cancer. The survival analysis was censored on 31 December 2016, and deaths occurring up to that time were considered events. In general, overall survival, rather than progression-free survival, is the most appropriate end-point of studies of HCC patients, most of whom have underlying liver disease, or some other serious disorder, especially as patients receive different types of curative and non-curative anti-cancer treatments [27-29]. Using multivariate Cox proportional hazards models, we estimated the hazard ratio (HR) for death of the familial group compared with the sporadic group as the reference control. The HRs were adjusted for age, gender, level of education, body mass index (BMI), smoking, alcohol consumption, etiology of liver disease, presence of cirrhosis, laboratory results related to liver function, tumor stage at diagnosis, and serum alpha-fetoprotein (AFP). A backward elimination approach involving candidate variables with *P*-values <0.10 in the univariate analysis was used in the multivariable analysis. Differences in clinical and pathologic parameters between the familial and sporadic groups were analyzed with the X^2 test or Fisher's exact probability test, as appropriate.

4

Stratified analyses were also performed by number of affected family members, and cancer stage. A two-sided P-value <0.05 was considered statistically significant.

RESULTS

Family histories of study subjects

Of the 5,484 HCC patients included, 1,859 (33.9%) had at least one relative with some form of cancer (Table 1); 1,823 had family histories in first-degree relatives and 36 in second-degree relatives.

When the family history was limited to HCC, 870 (15.9%) had a family history of HCC. 845 (15.4% of the entire cohorts) had family histories in one or more first-degree relatives and 25 in second-degree relatives. Nine of the 870 patients had both first- and second-degree family histories of HCC. 1,213 patients (22.1%) had family histories of non-HCC cancers.

Demographic and clinical characteristics according to presence or absence of a family history of HCC

Table 2 presents the baseline characteristics of patients and tumors at the time of HCC diagnosis. The median age of the entire subjects was 56 years (interquartile range [IQR], 49-63 years), and the majority of the patients were male (80.7%) and had HBV infections (80.6%). Liver cirrhosis was observed in 4,431 patients (80.8%). Females and younger patients, non-diabetics, and never-drinkers were more common among individuals with first-degree family histories of HCC than among those without such histories (Ps<0.05; Table 2). Those with first-degree family histories of HCC also had a higher proportion of non-HCC cancer histories (P=0.002). In addition, subjects with HBV or Child-Pugh class A were more common and hepatitis C virus (HCV) carriers were less common in the familial group (Ps<0.05). Size and multiplicity of tumors were not associated with a family history of HCC; BCLC stages were similar in the two groups (P=0.280), and TACE and surgical resection were the most common primary anti-HCC treatments in both groups. There was also no difference in the time interval between diagnosis of HCC and initiation of treatment in the two groups, this interval being generally less than one month in new cases (P=0.306) Curative therapies such as resection,

5

transplantation, and local ablation were initially chosen in 49.1% of the patients with a family history, significantly higher than the 44.0% among those without family histories (*P*<0.001), and the converse was true for non-curative options (50.9% vs. 56.0%; *P*<0.001; Table 2).

Table 1. Family Histories of Cancer in Patients with Hepatocellular Carcinoma

Family history	No. of patients (n=5,484)
Family history of any cancer	
Absent	3,625 (66.1%)
Present	1,859 (33.9%)
Degree of relatives with any cancer	
First degree	1,823 (98.1%)
Second degree	36 (1.9%)
No. of relatives with any cancer	
1 / ≥2	1,321 (71.1%) / 538 (28.9%)
No. of first degree relatives with any cancer	
0 / 1 / ≥2	36 (1.9%) / 1,305 (70.2%) / 518 (27.9%)
Family history of HCC	
Absent	4,614 (84.1%)
Present	870 (15.9%)
Degree of relatives with HCC	
First degree	845 (97.1%)
Second degree	25 (2.9%)
No. of relatives with HCC	
1 / ≥2	681 (78.3%) / 189 (11.7%)
No. of first degree relatives with HCC	
0 / 1 / ≥2	25 (2.9%) / 669 (76.9%) / 176 (20.2%)
Family history of cancers other than HCC	
Absent	4,289 (78.2%)
Present	1,213 (22.1%)
Degree of relatives with non-HCC cancers	
First degree	1,196 (98.6%)
Second degree	17 (1.4%)
No. of relatives with non-HCC cancers	
1 / ≥2	998 (82.3%) / 215 (17.7%)
No. of first degree relatives with non-HCC cancers	
0 / 1 / ≥2	17 (1.4%) / 986 (81.3%) / 210 (17.3%)

HCC, hepatocellular carcinoma.

