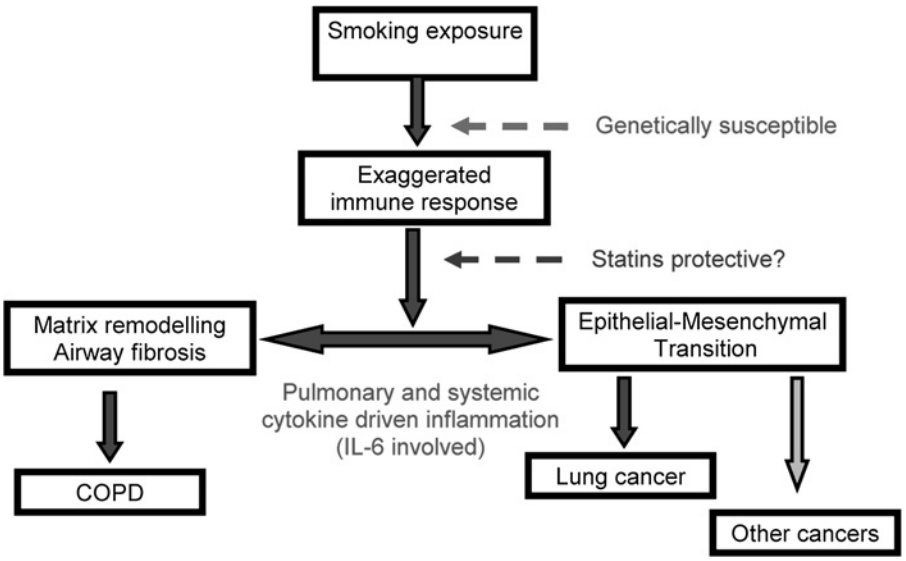

Figure 1 Relationship linking chronic obstructive pulmonary disease (COPD), lung cancer, extrapulmonary cancer and inflammation.

smoking effects, has been shown to be inversely correlated with the forced expiratory volume in 1 s in prospective studies.[3] In a murine model, overexpression of IL-6 resulted in the development of COPD (emphysema and airway fibrosis).[3] It has been proposed that elevated IL-6 is also associated with epithelial cancers through its growth-promoting effects[4] and the promotion of epithelial–mesenchymal transition (EMT), a well recognised feature of chronic inflammation and a precursor to malignant transformation in the lung.[3] Other cytokines involved in pulmonary inflammation are tumour necrosis factor alpha, IL-1β and IL-8,[3 4] which, together with growth factors like transforming growth factor beta 1 are implicated in EMT.[3] All of these pathways are mediated via guanosine triphosphatase (GTPase) signalling molecules (Rho Rac and Ras).[3] There is also growing interest in the role of systemic inflammation, which not only characterises COPD,[3] but may also be relevant in extrapulmonary epithelial cancers (eg, prostate, breast and colon).[4] These findings might partly explain the increased susceptibility of COPD patients to both lung cancer and extrapulmonary cancers (figure 1).[1]

In a recently published review of statins in COPD,[3] we suggest that the anti-inflammatory effects of statins, through inhibition of GTPases, may explain the protective effect of statin use on lung cancer incidence as reported in three large observational studies (OR 0.45–0.70)[3] and also by van Gestel *et al*[1] (OR 0.46–0.74). Studies show that statins can directly inhibit EMT through GTPase inhibition and inhibit the effects of IL-6, an effect that has been shown to block tumour progression.[4 5] We suggest that the anti-inflammatory actions of statins (eg, anti-IL-6 activity) could underlie the protective effects for both lung cancer[1 3] and extrapulmonary malignancies (figure 1).[1] These observations add considerable weight to existing data that suggest that statins may be very beneficial to patients with COPD.

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Authors' reply

We thank Drs Young and Hopkins for their interest in our study[1] and their interesting explanation for the results observed. It is indeed likely that the relationship between chronic obstructive pulmonary disease (COPD) and cancer (both pulmonary and extrapulmonary) is attributed to cytokine-induced inflammation mediated by guanosine triphosphatase (GTPase) signalling molecules. This is advocated by the results of Man *et al* who showed that the increased inflammatory state in patients with COPD is associated with future cancer mortality including extrapulmonary cancers.[2]

Statins are associated with reduced cardiovascular morbidity and mortality in patients with cardiovascular disease. Besides the reduction in low-density lipoprotein cholesterol levels, statins also reduce inflammation through reduced expression of inflammatory cytokines which is known as one of the pleiotropic effects of statins.[3 4] A recent double-blind placebo controlled trial in patients who had undergone vascular surgery showed that patients who were treated preoperatively with fluvastatins had significantly decreased levels of interleukin 6 at the time of surgery compared with the placebo group (−33% and −4%, respectively; $p<0.001$).[4] The same was observed for high-sensitivity C reactive protein, another marker of inflammation, which was decreased by 21% in the fluvastatin group and increased by 3% in the placebo group ($p<0.001$). Furthermore, patients with elevated inflammatory levels are more likely to benefit from statin therapy than those without elevated levels.[5] This might explain the increased beneficial effects of statins in patients with COPD and cancer observed in our study. Although the results of our study are in line with those of previous studies which suggest that statins might have an important role in patients with COPD (with or without cancer), further studies are needed before statin treatment can be recommended for patients with COPD.

