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Nonalcoholic Fatty Liver Disease and Mortality among Cancer Survivors

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Abstract

Background—Nonalcoholic fatty liver disease (NAFLD) may foster a tumor microenvironment that promotes cancer recurrence and progression. We examined the relationship between NAFLD and mortality among a sample of cancer survivors.

Methods—Ultrasonography was used to assess hepatic steatosis, and standardized algorithms were used to define NAFLD. Study endpoints included all-cause, cancer-specific, and cardiovascular-specific mortality.

Results—Among 387 cancer survivors, 17.6% had NAFLD. During a median of 17.9 years of follow up, we observed 196 deaths from all causes. In multivariable-adjusted regression models, NAFLD was associated with an increased risk of all-cause mortality [HR: 2.52, 95% CI: 1.47–4.34; *P*=0.001]. We observed 86 cancer-specific deaths. In multivariable-adjusted regression models, NAFLD was associated with an increased risk of cancer-specific mortality [HR: 3.21, 95% CI: 1.46–7.07; *P*=0.004]. We observed 46 cardiovascular-specific deaths. In multivariable-adjusted regression models, NAFLD was not associated with an increased risk of cardiovascular-specific mortality [HR: 1.04, 95% CI: 0.30–3.64, *P*=0.951].

Conclusion—NAFLD is associated with an increased risk of all-cause and cancer-specific mortality among cancer survivors. This novel observation warrants replication. Evaluating the efficacy of interventions, such as lifestyle modification through weight loss and exercise, to improve NAFLD in this population may be considered.

Keywords

hepatic steatosis; cancer progression; obesity; population-based; insulin resistance; metabolic syndrome

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1. INTRODUCTION

The prevalence of obesity has reached epidemic levels in the United States with one-in-three adults classified as obese [1]. Obesity is associated with an increased risk of developing cancer, experiencing cancer recurrence, and dying from cancer [2,3]. Obesity also contributes to a variety of hepatic abnormalities including nonalcoholic fatty liver disease (NAFLD), which is characterized by the accumulation of intrahepatic triglycerides [4]. Among the general population, 20–30% may have NAFLD [5,6], and NAFLD has been found to be associated with all-cause mortality in some [7], but not all studies [8].

Cancer survivors represent a unique population to study the relationship between NAFLD and mortality outcomes. NAFLD is a risk factor for the development of several types of cancer [9,10], and various agents used in the treatment of cancer are associated with an increased risk of developing NAFLD [11–13]. Specific to cancer survivors, NAFLD often co-exists with insulin resistance, type 2 diabetes, and the metabolic syndrome [4], which may foster a tumor microenvironment that promotes cancer recurrence and progression [14]. However, the relationship between NAFLD and mortality among people with a history of cancer has not been studied.

We examined the relationship between NAFLD and mortality among cancer survivors who participated in the Third National Health and Nutrition Examination Survey (NHANES III). NHANES III was a population-based study led by the United States Centers for Disease Control and Prevention that was designed to provide health information on a nationally-representative sample of males and females living throughout the United States [15]. In this hypothesis-generating study, we examined the influence of NAFLD as an independent predictor of all-cause and cause-specific mortality among cancer survivors.

2. METHODS

2.1. Population

Survey participants included males and females between the age of 20–74 years who completed the digestive diseases component of NHANES III (described below), and reported a prior diagnosis of non-skin-related cancer. All study participants provided written informed consent prior to completing any study-related procedures.