Table 2. Demographic and Hepatic Characteristics by Family History of Hepatocellular Carcinoma

Variable	Family History (n=845)	No family history (n=4,639)	*P* value
Demographic factor			
Male sex	656 (77.6%)	3,768 (81.2%)	0.015
Age, years	54 (49-61)	56 (49-64)	<0.001
Body mass index, kg/m^2	24.1 (22.1-26.1)	24.1 (22.1-26.1)	0.608
Alcohol consumption			0.007
Never	323 (38.2%)	1,515 (32.7%)	
Former	360 (42.6%)	2,140 (46.1%)	
Current	162 (19.2%)	984 (21.2%)	
Smoking status			0.201
Never	348 (41.2%)	1,762 (38.0%)	
Former	339 (40.1%)	1,959 (42.2%)	
Current	158 (18.7%)	914 (19.8%)	
Education, years			0.143
≤9	310 (36.7%)	1,857 (40.0%)	
10-12	298 (35.3%)	1,597 (34.4%)	
>12	237 (28.0%)	1,185 (25.6%)	
Diabetes	142 (16.8%)	975 (21.1%)	0.005
Hypertension	201 (23.8%)	1,250 (27.0%)	0.052
Family history of non-HCC cancers	219 (25.9%)	977 (21.1%)	0.002
Liver disease-related factor			
Etiology of liver disease			
Hepatitis B virus infection	762 (90.2%)	3,347 (72.1%)	<0.001
Hepatitis C virus infection	28 (3.3%)	513 (11.1%)	<0.001
Liver cirrhosis	690 (81.7%)	3741 (80.6%)	0.491
Ascites	87 (10.3%)	562 (12.1%)	0.132
Platelet count (X10^3/mm^3)	143 (98-190)	137 (94-189)	0.416
Serum albumin (g/dl)	3.7 (3.3-4.0)	3.6 (3.1-4.0)	<0.001
Serum bilirubin (mg/dl)	1.0 (0.8-1.4)	1.0 (0.8-1.5)	0.078
International normalized ratio (INR)	1.08 (1.03-1.17)	1.09 (1.03-1.19)	0.259
Serum creatinine (mg/dl)	0.8 (0.7-0.9)	0.8 (0.7-1.0)	0.256
Child-Pugh class			<0.001
Class A	710 (84.0%)	3,591 (77.4%)	
Class B	108 (12.8%)	860 (18.5%)	
Class C	27 (3.2%)	188 (4.1%)	

MELD score	8 (7-9)	8 (7-10)	0.003	
Tumor-related factor				
Number of tumors			0.716	
1	518 (61.3%)	2,830 (61.0%)		
2	153 (18.1%)	803 (17.3%)		
≥3	174 (20.6%)	1,006 (21.7%)		
Maximal tumor size (cm)	3.8 (2.1-7.7)	4.0 (2.0-8.0)	0.312	
Infiltrative type of tumor	85 (10.1%)	465 (10.0%)	0.975	
Vascular invasion	194 (23.0%)	1,209 (26.1%)	0.057	
Extra-hepatic metastasis	91 (10.8%)	552 (11.9%)	0.348	
Serum AFP (ng/ml)	58.6 (7.9-976.7)	54.0 (7.9-993.7)	0.063	
Cancer-related symptoms	907 (19.6%)	156 (18.5%)	0.470	
BCLC Stage				
Stage 0	90 (10.7%)	440 (9.5%)	0.280	
Stage A	344 (40.7%)	1,818 (39.2%)		
Stage B	112 (13.2%)	567 (12.2%)		
Stage C	272 (32.2%)	1,626 (35.0%)		
Stage D	27 (3.2%)	188 (4.1%)		
Initial anti-HCC treatment				
Surgical resection	338 (40.0%)	1,538 (33.2%)	<0.001	
Local ablation therapy	51 (6.0%)	377 (8.1%)	0.037	
Liver transplantation	26 (3.1%)	128 (2.8%)	0.607	
Transarterial chemoembolization	361 (42.7%)	2,118 (45.7%)	0.607	0.007*
Radiotherapy	3 (0.4%)	20 (0.4%)	>0.999	
Systemic chemotherapy	22 (2.6%)	106 (2.2%)	0.573	
Conservative management	44 (5.2%)	352 (7.6%)	0.014	

Data are presented as number (percentage) or median (interquartile range).

*P values for curative (i.e., surgical resection, local ablation, and liver transplantation) versus non-curative treatment.

HCC, hepatocellular carcinoma; MELD, model for end-stage liver disease; AFP, alpha-fetoprotein; BCLC, Barcelona Clinic Liver Cancer.

Effect of a family history of HCC on survival in patients with HCC

During a median observation period of 4.0 years (IQR 1.0-6.6 years), 3,228 of the 5,484 patients (58.9%) died of any cause. Of those who died, 89.4% (n=2,886) were treated and followed-up in our tertiary center for at least the last 6 months before death, and this proportion did not depend on the presence or absence of a family history of HCC (91.7% vs. 89.0%, *P*=0.083). The 3-, 5-, and 7-year estimated overall survival rates were 55.5%, 46.7%, and 41.1%, respectively in the entire population. Kaplan-Meier log-rank analysis revealed a significant increase of survival time in the patients with a history of HCC (52.1% vs. 45.7% at 5 years, *P*<0.001; Fig. 2A). In multivariate Cox models after adjustment for co-predictors (i.e., age, gender, family history of non-HCC cancer, smoking and drinking habitus, level of education, BMI, etiology of liver disease, presence of cirrhosis, Model for end-stage liver disease [MELD] score, platelet count, serum AFP levels, BCLC stage, and infiltrative type of tumor), a family history of HCC was independently associated with improved overall survival (adjusted hazard ratios [HRs], 0.89; 95% confidence interval [CI], 0.80 to 0.98, *P*=0.025; Table 3).

