Smoking and the risk of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection

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ABSTRACT

Introduction: It is unclear whether smokers are more vulnerable to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. This study aimed to evaluate the association between smoking and the risk of SARS-CoV-2 infection.

Methods: A matched case-control study was conducted using a large nationwide database. The case group included patients with SARS-CoV-2 infection confirmed by the Korea Centers for Disease Control and Prevention, and the control group was randomly sampled from the general Korean population in the National Health Insurance Service database by matching sex, age, and region of residence. Conditional logistic regression models were used to investigate whether the risk of infection with SARS-CoV-2 was affected by smoking status.

Results: A total of 4,167 patients with SARS-CoV-2 infection and 20,937 matched controls were enrolled. The proportion of ex-smokers and current smokers was 26.6% of the total participants. In multivariate analysis, smoking was not associated with an increased risk of SARS-CoV-2 infection (odds ratio [OR] = 0.56, confidence interval [CI] = 0.50–0.62). When ex-smokers and current smokers were analysed separately, similar results were obtained (current smoker OR = 0.33, CI = 0.28–0.38; ex-smoker OR = 0.81, CI = 0.72–0.91).

Conclusions: This study showed that smoking may not be associated with an increased risk of SARS-CoV-2 infection. Smoking tends to lower the risk of SARS-CoV-2 infection; however, these findings should be interpreted with caution.

IMPLICATIONS

It is unclear whether smokers are more vulnerable to coronavirus disease 2019. In this large nationwide study in South Korea, smoking tended to lower the risk of infection with severe acute respiratory syndrome coronavirus 2. However, these findings should be interpreted with caution, and further confirmatory studies are required.

INTRODUCTION

Coronavirus disease (COVID-19) is an infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The COVID-19 outbreak started in Wuhan, Hubei Province, China, in December 2019 and has been spreading globally since then. As of March 9, 2020, a total of 116,166,652 COVID-19 cases have been reported worldwide, including 2,582,528 deaths.[1]

Cigarette smoking increases the risk of important bacterial and viral infections through structural changes in the respiratory tract and a decrease in the immune response.[2] During the previous SARS outbreak (2002-2004), there was insufficient data on smoking and infection risk. One study reported that smoking did not increase the infection risk; however, no further studies have confirmed this.[3]

The invasion and replication of SARS-CoV-2 mainly occur in the respiratory tract.[4] Smoking weakens the mucociliary clearance and immune system of the airway, and makes SARS-CoV-2 easily penetrate the host cell.[5] Moreover, active cigarette smoking upregulates angiotensin-converting enzyme (ACE) 2, which is the host receptor for SARS-CoV-2 in the lower airway; thus, smoking may increase the risk of SARS-CoV-2 infection.[6,7] However, it is not well known whether smokers are more likely to get infected by SARS-CoV-2 or are more vulnerable to COVID-19. This study aimed to evaluate the association between smoking and the risk of SARS-CoV-2 infection.

METHODS

Data source

We used the Korean National Health Insurance Data and COVID-19 registry data from the Korea Centers for Disease Control and Prevention (KCDC). Korea has a unique insurance system provided by the National Health Insurance Service (NHIS). Nearly all individuals living in Korea are obliged to join the NHIS, and a large amount of medical information has been accumulated in the NHIS database. Recently, the NHIS provided the nationwide data on COVID-19 for research collaboration. The NHIS dataset for research on COVID-19 was based on insurance claims and comprised patients with SARS-CoV-2 infection, matched with the general population. This dataset includes various health-related variables, including sociodemographic information, diagnosis, medication, national health screening information (including smoking survey), and survival status. This study was approved by the Institutional Review Board of the NHIS Ilsan Hospital, Korea, and adhered to the tenets of the Declaration of Helsinki (NHIMC 2020-04-026). Owing to the retrospective nature of the study and the use of de-identified patient data from the database, the requirement for written informed consent was waived.

Study population

The COVID-19 registry data of the KCDC includes all COVID-19 cases in Korea to date. The first COVID-19 case in Korea was confirmed on January 20, 2020. The case group included patients with SARS-CoV-2 infection confirmed by the KCDC until April 16, 2020. All diagnoses in the registry data of the KCDC were confirmed by reverse transcription polymerase chain reaction testing for SARS-CoV-2. Patients under 40 years of age were

excluded because smoking information was not available at this age. The control group was randomly sampled from the general Korean population in the NHIS database by matching sex, age, and the region of residence, and the number of the control group was set to be five times that of the case group. Because all COVID-19 cases in Korea were included in the KCDC registry, it was considered that the control group did not have COVID-19.

