Air pollution: another cause of lung cancer

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In *The Lancet Oncology*, Ole Raaschou-Nielsen and colleagues[1] present the findings from individual data from 17 European cohorts and show that exposure to particulate matter air pollution increased the risk of lung cancer—particularly adenocarcinoma—with a suggestion of an effect even below the current European Union air pollution limit values (40 μg/m³ for particulate matter with an aerodynamic diameter <10 μm [PM_{10}] and 25 μg/m³ for particulate matter with a diameter <2·5 μm [$PM_{2·5}$]).

The design of their study is sophisticated and overcame several limitations of previous air pollution studies. Earlier studies examined the effect of air pollution on lung cancer by assessing geographical correlations (ie, between air pollution concentration data in communities and aggregate data on lung cancer), but they suffered from exposure misclassification and confounding (mainly by tobacco smoking). Subsequently, researchers tried to reduce these systematic errors by shifting to individual studies (case-control or cohort studies) with area-level exposure assessment or more precise individual-level exposure assessment. Raaschou-Nielsen and colleagues' took the next step by combining effect estimates from 17 cohorts with standardised protocols and undertaking a meta-analysis,[1] which increased the number of participants, who came from a wide range of European regions, and reduced the possibility of sampling and publication bias. This study also benefited from a high follow-up rate and adjustment of potential confounders, including a set of smoking variables. This study, therefore, should have reduced much of the systemic and random errors reported previously.

Even in the well known companion textbook for medical doctors,[2] air pollution is not listed as a cause of lung cancer. Although smoking is undoubtedly a strong risk factor, evidence for an association between air pollution exposure and lung cancer is also accumulating. Although the lung cancer risk associated with air pollution (eg, HR 1·22 [95% CI 1·03–1·45] per 10 μg/m³ increase in PM_{10} in this study) is much lower than that associated with smoking (relative risk [RR] 23·3 for currently smoking men and RR 12·7 for currently smoking women[3]), everybody is exposed to air pollution. Thus, the public health effect is quite large. For example, WHO estimated that smoking caused 5·1 million deaths and 71% of lung cancer worldwide in 2004, whereas air pollution caused 1·2 million deaths and 8% of lung cancer worldwide in the same year.[4]

Absence of safe thresholds is reported for health effects caused by both short-term exposure and long-term exposure to $PM_{2·5}$.[5] Even in Raaschou-Nielsen and colleagues' study,[1] raised point estimates were still reported below 10 μg/m³ of $PM_{2·5}$ (a current WHO air quality guideline for yearly $PM_{2·5}$ exposure[6]). Moreover, the investigators noted that the association between air pollution and lung cancer did not deviate statistically significantly from linearity.[1] These findings clearly support a possibility that "public health benefits will result from any reduction of $PM_{2·5}$ concentrations whether or not the current levels are above or below the limit values", as summarised by WHO.[5] Indeed, accountability studies that examined potential benefits of air pollution interventions (eg, planned actions such as reduction of fuel sulphur or regulation of vehicles and unplanned actions such as plant closures due to strikes) consistently showed that interventions reduced air pollution concentrations and improved health outcomes.[7]

So far, air pollution studies that have examined an association with lung cancer have mainly been done in Europe and North America, although several studies have emerged from other continents in recent years that also show associations between air pollutants and lung cancer risk.[8,9] However, an attempt such as Raaschou-Nielsen and colleagues' (ie, a meta-analysis of cohorts) has not been reported outside of Europe; future collaborative studies in other continents will thus provide further insights into the risk of lung cancer caused by air pollution exposure. Moreover, Raaschou-Nielsen and colleagues identified a relation between air pollution and the histological subtype of adenocarcinoma in particular;[1] however, in a previous study by the same investigator of three Danish cohorts,[10] a stronger association with squamous-cell carcinoma and small-cell carcinoma was reported than with adenocarcinoma. In view of the shift in frequency of lung cancer types (ie, from squamous-cell carcinoma to adenocarcinoma) and the different frequency distributions of types of lung cancer throughout the world,[3] future assessments of the association between air pollution and specific types of lung cancer are warranted.

At this stage, we might have to add air pollution, even at current concentrations, to the list of causes of lung cancer and recognise that air pollution has large effects on public health, although fortunately, like tobacco smoking, it is a controllable factor.

