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Research Article

Cancer Prevention Research

Higher Glucose and Insulin Levels Are Associated with Risk of Liver Cancer and Chronic Liver Disease Mortality among Men without a History of Diabetes

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Abstract

Insulin resistance likely increases the risk of chronic liver disease (CLD) and liver cancer, but long-term prospective studies with measured fasting glucose and insulin are lacking. We evaluated the associations of prediagnostic fasting glucose, insulin, and the homeostasis model assessment of insulin resistance (HOMA-IR) with liver cancer and CLD mortality in a prospective study of Finnish male smokers with extended follow-up time (≤22 years) and information on known risk factors using data from 138 incident primary liver cancer cases, 216 CLD deaths, and 681 matched controls. Fasting glucose and insulin were measured in baseline serum. We used unconditional logistic regression to estimate ORs and 95% confidence intervals adjusted for age, alcohol, education, smoking, body mass index, and hepatitis B and C viral status. Among those without self-reported diabetes, glucose was positively associated with liver cancer [quartile 3 vs. quartile 1 (Q3/Q1): OR = 1.88; 1.03–3.49; Q4/Q1: OR = 2.40; 1.33–4.35; P_{trend} = 0.002], and undiagnosed, biochemically defined, diabetes was associated with higher risk of liver cancer (OR = 2.95; 1.46–5.96) and CLD mortality (OR = 1.88; 1.00–3.56). Serum insulin and HOMA-IR were also positively associated with liver cancer (Q4/Q1: OR = 3.41; 1.74–6.66; P_{trend} < 0.0001; OR = 3.72; 1.89–7.32, P_{trend} < 0.0001, respectively) and CLD (OR = 2.51; 1.44–4.37; P_{trend} = 0.0002; OR = 2.31; 1.34–3.97; P_{trend} = 0.001, respectively), with stronger associations observed for liver cancer diagnosed >10 years after baseline. In conclusion, elevated fasting glucose and insulin and insulin resistance were independently associated with risk of liver cancer and CLD mortality, suggesting a potentially important etiologic role for insulin and glucose dysregulation even in the absence of diagnosed diabetes. *Cancer Prev Res; 9(11); 866–74. ©2016 AACR.*

Introduction

Chronic liver disease (CLD), including cirrhosis, is a major cause of death in the United States, especially among men (1). Liver cancer is the sixth most commonly occurring cancer and the second-leading cause of cancer-related mortality worldwide (2), and most cases of liver cancer are preceded by advanced liver disease (3). Although typically more common in developing countries, rates of liver cancer have increased rapidly in developed countries, including the United States and countries in Europe (4–7). Hepatitis B (HBV) and C (HCV) viruses, excessive alcohol intake, and aflatoxin exposure are strong risk factors for CLD (8) and liver cancer (4, 9). Much of the increase in liver cancer in Western countries has been ascribed to HCV (10, 11). However, 30% to 40% of liver cancers occur in patients without established risk factors (12).

In addition to HCV, obesity and diabetes may contribute to increasing liver cancer rates. Researchers have shown that diabetes is associated with a 2-fold increased risk of CLD (8), and a large body of evidence supports a positive association between diabetes and liver cancer (13–15). Several mechanisms are possible (16, 17), including that high insulin may have mitogenic effects (18). Patients with diabetes are also more likely to have hepatic steatosis (19, 20), either as simple nonalcoholic fatty liver disease or the more extreme form of nonalcoholic steatohepatitis. Fatty liver may increase liver cancer risk through excess inflammation, oxidative stress, and other mechanisms (20–23). Recent studies estimate that one third or more of the U. S. adults have fatty liver (24).

Although associations between diabetes and liver cancer have been widely reported (13, 14), some prior studies had limitations. Previous studies, many of which relied on self-reported diabetes, likely underestimated the prevalence of diabetes, and studies of undiagnosed diabetes or higher glucose in the absence of diabetes are lacking. In addition, studies have often not had complete ascertainment of possible confounding factors, such as alcohol intake, HBV, HCV, and obesity (25). Most studies with information on HBV and HCV were conducted in populations with high prevalence, limiting statistical power for examination of the diabetes association in HBV- and HCV-negative participants. Many previous studies employed a cross-sectional design or had only limited follow-up between diabetes assessment and cancer incidence, precluding evaluation of temporality (13, 26). This

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may be of particular concern as the liver plays a critical role in glucose and insulin metabolism, and cirrhosis can cause insulin resistance and diabetes (27). Finally, few studies examined associations between prediagnostic insulin concentrations and subsequent risk of liver cancer (28).

Because most cases of liver cancer develop in those with advanced CLD, it is possible to gain further insight into disease etiology by studying both endpoints. Thus, we examined the associations of prediagnostic fasting glucose, insulin, and the homeostasis model assessment of insulin resistance (HOMA-IR; refs. 29, 30) with primary liver cancer incidence or CLD mortality during up to 22 years of follow-up in the Alpha-Tocopherol, Beta-Carotene Cancer Prevention (ATBC) Study, a large prospective cohort with low HBV and HCV prevalence (31).

Materials and Methods

Participants

The ATBC study was a randomized, double-blind placebo-controlled, primary prevention trial designed to determine whether daily supplementation with α-tocopherol (50 mg/day), β-carotene (20 mg/day), or both would reduce the incidence of lung and other cancers in male smokers (31).

