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Non-smoking lung cancer and environmental exposure

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While lung cancer mortality has been decreasing in many countries due to tobacco control efforts, at least one quarter of global lung cancer cases occur among non-smokers. There is growing attention being paid to the role of environmental exposures, such as radon and air pollution, in lung cancer. Additionally, recent research efforts have sought to elucidate the distinct characteristics of and mechanisms involved in lung cancer among never smokers. Continued research on non-smoking lung cancer is critical to identifying new opportunities for intervention and addressing the global burden of lung cancer.

Key words: lung cancer, air pollution, prevention

Introduction

The story of lung cancer in the twentieth century has been dominated by the growth of the mass-produced cigarette. A familiar dynamic played out across many countries where a rise in cigarette smoking was followed, decades later, by a rise in lung cancer mortality. Eventually, as countries implement tobacco control measures, lung cancer mortality began to decrease [1]. In Poland, lung cancer mortality tripled among men between 1960 and the 1980s, but then began to fall as smoking dropped in response to the economic crisis of the 1980s and the tobacco control efforts of the 1990s [2]. By 2015, lung cancer mortality had nearly returned to the level it had been in 1960 (though this drop has not been seen among women to date) [3]. Worldwide, lung cancer incidence is twice as high on average among men compared with women, though this ratio varies across countries, and three to four times higher in transitioned versus transitioning economies. Thus, for example, the 2020 age standardized incidence rate per 100,000 for lung cancer among men varies from 49 in Eastern Europe to 2.8 in Western Africa [4]. These differences largely reflect trends in cigarette smoking; in the future these patterns may change as the number of cigarette smokers is projected to rise in Africa while it decreases in Europe.

However, it is estimated that at least one quarter of global lung cancer cases occur among non-smokers, though this proportion varies across populations with estimates ranging from less than 20% in the United States [5] to 40% or higher in Asia and Africa [6]. Recent headlines have called attention to an apparent rise in lung cancer among younger nonsmokers [7]. While it is not clear whether incidence of non-smoking lung cancer is in fact increasing, the reduction in cases attributable to smoking means that a greater proportion of new lung cancer cases are being diagnosed among non-smokers. This has, in turn, brought attention to other causes of lung cancer, from environmental exposures such as radon and air pollution [8].

Lung cancer is the leading cause of cancer mortality worldwide and is second only to female breast cancer in incidence. Among men, lung cancer remains the most frequently diagnosed form of cancer. In 2020 there were over 2.2 million new cases and around 1.8 million deaths, accounting for 11.4% of overall cancer incidence and 18% of deaths [9]. An estimated

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10–20% of lung cancers occur in non-smokers, yet this proportion varies widely across countries and populations. For example, in Asia the proportion of lung cancer attributable to smoking is estimated to be much lower, particularly among women where the majority of lung cancers occur in non--smokers [6]. Additionally, patterns of lung cancer attributable to smoking are changing over time; while lung cancer mortality attributable to smoking has been decreasing in the U.S. and Europe, it is increasing in other parts of the world, particularly in many low- and middle-income countries [10]. Thus, this paper seeks to summarize current knowledge and important questions around environmental causes of lung cancer.

History

Before the twentieth century, lung cancer was a very rare disease. It first attracted attention as an occupational disease of miners. Cobalt and nickel miners in Schneeberg, Saxony, had long been known to suffer from lung disease, referred to as "Schneeberg mountain sickness." In 1879, German physicians F.H. Harting and W. Hesse, conducted autopsies on 20 miners and described a pulmonary malignancy found in three quarters of them. It was not until the 1950s that radon exposure was understood to be the cause, but the Harting and Hesse work was significant in linking lung cancer to an external environmental exposure [11].

As lung cancer rates rose rapidly during the first half of the twentieth century, a number of potential culprits were suggested, including automobile exhaust, road tar, and industrial pollution, in addition to cigarette smoking. For example, lung cancer was more common among those who lived in urban, rather than rural areas, which suggested that the density of automobiles or industrial pollution could be important factors. Early epidemiologic studies of lung cancer used the case control method: investigators compared the smoking habits of a group of lung cancer patients with another group without lung cancer. The case control method was particularly useful where very little was known about disease etiology, as was the case for cancer, because it allowed investigators to make comparisons on countless suspected agents. But the strength of the relationship between cigarette smoking and lung cancer was so strong that it soon overshadowed other factors [12].

