Risk Factors for Hepatocellular Carcinoma by Age, Sex, and Liver Disorder Status: A Prospective Cohort Study in Korea

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BACKGROUND: To the authors’ knowledge, relatively little is known regarding the interaction of risk factors for hepatocellular carcinoma (HCC) with age, sex, and liver disorder status. METHODS: The authors followed 504,646 Korean patients aged 40 to 80 years who underwent routine health checkups between 2002 and 2003 until 2013 via linkage to national hospital discharge records. RESULTS: HCC occurred in 2744 individuals. In the sex-adjusted and age-adjusted analysis, cirrhosis increased the incidence of HCC by 42-fold, followed by hepatitis B virus (21-fold), hepatitis C virus (HCV; 19-fold), male sex (4.3-fold), and each 5-year age increment (1.24-fold). In the multivariable adjusted analysis, diabetes increased the risk of HCC by 80%, alcohol consumption ≥80 g/day increased the risk by 75%, alcohol consumption of 40 to 79 g/day increased the risk by 37%, and being a current smoker increased the risk by 25%. The multivariable adjusted hazard ratios of male sex and HCV were 6.27 and 5.72, respectively, at age <50 years, but were 2.09 and 22.51, respectively, at age ≥70 years. Each 20 g/day of alcohol consumption increased the risk of HCC by 6% (P = .11), 8% (P = .02), 16% (P < .001), and 30% (P < .001), respectively, in individuals aged <50 years, 50 to 59 years, 60 to 69 years, and 70 to 80 years. In individuals without a liver disorder, body mass index was found to be positively associated with HCC, whereas patients with a liver disorder demonstrated an inverse association. Women had higher adjusted hazard ratios associated with age and cirrhosis compared with men. CONCLUSIONS: With advancing age, the effects of alcohol use and HCV on the development of HCC become stronger, whereas the effect of male sex weakens. Lifetime moderate alcohol consumption may cause HCC in the elderly. Smoking increases the risk of HCC irrespective of viral hepatitis, and diabetes increases the risk of HCC independent of cirrhosis. Cancer 2018;124:2748-57. © 2018 American Cancer Society.

KEYWORDS: alcohol consumption, cirrhosis, hepatocellular carcinoma (HCC), liver cancer, viral hepatitis.

INTRODUCTION

Primary liver cancer, approximately 80% to 90% of which is accounted for by hepatocellular carcinoma (HCC), constituted 5.6% of cancer incidence and 9.1% of cancer-related deaths globally in 2012.1 The crude and age-standardized incidence of primary liver cancer in 2013 was 54.6 per 100,000 population and 34.0 per 100,000 population, respectively, in Korea.2 Cirrhosis, hepatitis B virus (HBV), and hepatitis C virus (HCV) infections are the most established risk factors for the development of HCC. Many health professionals consider alcohol use, smoking, and diabetes to be risk factors. However, some uncertainties remain. For example, according to a recent systematic review, it is unclear whether moderate alcohol use increases HCC risk.3 Although diabetes is suggested to be the most important risk factor for HCC in terms of population-attributable risk in the United States,4 considering the possibility of reverse causality, the question of whether diabetes increases the risk of HCC independently of cirrhosis has not been definitively answered.5,6 Despite strong sexual dimorphism and an age effect,7,8 relatively few studies to date have examined these associations by age and sex. It is unclear whether the impact of potential risk factors on the incidence of HCC differs in individuals with and without a prevalent liver disorder.

In the current prospective cohort study, we identified HCC incidence according to risk factors. We then examined the associations between potential risk factors and HCC and studied whether the associations differed by age, sex, or liver disorder status.9-11

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MATERIALS AND METHODS

Study Population and Follow-Up
Approximately 97% of Korean citizens are insured through the National Health Insurance Service (NHIS). The study cohort (514,795 individuals) was a random sample of approximately 10% of the 5.15 million NHIS beneficiaries aged 40 to 79 years in 2002 who received a health examination in 2002 or 2003. From this sample, 8458 individuals with preexisting cancer were excluded, as were 1691 subjects for whom information regarding alanine aminotransferase (ALT), aspartate aminotransferase (AST), and cardiometabolic factors (including fasting glucose and body mass index [BMI]) was missing. We followed the remaining 504,646 individuals until December 31, 2013 via record linkage to hospital discharge records from the NHIS (Fig. 1), in which certified health information managers review the medical records and assign standardized diagnosis codes. The completeness of the cancer incidence data from the NHIS is comparable to that of the Korea National Cancer Incidence Database, which was estimated to be 97.8%. All patients discharged from the hospital due to HCC (International Statistical Classification of Diseases and Related Health Problems, 10th revision [ICD-10] code C220) for the first time were considered as incident cases. According to Korean law, the NHIS can provide these routinely collected data without specific informed consent from the participants. We were granted access to the anonymized data by the NHIS. This study was approved by the institutional review board of Catholic Kwandong University.

Data Collection
Data were collected at the time of baseline health examinations from 2002 through 2003 through measurements and a questionnaire (Fig. 1). ALT and AST were measured using the nicotinamide adenine dinucleotide-ultraviolet (NADH-UV) absorption method or the Reitman-Frankel method. Fasting serum glucose was assayed using enzymatic methods. Blood pressure was measured using a standard mercury sphygmomanometer. BMI was calculated as the measured weight divided by the square of measured height (kg/m²). Smoking status, alcohol use, and history of cancer were assessed via a questionnaire. Individuals with a self-reported history of cancer or those who visited a medical institution for any cancer before the baseline health examination were considered to be individuals with a preexisting cancer. The health examinations and data collection followed a standard protocol documented by the government.