The ATBC cohort includes 29,133 Finnish male smokers, aged 50 to 69 years old, who were enrolled between April 1985 and June 1988. Individuals with a history of cirrhosis or chronic alcoholism were excluded from the study. Although supplementation ended in 1993, participants have been under follow-up since that time. ATBC was approved by the Institutional Review Boards of both the NIH (Bethesda, MD) in the United States and the National Public Health Institutes in Finland. All participants provided written informed consent.

Follow-up, outcome ascertainment, and control selection

Men diagnosed with primary incident liver cancer (ICD-9 = 155) were identified through the Finnish Cancer Registry, which provided close to 100% case ascertainment (32). Men who died from CLD (ICD-9 = 571) were identified through the Finnish Register of Causes of Death. For the current study, men who developed liver cancer and died of CLD were only included in the liver cancer analysis. Controls were alive and cancer free at the time of case diagnosis or death and were matched to cases (2:1) on age at randomization (±1 year), date of blood draw (±30 days), and sample availability.

With follow-up through December 31, 2007, 144 incident liver cancer cases, 218 CLD deaths, and 723 matched controls were identified in ATBC. For the current study, 138 incident liver cancer cases, 216 participants who died from CLD, and 681 matched controls had adequate baseline serum to measure insulin, and glucose and test for HBV and HCV, markers.

Data collection and laboratory analysis

Prior to randomization, at baseline, participants completed questionnaires detailing demographic information, lifestyle, and medical history, including whether they had been diagnosed with diabetes. Participant's height and weight were measured by trained study staff. Participants completed a food frequency questionnaire, which queried intake of alcohol and 275 other items. All participants donated a fasting (overnight) blood sample at baseline which was stored at −70°C.

The SAIC NCI-Frederick National Laboratory tested for HBV surface antigen (HBsAg), an indication of current HBV infection, antibody to hepatitis B core antigen (anti-HBc), an indication of whether a person has ever been infected, and for antibody to HCV (anti-HCV) an indication of current infection with HCV. HBsAg was tested using an enzyme immunoassay (Bio-Rad Laboratories). Anti-HBc and anti-HCV were tested using ELISA (Ortho Clinical Diagnostics). We included a panel of samples with known HBV and HCV positivity, and concordance with known status was perfect.

Insulin and glucose were measured in baseline serum by the Immunochemical Core Laboratory at the Mayo Clinic (Rochester, MN). Insulin was measured using a two-site immunoenzymatic assay on the Dxl automated immunoassay system from Beckman Instruments. The interassay coefficient of variation (CV) for a pooled quality control sample included in each batch (8% of the overall samples) was 3.2%, with a range across batches of 1.5% to 5.7%. Serum glucose was measured on the Roche Cobas c311 (Roche Diagnostics) utilizing a hexokinase reagent from Boehringer Mannheim. The interassay CV was 0.6%, with a range across batches of 0.1% to 2.1%. HOMA-IR (fasting insulin × fasting glucose/22.5, with fasting insulin expressed in μU/mL and fasting glucose expressed in mmol/L) was calculated as described previously (29).

A subset of serum samples from cohort participants ($n = 50$) was tested for the presence of aflatoxin–albumin adducts at the University of Leeds (Leeds, England). As expected in the Finnish population, we found no evidence for exposure in this subset (data not shown); therefore, we did not measure aflatoxin exposure in our larger case–control set.

Statistical analysis

Diabetes was defined by either self-report or having fasting glucose ≥126 mg/dL (33). For glucose, insulin, and HOMA-IR, we used quartiles with cut-off points based on the distribution of the controls who did not report diabetes at baseline. We tested for differences in the distribution of potential risk factors between cases and controls using the χ^2 and the Wilcoxon rank tests for categorical and continuous variables, respectively. Among controls who did not report a diagnosis of diabetes at baseline, we also examined baseline characteristics by median glucose, insulin, and HOMA-IR using the Mantel–Haenszel χ^2 or Fisher exact test for categorical variables and the Jonckheere–Terpstra test for continuous variables.

ORs and 95% confidence intervals (95% CI) were calculated using unconditional logistic regression models. Results were similar using conditional logistic regression models (data not shown). We present ORs from age (years)-adjusted models and from models that were additionally adjusted for alcohol intake (≤2.8, >2.8 to ≤11, >11 to ≤26, >26 to ≤44, >44 g/day), body mass index (BMI, <18.5, 18.5 to <25, 25 to <30, 30 to <35, ≥35 kg/m^2), anti-HBc, HBsAg, anti-HCV, education (elementary education or less), cigarettes per day, and duration of smoking (years). Tests for trend were conducted by treating quartiles as an ordinal variable in the model; statistical significance was then determined by the Wald test. Follow-up time began at the date of randomization and continued until the date of cancer diagnosis, death, or December 31, 2007, whichever came first. We also conducted time-stratified analyses by follow-up for the first 10 years or more than 10 years.

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We performed stratified analyses by median alcohol intake (≤11.3 vs. >11.3 g/day), BMI (≤26 vs. >26 kg/m^2), cigarettes per day (≤ 20 vs. >20), and years smoked (≤ 35 vs. >35). We used dichotomous cut-off points for HOMA-IR and insulin concentration, comparing participants in the fourth quartile (Q4) versus those in the first through third quartiles (Q1–3). Interactions were tested by comparing models with and without cross-product terms using likelihood ratio tests. We conducted sensitivity analysis excluding HBV- and HCV-positive participants.

Finally, among those who did not report a diagnosis of diabetes at baseline, we examined the joint effects of glucose-defined diabetes with insulin concentration and daily alcohol intake, as these factors may modify associations of diabetes with liver cancer and liver disease mortality. For insulin, we used a referent group of participants who did not have diabetes and had an insulin level <6.7 μU/mL, the 75th percentile in controls. For alcohol, the referent group included participants without diabetes and with below median alcohol intake.

