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Zhang, Xinyuan

Zhao, Longgang

Christopher, Cami

et al.

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Original Research Article

Association of dietary insulinemic and inflammatory potential with risk of liver cancer and chronic liver disease mortality in postmenopausal women: a prospective cohort study

Xinyuan Zhang [1], Longgang Zhao [1,2], Cami N. Christopher [3], Fred K. Tabung [3,4], Wei Bao [5], David O. Garcia [6], Aladdin H. Shadyab [7], Nazmus Saquib [8], Marian L. Neuhouser [9], Lesley F. Tinker [9], Xuehong Zhang [1,3,*]

[1] *Channing Division of Network Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, United States;* [2] *Department of Epidemiology and Biostatistics, Arnold School of Public Health, University of South Carolina, Columbia, SC, United States;* [3] *Department of Nutrition, Harvard T.H. Chan School of Public Health, Boston, MA, United States;* [4] *Department of Internal Medicine, The Ohio State University College of Medicine and Comprehensive Cancer Center, Columbus, OH, United States;* [5] *Institute of Public Health, Division of Life Sciences and Medicine, University of Science and Technology of China, Hefei, Anhui, China;* [6] *Department of Health Promotion Sciences, Mel & Enid Zuckerman College of Public Health, University of Arizona, Tucson, AZ, United States;* [7] *Herbert Wertheim School of Public Health and Human Longevity Science, University of California, San Diego, La Jolla, CA, United States;* [8] *Department of Clinical Sciences, College of Medicine, Sulaiman AlRajhi University, Al Bukayriyah, Saudi Arabia;* [9] *Division of Public Health Sciences, Fred Hutchinson Cancer Center, Seattle, WA, United States*

A B S T R A C T

Background: Low diet quality, diabetes, and chronic inflammation are risk factors of liver cancer and chronic liver disease (CLD), but the extent to which insulinemic and inflammatory diets are independently associated with risk of liver cancer and CLD mortality is unknown.

Methods: We conducted a prospective cohort analysis among 78,356 postmenopausal women in the Women's Health Initiative Observational Study. Two validated dietary indices, the empirical dietary index for hyperinsulinemia (EDIH) and the empirical dietary inflammation pattern (EDIP), were estimated from a food-frequency questionnaire. Incident cases of liver cancer and CLD mortality were adjudicated via review of medical records and linkage to National Death Index. Multivariable hazard ratios (HRs) with 95% confidence intervals (CIs) were calculated using Cox proportional hazards models, adjusted for age, diabetes, body mass index, and other covariates.

Results: During a median 22.1 y of follow-up, we documented 176 primary liver cancer cases and 156 CLD mortality cases. EDIH was positively associated with incident liver cancer ($HR_{Quartile\ 4\ vs.\ Quartile\ 1} = 1.68$; 95% CI: 1.00, 2.83; *P*-trend = 0.05) and CLD mortality ($HR_{Q4\ vs.\ Q1} = 2.28$; 95% CI: 1.25, 4.15; *P*-trend = 0.02) in the multivariable model. EDIP was also positively associated with liver cancer ($HR_{Q4\ vs.\ Q1} = 1.88$; 95% CI: 1.17, 3.03; *P*-trend = 0.009) and CLD mortality ($HR_{Q4\ vs.\ Q1} = 1.85$; 95% CI: 1.09, 3.15; *P*-trend = 0.007). Estimates remained significant and robust in sensitivity analyses. Further analyses indicated positive associations for refined grains, processed meat, sugary beverages, and eggs, and inverse associations for coffee/tea and poultry.

Conclusions: Dietary insulinemic and inflammatory potentials were independently associated with higher risk of liver cancer and CLD mortality in U.S. postmenopausal women. These findings suggest a potential role for diet modification to reduce risk of liver cancer and CLD.

Keywords: liver cancer, chronic liver diseases, mortality, empirical dietary index for hyperinsulinemia, EDIH, empirical dietary inflammation pattern, EDIP, prospective cohort study

Abbreviations: AHEI, Alternative Health Eating Index; CLD, chronic liver disease; DII, dietary inflammatory index; EDIH, empirical dietary index for hyperinsulinemia; EDIP, empirical dietary inflammation pattern; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HEI, Healthy Eating Index; ICC, intrahepatic cholangiocarcinoma; NAFLD, nonalcoholic fatty liver disease; RERI, relative excess risk due to interaction; TNFaR-2, tumor necrosis factor receptor 2; WHI, Women's Health Initiative.

* Corresponding author

E-mail address: xuehong.zhang@channing.harvard.edu (X. Zhang).

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Introduction

Liver cancer is a common lethal malignancy, and the incidence is on the rise at the global level, especially in high-income countries [1]. In the United States, liver cancer incidence has tripled since the early 1980s [2]. Liver cancer has many risk factors and the most common one is cirrhosis, the end result for most chronic liver diseases (CLD) [3]. CLD has contributed to over 1 million deaths worldwide each year, and the trend is increasing [3,4]. These trends underscore the urgent need for identifying the underlying reasons for this alarming increase and searching for modifiable risk factors for prevention. Women are usually at lower risk for liver cancer [1] and CLD [5] than men, yet evidence suggests that this sex disparity may disappear in postmenopausal women, for example, for severe fibrosis and hepatocellular carcinoma (HCC) survival [6]. The combination of age, hormone change, and other underlying factors may uniquely influence the development and progression of liver disease and thus require further studies in postmenopausal women.

