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Association between Smoking Cessation and the Risk of Cholangiocarcinoma and Ampulla of Vater Cancer: A Nationwide Cohort Study

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Keywords
Smoking cessation · Cholangiocarcinoma · Prevention · Diabetes · Prediabetes

Abstract

Introduction: The association between smoking cessation and intrahepatic and extrahepatic cholangiocarcinoma (iCCA and eCCA) risk is unclear. Furthermore, the association in individuals with preexisting risk factors is unknown. We aimed to investigate the association between smoking status (especially smoking cessation) and CCA risk according to individuals' glycemic status. ***Methods:*** In this nationwide cohort study, 9,520,629 adults without cancer who underwent national health screening by the Korean National Health Insurance Service in 2009 were followed up through 2018. The hazard ratios (HRs) and 95% confidence intervals (CIs) for CCA were estimated after adjusting for potential confounders. ***Results:*** During the 78.3 person-years of follow-up, 16,236 individuals were newly diagnosed with CCA. Quitters had a significantly lower risk of iCCA and eCCA compared to current smokers in all glycemic status groups (all $p < 0.01$). The HRs (95% CIs) for iCCA in current smokers and quitters were 1.33 (1.24–1.43) versus 0.98 (0.90–1.06) in individuals with normoglycemia, 1.49 (1.37–1.63) versus 1.17 (1.06–1.28) in individuals with prediabetes, and 2.15 (1.96–2.37) versus 1.58 (1.42–1.75) in individuals with diabetes, compared to never-smokers with normoglycemia. Current smokers with diabetes or prediabetes had a synergistically increased risk of iCCA (all $p < 0.01$). However, quitters with diabetes and prediabetes had an iCCA risk comparable to that of never-smokers. Analysis of eCCA yielded similar results. Smoking was not independently associated with the risk of the ampulla of Vater cancer. However, smoking combined with diabetes or prediabetes was associated with an increased risk of the ampulla of Vater cancer (all $p < 0.05$). ***Conclusion:*** Smoking cessation was associated with a reduced risk of CCA, despite the synergistically increased risk in current smokers with diabetes and prediabetes. Our findings suggest a crucial opportunity to reduce the risk of CCA. More individualized and intensive cancer prevention education is needed against CCA.

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Introduction

Cholangiocarcinoma (CCA) is a highly aggressive cancer of the biliary epithelial cells [1, 2]. The incidence and mortality rates of CCAs are increasing worldwide [1, 3]. However, CCA is still diagnosed at an advanced stage because of its silent presentation and absence of effective screening programs. The prognosis of CCA is dismal with a median overall survival of approximately 12 months [1, 4]. Moreover, most known risk factors for CCA are non-modifiable, including liver cirrhosis and bile duct abnormalities [2, 5]. Therefore, it is essential to determine the effect of modifying risk factors to reduce the growing disease burden of CCA.

Although smoking is a known risk factor for CCA [5–12], the effect of smoking cessation on CCA risk has not been established. Only one pooled analysis examined the association between smoking cessation and risk of intrahepatic CCA (iCCA) but reported no association, possibly due to insufficient statistical power (177 CCA cases in quitters) [7]. Furthermore, the data regarding whether the association between smoking or smoking cessation and CCA risk differs in individuals with pre-existing risk factors are lacking.

Diabetes and prediabetes, which affect 13.8% and 26.9% of adults in South Korea, respectively, are both associated with an increased risk of CCA [5, 13–15]. The prevalence of diabetes and prediabetes is rapidly increasing worldwide [16, 17]. Smoking and hyperglycemia may interact, indicating a common pathway for CCA carcinogenesis [18–23]. However, data are lacking regarding the effect of smoking and smoking cessation on CCA risk according to glycemic status. Analysis based on glycemic status can evaluate both the independent and interactive effects of smoking status and hyperglycemia on CCA risk.

Therefore, we investigated the association between smoking status (especially smoking cessation) and the risk of CCA according to individuals' glycemic status. We followed more than 9 million individuals in this nationwide cohort for 10 years using their national health screening and medical claims record data from the Korean National Health Insurance Service (NHIS). We analyzed each association individually based on the anatomical location of CCA, such as iCCA, extrahepatic CCA (eCCA), and ampulla of Vater cancer.

Patients and Methods

Data Source and Study Population

The Korean NHIS, the single insurer of healthcare services in Korea, covers approximately 97% of the South Korean population. In addition, the NHIS provides a standardized national health screening program for all citizens aged ≥40 years and all employees of any age at least every 2 years [24]. We used the NHIS database, which includes the national health screening program database (anthropometric measurements, a self-administered questionnaire on health-related behavior, and laboratory test results) and the national health claims database (medical treatment, prescription drugs, and disease diagnosis based on the International Classification of Diseases-10th Revision Clinical Modification (ICD-10-CM) code).

