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ORIGINAL ARTICLE

Association between metabolic syndrome and hepatobiliary cancers: A case-control study

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Abstract

Background The incidence of hepatobiliary cancer is steadily increasing. It is unclear if this rise is related to increasing trends in obesity, metabolic syndrome, and lifestyle changes.

Methods A case-control study was performed using the Health Improvement Network (THIN) database. Cases with a diagnosis of liver, bile duct, and gallbladder cancers were matched in a 1:2 fashion with controls and analyzed for potential associations between hepatobiliary cancer and obesity/metabolic syndrome.

Results Four thousand two hundred and eighty-seven patients (62% male, 38% female) with hepatobiliary cancers were matched with 8574 controls. On univariate analysis, body mass index (BMI), smoking, diabetes, alcohol consumption, ischemic heart disease, and hypertension were associated with hepatobiliary cancer. Statin use and non-smoking status had an inverse association. On multivariate analysis, BMI, diabetes, hypertension, ischemic heart disease, and insulin use were associated with the risk of hepatobiliary cancer. Statin use and non-smoking status were protective. On modeling BMI, each of diabetes and hypertension as a single covariate, there was a significant association with hepatobiliary cancer (1.59 [1.49–1.69], $p < 0.001$) which persisted despite adjusting for increasing age (1.006 [1005–1.006], $p < 0.001$) and background liver cirrhosis (1.037 [1.03–1.044], $p < 0.001$).

Conclusions Obesity and metabolic syndrome are associated with the risk of hepatobiliary cancer. Statin use seems to be protective.

Keywords Hepatobiliary cancer · Hepatocellular cancer · Cholangiocarcinoma · Metabolic syndrome · Diabetes · Obesity

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Bullet points of the study highlights

What is already known?

- Metabolic syndrome refers to a combination of obesity, Type II diabetes, dyslipidemia, and insulin resistance.
- Metabolic syndrome is known to be associated with the development of visceral cancers.
- The incidence of hepatobiliary cancers has been increasing steadily and it is unclear if this increase is as a consequence of an increase in the prevalence of metabolic syndrome.

What is new in this study?

- This is the first population-based study that demonstrates a significant association between metabolic syndrome and hepatobiliary cancer.
- Statin use seems protective against hepatobiliary cancer.

What are the future clinical and research implications of the study findings?

- The global epidemic of obesity and metabolic syndrome is a significant public health issue.
- This has the potential to result in an ongoing and sustained increase in the incidence of hepatobiliary cancers over the next few decades making this a public health emergency.
- Population-based trials of statins may help determine if they have a true chemopreventative effect against the development of hepatobiliary cancer.

Introduction

The incidence of hepatobiliary and gallbladder cancers has been progressively increasing over the last two decades without any clear cause. The age-standardized incidence rates of liver cancers have increased by over 200% over the last three decades [1, 2]. There have been similar increasing trends in the incidence of bile duct and gallbladder cancers [3, 4]. It is unclear if this rise is related to increasing trends in obesity, metabolic syndrome, and lifestyle changes (smoking and alcohol consumption levels) [5].

Metabolic syndrome refers to a constellation of clinical conditions, principally obesity, type II diabetes mellitus, hypertension, and dyslipidemia, characterized by insulin resistance [6]. Metabolic syndrome has been suggested to be causal in the development of several cancers, including liver cancer. Results from the Nurses Health Study has suggested that type II diabetes is independently associated with risk of hepatocellular carcinoma [7]. A case-control study from China suggested an association between metabolic syndrome and biliary tract cancers (gallbladder cancers and cholangiocarcinoma) [8]. The sample sizes in both case-control studies were relatively small and a population-based study examining the relationship between metabolic syndrome and primary liver, gallbladder, and biliary tract cancers has not been previously conducted. We used the Health Improvement Network (THIN) database to examine this issue [9].