Demographic factors and outcomes

In both case and control groups, information on sex, age, region of residence, and household income was collected as of 2019, and the data on comorbidities were collected for one year in 2019. Comorbidities were categorized into respiratory disease (asthma, J45-46; chronic obstructive pulmonary disease [COPD], J43-44; bronchiectasis, J47), heart disease (ischemic heart disease, I20-25, congestive heart failure, I50), diabetes mellitus (E10-14), hypertension (I10), and cancer (C00-97) according to the International Classification of Diseases, Tenth Revision.

The NHIS dataset includes information on national health screening, which is mandatory for most Korean citizens every two years. Personal smoking information was obtained through a smoking survey included in the national health screening program. The most recent health screening data prior to the time of enrollment were used to obtain smoking information. Smoking information was obtained through the following questionnaire: “Have you ever smoked more than five packs of cigarettes in your life?” The answers were divided into three categories: no, quit now, or currently smoking. The risk of infection with SARS-CoV-2 was analysed according to smoking status, which was categorized as never-smoker, ever-smoker, and current smoker.

Statistical analysis

Descriptive statistics were performed for all variables. Differences between the two groups were assessed using the chi-square test. Conditional logistic regression analyses that were conditioned on sex, age, and region of residence were performed to determine whether smoking was associated with the risk of infection with SARS-CoV-2. Two models were used to analyze the risk of infection: the first model (Model 1) compared two groups (never- versus ever- or current smokers); the other model (Model 2) compared three groups (never versus ever versus current smokers). Other variables (household income and comorbidities), except smoking, were the same for Models 1 and 2. *Statistical significance was set at* $P < 0.05$. All statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA).

RESULTS

Baseline characteristics

A total of 4,167 patients with SARS-CoV-2 infection were included (Table 1). The matched control group consisted of 20,937 participants. Of the total subjects, 8,814 (35.1%) were men. The age distribution was the highest in the 50s (34.0%), and those in their 60s and 40s were 24.7% and 23.3%, respectively. The incidence of SARS-CoV-2 infection was high in Daegu and Gyeongbuk, which are located in the southeastern region of South Korea. In the univariate analysis, lower income levels were associated with the risk of infection with SARS-CoV-2, especially in the Medicaid group. Among the five categories of comorbidities,

respiratory diseases were more frequent in patients with SARS-CoV-2 infection, while hypertension was less frequent. Heart disease, diabetes mellitus, and cancer did not differ between the case and control groups.

Smoking and risk of SARS-CoV-2 infection

The proportion of smokers (ex and current) was 26.6% of the total subjects and 21.6% and 27.6% in the case and control groups, respectively. In the conditional logistic regression analysis, smoking was not associated with an increased risk of SARS-CoV-2 infection (adjusted odds ratio [OR] = 0.56, confidence interval [CI] = 0.50–0.62) (Table 2). When ex- and current smokers were analysed separately, similar results were obtained (smoker-adjusted OR = 0.33, CI = 0.28–0.38; ex-smoker adjusted OR = 0.81, CI = 0.72–0.91). Among other variables, low household income and respiratory diseases were associated with an increased risk of infection with SARS-CoV-2, while hypertension was associated with a decreased risk of infection (Table 3).

DISCUSSION

This large population-based study found that smoking was associated with a reduced risk of SARS-CoV-2 infection. These results were the same for both current and ex-smokers, even after adjusting for all available confounding variables. However, these findings should be interpreted cautiously.

Early epidemiologic studies of COVID-19 in China have revealed that the proportion of smokers is larger than that of nonsmokers in the general population.[8-10] Subsequently, a cross-sectional study revealed that active smoking was linked with decreased odds of a positive COVID-19 result,[11] and another study from the US and China also found a lower prevalence of smokers in hospitalized patients with COVID-19.[12-14] This may indicate that the risk of SARS-CoV-2 infection in smokers is not higher than that in non-smokers.