The data collection methods for smoking and alcohol use are described in more detail in the Supporting Information. Alcohol consumption was estimated using methods similar to our previous study. Alcohol consumption frequency was categorized into 4 groups for analysis: almost daily, 3 to 4 days per week, 2 days per month to 2 days per week (2-3/month and 1-2/week combined), none, and missing data. The alcohol use amount (g of ethanol/day) was classified into 4 to 5 groups: none, <10, 10 to 39, ≥40 (40-79, ≥80), and missing data.

Medical Risk Factors at Baseline
We considered individuals to have prevalent disease at baseline if they visited a medical institution for the diagnosed diseases at least once within 6 months before or 2 months after the baseline health examination date. The medical risk factors for HCC were selected using the following ICD-10 codes: B15 to B19 (viral hepatitis); B16, B180, and B181 (HBV infection); B171 and B182 (HCV infection); E10 to E14 (diabetes); K70 to K76 (nonviral liver disease); K70 (alcoholic liver disease [ALD]); K74 (cirrhosis); and K758 and K760 (nonalcoholic fatty liver disease [NAFLD] and nonalcoholic steatohepatitis [NASH]).

Statistical Analysis
Smoking status was categorized as never, former, or current smoker (<1 pack/day or ≥1 pack/day) and missing data. Diabetes status was categorized as normoglycemia (fasting glucose <100 mg/dL), impaired fasting glucose (100-125 mg/dL), and diabetes (≥126 mg/dL or prevalent diabetes). The fasting glucose level also was analyzed as a continuous variable (per increase of 18 mg/dL [1.0 mmol/L]) to test a dose-risk relationship in the range of 90 to 299 mg/dL. BMI was categorized as <18.5, 18.5 to 24.9, 25 to 29.9, and ≥30 kg/m², and also was analyzed as a continuous variable (per 5-kg/m² increase).

The hazard ratios (HRs) for HCC incidence were calculated using Cox proportional hazards models stratified by age at baseline (40-44 years, 45-54 years, 55-64 years, 65-74 years, and 75-80 years). The multivariable analysis was adjusted for age at baseline (continuous variable; per 5 years older age), sex, smoking status, alcohol use, diabetes status, BMI, physical activity (at least once a week; yes or no), income status (deciles; <4 [low income], 4-7, and 8-10 [high income]), HBV infection, HCV infection, and cirrhosis. Variables in the same category (such as alcohol use frequency categories and increments of 20 g of ethanol/day) were not simultaneously included in the analysis.

A stratified analysis by age, sex, and liver disorder status was performed. Individuals with viral hepatitis, nonviral liver disease, an ALT level ≥40 IU/L, or an AST level ≥40 IU/L were termed the “liver disorder group,”
and individuals with no known liver disease, an ALT level < 40 IU/L, and an AST level < 40 IU/L were termed the “normal liver group” and were analyzed separately.

Formal interaction tests used an inverse-variance weighted average method. The 95% confidence intervals (95% CIs) of HCC incidence were calculated using the Wilson score method. All P values were 2-sided. All analyses were performed using SAS statistical software (version 9.4; SAS Institute Inc, Cary, North Carolina).

RESULTS

General Characteristics
During the mean 10.5 years of follow-up of 504,646 individuals (45.7% of whom were women) with a mean age of 53.0 years (±9.7 years), 2744 individuals were diagnosed with HCC. The individuals who developed HCC during follow-up tended to be older at baseline, men, current smokers, heavy alcohol users, low-income earners, and diabetics (Table 1). The crude incidence of HCC per 100,000 person-years was 52 (95% CI, 50-54) in all participants, 20 in women, 78 in men, 103 in individuals with diabetes, 19 in those with normal ALT and AST levels, and 231 in individuals with abnormal ALT or AST levels (see Supporting Table S1). The annual HCC incidence (per 100 person-years) was 2.6%, 1.0%, and 1.1%, respectively, in individuals with cirrhosis (1024 individuals), HBV infection (2627 individuals), and HCV infection (495 individuals) at baseline.

Risk Factors and HCC
In the sex-adjusted and age-adjusted analysis, comorbid cirrhosis increased the risk of HCC most strongly (42-
Comorbid liver disease
Diabetes status
BMI, kg/m²
Physical activity
Smoking status
Alcohol use, g ethanol/d
Cancer

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Table 1. Study Population Characteristics and HRs for HCC