The relationship between family history and outcomes according to the number of family members with HCC was also investigated. Although the majority of patients with a family history reported only one affected relative, there was a significant trend for an increased reduction in death risk with increasing number of affected family members after adjustment for demographic and tumoral factors (*P* for trend=0.018; Fig. 2B).
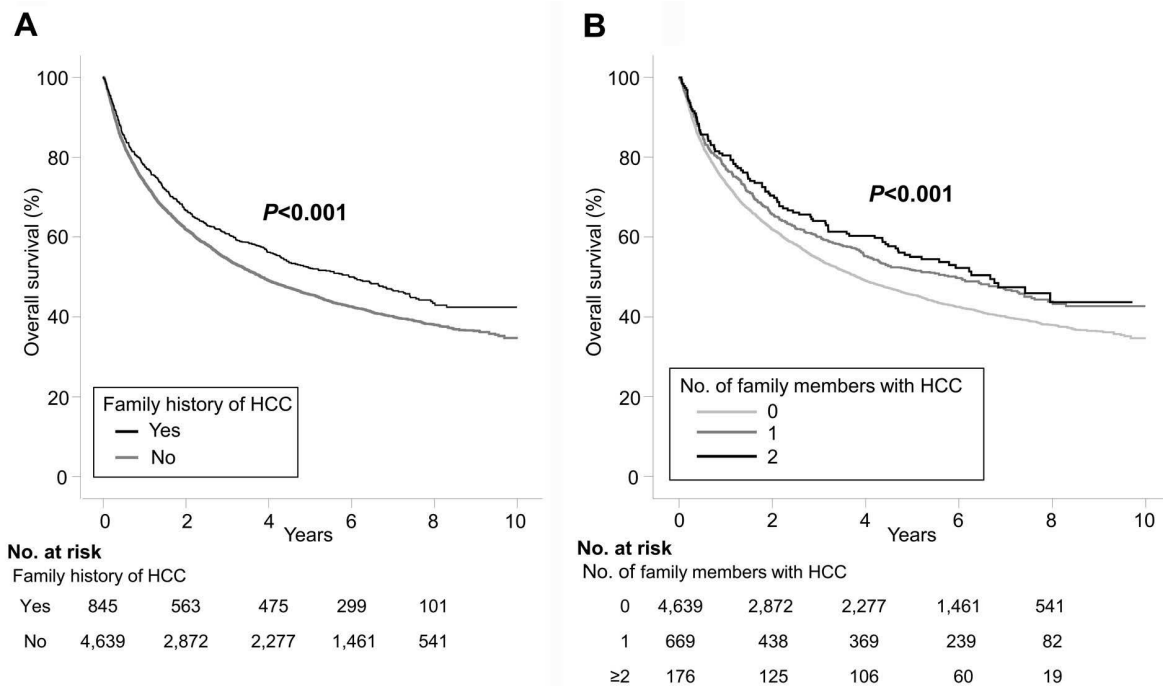
Figure 2. (A) Association between presence of family history and overall survival. A first degree family history was significantly associated with longer survival of HCC patients, **(B)** Overall survival according to number of family members with a history of HCC. There was a significant trend for improved survival with increasing number of affected family members.

Table 3. Effect of Family History of HCC on Overall Survival in the Entire Population

Variable	Univariate analysis			Multivariate analysis		
	HR	95% CI	*P*	HR	95% CI	*P*
Family history of HCC	0.83	0.75-0.92	<0.001	0.89	0.80-0.98	0.025
Family history of non-HCC cancers	0.93	0.85-1.01	0.076	0.98	0.90-1.07	0.695
Male sex	1.26	1.15-1.38	<0.001	1.22	1.11-1.35	<0.001
Age ≥60 years	1.16	1.09-1.25	<0.001	1.35	1.25-1.45	<0.001
Current alcohol drinking	1.06	0.98-1.15	0.173	-	-	-
Current smoking habitus	1.14	1.05-1.24	0.002	1.14	1.04-1.24	0.005
Education, years						
≤9	1			1		
10-12	0.91	0.84-0.99	0.019	0.94	0.87-1.02	0.134
>12	0.74	0.68-0.81	<0.001	0.81	0.74-0.89	<0.001
Body mass index						
<25.0 kg/m^2	1			1		
25.0-29.9 kg/m^2	0.79	0.73-0.85	<0.001	0.84	0.77-0.90	<0.001
≥30 kg/m^2	1.07	0.91-1.26	0.428	1.10	0.93-1.29	0.274
Diabetes	1.05	0.97-1.15	0.220	-	-	-
Hypertension	0.94	0.87-1.02	0.114	-	-	-
HBV infection	0.88	0.82-0.95	0.001	1.00	0.91-1.10	0.167
HCV infection	1.25	1.12-1.39	<0.001	1.27	1.14-1.42	<0.001
Liver cirrhosis	1.28	1.17-1.40	<0.001	1.23	1.12-1.36	<0.001
MELD score						
≤8	1			1		
9-10	1.54	1.41-1.68	<0.001	1.45	1.32-1.58	<0.001
11-14	2.06	1.87-2.27	<0.001	1.91	1.74-2.11	<0.001
≥15	2.45	2.17-2.76	<0.001	1.56	1.33-1.81	<0.001
Platelet count <100k/mm^3	0.98	0.91-1.05	0.541	-	-	-
Serum AFP ≥100 ng/ml	2.04	1.91-2.19	<0.001	1.63	1.52-1.75	<0.001
BCLC stage						
Stage 0	1			1		
Stage A	1.68	1.41-2.01	<0.001	1.59	1.33-1.90	<0.001
Stage B	3.48	2.88-4.20	<0.001	3.10	2.56-3.75	<0.001
Stage C	7.11	5.99-8.45	<0.001	5.31	4.44-6.34	<0.001
Stage D	7.59	6.06-9.50	<0.001	5.36	4.12-6.97	<0.001
Infiltrative type of tumor	4.27	3.88-4.71	<0.001	2.24	2.02-2.48	<0.001

HCC, hepatocellular carcinoma; HR, hazard ratio; CI, confidence interval; HBV, hepatitis B virus; HCV,

hepatitis C virus, MELD, model for end-stage liver disease; AFP, alpha-fetoprotein; BCLC, Barcelona Clinic Liver Cancer.