2.2. Exposure Ascertainment

Gallbladder ultrasonography was collected as part of the digestive diseases component of NHANES III. Between 2009 and 2010, archived digitized gallbladder ultrasound exam videotapes that were collected between 1988 and 1994 were reviewed to grade the presence of fat within the hepatic parenchyma. Hepatic steatosis was evaluated using five criteria: 1) parenchymal brightness; 2) liver to kidney contrast; 3) deep beam attenuation; 4) bright vessel walls, and 5) gallbladder wall definition. Following a standardized algorithm [16], an overall grading of hepatic steatosis was recorded based on the number of ultrasound findings, and classified as normal, mild, moderate, or severe by technicians who were blinded to participant outcomes. The overall grading was then categorized into a binary

steatosis variable: absent (normal or mild hepatic steatosis) or present (moderate or severe hepatic steatosis). The intra- and inter-rater reliability rates for steatosis grading were 0.913 and 0.887, respectively [17]. Consistent with prior studies using this dataset [8], we defined NAFLD as the presence of moderate or severe hepatic steatosis with normal liver enzymes (alanine aminotransferase ≤40 U/L for males and ≤31 U/L for females; aspartate aminotransferase ≤37 U/L for males and ≤31 U/L for females).

2.3. Endpoint Ascertainment

Vital status and cause of death were identified using the National Death Index publicly-released database with follow up through December 31, 2011. Participants were linked to the National Death Index database using a probabilistic matching algorithm that included 12 identifiers including Social Security Number, sex, date of birth, race, state of residence, and marital status [18]. The National Center for Health Statistics found that 96.1% of deceased participants and 99.4% of living participants were correctly classified using the probabilistic matching algorithm [19]. We censored study participants who were not matched with a death certificate at the end of the follow-up period. The publicly-released survival data are nearly identical to the restricted-use NHANES III linked mortality file [20]. Causes of death were categorized using 113 grouped recodes from the International Classification of Diseases, 10th Edition (ICD-10). Cancer-specific mortality was categorized using ICD-10 codes C00–C97. Cardiovascular-specific mortality was categorized using ICD-10 codes I00–I079.

2.4. Covariate Ascertainment

Demographic variables (including date of birth and gender) and clinical variables (including type of cancer, date of diagnosis, smoking history, and comorbid health conditions [e.g., hypertension, hyperlipidemia, diabetes, myocardial Infarction, stroke, and congestive heart failure]) were self-reported. Behavioral variables included a measure of regular physical activity, defined as moderate or vigorous intensity activity on one or more days in the past week; alcohol consumption and the healthy eating index were calculated from a 24-hour food recall. The healthy eating index forms a score than ranges from 0 to 100 to quantify aspects of a healthy diet [21,22]. Self-rated health was reported on a 0 to 100 scale, with higher scores indicating better perceived health [23]. Height, body mass, and waist circumference were measured by study technicians. Body mass index (BMI) was calculated as body mass divided by the square of height. Systolic and diastolic blood pressure was obtained by study technicians following standardized operating procedures [24]. Study participants underwent a venipuncture using a sterile technique. Blood samples were stored and assayed following standardized laboratory procedures that have been described in detail [25,26]. Metabolic measures included glucose, insulin, insulin resistance [calculated using the homeostatic model assessment (HOMA-IR) [27]], glycated hemoglobin, and creatinine. Lipid measures included total cholesterol, high- and low-density lipoprotein cholesterol, and triglycerides. Liver function measures included alanine aminotransferase, aspartate aminotransferase, γ-glutamyl transferase, total bilirubin, and albumin.

2.5. Statistical Analysis

Continuous variables are presented as means (standard error), and categorical variables are presented as percentages (%). We fit Cox proportional hazards regression models to estimate

the hazard ratio (HR) and 95% confidence interval (95% CI) between NAFLD and each of the three outcomes: all-cause, cancer-specific, and cardiovascular-specific mortality. Univariate subgroup analyses were conducted with all-cause mortality due to the reduced number of cancer-specific and cardiovascular-specific events in subgroup strata. Given the hypothesis-generating nature of this study, we considered a variety of covariates on the basis of biological plausibility of confounding the relationship between NAFLD and mortality. Covariates ultimately included in multivariable-adjusted models were selected on the basis of statistical evidence of confounding the relationship between NAFLD and mortality. We visualized log-log plots to confirm the assumption of proportional hazards. Sample weights were incorporated into all analyses to account for nonresponse bias, multistage sampling probabilities, and the subpopulation of participants included in this analytic sample. Stata SE v.14.1 statistical software was used for all analyses. Two-sided statistical significance was $P<0.05$.