| Variable/Group | Total Cohort | HCC Cases | Adjusted for Sex and Age | Multivariable Adjusted |
|----------------|-------------|-----------|--------------------------|-----------------------|
|                | N = 504,646 | n = 2744   | P^ | HR | 95% CI  | P | HR | 95% CI  |
| Age, y         |             |           |   |    |         |   |    |         |
| Per 5-7 older  | 53.0 ± 9.7  | 56.0 ± 9.4 | <.001 | 1.24 | 1.16-1.33 | <.001 | 1.25 | 1.17-1.34 |
| Sex            |             |           |   |    |         |   |    |         |
| Men vs women   |             |           |   |    |         |   |    |         |
| Never smoker   | 274,265 (54.3) | 2259 (82.3) | <.001 | 4.30 | 3.90-4.75 | <.001 | 3.67 | 3.28-4.11 |
| Former smoker  | 42,813 (8.5)  | 313 (11.4)  | .671 | 1.03 | 0.90-1.17 | .590  | 1.04 | 0.91-1.18 |
| Current smoker | 117,215 (23.2) | 983 (35.8)  | <.001 | 1.26 | 1.15-1.38 | <.001 | 1.25 | 1.14-1.38 |
| Missing data   | 21,362 (4.2)  | 120 (4.4)   | .511 | 1.06 | 0.88-1.29 | .375  | 0.91 | 0.73-1.13 |
| Alcohol use, g ethanol/d |     |           |   |    |         |   |    |         |
| None           | 278,925 (55.3) | 1251 (45.6) | <.001 | 1.00 | Reference | 1.00 | Reference |
| <10            | 100,871 (20.0) | 521 (19.0)  | <.001 | 0.83 | 0.75-0.93 | .080  | 0.91 | 0.82-1.01 |
| 10-39          | 89,039 (17.6) | 622 (22.7)  | .270 | 0.94 | 0.85-1.05 | .491  | 1.04 | 0.93-1.16 |
| ≥40            | 24,120 (4.8)  | 279 (10.2)  | <.001 | 1.43 | 1.25-1.64 | <.001 | 1.46 | 1.27-1.68 |
| Missing data   | 11,691 (2.3)  | 71 (2.6)    | .181 | 1.18 | 0.93-1.50 | .102  | 1.26 | 0.96-1.66 |
| Physical activity |             |           |   |    |         |   |    |         |
| None           | 297,094 (58.9) | 1612 (58.7) | .894 | 1.15 | 1.07-1.25 | .013  | 1.10 | 1.02-1.19 |
| Income status, decile |     |           |   |    |         |   |    |         |
| <4 (low income)| 116,187 (23.0) | 708 (25.8)  | <.001 | 1.35 | 1.22-1.48 | <.001 | 1.33 | 1.21-1.47 |
| ≥4-7           | 164,450 (32.6) | 943 (34.4)  | <.001 | 1.20 | 1.10-1.31 | <.001 | 1.16 | 1.06-1.27 |
| >7 (high income)| 224,009 (44.4) | 1093 (39.8) | 1.00 | Reference | 1.00 | Reference |
| BMI, kg/m²     |             |           |   |    |         |   |    |         |
| <18.5          | 11,494 (2.3)  | 70 (2.6)    | .811 | .700 | 1.05 | 0.82-1.33 | .793  | 1.03 | 0.81-1.31 |
| 18.5-24.9      | 315,741 (62.6) | 1714 (62.5) | 1.00 | Reference | 1.00 | Reference |
| 25-29.9        | 162,884 (32.3) | 880 (32.1)  | .567 | .98 | 0.90-1.06 | .837  | 0.99 | 0.91-1.08 |
| ≥30            | 14,527 (2.9)  | 80 (2.9)    | .068 | 1.23 | 0.98-1.54 | .175  | 1.17 | 0.93-1.46 |
| Diabetes status|             |           |   |    |         |   |    |         |
| Normoglycemia  | 339,160 (67.2) | 1548 (56.4) | <.001 | 1.00 | Reference | 1.00 | Reference |
| Impaired fasting glucose |     |           |   |    |         |   |    |         |
| Diabetes       | 52,076 (10.3) | 545 (19.9)  | <.001 | 1.82 | 1.65-2.01 | <.001 | 1.80 | 1.63-1.99 |
| Comorbid liver disease |     |           |   |    |         |   |    |         |
| Any viral hepatitis | 4,529 (0.9) | 362 (13.2)  | <.001 | 17.37 | 15.54-19.40 | <.001 | 6.82 | 5.26-8.84 |
| Hepatitis B virus infection | 2,627 (0.5) | 255 (9.3)   | <.001 | 20.90 | 18.36-23.79 | <.001 | 11.98 | 10.36-13.87 |
| Hepatitis C virus infection | 495 (0.1) | 55 (2.0)    | <.001 | 18.45 | 14.89-25.41 | <.001 | 9.02 | 6.87-11.85 |
| Nonviral liver disease | 14,039 (2.8) | 493 (18.0)  | <.001 | 6.89 | 6.25-7.60 | <.001 | 3.33 | 2.93-3.79 |
| Cirrhosis      | 1,024 (0.2)  | 215 (7.8)   | <.001 | 41.98 | 36.50-48.28 | <.001 | 18.56 | 15.83-21.76 |
| Alcoholic liver disease | 2,815 (0.6) | 76 (2.8)    | <.001 | 3.65 | 2.91-4.59 | <.001 | 1.82 | 1.43-2.30 |
| NASH/NAFLD     | 1,987 (0.4)  | 16 (0.6)    | .112 | .160 | 1.42 | 0.87-2.32 | .222  | 0.73 | 0.44-1.21 |

Abbreviations: 95% CI, 95% confidence interval; BMI, body mass index; HCC, hepatocellular carcinoma; HR, hazard ratio; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis.

Data were expressed as the mean (± standard deviation), number (%), or HR (95% CI).

*Adjustment for age at baseline, sex, smoking status, alcohol use, physical activity, income status, BMI, diabetes status, cirrhosis, and hepatitis B virus and hepatitis C virus infection.

