EDITORIAL

A to J Risk Factors for Lung Cancer: The Terrible Ten

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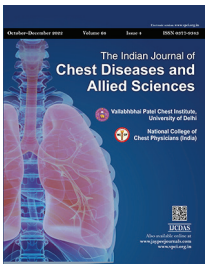

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Abbreviations used in this Article

LC = Lung cancer; LDCT = Low-dose computed tomography; PAH = Polycyclic aromatic hydrocarbons; RR = Relative risk; ER = Estrogen receptors.

To the Editor,

Lung cancer (LC) is the most common and deadliest cancer in the world. Low-dose computed tomography (LDCT) of the lung is a proven strategy for the screening of lung cancer. However, due to issues such as cost, logistic constraints, and concerns regarding high false-positive rates owing to wider prevalence of tuberculosis, it is seldom used in developing countries.[1] In the absence of screening, only a sound understanding of the complex epidemiological, etiological, and molecular-pathological aspects of LC will enable clinical and scientific progress against this deadly disease, regardless of technological advances. We hope this letter will be particularly helpful to the residents and specialists to broaden their knowledge and easily remember these terrible 10 risk factors (Table 1) for the comprehensive management of LC.

*A*sbestos, *A*lcohol, and *A*ir Pollution

Exposure to asbestos in all forms (amphiboles more than chrysotile) is a proven risk factor for LC.[2] In India, occupational exposure to asbestos among firefighters, industrial workers, shipyard, and construction-site workers still exists as a major risk factor for LC, besides occupational lung diseases (asbestosis, pleural plaques, and pleural effusion) and malignant mesothelioma of the pleura. Alcohol intake is associated with smoking and thus is difficult to directly attribute as a risk factor for LC. However, heavy alcohol consumption may lead to an increased risk of LC independent of smoking.[3] Air pollution includes a variety of sources, including motor vehicles, industries, wood, and kerosene stove burning (still prevalent in rural India), all of which can generate toxic polycyclic aromatic hydrocarbons (PAH), which are carcinogenic. Exposure to combustion-related fine particulate matter air pollution (PM 2.5) is an environmental risk factor for lung cancer and cardiopulmonary mortality.[4]

Table 1: "A to J" risk factors for lung cancer

A	Asbestos, alcohol, and air pollution
B	Burning of coal
C	Cigarette smoking and second-hand smoke
D	Diesel exhaust and diet
E	E-cigarette, exposure to radon, and emphysema
F	Family history
G	Genetic
H	Hormonal – estrogen
I	Ionizing radiation, infections, and injury to lung
J	Jobs related – occupational exposures to arsenic, silica, and chromium

*B*urning of Coal

Coal is still used as a fuel for indoor and outdoor cooking and locomotives, even though the developed countries have shifted to nonconventional sources of energy. Coal burning can lead to an increased release of PAH, benzo[a]pyrene, and fine particulate matter, all of which are carcinogenic. This led to the International Agency for Research on Cancer classifying household combustion of coal as carcinogenic (group I) to humans.

*C*igarette Smoking and second-hand Smoke

Cigarette smoking has been associated with LC for generations. Although cigarette smoking is most common, the risk for LC also persists with smoking pipes, cigars, hookahs, etc. In fact, the risk of LC is higher with use of Bidis and Hookahs, which may also be the reason for the shift from squamous cell carcinoma to adenocarcinoma as the most common type of LC in current times. A plausible explanation is that these forms of smoking require

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deeper inhalation causing carcinogens to go to the periphery of the lung causing adenocarcinoma. All pathological types of LC have smoking as a common risk factor. Passive smoking, also called second-hand smoke, carries a risk of developing lung cancer. In the case of a smoking spouse, this risk is probably related to the number of cigarettes smoked [relative risk, (RR) ¼ 1.1–3.4] and the number of years married (RR ¼ 0.9–3.3).[5]