We identified 10,585,844 individuals aged ≥20 years who underwent the NHIS health examinations from January 1 to December 31, 2009. Figure 1 shows the flowchart of the study population selection. To minimize the effect of preexisting disease, we excluded participants with a prior diagnosis of cancer before cohort entry (n = 151,128) and those who developed any cancer or died within 1 year after cohort entry (n = 86,691). We also excluded participants with missing data (n = 827,396). Finally, a total of 9,520,629 individuals were enrolled in the study. The study participants were followed up until the date of CCA development, death, or December 31, 2018, whichever occurred first.

The study was approved by the Institutional Review Board of the Samsung Medical Center, Seoul, Korea (approval no: SMC2019-08-106), and the NHIS Big Data Steering Department (NHIS-2021-1-719), and followed the principles of the Declaration of Helsinki. The requirement for written informed consent was waived because the NHIS data contain anonymized data that follow the guidelines of the Personal Data Protection Act.

Definition of Smoking and Glycemic Status

Smoking status was defined using a standardized self-administered questionnaire during the NHIS health screening (online suppl. Table S1; for all online suppl. material, see www.karger.com/doi/10.1159/000529609). Participants were classified as never-smokers, quitters, or current smokers. Never-smokers were defined as those who had smoked <100 cigarettes. When asked if they had smoked at least 100 cigarettes, those who responded "Yes, but I quit" were defined as quitters. Quitters and current smokers were questioned about the average number of cigarettes per day and the duration of smoking (in years). An individual's cumulative years of exposure to tobacco were measured in pack-years and calculated as the number of packs of cigarettes smoked per day multiplied by the number of years the person had smoked. For national health screening, healthcare professionals performed blood tests for each participant, which included an assessment of the fasting plasma glucose level, in the NHIS-certified hospitals that were subjected to quality control measures. The glycemic status of the participants was classified as normoglycemia (fasting plasma glucose level <100 mg/dL), prediabetes (fasting plasma glucose level of 100–125 mg/dL), and diabetes. Diabetes was defined as a fasting glucose level of ≥126 mg/dL or at least one claim per year for the prescription of oral and injectable antidiabetic medication under ICD-10-CM codes (E11–E14) [14, 24, 25].

Identification of New CCA Cases

The endpoint of this study was a newly diagnosed CCA. We identified new cases of CCA from January 2009 to December 2018 using ICD-10-CM codes (C22.1 for iCCA, C24.0 for eCCA, and C24.1 for ampulla of Vater cancer) during hospitalization, and a