Further studies have reported that smoking was associated with a lower risk of SARS-CoV-2 infection. A cohort study involving aircraft carrier crews found that current smokers had a lower OR of 0.64 (95% CI 0.49-0.84) for COVID-19 occurrence compared to that of nonsmokers.[15] Another study including 38 European countries showed a negative association between smoking prevalence and COVID-19 after controlling for confounding factors.[16] One study using a national internet-based survey in Italy found a dose-dependent decrease in SARS-CoV-2 infection in current smokers. In this study, the OR for SARS-CoV-2 infection was 0.76 (95% CI 0.55-1.05) in mild smokers, 0.56 (95% CI 0.42-0.73) in moderate smokers, and 0.38 (95% CI 0.27-0.53) in heavy smokers.[17] A meta-analysis showed that current smokers had a reduced risk of SARS-CoV-2 infection (relative risk 0.74, 95% CI 0.58-0.93); however, former smokers did not have a significant association.[18] Although direct comparison is limited due to differences in study methods, these patterns of previous studies are quite similar to those of our study.

These findings have suggested a ‘smoker’s paradox’, and there are possible mechanisms by which smoking has potential protective effects on the severity of COVID-19.[19] The protective effects of smoking include an anti-inflammatory effect of nicotine,[20] a blunted immune response in smokers,[21] and increased nitric oxide in the respiratory tract.[22] Leung et al. analysed the protein expression of ACE-2 in the resected lung tissue specimen of patients with COVID-19.[6] Although ACE-2 gene expression was higher in active smokers, the protein

intensity of epithelial ACE-2 was similar to that of never smokers. This may be one reason why the risk of SARS-CoV-2 infection was not higher in healthy smokers. Moreover, some studies reported that the immune system of smokers is more tolerant and less reactive compared to that of never smokers via attenuation of normal defensive function of the immune system.[23,24] These studies also revealed that exposure to smoke could modulate the adaptive immune responses and reduce systemic levels of several immune or inflammatory markers compared to those in never smokers.

However, this reverse association between smoking and SARS-CoV-2 infection requires careful interpretation. The method of collecting information related to smoking status and patterns of healthcare utilization might be the reasons why smoking groups showed lower positivity for COVID-19. Because the information on smoking history was based on the national health examination questionnaire, it is possible that the examinee did not provide accurate information or the smoking status changed after the health examination. In addition, smokers with symptoms tend to have high medical utilization rates, but symptom-free healthy smokers tend to have low compliance with drug prescriptions or preventive care screening.[25-28] Therefore, smokers can get tested more because of their symptoms suggestive of COVID-19.[11,29] For example, both smoking and COVID-19 can cause cough, and smokers with smoking-related cough can be tested even when they do not have COVID-19.[30] In addition, testing for acute infection requires collecting swabs of the mucosal epithelium, which can be disrupted in smokers, and this lead to alter the sensitivity of assays.[11]

In Korea, the initial outbreak of COVID-19 had a unique feature. During our study period, a cluster infection in one religious group accounted for half of all patients with COVID-19 in Korea. A high proportion of transmission was due to close contact in the same place, and this feature could overwhelm the individual characteristics of disease susceptibility. Additionally, our study included individuals over 40 years of age, because Korean national health screening

was recommended in these age groups. A recent study from the US reported an increased risk of COVID-19 in young smokers. In this study, the risk of COVID-19 was associated with e-cigarettes and the dual use of e-cigarettes and cigarettes among young smokers aged 13-24 years.[31]

Some previous studies have strongly encouraged smoking cessation to flatten the COVID-19 outbreak and reduce mortality.[32-34] However, the association between smoking and the severity of COVID-19 remains unclear. A study from Italy demonstrated that active smoking was not associated with COVID-19 severity.[35] In contrast, another study from the UK reported that smokers have a decreased risk of both COVID-19 and ICU admission compared to that of non-smokers.[36] More recent study from the US also found that cumulative exposure to smoking is a risk factor for hospital admission and mortality.[37] Several meta-analyses also reported conflicting results. Lippi et al. reported that active smoking is not associated with the severity of COVID-19 in Chinese patients during the early COVID-19 outbreak.[38] However, an updated meta-analysis using the same Chinese studies found increased severity of COVID-19 in active smokers with a pooled OR of 2.2 (95% CI 1.31-3.67).[39] More recent meta-analyses tend to report that smoking is associated with poor clinical outcomes.[18,40,41]

When these reports are combined, the risk of poor clinical outcomes in COVID-19 tends to increase in smokers, while the risk of SARS-CoV-2 infection seems to be reduced. However, the decreased risk of infection cannot justify the dangers of smoking itself, such as an increased risk of respiratory infection and progression of COPD or lung cancer. Moreover, there are several studies on high under-diagnosis rate of COPD among smokers in the primary care setting.[42,43] Thus, possible vulnerability to COVID-19 among smokers who have risk factors for COPD, such as predisposing host factors, > 20 pack-years of smoking, and occupational dust or fume exposure, should be emphasised.[44] Furthermore, the virus can be spread during smoking through crowding in a certain space, talking without wearing a facial

mask, bronchial toileting behaviours, such as coughing or spitting phlegm, or hand-to-mouth movement of smokers.

