

## Effects of cigarette smoking on the respiratory epithelium and its role in the pathogenesis of chronic rhinosinusitis

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### Summary

The increasing consumption of cigarettes has aroused concerns about the development and worsening of diseases, particularly those related to the respiratory tract. **Aim:** In this paper we review the evidence suggesting the effects of cigarette smoking on the respiratory epithelium and its role in the pathogenesis in chronic rhinosinusitis. **Conclusions:** Although there is evidence supporting a link between smoking and CRS, studies suggest that there might be individual susceptibility to cigarette smoking causing the development and/or maintenance of CRS. Proper patient educations to quit smoking as well as reinforcement of anti-smoking campaigns are extremely important to control this disease of major socio-economic impact.

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## INTRODUCTION

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Cigarette smoking is associated with the main current preventable cause of death, with growing importance especially in developing countries, such as Brazil. In its most recent publication on smoking, the World Health Organization pointed out that, among the eight main causes of death in the world today, six are associated with tobacco exposure, among them we stress inflammatory and infectious diseases of the respiratory tract.<sup>1</sup> According to data from the Ministry of Health (2006), 16.2% of the adult Brazilian population smoke cigarettes daily.<sup>2</sup> Despite the broad advertisement in the media about the harmful effects of cigarette smoking, very little is known about the association between cigarette exposure and the development of associated disorders such as chronic rhinosinusitis (CR). A better understanding of the physiopathogenic mechanisms involved in CR could lead to better treatment for these patients.<sup>3,4</sup>

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## OBJECTIVES

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In the present paper we reviewed the evidence pointing towards the cigarette smoke effects on the respiratory epithelium as well as its role on the pathophysiology of chronic rhinosinusitis.

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## METHOD

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Traditional asystematic review of papers indexed on the LILACS and MEDLINE databases from 1960 to 2009.

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## LITERATURE REVIEW

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1) Cigarette smoking effects on the respiratory epithelium

The epithelium coating the upper respiratory tract acts as a first line of defense against invasive agents (pollutants, allergens, microorganisms), and it can cause upper airway symptoms and diseases when in contact with these agents.<sup>5</sup>

Inhaled cigarette smoke, both passively as well as actively, has been associated with chronic irritation and discomfort on the eyes, nose and oropharynx.<sup>6</sup> Since 1964, when a report was published about smoking by the U.S. Department of Health, there already was evidence of cigarette smoking as a factor that worsened and prolonged rhinosinusitis.<sup>7</sup>

Cigarette combustion produces a smoke with more than 4000 noxious components, including gas and particulate substances - among them we have acrolein, formaldehyde, carbon monoxide, nicotine, cotinin; acetaldehyde, phenol and potassium cyanide<sup>8</sup>, and many of these components are provenly toxic to the respiratory epithelium.<sup>9</sup>

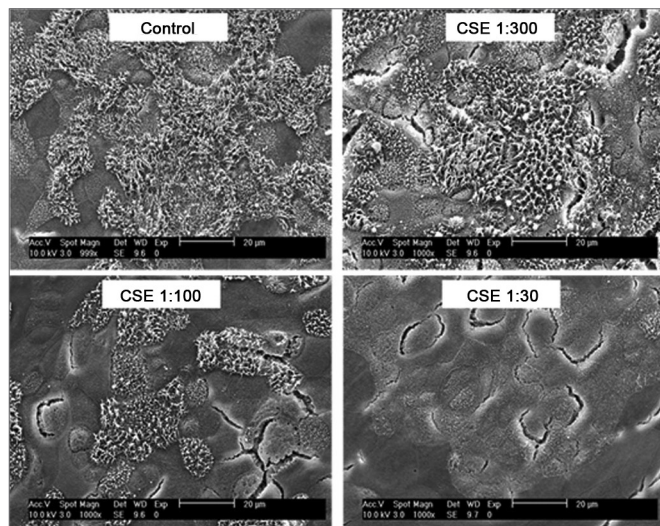
One of the possible explanations for cigarette smoke participating in the pathophysiology of CR is based on mucociliary transport alterations. Oral<sup>10</sup> as well as nasal inhalation<sup>11</sup> of cigarette smoke causes a deep reduction in mucociliary transport in vivo. Agius et al.<sup>12</sup> showed that cotinin, a toxic metabolite of nicotine is capable of significantly reducing the ciliary beat of epithelial cells in vitro. In 2009, Cohen et al., also reported on the exposure of epithelia cell cultures to the particulate phase of cigarette smoke reducing ciliary beat increase when stimulated.<sup>13</sup> Besides in vitro evidence, the exposure to cigarette smoke also harms mucociliary transport in humans, both in acute exposure<sup>14</sup> as well as in its chronic counterpart.<sup>15,16</sup>