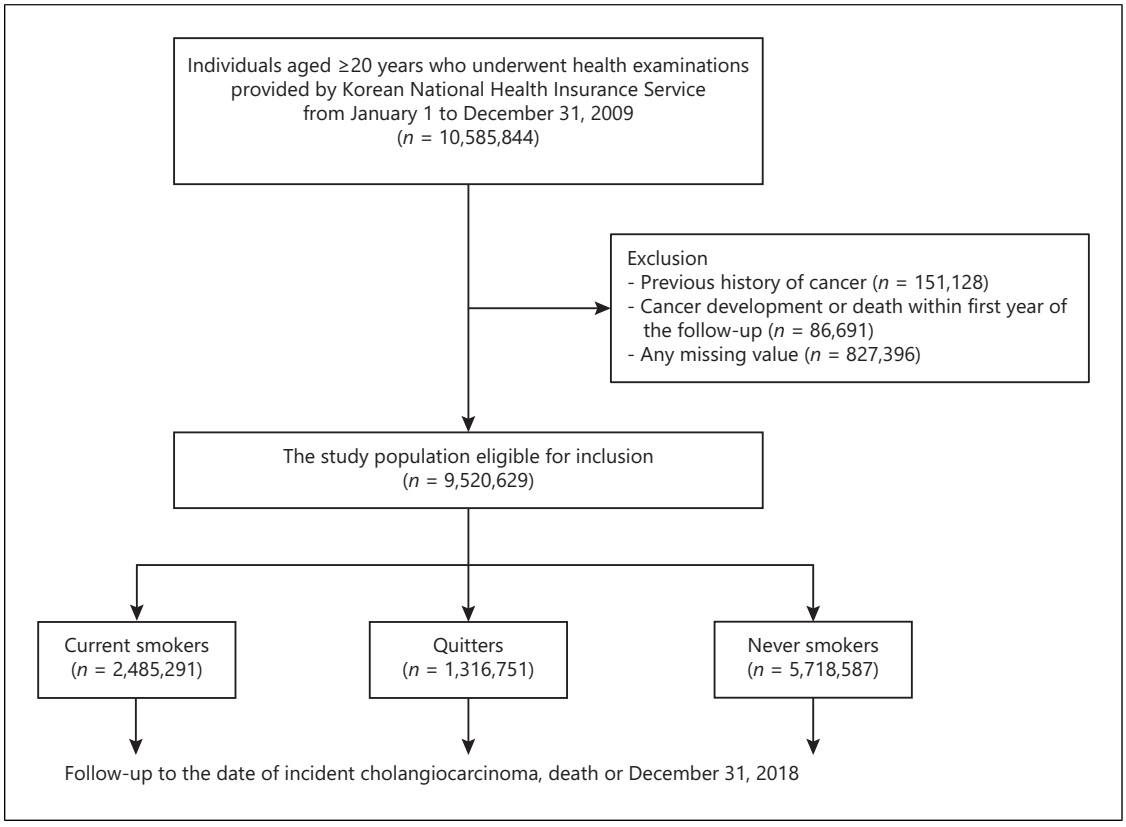

Fig. 1. Flowchart of the study population. Glycemic status: normoglycemia, prediabetes, and diabetes.

special reimbursement code for cancer (V193). Since 2006, the NHIS policy has enhanced health coverage for intractable diseases including cancer. Physicians and medical institutions need to confirm a cancer diagnosis for V193 code to reduce the copayment rate to 5% for cancer-related examinations and treatments. The NHIS registers all patients with a confirmed diagnosis of cancer using the reimbursement code (V193).

Definition of the Clinical Variables

Height, weight, and waist circumference were measured by healthcare professionals. Body mass index (BMI) was calculated by dividing the weight by height squared (kg/m^2). Systolic and diastolic blood pressure (BP) was measured in a seated position after at least 5 min of rest. Blood samples were collected after overnight fasting to analyze serum levels of glucose and total cholesterol. Lower income status included those in the lowest quartile of the required insurance fee or those who received free medical care.

Information on alcohol consumption and physical activity was obtained using standardized self-administered questionnaires. Alcohol consumption behavior was classified according to the average amount of alcohol consumed per day as follows: none, light-to-moderate (<30 g of alcohol per day), or heavy (≥30 g of alcohol per day) [25]. Regular physical activity was defined as performing ≥20 min of vigorous-intensity physical activity at least 3 times/week or ≥30 min of moderate-intensity physical activity at least 5 times/week.

Hypertension was defined as a systolic BP ≥140 mm Hg, diastolic BP ≥90 mm Hg, or ICD-10-CM codes (I10–I13 and I15) with claims for antihypertensive medications. Dyslipidemia was defined based on serum total cholesterol levels ≥240 mg/dL or ICD-10-CM code (E78) with claims for lipid-lowering drug prescriptions. The factors associated with CCA were defined using the following ICD-10-CM codes: choledochal cysts, Q44.4; primary sclerosing cholangitis, K83.01; primary biliary cirrhosis, K74.3; liver flukes, B66.0, B66.1, and B66.3; fibrosis and cirrhosis of the liver, K74; and alcoholic cirrhosis of the liver, K70.3.

Statistical Analysis

The baseline characteristics of the study participants were compared according to smoking status using ANOVA for continuous variables and the χ^2 test for categorical variables. Participants were censored on the date of CCA diagnosis, date of death, or December 31, 2018. CCA incidence rates were calculated by dividing the number of incident cases by the number of person-years in each exposure group. We used the Cox proportional hazard model to compute hazard ratios (HRs) and 95% confidence interval (CI) to estimate the risk of CCA according to smoking status and glycemic status. Model 1 was adjusted for age and sex. Model 2 was additionally adjusted for BMI, alcohol consumption, physical activity, income, hypertension, dyslipidemia, choledochal cysts, primary sclerosing cholangitis, primary biliary cirrhosis, liver flukes, liver fibrosis, and liver cirrhosis. We also analyzed this

association according to the pack-years of smoking. In addition, additive interactions were examined using the relative excess risk due to interaction (RERI), which indicates whether the interactive effects of smoking and glycemic status were greater than the additive effect when both risk factors were present [26]. RERI was computed for binary variables as the difference between the additive and observed risks for risk factors A and B (RERI = HR_{AB}–HR_A–HR_B+1). RERI = 0 represents no interaction or exact additivity; <0 represents a negative or sub-additive interaction; >0 represents a positive or synergistic interaction [27]. All statistical tests were two-sided, and statistical significance was set at $p < 0.05$. All statistical analyses were performed using the SAS software, version 9.3 (SAS Institute, Cary, NC, USA).

Results

Baseline Characteristics of the Study Population

We followed up 9,520,629 participants for a mean of 8.2 years (78.3 million person-years). During the follow-up period, 16,236 patients were newly diagnosed with CCA. Table 1 shows the baseline characteristics of the study population according to the smoking status. The mean age of current smokers was the lowest ($p < 0.01$). The proportion of men was similar between the quitters and current smokers. Current smokers had the highest proportion of heavy drinkers ($p < 0.01$). Quitters had the highest BMI and the highest proportions of hypertension, dyslipidemia, and diabetes (all $p < 0.01$).