All analyses were conducted with SAS version 9.3. All statistical tests were two-sided.

Results

Baseline characteristics are shown in Table 1 for participants who developed liver cancer or who died from CLD and their matched controls. The age ranges of cases and controls were similar for both endpoints. Both case groups drank more alcohol than controls, although this difference reached statistical significance only for CLD mortality where above, as compared with below, median alcohol intake was associated with more than a 4-fold increased odds of CLD mortality. Relative to controls, those who developed liver cancer had a longer smoking duration, whereas those who died from CLD tended to smoke more cigarettes per day but had similar smoking duration. A very low proportion of study participants tested positive for HBV or HCV; nevertheless, the prevalence of anti-HBc but not HBsAg was higher in liver cancer cases, and the prevalence of anti-HCV was higher in both liver cancer and liver disease mortality cases as compared with controls.

Participants who developed liver cancer were more likely than controls to be obese at baseline, yet no difference was observed for CLD. The prevalence of diabetes, defined as either having a self-report or a glucose ≥126 mg/dL, was higher in liver cancer (21.0%) and CLD cases (14.4%) than in their matched controls (7.1% and 9.4%, respectively). Among those who did not report a diabetes diagnosis at baseline, a higher percentage of liver cancer (12.1%) and CLD cases (10.6%) relative to controls (4.1% and 5.4%, respectively) had glucose ≥126 mg/dL. Finally, fasting insulin concentrations were higher in both case groups relative to controls, as were HOMA-IR scores (Table 1).

Distributions of baseline characteristics by median glucose, insulin, and HOMA-IR among controls who did not report a previous diagnosis of diabetes are shown in Table 2. The prevalence of overweight and obesity were associated with higher glucose and insulin concentrations and higher HOMA-IR scores. As expected, insulin concentration tended to be higher among those with higher glucose concentration.

Tables 3 and 4 show the associations for prediagnostic diabetes, fasting concentration of glucose or insulin, and HOMA-IR with liver cancer or CLD. Diabetes, defined either by self-report or fasting glucose, was associated with both liver cancer (Table 3: OR = 2.79; 95% CI, 1.65–4.75) and CLD mortality (Table 4: OR = 1.83; 95% CI, 1.09–3.10) in multivariable models. ORs for self-reported diabetes and glucose-defined diabetes were of similar magnitude and direction for liver cancer, but for CLD mortality, the OR for

Table 1. Baseline characteristics of cases and controls in ATBC

	Liver cancer			CLD deaths		
Baseline characteristics	**Cases[a] (*n* = 138)**	**Controls[a] (*n* = 253)**	**OR (95% CI)[b]**	**Cases[a] (*n* = 216)**	**Controls[a] (*n* = 428)**	**OR (95% CI)[b]**
Entry age (years)	58 (55–62)	57 (54–61)	1.03 (0.99–1.07)	55 (52–58)	55 (51–58)	1.00 (0.96–1.04)
Cigarettes/day	20 (15–25)	20 (13–20)	1.03 (1.01–1.06)	23 (15–25)	20 (15–25)	1.03 (1.01–1.05)
Smoking duration	40 (34–43)	37 (30–42)	1.02 (1.00–1.05)	35 (30–40)	35 (30–40)	1.00 (0.98–1.03)
Alcohol, >11.3 g/day[c]	71 (54.6%)	115 (47.7%)	1.36 (0.89–2.10)	157 (81.8%)	205 (51.6%)	4.25 (2.80–6.46)
HBV, antibody to core antigen, yes	22 (15.9%)	17 (6.7%)	2.52 (1.38–4.96)	14 (6.5%)	27 (6.3%)	1.04 (0.53–2.05)
HBV, surface antigen, yes	2 (1.5%)	3 (1.2%)	1.26 (0.21–7.67)	1 (0.5%)	1 (0.2%)	2.00 (0.12–32.07)
HCV, antibody, yes	6 (4.4%)	2 (0.8%)	5.44 (1.08–27.39)	6 (2.8%)	2 (0.5%)	6.22 (1.24–31.20)
BMI						
<18.5 kg/m^2	2 (1.5%)	1 (0.4%)	4.62 (0.40–53.08)	2 (0.9%)	1 (0.2%)	3.99 (0.36–44.6)
18.5 to <25 kg/m^2	38 (27.5%)	93 (36.8%)	1.00	77 (35.7%)	154 (36.0%)	1.00
25 to <30 kg/m^2	63 (45.7%)	120 (47.4%)	1.30 (0.80–2.12)	100 (46.3%)	203 (47.4%)	0.98 (0.68–1.42)
30 to <35 kg/m^2	28 (20.3%)	37 (14.6%)	1.85 (1.00–3.45)	31 (14.4%)	62 (14.5%)	1.00 (0.60–1.67)
≥35 kg/m^2	7 (5.1%)	2 (0.8%)	8.39 (1.67–42.29)	6 (2.7%)	8 (1.9%)	1.50 (0.50–4.47)
Elementary education or less	103 (74.6%)	192 (75.9%)	0.94 (0.58–1.52)	154 (71.3%)	339 (79.2%)	0.65 (0.45–0.95)
Self-reported diabetes, yes	14 (10.1%)	8 (3.2%)	3.35 (1.37–8.23)	9 (4.2%)	18 (4.2%)	0.99 (0.44–2.25)
Glucose ≥126 mg/dL[d]	15 (12.1%)	10 (4.1%)	3.44 (1.49–7.96)	22 (10.6%)	22 (5.4%)	2.10 (1.13–3.88)
Either self-reported or glucose ≥126 mg/dL	29 (21.0%)	18 (7.1%)	3.53 (1.88–6.65)	31 (14.4%)	40 (9.4%)	1.63 (0.99–2.68)
Glucose (mg/dL)[d]	103 (95–113)	98 (92–106)	1.03 (1.02–1.04)	101 (93–111)	99 (93–106)	1.00 (1.00–1.01)
Insulin (μU/mL)[d]	7.0 (3.8–11.2)	4.3 (2.8–6.5)	1.16 (1.10–1.22)	4.3 (2.9–6.6)	5.4 (3.2–9.5)	1.06 (1.03–1.09)
HOMA-IR[d]	1.9 (0.9–3.3)	1.1 (0.7–1.6)	1.65 (1.38–1.98)	1.1 (0.7–1.7)	1.3 (0.8–2.5)	1.18 (1.07–1.30)