3. RESULTS

3.1. Characteristics Associated with NAFLD

Among the 387 cancer survivors included in this analysis, 68 (17.6%) had NAFLD. Cancer survivors with NAFLD were older (55.4 *vs* 50.7 years; $P=0.043$), with higher fasting insulin (117.0 *vs* 62.2 pmol/L; $P=0.001$), insulin resistance (5.9 *vs* 2.8; $P=0.012$), body mass index (31.1 *vs* 25.4 kg/m^2; $P<0.001$), waist circumference (106.4 *vs* 89.5 cm; $P<0.001$), systolic (130.1 *vs* 121.8 mm Hg; $P=0.004$) and diastolic (76.8 *vs* 73.0 mm Hg; $P=0.029$) blood pressure, lower high-density lipoprotein cholesterol (1.1 *vs* 1.4 mmol/L; $P<0.001$), higher triglycerides (2.6 *vs* 1.6 mmol/L; $P=0.007$), and poorer self-rated overall health (44.6 *vs* 54.9; $P=0.012$; Table 1).

3.2. NAFLD and Mortality

During a median of 17.9 years of follow up [interquartile range: 10.4–20.2], we observed 196 deaths from all causes (50.6% of the cohort). NAFLD was associated with an increased risk of all-cause mortality [HR: 2.52, 95% CI: 1.47–4.34; $P=0.001$]; (Table 2). The all-cause mortality rate per 100 person-years of follow up was 4.15 and 2.28 among patients with and without NAFLD, respectively. We observed 86 cancer-specific deaths (44% of all deaths). NAFLD was associated with an increased risk of cancer-specific mortality [HR: 3.21, 95% CI: 1.46–7.07; $P=0.004$]. The cancer-specific mortality rate per 100 person-years of follow up was 1.82 and 0.94 among patients with and without NAFLD, respectively. We observed 46 cardiovascular-specific deaths (23% of all deaths). NAFLD was not associated with an increased risk of cardiovascular-specific mortality [HR: 1.04, 95% CI: 0.30–3.64, $P=0.951$]. The cardiovascular-specific mortality rate per 100 person-years of follow up was 0.86 and 0.51 among patients with and without NAFLD, respectively. Excluding patients with a history of myocardial infarction or congestive heart failure at baseline did not substantively shift effect estimates for cardiovascular-specific mortality [HR: 0.78, 95% CI: 0.21–2.87, $P=0.717$].

3.3. NAFLD and Mortality Subgroups

Age modified the relationship between NAFLD and all-cause mortality ($P_{interaction}$=0.027), such that younger cancer survivors (<60 years) with NAFLD were more likely to die than older cancer survivors with NAFLD [HR: 3.15, 95 % CI: 1.42–6.97; P=0.005; (Table 3)]. Body mass index also modified the relationship between NAFLD and all-cause mortality ($P_{interaction}$=0.040), such that cancer survivors with NAFLD who were overweight or obese (≥25 kg/m^2) were more likely to die than normal weight cancer survivors with NAFLD [HR: 2.08, 95 % CI: 1.24–3.48; P=0.005].

4. DISCUSSION

In this sample of long-term cancer survivors aged 20–74 years, approximately one-in-five had NAFLD, and the presence of NAFLD was independently associated with a two- to three-fold increased risk of all-cause and cancer-specific mortality. Younger and overweight or obese cancer survivors may be particularly vulnerable to the deleterious effects of NAFLD. At baseline, cancer survivors with NAFLD were more likely to be older, have a higher body mass index and waist circumference, be insulin resistant, with higher blood pressure, elevated triglyceride concentrations, low high-density lipoprotein cholesterol concentrations, and with poorer self-rated overall health. These findings provide additional evidence to strengthen the rapidly growing literature suggesting that obesity-related metabolic complications are common after cancer therapy and are negative prognostic factors for cancer survivors [2,3].

