Respiratory cancers and pollution

N. DING, N. ZHOU, M. ZHOU, G.-M. REN

Department of Respiratory, Xuzhou First People’s Hospital, Xuzhou, Jiangsu, China

Abstract. – BACKGROUND: Cancer is the major public health problem worldwide, irrespective of the socio-economic status of the countries. Even though the overall mortality from cancer is higher in the western countries, the cancer burden is on the rise in under-developed countries, with a projected 81-100% increase by 2030, mostly due to pollution and tobacco use. Respiratory cancers affect the lung, larynx, trachea, and bronchus and depending on the location of the cancer, the symptoms change and also the risks, incidence and survival outcomes differ accordingly. Besides tobacco use, chronic exposure to household pollution is known to be associated with elevated risk of lung cancer and other cancers. Women and children living in severe poverty in the underdeveloped countries are exposed most to household air pollution and, thus, suffer its consequences maximally, and household air pollution, specifically arising from solid fuel burning, which accounts for nearly 4 million deaths throughout the world annually. Cancers affecting the respiratory tract, including both nasopharyngeal cancer and lung cancer, are strongly associated with pollution from coal and other solid fuel burning. Lung cancer, which is of two types, small cell lung carcinoma and the non-small cell lung cancer, is the most common and fatal cancer. Even though tobacco has been viewed as the major risk for respiratory cancers, it is now evident that household pollution, exposure to asbestos, chromium and arsenic etc, all pose a significant risk for respiratory cancers. Preventive steps to curtail the many sources of air pollution by improving living conditions and reducing the occupational exposure hazards like welding, industrial work etc., are markedly needed to control the incidence of respiratory cancers.

Key Words: Respiratory cancers, Asbestos, Household pollution, Lung cancer, Mesothelioma, Fuel burning, Laryngeal cancer, Upper airway cancers, Multiple primary lung cancer.

Introduction

Cancer is the major public health problem worldwide, both high-income countries and under-developed countries. Even though studies on cancer statistics indicate that the overall mortality from cancer is higher in the high-income countries, with the spread of tobacco use, the cancer burden is on the rise in under-developed countries, with 81-100% increase projected by 2030, in comparison to 2008. Besides tobacco use, household pollution is a relatively major threat to health in under-developed countries. It is important to realize that each day approximately 3 billion people worldwide are exposed to toxic levels of household pollution that comes from the use of solid fuels, such as biomass fuels and coal for combustion, which causes the release of toxic levels of carbon monoxide and particulate matter. Long-term exposure to household pollution is known to be associated with elevated risk of lung cancer and other cancers. The major environmental cause of death worldwide is air pollution, in particular, the household air pollution, which accounts for nearly 4 million deaths annually and women and children living in severe poverty in third world countries are exposed most to household air pollution and, thus, suffer its consequences maximally. Cancers affecting the respiratory tract, including both nasopharyngeal cancer (Figure 1) and lung cancer, are strongly associated with pollution from coal and other solid fuel burning. Respiratory cancers include cancers of the lung, larynx, trachea, and bronchus and depending on the location of the cancer, the symptoms change. The risks, incidence and survival outcomes differ considerably.

Laryngeal Cancer

Laryngeal cancer incidence is more frequent in men than in women and there is expected geographical variation in its incidence. While most laryngeal cancers are squamous and originate in the glottis region, supraglottic and subglottic tumours are rare. The disease mainly affects elderly people and it has been observed that the age-standardized relative survival rate was 84% after 1 year and 64% after 5 years among male patients diagnosed in 2000-2001, and this survival
improved significantly since the 1980s. Even though the incidence of laryngeal cancer is lower among women, survival was poorer than for men8. As for all the respiratory cancers, tobacco is the main risk factor for laryngeal cancer and a combination with alcohol has a synergistic effect on the risk of laryngeal cancer9.

**Lung Cancer**

Lung cancer is the leading cause of cancer mortality worldwide than any other cancer, with 18 million new cases and 15 million deaths in 201210. Lung cancer is the most common cancer among men in most countries and is on the increasing trend among women, being the third most common cancer in women after breast and colorectal cancers, particularly in Western countries11. Age-standardized incidence is higher in industrialized countries (30.8 per 100,000 person-years) as compared with under developed countries (20.0 per 100,000), although countries such as China have higher incidence rates (36.1 per 100,000)6. Since lung cancer is often fatal, the trends in incidence and mortality are closely similar12. Overall trends of both incidence and mortality among men reached a plateau in the early 1970s, and since then there has been a decline in both12. On the other hand, increasing lung cancer trends were seen in women till the end of the 1980s, after which the rates remained stable. Lung cancer as a cause tops the cancer-related deaths worldwide, despite significant advances in the diagnostic, therapeutic, and supportive care strategies13.