Association of Smoking and Smoking Cessation with the Risk of CCA according to Glycemic Status

Table 2 and online supplementary Figure S1 show the risk of iCCA according to smoking and glycemic status compared to never-smokers with normoglycemia (reference group). Quitters had a reduced risk of iCCA compared to current smokers in all glycemic status groups (all $p < 0.01$ in models 1 and 2). In individuals with normoglycemia, current smokers had a 33% increased risk of iCCA (HR, 1.33; 95% CI, 1.24–1.43), whereas the risk of iCCA did not increase in the quitters (HR, 0.98; 95% CI, 0.90–1.06). In individuals with prediabetes, current smokers had a 49% increased risk of iCCA (HR, 1.49; 95% CI, 1.37–1.63), whereas quitters with prediabetes had a 17% increased risk (HR, 1.17; 95% CI, 1.06–1.28). In individuals with diabetes, current smokers had a more than 2-fold increased risk of iCCA (HR, 2.15; 95% CI, 1.96–2.37), while quitters had a 58% increased risk (HR, 1.58; 95% CI, 1.42–1.75).

The risk of iCCA increased as the glycemic status worsened (p for trend <0.01). Moreover, current smokers with diabetes or prediabetes had a synergistically increased risk of iCCA above the sum of these individual risks (RERI, 0.46 and 0.09, respectively; all $p < 0.01$).

As shown in Table 2 and online supplementary Figure S2, analysis of eCCA showed similar results. Quitters had a reduced risk of eCCA compared to current smokers in all glycemic status groups (all $p < 0.01$ in models 1 and 2). Significant synergistic interactions between current smoking and diabetes or prediabetes on eCCA risk were observed (RERI, 0.42 and 0.20, respectively; all $p < 0.01$). The RERI of current smoking and glycemic status on the risk of iCCA and eCCA increased as the glycemic status worsened (p for trend <0.01).

Online supplementary Table S2 shows the association between smoking status and the risk of the ampulla of Vater cancer according to the glycemic status. Smoking, prediabetes, and diabetes were not independently associated with an increased risk of the ampulla of Vater cancer after adjusting for potential confounders (model 2). However, current smokers with diabetes and prediabetes had an increased risk of the ampulla of Vater cancer compared to never-smokers with normoglycemia (model 2, HR, 95% CI: 1.46, 1.13–1.88 and 1.40, 1.13–1.72, respectively).

Association of Smoking and Smoking Cessation with the Risk of CCA According to Glycemic Status and Smoking Pack-Years

Among individuals with a smoking history of ≥20 pack-years, quitters had a reduced risk of iCCA compared to current smokers, regardless of glycemic status (Fig. 2a; online suppl. Table S3, all $p < 0.01$).

Quitters had a comparable iCCA risk to never-smokers, regardless of glycemic status, especially if a smoking history of <20 pack-years (Fig. 2b, all $p > 0.05$). As shown in Figure 2a, current smokers of ≥20 smoking pack-years and diabetes had the highest risk and a 2.3-fold increased risk of iCCA compared with never-smokers with normoglycemia (HR, 2.28; 95% CI, 2.04–2.54).

Figure 3 and online supplementary Table S4 show that quitters had a reduced risk of eCCA compared to current smokers among individuals with a smoking history of ≥20 pack-years (all $p < 0.01$). Current smokers of ≥20 smoking pack-years and diabetes had the highest risk and a 2.3-fold increased risk of eCCA compared with never-smokers with normoglycemia (HR, 2.00; 95% CI, 1.75–2.29). Analysis of the ampulla of Vater cancer is presented in online supplementary Table S5.

Discussion

In this nationwide cohort study, we found that smoking cessation was significantly associated with a reduced risk of iCCA and eCCA. Current smoking was

Table 1. Baseline characteristics of the study population according to the smoking status