The prevalence of NAFLD in our population-based sample was 17.6%, which is similar to prior estimates ranging between 20 and 30% in the general population [5,6]. Prior studies have provided contrasting evidence on the prognostic importance of NAFLD, which may be due, in part, to varying definitions of NAFLD. Several studies have concluded that the rate of all-cause mortality among people with NAFLD is two- to four-fold higher than that of the general population [7,28–31]. Conversely, several studies have concluded that the rates of all-cause mortality are not elevated among people with NAFLD [8,32]. Many studies have concluded that NAFLD is associated with an increased risk of hepatic-specific [7,29], and cardiovascular-specific mortality [7,28,31]. Fewer studies have examined cancer-specific mortality, and those these studies have reached conflicting conclusions [8,28,31]. NAFLD is a recognized risk factor for the development of hepatocellular carcinoma (primary liver cancer) [9]. Recent evidence has also implicated NAFLD as a risk factor for the development of a variety of other extra-hepatic malignancies in the gastrointestinal tract (i.e., colorectal, esophageal, gastric, and pancreatic), as well as kidney and breast cancer [10]. Many of the hypothesized mechanisms that link NAFLD to cancer risk, may also be implicated in the relationship of NAFLD with survival.

To our knowledge, there has not been a study that examined the influence of NAFLD on mortality outcomes among people with a history of cancer. Cancer survivors represent a unique population to study the relationship between NAFLD and mortality outcomes as various agents used in the treatment of cancer are associated with an increased risk of developing NAFLD. For example, breast cancer survivors treated with tamoxifen are more likely to develop hepatic steatosis compared to patients treated with anastrozole over a three-

year period (41.1 *vs* 14.6%; $P<0.001$) [11]. Colorectal cancer survivors treated with oxaliplatin and irinotecan are at an increased risk of developing steatohepatitis, sinusoidal dilation [12], and reductions in the density of liver parenchyma [13]. In some patients, NAFLD resolves when treatment is withdrawn, suggesting that the effects of cancer therapy on hepatic metabolism may be reversible [33].

Lifestyle changes through weight loss and exercise represent the cornerstone to the effective management of NAFLD [34]. Weight gain is associated with the progression of NAFLD [35]. Conversely, a weight loss of 5–7% is associated with improvements in steatosis, lobular inflammation, ballooning, and NAFLD activity scores [36,37]. Weight loss through caloric restriction is associated with an average 40% reduction in liver fat [34]. Exercise without concurrent dietary modification and in the absence of changes in body mass is associated with reductions intra-hepatic lipid content, alanine aminotransferase, and aspartate aminotransferase [38,39]. The magnitude of benefit with exercise is greater among people with a higher BMI [39]. This may be particularly relevant to cancer survivors, as our subgroup analyses demonstrated that overweight or obese (BMI ≥ 25 kg/m^2) cancer survivors with NAFLD were more likely to die than normal weight (BMI <25 kg/m^2) cancer survivors with NAFLD. Observational studies suggest that lifestyle behaviors related to improving energy balance such as physical activity, diet, and weight management are associated lower disease recurrence and mortality rates among cancer survivors [40]. Though the specific biologic mechanisms through which lifestyle behaviors improve cancer outcomes have not been elucidated, it is plausible that one mechanism may include improvements in hepatic-related lipid metabolism.

We acknowledge several limitations to this study. Ultrasonography was conducted at a single time point, such that we are unable to describe changes in NAFLD over time. Ultrasonography was conducted among participants aged 20–74 years, therefore we are unable to comment on the role of NAFLD among older cancer survivors. It is unknown if the cancer survivors in our sample had NAFLD prior to their diagnosis of cancer or developed NAFLD after their diagnosis of cancer, or perhaps, in part, due to cancer therapy. We also attempted to examine the relationship between nonalcoholic steatohepatitis (i.e., NASH) with mortality outcomes; however, our sample size was limited which reduced our statistical power and precluded our ability to conduct an informative analysis. We also did not have several cancer-specific characteristics, such as disease stage and cancer treatment history. It is plausible that the inclusion of these covariates would attenuate our effect size estimates. The calculation of the healthy eating index precluded us from parsing out specific dietary components that may modify the relationship between NAFLD and mortality (such as whole grains *vs* refined grains). Additional research is now needed to clarify the cancer-specific and stage-specific importance of NAFLD on cancer outcomes.

