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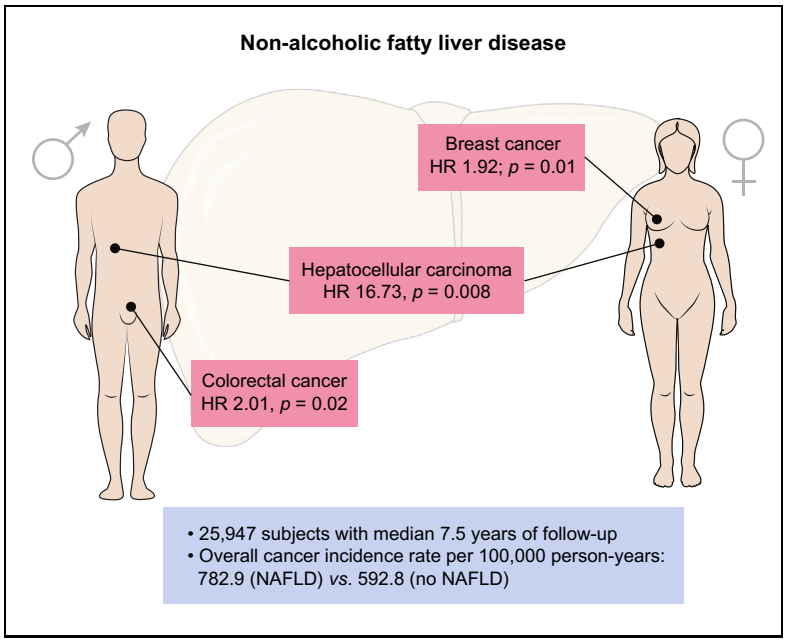
Graphical abstract



Highlights

- NAFLD was associated with HCC development.
- NAFLD was associated with colorectal cancer development in males.
- NAFLD was associated with breast cancer development in females.
- High NFS and high FIB-4 score were associated with developing all cancers and HCC.

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Lay summary

Non-alcoholic fatty liver disease (NAFLD) is associated with developing hepatocellular carcinoma (HCC). There have been limited data on the association between NAFLD and extrahepatic cancers. This study demonstrated that patients with NAFLD showed a higher association with the development of HCC, colorectal cancer in males, and breast cancer in females. A high NAFLD fibrosis score and a high fibrosis-4 score showed a strong association with the development of all cancers and HCC.

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Association between non-alcoholic fatty liver disease and cancer incidence rate

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See Editorial, pages 10–12

Background & Aims: Little is known about the association between non-alcoholic fatty liver disease (NAFLD) and cancer development. This study investigated the cancer incidence rates in NAFLD and analysed the association between NAFLD and cancer development.

Methods: This historical cohort study included subjects who were followed up for >1 year after having a heath checkup at a tertiary hospital in Korea from September 1, 2004 to December 31, 2005. NAFLD was diagnosed by ultrasonographic detection of hepatic steatosis in the absence of other known liver disease, including alcoholic or viral hepatitis. Cox proportional hazards regression model was conducted to assess the association between NAFLD and cancer development.

Results: Of 25,947 subjects, 8,721 (33.6%) had NAFLD. During the total follow-up of 164,671 person-years (median 7.5 years), the cancer incidence rate of the NAFLD group was higher than that of the non-NAFLD group (782.9 *vs.* 592.8 per 100,000 person-years; hazard ratio [HR] 1.32; 95% confidence interval [CI] 1.17–1.49; p <0.001). When demographic and metabolic factors were adjusted for, NAFLD showed a strong association with three cancers: hepatocellular carcinoma ([HCC]; HR 16.73; 95% CI 2.09–133.85; p = 0.008), colorectal cancer in males (HR 2.01; 95% CI 1.10–3.68; p = 0.02), and breast cancer in females (HR 1.92; 95% CI 1.15–3.20; p = 0.01). A high NAFLD fibrosis score (NFS) and a high fibrosis-4 (FIB-4) score were associated with the development of all cancers and HCC.

Conclusion: NAFLD was associated with the development of HCC, colorectal cancer in males, and breast cancer in females. A high NFS and a high FIB-4 score showed a strong association with the development of all cancers and HCC.

Lay summary: Non-alcoholic fatty liver disease (NAFLD) is associated with developing hepatocellular carcinoma (HCC). There have been limited data on the association between NAFLD and extrahepatic cancers. This study demonstrated that patients with NAFLD showed a higher association with the development of HCC, colorectal cancer in males, and breast cancer in females. A high NAFLD fibrosis score and a high fibrosis-4 score showed a strong association with the development of all cancers and HCC.

Introduction

Non-alcoholic fatty liver disease (NAFLD) is one of the most common chronic liver diseases globally, with an estimated prevalence of 25.2%.[1] NAFLD may progress to non-alcoholic steatohepatitis (NASH), cirrhosis, and hepatocellular carcinoma (HCC).[1–3] Moreover, NAFLD is strongly associated with insulin resistance, the metabolic syndrome, diabetes, and cardiovascular disease, indicating that NAFLD is a multisystem disease with extrahepatic complications.[4–6]

Several studies have shown that the second-most frequent cause of death after cardiovascular disease among patients with NAFLD is malignancy.[2,7] Recent data have shown that NAFLD is an attributable cause of HCC and indicated that the number of cases of NAFLD-related HCC in the United States increased 9% each year from 2004 to 2009.[8] Moreover, a cross-sectional study has demonstrated that patients with NAFLD, particularly those with NASH, are more likely to develop advanced colorectal neoplasms than healthy controls.[9] Although previous studies have confirmed the association between NAFLD and the development of colorectal cancers, the association between them over a long period of follow-up has not been demonstrated.[9,10] In addition, little attention has been given to an association between NAFLD and other extrahepatic cancers.