Our study is a large population-based study to evaluate the association between smoking status and the risk of SARS-CoV-2 infection. However, this study has several limitations. First, as a pandemic, the risk of SARS-CoV-2 infection is highly affected by exposure to the virus. Our study did not capture the exposure status due to the limitations of the data source. A non-smoker who attended a gathering of a large crowd would have a higher risk of disease than that of a smoker staying at home all the time. Our study could not limit the time window to when social distance ordering was in place to adjust for possible exposure. Second, our study might not reflect the current smoking habits of the subjects at the time of SARS-CoV-2 infection. This study used the patient's smoking information using a smoking survey included in the national health screening. Therefore, it was difficult to accurately evaluate the smoking status at the time of SARS-CoV-2 infection. Third, our study did not include young COVID-19 patients. Smoking information was obtained through a smoking survey on the national health screening dataset. Korean national health screening was only recommended for individuals over 40 years of age. Therefore, it may be difficult to apply our results to COVID-19 patients of all ages. Fourth, this study analysed only patients diagnosed during the early period of the COVID-19 outbreak. The initial spread of COVID-19 in Korea was largely affected by cluster infection within one religious group. The pattern of SARS-CoV-2 transmission might have changed during the course of the pandemic.

In conclusion, this case-control study based on the general Korean population showed that smoking may not be associated with the risk of SARS-CoV-2 infection. Smoking tends to lower the risk of infection with SARS-CoV-2; however, this finding should be interpreted with caution and should not be used to encourage people to smoke.

COMPETING INTERESTS

None.

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Table 1. Baseline demographics of patients with SARS-CoV-2 infection and matched controls

Variables	Patients with SARS-CoV-2	Controls	P-value
Total	4,167	20,937	
Male	1,444 (34.7)	7,370 (35.2)	0.499
Age			0.083
40-49	997 (23.9)	4,885 (23.2)	
50-59	1,454 (34.9)	7,083 (33.8)	
60-69	1,031 (24.7)	5,181 (24.8)	
70-79	465 (11.2)	2,579 (12.3)	
≥80	220 (5.3)	1,239 (5.9)	
Region of residence			0.321
Seoul	223 (5.4)	1,012 (4.8)	
Busan	47 (1.1)	263 (1.3)	
Daegu	2,720 (65.3)	13,499 (64.5)	
Incheon	46 (1.1)	220 (1.1)	
Gwangju	11 (0.3)	57 (0.3)	
Daejeon	14 (0.3)	109 (0.5)	
Ulsan	17 (0.4)	97 (0.5)	
Sejong	19 (0.5)	125 (0.6)	
Gyeonggi	244 (5.9)	1,220 (5.8)	
Gangwon	27 (0.7)	145 (0.7)	
Chungcheongbuk	26 (0.6)	118 (0.6)	
Chungcheongnam	56 (1.3)	294 (1.4)	
Jeollabuk	4 (0.1)	51 (0.2)	
Jeollanam	5 (0.1)	56 (0.3)	
Gyeongsangbuk	634 (15.2)	3,267 (15.6)	
Gyeongsangnam	72 (1.7)	365 (1.7)	
Jeju	2 (0.1)	39 (0.2)	
Household income			<0.001
Medicaid	360 (8.6)	589 (2.8)	
1st quintile	826 (19.8)	3,846 (18.4)	
2nd quintile	562 (13.5)	2,732 (13.1)	
3rd quintile	594 (14.3)	3,319 (15.9)	
4th quintile	782 (18.8)	4,431 (21.2)	
5th quintile	1,043 (25.0)	6,020 (28.8)	
Respiratory disease	486 (11.7)	2,171 (10.4)	0.013
Heart disease	302 (7.3)	1,529 (7.3)	0.900
Diabetes mellitus	848 (20.4)	4,146 (19.8)	0.418
Hypertension	1,252 (30.1)	6,750 (32.2)	0.006
Cancer	254 (6.1)	1,391 (6.6)	0.192
Smoking			<0.001
Never	3,269 (78.5)	15,156 (72.4)	
Ex-	618 (14.8)	2,878 (13.8)	
Current	280 (6.7)	2,903 (13.9)	

Values are presented as number (%).

