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Tobacco Products and the Risks of SARS-CoV-2 Infection and COVID-19

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Implications: This commentary addresses the state of the evidence on tobacco products, nicotine, and COVID-19. The evidence of the effects of smoking on respiratory infections and the immune system in general are examined and the current understanding of tobacco products and risk for SARS-CoV-2 infection and the course of COVID-19 is addressed.

Introduction

This commentary is written as the pandemic of COVID-19 continues in much of the world without a foreseeable end. SARS-CoV-2, the pandemic's causal agent, is a respiratory virus that binds to the angiotensin-converting enzyme 2 (ACE2) receptors in the respiratory tract. The resulting spectrum of illness ranges from being asymptomatic (but infectious) to severe and fatal adult respiratory distress syndrome. Diverse factors have been linked to more severe disease and death, including age, underlying heart and lung disease, obesity, and diabetes.[1] Sociodemographic factors are also determinants of higher risk: for example, those in minority groups, working in service industry jobs, and receiving low incomes.

Use of tobacco products has also been examined as a determinant of the course of SARS-CoV-2 infection and the prognosis of COVID-19.[2] If use of tobacco products increases risk for SARS-CoV-2 infection and poor outcomes from COVID-19, the juxtaposition of the two pandemics—tobacco products and COVID-19—represents an opportunity to reduce morbidity and mortality from COVID-19 through tobacco control. Based on observational evidence and insights from receptor biology, the hypothesis has also been advanced that nicotine may reduce the likelihood of SARS-CoV-2 infection.[3]

This commentary addresses the state of the evidence on tobacco products generally and nicotine specifically and COVID-19. At this point in the pandemic, the evidence remains incomplete and much of it exists in the form of preprints that have not been peer-reviewed. Nonetheless, papers on tobacco products, nicotine, and COVID-19 are numerous with 76 identified in PubMed and a further 77 in the Medrxiv server and 26 in Biorxiv in searches done on September 9, 2020.

Evidence on Smoking, the Immune System and Respiratory Infections

The effect of smoking on respiratory defense mechanisms and the immune system has been investigated for decades as has risk for respiratory infections.[4] Strong causal conclusions have been reached in Surgeon Generals' reports on the topic. Relevant Surgeon General conclusions are as follows:

- The evidence is sufficient to infer that cigarette smoking compromises the immune system and that altered immunity is associated with increased risk for pulmonary infections.[4]
- The evidence is sufficient to infer a causal relationship between smoking and acute respiratory illnesses, including pneumonia, in persons without underlying smoking-related chronic obstructive lung disease.[4]

The respiratory tract has multiple defenses against inhaled pathogens, such as the SARS-CoV-2 virus, including the filter posed by the upper airway, the mucociliary system that clears the airways, scavenging macrophages, and the immune system. As reviewed in the 2014 Surgeon General's report, these defenses are compromised in active smokers and the 2014 report concluded that the immune system is sufficiently compromised by smoking to increase risk for respiratory infections.[4]

Considering influenza as an example, recent systematic reviews show increased risk in smokers for infection and for a less favorable clinical course.[5,6] A systematic review and meta-analysis published in 2019 on tobacco smoking and community-acquired pneumonia estimated significantly increased risks for current smokers and for former smokers compared with never smokers.[7]

Smoking, Nicotine, SARS-CoV-2, and COVID-19

Do the general conclusions in the Surgeon General's reports apply to SARS-CoV-2 and COVID-19? Here, the story becomes complex with regard to smoking, nicotine, and the ACE2 receptor. The spike protein of the virus binds specifically to the ACE2 receptor, which is upregulated, ie, more abundant, in smokers.[8] Other general changes in the lungs of smokers may also be relevant: impaired mucociliary clearance, increased permeability of the epithelial lining of the airways, and airways inflammation. Together, these smoking-related changes in the respiratory tract would be expected to increase risk for infection and for more severe COVID-19. The likelihood of "cytokine storm," excessive release of inflammatory cytokines and chemokines considered to result in the most severe forms of COVID-19, may also be increased by smoking-induced systemic inflammation.[9]

In contrast, pharmacological effects of nicotine might decrease risk for SARS-CoV-2 infection. Tindle et al. suggest that nicotine itself may down regulate the ACE2 receptors through effects on the renin–angiotensin–aldosterone system, although receiving an antihypertensive agent that blocks ACE does not change risk for COVID-19.[10] Beneficial anti-inflammatory effects of nicotine have also been proposed from its activation of nicotinic acetylcholine receptors.