The aim of this study was to identify the incidence rates of various cancers in patients with NAFLD and the association between NAFLD and cancer development. Furthermore, the study aimed to investigate whether the severity of NAFLD based on noninvasive fibrosis scores is related to cancer development.

Patients and methods

Study population

A historical cohort study was conducted on the subjects who underwent a comprehensive health checkup from September

Keywords: Cancer; Incidence rate; Noninvasive fibrosis score.
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1, 2004 to December 31, 2005 at the Health Screening and Promotion Center at Asan Medical Center, a tertiary referral hospital in Korea. This study includes subjects who had not developed cancer within one year from their health checkup and who were followed up at our hospital for >1 year until December 31, 2015 (n = 33,985).

Exclusion criteria were excessive alcohol consumption (alcohol intake ≥30 g/day for men and ≥20 g/day for women; n = 4,533); positive serology for hepatitis B virus surface antigen (n = 1,511); hepatitis C virus, or HIV (n = 225); missing data for abdominal ultrasound, anthropometry, or metabolic parameters (n = 238); previous history of cancer or diagnosis of cancer at baseline (n = 1,166); previous history of organ transplantation (n = 11); liver cirrhosis on abdominal ultrasound (n = 14); and chronic kidney disease with a glomerular filtration rate <30 ml/min (n = 14). Subjects who had not visited our hospital for >2 years from the date of their last follow-up and returned to the hospital after their cancer diagnosis were excluded to avoid overestimation of cancer incidence rate (n = 326). A total of 25,947 subjects were finally analysed (Fig. 1).

This study was approved by the Institutional Review Board of Asan Medical Center (IRB No. 2015–0882).

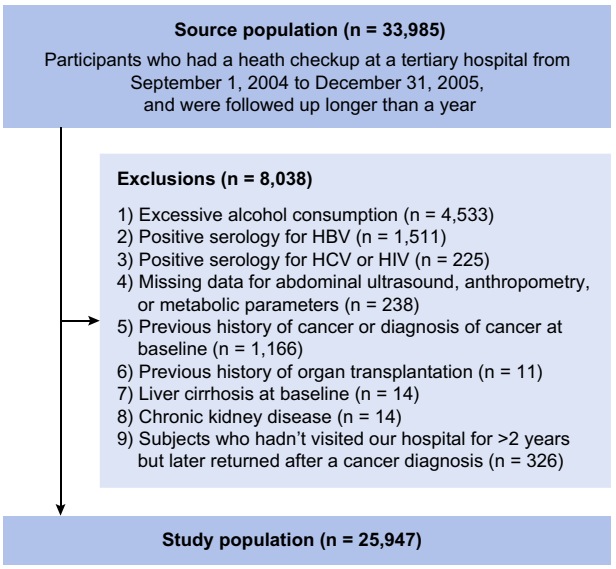

Fig. 1. Patient flow diagram.

Clinical assessment

All study subjects had a comprehensive health assessment, including medical history taking, physical examination, laboratory testing, and abdominal ultrasound at baseline. Information on smoking and alcohol intake, past medical history, and current drug history was extracted from a standardized questionnaire filled in by the subjects. Anthropometric measurements, including body weight and body height, were collected. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. Waist circumference was measured at the midpoint between the lower border of the rib cage and the iliac crest. After an overnight fast, blood samples were taken and analysed by standard laboratory procedures for aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transferase (GGT), total cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, triglycerides, fasting blood glucose, and glycated haemoglobin (HbA1c). Serum markers of hepatitis virus infection, including HBsAg and anti-HBs, anti-HCV, and anti-HIV antibodies, were measured using commercially available enzyme immunoassays (Abbott Laboratories, Chicago, IL).

Subjects who had a fasting blood glucose ≥126 mg/dl, HbA1c ≥6.5, or treatment for diabetes were defined as diabetic. Hypertension was defined as a systolic blood pressure ≥140 mmHg, diastolic blood pressure ≥90 mmHg, or treatment for hypertension. Metabolic syndrome was defined as the presence at least three of the following: central obesity (waist circumference ≥90 cm in men and ≥80 cm in women); blood pressure ≥130/85 mmHg or treatment for hypertension; fasting glucose ≥100 mg/dl or treatment for diabetes; serum triglycerides >150 mg/dl; or HDL cholesterol <40 mg/dl for men and <50 mg/dl for women.

Abdominal ultrasound and assessment of disease severity

Abdominal ultrasonography was performed to diagnose NAFLD by experienced clinical radiologists at the Health Screening and Promotion Center of Asan Medical Center. Ultrasonographic signs of hepatic steatosis included bright parenchyma, liver-to-kidney contrast, deep beam attenuation, and bright vessel walls.[11] Hepatic steatosis was classified into mild, moderate, or severe.