	Current smokers	Quitters	Never-smokers	*p* values
	(*N* = 2,485,291)	(*N* = 1,316,751)	(*N* = 5,718,587)	
Age, mean±SD, years	42.7±12.4	48.7±12.9	48.5±14.5	<0.01
Age ≥65 years, *n* (%)	154,789 (6.2)	168,746 (12.8)	885,041 (15.5)	<0.01
Sex, *n* (%)				
Male	2,338,894 (94.1)	1,248,448 (94.8)	1,596,954 (27.9)	<0.01
Female	146,397 (5.9)	68,303 (5.2)	4,121,633 (72.1)	
Smoking pack-years, *n* (%)				
<20	1,640,725 (66.0)	926,062 (70.3)	–	<0.01
≥20	844,566 (34.0)	390,689 (29.7)	–	
Alcohol consumption, *n* (%)				
None	573,601 (23.1)	383,519 (29.1)	3,930,535 (68.7)	<0.01
Light-to-moderate	1,466,803 (59.0)	756,008 (57.4)	1,648,058 (28.8)	
Heavy	444,887 (17.9)	177,224 (13.5)	139,994 (2.5)	
Regular physical activity, *n* (%)	403,466 (16.2)	330,831 (25.1)	962,659 (16.8)	<0.01
Anthropometric measurement, mean±SD				
Body mass index, kg/m^2	23.9±3.3	24.3±2.9	23.5±3.3	<0.01
Waist circumference, cm	82.7±8.3	84.1±7.8	78.3±9.2	<0.01
Systolic BP, mm Hg	123.5±14.1	125.2±14.3	121.3±15.5	<0.01
Diastolic BP, mm Hg	77.5±9.8	78.3±9.8	75.4±10.1	<0.01
Laboratory findings, mean±SD				
Fasting glucose, mg/dL	98.1±26.4	100.3±25.1	96.1±22.3	<0.01
Total cholesterol, mg/dL	194.7±36.8	196.3±36.4	195.1±37.1	<0.01
Low-income status, *n* (%)	409,374 (16.5)	180,456 (13.7)	1,275,667 (22.3)	<0.01
Comorbidities, *n* (%)				
Diabetes	215,661 (8.7)	145,960 (11.1)	461,125 (8.1)	<0.01
Hypertension	542,753 (21.8)	416,287 (31.6)	1,485,406 (26.0)	<0.01
Dyslipidemia	383,921 (15.5)	262,491 (19.9)	1,075,161 (18.8)	<0.01

BP, blood pressure; SD, standard deviation.

associated with a synergistically increased risk of iCCA and eCCA in individuals with diabetes and prediabetes. Nevertheless, quitters with diabetes or prediabetes had a CCA risk comparable to that of never-smokers with diabetes or prediabetes. No association between smoking and the risk of the ampulla of Vater cancer was observed. However, smoking was associated with an increased risk of the ampulla of Vater cancer when combined with either diabetes or prediabetes. Our findings suggest a crucial opportunity to significantly reduce CCA risk, particularly in individuals at an increased risk.

There have been limited data on whether smoking cessation could reduce the risk of CCA. To the best of our knowledge, only one pooled analysis from 14 cohort studies examined the association between smoking cessation and the risk of iCCA but did not demonstrate this association [7]. This could explain a relatively small number of patients with iCCA (177 cases in quitters and 60 cases in current smokers), which limited the statistical power to detect the association. We present new evidence of the beneficial effect of smoking cessation on CCA risk. This effect was consistently substantial in individuals with diabetes and prediabetes who had a synergistically increased risk of CCA.

Potential biological mechanisms can explain the beneficial effects of smoking cessation on CCA risk. Current smoking can cause persistent cumulative damage and increase the risk of CCA [28]. Conversely, smoking cessation may limit further damage and lead to the reactivation of normal cells that are not damaged by tobacco carcinogens [29]. Nevertheless, it is unclear why the effect of smoking on CCA risk differs according to the glycemic status. Some tobacco carcinogens, such as N-nitrosamines, polycyclic aromatic hydrocarbons, volatile organics, and aromatic amines, may act on the biliary tract through blood and bile juices [18]. Hyperglycemia may stimulate glycosylation of proteins and the production of free radicals, causing oxidative stress, and may promote the carcinogenic effect of smoking on CCA [19, 20]. In addition,

Table 2. Association between smoking status and the risk of intrahepatic and extrahepatic cholangiocarcinoma according to the glycemic status