Dietary factors have been associated with liver cancer and CLD risk [7]. For example, large-scale epidemiological studies found that lower scores of commonly used diet quality indices, for example, the Healthy Eating Index-2010 (HEI-2010), Alternative Health Eating Index (AHEI), Alternate Mediterranean Diet, and Dietary Approaches to Stop Hypertension, were associated with higher liver cancer and CLD mortality risk with no significant heterogeneity by sex and race/ethnicity [8–11]. An empirical dietary index for hyperinsulinemia (EDIH) and an empirical dietary inflammation pattern (EDIP) were developed to capture the overall ability of dietary components to contribute to chronic insulin hypersecretion and systemic inflammation, respectively [12–14]. It is well documented that diabetes and chronic inflammation are risk factors of liver cancer and CLD [15,16], but whether the insulinemic and inflammatory potential of diet are associated with higher risk of the diseases requires further investigation [17].

In a large prospective cohort of postmenopausal women, we aimed to test our hypothesis that higher dietary insulinemic and inflammatory potential would be associated with higher risk of liver cancer and CLD mortality.

Methods

Study population

The Women's Health Initiative (WHI) comprised 161,808 postmenopausal women aged 50–79 y who were enrolled at 40 clinical centers in the United States between 1993 and 1998 (baseline). Detailed information on study design and population characteristics are described elsewhere [18,19]. The WHI protocol was approved by the institutional review boards at the Clinical Coordinating Center at the Fred Hutchinson Cancer Research Center in Seattle, WA, and all 40 sites. All participants signed written informed consent.

For this analysis, we started by including the 93,676 women in the WHI Observational Study. We then excluded participants with history of cancer except for nonmelanoma skin cancer ($N = 12,075$), missing in dietary or main lifestyle factors ($N = 81$), or implausible total energy intake (<600 kcal/d or >5,000 kcal/d; $N = 3,164$), leaving 78,356 participants in the final analytic cohort for this study (Figure 1).

Assessment of diet, EDIP, and EDIH scores

At baseline, a validated food-frequency questionnaire (FFQ) including 122 food items and 19 adjustment questions was used to estimate average daily foods or nutrients intake over the previous 3-mo period [20]. This FFQ has been validated against four 24-h dietary recalls and a 4-d food record (mean correlation coefficient = 0.56) [20].

The development and validation of the EDIH and EDIP scores in this study have been described previously and examined in several publications [12,13,21–23]. Briefly, EDIH is a weighted sum of 18 food groups most predictive of plasma C-peptide concentrations, a marker of systemic inflammation [13,21], and EDIP is a weighted sum of 18 food groups most predictive of plasma inflammatory biomarkers, including interleukin 6 (IL-6), C-reactive protein (CRP), and tumor necrosis factor receptor 2 (TNFaR-2) [12,22]. Detailed list of foods in food groups and corresponding weights in the calculation of scores are listed in Supplemental Table S1.

Outcome ascertainment

Incident cases of liver cancer and CLD mortality were ascertained through March 6, 2021. Liver cancer was identified from annual self-reported questionnaires and then adjudicated by medical record review with 86% of adjudicated liver cancer cases pathologically confirmed [24,25]. According to the International Classification of Diseases (ICD) code 9th and 10th versions, liver cancer subtypes were identified as secondary outcomes, including HCC (ICD-9: 155.0 and 155.2; ICD-10: C22.0 and C22.9) and intrahepatic cholangiocarcinoma (ICC; ICD-9: 155.1; ICD-10: C22.1).

Cause of death was recorded by medical record or death certificate review and coded according to the ICD codes [24]. National Death Index queries provided additional information and information on deaths was more than 98% complete [26]. CLD mortality was defined as death from alcoholic liver diseases, nonalcoholic fatty liver disease (NAFLD), liver fibrosis, cirrhosis, and chronic hepatitis (ICD-9: 571;

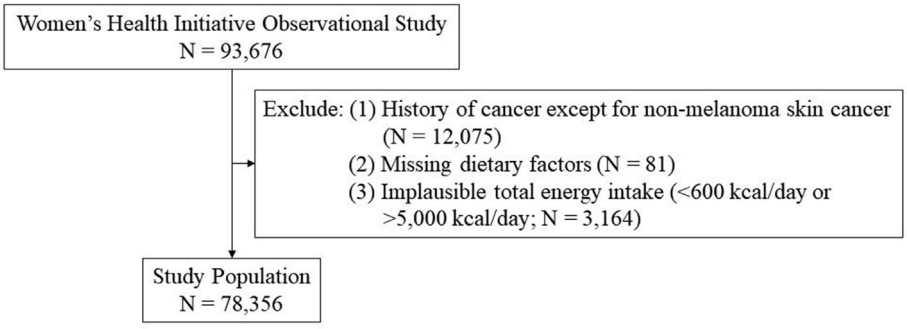

FIGURE 1. Flowchart of the study on dietary insulinemic and inflammatory potential with risk of liver cancer and chronic liver disease mortality in the Women's Health Initiative Observational Study.