The severity of liver fibrosis was assessed by two noninvasive markers in patients with NAFLD. The NAFLD fibrosis score (NFS) was calculated as follows: $-1.675 + 0.037 \times$ age (years) $+ 0.094 \times$ BMI (kg/m^2) $+ 1.13 \times$ impaired fasting glucose or diabetes (yes = 1, no = 0) $+ 0.99 \times$ AST/ALT ratio $-0.013 \times$ platelets ($\times 10^9$/L) $- 0.66 \times$ albumin (g/dl).[12] A low NFS (<−1.455) strongly suggests the absence of liver fibrosis.[12] The fibrosis-4 (FIB-4) score was calculated as follows: age (years) × AST (U/L)/(platelet count [$\times 10^9$/L] × ALT [U/L]$^{1/2}$).[13] A low FIB-4 score (<1.45) serves as a strong predictor of the absence of liver fibrosis.[13]

Outcomes and follow-up

The primary outcome of interest was cancer incidence rate. The follow-up began one year after the health checkup. Cancer incidence rates were calculated from the cancers found from one year after the subjects' first general health checkup to the date of cancer diagnosis, the last follow-up date, or December 31, 2015. This was because the study population included the subjects who had not developed cancer within a year from their health checkup and who were followed up at our hospital for >1 year. Primary cancers were diagnosed with pathological and/or radiological confirmation at Asan Medical Center, and were cross referenced with information from the Korean National Health Insurance Service database that covers >99% of the entire Korean population.[14] Second primary cancers, which are new primary cancers that occur in patients with a previous diagnosis of cancer, were not taken into account in this study. The total follow-up frequency from the index date was 12.5 for NAFLD and 9.6 for non-NAFLD subjects. The median follow-up frequency was 1.0/year for NAFLD and 0.9/year for non-NAFLD subjects.

Statistical analysis

The characteristics of the study subjects at baseline were compared using a chi-square test and *t* test for categorical and

Table 1. Baseline characteristics of the study subjects.

Characteristic	Total (n = 25,947)			Male (n = 13,966)			Female (n = 11,981)		
	NAFLD (n = 8,721)	No NAFLD (n = 17,226)	*p* value	NAFLD (n = 6,199)	No NAFLD (n = 7,767)	*p* value	NAFLD (n = 2,522)	No NAFLD (n = 9,459)	*p* value
Age, years	50.1 ± 9.7	46.9 ± 10.2	<0.001	48.9 ± 9.5	47.8 ± 10.3	<0.001	53.2 ± 9.5	46.1 ± 10.0	<0.001
Gender, male (%)	6,199 (71.1%)	7,767 (45.1%)	<0.001	–	–	–	–	–	–
BMI, kg/m^2	25.7 ± 2.6	22.7 ± 2.5	<0.001	25.8 ± 2.5	23.4 ± 2.4		25.4 ± 3.0	22.1 ± 2.5	<0.001
Smoking*			<0.001			<0.001			0.01
Never	3,493 (41.6%)	10,089 (61.5%)		1,305 (21.4%)	1,903 (24.9%)		2,188 (95.0%)	8,186 (93.5%)	
Past	2,718 (32.4%)	3,430 (20.9%)		2,668 (43.8%)	3,171 (41.4%)		50 (2.2%)	259 (3.0%)	
Current	2,184 (26.0%)	2,883 (17.6%)		2,120 (34.8%)	2,580 (33.7%)		64 (2.8%)	303 (3.5%)	
Fasting glucose, mg/dl	102.8 ± 23.5	93.1 ± 15.0	<0.001	103.2 ± 22.9	95.8 ± 17.1	<0.001	102.1 ± 24.8	90.9 ± 12.6	<0.001
Diabetes†	1,414 (16.2%)	760 (4.4%)	<0.001	998 (16.1%)	492 (6.3%)	<0.001	416 (16.5%)	268 (2.8%)	<0.001
Hypertension†	2,817 (32.3%)	2,916 (16.9%)	<0.001	1,923 (31.0%)	1,636 (21.1%)	<0.001	894 (35.4%)	1,280 (13.5%)	<0.001
Total cholesterol, mg/dl	200.7 ± 34.5	187.0 ± 32.7	<0.001	199.0 ± 33.2	187.0 ± 31.8	<0.001	205.1 ± 37.3	187.1 ± 33.4	<0.001
LDL cholesterol, mg/dl	132.7 ± 30.2	118.5 ± 29.0	<0.001	131.8 ± 29.0	121.2 ± 28.1	<0.001	134.7 ± 32.9	116.3 ± 29.5	<0.001
HDL cholesterol, mg/dl	48.1 ± 10.7	57.0 ± 13.5	<0.001	46.2 ± 9.7	52.2 ± 11.8	<0.001	52.6 ± 11.7	61.0 ± 13.5	<0.001
Triglyceride, mg/dl	169.0 ± 101.8	105.2 ± 58.3	<0.001	176.1 ± 104.9	120.1 ± 63.7	<0.001	151.8 ± 91.5	93.0 ± 50.2	<0.001
ALT, U/L	30.7 ± 21.6	17.8 ± 11.5	<0.001	33.6 ± 22.8	20.8 ± 10.7	<0.001	23.6 ± 16.2	15.3 ± 11.6	<0.001
GGT, U/L	36.5 ± 30.2	23.3 ± 20.2	<0.001	41.1 ± 28.6	30.6 ± 24.0	<0.001	25.2 ± 31.2	17.3 ± 13.7	<0.001
Metabolic syndrome	3,443 (39.5%)	1,709 (9.9%)	<0.001	2,244 (36.2%)	823 (10.6%)	<0.001	1,199 (47.5%)	886 (9.4%)	<0.001

