Lung Cancer: A Brief Review

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ABSTRACT
The rate of mortality due to cancer in India is alarming with about 806000 existing cases by the end of the last century. Cancer is the second most common disease in India responsible for maximum mortality with about 0.3 million deaths per year. This is owing to the poor availability of prevention, diagnosis and treatment of the disease. All types of cancers have been reported in Indian population including the cancers of skin, lungs, breast, rectum, stomach, prostate, liver, cervix, esophagus, bladder, blood, mouth etc. The cause may be internal (genetic, mutations, hormonal, poor immune conditions) and external or environmental factors (food habits, industrialization, over growth of population, etc.). Lung cancer is the leading worldwide cause of cancer deaths. Smoking is the dominant cause of lung cancer and in the beginning of the century, lung cancer was considered to be rare but now it has reached epidemic proportions. Lung cancer is the uncontrolled growth of abnormal cells in one or both of the lungs. While normal cells reproduce and develop into healthy lung tissue, cancer cells reproduce faster and never grow into normal lung tissue. Cancer cells (tumors) formed grow and interfere with the lung functions. Cancer cells can spread from the tumor into the bloodstream or lymphatic system where they can spread to other organs. Novel chemoprevention strategies have proved to be promising. In view of these facts, the present article describes the status of lung cancer which is the most common cause of major cancer incidence and mortality in men, whereas in women it is the third most common cause of cancer incidence and the second most common cause of cancer mortality.

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INTRODUCTION:
In India, around 5,55000 people died of cancer in 2010, according to estimates published in the Lancet today [1]. Cancer is the second most common disease after cardiovascular disorders for maximum deaths in the world [2]. In spite of good advancements for diagnosis and treatment, cancer is still a big threat to our society [3].

Cancer begins when cells in a part of the body start to grow out of control or it is caused by unregulated proliferation of abnormal cells [4]. The abnormal cells are termed cancer cells, malignant cells or tumor cells. Many cancers and the abnormal cells compose the cancer tissue. Cancer is identified by the name of the tissue that the abnormal cells originated from eg. breast cancer, colon cancer etc. Frequently, cancer cells can break away from this original mass of cells, travel through the blood and lymph systems, and lodge in other organs where they can again repeat the uncontrolled growth cycle. This process of cancer cells leaving an area and growing in another body area is termed metastatic spread or metastatic disease. It happens when the cancer cells get into the bloodstream or lymph vessels of our body. Cancer is a complex genetic disease that is caused primarily by environmental factors that mutate genes encoding critical cell-regulatory proteins [5].

In terms of behavior, tumors are either ‘benign’ or ‘malignant’. Benign tumors are generally slow-growing expansive masses that compress rather than invade surrounding tissue. Malignant tumors are usually rapidly growing, invading surrounding tissue and, most significantly, colonizing distant organs. The suffix ‘oma’ usually denotes a benign tumor, and tumors of glandular epithelia are called ‘adenomas’ (e.g. colonic adenoma). Tumors of surface epithelia are called ‘papillomas’ (e.g. skin papilloma). Leukemia and lymphomas are malignant tumors of bone marrow and lymphoid tissue respectively, and malignant melanoma derives from the melanin-producing cells of the skin [6].

Stage I soft tissue sarcomas are low-grade tumors of any size. Small (less than 5 cm or about 2 inches across) tumors of the arms or legs may be treated with surgery alone. Most stage II and III sarcomas are high-grade tumors. They tend to grow and spread quickly. Even when these sarcomas have not yet spread to lymph nodes, the risk of spread (to lymph nodes or distant sites) is very high. These tumors also tend to grow back in the same area after they are removed. A sarcoma is considered stage IV when it has spread to distant sites (M1). Stage IV sarcomas are rarely curable. But some patients may be cured if the main tumor and all of the metastases (areas of cancer spread) can be removed by surgery [7].

Cancer was estimated to account for about 7 million deaths (12% of all deaths) worldwide in 2000, only preceded by cardiovascular diseases (30% of all deaths), and by infectious and
parasitic diseases (19%). Cancer was also estimated to account for almost 6% of the entire global burden of disease in that same year. More than 70% of all cancer deaths occurred in low- and middle-income countries and, although the risk of developing/dying from it is still higher in the developed regions of the world [8].

In India, the International Agency for Research on Cancer estimated indirectly that about 635000 people died from cancer in 2008, representing about 8% of all estimated global cancer deaths and about 6% of all deaths in India. UV radiation was estimated to cause 60,000 deaths in 2000. 48,000 of those were melanomas and 12,000 basal and squamous skin carcinomas. Arsenic in drinking-water was estimated to cause 3,700 deaths from lung, bladder and skin cancers in Bangladesh alone, which is probably the most impacted country (9). The World Health Organization estimated that if unchecked, annual global cancer deaths could rise to 15 million by 2020. 39.6% of cancers in men occurred in those who were illiterate muslim men had higher age-standardised mortality ratios for most cancers than did Hindus and other religious groups [10].