*Analysis of variance test was used for age and the chi-square test was used for other variables.

fold), followed by HBV (21-fold) and HCV (19-fold) infection (Table 1). Male sex (4.3-fold) and older age (1.24-fold per 5-year older age) were found to be associated with higher risk of HCC, as well as physical inactivity and low economic status. Impaired fasting glucose and diabetes at baseline were associated with elevated risk (by 10% and 82%, respectively) (Table 1), and a dose-risk relation was observed between fasting glucose and HCC (Table 2). In the sex-adjusted and age-adjusted analysis, current smoker status (26% increased risk), alcohol intake ≥40 g/day (43%) (especially ≥80 g/day [86%]), and alcohol use frequency ≥5 times/week (45%) were associated with a greater HCC risk compared with never smokers and nondrinkers. Each increase of 20 g/day in alcohol intake was associated with a 12% higher risk of HCC.

In the multivariable adjusted analysis including HBV and HCV infections and cirrhosis, the estimated relative risks modestly changed for each risk factor, with the exception of liver disease-related factors, for which the HRs were halved (Tables 1 and 2).

Analysis According to Age, Sex, and Liver Disorder

The multivariable adjusted HRs associated with men, in comparison with women, decreased with age (6.27 vs 2.09 in those aged <50 years vs ≥70 years), whereas the
HRs associated with HCV infection (5.40 vs 22.51 in individuals aged <50 years vs ≥70 years) and alcohol use (1.15 vs 2.45 in those aged <50 years vs ≥70 years who drank ≥40 g/day) increased with age (Table 3). After excluding cirrhosis and other viral hepatitis, the multivariable adjusted HRs of HCV infection were 11.3, 18.1, 25.3, and 75.2, respectively, in the patients aged <50 years, 50 to 59 years, 60 to 69 years, and ≥70 years. Current smoking status and diabetes generally were associated with higher HCC risk across age groups (see Supporting Table S2).

In the alcohol analyses by age group, intake of ≥80 g/day was associated with a higher HCC risk in individuals aged <60 years (HR, 1.46; 95% CI, 1.08-1.98), whereas the categories of alcohol intake of ≥10 g/day demonstrated such associations in those aged ≥70 years. The HRs for each 20 g/day of alcohol consumption were 1.06 (P = .11), 1.08 (P = .02), 1.16 (P < .001), and 1.30 (P < .001), respectively, in individuals aged <50 years, 50 to 59 years, 60 to 69 years, and 70 to 80 years. Each 40-g alcohol consumption/drinking day was associated with a 10% and 42% higher risk of HCC, respectively, in individuals aged 60 to 69 years and 70 to 80 years.

In the sex-stratified analysis, women were found to have higher HRs associated with age and cirrhosis compared with men. Although the HR of high alcohol consumption for HCC was found to be greater than unity only in men, formal interaction tests revealed no statistical difference in the HRs of variables related to alcohol use (Table 4) (see Supporting Table S3).

Subjects with no liver disease were found to have higher HRs associated with age and male sex than liver disorder group (1.43 vs 1.22 per each 5-year older age; 3.77 vs 2.19 in men vs women) (Table 5). In the normal

### Table 2. Additional Alcohol-Related, Smoking-Related, and Metabolic Factors and HRs for HCC

| Variable/Group | Total Cohort | HCC Cases | Adjusted for Sex and Age | Multivariable Adjusteda |
|----------------|--------------|-----------|--------------------------|-------------------------|
|                | N = 504,646  | n = 2744   | Pd                        |                         |
| Smoking status |              |           | P  | HR  | 95% CI  | P  | HR  | 95% CI  |
| Never smoker   | 323,256 (64.1) | 1328 (48.4) | <.001 | 1.00 | Reference | 1.00 | Reference |
| Former smoker  | 42,813 (8.5)  | 313 (11.4)  | .691  | 1.03 | 0.90-1.17 | .516 | 1.04 | 0.92-1.19 |
| Moderate smoker, <1 pack/d | 91,484 (18.1) | 830 (30.2)  | <.001 | 1.35 | 1.23-1.48 | <.001 | 1.36 | 1.24-1.50 |
| Heavy smoker, ≥1 pack/d | 25,731 (5.1)  | 153 (5.6)   | .981  | 0.93 | 0.78-1.10 | .179 | 0.89 | 0.74-1.06 |
| Missing data   | 21,362 (4.2)  | 120 (4.4)   |           |             |           |             |           |
| Alcohol use, frequency | | | | | | | |
| None           | 278,925 (55.3) | 1251 (45.6) | <.001 | 1.00 | Reference | 1.00 | Reference |
| 2/mo to 2/wk   | 158,821 (31.5) | 882 (32.1)  | <.001 | 0.85 | 0.78-0.94 | .166 | 0.94 | 0.85-1.03 |
| 3-4 times/wk   | 35,279 (7.0)  | 276 (10.1)  | <.001 | 1.01 | 0.88-1.15 | .194 | 1.10 | 0.95-1.26 |
| Almost daily    | 22,120 (4.4)  | 284 (10.3)  | <.001 | 1.45 | 1.27-1.66 | <.001 | 1.49 | 1.30-1.71 |
| Missing data   | 9501 (1.9)    | 51 (1.9)    |           |             |           |           |           |
| Alcohol use, g ethanol/d | | | | | | | |
| None           | 278,925 (55.3) | 1251 (45.6) | <.001 | 1.00 | Reference | 1.00 | Reference |
| <10            | 100,871 (20.0) | 521 (19.0)  | <.001 | 0.83 | 0.75-0.93 | .078 | 0.91 | 0.82-1.01 |
| 10-39          | 89,039 (17.6) | 622 (22.7)  | <.001 | 0.94 | 0.85-1.05 | .497 | 1.04 | 0.93-1.15 |
| 40-79          | 18,934 (3.8)  | 199 (7.3)   | <.001 | 1.31 | 1.12-1.52 | <.001 | 1.37 | 1.17-1.61 |
| ≥80            | 5186 (1.0)    | 80 (2.9)    | <.001 | 1.86 | 1.48-2.34 | <.001 | 1.75 | 1.38-2.20 |
| Missing data   | 11,691 (2.3)  | 71 (2.6)    |           |             |           |           |           |
| Heavy alcohol use | | | | | | | |
| ≥80 g ethanol/d vs <80 | 5186 (1.0) | 80 (2.9) | <.001 | 1.94 | 1.55-2.42 | <.001 | 1.71 | 1.37-2.14 |
| Alcohol use 2 | 492,955 (100.0) | 2673 (100.0) | <.001 | 1.12 | 1.08-1.15 | <.001 | 1.12 | 1.08-1.15 |
| Per 20 g/d increase | 492,955 (100.0) | 2673 (100.0) | <.001 | 1.26 | 0.94-1.65 | <.001 | 1.04 | 0.74-1.47 |
| Per 40 g/drinking d increase | 492,955 (100.0) | 2673 (100.0) | .096 | 1.04 | 0.99-1.08 | .004 | 1.06 | 1.02-1.11 |
| Fasting glucose 2 | 285,127 (100.0) | 1716 (100.0) | <.001 | 1.12 | 1.09-1.14 | <.001 | 1.12 | 1.09-1.14 |
| BMI 2 | 504,646 (100.0) | 2744 (100.0) | .986 | 1.00 | 0.94-1.07 | .694 | 1.01 | 0.95-1.08 |