There are two types of lung cancer, the small cell lung cancer (SCLC; or oat cell cancer), which accounts about 20% of all lung cancer cases and the non small cell lung cancer (NSCLC), which accounts for ~80% cases14. SCLC, even though less common, is highly tumorigenic and metastatic in the primary and secondary bronchi, and strongly relates to smoking15. Histologically, non-small-cell type comprises 80-85% of all lung neoplasms, and this includes three major sub-types, viz., adenocarcinoma (40%), squamous cell carcinoma (25%), and large cell lung carcinoma (15%)16. Nearly 70% of the patients with non-small-cell lung cancer (NSCLC) present locally advanced or metastatic disease at the time of diagnosis16. The concept of multiple primary lung cancer (MPLC) has been developed as the patients who received successful treatments for NSCLC or SCLC have a high risk of developing a secondary metastatic tumor at a distant site through the lymphatic or circulatory system14. Second primary tumors can be either synchro-
nous, i.e., they are detected/resected simultaneously or metachronous, i.e., they are detected subsequent to the primary lesion. There is approximately 1-15% risk of developing MPLIC per patient per year \(^{17-19}\), according to the Martini and Melamed criteria for diagnosing second primary lung cancers. The Martini and Melamed criteria\(^ {20}\) are defined on the basis of tumor characteristics, including morphology, location, presence or absence of carcinoma in situ, vascular invasion and metastasis. However, these criteria cannot differentiate between metastasis and a second primary lung cancer\(^ {21}\). Despite the introduction of diagnostic procedures that are more sensitive, including CT or positron emission tomography scanning and fluorescence endoscopy to improve the detection of MPLIC, there are no uniform guidelines for MPLIC diagnosis\(^ {22}\). It has been recommended that the use of clinicopathological criteria together with genetic profiling\(^ {23}\) is a better approach for differentiating between independent and clonal tumors\(^ {24}\).

**Mesothelioma**

Mesothelioma is a rare cancer that develops from the mesothelium, the protective lining that covers many of the internal organs, in particular, the pleura. There has been a steady rise in the number of mesothelioma deaths since the 1960s. Mesothelioma is also more common in men who account for \(\sim 85\%\) of mesothelioma-related deaths each year\(^ {25}\). There is nearly 30-40 years latency for this cancer because of which most cases occur at older ages, and the survival is very poor\(^ {6}\). A recent retrospective study from Turkey on 400 mesothelioma patients showed that asbestos and erionite exposure is a major risk for malignant pleural mesothelioma\(^ {26}\).

**Upper Airway Cancers**

Upper airway cancers are relatively less common than lung cancer in developed countries. However, about 70% of all the upper airway cancer cases diagnosed worldwide occur in underdeveloped countries. According to the International Agency for Research on Cancer, in the year 2012, the estimated new cases of upper airway cancers were about 386,000, with 230,000 deaths\(^ {6}\). The tumors of the larynx and nasopharynx accounted for 63% of all cases and 58% of deaths. The major risk factors for upper airway cancers include the use of tobacco and alcohol\(^ {27}\). The strong geographical variation of upper airway cancers, in particular nasopharyngeal carcinoma, can partially be due to differences in genetic susceptibility\(^ {28}\) and the nature of viral infections\(^ {29}\).

**Respiratory Cancer Risks**

Several epidemiological studies linked Chromium (VI) compounds, including the chromates of potassium, sodium, calcium, and strontium, to lung cancer and thus these compounds have been classified as human carcinogens by the International Agency for Research on Cancer (IARC). Besides, in vivo studies in experimental animals and in vitro mutagenicity and genotoxicity assays provided strong support for this conclusion and a tolerable limit for Cr (VI) concentration of \(\sim 1\) mg/m\(^3\) workplace is suggested based on several studies\(^ {30}\).

Tobacco is the main risk factor for laryngeal cancer and exerts a synergistic effect on the risk of laryngeal cancer when combined with alcohol\(^ {7}\). Similar risk is also associated with upper airway cancers\(^ {27}\). The role of asbestos and laryngeal cancer remains controversial and several studies concluded that the evidence for such association is weak and that increased risk seen in some studies can be due to insufficient adjustment for alcohol and tobacco consumption\(^ {31}\). About 96% to 98% of mesothelioma cases in men are due to asbestos exposure\(^ {32}\). There is considerable evidence showing increased lung cancer in asbestos-exposed workers.