ICD-10: K70, K73, K74, K75.8, and K76.0). Liver cancer mortality was not included in CLD mortality.

Covariate assessment

We selected, *a priori,* the relevant covariates according to the literature examining the relationship between diet and liver cancer [27]. Information on covariates reported via questionnaires at baseline included age, race, ethnicity, education, physical activity, smoking status, personal and family medical histories of cancer, and nonsteroidal anti-inflammatory drugs use (NSAID). Total energy intake, AHEI, and alcohol intake were calculated from the FFQ. Participants' weight and height were measured by trained staff and used to calculate body mass index (BMI, in kg/m^2). In a WHI ancillary study, serum hepatitis B virus (HBV) surface antigen and hepatitis C virus (HCV) antibody levels were assessed in 360 WHI participants [28].

Statistical analysis

EDIH and EDIP scores were classified into quartile categories. Participants characteristics at baseline were described according to quartiles of dietary indices as mean (SD) for continuous variables and number (percentage) for categorical variables.

Cox proportional hazards regression models were used to estimate HRs and 95% CIs for incident liver cancer and CLD mortality. Person-years of follow-up were calculated from baseline to the date of liver cancer diagnosis (for liver cancer analyses) or death (for CLD mortality analyses), loss to follow-up, or end of study period (March 6, 2021), whichever came first. The proportional hazards assumption was evaluated by testing an interaction term of exposures and follow-up time, with no violations observed. Model 1 was adjusted for age (continuous) and energy intake (kcal/d, in quartiles); model 2 was further adjusted for race (White, Black, other), ethnicity (Hispanic, non-Hispanic), education (below college, college, postgraduate), physical activity (metabolic equivalent task-h/wk, in quartiles), smoking status (never, <5 pack-y, 5–<20 pack-y, ≥20 pack-y), alcohol intake (never, past, <1 drink/mo, <1 drink/wk, 1–<7 drinks/wk, ≥7 drinks/wk), liver disease (yes, no), hormone therapy (never, past, current), NSAID use (yes, no), and family history of cancer (yes, no). In model 3, the main model, we further adjusted for the AHEI (in quartiles), BMI (<25, 25–<30, ≥30 kg/m^2), and diabetes (yes, no). Tests for linear trend were performed using the quartile medians of the scores as a continuous variable.

In secondary analyses, we examined HCC and ICC separately. In sensitivity analyses, we excluded cases that occurred in the first 2 y of follow-up to limit reverse causality (2-y lag analyses). We also excluded participants with self-reported liver disease at baseline or chronic hepatitis B/C infection. Among WHI participants with data on HBV/HCV infection status, we tested its correlations with the main exposure (EDIH and EDIP) to further evaluate to what extent HCV/HCV status might influence our findings.

To test the joint association and additive interaction between these 2 dietary indices, we dichotomized EDIH and EDIP at their medians and cross-classified the participants into 4 categories. The relative excess risk due to interaction (RERI) was calculated [29]. Food group components of the EDIH and EDIP indices were examined as secondary exposures. We also tested the multiplicative interactions between the dietary indices and age, smoking status, alcohol intake, BMI, waist circumference, diabetes, hypertension, and history of liver disease by including corresponding multiplicative terms in the main model.

All analyses were performed in SAS 9.4 (SAS institute Inc., Cary, NC). Statistical tests were 2 sided and $P < 0.05$ was set for statistical significance.

Results

The study population included 78,356 postmenopausal women with a mean age of 63.4 (SD: 7.3) y at baseline. Compared with participants with lower EDIH and EDIP scores (healthier diet), those in the highest quartile category (most unhealthy diet) were more likely to be Black, be Hispanic, have higher BMI, and have a history of diabetes; they tended to have less education, recreational physical activity, and alcohol intake (Table 1). Differences in total energy intake were found across the quartiles.

Associations between EDIH, EDIP, and liver cancer

During a median 22.1 y of follow-up, we documented 176 incident liver cancer cases and 156 CLD mortality cases. A higher EDIH score was positively associated with incident liver cancer risk (Table 2). The HR comparing the highest (Q4) vs. lowest quartile (Q1) was 1.68 (95% CI: 1.00, 2.83; *P*-trend = 0.05) in the main model (model 3). The association was further attenuated in the 2-y lag analysis ($HR_{Q4\ vs.\ Q1}$ = 1.50; 95% CI: 0.87, 2.58; *P*-trend = 0.13). A higher EDIP score was also positively associated with liver cancer risk ($HR_{Q4\ vs.\ Q1}$ = 1.88; 95% CI: 1.17, 3.03; *P*-trend = 0.009). We observed similar associations in the 2-y lag analysis.

Among the liver cancer cases, 126 were diagnosed as HCC and 48 were ICC. We observed similar patterns of a trend toward positive association between EDIH, EDIP, and risk of HCC and ICC (Supplemental Table S2). For HCC, the multivariable-adjusted $HR_{Q4\ vs.\ Q1}$ was 1.53 (95% CI: 0.82, 2.88; *P*-trend = 0.30) for EDIH and 1.87 (95% CI: 1.06, 3.33; *P*-trend = 0.04) for EDIP. For ICC, due to small case numbers, only a trend toward positive association with EDIH (*P*-trend = 0.03) and marginally positive association with EDIP (*P*-trend = 0.08) was observed.