Abbreviations: 95% CI, 95% confidence interval; BMI, body mass index; HCC, hepatocellular carcinoma; HR, hazard ratio.
Data were expressed as the number (%), or HR (95% CI).
Variables of the same category (such as alcohol use frequency and alcohol use in g ethanol/day) were not mutually adjusted for in the multivariable analysis.
aAdjustment for age at baseline, sex, smoking status, alcohol use, physical activity, income status, BMI, diabetes status, cirrhosis, and hepatitis B virus and hepatitis C virus infection.
bChi-square test.
cMissing data regarding alcohol use were excluded.
dAnalysis was restricted to 90 to 299 mg/dL.
TABLE 3. HRs[^3] for HCC Incidence According to Age Group

| Variable                      | 40 to 49 Years | 50 to 59 Years | 60 to 69 Years | 70 to 80 Years | P^interaction |
|-------------------------------|----------------|----------------|----------------|----------------|---------------|
| Age Group                    |                |                |                |                |               |
|                               | No. of Cases   | HR  95% CI     | No. of Cases   | HR  95% CI     | No. of Cases   | HR  95% CI     | No. of Cases   | HR  95% CI     |               |
| Sex                           | Men vs. women  | 719 6.27 4.77-8.23 | 750 3.57 2.92-4.37 | 603 3.25 2.69-3.94 | 187 2.09 1.54-2.83 | <.001 |
| Alcohol use, g ethanol/d      | None           | 285 1.00 Reference    | 384 1.00 Reference    | 430 1.00 Reference    | 152 1.00 Reference    |               |
|                               | <10            | 183 0.91 0.75-1.10 | 198 0.98 0.82-1.18 | 99 0.71 0.57-0.89 | 41 1.24 0.86-1.79 | .043 |
|                               | ≥40            | 75 1.15 0.88-1.51 | 82 1.18 0.92-1.52 | 96 1.98 1.56-2.51 | 26 2.45 1.56-3.85 | <.001 |
|                               | ≥80            | 20 1.46 0.92-2.33 | 27 1.46 0.98-2.19 | 23 1.86 1.21-2.85 | 10 4.36 2.24-8.46 | .035 |
|                               | Missing data   | 18 20 | 22 | 11 |               |
| Alcohol use, frequency        | None           | 285 1.00 Reference    | 384 1.00 Reference    | 430 1.00 Reference    | 152 1.00 Reference    |               |
|                               | 2/mo to 2/wk   | 346 0.92 0.77-1.09 | 322 0.96 0.82-1.13 | 158 0.80 0.66-0.97 | 56 1.40 1.01-1.95 | .039 |
|                               | 3-4/wk         | 95 1.05 0.82-1.34 | 104 1.19 0.95-1.50 | 53 0.82 0.61-1.10 | 24 2.08 1.32-3.29 | .008 |
|                               | Almost daily    | 48 1.20 0.88-1.65 | 75 1.21 0.93-1.57 | 125 1.91 1.54-2.37 | 36 1.79 1.20-2.66 | .019 |
|                               | Missing data   | 15 17 | 16 | 3 |               |
| Alcohol use[^b]               | Per 20 g/d     | 771 1.06 0.99-1.13 | 882 1.08 1.01-1.14 | 760 1.16 1.09-1.23 | 260 1.30 1.18-1.43 | .002 |
| Alcohol use[^b]               | Per 40 g/drinking d | 771 0.99 0.92-1.06 | 882 1.05 0.98-1.13 | 760 1.10 1.01-1.21 | 260 1.45 1.24-1.69 | <.001 |
| Comorbidity                   | HCV infection  | 6 5.72 2.55-12.84 | 13 5.40 3.06-9.51 | 22 11.43 7.37-17.72 | 14 22.51 12.29-41.3 | .003 |

Abbreviations: 95% CI, 95% confidence interval; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HR, hazard ratio; P^interaction, P value for interaction test between age groups.

