Editorial

How to prevent most deaths from lung cancer: control cigarette smoking and air pollution

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The lung is a remarkable organ exchanging oxygen and carbon dioxide across a surface area the size of a tennis court (1). It is also the portal of entry for numerous carcinogens. An adult inhales approximately 10,000 liters of air daily, exposing the airways and alveoli to the contaminants in each breath. Consider airborne particles: in clean indoor air (5–10 μg/m^3 of $PM_{2.5}$—particulate matter less than 2.5 μm in aerodynamic diameter), a breath contains approximately 2 million particles, while in polluted urban air at 200 μg/m^3 there are 40 million particles; multiplying by 10,000 provides an estimate of the total number of particles inhaled in a day. These 10,000 breaths are taken in many different places, depending on how and where time is spent: offices and factories, outdoors at home, and indoors while cooking and in other locations in homes. The contaminants inhaled vary widely, reflecting the sources of air pollution where breathing takes place and, of course, the involuntary and voluntary inhalation of tobacco smoke. While the lung has an elegant set of defense mechanisms, extending from the nose to the alveoli, which contend with inhaled gases and particles, these defenses, may be overwhelmed at high concentrations and even pollutants at lower concentrations may cause injury if exposure is sustained.

With this background, consider air pollution, smoking, and lung cancer. Smoking is a long-established cause of lung cancer and, today, in most places the majority of cases are attributable to cigarette smoking. The carcinogenicity of tobacco smoke is fully consistent with the rich combustion mixture that cigarette smokers inhale, which contains numerous known carcinogenic agents and also compounds that have high oxidative and inflammatory activity. For comparison with ambient air pollution, the concentration of small particles in tobacco smoke is 5 billion particles/cm^3 (2). Finding the causal link of smoking with lung cancer was an early triumph of epidemiologists in establishing the causes of noncommunicable diseases and motivating the implementation of tobacco control. More than a half-century after this causal association was established, however, there are still approximately 800 million smokers globally. In 2017, there were 1.88 million deaths from lung cancer worldwide, of which 1.19 million were attributable to tobacco smoking (3). The comparison scenario or counterfactual is that all smokers were instead lifelong nonsmokers.

In the 21st century, air pollution has emerged as a major cause of lung cancer, reflecting worsening air pollution and the growth of urban populations (4,5). In today's world, combustion sources of air pollution predominate, both indoors and outdoors, and combustion processes, whether fires or sophisticated industrial processes, generate carcinogens. Numerous well-characterized carcinogens are present in indoor and outdoor air, including benzo-a-pyrene and other polycyclic aromatic hydrocarbons (PAHs), benzene, and dioxin (2,6). Samples of particles collected in outdoor air have mutagenic activity; i.e., they cause mutations in DNA, which is fundamental to carcinogenesis (7). Air pollution also causes inflammation in the lungs, which may contribute to increased cancer risk through non-specific pathways. Evidence on air pollution and lung cancer also comes from animal bioassays, largely directed at specific sources and contaminants such as diesel exhaust and fibers.

And, of course epidemiologists have been investigating air pollution and lung cancer for decades. Historically, as the 20th century epidemic of lung cancer began, there were two extant hypotheses as to its origins: tobacco smoking and air pollution. In introducing their 1950 paper providing the

preliminary results of their lung cancer case-control study in London, Doll and Hill wrote: "Two main causes have from time to time been put forward: (I) a general atmospheric pollution from the exhaust fumes of cars, from the surface dust of tarred roads, and from gas-works, industrial plants, and coal fires; and (II) the smoking of tobacco." (8).