The Health Improvement Network The THIN database is a large United Kingdom (UK) primary care database, which includes computerized anonymized longitudinal patient records over the period 1980–2015, retrieved from over 300 primary care centers in the UK [9]. There are over 5 million patients registered with THIN primary care centers, and the patient population is regionally and demographically representative of the UK. The data is organized by individual primary care centers, and each patient is identified by a computer-generated unique identifier within the center. Participating primary care practitioners systematically record each patient episode or clinical encounter as part of their routine practice, which is automatically anonymized and prospectively recorded by the THIN software. This ensures that no identifying information (such as name, address, date of birth, postcode) leaves the individual primary care center. The THIN database holds detailed clinical, anthropometric, and drug therapy data for each patient.

Assuming a population prevalence of hepatobiliary cancer of 8 per 100,000 and a relative risk of mortality of 1.52 (95% CI 1.13–2.05) in men and 1.62 (1.40–1.87) in women with increasing BMI levels, we determined that a sample size of at least 10,023 patients would provide sufficient power at type I (α) error rate of 0.05 and a type II (β) error rate of 0.1 to examine the association between hepatobiliary cancer and metabolic syndrome [2, 10].

Methodology

Sample size

All patients over the age of 20 years with diagnosis codes for "liver cancer," "bile duct cancer," and "gallbladder cancer" were identified from the THIN database to constitute the

primary dataset for "hepatobiliary cancer." All diagnostic codes of peri-ampullary cancer and pancreatic cancer were excluded. These cases were matched with "controls" in a 1:2 fashion, by age, practice (e.g. general practitioner [GP]), and gender, with at least 1 year of follow up on the database. Hepatobiliary cancers were further stratified into primary hepatocellular cancers, gallbladder cancers, intrahepatic cholangiocarcinomas, and extrahepatic cholangiocarcinomas.

Data on co-morbidities, drug history (medication for diabetes, aspirin and statin use), anthropometric data (weight, body mass index [BMI]), and data on smoking and alcohol consumption were extracted from the database. Patients with diagnosis codes for type I diabetes were excluded from the initial database search. Drug history was additionally analyzed in terms of the numbers of prescriptions (with drug quantities prescribed) of each drug over a temporal distribution within the database.

Categorical data such as BMI were initially log-transformed for analysis. Continuous and categorical data were then compared between groups using the chi-squared (χ^2) test. Logistic regression analysis was used in univariate and multivariate models to understand the effect of each covariate on the risk of developing hepatobiliary cancer. These analyses were initially conducted on the entire dataset of hepatobiliary cancers and subsequently on each cancer subtype. Covariates that were adjusted for in the model included age, BMI (log-transformed), smoking (categorized as non-smoker, ex-smoker and current smoker), alcohol consumption in units/week, co-morbidities (diabetes mellitus, hypertension and ischemic heart disease), and the use of prescribed medication for diabetes (insulin and antihyperglycemic drugs such as metformin, sulfonylureas, and thiazolidinediones).

Ethics approval to use the THIN dataset was sought and obtained from the Health Research Authority (HRA) in the UK in 2016 (approved 27 June 2016). The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in approval by the HRA.

Results

Data extraction from the THIN dataset yielded 4287 cancers with codes for liver, gallbladder, and bile duct cancers (cholangiocarcinoma). These patients were age and gender-matched with 8574 controls (total sample size of 12,861 patients). The cancers were further subdivided into primary hepatocellular cancers (70%), gallbladder cancers (23%), intrahepatic cholangiocarcinomas (1.1%), and extrahepatic cholangiocarcinomas (5.9%). Cases and controls had 101,705 and 216,071 patient-years of time respectively on the THIN dataset. There was a slight preponderance of males in both case and control cohorts (Table 1). Mean BMI was similar across both case and control groups, although there were a greater number of controls with BMI between 25 and 29.9 kg/m^2 (Table 1). Obese and morbidly obese patients (BMI > 30 kg/m^2) were also more common among the cases compared to controls. Overall, there were a greater proportion of cases with BMI > 25 kg/m^2 compared to controls (cases 71.5%, controls 64.9%, $p < 0.001$, χ^2 test).

There were more smokers in the case group (Table 1), although the control group had more non-smokers and ex-smokers. There was no difference in the mean alcohol consumption in either group. There were more patients with diabetes mellitus, hypertension, and ischemic heart disease in the case group compared to the controls (Table 1). Aspirin and statin use were not significantly different in either group (Table 1).

