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LETTER TO THE EDITOR

Cigarette smoking and COVID-19



In a recent editorial published on tobacco and COVID-19, the Sociedade Portuguesa de Pneumologia raises doubts and caution about the data coming from the medical and scientific community regarding the hypothesis that cigarette smoking or nicotine could be ''protective'' against COVID-19, recommending that this information should not be taken as an invitation to start smoking or to delay giving it up to avoid SARS-CoV-2 infection or its complications.¹

The role of cigarette smoking/nicotine (or whatever else is contained within cigarette smoke) in the scientific discussion on COVID-19 ignores the fact that smoke cessation has to be discouraged to avoid COVID-19 pulmonary complications (this seems obvious for scientists and physicians) but references the scientific importance of the strong epidemiological data coming from all the countries that hospitalized patients with SARS-CoV-2 related pneumonia show quite low percentages of active smokers.^{2,3}

Based on this we have to strongly support the importance of understanding of the possible mechanisms characterizing these aspects, i.e. how cigarette smoking dampens the inflammatory response during infection by SARS-CoV-2 strongly reducing the severe complications of SARS-CoV-2 infection, mainly nterstitial pneumonia and ARDS. The reported evidence that among COVID-19 patients, those who are (and/or were) smokers show worse clinical progression with respect to never smokers is not in contradiction with the huge number of studies showing that there are few active smokers among hospitalized patients with SARS-CoV-2 related pneumonia.⁴⁻⁶ However it is guite strange that a scientific society does not seem to understand the important scientific implications of such observations, bearing in mind that of course cigarette smoking has to be discouraged due to its well known dangerous effects.

Thus we have to consider, without any preconceived position, on the one hand the notorious unhealthy effects of cigarette smoking, and on the other the possible important scientific information coming from different countries in the world showing that active smokers are somehow 'protected' from the severe complications of SARS-CoV-2 infection, namely interstitial pneumonia and ARDS.

In this context a very recent paper reported decreased levels of the SARS-CoV-2 receptor ACE2 in both bronchial and alveolar epithelial cells from cigarette smoking-exposed versus air-exposed mice.⁷ Furthermore and more importantly, cigarette smoking treatment did not affect ACE2 levels but potently inhibited SARS-CoV-2 replication in Calu3 cells in vitro.⁷ On the other hand previous studies have reported the opposite effects of cigarette smoking on ACE2 expression in the lung,⁸ thus underlying the urge for further investigations to finally clarify the role of cigarette smoking on SARS-CoV-2 infection and its severe respiratory complications.

Science proceeds by criticism and by analyzing objective data coming from scientists. In 1939 Winston Churchill said "Criticism may not be agreeable, but it is necessary. It fulfils the same function as pain in the human body; it calls attention to the development of an unhealthy state of things. If it is heeded in time, danger may be averted; if it is suppressed, a fatal distemper may develop".⁹

In the case of active smoking and COVID-19, to hide ones head in the sand will not help rapid scientific progress in the discovery of the pathophysiology of this disease and of its possible therapeutic strategies.

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Conflict of interest

The authors have no conflict of interest to declare.

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Tobacco and COVID-19: A position from Sociedade Portuguesa de Pneumologia. Authors' reply

We read with great interest the letter by Rossato and Di Vincenzo¹ commenting on our editorial ''Tobacco and COVID-19: A position from Sociedade Portuguesa de Pneumologia'' published in Pulmonology in December 2020.² We would like to thank the authors for the challenging discussion points and we acknowledge that, as in all fields of science, new data are continuously being collected and interpreted and we are still far from definitive conclusions about how smoking really impacts COVID-19.

The observations that report a low rate of smokers among COVID-19 patients are pertinent but have yet to be confirmed by good quality epidemiological studies designed to address this question. As we mentioned, a high number of studies does not report smoking status or does not distinguish never-smokers from missing data and this may pose considerable bias.² At the present time, we cannot rule out the hypothesis that smoking may not constitute a strong risk factor for COVID-19, but we have to further specify what questions we are posing: what is the difference in risk between present smokers and having a past history? Are smokers more prone to contract SARS-Cov-2 infection in general? We do not have enough information concerning asymptomatic infection and smoking, and we know there may be a bias toward higher testing rates in smokers,³ due to higher rates of respiratory symptoms. An interesting study in *Nature*⁴ shows that there are difficulties in correctly adjusting for other covariates - depending on the covariates included, a smoking history could either be associated with a higher risk of COVID-19 (age and sex adjusted only) or lower risk (fully adjusted model). After adjusting only for demographic factors (age, sex, deprivation and ethnicity), the authors found a non-significant positive hazard ratio for current smoking (HR 1.07 (0.98-1.18)), excluding any protective effect of nicotine and suggesting that any increased risk with current smoking is likely to be small.

Rossato and Di Vincenzo also quote the new paper by Tomchaney et al.,⁵ reporting conflicting new results that show decreased expression of ACE2 receptors in both bronchial and alveolar epithelial cells exposed to cigarette smoke. These are puzzling data that still wait peer-review and publication. Animal studies are undoubtedly important to open new pathophysiologic hypothesis; however, we still face uncertainties as to the real role of ACE-2 receptor modulation and the risk of infection. One of the problems concerns tobacco smoke, a mixture of thousands of chemicals interacting together, and the presumptive role of nicotine. The studies by Russo et al.⁶ have thrown some light on how isolated nicotine may facilitate SARS-Cov-2 infection: nicotine, even at low concentrations, increases ACE-2 levels in bronchial cells. Besides, they showed that ACE-2 increase is specifically mediated by α 7-nAChR, suggesting that smoking may promote cellular uptake mechanisms of SARS-CoV-2 through α 7-nAChR signaling. The presence of this receptor in neuronal tissues also raises questions about the impact of smoking in COVID-19 pathophysiology in several organs, including the brain.

In the absence of well-designed studies, with large populations, any hypothesis on the effect of smoking or nicotine in the risk of COVID-19 remains unproven. More than five decades of research in vast population-based studies were needed to establish the causative effect of tobacco in several deadly diseases. Our minds should be open to change, but in the present state of knowledge, we stand with the WHO and adopt a cautious recommendation against any putative protective effect of smoking.

Conflicts of interest

The authors have no conflicts of interest to declare.

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