There are multiple strengths to this study. The main strength is the sampling design, which is representative of the US population of cancer survivors aged 20–74 years. Our classification of NALFD was determined based on ultrasonography, which reliably and accurately characterizes NAFLD [41], and has been utilized in this dataset previously [8]. Our multivariable-adjusted Cox regression models considered a variety of covariates that may

confound the relationship between NALFD and mortality in this population, including demographic, clinical, and behavioral characteristics.

5. CONCLUSION

In conclusion, we found that the presence of NAFLD among cancer survivors is associated with an increased risk of all-cause and cancer-specific mortality. Younger cancer survivors and those who are overweight or obese may be particularly prone to the deleterious effects of NAFLD on survival. Several demographic, anthropometric, and metabolic factors were associated with NAFLD among cancer survivors. Additional research is necessary to replicate these findings in specific cancer sites, and to test interventions, such as dietary modification or exercise, that may improve NAFLD and potentially improve patient outcomes.

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Table 1

Characteristics of study participants

Characteristic	Overall (n=387)[Mean ± SE) or (%)]	Nonalcoholic Fatty Liver Disease		*P*
		No (n=319)	Yes (n=68)	
Demographics				
Age, yr	51.6±1.11	50.7±1.3	55.4±2.0	0.043
Gender, %				
Male	28.0	27.1	32.3	0.504
Female	72.0	72.9	67.7	
Cancer				
Type of Cancer, %				
Breast	22.1	22.7	19.2	0.713
Gastrointestinal	11.8	11.4	13.9	
Genitourinary	13.0	12.1	17.0	
Gynecologic	29.1	30.7	22.1	
Lung	2.2	2.7	0.0	
Hematologic	5.3	4.8	7.8	
Other, Missing, or Can’t Remember	16.5	15.7	20.0	
Time Since Cancer Diagnosis, yr	9.2±0.5	9.0±0.6	9.8±1.5	0.623
Comorbidity				
Comorbid Health Conditions, %				
Hypertension	35.4	32.9	46.7	0.105
Hyperlipidemia	28.2	28.5	27.0	0.841
Diabetes	6.8	5.6	12.0	0.126
Myocardial Infarction	5.8	6.1	4.5	0.600
Stroke	2.0	1.6	3.5	0.294
Congestive Heart Failure	3.6	2.7	7.7	0.064
Metabolic				
Glucose, mmol/L	5.7±0.17	5.6±0.19	6.1±0.37	0.260
Insulin, pmol/L	72.4±4.7	62.2±3.4	117.0±16.8	0.001
HOMA-IR	3.4±0.3	2.8±0.3	5.9±1.2	0.012
Glycated Hemoglobin, %	5.5±0.09	5.5±0.1	5.7±0.2	0.321
Body Mass Index, kg/m^2	26.5±0.4	25.4±0.4	31.3±1.1	<0.001
Waist Circumference, cm	92.6±1.2	89.5±1.1	106.4±2.8	<0.001
Systolic Blood Pressure, mmHg	123.3±1.2	121.8±1.4	130.1±2.5	0.004
Diastolic Blood Pressure, mmHg	73.7±0.6	73.0±0.7	76.8±1.6	0.029
Creatinine, μmol/L	93.3±1.2	92.4±1.3	97.2±2.9	0.126
Lipid				
Total Cholesterol, mmol/L	5.6±0.07	5.6±0.08	5.6±0.20	0.995
HDL, mmol/L	1.3±0.03	1.4±0.03	1.1±0.03	<0.001
LDL, mmol/L	3.4±0.1	3.4±0.1	3.4±0.2	0.942
Triglycerides, mmol/L	1.8±0.1	1.6±0.1	2.6±0.3	0.007