Among patients with diabetes in the study cohort, insulin use was more common in the case group compared to the controls (Supplementary Table 1). The prevalence of oral antihyperglycemic drugs was also more common in the case group compared to controls (Supplementary Table 1).

Only a small proportion of the study cohort had diagnosis codes for non-alcoholic fatty liver disease (NAFLD) (2.1% cases), cirrhosis (12.8% cases), and viral liver disease (5.9% cases).

Univariate analysis

On univariate logistic regression analysis (Table 2), BMI, smoking, alcohol consumption, diabetes mellitus, hypertension, and ischemic heart disease were associated with risk of hepatobiliary cancer. Interestingly, age was inversely associated with hepatobiliary cancer. Non-smokers also had a lower risk of hepatobiliary cancer. Aspirin use was not protective but there was an inverse association with statin use and the risk of hepatobiliary cancer. Insulin use was strongly associated with risk of hepatobiliary cancer, as was the use of oral antihyperglycemic medication (Table 3). The use of insulin and oral antihyperglycemic medication or combinations of different oral antihyperglycemic medication were not associated with any significant risk of hepatobiliary cancer.

Expectedly, NAFLD (odds ratio 5.00 [3.41–7.35], $p < 0.001$) and cirrhosis (37.93 [26.64–54.01], $p < 0.001$) were strongly associated with risk of hepatobiliary cancer.

In order to understand if the above risks related to all hepatobiliary cancers or specifically hepatocellular carcinoma, univariate logistic regression analysis was conducted on each cancer subtype within the hepatobiliary cancer dataset.

Hepatocellular carcinoma

On univariate analysis (Table 3), BMI was strongly associated with the risk of developing hepatocellular carcinoma. Age was inversely associated, and non-smoking status was protective. Diabetes, hypertension, and ischemic heart disease were associated with risk of developing hepatocellular carcinoma.

Table 1 Demographic information about the study cohort

	Cases	Controls	*p*-value
Age (mean) years	72	75	NS
Male gender (%)	62	62	NS
BMI (mean) kg/m2	29.2	28.6	NS
BMI < 18.5 (*n* %)	434 (10.1)	1229 (14.3)	p < 0.001
BMI 18.5–24.9 (*n* %)	787 (18.4)	1776 (20.7)	*p* = 0.01
BMI 25.0–29.9 (*n* %)	1420 (33.1)	3058 (35.7)	*p* = 0.05
BMI 30–34.9 (*n* %)	999 (23.3)	1593 (18.6)	*p* < 0.001
BMI > 35 (*n* %)	647 (15.1)	918 (10.7)	*p* < 0.001
Smokers (*n* %)	1698 (39.6)	2188 (25.5)	*p* < 0.001
Ex-smokers (*n* %)	1606 (37.5)	3967 (46.3)	*p* < 0.001
Non-smokers (*n* %)	679 (15.8)	1629 (19)	*p* < 0.001
Alcohol (units per week), (mean, range)	8 (0–210)	6 (0–170)	0.557
Diabetes (*n* %)	1502 (35)	1652 (19.3)	*p* < 0.001
Hypertension (*n* %)	2213 (51.6)	3982 (46.4)	*p* = 0.001
Ischemic heart disease (*n* %)	827 (19.3)	806 (9.4)	*p* < 0.001
Aspirin use (*n* %)	1818 (42.4)	3444 (40.2)	*p* = 0.06
Statin use (*n* %)	1707 (40)	3567 (41.6)	*p* = 0.11

NS non-significant

Aspirin consumption and smoking were not associated, but insulin and metformin were associated with risk of hepatocellular cancer.

Gallbladder cancer

Gallbladder cancer was seen to be associated with increasing BMI (Table 3). Age and non-smoking status had an inverse association with the risk of gallbladder cancer. As with hepatocellular cancer, diabetes, hypertension, and ischemic heart disease were associated with risk of gallbladder cancer. Aspirin had no association, and statin use had a strong inverse association with gallbladder cancers. Insulin and metformin use were associated with risk of gallbladder cancer.