Cigarette smoking is also associated with profound changes in mucous production mechanisms. Chronic exposure to this smoke causes metaplastic alterations to the respiratory mucosa with an increase in the number and size of goblet cells and consequent increase in upper airway secretion.<sup>17,18</sup> Cohen et al.<sup>13</sup> and Kreindler et al.<sup>19</sup> also showed in vitro that exposure to cigarette smoke inhibits chloride transport in epithelial cells, causing physiological alterations similar to those found in patients with cystic fibrosis.

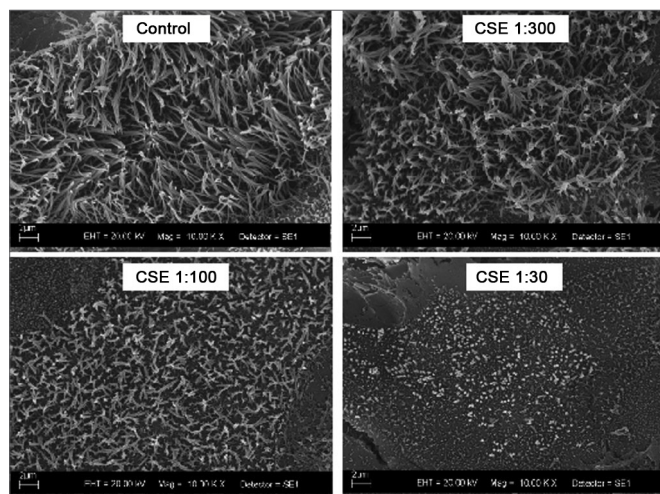
Besides functional alterations, cigarette smoke causes important structural alterations to the respiratory epithelium. Different studies have shown that cigarette smoke causes a reduction in cell viability and induction of apoptosis in respiratory hair cells<sup>20</sup>, opposite mitogenic effects or pro-apoptotic depending on the cigarette smoke concentration<sup>21</sup> or even an impairment on epithelial regeneration upon injury.<sup>22</sup> Animal studies have shown that chronic and intermittent exposure to cigarette smoke cause morphological alterations to the epithelium of the entire respiratory tract, from hyperplasia in lower concentrations, all the way to loss of cilia and metaplasia with keratinization in higher concentrations, and also submucosal thickening and inflammation with neutrofilic and mononuclear inflammatory cells infiltrate.<sup>23</sup> Also, Hamm et al.<sup>24</sup> showed that the cigarette-induced respiratory mucosa inflammatory reaction persists even after seven months of recovery. Studies carried out with smokers have confirmed these findings in animal models, showing alterations in the respiratory epithelium as an enlargement of the naked epithelium,<sup>25</sup> a greater prevalence of hyperplasia and cell atypias<sup>26</sup> and ultrastructural cilia abnormalities<sup>27</sup>.

Besides the alterations caused on the differentiated tissues, Tamashiro et al.<sup>28</sup> showed that the cigarette smoke has a negative impact on the ciliogenesis process in a dose-dependent fashion to the respiratory epithelium in the maturation and differentiation phases. Using respiratory epithelium cell cultures obtained from the nasal septum of mice, they showed that the respiratory epithelium exposure to the particulate phase as well as the gas phase of cigarette smoke causes a significant reduction in the

percentage of cilia development (Figure 1), as well as reduction in their size (Figure 2). Therefore, these authors suggest that there must be more than one toxic substance in the cigarette smoke, particulate and gaseous phases, involved in ciliogenesis block.



**Figure 1.** Scanning electron microscopy photographs showing the dose-dependent effect of cigarette smoke on the percentage of ciliated area after exposure to reducing dilutions of Cigarette Smoke Extract (CSE).



**Figure 2.** Scanning electron microscopy photographs showing the dose-dependent effect of cigarette smoke on cilia size after exposure to decreasing dilutions of the Cigarette Smoke Extract (CSE).