It is generally considered that the overwhelming risk factor for lung cancer is cigarette smoking\(^ {33}\), which probably accounts for \(\sim 90\%\) of the disease burden in developed countries\(^ {16}\). However, in many underdeveloped countries, where the smoking epidemic is relatively recent, but there is widespread use of solid fuels, causing emissions that can account for \(\sim 17\%\) of all lung cancer deaths in men and 22% in women\(^ {34}\). Several studies conducted in China, India, Nepal, Taiwan and Japan showed that individuals exposed to coal smoke had a greater risk of lung cancer compared with people exposed to wood and mixed solid fuels\(^ {1}\). Among the subtypes of lung cancer, adenocarcinoma but not the squamous-cell carcinoma to be significantly associated with ambient particulate air pollution\(^ {35}\). Studies showed that carcinogenicity of different types of coal could vary significantly. For example, a large retrospective cohort study that followed 20,000 residents from Xuanwei county in southwestern China for 20 years during 1976-96, observed that the use of bituminous coal in-
creased lung cancer mortality by 36-fold in men and 99-fold in women compared with anthracite coal users.

Emissions from burning coal and those from solid fuels have been classified as known (group 1) carcinogens and as probable (group 2A) carcinogens by IARC (Table I). In 2000, approximately 200 million people used coal for household cooking in east Asia, in particular, from China and ~25 million from south Asian countries. Even though, the proportion of people using solid fuel in urban China has decreased significantly over the last two decades, from 64% in 1990, to 46% in 2010, nearly two-thirds of people still use solid fuels for cooking and heating in rural China. While mainly two types of coal, the predominantly smoky coal (bituminous coal), and the smokeless coal (anthracite, which is low in sulfur but high in carbon) are used in China, the use of wood is more common in south Asian countries, particularly India, Pakistan, Bangladesh, and Nepal and also sub-Saharan African countries. Nearly 30% of the total solid fuel worldwide is used in India alone. Considering that the emissions from the solid fuels contain high levels of various carcinogens, it is quite possible that prolonged exposure of people to higher doses of smoke imposes a greater risk of developing cancer.

There are differences in the types of coal on the basis of the types of emission products such as the volatility levels of benzene and formaldehyde, which vary the carcinogenicity. Thus, the emissions from bituminous coal have higher carcinogenic potential as they have increased polycyclic aromatic hydrocarbons, silica, nickel, and arsenic contents than the emissions from other types of coal such as anthracite.

### Mechanism of Coal and Wood Smoke Mediated Carcinogenesis

Polycyclic aromatic hydrocarbons with inhalable particles, volatile organic compounds, and some metals are the main carcinogenic components released from solid fuel (Table I). While the insoluble particles entering the extra-thoracic or tracheal regions are cleared by mucociliary mechanisms or via exhalation, those in alveolar regions likely undergo chemical transformations and lead to tumor formation following the uptake of particles by phagocytes and other cells. The deposited particles potentially initiate sustained inflammation, cell injury, cell proliferation, depletion of antioxidants, elevated production of reactive oxygen species, and gene mutation. Polycyclic aromatic hydrocarbons absorbed through the respiratory tract get distributed to most tissues, and are metabolized to epoxides, phenols, dihydrodiols, phenol dihydrodiol epoxides, quinines, and tetrals, which are known to bind the nitrogen bases in DNA and cause deleterious mutations and eventually transformation of the cell to a cancerous phenotype.

It has been suggested that inflammation is part of the etiology underlying cancer and that measuring inflammation using a marker such as suPAR (plasma-soluble urokinase plasminogen activator receptor) along with the established risk factors, such as age, sex, smoking, and alcohol consumption, could improve cancer risk stratification.

### Conclusions

Respiratory tract cancers, including nasopharyngeal cancer, mesothelioma and lung cancer,
are strongly associated with tobacco use and air pollution, in particular, from household coal and other solid fuel burning. Considering that each day nearly 3 billion people, mostly women and children worldwide are exposed to toxic levels of household pollution that comes from the use of solid fuels, the enormity of the respiratory cancer problem in under developed countries cannot be ignored. Besides, because of the improved diagnostic and surveillance measures there is an increase in the number of multiple primary lung cancer cases being identified worldwide among the ageing population. Lung cancer is the most common and fatal cancer whose risk is dependent not only on tobacco and household pollution but also on asbestos, chromium and arsenic, etc., which pose a major occupation-related risk. Overall attempts to curtail the many sources of air pollution by improving living conditions and reducing the hazards from occupations like welding, industrial work, etc. are desperately needed to control the incidence of respiratory cancers.

**Conflict of Interest**

The Authors declare that there are no conflicts of interest.

**References**