Cholangiocarcinoma	Glycemic status	Smoking status	*N*	Event, *n*	Person-years	IR*	Hazard ratio (95% CI)	
							Model 1	Model 2
Intrahepatic	Normoglycemia							
		Never-smokers	4,065,767	2,999	33,689,370	8.9	1 (reference)	1 (reference)
		Quitters	801,063	798	6,600,675	12.1	0.99 (0.91–1.08)	0.98 (0.90–1.06)
		Current smokers	1,666,390	1,291	13,707,710	9.4	1.34 (1.25–1.44)	1.33 (1.24–1.43)
	Prediabetes							
		Never-smokers	1,191,695	1,462	9,818,506	14.9	1.10 (1.04–1.17)	1.07 (1.01–1.14)
		Quitters	369,728	564	3,031,916	18.6	1.22 (1.11–1.34)	1.17 (1.06–1.28)
		Current smokers	603,240	699	4,925,929	14.2	1.56 (1.43–1.71)	1.49 (1.37–1.63)
	Diabetes							
		Never-smokers	461,125	1,156	3,704,247	31.2	1.43 (1.33–1.53)	1.36 (1.27–1.46)
		Quitters	145,960	454	1,165,693	38.9	1.66 (1.50–1.85)	1.58 (1.42–1.75)
		Current smokers	215,661	580	1,713,783	33.8	2.28 (2.08–2.50)	2.15 (1.96–2.37)
Extrahepatic	Normoglycemia							
		Never-smokers	4,065,767	2,190	33,689,493	6.5	1 (reference)	1 (reference)
		Quitters	801,063	536	6,600,812	8.1	0.90 (0.81–1.00)	0.88 (0.80–0.98)
		Current smokers	1,666,390	768	13,708,139	5.6	1.11 (1.02–1.22)	1.13 (1.03–1.23)
	Prediabetes							
		Never-smokers	1,191,695	1,039	9,818,757	10.6	1.06 (0.98–1.14)	1.02 (0.95–1.10)
		Quitters	369,728	357	3,032,048	11.8	1.04 (0.92–1.17)	0.99 (0.88–1.11)
		Current smokers	603,240	447	4,926,070	9.1	1.38 (1.24–1.54)	1.35 (1.21–1.50)
	Diabetes							
		Never-smokers	461,125	818	3,704,294	22.1	1.35 (1.25–1.47)	1.27 (1.17–1.38)
		Quitters	145,960	283	1,165,806	24.3	1.38 (1.22–1.58)	1.29 (1.13–1.47)
		Current smokers	215,661	355	1,713,940	20.7	1.91 (1.70–2.15)	1.81 (1.61–2.04)

Model 1: adjusted for age and sex. Model 2: adjusted for age, sex, body mass index, alcohol consumption, physical activity, income, hypertension, dyslipidemia, choledochal cysts, primary sclerosing cholangitis, primary biliary cirrhosis, liver flukes, liver fibrosis, and liver cirrhosis. CI, confidence interval; IR, incidence rate. *Incidence rate per 100,000 person-years.