Associations between EDIH, EDIP, and CLD mortality

Both EDIH and EDIP higher scores were strongly associated with a higher risk of CLD mortality (Table 2). The multivariable-adjusted $HR_{Q4\ vs.\ Q1}$ was 2.28 (95% CI: 1.25, 4.15; *P*-trend = 0.02) for EDIH and 1.85 (95% CI: 1.09, 3.15; *P*-trend = 0.007) for EDIP. Results remained similar in the 2-y lag analyses.

Sensitivity analyses

Excluding participants with self-reported liver disease at baseline (N = 1842) did not substantially change the results (Supplemental Table S3). In the subgroup of 177 participants with HBV/HCV assessments, neither EDIH nor EDIP was correlated with the HBV surface antigen or HCV antibody levels (Spearman correlation ranged 0.06–0.10, all $P > 0.05$). Excluding the HBV/HCV positive participants (N = 16) generated very similar results (Supplemental Table S3).

Joint associations between EDIH and EDIP

Although compared to participants with low EDIH and low EDIP (both <median), those with high EDIH and high EDIP (both ≥median) had the highest HR for liver cancer (1.71; 95% CI: 1.13, 2.60) and CLD

TABLE 1
Baseline characteristics of participants according to dietary insulinemic and inflammatory potential indices in the Women's Health Initiative Observational Study

	EDIH				EDIP			
	Quartile 1	Quartile 2	Quartile 3	Quartile 4	Quartile 1	Quartile 2	Quartile 3	Quartile 4
	$N = 19,589$	$N = 19,589$	$N = 19,589$	$N = 19,589$	$N = 19,589$	$N = 19,589$	$N = 19,589$	$N = 19,589$
Score	−0.15 (0.14)	0.06 (0.04)	0.21 (0.05)	0.55 (0.27)	−0.75 (0.28)	−0.35 (0.06)	−0.15 (0.06)	0.15 (0.20)
Age (y)	63.5 (7.3)	63.9 (7.3)	63.6 (7.3)	62.6 (7.3)	63.1 (7.2)	63.6 (7.3)	63.9 (7.4)	63.0 (7.5)
Race, *N* (%)								
White	17,142 (87.8)	16,470 (84.3)	16,415 (84.0)	15,713 (80.4)	17,998 (92.1)	17,377 (89.0)	16,351 (83.6)	14,014 (71.8)
Black	935 (4.8)	1373 (7.0)	1522 (7.8)	2108 (10.8)	676 (3.5)	997 (5.1)	1563 (8.0)	2702 (13.8)
Other	1447 (7.4)	1683 (8.6)	1612 (8.3)	1723 (8.8)	861 (4.4)	1155 (5.9)	1634 (8.4)	2815 (14.4)
Ethnicity, *N* (%)								
Hispanic	568 (2.9)	705 (3.6)	764 (3.9)	902 (4.6)	326 (1.7)	476 (2.4)	695 (3.6)	1442 (7.4)
Education, *N* (%)								
Below college	4578 (23.6)	5641 (29.0)	6245 (32.1)	7313 (37.7)	4607 (23.7)	5405 (27.8)	6160 (31.7)	7605 (39.2)
College	7436 (38.3)	7529 (38.7)	7560 (38.9)	7345 (37.8)	7754 (39.9)	7556 (38.8)	7549 (38.9)	7011 (36.1)
Postgraduate	7415 (38.2)	6274 (32.3)	5639 (29.0)	4751 (24.5)	7077 (36.4)	6494 (33.4)	5721 (29.4)	4787 (24.7)
Recreational physical activity (MET-h/wk)	17.7 (16.1)	14.7 (14.4)	12.7 (13.4)	10.3 (12.5)	16.5 (15.4)	14.7 (14.4)	13.4 (13.9)	10.9 (13.1)
Smoking status, *N* (%)								
Never	8758 (45.4)	10,010 (51.8)	10,440 (54.1)	10,254 (53.1)	8016 (41.5)	9344 (48.4)	10,677 (55.3)	11,425 (59.2)
<5 pack-y	3108 (16.6)	2913 (15.4)	2670 (14.1)	2491 (13.1)	2913 (15.5)	2995 (15.9)	2835 (15.0)	2439 (12.9)
5 to <20 pack-y	3188 (17.0)	2739 (14.5)	2544 (13.5)	2417 (12.8)	3354 (17.9)	2906 (15.4)	2420 (12.8)	2208 (11.6)
≥20 pack-y	3704 (19.7)	3209 (17.0)	3244 (17.2)	3782 (20.0)	4479 (23.9)	3583 (19.0)	2974 (15.7)	2903 (15.3)
Alcohol intake, serving/wk	4.23 (6.96)	2.13 (4.09)	1.96 (4.17)	1.91 (4.52)	5.13 (7.72)	2.52 (4.17)	1.62 (3.47)	0.95 (2.74)
Total energy intake (kcal/d)	1384 (476)	1355 (471)	1521 (488)	2024 (677)	1611 (559)	1499 (529)	1470 (555)	1705 (706)
AHEI	58.5 (9.9)	55.6 (9.3)	52.5 (9.4)	47.1 (9.9)	57.0 (10.3)	55.3 (9.9)	52.8 (9.7)	48.6 (10.3)
BMI, (kg/m^2)	25.5 (4.8)	26.5 (5.2)	27.4 (5.7)	29.4 (6.7)	26.3 (5.1)	26.7 (5.5)	27.1 (5.7)	28.7 (6.6)
Waist circumference (cm)	80.5 (11.6)	82.7 (12.4)	85.1 (13.1)	90.1 (15.0)	82.4 (12.3)	83.4 (12.9)	84.5 (13.5)	88.2 (14.8)
Self-reported diabetes, *N* (%)	571 (2.9)	882 (4.5)	1119 (5.7)	1575 (8.0)	631 (3.2)	855 (4.4)	1068 (5.5)	1593 (8.1)
Self-reported hypertension, *N* (%)	5243 (26.8)	6082 (31.0)	6632 (33.9)	7493 (38.3)	5361 (27.4)	5995 (30.6)	6588 (33.6)	7506 (38.3)
Self-reported liver disease, *N* (%)	437 (2.2)	447 (2.3)	460 (2.3)	498 (2.5)	453 (2.3)	432 (2.2)	463 (2.4)	494 (2.5)
Hormone replacement therapy, *N* (%)								
Never	7681 (39.2)	7425 (37.9)	7506 (38.4)	7972 (40.7)	7505 (38.3)	7419 (37.9)	7508 (38.4)	8152 (41.7)
Past	2585 (13.2)	2711 (13.9)	2669 (13.6)	2754 (14.1)	2604 (13.3)	2660 (13.6)	2798 (14.3)	2657 (13.6)
Current	9304 (47.5)	9438 (48.2)	9389 (48.0)	8843 (45.2)	9466 (48.4)	9487 (48.5)	9266 (47.3)	8755 (44.8)
NSAID use, *N* (%)	6855 (35.0)	7194 (36.7)	7543 (38.5)	7589 (38.7)	7375 (37.6)	7372 (37.6)	7245 (37.0)	7189 (36.7)
Family history of cancer, *N* (%)	12,386 (63.2)	12,379 (63.2)	12,448 (63.5)	12,299 (62.8)	12,700 (64.8)	12,467 (63.6)	12,304 (62.8)	12,041 (61.5)