At the same time, however, air pollution was gaining attention as a growing public health threat. In the U.S., during a smog episode at Donora, Pennsylvania, in 1948, at least 20 people died, and thousands suffered adverse respiratory effects triggered by a combination of weather conditions and pollution generated by a nearby steel plant. Additionally, Los Angeles, New York, and other cities were also facing growing challenges with air pollution. The 1955 Air Pollution Control Act, the first national legislation on air pollution, established a nationwide air sampling network to provide valuable data. Epidemiologist and occupational health expert Thomas Mancuso of the Ohio State Department of Health argued that air pollution was a likely contributor to urban lung cancer, emphasizing that urban areas were associated with higher lung cancer incidence even after accounting for cigarette smoking. In 1958, headlines in the national news warned – "US links cancer to air in cities", "Dirty air linked to cancer – aid seeks health drive", "smog is termed a cancer cause".

In June 1962, the U.S. Surgeon General released a 450-page report on motor vehicles, air pollution, and health. The report described statistical studies comparing lung cancer mortality across different cities and urban versus rural conditions, noting that the patterns recorded could not be entirely explained by differences in smoking prevalence. "It would appear, therefore, that there is evidence that air pollutants, related to vehicular emissions, play a role, at least as a co-factor, in the production of lung cancers under these conditions," the report concluded [13]. It is noteworthy that this report appeared two years before the landmark 1964 report of the Surgeon General on Smoking and Health in 1964, which concluded that smoking is a cause of lung cancer [14]. Both reports did eventually lead to policies controlling tobacco smoking and air pollution, though the 1964 report on smoking generated much more attention at the time.

Environmental causes

The International Agency for Research on Cancer (IARC) has identified several environmental exposures associated with lung cancer as known human carcinogens. Outdoor air pollution (including particulate matter in air pollution), diesel exhaust, radon, household coal combustion, secondhand smoke, and asbestos are all classified as class 1 carcinogens for which sufficient evidence is available of their carcinogenicity in humans [15]. Additionally, a range of air pollutants, such as polycyclic aromatic hydrocarbons, have been individually reviewed for carcinogenicity by IARC since the 1980s.

When IARC first classified outdoor air pollution and particulate matter as class 1 carcinogens in 2013, they cited the findings from large case control and cohort studies dating back to the 1970s [16]. The American Cancer Prevention Study, for example, followed over 500,000 people for over 20 years. The European Study of Cohorts for Air Pollution Effects (ESCAPE) study was also cited. These large cohort studies were important for having detailed information on cigarette smoking to rule it out as a potential confounder. Additionally, the IARC report cited other forms of evidence supporting the effects of air pollution on cancer. In particular, ambient air pollution contains specific chemical agents known to cause cancer (including arsenic, cadmium, benzene, beryllium, and polycyclic aromatic hydrocarbons, such as benzo[a]pyrene), and human exposure to outdoor air pollution is associated with forms of genetic damage that are predictive of cancer in humans.

However, characterizing the burden of lung cancer attributable to air pollution, distinct from cigarette smoking, remains

challenging. According to estimates from the Global Burden of Disease, the proportion of lung cancer deaths worldwide attributable to outdoor ambient PM2.5 (known as "fine particulate matter") air pollution was 14% in 2017, ranging from 4.7% in the United States to 20.5% in China [17]. A recent meta-analysis of the relative risk of lung cancer associated with PM2.5 exposure showed a higher risk for former smokers and never smokers compared with current smokers; the authors suggested that this may be due to the effect of PM2.5 being obscured by cigarette smoking in current smokers [18]. In another meta-analysis, Huang and colleagues, using data from 17 studies from different countries, found a relative risk of 1.11 for each 10 $\mu g/m^3$ increase in exposure to PM2.5; in other words, each 10 $\mu g/m^3$ unit increase in PM2.5 exposure was associated with an 11% increase in lung cancer [19]. However, as this was a pooled estimate based on multiple studies, the actual relative risk may vary across countries with different exposure patterns and competing risks. For example, relative risks tended to be higher in studies from Asia compared with Europe.

While radon is also a known cause of lung cancer, there remains controversy over the extent of the burden. Radon exposure has been clearly linked to lung cancer among uranium miners who experience high levels of occupational exposure. However, the level of radon exposure in homes is much lower and the extent of its role in the development of lung cancer remains unclear. In a meta-analysis of 13 case control studies, the authors estimated the excess risk associated with home-based exposure to radon across different exposure levels. They found excess risk associated with home exposure and also concluded that the risk from radon was 25 times higher among smokers compared with non-smokers. Based on this information, the authors estimated that radon exposure might be responsible for up to two percent of lung cancer deaths in Europe [20].