[a]Median (IQR) for continuous variables; n (column %) for categorical variables.
[b]Models, other than the models for entry age, are age adjusted.
[c]Median level of alcohol consumption was 11.3 g/day.
[d]Restricted to participants who did not report a diagnosis of diabetes at baseline.

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Table 2. Baseline characteristics of controls ($n = 655$) by median glucose, insulin, and HOMA-IR among participants who did not report a previous diagnosis of diabetes.

	Glucose[a]			Insulin[a]			HOMA-IR[a]		
Baseline characteristics	**≤99 mg/dL ($n = 346$)**	**>99 mg/dL ($n = 309$)**	**P^b**	**≤4.3 μU/mL ($n = 337$)**	**>4.3 μU/mL ($n = 318$)**	**P^b**	**≤1.05 ($n = 327$)**	**>1.05 ($n = 328$)**	**P^b**
Entry age (years)	56 (52–59)	56 (52–59)	0.36	56 (52–59)	56 (52–60)	0.16	56 (51–58)	56 (52–60)	0.04
Cigarettes/day	20 (15–25)	20 (15–25)	0.43	20 (15–24)	20 (15–25)	0.36	20 (15–25)	20 (15–25)	0.71
Smoking duration	35 (30–40)	35 (30–40)	0.43	35 (30–40)	35 (30–40)	0.56	35 (30–40)	35 (30–40)	0.23
Alcohol, >11.3 g/day	156 (47.7%)	156 (54.2%)	0.11	166 (52.4%)	146 (49.0%)	0.40	165 (53.6%)	147 (47.9%)	0.16
HBV, antibody to core antigen, yes	24 (6.9%)	19 (6.2%)	0.68	18 (5.3%)	25 (7.9%)	0.19	18 (5.5%)	25 (7.6%)	0.27
HBV, surface antigen, yes	4 (1.2%)	0 (0%)	0.13	2 (0.6%)	2 (0.6%)	1.00	2 (0.3%)	2 (0.3%)	1.00
HCV, antibody, yes	3 (0.9%)	1 (0.3%)	0.63	1 (0.3%)	3 (0.9%)	0.36	1 (0.3%)	3 (0.9%)	0.62
BMI			<0.0001			<0.0001			<0.0001
<18.5 kg/m^2	0 (0%)	2 (0.7%)		2 (0.6%)	0 (0%)		2 (0.6%)	0 (0%)	
18.5 to <25 kg/m^2	153 (44.2%)	84 (27.2%)		182 (54.0%)	55 (17.3%)		177 (54.1%)	60 (18.3%)	
25 to <30 kg/m^2	156 (45.1)	157 (50.8%)		138 (41.0%)	175 (55.0%)		135 (41.3%)	178 (54.3%)	
30 to <35 kg/m^2	34 (9.8%)	60 (19.4%)		15 (4.4%)	79 (24.8%)		13 (4.0%)	81 (24.7%)	
≥35 kg/m^2	3 (0.9%)	6 (1.9%)		0 (0%)	9 (2.8%)		0 (0%)	9 (2.7%)	
≤Elementary education	264 (76.3%)	244 (79.0%)	0.42	264 (78.3%)	244 (76.7%)	0.62	258 (78.9%)	250 (76.2%)	0.41
Glucose (mg/dL)	93 (89–97)	106 (103–114)	nd	96 (90–102)	102 (97–111)	<0.0001	95 (90–100)	103 (98–112)	nd
Insulin (μU/mL)	3.4 (2.4–5.2)	5.5 (3.7–8.3)	<0.0001	2.9 (2.3–3.5)	6.7 (5.3–8.8)	nd	2.9 (2.3–3.5)	6.5 (5.2–11.9)	nd
HOMA-IR	0.8 (0.5–1.2)	1.5 (1.0–2.3)	nd	0.7 (0.5–0.9)	1.7 (1.3–2.4)	nd	0.7 (0.5–0.9)	1.7 (1.3–2.3)	nd

Abbreviation: nd, not determined.

[a]Restricted to participants who did not report a diagnosis of diabetes at baseline.

[b]*P* value for Mantel–Haenszel χ^2 test or Fisher exact test for categorical variables and Jonckheere–Terpstra test for continuous variables.

self-reported diabetes, although positive, was not statistically significant.