Table 2 Univariate analysis of factors associated with hepatobiliary cancers

	Univariate odds ratio (OR) (95% CI)	*p*-value
Log body mass index	3.22 (2.58–4.03)	*p* < 0.001
Age	0.986 (0.984–0.989)	*p* < 0.001
No smoking history	0.80 (0.73–0.89)	*p* < 0.001
Smoking (current + previous)	1.85 (1.71–2.01)	*p* < 0.001
Alcohol	1.013 (1.01–1.016)	*p* < 0.001
Diabetes	2.12 (1.94–2.31)	*p* < 0.001
Hypertension	1.23 (1.14–1.32)	*p* < 0.001
Ischemic heart disease	2.06 (1.85–2.29)	*p* < 0.001
Aspirin	0.99 (0.99–1.00)	*p* = 0.06
Statin	0.99 (0.997–0.998)	*p* < 0.001
Insulin	2.93 (2.51–3.42)	*p* < 0.001
Metformin	1,01 (1.008–1.014)	*p* < 0.001
Sulfonylureas	1.011 (1.005–1.016)	*p* < 0.001
Thiazolidinedione	1.007 (1.002–1.012)	*p* = 0.003
Combination therapy for diabetes	1.00 (0.99–1.002)	*p* = 0.40

Intrahepatic cholangiocarcinoma

Intrahepatic cholangiocarcinoma was strongly associated with increasing BMI (Table 3). Smoking, diabetes, ischemic heart disease, and insulin use were associated with risk of intrahepatic cholangiocarcinoma, and non-smoking status had an inverse association.

Extrahepatic cholangiocarcinoma

Increasing BMI had a strong association with extrahepatic cholangiocarcinoma, as did the presence of diabetes mellitus and the use of medication for diabetes (Table 3).

Multivariate analysis

On multivariate analysis (Table 4), BMI, diabetes, hypertension, ischemic heart disease, and insulin use were associated with the risk of developing hepatobiliary cancer. Age and non-smoking status were inversely associated, and statin use was protective.

On examining the cancer subtypes in a separate multivariate model (Table 5) with covariates that demonstrated significant association in the initial univariate analysis, increasing BMI, diabetes, alcohol consumption, hypertension, ischemic heart

Table 3 Univariate analysis of risk factors for subtypes of hepatobiliary cancers in the study

	Hepatocellular cancer univariate OR (95% CI)	*p*-value	Gallbladder cancer univariate OR (95% CI)	*p*-value	Extrahepatic cholangiocarcinoma univariate OR (95% CI)	*p*-value	Intrahepatic cholangiocarcinoma univariate OR (95% CI)	*p*-value
Log BMI	2.03 (1.63–2.55)	$p < 0.001$	2.15 (1.62–2.86)	$p < 0.001$	2.01 (1.35–3.00)	$p = 0.001$	2.73 (1.59–4.67)	$p < 0.001$
Age	0.989 (0.986–0.992)	$p < 0.001$	0.989 (0.985–0.994)	$p < 0.001$	0.993 (0.984–1.002)	$p = 0.14$	0.98 (0.96–0.99)	$p = 0.43$
No smoking history	0.85 (0.77–0.95)	$p = 0.005$	0.80 (0.67–0.96)	$p = 0.015$	0.63 (0.43–0.91)	$p = 0.015$	1.81 (0.95–3.44)	$p = 0.072$
Smoking (current + previous)	1.10 (1.00–1.22)	$p = 0.051$	1.16 (0.98–1.36)	$p = 0.077$	1.43 (1.03–1.99)	$p = 0.033$	0.59 (0.32–1.01)	$p = 0.097$
Alcohol	1.01 (1.01–1.013)	$p < 0.001$	No data		No data		No data	
Diabetes	1.98 (1.81–2.16)	$p < 0.001$	1.69 (1.47–1.94)	$p < 0.001$	1.87 (1.45–2.42)	$p < 0.001$	2.17 (1.21–3.91)	$p = 0.01$
Hypertension	1.22 (1.12–1.32)	$p < 0.001$	1.19 (1.04–1.35)	$p = 0.01$	No data		No data	
Ischemic heart disease	2.11 (1.89–2.36)	$p < 0.001$	1.54 (1.30–1.83)	$p < 0.001$	1.65 (1.20–2.26)	$p = 0.002$	No data	
Aspirin	1.00 (0.99–1.00)	$p = 0.20$	0.99 (0.998–1.00)	$p = 0.27$	0.99 (0.99–1.002)	$p = 0.484$	1.00 (0.998–1.003)	$p = 0.87$
Statin	0.998 (0.997–0.999)	$p < 0.001$	0.997 (0.996–0.999)	$p < 0.001$	0.999 (0.996–1.001)	$p = 0.325$	1.00 (0.995–1.01)	$p = 0.91$
Insulin	2.40 (2.05–2.80)	$p < 0.001$	1.63 (1.28–2.07)	$p < 0.001$	2.34 (1.59–3.45)	$p < 0.001$	4.2 (2.03–8.78)	$p < 0.001$
Metformin	1.008 (1.006–1.01)	$p < 0.001$	1.006 (1.002–1.010)	$p = 0.003$	1.006 (0.99–1.01)	$p = 0.09$	1.01 (1.001–1.02)	$p = 0.03$
Sulfonylureas	1.008 (1.002–1.013)	$p = 0.005$	1.007 (0.999–1.01)	$p = 0.08$	0.99 (0.97–1.02)	$p = 0.56$	1.02 (1.01–1.04)	$p < 0.001$
Thiazolidinedione	1.006 (1.002–1.011)	$p = 0.009$	1.004 (0.997–1.01)	$p = 0.27$	0.99 (0.98–1.04)	$p = 0.94$	1.01 (0.98–1.03)	$p = 0.72$