Survival analysis stratified by stage of HCC

We further analyzed the prognostic effect of a family history of HCC in patients who were at different initial stages of HCC when diagnosed. A family history of HCC was positively correlated with overall survival in patients with BCLC 0 or A stage HCC (adjusted HR 0.83, 95% CI 0.69-0.99; P=0.042), as shown in Table 4 and Fig. 3. The proportion of cases receiving curative treatment was also higher in early-stage patients with a family history (72.6% vs. 63.3%; P<0.001). In terms of specific anti-cancer treatments, surgical resection was more frequently performed in patients with familial histories than in those without histories (58.5% vs. 47.3%, P<0.001; Fig. 4). On the other hand, TACE treatment were more common in the latter group (26.7% vs. 35.0%, P=0.001).

When the analysis was restricted to patients with advanced stage HCC, we observed no relationship between survival and family history (HRs [95% CIs] 0.88 [0.68-1.13] for BCLC B stage; 0.98 [0.85-1.12] for BCLC C stage; and 0.77 [0.48-1.24] for BCLC D stage; Ps>0.05). Among the patients with more advanced HCC, the primary treatment pattern was similar in the two groups (curative vs. non-curative treatments 25.8% vs. 24.5%, P=0.603).

Table 4. Effect of Family History of HCC on Overall Survival in a Stage-Stratified Survival Analysis

|	BCLC 0 or A		BCLC B		BCLC C		BCLC D	
	Family member with HCC		Family member with HCC		Family member with HCC		Family member with HCC	
	Yes	No	Yes	No	Yes	No	Yes	No
No. at risk	434	2,258	112	567	272	1,626	27	188
Number of death	132 (30.4%) †	887 (39.3%)	70 (62.5%)	389 (68.6%)	227 (83.5%)	1,359 (83.6%)	19	145
Unadjusted HR	0.73 (0.61-0.88)†	1 (reference)	0.88 (0.68-1.13)	1 (reference)	0.98 (0.85-1.12)	1 (reference)	0.77 (0.48-1.24)	1 (reference)
Adjusted HR*	0.83 (0.69-0.99)†	1 (reference)	-	-	-	-	-	-

* Multivariate HRs and 95% CIs are adjusted for age, sex, habitus of alcohol and smoking, hypertension, diabetes, body mass index, family history of non-hepatocellular cancers, etiology of chronic liver disease, presence of liver cirrhosis, MELD score, platelet count, serum alpha-fetoprotein, BCLC stage (only BCLC 0-A subgroup), and infiltrative tumor type.