Causes of lung cancer may also act together through synergistic interactions to increase risk. Under a multicausal model, environmental exposures may interact with cigarette smoking to multiply the risk of lung cancer. For example, as early as the 1960s it was noted that while occupational exposure to asbestos and cigarette smoking were associated with lung cancer, those who smoked and also worked with asbestos had many times the lung cancer risk of those only exposed to one of the two carcinogens [21]. Thus, while it is correct to say that smoking causes most cases of lung cancer, environmental exposures can also contribute substantially and should not be underestimated. Recent attention to the potential long term health impacts of climate change also highlights the importance of continuing to monitor air pollution and other environmental factors for lung cancer [22].

Non-smoking lung cancer

There has been increased attention to understanding lung cancer in never smokers (typically defined as those who have smoked less than 100 cigarettes in their lifetime), though research remains limited. Because lung cancer has been so strongly linked to cigarette smoking, non-smoking patients are particularly confused to learn about their diagnosis and seek answers. One important analysis, derived from 35 databases around the world (13 cohorts and 22 cancer registries on lung cancer), indicates that death rates among never-smokers with lung cancer are greater in men, African Americans, and Asians living in Asia, compared with those of European ancestry [23].

Courad and colleagues [24] reported the results of one of the largest prospective European trials conducted in lung cancer in never-smokers (defined as less than 100 cigarettes in a lifetime). The study recruited 384 French patients in 75 participating centers, each individually contacted to perform an interview on risk exposure. The authors showed that 13% of patients had been exposed to at least one occupational carcinogen (men 35%, women 8%), whereas domestic exposure (passive smoking and cooking oil) was higher in women (41% *versus* 18% for exposure to cooking oil fumes). Domestic exposure to passive smoking, 62% of which began during childhood, was significantly more frequent among women than men (64% *versus* 38%). Overall, it appears men are more exposed to occupational carcinogens and women more exposed to domestic carcinogens.

More than one third of all newly diagnosed lung cancers and nearly 40% of deaths globally occurred in China, and the number is expected to increase in the future [25]. While smoking prevalence is high among men in China, it is very low among women, who also suffer a high burden of lung cancer. High lung cancer mortality among non-smoking women in China has been attributed to household air pollution from cooking and the use of coal for heating [26]. Lung cancer among women in China has historically been higher in the northeast of the country, where indoor heating exposure would be expected to be higher [27, 28]. Geographic studies have also linked ambient air pollution levels to lung cancer mortality in China [29]. A recent analysis also estimated that (based on 2,005 figures) 13.7% of lung cancer deaths (10% for men and 18% for women) could be attributed to PM2.5 exposure [30].

There are two primary forms of lung cancer:

- small cell lung cancer, which is found almost exclusively in cigarette smokers, and
- non-small cell lung cancer, which is the most common form of lung cancer, and appears in smokers and non-smokers.

Adenocarcinoma, the most frequent type of non-small cell lung cancer, starts in the cells of mucus making glands in the lining of the airways. Recent reports in popular media have highlighted "a surge in 'non- smoking' lung cancer" in China [31], noting a rise in adenocarcinoma relative to other lung cancer subtypes since 2000. While the increase in adenocarcinoma has been attributed by some to high levels of ambient air pollution

in China, this shift is likely partly explained by changes in cigarette smoking behavior. A similar shift in lung cancer histology was seen in previous decades in the U.S. and European countries and attributed to changes in cigarette design [32]. During the 1960s and 1970s, tobacco companies increasingly marketed "light" and low-tar cigarette brands with lower machine-measured levels of tar and nicotine, and these brands came to dominate the market in large part due to the perception that they were less harmful than other cigarettes. As smokers switched to low-tar cigarettes, they tended to inhale more deeply, transporting carcinogens more distally into the lungs where adenocarcinomas arise. At the same time, greater use of reconstituted tobacco, with higher concentrations of nitrosamines, may have also contributed to a shift towards adenocarcinomas. China has experienced a similar shift towards "low tar" cigarettes, though more recently. Thus, it is likely that the increase in adenocarcinomas relative to other lung cancer subtypes is attributable, at least in part, to changes in cigarette design and smoking behavior. At the same time, long term air pollution exposure may also account for some portion of adenocarcinomas [33]. A similar pattern has been seen in other LMICs, such as India, and also linked to tobacco use patterns [34].