Values are expressed as means ± standard deviation or number (%).
ALT, alanine aminotransferase; BMI, body mass index; GGT, gamma-glutamyl transferase; HDL, high-density lipoprotein; LDL, low-density lipoprotein; NAFLD, nonalcoholic fatty liver disease.
* Information regarding smoking status was obtained for 24,797 subjects (95.6%).
† Hypertension was defined as systolic blood pressure ≥140 mmHg, diastolic blood pressure ≥90 mmHg, or receiving treatment for hypertension; diabetes was defined as a fasting blood glucose ≥126 mg/dl, HbA1c ≥6.5, or receiving treatment for diabetes.

continuous variables, respectively. Incidence rates were computed by dividing the number of newly diagnosed cancers during the study period by the total observation time. A Poisson regression model was used to estimate the incidence rate ratio (IRR) of cancer development in patients with NAFLD compared to controls without NAFLD. Univariate, age- and sex-adjusted, and multivariable analyses were carried out to investigate the association between NAFLD and cancer development using Cox proportional hazards regression model. In identifying the association between the severity of NAFLD and cancer development, univariate and multivariable analyses were also performed. Variables used in the multivariable analyses were age, sex, smoking status, diabetes, hypertension, and serum levels of GGT, HDL cholesterol, LDL cholesterol, and triglycerides.

A *p* value of <0.05 was considered statistically significant. All statistical analyses were performed with SAS (version 9.3, SAS, Cary, NC) and R (version 3.3.2, http://www.r-project.org) software.

For further details regarding the materials used, please refer to the CTAT table and supplementary information.

Results

Characteristics of the study population

The study population comprised 25,947 subjects who met the inclusion criteria (Fig. 1). The prevalence of NAFLD was 33.6% (n = 8,721). The baseline characteristics of the study subjects are presented (Table 1). Compared to subjects without NAFLD, those with NAFLD were older (mean age 50 *vs.* 47 years, *p* <0.001); more likely to be male (71.1% *vs.* 45.1%, *p* <0.001), smokers (58.4% *vs.* 38.5%, *p* <0.001), diabetic (16.2% *vs.* 4.4%, *p* <0.001), and hypertensive (32.3% *vs.* 16.9%, *p* <0.001); and more likely to have higher levels of fasting glucose (102.8 *vs.* 93.1 mg/dl, *p* <0.001), total cholesterol (200.7 *vs.* 187.0 mg/dl, *p* <0.001), serum ALT (30.7 *vs.* 17.8 U/L, *p* <0.001), and GGT (36.5 *vs.* 23.3 U/L, *p* <0.001).

Incidence rates of cancer

The median follow-up duration was 7.5 years (interquartile range [IQR] 3.2–9.3 years), contributing 164,671 person-years of follow-up. During the follow-up period, 440 subjects (5.0%) with NAFLD and 643 subjects (3.7%) without NAFLD developed malignancies. The overall cancer incidence rate was significantly higher in the NAFLD group (782.9 [95% confidence interval (CI) 711.5–859.7] per 100,000 person-years) than in the non-NAFLD group (592.8 [95% CI 547.8–640.4] per 100,000 person-years; IRR 1.32; 95% CI 1.17–1.49; *p* <0.001; Table 2).

Details of the cancer incidence rates are provided (Table 2). Subjects with NAFLD had significantly higher cancer incidence rates in three specific cancers than those without NAFLD: HCC (23.1 *vs.* 0.9 per 100,000 person-years; IRR 25.09; 95% CI 3.28–191.83; *p* = 0.002), colorectal cancer (69.4 *vs.* 34.1 per 100,000 person-years; IRR 2.04; 95% CI 1.30–3.19; *p* = 0.002), and breast cancer in female subjects (181.6 *vs.* 102.5 per 100,000 person-years; IRR 1.77; 95% CI 1.15–2.74; *p* = 0.01). There was no significant difference in the incidence rates of cancers of the thyroid, oesophagus, stomach, pancreas, biliary tract, lung, kidney, bladder, or uterus; non-Hodgkin lymphoma; leukemia; or other rare tumors.

When stratified by gender, male subjects with NAFLD had significantly higher incidence rates of HCC (30.3 *vs.* 2.0 per 100,000 person-years; IRR 14.80; 95% CI 1.93–113.85; *p* = 0.01; Table 3) and colorectal cancer (85.7 *vs.* 38.8 per 100,000 person-years; IRR 2.21; 95% CI 1.26–3.87; *p* = 0.006), whereas female subjects with NAFLD had a significantly higher incidence rate of breast cancer (181.6 *vs.* 102.5 per 100,000 person-years; IRR 1.77; 95% CI 1.15–2.74; *p* = 0.01). Among female subjects, the incidence rate of colorectal cancer did not differ between the NAFLD and control group.