Results including variables with a P^interaction ≥ .05 are presented in Supporting Table S2.

[^3]: Adjustment for age at baseline, sex, smoking status, alcohol use, physical activity, income status, body mass index, diabetes status, cirrhosis, and hepatitis B virus and HCV infection.
[^b]: Missing data regarding alcohol use were excluded.
### TABLE 4. HRs\(^a\) for HCC Incidence According to Sex

| Variable          | Group                  | Men N = 274,265 | N | P   | HR   | 95% CI        | P   | HR    | 95% CI        | Pinteraction |
|-------------------|------------------------|-----------------|---|-----|------|--------------|-----|-------|--------------|--------------|
| Age, y            | Per 5-y older          | 2259            | .001 | .012 | 1.20 | 1.11-1.30    |     | 485   | .001 | 1.47 | 1.24-1.73 | .034         |
| Comorbidity       | Cirrhosis              | 169             | .001 | 15.62| 13.85-19.70 |     | 46    | .001 | 36.22 | 24.87-52.75 | <.001        |
| BMI Per 5 kg/m\(^2\) increase | 2259                  | .298            | .96  | .89-1.04 |   | 485   | .028 | 1.17  | 1.02-1.34 | .015         |

Abbreviations: 95% CI, 95% confidence interval; BMI, body mass index; HCC, hepatocellular carcinoma; HR, hazard ratio; P\(_{interaction}\), P value for interaction test between sex groups.

Results including variables with a P\(_{interaction}\) ≥ .05 are presented in Supporting Table S3.

\(a\) Adjustment for age at baseline, sex, smoking status, alcohol use, physical activity, income status, BMI, diabetes status, cirrhosis, and hepatitis B virus and hepatitis C virus infection.

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### TABLE 5. HRs\(^a\) for HCC Incidence According to Liver Disorder Status

| Variable          | Group                  | Normal Liver Group N = 415,461 | N | P   | HR   | 95% CI        | P   | HR    | 95% CI        | Pinteraction |
|-------------------|------------------------|--------------------------------|---|-----|------|--------------|-----|-------|--------------|--------------|
| Age, y            | Per 5-y older          | 702                           | .015 | .043 | 1.43 | 1.25-1.64    |     | 2042  | .001 | 1.22 | 1.12-1.32 | .046         |
| Sex               | Men vs. women          | 552                           | .001 | 3.77 | 3.06-4.85 |     | 1707  | .001 | 2.19 | 1.92-2.50 | <.001        |
| Alcohol use, frequency | None                  | 323                           | 1.00 | Reference |     | 928   | 1.00 | Reference |     | 269   | <.001 | 1.22 | 1.12-1.32 | .046         |
| Alcohol use, alcohol use, g ethanol/d | 2/mo to 2/wk | 246 | .497 | 1.07 | 0.89-1.28 |   | 636   | .005 | 0.85 | 0.76-0.95 | .042         |
| Alcohol use, alcohol use, g ethanol/d | 3-4 times/wk | 60 | .971 | 1.01 | 0.75-1.34 |   | 216   | .175 | 0.90 | 0.76-1.05 | .495         |
| Alcohol use, alcohol use, g ethanol/d | Almost daily | 60 | .021 | 1.40 | 1.05-1.87 |   | 224   | .660 | 0.97 | 0.82-1.13 | .025         |
| Alcohol use, alcohol use, g ethanol/d | Missing data | 13 | .520 | 1.23 | 0.65-2.34 |   | 38    | .787 | 1.05 | 0.72-1.53 | .675         |
| Alcohol use, alcohol use, g ethanol/d | ≥80 | 17 | .009 | 1.91 | 1.18-3.10 |   | 64    | .769 | 1.04 | 0.81-1.34 | .028         |
| Comorbidity       | Viral hepatitis        | 362                           | .015 | .215 | 1.67-2.77 |     | 255   | .001 | 4.41 | 3.85-5.07 | .001         |
| Comorbidity       | HBV infection          | 55                            | .001 | 3.75 | 2.86-4.92 |     | 55    | .001 | 3.75 | 2.86-4.92 | .001         |
| Comorbidity       | HCV infection          | 493                           | .740 | 1.02 | 0.90-1.16 |     | 493   | .740 | 1.02 | 0.90-1.16 | .001         |
| Comorbidity       | Nonviral liver disease | 215                           | .001 | 8.17 | 7.05-9.48 |     | 215   | .001 | 8.17 | 7.05-9.48 | .001         |
| Comorbidity       | Cirrhosis              | 76                            | .311 | 0.99 | 0.70-1.12 |     | 76    | .311 | 0.99 | 0.70-1.12 | .001         |
| Comorbidity       | Alcoholic liver disease | 16                           | .001 | 0.37 | 0.22-0.60 |   | 16    | .001 | 0.37 | 0.22-0.60 | .001         |
| BMI, kg/m\(^2\)  | <18.5                  | 18                            | .811 | 0.94 | 0.59-1.52 |   | 52    | .772 | 1.04 | 0.79-1.38 | .724         |
| BMI, kg/m\(^2\)  | 18.5-24.9              | 436                           | 1.00 | Reference |     | 1278  | 1.00 | Reference |     | 1278  | 1.00 | Reference |     |
| BMI, kg/m\(^2\)  | 25-29.9                | 234                           | .033 | 1.19 | 1.01-1.40 |   | 646   | .001 | 0.67 | 0.61-0.73 | .001         |
| BMI, kg/m\(^2\)  | ≥30                    | 14                            | .636 | 1.14 | 0.67-1.94 |   | 66    | .001 | 0.61 | 0.48-0.79 | .040         |
| BMI Per 5-kg/m\(^2\) increase | 702                    | .014 | 1.17 | 1.03-1.32 |   | 2042  | .001 | 0.70 | 0.65-0.76 | .001         |
| In men            | Per 5-kg/m\(^2\) increase | 552              | .011 | 1.19 | 1.04-1.37 |   | 1707  | .001 | 0.66 | 0.61-0.72 | <.001        |
| In women          | Per 5-kg/m\(^2\) increase | 150              | .530 | 1.09 | 0.84-1.40 |   | 335   | .061 | 0.85 | 0.72-1.01 | .122         |
| In those with cirrhosis or viral hepatitis | BMI Per 5-kg/m\(^2\) increase | 517       | .484 | 1.06 | 0.91-1.23 |   | 517   | .484 | 1.06 | 0.91-1.23 | .001         |