There is increasing documentation that lung cancer in never smokers is different from lung cancer seen in smokers. For example, in Taiwan, where never smoking patients are predominant (53%), especially among females (93%), lung cancer tends to have an earlier onset at younger ages with a predominance of *EGFR* mutations [35]. Recent studies have revealed that lung cancer in never smokers exhibits a distinct pattern of oncogenic mutations and a distinct natural history compared with lung cancer caused by smoking [36]. Last year, an international team of researchers, led by investigators at the National Cancer Institute, completed whole genome sequencing of tumor and normal tissue from 232 never smokers diagnosed with non-small cell lung cancer (primarily adenocarcinomas). By looking at patterns of mutations, they identified three distinct subtypes of lung cancer in never smokers:

- the "piano" subtype, which has the fewest mutations and grows very slowly,
- the "mezzo-forte" subtype, which exhibits chromosomal changes and mutations in the growth factor receptor gene *EGFR*, and
- the "forte" subtype, which exhibits a phenomenon known as whole genome doubling, typically seen in lung cancer in smokers [37].

These findings provide clues to the origins of these distinct tumor subtypes and might help to develop treatments that target specific pathways through which these cancers develop. Another genomic study, comparing adenocarcinoma cells from smoking and never-smoking lung cancer patients, found that the tumors from never-smokers were more likely to contain driver mutations, alterations in certain genes that drive oncogenesis. A number of clinical therapies have been developed recently that target driver mutations and show promise for treating lung cancer [38].

A new study from investigators at the Francis Crick Institute recently provided some novel findings on the mechanisms by which air pollution may cause lung cancer. The researchers observed that cancer-driving mutations in *EGFR* genes found in lung cancer are also frequently present in normal tissue in patients without cancer, suggesting that some additional step was involved. They hypothesized that inhaled PM2.5 particles produced an inflammatory response in the lungs which activates the mutated cells. They tested this idea in mice with *EGFR* mutant cells and found that the mice exposed to air pollution were more likely to develop lung cancer than those not exposed [39]. The findings depart from the conventional model that cancer develops from an accumulation of mutations due to repeated air pollution exposure. While the mutations are a necessary step in the process, air pollution may in fact cause lung cancer through a different route, by triggering an inflammatory response. These findings are also noteworthy because they suggest another possible route for intervention to prevent cancer through controlling the immune response.

Discussion

The growth in lung cancer caused by environmental exposures seen in non-smokers is likely to continue under current trends. Both indoor and outdoor air pollution are important contributors to the global burden of lung cancer, and multiple exposures may interact together in a synergistic manner. However, reducing exposure to air pollution should reduce the future lung cancer burden. That said, while strategies exist to reduce exposure, implementing these measures involves additional challenges which should be addressed through further research. For example, the use of cleaner cooking stoves could reduce indoor air pollution exposure, but large-scale replacement of home stoves with new stoves and fuel requires education and support for adoption [40]. Future research in implementation science can help address this gap between discovery and public health impact.

Greater efforts are needed to reduce the global burden of lung cancer. According to the Surveillance, Epidemiology, and End Results (SEER) database, maintained by the U.S. National Cancer Institute, the 5-year survival rate for patients with lung cancer is 26% (though it rises to 64% when identified at a localized stage). This figure reflects the experience in the United States, but may be different in other countries, particularly where capacity for diagnosis is limited. Regular screening for lung cancer with low-dose computed tomography has so far only been shown to be beneficial in high-risk patients with a history of cigarette smoking [41]. Moreover, while there have been some efforts to amplify the voices of lung cancer patients, lung cancer has not received the focused advocacy and attention other cancers have. Lung cancer patients are

more likely to experience stigma; while experience may differ between smoking and non-smoking patient, patients report discomfort sharing a lung cancer diagnosis regardless of their smoking history [42].

Conclusions

The good news is that ongoing research continues to elucidate the mechanisms of lung cancer and suggest new opportunities for intervention. As recent work on the role of air pollution in *EGFR*-mutant cancers shows, there is still more to learn about how environmental exposures cause lung cancer. Increased understanding of these cancers, and the distinct characteristics of non-smoking lung cancer, may reveal new approaches to address the global burden of lung cancer.

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