Association between NAFLD and cancer development

On univariate analysis, the subjects with NAFLD showed higher association with the development of all cancers than those

Table 2. Cancer incidence rates in subjects with and without NAFLD.

	No. of cancer	Cancer incidence rates per 100,000 person-years				*p* value
		All	NAFLD	No NAFLD	IRR (95% CI)	
All cancers	1,083	657.7	782.9	592.8	1.32 (1.17–1.49)	<0.001
Thyroid	218	132.4	126.3	135.5	0.93 (0.70–1.24)	0.63
Digestive system						
Esophagus	8	4.9	7.1	3.7	1.93 (0.48–7.72)	0.35
Stomach	162	98.4	119.2	87.6	1.36 (1.00–1.86)	0.053
Colon and rectum	76	46.2	69.4	34.1	2.04 (1.30–3.19)	0.002
Hepatocellular carcinoma	14	8.5	23.1	0.9	25.09 (3.28–191.83)	0.002
Pancreas	24	14.6	16.0	13.8	1.16 (0.51–2.65)	0.73
Biliary	23	14.0	17.8	12.0	1.49 (0.65–3.39)	0.35
Lung	83	50.4	60.5	45.2	1.34 (0.87–2.07)	0.19
Breast*	91	119.7	181.6	102.5	1.77 (1.15–2.74)	0.01
Kidney and real pelvis	42	25.5	35.6	20.3	1.76 (0.96–3.22)	0.07
Bladder	30	18.2	26.7	13.8	1.93 (0.94–3.95)	0.07
Uterus, cervical, ovary*	22	28.9	48.4	23.5	2.06 (0.86–4.91)	0.10
Prostate†	118	133.2	126.0	138.9	0.91 (0.63–1.31)	0.60
Non-Hodgkin lymphoma	49	29.8	28.5	30.4	0.94 (0.52–1.70)	0.83
Leukemia	16	9.7	10.7	9.2	1.16 (0.42–3.19)	0.78

Follow-up duration, 164,671 person-years; no NAFLD group, 108,476 person-years; NAFLD group, 56,195 person-years.
CI, confidence interval; IRR, incidence rate ratio; NAFLD, nonalcoholic fatty liver disease.
The incidence rate ratios and *p* values represent the NAFLD group compared with the non-NAFLD group using a Poisson regression model.
* Incidence rate of cancer was calculated among females (76,052 person-years; no NAFLD group: 59,532 person-years, NAFLD group; 16,520 person-years).
† Incidence rate of cancer was calculated among males (88,619 person-years, no NAFLD group: 48,944 person-years, NAFLD group; 39,675 person-years).

Table 3. Cancer incidence rates in subjects with and without NAFLD by gender.

	Male					Female				
	Cancer incidence rates per 100,000 person-years				*p* value	Cancer incidence rates per 100,000 person-years				*p* value
	All	NAFLD	No NAFLD	IRR (95% CI)		All	NAFLD	No NAFLD	IRR (95% CI)	
All cancers	740.3	801.5	690.6	1.16 (1.00–1.35)	0.05	561.5	738.5	512.3	1.44 (1.17–1.78)	0.001
Thyroid	95.9	105.9	87.9	1.21 (0.79–1.84)	0.39	174.9	175.5	174.7	1.01 (0.67–1.52)	0.98
Digestive system										
Esophagus	9.0	10.1	8.2	1.23 (0.31–4.93)	0.77	–	–	–	–	–
Stomach	139.9	136.1	143.0	0.95 (0.67–1.36)	0.78	50.0	78.7	42.0	1.87 (0.96–3.66)	0.07
Colon and rectum	59.8	85.7	38.8	2.21 (1.26–3.87)	0.006	30.2	30.3	30.2	1.00 (0.37–2.70)	0.99
Hepatocellular carcinoma	14.7	30.3	2.0	14.80 (1.93–113.85)	0.01	1.3	6.1	–	–	–
Pancreas	16.9	15.1	18.4	0.82 (0.29–2.31)	0.71	11.8	18.2	10.1	1.80 (0.45–7.20)	0.41
Biliary	13.5	15.1	12.3	1.23 (0.40–3.83)	0.72	14.5	24.2	11.8	2.06 (0.60–7.03)	0.25
Lung	67.7	78.1	59.3	1.32 (0.80–2.19)	0.28	30.2	18.2	33.6	0.54 (0.16–1.82)	0.32
Breast*	–	–	–	–	–	119.7	181.6	102.5	1.77 (1.15–2.74)	0.01
Kidney and real pelvis	38.4	40.3	36.8	1.10 (0.56–2.15)	0.79	10.5	24.2	6.7	3.60 (0.90–14.41)	0.07
Bladder	28.2	30.3	26.6	1.14 (0.52–2.50)	0.75	6.6	18.2	3.4	5.41 (0.90–32.35)	0.07
Uterus, cervical, ovary*	–	–	–	–	–	28.9	48.4	23.5	2.06 (0.86–4.91)	0.10
Prostate†	133.2	126.0	138.9	0.91 (0.63–1.31)	0.60	–	–	–	–	–
Non-Hodgkin lymphoma	31.6	27.7	34.7	0.80 (0.37–1.70)	0.56	27.6	30.3	26.9	1.13 (0.41–3.07)	0.82
Leukemia	11.3	7.6	14.3	0.53 (0.14–2.04)	0.36	7.9	18.2	5.0	3.60 (0.73–17.85)	0.12

