The Relationship Between Emphysema on CT Scan and Lung Cancer

To the Editor:

I commend Maldonado and colleagues1 for their extended reanalysis of lung cancer screening data to explore the association between emphysema on CT scan and lung cancer in a recent issue of CHEST (December 2010). Attempts to validate previously published findings are all too rare. The authors report the absence of a clear relationship between emphysema (quantitative or dichotomous) and the odds of lung cancer. As mentioned in the discussion, these findings differ from the more than threefold risk associated with emphysema found in two independent prospective cohort studies.2,3 Exploring why such different observations were made will help advance our understanding of the seemingly complex relationship between lung cancer, COPD, and emphysema on chest CT scans.

Maldonado et al2 acknowledge that Wilson et al3 observed an all-or-none effect, with even trace (<10%) or mild (10%-20%) emphysema increasing the risk of lung cancer. Yet their dichotomous analysis uses a threshold for emphysema at ≥15%. I would be interested to know the crude and adjusted impact of any emphysema (ie, >0%), as this was the threshold used by de Torres et al2 and Wilson et al.3 Indeed, from the data provided in Table 2 of the article by Maldonado et al2 with a threshold of ≥5%, the crude OR of lung cancer in the presence of emphysema is 1.7 (1.0-2.9). It may be that automated techniques or the threshold of ~900 Hounsfield units generate too many false-positive diagnoses of minimal emphysema, a disease severity clinically important with respect to lung cancer risk.

Conversely, it is possible that the automated quantification technique used by Maldonado et al2 eliminated a potential observer bias in the studies of de Torres et al2 and Wilson et al.3 Lung cancer cases that were detected on the initial screening scan were presumably apparent to the CT scan readers (eg, masses, adenopathy) and may have influenced their assessment of emphysema. Such a bias could spuriously create a false association with lung cancer.

In summary, the work by Maldonado et al2 forces us to refine our understanding of the relationship between emphysema on CT scan and lung cancer and raises new research questions. Perhaps the application of their quantitative algorithm to the datasets of de Torres et al2 or Wilson et al3 or the manual grading of emphysema within their dataset would advance our understanding.

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References


Response

To the Editor:

We appreciate Dr Smith’s very insightful comments on our data recently published in CHEST (December 2010)1 on the relationship between radiographic evidence of emphysema and risk of lung cancer. As mentioned, our results contrast with those of two independent retrospective studies using qualitative or semiquantitative visual assessment of emphysema as opposed to the automated CT scan quantification based on threshold detection techniques used in our study.2,3

The conventional wisdom is that, in the majority of cases, continuous data should be analyzed as continuous because conversion to categoric variables will almost systematically result in loss of power. As such, we analyzed the quantity of emphysema as a risk factor for lung cancer as a continuous variable, with adjunct analyses of emphysema as a discrete variable. We agree, however, that should an all-or-none effect of emphysema on lung cancer risk be confirmed, analyzing our data as a dichotomous variable (emphysema vs no emphysema) could theoretically make sense and could unmask a signal not otherwise evident. Indeed, the crude OR calculated by Dr Smith using a threshold of 5% is 1.7 (1.0-2.9). The use of a density threshold method makes a comparison between emphysema and nonemphysema groups impossible (because having no voxel <~900 Hounsfield units is improbable in any data set), but using an arbitrarily defined threshold of 5%, the adjusted OR is 1.85 (1.05-3.26), P = .034.

This result seems to support Dr Smith’s suggestion and would be consistent with previously published results by Wilson et al2 (whose data do suggest an absence of “dose-effect” between emphysema and lung cancer) and de Torres et al2 (who analyzed radiographic evidence of emphysema as a dichotomous variable). Another explanation for this result could be that reclassifying subjects with <5% emphysema as “no emphysema” improves the signal/noise ratio by eliminating a number of false positives (subjects without emphysema but with the presence of low-density voxels “read” as emphysema by our automated emphysema quantification system). Obviously, this result may also be spurious, a consequence of multiple hypothesis testing, or the result of chance alone.

Automated quantitative analysis of emphysema is a powerful tool, yet it still requires standardization. However, it does eliminate the risk of observer bias, a potential issue with the two mentioned studies. We agree that the relationship between radiographic evidence of emphysema and risk of lung cancer remains to be clarified, and that further research, using both visual assessment and automated CT scan quantification, is warranted.