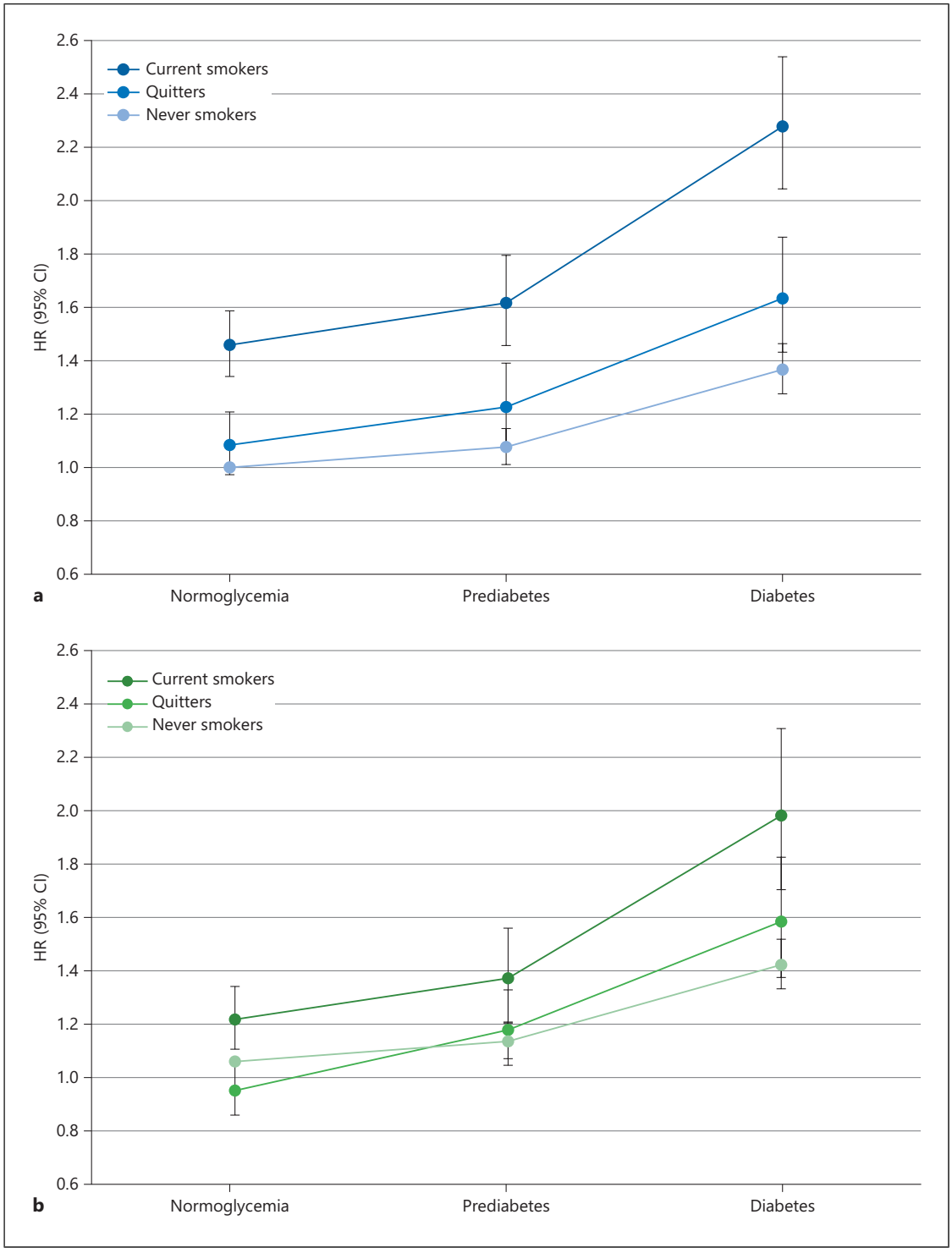

Fig. 2. Association of current smoking and smoking cessation with the risk of intrahepatic cholangiocarcinoma according to glycemic status in smokers of ≥20 pack-years (**a**) and <20 pack-years (**b**). HRs and 95% CIs were adjusted for age, sex, body mass index, alcohol consumption, physical activity, income, hypertension, dyslipidemia, choledochal cysts, primary sclerosing cholangitis, primary biliary cirrhosis, liver flukes, liver fibrosis, and liver cirrhosis. CI, confidence interval; HR, hazard ratio.