Among participants who did not report a previous diagnosis of diabetes, both liver cancer (Table 3) and CLD mortality (Table 4) were positively associated with insulin concentration and HOMA-IR. Relative to Q1, risk estimates for insulin and HOMA-IR were elevated in Q4 for liver cancer (OR = 3.41; 95% CI, 1.74–6.66; $P_{trend} < 0.0001$; and OR = 3.72; 95% CI, 1.89–7.3; $P_{trend} < 0.0001$, respectively) and CLD mortality (OR = 2.51; 95% CI, 1.44–4.37; $P_{trend} = 0.0002$; and OR = 2.31; 95% CI, 1.34–3.97; $P_{trend} = 0.001$, respectively). For glucose, participants in Q3 [median glucose = 103 mg/dL; interquartile range (IQR) = 101–104] as well as those in Q4 (median glucose = 114 mg/dL; IQR = 110–124) were at higher risk of liver cancer relative to Q1 (OR = 1.88; 95% CI, 1.03–3.49 and OR = 2.40; 95% CI, 1.33–4.35, respectively). However, no association was observed for glucose and CLD mortality ($P_{trend} = 0.064$).

In analyses stratified by follow-up time, the association between diabetes and liver cancer appeared similar in each follow-up period (Table 3). The associations for glucose, insulin concentration, and HOMA-IR appeared stronger in liver cancer cases that occurred more than 10 years after baseline than in cases that occurred in the first 10 years of follow-up. The pattern was different for CLD where associations with glucose appeared stronger for deaths in the first 10 years (than for deaths more than 10 years after baseline). In contrast, the ORs for CLD with insulin and HOMA-IR appeared similar in each follow-up period (Table 4).

We observed similar associations for diabetes, insulin, and HOMA-IR with each endpoint after excluding HBV- and HCV-positive participants. We also observed similar associations for diabetes, insulin, and HOMA-IR with each endpoint across strata defined by baseline alcohol use, BMI, and smoking history (Supplementary Table S1). Of all the examined stratifications, four deviations from homogeneity were observed; owing to relatively small sample sizes and multiple comparisons, these results should, however, be interpreted with caution.

Finally, we examined the joint effects of biochemically defined diabetes with insulin concentration and daily alcohol intake (Table 5). In these analyses, we observed little evidence for an association with diabetes among participants with lower insulin concentration, although there were few cases in this group. Among participants without diabetes, we observed some evidence for an association of insulin concentration with liver cancer and CLD. The highest ORs were among participants who had both higher insulin concentration and diabetes. For alcohol, we observed similar ORs for diabetes and liver cancer among those with high and low alcohol intake. In contrast, participants with higher alcohol intake and diabetes had more than 2-fold higher odds of CLD mortality than those with lower alcohol intake and diabetes. These observed differences should, however, be interpreted with caution as multiple comparisons were made and *P* values were greater than 0.05 for statistical tests of multiplicative and additive interactions for diabetes with insulin or alcohol intake.

Discussion

In our study, among Finnish male smokers without a prior diabetes diagnosis, higher glucose concentration was associated with increased risk of incident liver cancer, and higher insulin concentration or higher HOMA-IR was associated with increased risk of incident liver cancer and CLD mortality during 22 years of follow-up. These associations were independent of other CLD and liver cancer risk factors, including HBV and HCV status, alcohol intake, BMI, and smoking history.

Many previous studies have observed associations between diabetes and liver cancer, using a number of different study designs, including case–control, record linkage, and prospective cohorts (13). Similar to our estimate for self-reported diabetes (OR = 2.48; 95% CI, 1.20–5.12), a recent meta-analysis reported summary RR estimates for hepatocellular carcinoma and primary liver cancer of 2.06 (95% CI, 1.64–2.60) and 1.75 (95% CI, 1.25–2.47), respectively (13). In the

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Table 3. ORs and 95% CIs for diabetes, glucose, insulin, and insulin resistance with primary incident liver cancer over 22 years of follow-up in a nested case–control study from the ATBC cohort

Diabetes	Self-reported diabetes only			Fasting glucose ≥126 mg/dL only[a]			Self-report or fasting glucose ≥126 mg/dL		
	No (ref)	Yes		No (ref)	Yes		No (ref)	Yes	
	Controls/cases	Controls/cases	OR (95% CI)	Controls/cases	Controls/cases	OR (95% CI)	Controls/cases	Controls/ cases	OR (95% CI)
Age adjusted	655/124	26/14	2.59 (1.29–5.18)	623/109	32/15	3.11 (1.61–6.03)	623/109	58/29	2.97 (1.80–4.90)
Multivariable model[b]	655/124	26/14	2.48 (1.20–5.12)	623/109	32/15	2.95 (1.46–5.96)	623/109	58/29	2.79 (1.65–4.75)
>0 to 10 years of follow-up[b]	655/57	26/8	3.45 (1.38–8.63)	623/51	32/6	2.69 (0.93–7.80)	623/51	58/14	3.14 (1.51–6.54)
>10 years of follow-up[b]	655/67	26/6	1.95 (0.73–5.21)	623/58	32/9	3.07 (1.34–7.05)	623/58	58/15	2.61 (1.34–5.09)

Glucose (mg/dL)[a]	Q1 (ref; 89, 86–92)[c] Controls/ cases	Q2 (97, 95–98)[c] Controls/cases	OR (95% CI)	Q3 (103, 101–104)[c] Controls/cases	OR (95% CI)	Q4 (114, 110–124)[c] Controls/cases	OR (95% CI)	P_{trend}
Age adjusted	193/25	153/20	1.05 (0.56–1.98)	155/34	1.69 (0.96–2.98)	154/45	2.30 (1.34–3.96)	0.001
Multivariable model[b]	193/25	153/20	1.28 (0.66–2.49)	155/34	1.88 (1.03–3.49)	154/45	2.40 (1.33–4.35)	0.002
>0 to 10 years of follow-up[b]	193/18	153/11	1.26 (0.53–3.01)	155/12	1.07 (0.45–2.50)	154/16	1.40 (0.61–3.21)	0.511
>10 years of follow-up[b]	193/7	153/9	1.74 (0.62–4.90)	155/22	3.83 (1.55–9.45)	154/29	4.82 (1.99–11.70)	<0.0001

