

Respiratory cancers and pollution

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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 un-

der-developed countries. Even though studies on cancer statistics indicate that the overall mortality from cancer is higher in the high-income countries¹, 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 2008². Besides tobacco use, household pollution is a relatively major threat to health in under-developed countries³. 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^{4,5}. 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 maximally⁶. 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 rare⁷. 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 2000-2001⁸, and this survival

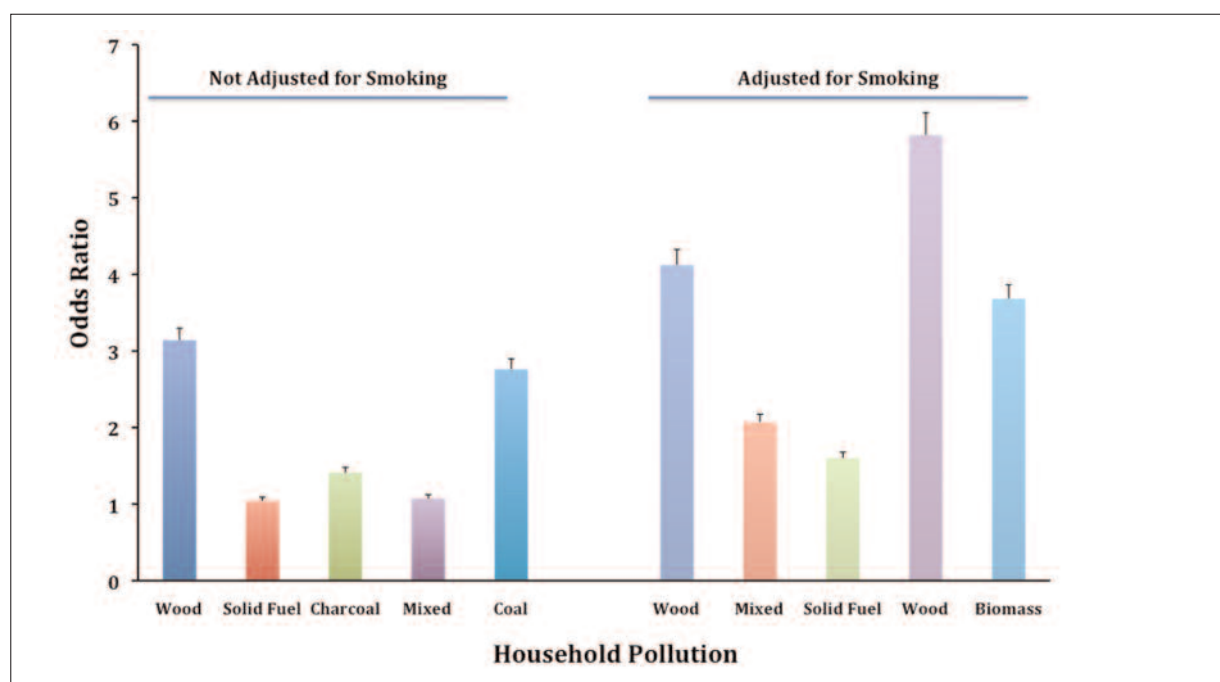


Figure 1. The link between nasopharyngeal cancer and exposure to household air pollution without and with adjustment for tobacco smoking status, expressed as Odds Ratio.

improved significantly since the 1980s. Even though the incidence of laryngeal cancer is lower among women, survival was poorer than for men⁹. 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 1.8 million new cases and 1.5 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 both⁹. 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 subtypes, 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 MPLC per patient per year¹⁷⁻¹⁹, according to the Martini and Melamed criteria for diagnosing second primary lung cancers. The Martini and Melamed criteria²⁰ 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 cancer²¹. 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 MPLC, there are no uniform guidelines for MPLC diagnosis²². It has been recommended that the use of clinicopathological criteria together with genetic profiling²³ is a better approach for differentiating between independent and clonal tumors²⁴.

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 ~85% of mesothelioma-related deaths each year²⁵. There is nearly 30-40 years latency for this cancer because of which most cases occur at older ages, and the survival is very poor⁹. A recent retrospective study from Turkey on 400 mesothelioma patients showed that asbestos and erionite exposure is a major risk for malignant pleural mesothelioma²⁶.

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 under developed 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 deaths⁶. 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 alcohol²⁷. The strong geographical variation of upper airway cancers, in particular nasopharyngeal carcinoma,

can partially be due to differences in genetic susceptibility²⁸ and the nature of viral infections²⁹.

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 ~1 mg/m³ workplace is suggested based on several studies³⁰.

Tobacco is the main risk factor for laryngeal cancer and exerts a synergistic effect on the risk of laryngeal cancer when combined with alcohol⁹. Similar risk is also associated with upper airway cancers²⁷. 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 consumption³¹. About 96% to 98% of mesothelioma cases in men are due to asbestos exposure³². 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 smoking³³, which probably accounts for ~90% of the disease burden in developed countries¹⁶. However, in many under developed countries, where the smoking epidemic is relatively recent, but there is widespread use of solid fuels, causing emissions that can account for ~17% of all lung cancer deaths in men and 22% in women³⁴. 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 fuels⁴. Among the subtypes of lung cancer, adenocarcinoma but not the squamous-cell carcinoma to be significantly associated with ambient particulate air pollution³⁵. 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 users³⁶.

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 China³⁷ 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 2010³, nearly two-thirds of people still use solid fuels for cooking and heating in rural China³⁸. 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 alone⁴. 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 cancer³⁸. 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 carcinogenicity³⁸. 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 anthracite³.

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 tracheothoracic 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 tetrols, which are known to bind the nitrogen bases in DNA and cause deleterious mutations and eventually transformation of the cell to a cancerous phenotype³⁹. It has been suggested⁴⁰ that inflammation is part of the etiology underlying cancer and that measuring inflammation using a marker such as sPAP (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,

Table I. Compounds present in emissions from combustion of wood or coal.

Polycyclic aromatic hydrocarbons, organic compounds or metals	Emission source	Carcinogenicity assessment		
		IARC Group	Humans	Animals
Benz(a)anthracene	Wood and coal	2B*	Inadequate	Sufficient
Benzo(b)fluoranthene	Coal	2B	Inadequate	Sufficient
Benzo(a)pyrene	Wood and coal	1	Inadequate	Sufficient
Cyclopenta(c,d)pyrene	Coal	2A	Inadequate	Sufficient
Benzene	Wood and coal	1	Sufficient	Sufficient
Formaldehyde	Wood and coal	1	Sufficient	Sufficient
Arsenic	Wood and coal	1	Sufficient	Sufficient

*International Agency for Research on Cancer carcinogenicity groups: 2A, probably carcinogenic to human beings; 2B, possibly carcinogenic to human beings; 1, carcinogenic to human beings.

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.

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