While the early epidemiological studies quickly documented the strong and causal link of smoking with lung cancer, the initial investigations of air pollution, using primarily ecological approaches, provided suggestive but not confirmatory findings as did the initial case-control and cohort studies. Epidemiological research on air pollution and lung cancer is complicated by accurately assessing exposure to air pollution, which is sustained across the life course and in multiple environments (7). Initial studies used the simplistic approaches available at the time: current residential location and respondent assessment of exposures and proximity to sources. Over time, increasingly sophisticated approaches have been used to assess exposures for epidemiological studies that draw on monitoring data, land-use information, and satellite measurements of optical density of the air, used to estimate particulate matter concentrations. With these approaches, exposures have now been investigated for large cohorts with the finding that ambient particulate matter is associated with increased lung cancer risk (9,10). Hamra *et al.* pooled 18 studies, finding that lung cancer risk increased by 9 percent per 10 μg/m^3 increase in $PM_{2.5}$ (10). Based on a comprehensive review, the International Agency for Research on Cancer (IARC) classified both ambient air pollution and particulate matter air pollution as known human carcinogens (Group 1) in Monograph 109 (7).

For ambient air pollution, there is also a substantial burden of avoidable lung cancer mortality, estimated at 265,000 for 2017 (3). However, for air pollution the counterfactual scenario is a level of $PM_{2.5}$ below 5.9 μg/m^3. This scenario cannot be achieved in most industrialized countries and is far out of reach for low- and middle-income countries where annual average $PM_{2.5}$ concentrations reach 100 μg/m^3 in many locales, well above the current World Health Organization guideline of 10 μg/m^3.

For both the clinical and public health communities, lung cancer is a disease to be prevented, as overall five-year survival is at about 18.6% in high-income countries where state-of-art care can be accessed (11). There are promising new targeted therapies, but the costs are enormous, making them out of reach for the majority of lung cancer victims. Screening with CT scans has been shown to be efficacious but its impact on lung cancer mortality in real-world settings remains uncertain (12).

We are left with primary prevention as the path to reducing the global burden of lung cancer and the attributable burden constitutes the majority of cases, combining the 1.19 million from smoking with the 265,000 from outdoor air pollution. While the combined figure of over 1.4 million likely "double counts" some lung cancer deaths, most cases that are currently attributable to a specific etiological agent are covered, except for household air pollution and radon with 85,000 and 88,000 attributable lung cancer deaths, respectively (3). And, we have effective mitigation approaches for both smoking and air pollution, and for indoor radon as well.

For smoking, there has been success with the steady decline of tobacco smoking in high-income countries leading to decline in lung cancer mortality. However, that decline may be interrupted by the allure of nicotine delivered by electronic nicotine delivery systems and efforts by the multinational tobacco industry to penetrate into new markets, including Africa and women everywhere. The Framework Convention on Tobacco Control represents a critical global barrier to reining in the tobacco companies (13). The counterfactual of a world without smokers represents a goal that could be achieved, albeit not quickly.

For ambient air pollution, there is a range of regulatory control strategies that are evidence-based (14). In higher-income countries such regulations have made a difference, dropping average particulate matter concentrations by as much as 90%. However, the lung cancer burden from air pollution is now driven by exposures to people in India and China, both countries where there has been substantial industrialization and the rise of large vehicle fleets. Long-standing sources of air pollution also persist—burning of biomass fuels for heating and cooking and open trash-burning. Many countries lack adequate pollution monitoring, regulations, and infrastructure for air quality management. Reduction of air pollution may be achieved slowly, in part because of concern about the extremely high pollution levels experienced in some cities and regions in China and India. Achieving emissions commitments made under the Paris Agreement will help, but how and when these commitments will be met is quite uncertain. For ambient air pollution, the counterfactual used for the Global Burden of Disease estimates cannot be reached.

Could more research be of benefit? A question almost always answered affirmatively. However, for both smoking and air pollution, the evidence on causation is sufficient and

risks have been quantified with reasonable certainty. The estimates of burden from these two exposures are credible. Advances in understand of the molecular biology of lung cancer could be useful if "signatures" for those cancers caused by air pollution and/or smoking were identified. A new level of certainty of attribution could then be made, one that might further strengthen the rationale for exposure reduction. In the meantime, we need to aggressively use the suite of measures that have proven effective for controlling tobacco use and mitigating air pollution.

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