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1 Raaschou-Nielsen O, Andersen ZJ, Beelen R, et al. Air pollution and lung cancer incidence in 17 European cohorts: prospective analyses from the European Study of Cohorts for Air Pollution Effects (ESCAPE). *Lancet Oncol* 2013; published online July 10. http://dx.doi.org/10.1016/S1470-2045(13)70279-1.
2 Longo DL. Harrison's principles of internal medicine, 18th edn. New York: McGraw-Hill, 2012.
3 Thun M, Henley S. Tobacco. In: Schottenfeld D, Fraumeni JF, eds. Cancer epidemiology and prevention, 3rd edn. Oxford: Oxford University Press, 2006: 217–42.
4 WHO. Global health risks: mortality and burden of disease attributable to selected major risks. Geneva: World Health Organization, 2009.
5 WHO. Review of evidence on health aspects of air pollution—REVIHAAP project—first results. Denmark: World Health Organization Regional Office for Europe, 2013.
6 WHO. Air quality guidelines: global update 2005—particulate matter, ozone, nitrogen dioxide, and sulfur dioxide. Copenhagen: World Health Organization, 2006.
7 Henschel S, Atkinson R, Zeka A, et al. Air pollution interventions and their impact on public health. *Int J Public Health* 2012; **57:** 757–68.
8 Hales S, Blakely T, Woodward A. Air pollution and mortality in New Zealand: cohort study. *J Epidemiol Community Health* 2012; **66:** 468–73.
9 Yorifuji T, Kashima S, Tsuda T, et al. Long-term exposure to traffic-related air pollution and the risk of death from hemorrhagic stroke and lung cancer in Shizuoka, Japan. *Sci Total Environ* 2013; **443:** 397–402.
10 Raaschou-Nielsen O, Bak H, Sørensen M, et al. Air pollution from traffic and risk for lung cancer in three Danish cohorts. *Cancer Epidemiol Biomarkers Prev* 2010; **19:** 1284–91.

Glioblastoma: bridging the gap with gene therapy

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Adult glioblastoma is the most common primary brain tumour. It is characterised by substantial morbidity and mortality despite multimodal therapy with surgical resection and adjuvant radiochemotherapy as standard care.[1] The poor prognosis is largely due to the disease's high frequency of recurrence, which is indicative of its intrinsic invasive properties into the peritumoral zone.[2] Consequently, an unmet need exists to improve local control of glioblastoma beyond the margin of resection and to explore new treatment options targeted peritumouraly. Local therapies that can be applied during surgery are therefore well-suited to bridge the gap between initial surgical resection and subsequent radiochemotherapy. In *The Lancet Oncology*, Manfred Westphal and colleagues[3] explore the use of so-called suicide gene therapy to address this treatment gap, describing the results of a randomised, open-label phase 3 trial (ASPECT) for the treatment of operable high-grade glioblastoma. This trial was based on previous phase 1 and phase 2 trials[4–6] and relies on local injection into the resection cavity of a replication-deficient adenoviral vector encoding a herpes simplex virus thymidine kinase (*HSV-tk*) gene to selectively eliminate any residual glioblastoma cells. The HSV-TK catalyses the conversion of a non-toxic ganciclovir prodrug into a toxic nucleotide analogue that is incorporated into the DNA of dividing cancer cells, prompting apoptosis. This approach overcomes the typical inaccessibility of glioblastoma tumour, and brain-infiltrating, cells to most systemic therapies. Moreover, preclinical studies indicate that both the *HSV-tk* gene-modified cells and adjacent, non-modified dividing cells are eliminated through a so-called bystander effect that enhances the overall anti-tumour effect. This bystander effect is probably mediated by intercellular trafficking of the toxic ganciclovir metabolites through gap junctions or immune mechanisms.[7,8] Another advantage is that normal neurons do not proliferate and are therefore resistant to the ganciclovir metabolites, which improves the tumour selectivity of this treatment strategy.

The specific objective of the ASPECT trial was to determine whether ganciclovir with adenoviral HSV-tk gene therapy was better than standard care, with time to death or re-intervention as the composite primary endpoint. After the ASPECT trial had begun, temozolomide emerged as a new and effective treatment for glioblastoma and was included in both the treatment and control groups. Consequently, this invalidated the initial statistical analysis strategy. A post-hoc multivariate statistical analysis based on a Cox's proportional hazards model was therefore needed for the composite primary endpoint, which