BMI body mass index

Table 4 Multivariate analysis of factors associated with the risk of development of hepatobiliary cancer

	Hepatocellular cancer multivariate OR (95% CI)	*p*-value	Gallbladder cancer multivariate OR (95% CI)	*p*-value	Extrahepatic cholangiocarcinoma multivariate OR (95% CI)	*p*-value	Intrahepatic cholangiocarcinoma multivariate OR (95% CI)	*p*-value
Log BMI	1.31 (1.04–1.64)	$p = 0.02$	1.74 (1.30–2.34)	$p < 0.001$	1.73 (1.09–2.73)	$p = 0.02$	2.39 (1.31–4.35)	$p = 0.004$
Age	0.986 (0.982–0.989)	$p < 0.001$	0.986 (0.981–0.992)	$p < 0.001$				
No smoking history	0.94 (0.84–1.05)	$p = 0.26$	0.83 (0.69–0.990)	$p = 0.05$	0.66 (0.45–0.97)	$p = 0.03$		
Diabetes	1.85 (1.65–2.06)	$p < 0.001$	1.73 (1.49–2.01)	$p < 0.001$	1.73 (1.33–2.72)	$p = 0.02$	1.29 (0.59–2.56)	$p = 0.58$
Hypertension	1.21 (1.10–1.33)	$p < 0.001$	1.21 (1.05–1.39)	$p = 0.008$				
Ischemic heart disease	2.45 (2.17–2.76)	$p < 0.001$	1.72 (1.43–2.06)	$p < 0.001$	1.41 (1.02–1.94)	$p = 0.04$		
Statin	0.993 (0.992–0.994)	$p < 0.001$	0.993 (0.991–0.995)	$p < 0.001$				
Insulin	1.52 (1.27–1.82)	$p < 0.001$			1.61 (1.04–2.45)	$p = 0.03$	2.90 (1.20–7.02)	$p = 0.02$

BMI body mass index

disease, and insulin use were associated with risk of developing hepatocellular cancer.

Gallbladder cancer was associated with increasing BMI, diabetes, hypertension, and ischemic heart disease. Age and statin use were inversely associated with hepatocellular cancer and gallbladder cancer. Extrahepatic cholangiocarcinoma was associated with increasing BMI, diabetes, ischemic heart disease, insulin use, while non-smoking status was protective. Intrahepatic cholangiocarcinoma was also associated with increasing BMI and insulin use.

Survival

To understand the effect of metabolic syndrome on hepatobiliary cancer, increasing BMI, diabetes, and hypertension were modeled as a single covariate and were seen to be strongly associated with hepatobiliary cancer (odds ratio 1.59 [1.49–1.69], p <0.001). This association persisted despite adjusting for age (1.006 [1005–1.006], $p < 0.001$) and background liver cirrhosis (1.037 [1.03–1.044], $p < 0.001$). The combination of metabolic syndrome (high BMI, diabetes, and hypertension), with pre-existing liver cirrhosis, was strongly predictive of the risk of hepatobiliary cancer (13.02 [8.04–21.1], $p < 0.001$), and this risk was seen to increase with age.