Males: follow-up duration, 88,619 person-years, no NAFLD group: 48,944 person-years, NAFLD group; 39,675 person-years
Females: follow-up duration, 76,052 person-years; no NAFLD group: 59,532 person-years, NAFLD group; 16,520 person-years
The incidence rate ratios and p values represent the NAFLD group compared with the non-NAFLD group using a Poisson regression model.
NAFLD, nonalcoholic fatty liver disease; CI, confidence interval; IRR, incidence rate ratio.
* Incidence rate of cancer was calculated among females.
† Incidence rate of cancer was calculated among males.

without NAFLD (hazard ratio [HR] 1.32; 95% CI 1.17–1.49; p <0.001; Table 4). After adjusting for age and sex, NAFLD had a significant association with three specific cancers: HCC (HR 15.86; 95% CI 2.07–121.33; $p = 0.008$), colorectal cancer in males (HR 2.13; 95% CI 1.22–3.74; $p = 0.008$), and breast cancer in females (HR 1.90; 95% CI 1.20–3.01; $p = 0.006$; Table 4). The results of multivariable analysis were consistent. After adjusting for demographic and metabolic factors, NAFLD had a strong association with HCC (HR 16.73; 95% CI 2.09–133.85; $p = 0.008$; Table 4), colorectal cancer in males (HR 2.01; 95% CI 1.10–3.68; $p = 0.02$), and breast cancer in females (HR 1.92; 95% CI 1.15–3.20; $p = 0.01$). To further investigate the impact of obesity on the development of breast cancer, the subjects were stratified as obese (≥25 kg/m^2) or non-obese according to their BMI. In multivariable analyses, there were no significant associations between NAFLD and breast cancer among the obese

Table 4. Association between NAFLD and development of cancers.

	Univariate analysis		Age and sex-adjusted analysis		Multivariable analysis	
	HR (95% CI)	*p* value	HR (95% CI)	*p* value	HR (95% CI)	*p* value
All cancers	1.32 (1.17–1.49)	<0.001	1.10 (0.97–1.25)	0.13	1.08 (0.94–1.24)	0.27
Stomach	1.36 (0.99–1.86)	0.06	0.99 (0.72–1.36)	0.96	0.98 (0.69–1.38)	0.91
Colon and rectum	2.04 (1.30–3.20)	0.002	1.57 (0.99–2.48)	0.05	1.45 (0.88–2.38)	0.15
Male (n = 53)	2.21 (1.26–3.88)	0.006	2.13 (1.22–3.74)	0.008	2.01 (1.10–3.68)	0.02
Female (n = 23)	1.01 (0.37–2.71)	0.99	0.66 (0.24–1.81)	0.41	0.63 (0.21–1.89)	0.41
Hepatocellular carcinoma	24.83 (3.25–189.83)	0.002	15.86 (2.07–121.33)	0.008	16.73 (2.09–133.85)	0.008
Breast	1.77 (1.14–2.73)	0.01	1.90 (1.20–3.01)	0.006	1.92 (1.15–3.20)	0.01

The hazard ratios and *p* values represent the NAFLD group compared to the non-NAFLD group using a Cox proportional hazards regression model.
Multivariable analyses were adjusted for age, gender, smoking status, diabetes, hypertension, GGT, HDL cholesterol, LDL cholesterol, and triglycerides.
CI, confidence interval; GGT, gamma-glutamyl transpeptidase; HDL, high-density lipoprotein; HR, hazard ratio; LDL, low-density lipoprotein; NAFLD, nonalcoholic fatty liver disease

subjects (HR 1.06; 95% CI 0.45–2.49; $p = 0.90$), whereas the non-obese subjects showed a substantially greater association between them (HR 2.40; 95% CI 1.27–4.54; $p = 0.007$).

Association between severity of NAFLD and cancer development

On univariate and multivariable Cox analyses, the subjects with a high NFS (≥−1.455; adjusted HR 1.87; 95% CI 1.54–2.28; p <0.001) or a high FIB-4 score (≥1.45; adjusted HR 1.74; 95% CI 1.42–2.13; p <0.001) showed a stronger association with the development of all cancers than those with a low NFS (<−1.455) or a low FIB-4 score (<1.45) among the NAFLD subjects (n = 8,721) (Table 5). The severity of hepatic steatosis detected on ultrasound was not significantly associated with cancer development (adjusted HR 0.99; 95% CI 0.82–1.20; p = 0.92).

The association between the severity of NAFLD and the development of each cancer was further analysed. Although the severity of NAFLD was significantly associated with HCC, it was not associated with colorectal cancer or breast cancer. A high NFS (adjusted HR 5.64; 95% CI 1.49–21.44; $p = 0.01$) or a high FIB-4 score (adjusted HR 13.99; 95% CI 3.00–65.23; p = 0.001) showed strong association with HCC (Table 5). The association between hepatic steatosis detected on ultrasound and HCC development was also found (adjusted HR 3.39; 95% CI 1.00–11.43; $p = 0.049$).