Insulin (μU/mL)[a]	Q1 (ref) 2.4 (1.9–2.6)[c] Controls/cases	Q2 3.6 (3.3–4.0)[c] Controls/cases	OR (95% CI)	Q3 5.3 (4.8–5.8)[c] Controls/ cases	OR (95% CI)	Q4 8.7 (7.5–11.2)[c] Controls/cases	OR (95% CI)	P_{trend}
Age adjusted	175/20	162/17	0.91 (0.46–1.82)	155/21	1.15 (0.60–2.22)	163/66	3.42 (1.97–5.94)	<0.0001
Multivariable model[b]	175/20	162/17	0.96 (0.47–1.96)	155/21	1.14 (0.55–2.33)	163/66	3.41 (1.74–6.66)	<0.0001
>0 to 10 years of follow-up[b]	175/14	162/11	0.87 (0.36–2.12)	155/9	0.52 (0.19–1.45)	163/23	1.22 (0.47–3.19)	0.816
>10 years of follow-up[b]	175/6	162/6	1.05 (0.32–3.39)	155/12	2.20 (0.77–6.29)	163/43	7.42 (2.79–19.76)	<0.0001

HOMA-IR[a]	Q1 (ref) 0.51 (0.42–60)[c] Controls/cases	Q2 0.85 (0.76–0.94)[c] Controls/cases	OR (95% CI)	Q3 1.32 (1.20–1.51)[c] Controls/cases	OR (95% CI)	Q4 2.39 (2.07–3.35)[c] Controls/cases	OR (95% CI)	P_{trend}
Age adjusted	166/18	163/18	1.00 (0.50–2.01)	163/20	1.05 (0.53–2.08)	163/68	3.70 (2.09–6.55)	<0.0001
Multivariable model[b]	166/18	163/18	1.04 (0.50–2.13)	163/20	0.97 (0.46–2.04)	163/68	3.72 (1.89–7.32)	<0.0001
>0 to 10 years of follow-up[b]	166/12	163/11	0.94 (0.38–2.35)	163/10	0.58 (0.21–1.63)	163/24	1.60 (0.62–4.14)	0.390
>10 years of follow-up[b]	166/6	166/7	1.13 (0.36–3.54)	163/10	1.50 (0.51–4.46)	163/44	6.87 (2.60–18.17)	<0.0001

[a]Restricted to participants who did not report a diagnosis of diabetes at baseline.

[b]Multivariable models are adjusted for age (years), cigarettes per day, duration of smoking (years), alcohol intake (≤2.8, >2.8 to ≤11, >11 to ≤26, >26 to ≤44, >44 g/day), anti-HBc, HBsAg, anti-HCV, BMI (<18.5, 18.5 to <25, 25 to <30, 30 to <35, ≥35 kg/m^2), and education (elementary education or less, more than elementary education).

[c]Median and IQR among controls.

Table 4. ORs and 95% CIs for diabetes, glucose, insulin, and insulin resistance with CLD mortality over 22 years of follow-up in a nested case–control study from the ATBC cohort

	Self-reported diabetes only			Fasting glucose ≥126 mg/dL only[a]			Self-report or fasting glucose ≥126 m/dL		
	No (ref)	Yes		No (ref)	Yes		No (ref)	Yes	
Diabetes	**Controls/cases**	**Controls/cases**	**OR (95% CI)**	**Controls/ cases**	**Controls/cases**	**OR (95% CI)**	**Controls/cases**	**Controls/cases**	**OR (95% CI)**
Age adjusted	655/207	26/9	1.12 (0.51–2.43)	623/185	32/22	2.31 (1.31–4.08)	623/185	58/31	1.81 (1.13–2.89)
Multivariable model[b]	655/207	26/9	1.67 (0.71–3.94)	623/185	32/22	1.88 (1.00–3.56)	623/185	58/31	1.83 (1.09–3.10)
>0 to 10 years of follow-up[b]	655/109	26/7	2.42 (0.93–6.30)	623/92	32/17	3.33 (1.62–6.85)	623/92	58/24	3.08 (1.70–5.58)
>10 years of follow-up[b]	655/98	26/2	0.70 (0.15–3.40)	623/58	32/9	0.71 (0.26–1.99)	623/93	58/7	0.72 (0.30–1.72)

	Q1 (ref) (89, 86–92)[c]	Q2 (97, 95–98)[c]		Q3 (103, 101–104)[c]		Q4 (114, 110–124)[c]		
Glucose (mg/dL)[a]	**Controls/cases**	**Controls/cases**	**OR (95% CI)**	**Controls/cases**	**OR (95% CI)**	**Controls/cases**	**OR (95% CI)**	**P_{trend}**
Age adjusted	193/58	153/32	0.68 (0.42–1.10)	155/47	1.00 (0.64–1.55)	154/70	1.54 (1.02–2.31)	0.019
Multivariable model[b]	193/58	153/32	0.76 (0.45–1.29)	155/47	1.00 (0.62–1.64)	154/70	1.49 (0.93–2.37)	0.064
>0–10 years of follow-up[b]	193/27	153/14	0.74 (0.35–1.56)	155/25	1.24 (0.65–2.36)	154/43	2.08 (1.14–3.80)	0.007
>10 years of follow-up[b]	193/31	153/18	0.74 (0.38–1.44)	155/22	0.83 (0.44–1.58)	154/27	1.02 (0.54–1.90)	0.929