In the case group, 2486 patients (57.9%) died at a median of 6 months after diagnosis of hepatobiliary cancer (mean 11 months, range 1–222 months). On Kaplan-Meier analysis, there was a significant difference between the case and the control groups in survival (hazard ratio 8.46 [7.78–9.2], $p < 0.001$), with much lower survival in the case-cohort (Fig. 1).

Table 5 Multivariate analysis of the factors associated with the risk of developing cancer within the subtypes of hepatobiliary cancer

	Multivariate OR (95% CI)	*p*-value
Log body mass index	1.99 (1.57–2.52)	$p < 0.001$
Age	0.982 (0.979–0.985)	$p < 0.001$
Non-smoking status	0.77 (0.63–0.94)	$p = 0.01$
Smoking	0.90 (0.75–1.08)	$p = 0.25$
Alcohol	0.98 (0.91–1.07)	$p = 0.67$
Diabetes mellitus	2.12 (1.92–2.36)	$p < 0.001$
Hypertension	1.23 (1.13–1.34)	$p < 0.001$
Ischemic heart disease	2.91 (2.58–3.28)	$p < 0.001$
Statin	0.991 (0.990–0.993)	$p < 0.001$
Insulin	1.70 (1.42–2.04)	$p < 0.001$
Metformin	1.002 (0.998–1.006)	$p = 0.26$
Sulfonylureas	1.004 (0.999–1.01)	$p = 0.13$
Thiazolidinediones	1.00 (0.996–1.07)	$p = 0.73$

Discussion

In this study, we observed a striking association between metabolic syndrome and hepatobiliary cancer. This association corroborates the evidence thus far in the literature and highlights that the association between increasing BMI and hepatobiliary cancer is preserved for primary liver cancers, gallbladder cancers, and bile duct cancers.

There is a body of evidence linking metabolic syndrome to the development of liver cancers, and the strength of this association seems to be driven by type 2 diabetes and specifically, insulin resistance [11]. Insulin resistance in type 2 diabetes can propagate tumorigenesis by inhibiting apoptosis and stimulating cellular proliferation by activation of the Wnt-signaling pathway and by the production of reactive oxygen species that can facilitate cellular lipid peroxidation and damage [12, 13].

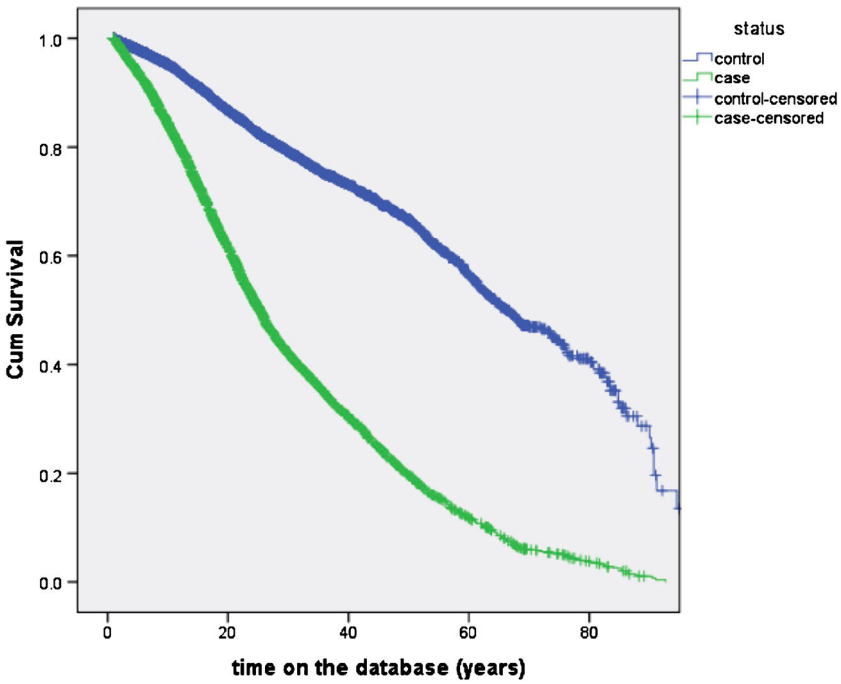

Fig. 1 Survival curves of case and control cohorts with increasing time on the database