Types of cancer-The cancers that most frequently affect the man in India are-
(a) Gastric carcinoma accounts 10% in worldwide. Chronic H. pylori infection is the most important cause of distal gastric adenocarcinoma [11]. It commonly generates chronic gastritis, and over several decades may induce mucosal atrophy, which in some patients precedes the development of cancer [12,13].

(b) Colorectal cancer- Cancers that start in the cells that line inside the colon (the longest part of the large intestine) and rectum (the last few inches of the large intestine before the anus) are called colorectal cancers. The colon and rectum form the large intestine (large bowel), which is the last portion of the digestive system. It usually starts from a pre-cancerous growth called a polyp and grows slowly, usually in a predictable way [14].

(c) Oral cancer-consumption of different form of tobacco as areca nut, smokeless tobacco and paan and alcohol consumption cause oral cancer [15].

(d) Breast cancer- Breast cancer is a malignant tumor that starts in the cells of the breast and is a group of cancer cells that can grow into (invade) surrounding tissues or spread (metastasize) to distant areas of the body[16]. The disease occurs almost entirely in women, but men can get it, too. Simply being a woman is the main risk factor for developing breast cancer. Men can develop breast cancer, but this disease is about 100 times more common among women. About 5% to 10% of breast cancer cases are thought to be hereditary, resulting directly from gene defects (called mutations) inherited from parent than men [17].
(e) Gynecologic cancer in pregnancy - it may affect reproductive tract and foetalous. It is estimated that this type of cancer is responsible for 19% death of the worldwide [18]. Both cervical gland and stroma undergo physiological changes during pregnancy [19].

(f) Cervical cancer - Human PapilomaVirus (HPV) is responsible for cervical cancer transmitted sexually. Current HPV vaccines are designed to protect against two of the most common cancer-causing strains of HPV, 16 and 18, which cause over 70 percent of cervical cancer globally which are transmitted through sexual exposure. HPV vaccines must be given to girls before they are sexually active. Since 2006, more than 35 governments worldwide have introduced HPV vaccines in their national health and immunization program [20].

**LUNG CANCER**

Lung cancer was rare in the beginning of the last century [21] but later on it was diagnosed in various patients. Banker et al. [22] reported about 9210 consecutive autopsies of lung cancer patients in 1970, which were 14.4% of all cancer types. But, nowadays, it has become almost epidemic resulting in greater number of deaths than those caused by colorectal, breast and prostate cancers [23].

Cigarette smoking is by far the most important cause of lung cancer, and the risk from smoking increases with the number of cigarettes smoked and the length of time spent smoking [24]. Other recognized causes include radon[25] second hand smoke[26] and some occupational chemicals and air pollutants like benzene,[27] formaldehyde,[28] and diesel air pollution[29]. Asbestos, a product used in insulation and manufacturing for years, is also an important cause of lung cancer [30]. It has been estimated that active smoking is responsible for close to 90 percent of lung cancer cases; radon causes 10 percent, occupational exposures to carcinogens account for approximately 9 to 15 percent and outdoor air pollution 1 to 2 percent. Because of the interactions between exposures, the combined attributable risk for lung cancer exceeds 100 percent [31].

**Evolution of lung cancer**

75.6% of Indians are literate; amongst these, the literacy rates are 75.6% and 54.0% for men and women respectively [32]. The more illiterate the individual, the higher is the indulgence in tobacco use and smoking [33].

Historically, in India, tobacco was introduced in Karnataka by the Portuguese during A.D 1600 [34-35]. A couple of centuries later, the British introduced commercially produced cigarettes and established tobacco production in the country. Beedi (0.2-0.3gm of tobacco wrapped in a temburni leaf and tied with a small string) smoking was reported as early as 1711 in India [36].
One of the reasons for increased beedi consumption was the call for boycott of imported cigarettes as part of swadeshi movement (movement to boycott foreign goods) that enhanced a shift from cigarettes to beedies [34, 37].

Lung cancer was not recognized as a disease until 1761; the first link between lung cancer and smoking was reported way back in 1929 by physician Fritz Lickint from Germany [38]. The death toll due to lung cancer is projected to rise to ten million by 2030 with 7 out of 10 deaths in the developing world [39].

