Chronic Obstructive Pulmonary Disease and Risk of Lung Cancer: The Importance of Smoking and Timing of Diagnosis

To the Editor:

We read with interest the article by Powell et al.[1] on the risk of lung cancer (LC) in patients with chronic obstructive pulmonary disease (COPD). The authors literally concluded that "… a diagnosis of COPD is strongly associated with a diagnosis of LC, however, this association is largely explained by smoking habit, strongly dependent on the timing of COPD diagnosis, and not specific to COPD. It seems unlikely, therefore, that COPD is an independent risk factor for lung cancer."[1] We congratulate the authors for their study but respectfully disagree regarding their interpretation of results and conclusions for the reasons explained below.

Using a U.K. general practice database (Health Improvement Network), Powell et al.[1] identified 11,888 incident cases of LC, 23% of whom had a prior diagnosis of COPD compared with only 6% of 37,605 controls matched for age, sex, and practice. The odds ratio (OR) of LC in patients who had COPD diagnosed within 6 months of their cancer diagnosis were 11-fold those of patients without COPD (11.47, 95% confidence interval [CI]: 9.38–14.02). When, for reasons unclear to us, analysis was restricted to those cases with COPD diagnosed more than 10 years before LC diagnosis with, importantly, adjustment for smoking, the OR decreased to 2.18 (95% CI: 1.87–2.54). Given that the OR is the ratio of the odds of an event occurring in one group to the odds of it occurring in another group, we think that these remarkable results should be interpreted differently because they: (1) confirm that smoking is a major risk factor for both COPD and LC (OR: 11.47) and (2) demonstrate that, after adjusting for smoking and time since COPD diagnosis, the risk of developing LC is 2.18 times higher in smokers with COPD and that this is statistically significant (95% CI: 1.87–2.54). In other words, those smokers who are susceptible to the effects of smoking and develop COPD (not all smokers) have more than twice the risk of developing LC than smokers who manage to preserve their lung function within the normal range despite their habit. To put it simply, these results clearly show that COPD is an independent risk factor for LC. This interpretation is opposite to that offered by Powell et al.[1] but potentially very important in any program of LC screening[2] in which cost–benefit ratio is proportional to the specific population screened.[3]

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Chronic Obstructive Pulmonary Disease and Risk of Lung Cancer: The Importance of Smoking and Timing of Diagnosis

To the Editor:

We thank Drs. Molins and Agusti for their interest in our article[1] and for their comments. We agree entirely that our results are of great importance in the lung cancer screening setting. In our view, however, this is because of the strength of the unadjusted association between chronic obstructive pulmonary disease (COPD) and lung cancer, and the fact that COPD is essentially an excellent marker for smoking. Diagnoses of COPD could potentially identify patients who do not admit to either their smoking habit or the quantity.

The idea that smokers who develop COPD are the ones who are susceptible to lung cancer, and those who smoke but do not develop COPD are less likely to develop lung cancer, is not unreasonable. In our opinion, however, the evidence for an independent association is weak as it relies on adjustment for a confounder, which in itself increases the risk of lung cancer more than 15-fold, and which is measured almost exclusively by patient reported quantity smoked. Since at least the 1950s, we have known that cigarette smoking is harmful, and smoking cessation is widely promoted during medical consultations. It is highly likely that smoking quantity

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and duration are under-reported by patients and therefore impossible to completely exclude from any estimate of the association between the two diseases which are both strongly related to smoking.

Although we accept that our study does not completely exclude an independent effect of COPD on the risk of lung cancer, our own opinion is that the remaining association can be explained by residual confounding and that any truly independent effect would be very small, and certainly lower than a twofold increase. The importance of our interpretation lies in the allocation of resources in lung cancer research, which we believe should not be focused on the pursuit of a potential molecular link, but rather on early detection, novel and improved treatments, and smoking cessation.

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Balancing Radiation Pneumonitis Versus Locoregional Tumor Control in Non–Small-Cell Lung Cancer

To the Editor:

With great interest, we read the recent publication by Vinogradskiy et al.[1] The authors apply their radiation pneumonitis prediction model combining dose-volume and genetic components (single-nucleotide polymorphisms [SNPs]) for isotoxic mean lung dose determination. The five SNPs were found to predict for radiation pneumonitis and interestingly, they do not directly relate to lung injury, but rather to cellular repair and the tumor microenvironment.

The authors state that radiation pneumonitis is the dominant dose-limiting constraint in thoracic radiotherapy. This may have been the case for the cohort studied for 19% of the patients, mostly treated with three-dimensional conformal radiotherapy developed radiation pneumonitis of grade 3 or higher. With the introduction of highly conformal radiotherapy delivery techniques and by abandoning elective nodal irradiation, acute grade 3 esophagitis is increasingly the dose-limiting toxicity based both on clinical experience[2] and in silico studies.[3] As opposed to radiation pneumonitis, this burdensome side effect is not fatal but gradually develops during the course of (chemo)radiotherapy, lasting for several weeks thereafter necessitating analgesic medication and dietary alterations in the majority of patients. Moreover, late esophageal sequelae may develop, adversely influencing the patients' quality of life.

Vinogradskiy et al.[1] found that on the basis of the isotoxic physico-genetic model a reduction in prescribed dose would be necessary in 26 of the 141 patients studied. All but one of these patients belonged to the cohort that developed radiation pneumonitis. The mean clinically prescribed dose to this pneumonitis population was 64.7 Gy as opposed to 51.8 Gy predicted to be safe by the model. For a subset of the remaining patients, the dose could be slightly increased or decreased. This finding is intriguing keeping in mind that dose escalation in lung radiotherapy is thought to substantially increase local tumor control and ultimately survival.[4] Instead of decreasing the dose to prevent patients from developing unwanted side effects, more tailored solutions are feasible. van Baardwijk et al.[5] successfully pioneered an individualized approach escalating dose to maximal tolerance while keeping within the normal-tissue constraints, both theoretically and clinically. Both acute and late toxicity were acceptable. Additionally, MAASTRO clinic is currently conducting a randomized phase II trial including 18F-fluorodeoxyglucose-positron emission tomography information for tumor (subvolume) boosting (NCT01024829). On the basis of a recent in silico study,[3] Radboud University Nijmegen Medical Centre is carrying out the Individualized Dose Escalation in Advanced stage non-small cell Lung cancer using Volumetric Modulated Arc Therapy (IDEAL-VMAT) study (NCT01577212), whereby the irradiation dose is increased on an individual basis, taking into account multiple normal-tissue constraints.

For patients with both an unfavorable genetic profile and dose distribution, the radiation dose that can be safely administered on the basis of the proposed model is probably not curative. Therefore, the treating radiation oncologist may opt for a palliative protocol thereby decelerating tumor progression and alleviating tumor-associated complaints while preventing patients from unnecessary treatment-related side effects.

In summary, this article on model-based prescription provides new, yet prospectively unvalidated, tools for individualized dose-prescription in non–small-cell lung cancer patients. Radiation oncologists are encouraged to enhance radiation dose in patients with a favorable profile while seeking alternative therapeutic options in the remaining patients.

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