The Observational Evidence

Speculation about smoking, vaping, and COVID-19 began early in the pandemic. Although prior evidence, eg, the conclusions of the Surgeon Generals' reports, lead to the hypothesis that smoking would increase risk for COVID-19 and poorer outcomes in those with the disease, several observations raised the competing hypothesis that smoking might decrease risk. Clinical series of patients early in China's epidemic showed a substantially lower prevalence of smoking than in the general population.[2] A similar observation was made at a hospital in France, leading to the implementation of a trial of nicotine administration among hospital workers and patients.[11–13]

The relevant literature is being tracked by Simons et al. in a "living evidence" review that is in its 7th version at present.[2] Research on the topic has been complicated by the restraints posed by the pandemic, including obtaining high-quality data in the context of acute, severe illness. Through August 25, 2020, the authors had identified 233 studies, of which 32 were considered "good" or "fair" in quality and were included in meta-analyses. Current smokers were at 25% reduced risk for infection and former smokers had increased risk for hospitalization, greater disease severity, and dying. Notably, the low prevalence of smoking in some of the studies, compared with national data, may reflect incomplete smoking information and possibly confounding by age with older patients being less likely to be actively smoking.

There are multiple, not exclusive, pathways by which tobacco smoking could increase risk for SARS-CoV-2 infection and poorer outcomes for COVID-19. There are the general effects of smoking on host defenses, the increased inflammation in smokers and the specific effects on the ACE2 receptor. Also, smoking causally increases the frequency of chronic diseases linked to increased risk for poor outcomes in COVID-19: chronic obstructive pulmonary disease, coronary heart disease, and type 2 diabetes mellitus. Increased risk for more severe COVID-19 could be mediated through smoking-caused chronic diseases.

The findings of the OpenSAFELY Study of 17 million people in the United Kingdom provide insights with regard to these pathways.[1] For the outcome of death while hospitalized, there was a steep positive gradient with age, and risk was also increased by the presence of a lung disease other than asthma (presumably chronic obstructive pulmonary disease), heart disease, diabetes, and obesity. With regard to tobacco smoking, risk depended on the model considered, either age- and sex-adjusted only or fully adjusted with inclusion of the disease-status variables (Table 1). For current smoking, the estimate changed from above to below one with adjustment for additional risk factors, suggesting that the effect of being a current smoker could be mediated by the chronic diseases caused by smoking. For former smokers, the risk remained increased with adjustment, perhaps reflecting the poorer health status of former smokers in general who were motivated to quit by declining health status.

With regard to vaping, the review by Simons et al. did not call out findings of specific studies. The same general mechanisms as for smoking have been cited as potentially leading to increased risk for COVID-19 from vaping, but evidence is lacking.[9] The results from a national, Internet-based panel have received substantial attention; this cross-sectional survey based on self-report of COVID-19 diagnosis, testing, and symptoms showed strong associations of diagnosis with vaping, smoking, and dual product use.[14] This study is limited by the source of the study population, its reliance on self-report, and the cross-sectional design. Nonetheless, the associations found are strong and warrant follow-up research. A nexus of the COVID-19 pandemic with EVALI has not yet emerged.[15]

Next Steps

There is no need to call for more research. It is needed and will be carried out. However, there is a need for high-quality investigations that will meet quality criteria for evidence reviews. Recall that in the dynamic review by Simons et al., only 32 of 233 studies met the bar of "good" or "fair" evidence.[2] Prospectively planned investigations are needed that meet the challenges of exposure and outcome assessment. Specific hypotheses should be targeted, ie, tobacco products increase risk for: SARS-CoV-2 infection, incidence of COVID-19, more severe COVID-19, and mortality from COVID-19. The question of a beneficial effect of nicotine is being addressed in trials in France.[16]

In this misinformation era, there is a need for timely evidence. Initial speculation about a beneficial effect of nicotine led to a run on nicotine-replacement therapy. While the evidence on use of tobacco products and COVID-19 remains limited, the prior causal conclusions on smoking and the immune system and risk for respiratory infection stand. The pandemic brings an opportunity to accelerate cessation of use of tobacco products, even as research continues.

Table 1. Hazard Ratios (HR) for In-Hospital Death in the OpenSAFELY Study

	COVID-19 death HR (95% CI)	
	Age–sex adjusted	Fully adjusted
Never smoker	1.00 (ref)	1.00 (ref)
Former smoker	1.43 (1.37–1.49)	1.19 (1.14–1.24)
Current smoker	1.14 (1.05–1.23)	0.89 (0.82–0.97)

CI = confidence interval. Source: Williamson et al.[1]

Supplementary Material

A Contributorship Form detailing each author's specific involvement with this content, as well as any supplementary data, are available online at https://academic.oup.com/ntr.

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Declaration of Interests

None declared.

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