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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.

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.

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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 $\leq$40 U/L for males and $\leq$31 U/L for females; aspartate aminotransferase $\leq$37 U/L for males and $\leq$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-h 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