*D*iesel Exhaust and *D*iet

Diesel exhaust exposure has been shown to increase the risk of LC by an odds ratio of 1.3 times.[6] Dietary habits such as a greater consumption of fruits and vegetables might have a protective role for LC, though the effect is doubtful. The association may be stronger for fruits than vegetables, and more robust for women than men. In addition, increased consumption of red meat, processed meat, meat mutagens, and oils can increase exposure of nitrosamines that can be potential carcinogens.[7]

E-cigarette, *E*xposure to Radon, and *E*mphysema

E-cigarette devices and vaping fluids demonstrably contain a series of both definite and probable substances, including nicotine derivatives and aldehydes/other complex organic compounds, which lead to LC. These arise both as constituents of the e-liquid and as a result of pyrolysis/complex organic reactions in the electronic cigarette device. Various studies demonstrate *in vitro*-transforming and cytotoxic activity of these derivatives. E-cigarette device use has been significantly increasing, particularly among the younger generations and nonsmokers, and is an area of significant concern for the future. Many countries have enforced a strict ban on the use of E-cigarettes solely based on this reason.[8] Radon, a heavy colorless and odorless radioactive natural gas, is present in the soil in many areas and also identified in concrete with a half-life of 3.8 days. The decay products, polonium 214 and 218, present radioactive hazards, which may accumulate on floors and in basements. The odds ratios for LC increase with increasing radon exposure, especially with mutations in p53. Residential exposure to radon can significantly increase the risk of LC in a dose–response manner.[9] Impaired pulmonary function, even in the absence of cigarette smoking, is associated with an increased risk of developing LC. There is an odds ratio of 1.9 association between both emphysema and LC.[10]

*F*amily History

In a patient of LC with a positive family history, the chances for a second primary lung malignancy are higher than those without (RR: 11 vs. 2.5, respectively). Rare Mendelian cancer syndromes of some tumor suppressor genes such as Li-Fraumeni syndrome, Bloom syndrome, and Werner syndrome are associated with a marked increased lung cancer risk, especially among tobacco smokers.[11]

*G*enetic Susceptibility

Since only approximately one in seven smokers develop LC, individuals probably differ in terms of their susceptibility to lung malignancy. Single-gene polymorphisms involving phase I and II enzymes of the xenobiotic metabolism and DNA repair mechanisms are involved in lung carcinogenesis, and those individuals could carry a higher risk if they concurrently smoke and have lower dietary intake of fruits and vegetables. In theory, a future application may be genetic screening for high-risk alleles as a basis for LC detection.[12]

*H*ormonal

Estrogen receptors (ER) are consistently found in LC tissues and cell lines, especially adenocarcinoma, and mostly in the form of the ER beta. Estrogen has been reported to adversely affect the prognosis of LC patients [ref]. Possible explanations that women may be more susceptible to LC than men include (i) involvement of ER beta in growth stimulation and differential expression of the X-chromosome-linked "gastrin-releasing peptide receptor" with earlier activation to tobacco exposure than in men.[13]

*I*onizing Radiation, *I*nfections, and *I*njury to Lung

The etiological role of infectious agents in the development of lung carcinoma is an intriguing area of clinical and epidemiological research. While strong associations are not present in LC, viruses (human papillomavirus, Epstein–Barr virus, and human immunodeficiency virus), bacteria (*Chlamydophila pneumoniae*, mycobacteria), or fungi (*Microsporum canis*) may play an etiological role in rare cases.[14]

*J*ob-related (Occupational)

The most important study on occupational exposure is a north European study covering 45 years, published in 2009. It included 15 million people aged 30–64 years from Denmark, Finland, Iceland, Norway, and Sweden. The cancer incidence data by occupational category analysis revealed the highest LC risk in male waiters, seamen, tobacco workers, miners and quarry workers, cooks and stewards, chimney sweeps, plumbers, and beverage-manufacturing workers.[15]

To conclude, LC has multiple risk factors that are not only limited to tobacco smoking. Whereas tobacco cessation programs have a long way to go, focusing on environmental exposures, air pollution, and stressing upon a healthy diet can also help prevent LC worldwide. Global focussed interventions are the need of the hour to mitigate and reduce the huge burden of morbidity and mortality due to LC.

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