The presence of intravisceral fat in the liver in NAFLD is known to propagate fibrosis, with regression of fibrosis on improvement in glycemic control [14]. However, there is growing acknowledgment that hepatocellular cancer can develop in non-cirrhotic livers with pathological studies suggesting that such cancers develop from liver cell adenomas in patients with metabolic syndrome, rather than a fibrosis-cirrhosis sequence [15, 16].

In this study, only 12.8% and 2.1% of the cohort had cirrhosis and NAFLD, respectively. This may represent undercoding of patients within the dataset, but the quality of the THIN dataset has been validated previously and there is a possibility that this represents a general under-diagnosis of fatty liver disease within the population [17]. It is also plausible that a majority of cancers within the dataset that arose in non-NAFLD patients could follow an alternate pathway to the development of cancer. The presence of cirrhosis clearly poses an additional risk factor to cancer progression, and this effect is more pronounced with increasing age, as we have demonstrated.

We observed that age had an inverse association with risk of hepatobiliary cancers, and this risk was preserved in cancer subtypes within the study. Age is known to be a risk factor for the development of hepatobiliary cancers [18]. It is possible that this effect is due to a peak in the incidence of hepatobiliary cancers in the 60 to 80-year age group and a decrease in the incidence with increasing age. Indeed, the case-cohort within the study had lower survival compared to the control group. The narrow confidence intervals for age, and the consistent odds ratios around 1.0 would additionally suggest that the inverse effect of age on the risk of hepatobiliary cancer is closer to a neutral risk.

Insulin and antihyperglycemic medication used in diabetes have been reported to be associated with risk of hepatocellular cancer [19, 20]. Uniquely, metformin is thought to exert a protective effect against development of hepatocellular cancer [19]. The proposed anti-cancer molecular action of metformin is mainly associated with the inhibition of the mammalian target of rapamycin complex 1 (mTORC1) [21]. The mTOR pathway plays a pivotal role in metabolism, growth, and proliferation of cancer cells, and metformin is thought to inhibit the mTORC 1 pathway. We found that insulin and metformin were consistently associated with risk of hepatobiliary cancer.

We found that statin use was protective against hepatobiliary cancer. There has been interest in the chemo-preventative effects of statins in other cancer types [22]. Statins are hypothesized to upregulate proapoptotic proteins, reduce cell proliferation, and enhance apoptosis through signaling G-proteins through the inhibition of HMG-CoA reductase, which reduces levels of mevalonate, an important precursor to isoprenoids which have critical effects on cell growth in vitro [23]. Preclinical studies have suggested that statins can inhibit angiogenesis and suppress tumorigenesis by facilitating apoptosis [24, 25]. Statins have been found to have a protective effect in colorectal cancer and prostate cancer [26–28], although no association has been noted with breast, stomach, and pancreatic cancer [29–31]. Recent case-control studies have, however, suggested a significant risk reduction with statin use for hepatocellular cancer [28] and cholangiocarcinoma [32], similar to our results.

Our study has some limitations. This study was performed on a database and is subject to the quality of data within the dataset. However, the THIN database is updated continually, thus limiting the possibility of missing data on confounders.

An additional strength of our study included detailed prescription data. We were able to examine the prescription patterns of different drugs within the dataset over a temporal timeframe and understand their impact on hepatobiliary cancer.

In conclusion, our study demonstrates that increasing BMI, as part of metabolic syndrome, is an independent risk factor for the development of hepatobiliary cancer.

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Compliance with ethical standards

Conflict of interest SM, and RM declare that they have no conflict of interest.

Ethical clearance The authors declare that the study was performed in a manner conforming to the Helsinki declaration of 1975, as revised in 2000 and 2008 concerning human and animal rights, and the authors followed the policy concerning informed consent as shown on Springer.com.

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