Values are means (SDs) for continuous variable and *N* (%) for categorical variables. Categorical variables may not add up to 100% because missingness was not counted.

Abbreviations: AHEI, Alternative Healthy Eating Index; EDIH, empirical dietary index for hyperinsulinemia; EDIP, empirical dietary inflammation pattern; MET, metabolic equivalent of task; NSAID, nonsteroidal anti-inflammatory drug.

mortality (1.71; 95% CI: 1.08, 2.72), the RERI showed no additive effect between the 2 indices (both $P > 0.05$; Supplemental Table S4).

Subgroup analyses

We did not find interactive effects between the dietary indices and other risk factors except for EDIH and BMI in the analysis for liver cancer (P-interaction = 0.03; Supplemental Table S5). After stratifying by BMI, the positive association between a higher EDIH score and liver cancer was stronger in the under/normal weight group with BMI <25 kg/m^2 ($N = 31,916$; adjusted HR = 2.44; 95% CI: 1.08, 5.52; P-trend = 0.02; Table 3). No significant interaction was found between EDIP and BMI (P-interaction = 0.48; Table 3).

Among the food groups included in the calculation of EDIH and EDIP (Table 4), we found that per serving increase in refined grain intake was associated with higher risk of liver cancer (adjusted HR = 1.33; 95% CI: 1.11, 1.58), whereas higher intake of coffee or tea was marginally associated with lower risk of liver cancer (adjusted HR = 0.92; 95% CI: 0.83, 1.01). A higher intake of processed meat (adjusted HR = 1.99; 95% CI: 1.46, 2.71), sugary beverages (including both low- and high-energy soft drinks, adjusted HR = 1.25; 95% CI: 1.06, 1.48), or eggs (adjusted HR = 1.84; 95% CI: 1.06, 3.19) were associated with higher risk of CLD mortality, while a higher intake of poultry (adjusted HR = 0.46; 95% CI: 0.21, 1.00) or coffee or tea (adjusted HR = 0.90; 95% CI: 0.81, 1.00) were associated with lower risk of CLD mortality.

Discussion

In this large prospective cohort of postmenopausal women, higher EDIH and EDIP scores were associated with higher risk of liver cancer and CLD mortality, independent of other risk factors including BMI and diabetes. These associations remained robust in sensitivity analyses.