†P value<0.05

HCC, hepatocellular carcinoma; BCLC, Barcelona clinic liver cancer; MELD, model for end-stage liver disease.
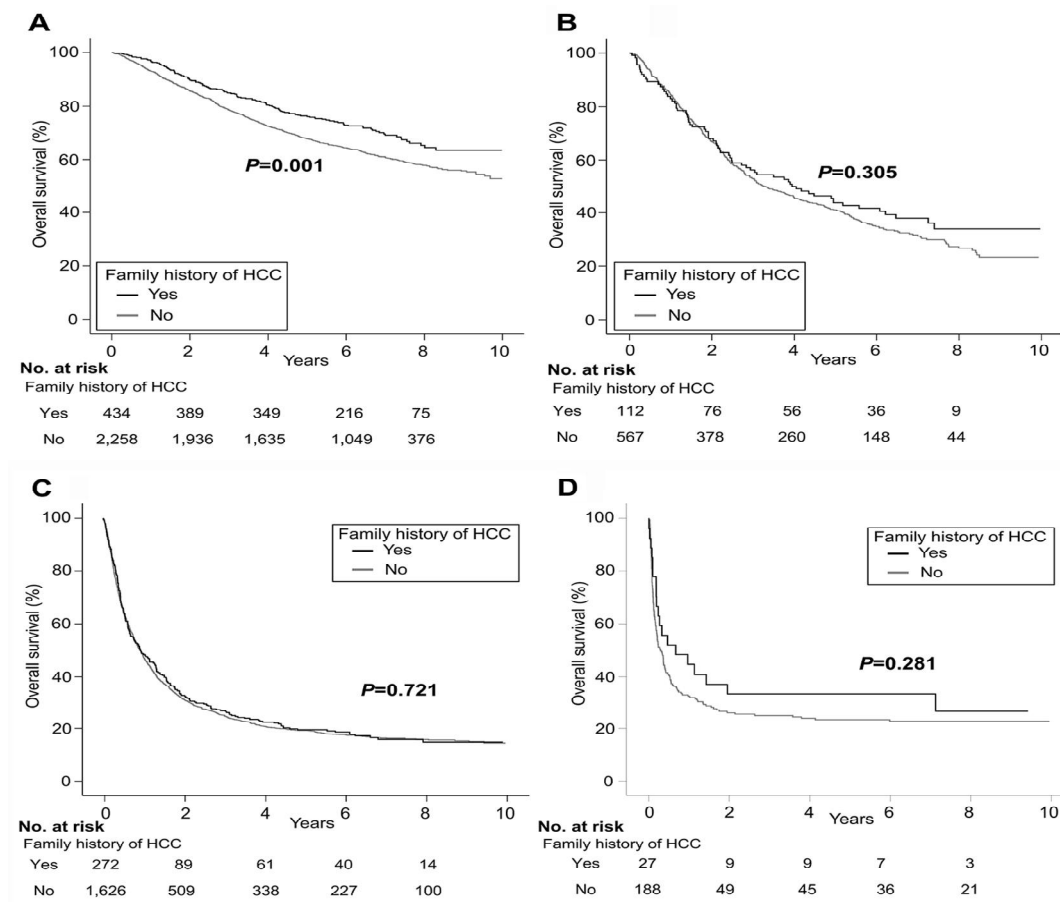
Figure 3. Presence of a family history of HCC and overall survival stratified into BCLC stage ([A] BCLC stage 0 or A, [B] BCLC stage B, [C] BCLC stage C, and [D] BCLC stage D). A family history was associated with better outcomes in patients with BCLC 0-A stage HCC, but not in those with BCLC stages B-D.
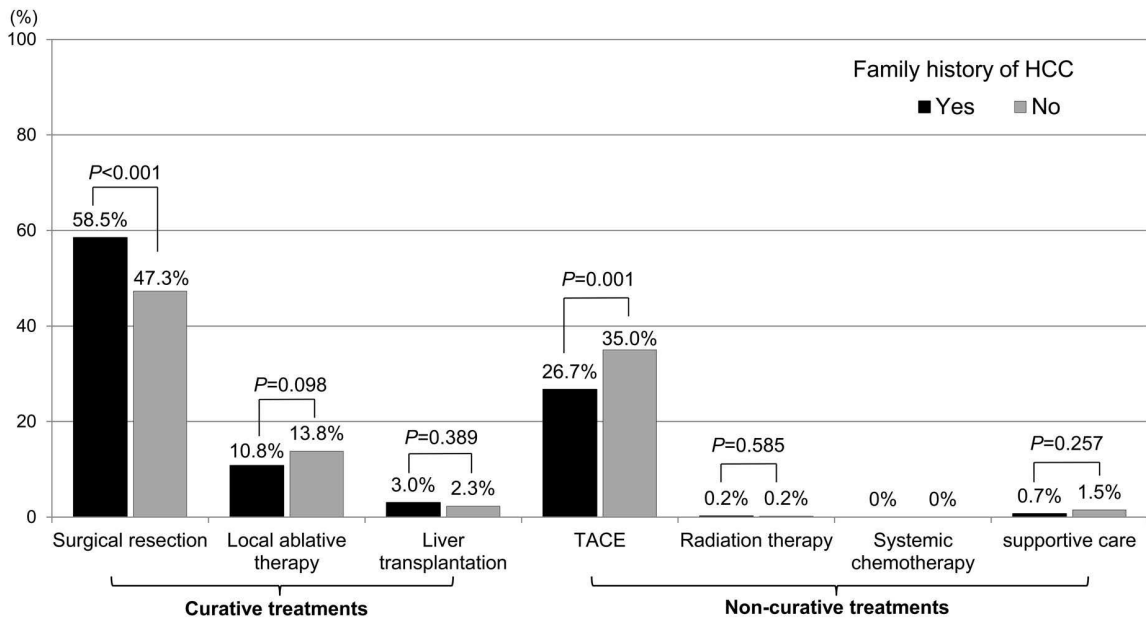
Figure 4. Anti-HCC treatments according to presence of a family history of HCC in patients with BCLC 0-A stage HCC. The proportion of patients undergoing curative resection was significantly higher in the group with familial clustering of HCC, whereas treatment with TACE was more prevalent in the sporadic HCC cases.

DISCUSSION

Several studies have demonstrated that a family history of HCC increases the risk of developing HCC, after adjusting for proven risk factors including HBV and HCV infection [13,17]. Familial aggregation of liver cancer has been frequently reported, although there have been no suggestions of an underlying genetic predisposition for hepatic neoplasms [12,14,30]. However, the influence of a family history of HCC on subsequent outcomes in patients with the established disease is controversial [19,31]. In this large, well-characterized, hospital-based cohort study, the incidence of a family history in a new HCC series was about 16%, and familial clustering of HCC was associated with a reduced risk of overall mortality in patients with the disease. Curative treatment, especially surgical resection, was also more common in patients with a positive family history.

The role of family history has been investigated as a prognostic factor in several types of malignancy, and diverse correlations have been observed [6,8,9,32]. The presence of familial cancer in stomach, breast, prostate, and colon cancer patients had protective effects, as in our HCC series, but no such effects were seen for brain and ovarian cancers [6,8,9]. The univariate findings in a study by a group in Hong Kong pointed to better survival in familial HCC patients (who accounted for approximately 10% of the total), especially in an early-stage non-metastatic sub-cohort, a result that appears to resemble the present findings based on a more intensive and less confounded analysis [19]. Although another Chinese investigation with 12% familial cases did not find a significant relationship between family history of HCC and survival after resection, the fact that it was restricted to surgical patients limits its generalizability [31].