Abbreviations: 95% CI, 95% confidence interval; BMI, body mass index; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HR, hazard ratio; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; P\(_{interaction}\), P value for interaction test between liver disorder status groups.

Results including variables with P\(_{interaction}\) ≥ .05 are presented in Supporting Table S4.

\(a\) Adjustment for age at baseline, sex, smoking status, alcohol use, physical activity, income status, BMI, diabetes status, cirrhosis, and hepatitis B virus and hepatitis C virus infection.
liver group, BMI was found to have positive associations with HCC, whereas an inverse association was found in those with a liver disorder, especially in men or in those who had a liver disorder other than cirrhosis or viral hepatitis (Table 5) (see Supporting Table S4). Heavy alcohol consumption (≥80 g/day) was associated with a higher risk in the normal liver group, but not in the liver disorder group. Cirrhosis and viral hepatitis, but not ALD and NASH/NAFLD, were associated with a further excess risk of HCC in the liver disorder group. In both groups, current smoker status and diabetes were associated with a higher risk of HCC (see Supporting Table S4).

DISCUSSION
The incidence of HCC per 100,000 person-years was 52 in the current study participants, which is more than 2-fold higher than the corresponding incidence in Asian-American individuals in the United States. With advancing age, the effects of alcohol use and HCV in the development of HCC became stronger, whereas the effect of male sex weakened. Alcohol use of ≥40 g/day was associated with an increased risk of HCC in all participants, whereas alcohol use of 10 to 39 g/day as well as ≥40 g/day was associated with higher risk in the elderly aged ≥70 years. Smoking and diabetes were associated with a higher HCC risk both in the patients with normal liver and those with liver disorders. BMI was found to be positively associated with HCC in individuals without a liver disorder, whereas those with a liver disorder demonstrated an inverse association.

HBV and HCV infections, the second strongest risk factors after cirrhosis, increased HCC risk by approximately 20-fold in the sex-adjusted and age-adjusted analysis and in the multivariable adjusted analysis after excluding cirrhosis and other viral hepatitis. The HRs of HCV infection, but not HBV infection, increased with age. In the elderly, HCV infections had a markedly higher risk in accordance with previous findings that patients with HCV mostly develop cirrhosis and HCC at ages ≥60 years, irrespective of the age at which they were infected.16-18

Men are known to be at a higher risk of HCC compared with women.8,19 However, to the best of our knowledge, the finding that the multivariable adjusted relative risk of male sex decreased with age in middle-aged and elderly individuals is novel. The protective role of estrogen has been suggested as an explanation for sexual dimorphism.7 Our sex-specific analysis revealed that women did not have lower HRs of risk factors, including viral hepatitis and cirrhosis, compared with men. These findings suggest that women have a lower incidence of HCC because being a woman, especially a young woman, per se has protective effects against the development of HCC and the effects of every risk factor, not just certain risk factors such as HCV,18 are delayed, ameliorated, or prevented. The potential molecular mechanisms remain to be elucidated.7

The associations between alcohol use and HCC varied by age and liver disorder status. Age-stratified analysis revealed that the effects of alcohol on HCC became stronger with age. At age <60 years, only heavy intake (≥80 g/day) was found to elevate the risk of HCC; however, at age ≥70 years, even a light-to-moderate intake of 10 to 39 g/day was associated with an increased risk. This is a novel finding. The threshold effects similarly observed for ALD and cirrhosis20,21 may be a potential mechanism. If alcoholic HCC develops through alcoholic cirrhosis after lifetime alcohol consumption reaches a certain very high level (threshold), such as 500 kg of ethanol (which moderate drinkers only can reach at an older age), the risks associated with alcohol would become greater with age. In addition, the probable higher percentage of alcoholic HCC in older subjects in Korea may partly explain this finding.