SARS-CoV-2=severe acute respiratory syndrome coronavirus 2.

Table 2. Association between smoking and risk of SARS-CoV-2 infection

Variables	Number (% of cases)	Unadjusted[a]		Adjusted[b]	
		OR (95% CI)	P-value	OR (95% CI)	P-value
Never vs others					
Never	18,425 (17.7)	1		1	
Ex- or current	6,679 (13.4)	0.559 (0.502, 0.622)	<0.001	0.557 (0.500, 0.620)	<0.001
Never vs ex- vs current					
Never	18,425 (17.7)	1		1	
Ex-	3,496 (17.7)	0.779 (0.691, 0.878)	<0.001	0.810 (0.718, 0.914)	0.001
Current	3,183 (8.8)	0.344 (0.296, 0.399)	<0.001	0.328 (0.282, 0.381)	<0.001

[a]Calculated by conditional logistic regression (conditioned on sex, age, and region of residence).

[b]Adjusted for household income, respiratory disease, heart disease, diabetes mellitus, hypertension, and cancer.

SARS-CoV-2=severe acute respiratory syndrome coronavirus 2; OR=odds ratio; CI=confidence interval.

Table 3. Conditional logistic regression for risk factors of SARS-CoV-2 infection[a]

Variables	Number (% of cases)	Unadjusted		Adjusted			
		OR (95% CI)	P-value	Model 1 (Never vs others)		Model 2 (Never vs ex- vs current)	
				OR (95% CI)	P-value	OR (95% CI)	P-value
Household income							
Medicaid	949 (37.9)	3.535 (3.041, 4.109)	<0.001	3.548 (3.047, 4.131)	<0.001	3.793 (3.252, 4.423)	<0.001
1st quintile	4,672 (17.7)	1.232 (1.111, 1.365)	<0.001	1.256 (1.133, 1.393)	<0.001	1.295 (1.167, 1.437)	<0.001
2nd quintile	3,294 (17.1)	1.172 (1.044, 1.316)	0.007	1.181 (1.052, 1.327)	0.005	1.216 (1.082, 1.366)	0.001
3rd quintile	3,913 (15.2)	1.015 (0.907, 1.136)	0.797	1.023 (0.914, 1.145)	0.691	1.045 (0.933, 1.170)	0.446
4th quintile	5,213 (15.0)	1.018 (0.919, 1.128)	0.729	1.036 (0.935, 1.148)	0.501	1.055 (0.952, 1.170)	0.308
5th quintile	7,063 (14.8)	1		1		1	
Respiratory disease							
No	22,447 (16.4)	1		1		1	
Yes	2,657 (18.3)	1.147 (1.030, 1.277)	0.012	1.141 (1.022, 1.273)	0.019	1.148 (1.028, 1.281)	0.014
Heart disease							
No	23,273 (16.6)	1		1		1	
Yes	1,831 (16.5)	1.042 (0.912, 1.191)	0.545	1.026 (0.893, 1.178)	0.720	1.016 (0.884, 1.167)	0.826
Diabetes mellitus							
No	20,110 (16.5)	1		1		1	
Yes	4,994 (17.0)	1.042 (0.912, 1.191)	0.545	1.026 (0.893, 1.178)	0.720	1.016 (0.884, 1.167)	0.826

Hypertension							
No	17,102 (17.0)	1		1		1	
Yes	8,002 (15.6)	0.933 (0.861, 1.012)	0.093	0.900 (0.826, 0.979)	0.015	0.885 (0.813, 0.964)	0.005
Cancer							
No	23,459 (16.7)	1		1		1	
Yes	1,645 (15.4)	0.920 (0.799, 1.059)	0.245	0.924 (0.802, 1.066)	0.279	0.915 (0.793, 1.055)	0.222
Never vs others							
Never	18,425 (17.7)	1		1		-	
Others	6,679 (13.4)	0.559 (0.502, 0.622)	<0.001	0.557 (0.500, 0.620)	<0.001	-	-
Never vs ex- vs current							
Never	18,425 (17.7)	1		-		1	
Ex-	3,496 (17.7)	0.779 (0.691, 0.878)	<0.001	-	-	0.810 (0.718, 0.914)	0.001
Current	3,183 (8.8)	0.344 (0.296, 0.399)	<0.001	-	-	0.328 (0.282, 0.381)	<0.001

[a]Conditioned on sex, age, and region of residence.

SARS-CoV-2=severe acute respiratory syndrome coronavirus 2; OR=odds ratio; CI=confidence interval.