There are some possible explanations for the association between familial cancer clusters and prognoses. First, cancer patients with a family history may more often present with early-stage disease, perhaps because they adhere more rigorously to cancer screening through greater awareness of the implications of the disease, as has been found in studies of prostate, breast, and gastric cancer [9,33-35]. However, a family history did not influence the initial profile of tumor stages among our new HCC cases, and the familial effect persisted after controlling for differences in stage. Second, genetic differences in inherent tumor biology between patients with and without a family history may

17

influence cancer mortality [36]. A Swedish population-based study found a higher proportion of indolent subtypes in familial leukemia, whereas familial cases of ovarian cancers had a more aggressive course with poorer survival [6]. Functional genetic or immunologic polymorphisms may well determine not only susceptibility to specific diseases, but also individual responses to cancer treatment.[37] Third, health-related behavioral changes including regular physical activity, stopping smoking and drinking, and a healthy diet and nutrition may contribute to the superior disease course, since these factors have been shown to have anti-cancer effects in HCC [38-40].

On the other hand, the beneficial effect of a family history in our study appeared greater among patients with early cancers. Since, unlike intermediate or advanced HCC, for which there is a single standard treatment, early-stage HCC can be treated in a variety of ways, from radical resection or liver transplantation with more curative intent, to less potent but more convenient interventional procedures [18,24]. This association suggests that familial HCC patients are more likely to seek medical attention, a factor which is seldom controllable; they may therefore have a higher probability of, and even a preference for, undergoing more effective, albeit more invasive, treatment [35]. On the other hand, patients with no family history may have less understanding of the therapeutic options and prognoses, and less opportunity to consult someone with experience of HCC, which may influence doctor-patient decision-making regarding treatment modality. Our results show that the presence of a family history was closely associated with the receipt of formally recommended definitive surgery, rather than palliative TACE, as the initial therapy in equivalent early cases. In addition to accurate medical knowledge of therapeutic risks and benefits, a variety of factors including fear of complications related to surgery, concern about recurrence, and advice from the patient's family are usually involved in the choice of cancer treatment [41,42]. Our results suggest that such behavioral benefits associated with family history increase with increasing number of affected relatives. The absence of an association between presence of a family history and survival in patients who had opted for and received surgical resection in our and prior Chinese studies may indicate that a family history is mainly influential during clinical decision-making [19].

Several limitations of this study deserve comment. First, because we relied on self-reported family

histories, family history status may have been misclassified. However, self-reported data have repeatedly been shown to be reliable in prior studies [43,44]. Because the data on family history were collected at the time of first diagnosis of HCC, prior to the initial treatment, any errors in recall should not have influenced the association with patient outcome [45]. In addition, we tried to minimize ascertainment bias, and thus in the end only tested the familial effect of first-degree relatives, and the latter are presumably reported quite reliably [26,46]. Second, differences in adherence to medical management could introduce a certain bias. However, the interval between diagnosis and treatment among all the new cases, and the follow-up compliance in our center among the patient who ultimately died, was not affected by a family history of HCC during the period of observation, and indeed patient compliance is likely to be more reliable in a high-volume hospital like ours [47].

In conclusion, this investigation revealed that patients with HCC who had a first-degree family history of the disease survived better than those without such a family history. This familial benefit was stronger among early-stage patients, whose attitudes would have a greater impact on treatment decisions and subsequent outcomes than among those at a later stage. The molecular and genetic factors underlying familial-clustered HCC remain to be elucidated.

REFERENCES

[1]   Lu KH, Wood ME, Daniels M, Burke C, Ford J, Kauff ND, et al. American Society of Clinical Oncology Expert Statement: collection and use of a cancer family history for oncology providers. J Clin Oncol 2014;32:833-840.

[2]   Bratt O, Drevin L, Akre O, Garmo H, Stattin P. Family History and Probability of Prostate Cancer, Differentiated by Risk Category: A Nationwide Population-Based Study. J Natl Cancer Inst 2016;108.

[3]   Lowery JT, Ahnen DJ, Schroy PC, 3rd, Hampel H, Baxter N, Boland CR, et al. Understanding the contribution of family history to colorectal cancer risk and its clinical implications: A state-of-the-science review. Cancer 2016;122:2633-2645.

[4]   Altieri A, Bermejo JL, Hemminki K. Familial risk for non-Hodgkin lymphoma and other lymphoproliferative malignancies by histopathologic subtype: the Swedish Family-Cancer Database. Blood 2005;106:668-672.

[5]   Kupelian PA, Kupelian VA, Witte JS, Macklis R, Klein EA. Family history of prostate cancer in patients with localized prostate cancer: an independent predictor of treatment outcome. J Clin Oncol 1997;15:1478-1480.

[6]   Lee M, Reilly M, Lindstrom LS, Czene K. Differences in survival for patients with familial and sporadic cancer. Int J Cancer 2017;140:581-590.

[7]   Lindström LS, Hall P, Hartman M, Wiklund F, Grönberg H, Czene K. Familial concordance in cancer survival: a Swedish population-based study. The Lancet Oncology 2007;8:1001-1006.

[8]   Chan JA, Meyerhardt JA, Niedzwiecki D, Hollis D, Saltz LB, Mayer RJ, et al. Association of family history with cancer recurrence and survival among patients with stage III colon cancer. Jama 2008;299:2515-2523.