In the analysis stratified by liver disorder, only heavy drinkers (≥80 g/day) were found to have a higher risk in the normal liver group. It might take >10 years for HCC to develop in healthy alcohol drinkers consuming 40 to 79 g/day.16 The absence of an increased risk of heavy alcohol use in the liver disorder group suggests that heavy alcohol use and liver disease might not have synergistic effects on HCC,22-24 with the possible exception of HCV infection. In the sex-specific analysis, women were not found to have any higher risk associated with alcohol use. The findings of previous research that women with alcoholic cirrhosis had a markedly lower HCC incidence compared with their male counterparts may partly explain these results.25 However, because formal interaction tests demonstrated no statistically significant differences in the HRs related to alcohol use between the sexes, the absence of an association may have been caused by chance.

To the best of our knowledge, evidence still is lacking regarding whether smoking increases HCC independently of HBV and HCV infection,26 or in the HBV-negative and HCV-negative population.5 The absence of a higher risk associated with heavy smoking (≥1 pack/day) suggests the need for further investigation. However, the consistent associations of current smoker status in the sex, age, and liver disorder subgroups, and especially in the normal liver group, support the hypothesis that smoking is an independent risk factor.
A meta-analysis of 42 case-control and cohort studies reported an approximately 2.3-fold increased risk of HCC associated with diabetes independent of viral hepatitis and alcohol, but diabetes was not found to be associated with HCC in cirrhosis-adjusted studies. Diabetes develops as a complication of cirrhosis and thus the question of whether diabetes causes HCC independent of cirrhosis remains unclear. Diabetes remained associated with a 1.6-fold and 2-fold (HR, 2.05; 95% CI, 1.03-4.07) higher risk, respectively, in the patients with normal liver overall and in the normal liver group with an ALT level <20 IU/L and an AST level <20 IU/L. The severity of glucose intolerance, reflected by glucose levels, was found to be positively associated with HCC risk. These results suggest that diabetes is a risk factor of HCC, independent of cirrhosis or liver disease.

The association of BMI differed by baseline liver disorder status. BMI was found to be positively associated with a higher risk of HCC in the normal liver group, whereas in subjects with a liver disorder, BMI had inverse associations. The potentially different shape of associations with BMI between sexes seemed to disappear when stratified by liver disorder status. In individuals with potential liver damage, a lower BMI may be a good predictor of future HCC. The association between obesity and HCC may be more easily observed in populations with a higher percentage of obesity and NAFLD/NASH, such as Western populations or young adults.

The current study had one of the largest numbers of HCC cases, allowing for the careful consideration of the most important risk factors for HCC: cirrhosis and infection with HBV and HCV. This is a clear strength of the study. As a prospective cohort study, recall and selection biases related to the retrospective design were minimized, and detailed information concerning HCC incidence was provided. Nearly complete follow-up via record linkage to a national database is an additional strength. Furthermore, analyses of the associations between risk factors and HCC that were specific for age, sex, and liver disorder status provided novel findings.

However, the current study had limitations. First, the study population comprised Koreans aged 40 to 80 years, and the results may not necessarily be generalizable to younger people. Furthermore, approximately 50% to 75%, 10% to 20%, and <20%, respectively, of HCC cases in Korea were caused by HBV, HCV, and alcohol. The associations between risk factors and HCC may differ by region and ethnicity due to the varying distribution of HCC etiology. There also is evidence suggesting that ethnicity does not significantly affect HCC risk. Such results enhance the generalizability of the current study findings. Second, in the current study, individuals with viral hepatitis had mostly active chronic hepatitis, and the majority of inactive or subclinical infections most likely were classified as no hepatitis. Because inactive carriers have a higher risk of HCC compared with those who are negative for hepatitis B surface antigen, the HRs of HBV and HCV infections may have been underestimated, and the incidence of HCC in individuals without viral hepatitis may have been somewhat overestimated. Third, single measurements of risk factors were used in the current study; however, the associations with risk factors are unlikely to have been overestimated, considering the regression dilution effect. Fourth, data collected via questionnaire such as smoking status and alcohol use might vary in quality. However, in our validation analyses, alcohol and smoking measures were found to have strong positive associations with ALD and lung cancer incidence, respectively, and self-reported smoking status was shown to have satisfactory validity (kappa coefficient, 0.79) when compared with cotinine measurements in Korean populations; therefore, our measures were deemed reasonably valid and reliable. Finally, further information regarding cirrhosis and viral hepatitis, such as fibrosis stage and viral load, was not available. Therefore, the impact of such detailed information on HCC, or whether diabetes or other risk factors increased the risk of HCC independent of those factors, could not be examined.

Conclusions
Detailed information regarding HCC incidence according to risk factors may help to inform decision making in clinical and public health settings. Among individuals aged ≥40 years, it was found that as age advanced, sexual dimorphism (ie, the lower risk of female sex) in HCC development weakened, whereas the risks of alcohol use and HCV became greater. Moderate alcohol consumption in the elderly may increase the risk of HCC. Smoking increased the risk of HCC among individuals with or without viral hepatitis. Diabetes increased HCC development independent of cirrhosis or any prevalent liver disease, and the severity of glucose intolerance was found to be positively associated with HCC risk. BMI had positive associations with the risk of HCC in individuals with no liver disease at baseline, but an inverse association was noted among those with liver disease.

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AUTHOR CONTRIBUTIONS
Sang-Wook Yi: Conceptualization, data curation, formal analysis, funding acquisition, investigation, methodology, validation, writing-original draft, and writing-review and editing. Ja-Sung Choi: Investigation and writing-review and editing. Jee-Jeon Yi: Investigation and writing-review and editing. Yong-ho Lee: Writing-review and editing. Ki Jun Han: Writing-review and editing.

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