	Q1 (ref) 2.4 (1.9–2.6)[c]	Q2 3.6 (3.3–4.0)[c]		Q3 5.3 (4.8–5.8)[c]		Q4 8.7 (7.5–11.2)[c]		
Insulin (μU/mL)[a]	**Controls/cases**	**Controls/cases**	**OR (95% CI)**	**Controls/cases**	**OR (95% CI)**	**Controls/cases**	**OR (95% CI)**	**P_{trend}**
Age adjusted	175/45	162/33	0.79 (0.48–1.29)	155/45	1.15 (0.72–1.83)	163/84	2.09 (1.37–3.20)	<0.0001
Multivariable model[b]	175/45	162/17	0.88 (0.50–1.52)	155/45	1.37 (0.80–2.37)	163/84	2.51 (1.44–4.37)	0.0002
>0 to 10 years of follow-up[b]	175/20	162/19	1.04 (0.51–2.12)	155/24	1.53 (0.75–3.10)	163/46	2.85 (1.41–5.75)	0.002
>10 years of follow-up[b]	175/25	162/14	0.75 (0.36–1.60)	155/21	1.24 (0.60–2.56)	163/38	2.17 (1.06–4.42)	0.016

	Q1 (ref) 0.51 (0.42–0.60)[c]	Q2 0.85 (0.76–0.94)[c]		Q3 1.32 (1.20–1.51)[c]		Q4 2.39 (2.07–3.35)[c]		
HOMA-IR[a]	**Controls/cases**	**Controls/cases**	**OR (95% CI)**	**Controls/cases**	**OR (95% CI)**	**Controls/cases**	**OR (95% CI)**	**P_{trend}**
Age adjusted	166/46	163/33	0.72 (0.44–1.18)	163/42	0.97 (0.60–1.55)	163/86	1.98 (1.30–3.02)	0.0002
Multivariable model[b]	166/46	163/33	0.87 (0.50–1.53)	163/42	1.24 (0.71–2.17)	163/86	2.31 (1.34–3.97)	0.001
>0–10 years of follow-up[b]	166/23	163/16	0.70 (0.33–1.48)	163/23	1.23 (0.61–2.49)	163/47	2.24 (1.13–4.43)	0.005
>10 years of follow-up[b]	166/23	163/17	1.04 (0.50–2.17)	163/19	1.23 (0.58–2.62)	163/39	2.30 (1.12–4.71)	0.016

[a]Restricted to participants who did not report a diagnosis of diabetes at baseline.

[b]Multivariable models are adjusted for age (years), cigarettes per day, duration of smoking (years), alcohol intake (≤2.8, >2.8 to ≤11, >11 to ≤26, >26 to ≤44, >44 g/day), anti-HBc, HBsAg, anti-HCV, BMI (<18.5, 18.5 to <25, 25 to <30, 30 to <35, ≥35 kg/m^2), and education (elementary education or less, more than elementary education).

[c]Median and IQR among controls.

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Table 5. ORs and 95% CIs for the joint effects analysis of diabetes with fasting insulin levels[a] and alcohol consumption[b] with liver cancer incidence and chronic liver disease mortality among those without a self-reported history of diabetes at baseline

	No diabetes (glucose < 126 mg/dL)		Diabetes (glucose ≥126 mg/dL)		$P_{interaction}$	
	Controls/cases	OR (95% CI)	Controls/cases	OR (95% CI)	Multiplicative	Additive
Liver cancer[c]					0.606	0.421
Insulin ≤6.7 μU/mL	478/56	1.00 (ref)	14/2	1.54 (0.32–7.48)		
Insulin >6.7 μU/mL	145/53	2.91 (1.77–4.80)	18/13	7.17 (3.10–16.55)		
Chronic liver disease[c]					0.252	0.322
Insulin ≤6.7 μU/mL	478/120	1.00 (ref)	14/3	0.73 (0.19–2.90)		
Insulin >6.7 μU/mL	145/65	2.05 (1.32–3.18)	18/19	3.79 (1.75–8.22)		
Liver cancer[d]					0.694	0.944
Alcohol ≤11.3 g/day	291/47	1.00 (ref)	12/6	3.56 (1.21–10.50)		
Alcohol >11.3 g/day	296/55	1.24 (0.79–1.97)	16/8	3.32 (1.25–8.87)		
Chronic liver disease[d]					0.295	0.930
Alcohol ≤11.3 g/day	291/26	1.00 (ref)	12/5	4.52 (1.38–14.78)		
Alcohol >11.3 g/day	296/136	4.96 (3.08–7.99)	16/16	10.68 (4.63–24.65)		

[a]Above versus below the 75% of insulin in controls, 6.7 μU/mL.

[b]Above versus below the median level of alcohol consumption 11.3 g/day.

[c]Models are adjusted for age (years), cigarettes per day, duration of smoking (years), alcohol intake (≤2.8, >2.8 to ≤11, >11 to ≤26, >26 to ≤44, >44 g/day), anti-HBc, HBsAg, anti-HCV, BMI (<18.5, 18.5 to <25, 25 to <30, 30 to <35, ≥35 kg/m^2), education (elementary education or less, more than elementary education).