Lung cancer is the uncontrolled growth of abnormal cells in one or both of the lungs. Lung cancer arises from abnormal epithelial cells in the airways of the lungs. Epithelial cells form the covering over free surfaces in the body such as the airways [40]. While normal cells reproduce and develop into healthy lung tissue, these abnormal cells reproduce faster and never grow into normal lung tissue. Lumps of cancer cells (tumors) then form and grow. Besides interfering with how the lung functions, cancer cells can spread from the tumor into the blood stream or lymphatic system where they can spread to other organs [41]. Lung cancer surpassed breast cancer to become the leading cause of cancer deaths among women as well. In 2006, lung cancer had an age-adjusted death rate of 51.5 per 100,000 population in the U.S. and accounted for 31 and 26 percent of all male and female cancer deaths, respectively [42].

Mediators involved - The angiogenic process involves several cell types and mediators. Angiogenesis occurs in several physiological and pathological conditions, such as embryo development and wound healing, diabetic retinopathy and tumors. Inflammatory cells, namely monocytes/macrophages, T-lymphocytes and neutrophils, fully participate in the angiogenic process by secreting cytokines that may affect endothelial cell (EC) functions, including EC proliferation, migration and activation [43]. IL-1β promotes tumour growth by induction of angiogenic factors. TNF-α is a 17 kDa polypeptide and is a pleiotropic cytokine, initially shown to be secreted mainly by macrophages. However, it is now known that TNF-α is produced by many cell types, including stromal and malignant cells. Anti-TNF antibody treatment results in inhibition of cytokine/chemokine production, reduced angiogenesis and prevention of leukocyte infiltration, suggesting that all these actions may be useful in a biological therapy for cancer [44].

Symptoms - include a persistent cough, shortness of breath, wheezing, coughing up blood, chest pain and recurring pneumonia or bronchitis, dysphagia (difficulty in swallowing) [45].

Types of lung cancer
90% of lung content is air and only 10% is solid tissue; the latter’s significant components include the bronchi, bronchioles and alveoli [46]. There are 300 million alveoli and over a
million bronchioles and over 95% of lung cancer is bronchogenic carcinoma [47]. There are 40 types of cells in the lung of which 27 varieties make up the lung tissue itself [48]. Four amongst these are unique for the lung and include

**Non Small Cell Lung Cancer**
About 85% to 90% of lung cancers are non-small cell lung cancer (NSCLC). There are 3 main subtypes of NSCLC. The cells in these subtypes differ in size, shape, and chemical makeup when looked at under a microscope. But they are grouped together because the approach to treatment and prognosis (outlook) are very similar.

Squamous cell (epidermoid) carcinoma: About 25% to 30% of all lung cancers are squamous cell carcinomas. These cancers start in early versions of squamous cells, which are flat cells that line the inside of the airways in the lungs. They are often linked to history of smoking and tend to be found in the middle of the lungs, near a bronchus.

About 40% of lung cancers are adenocarcinomas. These cancers start in early versions of the cells that would normally secrete substances such as mucus. This type of lung cancer occurs mainly in people who smoke (or have smoked), but it is also the most common type of lung cancer seen in non-smokers. It is more common in women than in men, and it is more likely to occur in younger people than other types of lung cancer. Adenocarcinoma is usually found in the outer region of the lung. It tends to grow slower than other types of lung cancer, and is more likely to be found before it has spread outside of the lung.

Large cell (undifferentiated) carcinoma: This type of cancer accounts for about 10% to 15% of lung cancers. It may appear in any part of the lung. It tends to grow and spread quickly, which can make it harder to treat [49].

**Small cell lung cancer:**
About 10% to 15% of all lung cancers are small cell lung cancer (SCLC), named for the size of the cancer cells when seen under a microscope. Other names for SCLC are oat cell cancer, oat cell carcinoma, and small cell undifferentiated carcinoma. It is very rare for someone who has never smoked to have small cell lung cancer. SCLC often starts in the bronchi near the center of the chest, and it tends to spread widely through the body fairly early in the course of the disease [50].

**Pathophysiology of lung cancer**-
The epidermal growth factor receptor (EGFR) is a transmembrane glycoprotein with an extracellular ligand-binding domain and an intracellular domain possessing intrinsic tyrosine kinase (TK) activity [51]. After ligand binding, receptor dimerization leads to both activation of the TK domain and recruitment and phosphorylation of intracellular substrates, which drive
normal cell growth and differentiation [52-53]. EGFR is believed to play a critical role in neoplastic progression [54]. The EGFR was found to be over expressed in several types of tumors, including lung carcinomas [55].

Because cellular changes may begin in the lungs years before a diagnosis is made additional testing is recommended for those who are considered at risk [56].

Sputum cytology- This test looks at individual cells in sputum under a microscope and characterizes them as normal, pre-cancer (dysplasia), or early cancer.