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Diagnosing lung cancer earlier in the UK

We read with interest the article by Hubbard *et al* who raise late diagnosis as a key determinant of poor lung cancer survival in the UK.[1] We would like to highlight discrepancies in rates of radical treatment use as another contributory factor. Figures from the Eurocare 4 study[2] suggest 5-year survival figures in Northern Ireland have been higher than in England and Wales or Scotland (table 1).[2–4] This could reflect differences in patient demographics, disease, method of recording or treatment modality. There are no published data that directly compare the health or the stage at presentation of patients with lung cancer in relation to geographical location in the UK. If significant regional differences exist, one might expect to find evidence for differential survival from other cancers as well. Current data do not suggest a survival advantage for cancer patients in general from Northern Ireland over the rest of the UK.

Data on cancer survival in Northern Ireland are collected by the Northern Ireland Cancer Registry (NICR), a population-based registry collecting data from pathological records, hospital discharges and death registrations. Over the last decade the introduction of LUCADA in England and Wales, and CaPPS in Northern Ireland have made it possible to look for regional differences in cancer treatment. In Northern Ireland the number of patients included in CaPPS exceeds that recorded in recent years by the cancer registry. This would suggest most patients have been captured. One-year survival is likely to be influenced by palliative treatments, but 5-year survival is largely influenced by radical treatments, of which surgery is the mainstay. The use of radical radiotherapy may also have some influence, but comparative data are not available. We looked at the surgical resection rate and 5-year relative survival rate for lung cancer in Northern Ireland and compared them with those published for England, Wales and Scotland.[2–4]

Reported rates of surgical resection in all areas of Northern Ireland in 2004–08 exceeded the average for England and Wales for 2008. We believe this may offer a plausible reason for better 5-year survival differences and may be worthy of further study. Regional differences in lung cancer treatment are not new and are as yet unexplained.[5] Addressing the remediable differences in appropriate use of radical treatment in the UK may offer a more immediate potential improvement in lung cancer survival than early diagnosis.

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Authors' response

In our editorial we argue that, as a group, people with lung cancer in the UK present later and have a worse prognosis than people with lung cancer elsewhere in Europe.[1] We believe that delays in the early diagnostic process are central to this problem. At the moment, however, we do not understand enough about the early patient journey from the development of symptoms to initial investigations in primary care to try to intervene to improve the situation. We need to do this if we are to maximise the benefits of currently available treatments such as surgery. We believe that this is an area in urgent need of further research.

Weir *et al* make the point that that there is variation in the outcome for people with lung cancer within the UK and that the reasons for this are poorly understood.[2] In addition to delays in diagnosis, Weir *et al* argue that access to potentially curative surgical treatment may vary geographically and that this, though currently only a treatment option for a small minority of people, may also contribute to variations in survival. We agree.

It is clear that, in addition to understanding the cultural and health service factors which appear to lead to delays in lung cancer diagnosis in the UK, we also need to be sure that, once we have diagnosed lung cancer, people within the UK receive the highest quality of care. To do this we need to determine the extent to which variations in access to care exist, as well as what individual factors—such as comorbidity, performance status and stage—influence treatment decisions for people with lung cancer. The presence of the National Lung Cancer Audit, which now provides more than 5 years of data for people with lung cancer in the UK, is an important and unique tool to do this research. We hope that the analyses using the national audit which are currently being done by us and by other groups will help to shed some light on these questions.

Lung cancer remains an enormous public healthcare problem for the UK and we desperately need new effective treatments for people with lung cancer. We also need to study the diagnostic processes and the delivery of care for people with lung cancer to ensure that, at each stage, we maximise the benefits from the currently available treatments.

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Table 1 A comparison of regional surgical resection rate and 5 year survival

	Total number of lung cancers	Surgical resection rate	1995–99 mean age adjusted 5 year relative survival (SD)*
UK England	27815	10.8	8.6 (0.2)
UK Wales 2008			9.0 (0.9)
UK Scotland 2008	4058	10.6	8.0 (0.5)
UK Northern Ireland 2004–08	4786	12.8	10.2 (1.2)

*Difference in 5 year relative survival for cancers diagnosed between 1995–99 and 1990–94.