Discussion

In this observational study, we found that subjects with NAFLD had higher incidence rates of all cancers than those without NAFLD. The results of this study demonstrated that NAFLD was associated with the development of HCC, colorectal cancer in males, and breast cancer in females, which was consistently observed in univariate, age-sex-adjusted, and multivariable adjusted analyses. Furthermore, this study showed that a high NFS and a high FIB-4 score in the NAFLD group were associated with the development of all cancers and HCC. Thus, our findings suggest that NAFLD may have a strong association with extra-hepatic cancers, particularly colorectal and breast cancer, as well as with HCC.

A Danish cohort study with median 6-year follow-up evaluated cancer risk in patients with fatty liver and showed an increased risk of primary liver, colon, pancreatic, and kidney

Table 5. Association between severity of NAFLD and cancer development.

Outcome	Univariate analysis		Multivariable analysis	
	HR (95% CI)	*p* value	HR (95% CI)	*p* value
NFS: Low, <−1.455 (n = 6,562; reference), high and intermediate, ≥−1.455 (n = 2,159)				
All cancers	1.96 (1.62–2.37)	<0.001	1.87 (1.54–2.28)	<0.001
Hepatocellular carcinoma	9.61 (2.64–34.91)	0.001	5.64 (1.49–21.44)	0.01
Colon and rectum	1.45 (0.75–2.83)	0.27	1.40 (0.70–2.78)	0.34
Breast	0.79 (0.34–1.83)	0.58	0.76 (0.32–1.82)	0.54
FIB-4 score: Low, <1.45 (n = 7,007; reference), high and intermediate, ≥1.45 (n = 1,714)				
All cancers	1.88 (1.54–2.29)	<0.001	1.74 (1.42–2.13)	<0.001
Hepatocellular carcinoma	21.21 (4.70–95.68)	<0.001	13.99 (3.00–65.23)	0.001
Colon and rectum	1.72 (0.87–3.39)	0.12	1.64 (0.81–3.30)	0.17
Breast	1.69 (0.40–7.08)	0.48	1.80 (0.40–8.21)	0.45
Hepatic steatosis on ultrasound: Mild (n = 5,115; reference), moderate to severe (n = 3,606)				
All cancers	0.98 (0.81–1.19)	0.87	0.99 (0.82–1.20)	0.92
Hepatocellular carcinoma	3.18 (0.98–10.33)	0.054	3.39 (1.00–11.43)	0.049
Colon and rectum	0.99 (0.52–1.88)	0.98	1.15 (0.60–2.22)	0.67
Breast	1.61 (0.79–3.29)	0.19	1.76 (0.84–3.69)	0.14

NAFLD patients: 8,721, all cancers: 440
The hazard ratios and *p* values were calculated using a Cox proportional hazards regression model.
Multivariable analyses were adjusted for age, gender, smoking status, diabetes, hypertension, GGT, HDL cholesterol, LDL cholesterol, and triglycerides.
For the NFS, the model was not adjusted for age or diabetes.
For the FIB-4 score, the model was not adjusted for age.
CI, confidence interval; FIB-4, fibrosis-4; GGT, gamma-glutamyl transpeptidase; HDL, high-density lipoprotein; HR, hazard ratio; LDL, low-density lipoprotein; NAFLD, nonalcoholic fatty liver disease; NFS, NAFLD fibrosis score.

cancers in patients with NAFLD (n = 1,800) compared with the general population.[15] Nonetheless, the association between NAFLD and the development of extrahepatic cancers was not clearly demonstrated. In our large observational study, we not only assessed the overall incidence rates of each cancer, but we also found that NAFLD is associated with HCC, colorectal cancer in males, and breast cancer in females. These findings agree with the results of previous studies showing an association between NAFLD and HCC.[8,16–19] The incidence rate of HCC among NAFLD patients was 0.23 per 1,000 person-years in this study, which is lower than the incidence rate of 0.44 (range, 0.29–0.66) in a recent meta-analysis.[1] Excluding subjects with cirrhosis at baseline might have affected the incidence rate of HCC. Still, the relationship between NAFLD and extrahepatic cancers has not been fully demonstrated. A recently reported putative mechanism suggests that patients with NAFLD are more likely to have chronic inflammation with insulin resistance, which may generate a microenvironment suitable for developing cancers.[20–22] This includes increased insulin and insulin-like growth factor, decreased adiponectin, or increased proinflammatory cytokines, which may promote cancer through proliferative and anti-apoptotic effects and angiogenesis.[20]

Although the results of multivariable analyses did not show a significant association between NAFLD and colorectal cancer in all subjects and female subjects, a strong association between NAFLD and colorectal cancer was found in male subjects. This could have been because of the small number of female NAFLD subjects included in this study and the low incidence rate of colorectal cancer in females. Other studies have reported that patients with central obesity, metabolic syndrome, or diabetes have an increased risk of colorectal neoplasm.[23–25] In addition, a recent study of NAFLD, diagnosed by proton-magnetic resonance spectroscopy and liver histology, showed that patients with NASH are at the highest risk of having colorectal adenomas and advanced neoplasms.[9] Further studies that investigate the association between NAFLD and colorectal cancer in larger populations should be carried out to confirm our findings. Nevertheless, these observations highlight the need to identify groups at high risk of developing colorectal cancer in patients with NAFLD.