[9]   Han MA, Oh MG, Choi IJ, Park SR, Ryu KW, Nam BH, et al. Association of family history with cancer recurrence and survival in patients with gastric cancer. J Clin Oncol 2012;30:701-708.

[10]   Jobsen JJ, van der Palen J, Brinkhuis M, Ong F, Struikmans H. Long-term effects of first degree family history of breast cancer in young women: Recurrences and bilateral breast cancer. Acta Oncol 2016;55:449-454.

[11]   Stoffel EM, Mercado RC, Kohlmann W, Ford B, Grover S, Conrad P, et al. Prevalence and predictors of appropriate colorectal cancer surveillance in Lynch syndrome. Am J Gastroenterol 2010;105:1851-1860.

[12]   Hemminki K, Li X. Familial liver and gall bladder cancer: a nationwide epidemiological study from Sweden. Gut 2003;52:592-596.

[13]   Turati F, Edefonti V, Talamini R, Ferraroni M, Malvezzi M, Bravi F, et al. Family history of liver cancer and hepatocellular carcinoma. Hepatology 2012;55:1416-1425.

[14]   Yang Y, Wu QJ, Xie L, Chow WH, Rothman N, Li HL, et al. Prospective cohort studies of association between family history of liver cancer and risk of liver cancer. Int J Cancer 2014;135:1605-1614.

[15]   Loomba R, Liu J, Yang HI, Lee MH, Lu SN, Wang LY, et al. Synergistic effects of family history of hepatocellular carcinoma and hepatitis B virus infection on risk for incident hepatocellular carcinoma. Clin Gastroenterol Hepatol 2013;11:1636-1645 e1631-1633.

[16]   Wan DW, Tzimas D, Smith JA, Kim S, Araujo J, David R, et al. Risk factors for early-onset and late-onset hepatocellular carcinoma in Asian immigrants with hepatitis B in the United States. Am J Gastroenterol 2011;106:1994-2000.

[17]   Hassan MM, Kaseb A, Li D, Patt YZ, Vauthey JN, Thomas MB, et al. Association between hypothyroidism and hepatocellular carcinoma: a case-control study in the United States. Hepatology 2009;49:1563-1570.

[18]   Bruix J, Sherman M, American Association for the Study of Liver D. Management of hepatocellular carcinoma: an update. Hepatology 2011;53:1020-1022.

[19]   Dai WC, Fan ST, Cheung TT, Chok KSH, Chan ACY, Tsang SHY, et al. The impact of family history of hepatocellular carcinoma on its patients' survival. Hepatobiliary and Pancreatic Diseases International 2012;11:160-164.

21

[20] Kim HJ, Cho JH, Lyu Y, Lee SH, Hwang KH, Lee MS. [Construction and validation of hospital-based cancer registry using various health records to detect patients with newly diagnosed cancer: experience at Asan Medical Center]. J Prev Med Public Health 2010;43:257-264.

[21] Seo HJ, Oh IH, Yoon SJ. A comparison of the cancer incidence rates between the national cancer registry and insurance claims data in Korea. Asian Pac J Cancer Prev 2012;13:6163-6168.

[22] Shin SY, Lyu Y, Shin Y, Choi HJ, Park J, Kim WS, et al. Lessons Learned from Development of De-identification System for Biomedical Research in a Korean Tertiary Hospital. Healthc Inform Res 2013;19:102-109.

[23] Shin SY, Park YR, Shin Y, Choi HJ, Park J, Lyu Y, et al. A De-identification method for bilingual clinical texts of various note types. J Korean Med Sci 2015;30:7-15.

[24] Dufour JF, Greten TF, Raymond E, Roskams T, De T, Ducreux M, et al. Clinical Practice Guidelines EASL – EORTC Clinical Practice Guidelines : Management of hepatocellular carcinoma European Organisation for Research and Treatment of Cancer. Journal of Hepatology 2012;56:908-943.

[25] Shim JH, Han S, Shin YM, Yu E, Park W, Kim KM, et al. Optimal measurement modality and method for evaluation of responses to transarterial chemoembolization of hepatocellular carcinoma based on enhancement criteria. J Vasc Interv Radiol 2013;24:316-325.

[26] Ziogas A, Anton-Culver H. Validation of family history data in cancer family registries. American Journal of Preventive Medicine 2003;24:190-198.

[27] Huang L, Sanctis YD, Shan M, Bruix J, Llovet J, Cheng A-L, et al. Weak correlation of overall survival and time to progression in advanced hepatocellular carcinoma. Journal of Clinical Oncology 2017;35:233-233.

[28] Reig M, Rimola J, Torres F, Darnell A, Rodriguez-Lope C, Forner A, et al. Postprogression survival of patients with advanced hepatocellular carcinoma: rationale for second-line trial design. Hepatology 2013;58:2023-2031.

[29] Patel T, Harnois D. Assessment of response to therapy in hepatocellular carcinoma. Ann Med 2014;46:130-137.

[30] Liu L, Li L, Zhou S, Jiang Q, Chen S, Gao Y, et al. Familial correlations of onset age of hepatocellular carcinoma: A population-based case-control family study. PLoS ONE 2014;9:1-5.

[31] Y Z, J H, L X. Family history of hepatocellulcar carcinoma is not associated with its patients' prognosis after hepatectomy. World Journal of Surgical Oncology 2013;11.