The Nurses' Health Study (women aged 40–65 y in 1986) and the Health Professionals Follow-up Study (men aged 40–75 y in 1986) previously reported the associations between EDIH, EDIP, and risk of HCC. Specifically, in women, the multivariable-adjusted $HR_{top\ vs.\ bottom\ tertile}$ was 1.97 (95% CI: 1.06, 3.66; P-trend = 0.03) for EDIH and 3.53 (95% CI: 1.71, 7.30; P-trend <0.01) for EDIP [17]. Although a direct comparison cannot be made due to differences in population characteristics, these are consistent with our results on EDIH, EDIP, and risk of HCC. A moderate effect modification was found for

TABLE 2
Cox proportional hazards models of liver cancer and chronic liver disease mortality according to dietary insulinemic and inflammatory potential indices in the Women's Health Initiative Observational Study

	Dietary index				*P*-trend
	Quartile 1	Quartile 2	Quartile 3	Quartile 4	
Incident liver cancer					
EDIH					
Index median (IQR)	−0.11 (−0.20, −0.06)	0.06 (0.02, 0.09)	0.20 (0.16, 0.25)	0.46 (0.37, 0.63)	
Case *N*	31	41	52	52	
Model 1	1 (ref)	1.32 (0.83, 2.11)	1.77 (1.13, 2.76)	1.99 (1.24, 3.21)	0.003
Model 2	1 (ref)	1.32 (0.82, 2.12)	1.74 (1.10, 2.75)	1.89 (1.15, 3.10)	0.009
Model 3	1 (ref)	1.29 (0.81, 2.08)	1.66 (1.04, 2.64)	1.68 (1.00, 2.83)	0.05
2-y lag	1 (ref)	1.21 (0.74, 1.98)	1.53 (0.95, 2.48)	1.50 (0.87, 2.58)	0.13
EDIP					
Index median (IQR)	−0.67 (−0.85, −0.56)	−0.35 (−0.41, −0.29)	−0.15 (−0.20, −0.10)	0.09 (0.01, 0.21)	
Case *N*	31	41	45	59	
Model 1	1 (ref)	1.31 (0.82, 2.09)	1.45 (0.91, 2.29)	2.04 (1.32, 3.15)	0.001
Model 2	1 (ref)	1.33 (0.83, 2.14)	1.49 (0.92, 2.39)	2.02 (1.26, 3.22)	0.003
Model 3	1 (ref)	1.30 (0.81, 2.09)	1.43 (0.89, 2.31)	1.88 (1.17, 3.03)	0.009
2-y lag	1 (ref)	1.24 (0.75, 2.04)	1.54 (0.94, 2.51)	1.82 (1.10, 2.99)	0.01
Chronic liver disease mortality					
EDIH					
Case *N*	18	41	33	64	
Model 1	1 (ref)	2.28 (1.31, 3.97)	2.04 (1.15, 3.64)	4.55 (2.60, 7.95)	<0.001
Model 2	1 (ref)	2.20 (1.25, 3.85)	1.82 (1.01, 3.28)	3.30 (1.85, 5.89)	<0.001
Model 3	1 (ref)	2.02 (1.15, 3.55)	1.51 (0.83, 2.73)	2.28 (1.25, 4.15)	0.02
2-y lag	1 (ref)	2.03 (1.16, 3.56)	1.52 (0.84, 2.74)	2.21 (1.21, 4.03)	0.04
EDIP					
Case *N*	23	25	49	59	
Model 1	1 (ref)	1.08 (0.61, 1.90)	2.11 (1.29, 3.48)	2.63 (1.62, 4.27)	<0.001
Model 2	1 (ref)	1.14 (0.64, 2.02)	2.16 (1.29, 3.62)	2.22 (1.31, 3.75)	0.001
Model 3	1 (ref)	1.07 (0.60, 1.91)	1.97 (1.17, 3.32)	1.85 (1.09, 3.15)	0.007
2-y lag	1 (ref)	1.08 (0.60, 1.92)	1.94 (1.15, 3.27)	1.83 (1.07, 3.13)	0.008

Values presented for the models are hazard ratios (95% confidence intervals).
Model 1 was adjusted for age (continuous) and energy intake (kcal/d, in quartiles).
Model 2 was further adjusted for race (White, Black, other), ethnicity (Hispanic, non-Hispanic), education (below college, college, postgraduate), recreational physical activity (metabolic equivalent of task-h/wk, in quartiles), smoking status (never, <5 pack-y, 5–<20 pack-y, ≥20 pack-y), alcohol intake (never, past, <1 drink/mo, <1 drink/wk, 1–<7 drinks/wk, ≥7 drinks/wk), liver disease (yes, no), hormone replacement therapy (never, past, current), nonsteroidal anti-inflammatory drug (yes, no), and family history of cancer (yes, no).
Model 3 was further adjusted for the Alternative Healthy Eating Index (in quartiles), body mass index (<25, 25–<30, ≥30 kg/m^2), hypertension (yes, no), and diabetes (yes, no).
Abbreviations: EDIH, empirical dietary index for hyperinsulinemia; EDIP, empirical dietary inflammation pattern; IQR, interquartile range.

diabetes and BMI, which is also similar to our findings [17]. This earlier study did not include ICC, total liver cancer, or CLD mortality. Our study contributes to the limited prospective evidence on the association between dietary indices and end-stage liver outcomes, including liver cancer, its subtypes, and CLD mortality. Our findings provide evidence for reducing insulinemic and inflammatory potentials of diet for improving liver health, specifically among postmenopausal women who may have decreased hepatic ability of fatty acid oxidation and increased lipogenesis that in turn may induce inflammation [30].