Our present study demonstrated a strong association between NAFLD and breast cancer in females. However, the impacts of BMI and hormonal status were not clearly investigated, because multivariable analyses could not include BMI because of its strong correlation with NAFLD, the potential of multicollinearity cannot be ruled out. Indeed, several studies have found a strong association between obesity and the higher risk of several cancers, including breast cancer.[26,27] It has been suggested that disruptions in insulin metabolism, adipokines, and inflammation contribute to the effects of obesity in breast cancer.[28] An association between metabolic syndrome or hyperinsulinaemia and breast cancer has been also reported.[29–31] In our study, the association between NAFLD and the development of breast cancer was found in non-obese female subjects, whereas no association between them was found in obese female subjects. An explanation for these findings can be that obesity-related metabolic or hormonal derangement acts as the predominant mechanism behind the increased incidence rate of breast cancer. This suggests that the presence of NAFLD *per se* did not increase the incidence rate of breast cancer in obese subjects. The higher incidence rate of breast cancer found in non-obese NAFLD subjects could be explained by similar metabolic or hormonal derangement caused by NAFLD instead of obesity.

Although our subjects did not undergo liver biopsy, we found that noninvasive fibrosis scores were associated with the development of all cancers and HCC. A high NFS and a high FIB-4 score were associated with the development of all cancers. In addition, a high NFS or a high FIB-4 score showed strong association with the development of HCC, which corresponds with the results of previous studies.[16,32] However, no clear association between noninvasive fibrosis scores and the development of other cancers, including colorectal and breast cancer, was found in this study.

Although this study demonstrated higher cancer incidence rates in NAFLD patients, it has some unavoidable limitations. The study was based on observational data, potentially subjecting the findings to bias and confounding factors. Firstly, the Asan Medical Center is a tertiary referral hospital which covers about 15% of all cancer patients nationally, which implies the rate of patients returning to our hospital for cancer treatment might be higher than that of patients returning for other diseases after the follow-up loss. To avoid possible overestimation of the cancer incidence, we excluded 326 patients who did not visit our hospital for >2 years from the date of their last follow-up, but returned after their cancer diagnoses. Among these subjects, the most frequent cancer was of the thyroid, but there were some cases of stomach (n = 40), breast (n = 34), and colorectal cancer (n = 18) and one case of HCC. Even when these 326 patients were included in the analyses, the association between NAFLD and cancer incidence rates was consistent with our results (data not shown). Secondly, although this study showed that patients with NAFLD had higher incidence rates of cancer, our findings cannot be translated to cancer risk because the current study was not able to take death into account. The subjects with NAFLD may have had a higher rate of death before developing cancer, which may have served as a competing risk in our study. Thirdly, the subjects included in this cohort might have had a relatively high frequency of hospital visits and health screening, which might have affected the detection rate of cancer. In fact, it has been reported that higher frequency of health screening increases the detection rate and incidence rate of thyroid cancer in Korea.[33] However, it is not clear whether frequent health screening has the same effect on other cancers. Fourthly, our analysis may have had some surveillance bias, since patients with NAFLD visited the hospital more often than those without NAFLD. However, the median follow-up frequency of the study subjects was 1.0/year for NAFLD and 0.9/year for non-NAFLD subjects, which did not seem to bear any meaningful clinical significance. Lastly, fatty liver was assessed by abdominal ultrasound, which does not detect hepatic steatosis well when it is <20%.[34] It may have resulted in some errors in diagnosing NAFLD in this present analysis. Nevertheless, ultrasound is a practical and preferred first-line diagnostic method of NAFLD in a large population setting.[2] The prevalence of NAFLD in this study was 33.6%, similar to that of previous reports.[7,35]

In conclusion, this study has demonstrated that NAFLD was associated with higher incidence rates of cancer in general. Unadjusted, age-sex-adjusted, and multivariable adjusted analysis consistently showed that NAFLD was significantly associated with HCC, colorectal cancer in males, and breast cancer in females. In the NAFLD group, a high NFS or a high FIB-4 score showed a strong association with the development of all cancers

and HCC. These findings suggest that patients with NAFLD require multidisciplinary evaluation with attention given to the development of malignancy. Further studies are needed to specify which high-risk groups of patients with NAFLD carry a greater risk of developing cancers, including HCC, colorectal cancer, and breast cancer.

Author contributions

GA Kim, HC Lee, and J Choe were responsible for the concept and design of the study, the acquisition, analyses and interpretation of the data, and the drafting of the manuscript. MJ Kim performed the statistical analyses. MJ Lee, HS Chang, IY Bae, HK Kim, J An, JH Shim, KM Kim, and YS Lim helped with the acquisition of the data and critically revised the manuscript for important intellectual content.

Conflict of interest

The authors who have taken part in this study declared that they do not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

Please refer to the accompanying ICMJE disclosure forms for further details.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.jhep.2017.09.012.

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