Revisiting the Paradox of Smoking: Radioactivity in Tobacco Smoke or Suppressing the SARS-CoV-2 Receptor, Angiotensin-Converting Enzyme 2, via Aryl-Hydrocarbon Receptor Signal?

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Abstract
Despite current controversies, some reports show a paradoxical mitigating effect associated with smoking in individuals with symptomatic COVID-19 compared to the general population. To explain the potential mechanisms behind the lower number of hospitalized COVID-19 patients, it has been hypothesized that cigarette smoking may reduce the odds of cytokine storm and related severe inflammatory responses through cholinergic-mediated anti-inflammatory mechanisms. Japanese scientists have recently identified a potential mechanism behind the lower numbers of COVID-19 cases amongst smokers compared to non-smokers. However, we believe that this mitigative effect may be due to the relatively high concentration of deposited energy of alpha particles emitted from naturally occurring radionuclides such as Po-210 in cigarette tobacco. Regarding COVID-19, other researchers and our team have previously addressed the anti-inflammatory and immune-modulating effects of low doses of ionizing radiation. MC-simulation using the Geant4 Monte Carlo toolkit shows that the radiation dose absorbed in a spherical cell with a radius of .9 μm for a single 5.5 MeV alpha particle is about 5.1 Gy. This energy deposition may trigger both anti-inflammatory and anti-thrombotic effects which paradoxically lower the risk of hospitalization due to COVID-19 in smokers.

Keywords
radioactivity, smoking, tobacco, COVID-19, hospitalization, severity

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The purpose of this paper is to outline the perplexing connection between smoking and COVID-19. It is not intended to advocate or endorse smoking, which has known negative health consequences. The paper offers a hypothetical mechanism as well as some information of potential interest in the treatment of smokers who have contracted or are just presenting symptoms of COVID-19.

Addressing a Controversy

Smoking is the global leading cause of respiratory diseases. COVID-19, the disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), became a deadly pandemic without any widely accepted specific treatment after its identification in 2019. There are some reports suggesting smoking increases the severity of COVID-19. However, other reports paradoxically show a mitigative effect might be associated with patients smoking at a lower rate in individuals with symptomatic COVID-19 compared to the general population or a decreased severity of COVID-19 disease and death.

Moreover, a causal effect of smoking on the risk of severe COVID-19 is reported by some researchers, but Paleiron et al. have reported that current smoking status can be associated with a lower risk of developing severe COVID-19. However, they noted that smoking cannot be considered as efficient protection against infection and stated that the mechanisms behind the decreased susceptibility of smokers to SARS-CoV-2 require further research. Given this consideration, here we present some possible protective mechanisms of action of smoking in COVID-19.

Protective Mechanisms of Action

To explain the reason for the lower number of hospitalized patients, it has been hypothesized that cigarette smoking may have preventative effects on cytokine storm and severe related inflammatory responses through cholinergic-mediated anti-inflammatory mechanisms. In Italy, the very low number of COVID-19 patients who are smokers suggests that there is not a significant positive relationship between smoking and the prevalence of severe COVID-19. It has also been reported that the lower numbers of COVID-19 cases amongst smokers might be due to the effects of nicotine. It should be noted that nicotine has previously been reported to downregulate the ACE-2 receptor. However, other reports contradict the protective effects of nicotine, as claimed in some reports, and show that the effect of being a current smoker is possibly very small.

Recently Proposed Mechanisms

Researchers at Hiroshima University have identified a potential mechanism behind the lower numbers of COVID-19 cases amongst smokers compared to non-smokers. They reported that cigarette smoke extract (CSE) may suppress the expression of the angiotensin-converting enzyme 2 (ACE-2) receptor, (the receptor for SARS-CoV-2), which in turn would result in lower cellular entry of the virus (by decreasing available binding sites for the virus), thereby limiting the progression of the disease.

However, other researchers believed cigarette smoking may be related to COVID-19 through the link between nicotine and higher ACE-2 expression in different groups of cells such as lung and airway epithelium. Moreover, Voinisky et al. have reported that due to higher bronchial TMRSS4 levels (which codes for a protease that primes COVID-19 virus for entering cells), smokers are more susceptible to COVID-19 infection risk than non-smokers. Therefore, there is ongoing controversy over the effect of smoking on ACE-2 expression.

While the lower numbers of COVID-19 cases amongst smokers has been linked to nicotine, the report published by Hiroshima University introduces the potential effects of polycyclic aromatic hydrocarbons (PAHs) and activation of arylhydrocarbon receptors (AhRs). However, we believe that the lower numbers of COVID-19 cases amongst smokers can be due to the high concentration of deposited energy of alpha particles emitted from naturally occurring radionuclides such as Po-210 in cigarette tobacco. There are more than 6000 identified chemical compounds in tobacco and tobacco smoke. The presence of radioactive polonium-210 (210Po) and lead-210 (210Pb) in tobacco and tobacco smoke was identified a long time ago (Figure 1).

Radiation Energy Deposition

The activity of the alpha-emitting radionuclide 210Po is estimated to range from 5.5 to 17.8 mBq/cigarette with the mean value of 12.0 mBq/cigarette. 210Pb which is also present in cigarette smoke can also emit alpha particles. Besides 210Po, there are other radionuclides in cigarette smoke such as 238U, 232Th, 226Ra, 228Ra, 214Bi, and 40K. Due to the relatively high activity of 210Po and 210Pb in tobacco, smoking has been reported to increase the internal intake of both of these radionuclides and that results in an increase in the internal radiation dose, which may promote development of lung cancer. However, other researchers and our team have previously addressed the anti-inflammatory and immune-modulating effects of low doses of ionizing radiation. Given this consideration, smokers are constantly exposed to low doses of high linear energy transfer (LET) alpha particles due to inhalation of radionuclides such as 210Po and 210Pb in cigarette smoke. Therefore, the anti-inflammatory effects of localized radiation via alpha particles as well as the effect of low doses of radiation on reducing the risk of thrombosis are possibly involved in the lower number of hospitalized smokers than expected.

Mont Carlo Simulation

MC simulation, using Geant4 Monte Carlo toolkit [29], shows that the radiation dose absorbed in a spherical cell with a radius of .9 μm for a single 5.5-MeV alpha particle is about 5.1 Gy. Figure 2 shows the trajectory of alpha particles emitted from naturally occurring radionuclides such as Po-210 in cigarette tobacco. There are more than 6000 identified chemical compounds in tobacco and tobacco smoke. The presence of radioactive polonium-210 (210Po) and lead-210 (210Pb) in tobacco and tobacco smoke was identified a long time ago (Figure 1).
through a spherical cell of water. The alpha particles were emitted from a circular plane with a radius of .9 μm toward the cell. The extension of Geant4-DNA [30] was used to define a suitable model of physical interactions in micrometer scale. For alpha particles, the physics package of “G4EmDNAPhysics_option2” includes G4DNAIonElasticModel, G4DNA-MillerGreenExcitationModel, G4DNARuddIonisationModel, and G4DNADingfelderChargeDecrease.

Figure 1. The presence of radioactive polonium-210 and lead-210 in tobacco and cigarette smoke leads to exposure of the alveolar epithelial cells that line the small, spongy sacs (alveoli) to alpha particles that in turn leads to dense deposition of radiation energy in these cells. This phenomenon may trigger both anti-inflammatory and anti-thrombosis effects and eventually lower the risk of hospitalization due to COVID-19.

Figure 2. Monte Carlo simulation of the passage of 5.5 MeV alpha particles through a spherical volume of water as a cell with a radius of 0.9 μm.
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