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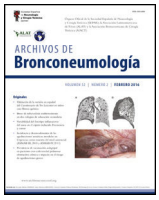

Editorial

Environmental pollution and lung cancer: The carcinogenic power of the air we breathe☆

Contaminación ambiental y cáncer de pulmón: el poder carcinogénico del aire que respiramos

Lung cancer (LC) is the cancer with the highest overall incidence and mortality: about 2.1 million new cases and 1.8 million deaths worldwide were recorded in 2018.[1] The scale of these data, despite modern therapeutic advances, means that prevention and early diagnosis must be promoted as central strategies in the control of this disease. In both cases, comprehensive recognition of the risk factors involved is essential.

It is clear beyond doubt that smoking is the main risk factor for LC, as confirmed in about 80% of these patients. However, other factors, such as environmental pollution, domestic pollution, occupational exposure, and even nutrition, cause an estimated 908,000 LC deaths per year, not far from the 1,190,000 LC deaths attributable to tobacco use.[2] Moreover, LC in non-smokers is an increasingly common occurrence that demands an examination of the real impact of air quality on the development of these malignant tumors. In this respect, environmental pollution could be related to 36% of LC deaths, accounting for 265,000 deaths annually attributable to this cause.[2,3]

We must assume that the air we breathe has a high concentration of pollutants, many of which cause cancer. In fact, in 2013, the World Health Organization (WHO) and the International Agency for Research on Cancer (IARC) classified air pollution as a human carcinogen (Group 1). Of all the atmospheric pollutants, particulate matter (PM) is the most harmful.[4] These particles are composed of a heterogeneous mixture of substances such as nitrates, sulfates, carbon, organic compounds, and metals. They are produced by both natural sources (fires, volcanic emissions, *etc.*) and human activity (transport, biomass burning, industrial, agricultural and livestock activities, *etc.*).[5] PM are classified according to their aerodynamic diameter: PM_{10} have a diameter smaller than 10 μm, and $PM_{2.5}$ have a diameter smaller than 2.5 μm. The ability of these particles to penetrate the airway depends on their aerodynamic diameter, although it is still unknown how much this factor could affect the risk of developing various associated diseases.

Numerous epidemiological studies have shown significant associations between environmental pollution and LC. The ESCAPE study, that pooled 17 European cohort studies, concluded that increased concentrations of PM in the environment increase the risk of LC. Specifically, for each 5 $\mu g/m^3$ increase in $PM_{2.5}$ and 10 $\mu g/m^3$ increase in PM_{10} in the environment, the risk of LC increased by 18% and 22%, respectively.[6] Hamra et al. confirmed similar relative risks in a meta-analysis of 18 cohort studies from Asia, North America and Europe.[7] The same scientific group also found that an increase in environmental concentration of NO_2 as a marker of exposure to road traffic also significantly increased the risk of LC.[8] All these cohorts clearly point to a significant epidemiological association, despite certain limitations such as the lack of an individual exposure model.

Research into the biological mechanisms involved in this association is complex, given the high diversity of pollutants and the different carcinogenic effects of each one. Epigenetics appear to play a central role in lung carcinogenesis, *i.e.*, environmental pollution can modulate the expression of different genes involved in tumor development. Specifically, exposure to PM activates inflammatory mediators and oxidative stress that induce mechanisms such as DNA methylation, histone modification, and micro-RNA.[9,10] These epigenetic processes could regulate gene expression, with overexpression of pro-oncogenes and underexpression of tumor suppressor genes. The final consequences of these genetic changes will involve activation of oncogenic pathways, such as sustained cell proliferation, resistance to cell death, and induction of angiogenesis, invasion, and metastases.

In this respect, *in vitro* and *in vivo* studies have shown that lung cells exposed to $PM_{2.5}$ secrete molecules as exosomes that can activate the Wnt/β-catenin pathway involved in tumor cell proliferation.[11] Exposure to PM also induces an increase in protease activity resulting in greater invasion and metastasis capacity.[12] A murine model has recently shown that animals exposed to PM developed a greater number of lung tumors, while simultaneously showing increased levels of more than 12 angiogenic factors, including MMP1, ILIβ and VEGF.[13] These epigenetic changes are detectable in biological fluids and could be used as disease biomarkers. Research into these biomolecules could have valuable clinical implications for early diagnosis and disease monitoring strategies.[14]

Another parallel line of investigation of interest may be the potential impact of environmental pollution on the prognosis of patients already diagnosed with cancer. Recent studies suggest

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that exposure to air contamination could affect the progression of established tumors, shortening survival in these patients. Although further studies are needed to confirm this suspicion, reports in both LC and other malignancies such as breast or liver cancers have already been published.[15–17]

In short, given the enormous burden of LC morbidity and mortality, prevention and early diagnosis strategies must be implemented, and the risk factors involved must be understood. Environmental pollution must be recognized as a cause of LC in the face of the solid epidemiological and biological evidence. The scientific community and respiratory medicine specialists in particular must take a leading role in disseminating this evidence in order to promote governmental strategies in the fight against air pollution.

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David Clofent,[a,*] Mario Culebras,[a] Karina Loor,[a] M. Jesús Cruz[a,b,c]

[a] *Servicio de Neumología, Hospital Universitario Vall d'Hebron, Barcelona, Spain*

[b] *CIBER Enfermedades Respiratorias (CIBERES), Madrid, Spain*

[c] *Departamento de Medicina, Universidad Autónoma de Barcelona, Barcelona, Spain*

[*] Corresponding author.

E-mail address: dclofent@vhebron.net (D. Clofent).