Cancer-protective effects of inhaled corticosteroids in COPD are likely related to modification of epithelial activation

To the Editor:

The article published by Raymakers *et al.* [1] presents a lung cancer-protective effect of inhaled corticosteroids (ICS) in patients with COPD. The authors suggest that this effect is due to "anti-inflammatory" properties of ICS on the airways. This may be partly true but, from what we have come to know of COPD pathogenesis, the situation is likely to be more nuanced and complicated than that.

We and others have published a number of papers on the characteristics of airway pathology in COPD patients [2–6]. We have found active epithelial–mesenchymal transition (EMT) as part of the gene reprogramming that occurs in epithelial basal cells, with subepithelial reticular basement membrane fragmentation and hypervascularity but underlying lamina propria fibrosis, hypovascularity and hypocellularity. In contrast to the airway wall, there is certainly innate immune activation in the airway lumen, and reactive oxygen species generated here may be a factor driving the EMT. However, we would suggest that it is the EMT and its related hypervascularity that is the driver of malignancy (so called type 3 EMT) in COPD. EMT also plays a role in progression and metastasis of lung cancers [7]. This may be a general paradigm for epithelial cancers, that incidentally make up 95% of human malignancy.

Further, our investigations have also suggested that ICS can reverse some of the airway wall pathology in COPD, including airway EMT [8, 9]. Therefore, it may well be that the cancer protection by ICS treatment demonstrated by Raymakers *et al.* [1] is not simply explained by an anti-inflammatory effect, but also perhaps mainly through an effect on EMT.

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COPD is an independent risk factor for lung cancer. Studies have suggested that inhaled corticostroids have reduced the incidence of lung cancer in these patients. This effect is likely related to modification of epithelial–mesenchymal transition (EMT). http://bit.ly/2Km4VK4

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