A dietary pattern that possesses hyperinsulinemic potential might increase risk of liver diseases. Abnormal glucose metabolism, for example, impaired fasting glucose and insulin resistance, causes DNA damage, hepatocyte iron overload, steatosis, and advanced fibrosis, which could progress to chronic, late-stage liver disease and liver cancer [16]. Another explanation is that insulin resistance results in chronic hyperinsulinemia and increase in bioavailable insulin-like growth factor 1, which could stimulate hepatic carcinogenesis [31]. Further adjusting for diabetes attenuated the association which remained statistically significant, and testing for the interaction between EDIH and diabetes generated nonsignificant results. This may suggest other metabolic pathways toward liver pathogenesis that are complicated by the hyperinsulinemic potential of diet. The EDIH was validated against serum C-peptide, a precursor to insulin [13]. Compared to other similar indices, for example, dietary glycemic index and glycemic load, C-peptide is closely related to the usual secretion of insulin and less an indicator of an immediate insulin response to diet [32]. Interestingly, liver and renal functions could interfere with the plasma measurement of insulin and C-peptide [32]. Although limited evidence link C-peptide directly to liver cancer risk, C-peptide levels were found to be higher in NAFLD and steatohepatitis [33], 2 early-stage CLD, and this risk might translate to subsequent liver cancer.

The liver is vulnerable to oxidative stress and inflammation. Chronic inflammation is a key element in the pathogenesis of CLD and liver carcinogenesis by subsequently inducing transcription, protein expression, cell apoptosis, and hepatic stellate cell activation [15]. Inflammatory cytokines might mediate the association between pro-inflammatory diet and liver disease. Levels of nutrients and bioactive components might also explain the association. A previous prospective cohort study in the Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial found that the dietary inflammatory index (DII), a score calculated based mostly on micronutrients, macronutrients, and some bioactive components [34], was associated with higher risks of

TABLE 3
Associations of dietary insulinemic and inflammatory potential indices with liver cancer risk, stratified by body mass index (BMI) status

	Dietary index				*P*-trend	*P*-interaction with BMI
	Quartile 1	Quartile 2	Quartile 3	Quartile 4		
EDIH						0.03
BMI <25 kg/m^2 (N = 31,916)						
Case, N	14	14	17	19		
Multivariable model	1 (ref)	1.15 (0.54, 2.44)	1.65 (0.78, 3.48)	2.44 (1.08, 5.52)	0.02	
BMI ≥25 kg/m^2 (N = 45,538)						
Case, N	17	26	35	33		
Multivariable model	1 (ref)	1.29 (0.69, 2.39)	1.60 (0.88, 2.91)	1.39 (0.71, 2.71)	0.35	
EDIP						0.48
BMI <25 kg/m^2 (N = 31,916)						
Case, N	14	21	13	16		
Multivariable model	1 (ref)	1.57 (0.79, 3.13)	1.01 (0.46, 2.21)	1.48 (0.68, 3.24)	0.50	
BMI ≥25 kg/m^2 (N = 45,538)						
Case, N	17	20	31	43		
Multivariable model	1 (ref)	1.11 (0.57, 2.14)	1.69 (0.91, 3.13)	2.19 (1.19, 4.05)	0.005	

Values presented for the models are hazard ratios (95% confidence intervals).
Multivariable model was adjusted for age (continuous) and energy intake (kcal/d, in quartiles), race (White, Black, other), ethnicity (Hispanic, non-Hispanic), education (below college, college, postgraduate), recreational physical activity (metabolic equivalent of task-h/wk, in quartiles), smoking status (never, <5 pack-y, 5–<20 pack-y, ≥20 pack-y), alcohol intake (never, past, <1 drink/mo, <1 drink/wk, 1–<7 drinks/wk, ≥7 drinks/wk), the Alternative Healthy Eating Index (in quartiles), liver disease (yes, no), hormone replacement therapy (never, past, current), nonsteroidal anti-inflammatory drug (yes, no), family history of cancer (yes, no), hypertension (yes, no), and diabetes (yes, no).
Abbreviations: EDIH, empirical dietary index for hyperinsulinemia; EDIP, empirical dietary inflammation pattern.

TABLE 4
Associations of food group components with liver cancer and chronic liver disease (CLD) mortality risk