[d]Models are adjusted for age (years), cigarettes per day, duration of smoking (years), anti-HBc, HBsAg, anti-HCV, BMI (<18.5, 18.5 to <25, 25 to <30, 30 to <35, ≥35 kg/m^2), education (elementary education or less, more than elementary education).

current study, the OR for diabetes either by self-report or serum glucose testing was 2.79 (95% CI, 1.65–4.75), indicating that people with undiagnosed diabetes are similarly at increased risk for liver cancer. Moreover, a trend ($P_{trend} = 0.002$) was observed for liver cancer across increasing quartiles of serum glucose, indicating that higher glucose concentrations, including those below 126 mg/dL (i.e., Q3: median glucose = 103 mg/dL; IQR = 101–104), are associated with higher odds of liver cancer. Another recent study observed a positive, albeit not statistically significant, association between categories of serum glucose and liver cancer, noting a limited sample size and imprecise risk estimates in the higher categories of serum glucose (34).

Previous findings for insulin and liver cancer, although more limited than for diabetes, are also consistent with our results. C-peptide, a marker of hyperinsulinemia, has been positively associated with liver cancer in a large European prospective cohort (35). High insulin concentrations have been associated with poorer prognosis in patients with liver cancer (36, 37), as well as liver disease progression (38) and poorer prognosis after liver transplant (39) among HCV$^+$ patients. Higher insulin concentrations have also been associated with liver cancer in a cohort of HBV carriers (28). Our observation of an association with higher fasting insulin among participants without diabetes is intriguing and suggests that insulin may promote carcinogenesis in the absence of diabetes. Previous results of an association between higher insulin concentrations and more rapid liver tumor growth (36) are also consistent with our findings, as are pharmacoepidemiologic studies (40). For example, a recent meta-analysis found that among patients with diabetes, prescribed insulin was associated with increased liver cancer risk, whereas metformin and thiazolidinedione were associated with decreased liver cancer risk (40). Such findings could, however, reflect confounding by indication.

Although numerous studies have explored the interrelationship between diabetes and nonalcoholic fatty liver disease (8, 24), associations of insulin and glucose with subsequent mortality from chronic liver disease, particularly among those without a prior diabetes diagnosis, are poorly understood. In the current study, we found stronger findings for diabetes, insulin, and HOMA-IR with liver cancer than with CLD mortality. It is possible that higher insulin and glucose levels may be more strongly related to subsequent liver cancer than fatal noncancer liver disease endpoints. In support, some studies have suggested that high glucose and insulin levels may promote liver tumor growth (36). However, the observed differences could also be due to chance.

Alternatively, associations with glucose and insulin concentrations could reflect reverse causality. Cirrhosis can cause diabetes (27), and previous findings suggest that blood insulin concentration and insulin resistance are affected by diminished insulin clearance from fatty liver (41). Although our study excluded participants manifesting cirrhotic symptoms at baseline, we lacked information on asymptomatic underlying liver disease at baseline. However, we consistently observed weaker associations for glucose, insulin, and HOMA-IR with liver cancers in the first 10 years of follow-up, when participants developing an endpoint would be more likely to have cirrhosis at baseline, than with liver cancers in years 11 to 22 of follow-up. If insulin resistance and diabetes at baseline were solely a reflection of advanced liver disease, then a higher risk of liver cancer would have been expected in the first decade of observation. These data, coupled with previous findings of associations with liver disease progression in the context of HCV (38, 39, 42), suggest that our results for liver cancer do not simply reflect the metabolic alterations of undiagnosed cirrhosis. In contrast, associations for self-reported diabetes and glucose were only apparent for CLD mortality that occurred within 10 years of baseline, suggesting more of a concern for reverse causality.

Key strengths of our study include its prospective design, 22-year follow-up, measured fasting glucose and insulin concentrations, ability to adjust for major liver cancer risk factors, including HBV, HCV, alcohol use, and smoking, and the exclusion of patients with cirrhosis and chronic alcoholism at baseline. Limitations include our relatively modest sample size, a lack of histology information for liver cancer cases, although the majority were likely hepatocellular carcinoma, and a single measurement of fasting glucose and insulin, which could lead to misclassification of the exposure. Although repeat measures are ideal, national

prevalence estimates generally rely on a single serum measurement to define undiagnosed diabetes (43). We were also unable to differentiate between type I and type II diabetes, although most diabetes would be type II in this older population. We lacked data on undiagnosed CLD at baseline, as discussed above. We also lacked data on incident CLD during follow-up, and the associations of diabetes and insulin concentrations with CLD risk may differ from those observed for CLD mortality. The ATBC study included only male smokers, which may affect the generalizability of our findings to women and to never-smokers. Although our measured levels of insulin in controls were consistent with those previously measured in the cohort (44–46), they were lower than those in U. S. population surveys (47). Future studies in populations with higher insulin levels are needed to extend and replicate these results.

In summary, participants in the ATBC cohort with higher glucose and insulin levels as well as those with diagnosed and undiagnosed diabetes were more likely to develop liver cancer and die from CLD over 22 years of follow-up. Associations were independent of known liver cancer and CLD risk factors and suggest a potentially important role for glucose and insulin homeostasis in liver cancer and CLD mortality.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

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Development of methodology: R.Z. Stolzenberg-Solomon

Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): S.J. Weinstein, P.R. Taylor, S. Männistö, D. Albanes, R.Z. Stolzenberg-Solomon

Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): E. Loftfield, N.D. Freedman, G.Y. Lai, R.Z. Stolzenberg-Solomon

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Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): N.D. Freedman, S.J. Weinstein, P.R. Taylor

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Cancer Prevention Research

Higher Glucose and Insulin Levels Are Associated with Risk of Liver Cancer and Chronic Liver Disease Mortality among Men without a History of Diabetes

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