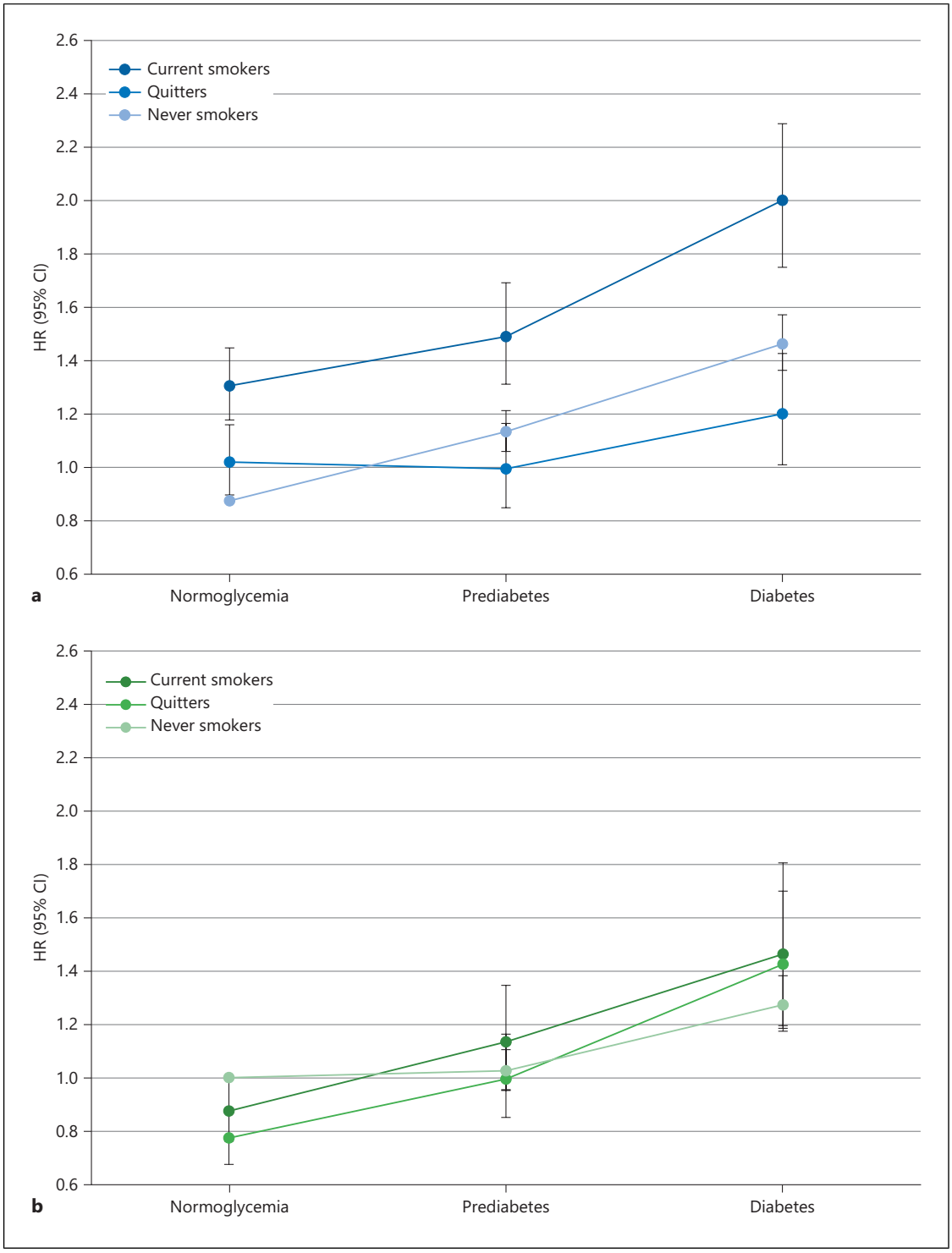

Fig. 3. Association of current smoking and smoking cessation with the risk of extrahepatic cholangiocarcinoma according to glycemic status in smokers of ≥20 pack-years (**a**) and <20 pack-years (**b**). HRs and 95% CIs were adjusted for age, sex, body mass index, alcohol consumption, physical activity, income, hypertension, dyslipidemia, choledochal cysts, primary sclerosing cholangitis, primary biliary cirrhosis, liver flukes, liver fibrosis, and liver cirrhosis. CI, confidence interval; HR, hazard ratio.

hyperglycemia can damage blood vessels and increase susceptibility to tobacco carcinogens [21]. The combination of smoking and diabetes may also promote biliary carcinogenesis through the synergism of chronic inflammation and oxidative stress [22, 23]. However, smoking cessation may reduce both the direct carcinogenic effect of smoking and the synergistic effect of current smoking and hyperglycemia on CCA risk.

Our study has several strengths. First, we used the longitudinally collected blood test results, lifestyle factors, anthropometric parameters, and comprehensive medical records. The Korean NHIS database accurately tracked the clinical course of the disease in the participants after cohort entry. Second, this population-based nationwide study is one of the largest cohort studies based on data from more than nine million individuals, with a follow-up period of 10 years. Third, analyses were performed after adjusting for significant confounders including various CCA-associated factors and BMI. Fourth, for a high diagnostic accuracy, we used both ICD-10-CM diagnostic codes (C code) and national registration codes (V codes) to identify CCA.

Our study has some limitations. First, smoking status was measured using standardized questionnaires prior to CCA development; however, biochemical validation was not performed. Misclassification and underreporting are possible; however, self-reported smoking status is generally accurate [30]. Second, data on the date of study participants quit smoking are unavailable due to a lack of data. We were not able to determine the duration of smoking cessation. Third, HbA1c data were not considered because they were unavailable in the NHIS database. Fourth, the pathological subtypes of CCA were not considered. However, the majority (>90%) of CCA are adenocarcinoma [2]. Fifth, our study is a large population-based study that included a single country population. The ethnic differences in the association between smoking status and CCA risk were not determined.

In conclusion, smoking cessation was significantly associated with a reduced risk of iCCA and eCCA. Current smoking was associated with a synergistically increased risk of iCCA and eCCA in individuals with diabetes and prediabetes. However, the risk of iCCA and eCCA in quitters with diabetes and prediabetes was comparable to that in never-smokers. Although smoking, prediabetes, and diabetes were not independently associated with the risk of the ampulla of Vater cancer, the combination of smoking with either diabetes or prediabetes was associated with an increased risk of the ampulla of Vater cancer. Given the lack of effective screening and the dismal prognosis of CCA, our findings suggest a crucial opportunity to significantly reduce the risk of CCA, especially in individuals at an increased risk. More individualized and intensive cancer prevention education should be underscored for individuals at an increased risk of CCA. Further studies are needed to elucidate the mechanisms underlying the interaction between smoking and hyperglycemia that promotes biliary carcinogenesis.

Statement of Ethics

The study was approved by the Institutional Review Board of the Samsung Medical Center, Seoul, Korea (approval No: SMC2019-08-106) and the NHIS Big Data Steering Department (NHIS-2021-1-719), and followed the principles of the Declaration of Helsinki. The requirement for written informed consent was waived because the NHIS data contain anonymized data that follow the guidelines of the Personal Data Protection Act.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Joo-Hyun Park: conceptualization, data curation, formal analysis, investigation, methodology, and writing – original draft, review, and editing. Jung Yong Hong: conceptualization, data curation, formal analysis, investigation, methodology, writing – original draft, review and editing, and supervision. Kyungdo Han: conceptualization, data curation, formal analysis, investigation, methodology, writing, review, and editing.

Data Availability Statement

The Korean National Health Insurance Data Service website (http://nhiss.nhis.or.kr) provides access to the data from the National Health Insurance Service (NHIS). To access the database, researchers must submit a study proposal for approval from each Institutional Review Board, which is then reviewed by the NHIS review committee. Further inquiries can be directed to the corresponding author.

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