Food group	Mean intake, serving/d	Liver cancer	CLD mortality
Positive components with EDIH/EDIP			
Processed meat	0.23	0.72 (0.40, 1.31)	1.99 (1.46, 2.71)
Red meat	0.44	0.87 (0.57, 1.32)	0.92 (0.62, 1.36)
Poultry	0.27	0.68 (0.35, 1.34)	0.46 (0.21, 1.00)
Sugary beverages	0.15	1.04 (0.77, 1.40)	1.25 (1.06, 1.48)
Margarine	0.03	0.55 (0.10, 3.06)	0.66 (0.13, 3.40)
Butter	0.37	0.99 (0.73, 1.33)	1.26 (0.97, 1.64)
Nondark fish	0.22	1.07 (0.51, 2.27)	0.58 (0.22, 1.50)
Eggs	0.13	1.67 (0.86, 3.23)	1.84 (1.06, 3.19)
Low-fat dairy	0.16	0.93 (0.54, 1.59)	0.81 (0.42, 1.55)
Cream soup	0.03	4.02 (0.96, 16.9)	0.24 (0.01, 3.83)
Tomatoes	0.54	1.06 (0.79, 1.43)	0.96 (0.69, 1.35)
French fries	0.05	0.57 (0.09, 3.44)	1.34 (0.41, 4.39)
Other vegetables	0.40	0.97 (0.67, 1.39)	0.78 (0.51, 1.21)
Refined grain	1.32	1.33 (1.11, 1.58)	1.00 (0.81, 1.22)
Inverse components with EDIH/EDIP			
Green leafy vegetables	0.89	0.92 (0.73, 1.16)	0.82 (0.62, 1.08)
Dark yellow vegetables	0.65	0.94 (0.69, 1.29)	0.68 (0.46, 1.02)
Wine	0.21	0.89 (0.55, 1.43)	0.87 (0.56, 1.36)
Coffee or tea	2.07	0.92 (0.83, 1.01)	0.90 (0.81, 1.00)
High-fat dairy	1.67	0.97 (0.89, 1.06)	0.96 (0.87, 1.05)
Whole fruit	2.82	0.95 (0.87, 1.05)	0.95 (0.86, 1.05)
Snack	0.37	0.89 (0.62, 1.28)	0.91 (0.64, 1.31)
Fruit juice	0.62	0.79 (0.60, 1.04)	0.94 (0.73, 1.21)
Pizza	0.05	0.50 (0.04, 6.88)	0.29 (0.02, 4.66)

Values presented for the models are hazard ratios (95% confidence intervals) per serving increase.
Multivariable model was adjusted for age (continuous) and energy intake (kcal/d, in quartiles), race (White, Black, other), ethnicity (Hispanic, non-Hispanic), education (below college, college, postgraduate), recreational physical activity (metabolic equivalent of task-h/wk, in quartiles), smoking status (never, <5 pack-y, 5–<20 pack-y, ≥20 pack-y), alcohol intake (never, past, <1 drink/mo, <1 drink/wk, 1–<7 drinks/wk, ≥7 drinks/wk), the Alternative Healthy Eating Index (in quartiles), liver disease (yes, no), hormone replacement therapy (never, past, current), nonsteroidal anti-inflammatory drug (yes, no), family history of cancer (yes, no), BMI (<25, 25–<30, ≥30 kg/m^2), hypertension (yes, no), and diabetes (yes, no).
Abbreviations: EDIH, empirical dietary index for hyperinsulinemia; EDIP, empirical dietary inflammation pattern.

primary liver cancer incidence and mortality [35]. EDIP captures the inflammatory potential of overall dietary pattern based on food groups and is validated against IL-6, CRP, and TNFaR-2. Compared to the scoring algorithm of DII, EDIP is a more straightforward index calculated from food groups and may be easier to translate into clinical practice.

Because of the likely crosstalk between inflammation and insulin resistance, for example, TNF-α and IL-6 contributing to insulin resistance as well as other metabolic dysregulations [36], we analyzed whether there is a synergic effect of EDIH and EDIP on liver outcomes. We did not find a significant interaction between EDIH and EDIP, which could suggest independent contributions on liver cancer and CLD mortality or could result from foods overlapping between the 2 dietary indices. Analyses of individual food groups and liver outcomes indicated positive associations with refined grains, processed meat, sugary beverages, and eggs, and inverse associations with coffee or tea, and poultry. Particularly, coffee or tea intake was inversely associated with both liver cancer and CLD mortality. This was consistent with the report from the World Cancer Research Fund and American Institute for Cancer Research that summarized the strong evidence of a decreased liver cancer risk with coffee intake [27]. According to this report, evidence for most dietary exposures, however, remained inconclusive. Nevertheless, it is important to replicate our findings in other cohorts to further validate them for use in recommendations or policies.

Our study has several strengths, including the prospective study design, confirmation of disease outcomes via medical records, and availability of extensive information on diet and relevant covariates. Our study also has limitations. First, self-reported dietary assessment was prone to measurement errors and the number of items in the FFQ was limited. Second, reverse causation might exist where diet changed as a result of disease status, but the lag analysis and sensitivity analysis excluding baseline liver disease demonstrated the robustness of results. Third, although the model was adjusted for diabetes, hypertension, and BMI, it was likely not adequate to fully account for the outcome effect due to the difference in metabolic syndrome, and information on histories of NAFLD is unknown. Last, there is potential confounding by hepatitis infection; however, in a subset of the participants with available assessments, EDIH/EDIP was not correlated with HBV or HCV infection status. This suggested that the observed associations are unlikely to be substantially confounded by HBV/HCV status.

In summary, we found that dietary insulinemic and inflammatory potentials were associated with higher risk of liver cancer and CLD mortality. Future clinical trials should consider dietary interventions to determine whether reduction of insulinemic and inflammatory diets may contribute to lower risk of future liver cancer and CLD mortality.

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Author Contributions

The authors' responsibilities were as follows – Xuehong Zhang: study concept and design; Xinyuan Zhang, LZ: analysis and interpretation of data; Xinyuan Zhang: drafting of the manuscript; and all authors: critical revision of the manuscript for important intellectual content.

Conflicts of Interest

The authors report no conflicts of interest.

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Data Availability

Data described in the manuscript, code book, and analytic code will be made available upon request pending application and approval of the Women's Health Initiative.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ajcnut.2023.07.009.

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