Spiral computerized tomography - Also known as a CT scan, this is a painless procedure in which a special imaging machine rotates rapidly around the body taking more than 100 pictures in less than a minute. The scan is so sensitive it can detect abnormalities smaller than a fingernail.

Gamma PET-This new technology uses sugar-bound radioisotopes to form precise images of tissues and internal structures.

Fluorescence Bronchoscopy- Using fluorescent light, this revolutionary tool causes normal tissue to glow green, while rust-colored areas indicate possible abnormalities. It can identify lung cancer in its earliest, most treatable stages, when the patient has an excellent chance for recovery [57-58].

Human eye is capable of detecting a single nodule as small as 3 mm, it is quite unusual for a solitary neoplasm less than 1 cm in diameter to be seen. Although 1 cm has generally been accepted as the size threshold of detectability for peripheral lung cancers it is suggested that for the prospective analysis of chest radiographs the threshold size of detectability may be much larger. In their series, the size of peripheral lung cancers at the initial time of prospective detection during routine screening ranged from 0.7 to 9.4 cm, with an average size of 2.4 cm. The shape of a nodule also plays a significant role in its detectability. If a peripheral lung cancer is spherical and sharply marginated, its edge will be enhanced by a negative Mach band. The presence of the negative Mach band will greatly increase the detectability of the nodule [59].

Mucoid impaction of bronchi refers to the accumulation of inspissated secretions within the bronchial lumen usually associated with bronchial dilatation or bronchiectasis [60-62]. Lung cancer is by far the most common cause of mucoid impaction caused by bronchial obstruction [60-63].

Radiologically, mucoid impaction of the bronchi distal to an obstructing tumor often is obscured by post obstructive pneumonia or collapse. However, if collateral ventilation occurs, so that the lung distal to the obstruction remains aerated, mucoid impaction may be visible on...
plain films or CT scans [64-66]. Double lesion sign, considered strong evidence against lung cancer, is defined as lobar or segmental atelectasis in two different lobes [67]. Pleural involvement in primary lung cancer is not uncommon, occurring in about 5% of cases. Usually this is manifested by pleural effusion. Typically a hilar or parenchymal mass is visible on the radiograph; however, a subtle hilar mass or small peripheral tumor may be relatively inapparent on the initial radiographs, especially when the effusion is large, leaving the impression that the pleural effusion is an isolated finding [67]. Invasion of one or more of the pulmonary arteries is common in lung cancer. This may result in decreased perfusion of the involved lung [68]. Invasion of the pulmonary artery will cause pulmonary infarction; this may be seen as a dumbbell-shaped opacity with the central mass representing the tumor and the peripheral mass representing the infarct [69]. Dysphagia is occasionally the presenting symptom in patients with lung cancer [70-71].

Chemotherapeutic measures; A number of airway stents are available for the palliation of dyspnoea. These include silastic stents for the trachea or main stem bronchi, silastic Y stents for use at the carinal level and expandable metal stents that can be used in the trachea and the main bronchi. Stents are commonly used in patients with endoluminal obstruction and extrinsic compression. Stents placed at lobar level are often not as successful as those placed for central lesions [72]. Breathlessness due to pleural effusion may be relieved by needle aspiration or more completely by drainage with a tube left indwelling for a period of time. Recurrence in days or weeks is common, so symptomatic relief is usually temporary. Although it has been assumed that chemotherapy drugs pass the blood-brain barrier poorly, a recent study [73] shows that small scaleseries of NSCLC and SCLC patients had response similar to those with tumours located elsewhere. Chemotherapy is effective at reducing pain caused by cerebral metastases in SCLC patients [74]. Brachytherapy is the delivery of radiation from an endobronchial source. A catheter is placed across the lesion, loaded with the appropriate radiation source, and this remains in place until the prescribed dose has been delivered [75].

**Conclusion**

Cancer cell growth is different from normal cell growth. Instead of dying, cancer cells continue to grow and form new, abnormal cells. Cancer cells can also invade (grow into) other tissues, something that normal cells cannot do. Growing out of control and invading other tissues is what makes a cell a cancer cell. About 75-80% of lung cancers are associated with smoking. Every three minutes someone is diagnosed with lung cancer. Scans like, CXR, CT, PET and blood tests, Bronchoscopies, Endobronchial ultrasound, Thoracentesis Endoscopic esophageal ultrasound, Mediastinoscopy and mediastinotomy have proved to be beneficial in the diagnosis of lung cancer.
of lung cancer beside new chem-preventive strategies which have shown progress in the intervention of pathogenesis lung cancer. Apart from them some life style modifications like stopping the use of tobacco may be helpful in the management and reduction of cases of lung cancer. Untill tobacco use is sharply decreased lung cancer will continue to be major killer.

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