Characteristic	Overall (n=387)[Mean ± SE) or (%)]	Nonalcoholic Fatty Liver Disease		*P*
		No (n=319)	Yes (n=68)	
Liver Function				
Alanine Aminotransferase, U/L	16.9±1.5	16.6±1.8	18.1±1.3	0.497
Aspartate Aminotransferase, U/L	21.6±1.2	21.6±1.5	21.2±1.6	0.858
γ-Glutamyl Transferase, U/L	31.5±3.9	29.4±4.6	40.7±5.7	0.123
Total Bilirubin, mol/L	9.8±0.5	9.5±0.5	10.6±1.4	0.486
Albumin, g/L	4.1±0.03	4.1±0.03	4.1±0.06	0.395
Behavioral				
Smoking Status, %				
Never	35.0	36.5	38.7	0.406
Former	39.2	37.1	48.5	
Current	25.8	26.4	22.7	
Regular Physical Activity, %	20.8	21.0	20.0	0.933
Healthy Eating Index, 0–100	65.6±0.8	66.0±1.0	63.6±1.4	0.160
Alcoholic Consumption, drinks/wk	0.9±0.1	0.9±0.1	0.8±0.3	0.779
Self-Reported Health, 0–100	53.0±1.9	54.9±2.1	44.6±3.5	0.012

Table 2

Relationship between nonalcoholic fatty liver disease and mortality

	All-Cause		Cancer-Specific		Cardiovascular-Specific	
	HR and 95% CI	***P***	**HR and 95% CI**	***P***	**HR and 95% CI**	***P***
Model 1[a]	1.87 (1.19–2.93)	0.007	1.94 (1.02–3.70)	0.045	1.76 (0.72–4.32)	0.217
Model 2[b]	2.02 (1.24–3.23)	0.005	2.03 (1.07–3.85)	0.031	1.72 (0.65–4.54)	0.272
Model 3[c]	2.62 (1.53–4.47)	<0.001	2.87 (1.17–6.98)	0.021	1.15 (0.35–3.82)	0.808
Model 4[d]	2.52 (1.47–4.34)	0.001	3.21 (1.46–7.07)	0.004	1.04 (0.30–3.64)	0.951

HR, Hazard Ratio. 95% CI, 95% Confidence Interval.

[a]Unadjusted.

[b]Adjusted for age.

[c]Adjusted for age, sex, type of cancer, time since cancer diagnosis, heart failure, waist circumference, insulin resistance, systolic blood pressure, and self-reported health.

[d]Adjusted for the variables in model 3, plus body mass index.

Table 3

Univariate subgroup relationships between nonalcoholic fatty liver disease and all-cause mortality

Subgroup	HR and 95% CI	*P*	$P_{interaction}$
Age			0.027
<60 yr	3.15 (1.42–6.97)	0.005	
≥60 yr	1.09 (0.67–1.78)	0.725	
Gender			0.751
Male	1.72 (0.90–3.29)	0.101	
Female	1.84 (1.04–3.27)	0.036	
Body Mass Index			0.040
<25 kg/m^2	0.48 (0.14–1.72)	0.262	
≥25 kg/m^2	2.08 (1.24–3.48)	0.005	
Waist Circumference			0.375
<88 (female) or <102 (male)	1.16 (0.48–1.79)	0.739	
≥88 (female) or ≥102 (male)	1.87 (1.04–3.36)	0.035	
Healthy Eating Index			0.424
<65	1.64 (0.84–3.12)	0.145	
≥65	2.29 (1.33–3.96)	0.003	
Regular Physical Activity			0.438
None	1.64 (0.99–2.72)	0.053	
Any	2.46 (0.99–6.10)	0.052	

HR, Hazard Ratio. 95% CI, 95% Confidence Interval.