## 2) Evidence of an Association Between Smoking and Chronic Rhinosinusitis

Considering that one of the endpoints of CR is the stasis of nasosinusal secretions secondary to a reduction in mucociliary transport, the alterations caused to the respiratory epithelium would justify a causal relationship of CR with smoking. Notwithstanding, despite the plausible pathophysiological relations, there is little clinical evidence

proving this association between smoking and CR.

Lieu and Feinstein (2000)<sup>29</sup>, doing a survey with the American population, observed that smokers had a higher prevalence of chronic or recurrent rhinosinusitis when compared to people who never smoked or who quit smoking. When they compared the relative risk between the groups, this study showed a risk 14% higher for smokers having chronic or recurrent rhinosinusitis, especially those who smoked more than 10 cigarettes per day. Under the viewpoint of the number of cigarettes necessary to cause an effect, we would need 62 active smokers in order to increase in one extra case of chronic rhinosinusitis. Similarly, Chen et al.<sup>30</sup> did a cross-sectional study between the years of 1996 and 1997 assessing 73,364 Canadian individuals. In such study they reported that smoking was associated to a higher prevalence of chronic rhinosinusitis, both in men and women. Despite a questionable reliability in both studies because they were based on a diagnostic evaluation from a questionnaire, these were the only populational evaluations so far that have identified risk factors for the development of chronic rhinosinusitis.

Other authors have also investigated the influence of cigarette smoke exposure in the postoperative recovery after endoscopic surgery of the paranasal sinuses. In a study with long follow up, Kennedy<sup>31</sup> showed that smoking was one of the most important factors which led to the need of a second treatment for recurrence. Other studies in adults have also shown that smoking has a negative impact on the postoperative outcome of nasosinusal endoscopic surgery when assessed under the viewpoint of symptoms, quality of life scores, endoscopic analysis and CT-scan findings.<sup>32,33,34</sup>

In the pediatric population, Kim et al.<sup>35</sup>, retrospectively assessed 97 patients submitted to paranasal sinuses surgery, and showed that children exposed to cigarette smoke had a worse postoperative outcome based on endoscopic analysis. Although the authors included children with asthma (4.1%) in their study, under multivariate analysis they concluded that asthma did not impact the postoperative success of paranasal sinuses endoscopic surgery ( $p=0.381$ ). By the same token, Ramadan and Hinerman<sup>36</sup> also showed that the children passively exposed to cigarette smoke had lower improvement rates (70%) when compared to non-exposed children (90%) one year after endoscopic surgery for CR. In this study, Ramadan & Hinerman excluded from the study those children with cystic fibrosis or immunodeficiency and the ones submitted to previous endoscopic surgery.

Another pathophysiological possibility of the association between smoking and CR would be the propensity to bacterial infection on the respiratory epithelium. Ertel et al.<sup>37</sup> showed that the respiratory tracts of smokers were preferentially colonized by Gram negative bacilli. In this

same study, the authors showed that this greater colonization is due to a greater resistance of Gram-negative bacteria to cigarette smoke when compared to Gram-positive.<sup>37</sup> Chronic exposure to cigarette smoke is also capable of increasing the adhesion of these bacteria to epithelial cells, possibly for altering the characteristics of the mucosal surface potentializing the binding of pathogenic bacteria.<sup>38,39</sup> This greater bacteria-epithelium interaction causes an increase in inflammatory reaction on the upper airways by mechanisms that do not depend on toxins.<sup>40</sup> Still, Tamashiro et al., in 2009, showed that the exposure to high concentrations of cigarette smoke stimulates the in vitro formation of pathogenic bacterial biofilms obtained from patients with CR.<sup>41</sup>

### FINAL REMARKS

Although there is data strengthening a link between smoking and CS, these studies point out that there must be an important individual susceptibility to cigarette smoke response insofar as the development of CS is concerned. At any rate, considering that the main objective of any treatment for patients with CS is to reestablish normal function of the nasosinusal mucosa and the evidence that cigarette smoking impairs mucociliary transport, reducing cilia beat, the ciliogenesis or epithelial regeneration process, a proper education for these patients towards interrupting cigarette smoking as well as reinforcing campaigns against smoking are extremely important to control this disease that has a major socio-economic impact.

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