[32] Melvin JC, Wulaningsih W, Hana Z, Purushotham AD, Pinder SE, Fentiman I, et al. Family history of breast cancer and its association with disease severity and mortality. Cancer Med 2016;5:942-949.

[33] Williams KP, Reiter P, Mabiso A, Maurer J, Paskett E. Family history of cancer predicts Papanicolaou screening behavior for African American and white women. Cancer 2009;115:179-189.

[34] Wallner LP, Sarma AV, Lieber MM, St Sauver JL, Jacobson DJ, McGree ME, et al. Psychosocial factors associated with an increased frequency of prostate cancer screening in men ages 40 to 79 years: the Olmsted County study. Cancer Epidemiol Biomarkers Prev 2008;17:3588-3592.

[35] Tracy KA, Quillin JM, Wilson DB, Borzelleca J, Jones RM, McClish D, et al. The impact of family history of breast cancer and cancer death on women's mammography practices and beliefs. Genetics in Medicine 2008;10:621-625.

[36] Dragani TA. Risk of HCC: Genetic heterogeneity and complex genetics. Journal of Hepatology 2010;52:252-257.

[37] Sampson JN, Wheeler WA, Yeager M, Panagiotou O, Wang Z, Berndt SI, et al. Analysis of Heritability and Shared Heritability Based on Genome-Wide Association Studies for Thirteen Cancer Types. J Natl Cancer Inst 2015;107:djv279.

[38] Humpel N, Magee C, Jones SC. The impact of a cancer diagnosis on the health behaviors of cancer survivors and their family and friends. Support Care Cancer 2007;15:621-630.

[39]   Patterson F, Wileyto EP, Segal J, Kurz J, Glanz K, Hanlon A. Intention to quit smoking: role of personal and family member cancer diagnosis. Health Educ Res 2010;25:792-802.

[40]   Hamed MA, Ali SA. Non-viral factors contributing to hepatocellular carcinoma. World Journal of Hepatology 2013;5:311-322.

[41]   Hawley ST, Griggs JJ, Hamilton AS, Graff JJ, Janz NK, Morrow M, et al. Decision involvement and receipt of mastectomy among racially and ethnically diverse breast cancer patients. Journal of the National Cancer Institute 2009;101:1337-1347.

[42]   Vornanen M, Konttinen H, Kaariainen H, Mannisto S, Salomaa V, Perola M, et al. Family history and perceived risk of diabetes, cardiovascular disease, cancer, and depression. Prev Med 2016;90:177-183.

[43]   Kerber RA, Slattery ML. Comparison of self-reported and database-linked family history of cancer data in a case-control study. Am J Epidemiol 1997;146:244-248.

[44]   Aitken J, Bain C, Ward M, Siskind V, MacLennan R. How accurate is self-reported family history of colorectal cancer? Am J Epidemiol 1995;141:863-871.

[45]   Fiederling J, Shams AZ, Haug U. Validity of self-reported family history of cancer: A systematic literature review on selected cancers. Int J Cancer 2016;139:1449-1460.

[46]   Mai PL, Garceau AO, Graubard BI, Dunn M, McNeel TS, Gonsalves L, et al. Confirmation of family cancer history reported in a population-based survey. J Natl Cancer Inst 2011;103:788-797.

[47]   Hebert-Croteau N, Brisson J, Lemaire J, Latreille J, Pineault R. Investigating the correlation between hospital of primary treatment and the survival of women with breast cancer. Cancer 2005;104:1343-1348.

국문요약

배경 및 목적 : 간세포암종(HCC) 가족력은 HCC의 위험 인자이자 흔한 특징이다. 본 연구는 처음으로 HCC 진단을 받은 환자의 생존율에 HCC 가족력이 어떤 영향을 미치는지 알아보고자 하였다.

방법 : 서울아산병원에 등록된 환자를 기반으로 한 본 코호트 연구는 처음으로 HCC 진단을 받은 5,484명의 환자를 대상으로 하였다. 숙련된 간호사가 인터뷰를 통해 암의 개별 가족 병력을 얻었으며, 3세대 가계도를 구축하였다. 다른 잠재적인 예측인자를 보정한 후, HCC 1촌 가족력이 있는 환자군과 없는 환자군을 비교하여 전체 생존 자료를 분석하였다.

결과 : 처음으로 HCC 진단을 받은 5,484명의 환자 중 845명(15.4%)이 HCC 1촌 가족력이 있었으며, HCC 가족력은 전체 코호트에서 더 높은 생존과 관련이 있었다(Hazard Ratio[HR] 0.89, 95% 신뢰 구간[CI] 0.80-0.98, p=0.025). HCC 병력을 가진 가족 수의 증가는 HCC로 인한 사망 위험을 유의하게 감소시키는 경향이 있는 것으로 관찰되었다(p for trend=0.018). 병기 분류 분석은 가족 병력의 존재가 (극)초기 병기 HCC 환자의 사망 위험 감소와 관련이 있음을 보여주었다(adjusted HR 0.83, 95% CI 0.69-0.99; p=0.042). 완치 진단을 받은 환자의 비율도 가족력이 있는 초기 병기 환자에게서 더 높았다 (72.6% vs. 63.3%; p<0.001).

결론 : HCC 1촌 가족력은 HCC 환자, 특히 근본적인 방법으로 치료할 수 있는 낮은 병기 환자의 생존율을 향상시키는 예후 인자이다.