

# CT-diagnosed emphysema and lung cancer mortality: novel association or old news?

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Hippocrates may well have appreciated the significance of the presence of emphysema, but it was not until the 17th century that Bonet<sup>1</sup> described the larger lungs of those with emphysema, to which he attributed their breathlessness. In 1821, Laennec connected emphysema to ageing, when he ascribed a subtly different definition to emphysema, describing it as “a breakdown of tissue in the parenchyma of the lungs as opposed to air trapped in the alveoli due to obstruction as occurs in asthma and chronic bronchitis” essentially considering emphysema to be an ‘independent finding’ to obstructive lung disease, although at postmortem.<sup>2</sup> Fast forward 200 years, and one could argue that even in 2016 the significance of emphysema on a CT scan in someone who does not have airflow obstruction or clinical symptoms of breathlessness is unclear.

Even the significance of emphysema among people with COPD and the association between emphysema and smoking are obscure. Around half of patients with COPD do not have significant emphysema,<sup>3</sup> and up to 10% of never smokers have evidence of emphysema at postmortem.<sup>4</sup> On the flip side, its presence is an important prognostic marker in COPD; emphysema is considered to be a risk factor for exacerbations,<sup>5</sup> disease progression<sup>6</sup> and incidence of and mortality associated with lung cancer, particularly in current smokers.<sup>7,8</sup>

So what then is the relevance of emphysema on CT in the general population, and is there any association with respiratory and lung cancer mortality? This is potentially an important question for two reasons; (1) because lung cancer and chronic respiratory disease are responsible for a large proportion of worldwide morbidity and mortality and (2) because recent studies on lung cancer screening have focused on high-risk populations. Currently, those high-risk populations

include people with COPD and current smokers, but not emphysema in isolation.<sup>9</sup> Roughly, one-third of smokers undergoing lung cancer screening have emphysema on CT,<sup>10</sup> so establishing a relationship in the general population has wide-reaching implications.

In this issue of *Thorax*, Oelsner *et al*<sup>11</sup> explore the association and describe the prognostic significance of assessing the percentage of emphysema on CT in the general population in a study of 6814 individuals aged 45–84 years without clinical cardiovascular disease who took part in the multi-ethnic study of atherosclerosis (MESA)<sup>12</sup> between 2000 and 2002. Emphysema was defined as per cent emphysema greater than the upper limit of normal using MESA reference equations and the study focused on death due to respiratory disease or lung cancer in a composite endpoint. Perhaps unsurprisingly, the 538 participants (8.6%) with emphysema on CT were older, more likely to be smokers, were more likely to have a prior clinical diagnosis of emphysema (6%) or asthma (18%) and had lower FEV<sub>1</sub>/FVC ratios. So, maybe not such an ‘independent’ finding.

The authors found that emphysema was strongly associated with increased respiratory and lung cancer mortality. Indeed, emphysema on CT conferred an almost threefold increased risk of respiratory disease mortality in adjusted models. While the association between respiratory mortality and clinical emphysema is not new, what is particularly interesting about this study is that it captures CT-diagnosed emphysema in the general population, the majority of whom do not have a known diagnosis of COPD, and around a third of whom are never smokers. While previous data do exist on the potential implications of emphysema detected on CT in never smokers,<sup>13</sup> this study provides more detailed novel data. Why does this matter? Does it simply suggest there is a lot of undiagnosed COPD out there? With an ageing population and the increasing availability of CT, more radiological emphysema will be found. The relationship between the degree of radiological emphysema and lung and

respiratory mortality in never and light smokers is therefore intriguing and likely to be COPD independent.

As with all new relationships, however, a degree of trepidation is required and large cohort studies of this nature are no exception. Numbers are small, particularly in the subgroup endpoints, CIs are wide and this is a secondary analysis of data collected for another purpose. The authors are clear about the limitations in the discussion and conclude that these data are hypothesis generating rather than definitive conclusions. One of the main unknowns is around the development of airflow obstruction or a diagnosis of COPD later on. Not all patients had spirometry or information regarding a diagnosis of COPD. Knowing that COPD is underdiagnosed in the general population, misclassification is likely. Nevertheless, the ability to find this association; that CT-detected emphysema in individuals without significant respiratory and smoking history and without airway limitation is associated with increased lung and respiratory mortality is something very few studies could do. MESA is unique in that regard, and the subsequent use of precollected data to answer important clinical questions in a time of cuts in research funding is an efficient use of resource.

So where do we go next? Perhaps as other large cohorts and resources such as UK Biobank develop,<sup>14</sup> more of these independent findings will be written about, or perhaps in another 200 years with the development of genomics, precision medicine and stem cell regeneration, future editorialists and respiratory physicians will wonder what all the fuss was about.

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