Review Article

Proceedings of Anticancer Research 2017; 1(1): 19-26

BIO-BYWORD SCIENTIFIC PUBLISHING PTY LTD

Proceedings of Anticancer Research

The global burden of lung cancer: A short review

Thamaraiselvan Rengarajan[1]*, Peramaiyan Rajendran[2], Natarajan Nandakumar[3]

1.Scigen Research & Innovation, Periyar Technology Business Incubator, Periyar Nagar, Thanjavur 613403, Tamilnadu, India.

2.Research fellow, China Medical University, Taichung, Taiwan 40402.

3.Department of Microbiology, Immunology and Genetics, Ben Gurion University of the Negev, Beer Sheva, 84105, P.O.B.653, Israel.

ARTICLE INFO

Article history:

Published online: 15th July, 2017

Key words:

Lung cancer

epidemiology

symptoms

detection

treatment

***Corresponding Author**

Dr. Thamaraiselvan Rengarajan, PhD., Scigen Research & Innovation, Periyar Technology Business Incubator, Periyar Nagar, Thanjavur 613403, Tamilnadu, India E-mail: thamarairaj2000@gmail.com

ABSTRACT

Lung cancer is the leading cause of cancer-related mortality in both men and women, and lung adenocarcinoma accounts for approximately 75-85% of all lung cancers. It is expected to cause 10 million deaths per year worldwide by the year 2030. A large number of lung cancers are associated with cigarette smoke, although other factors such as environmental influences and radon or nutrition may also be involved. Lung adenocarcinoma commonly develops resistance to radiation and chemotherapy, and often presents at stages too late for surgical intervention. The present review discuss about the epidemiology, etiology, pathogenesis, and chemoprevention of lung cancer.

Introduction

Cancer has been in existence since the first of our ancestors learned to log their life activities. Because technology and science have made such huge strides within the twentieth century, life spans have been greatly expanded. Usually, cancer is more likely to develop with the increase of age. Due to this fact, cancer has become a prevalent problem, affecting many in our society today (Asmis et al, 2008). Because cancer is one of the leading causes of death in this day and age, it must be explored, scrutinized and understood. The main reasons for the greater cancer burden of affluent societies are the earlier onset of the

tobacco epidemic, the earlier exposure to occupational carcinogens, and the Western nutrition and lifestyle. However, with increasing wealth and industrialization, many countries undergo rapid lifestyle changes that will greatly increase their future disease burden (WHO, 2004).

Carcinogenesis is a multistep process associated with accumulated genetic alterations in somatic cells (Hanahan & Weinberg, 2011). Tumour initiation begins through carcinogen-induced mutations, and the initiated cells may acquire a selective growth advantage as a result of mutations in genes that control cellular proliferation and death. During the tumour promotion phase, the initiated cells further expand clonally, and additional genetic damage develops through several mutations. These mutations may include the activation of proto-oncogenes or the inactivation of tumour suppressor genes (Rajendran et al., 2008). Progressive phenotypic changes and genomic instability continue during the phases of tumour progression and malignant conversion (Loeb et al., 2008). It has been estimated that a normal cell must acquire at least five or six mutations to become a cancer cell (Stratton et al., 2009). Reactive oxygen species may participate in the multistage carcinogenesis from initiation to malignant conversion by causing oxidative DNA damage and mutations in protooncogenes and tumour suppressor genes, and by activating signal transduction pathways (Klaunig et al., 2011).

Lung cancer

Lung cancer is one of the commonest malignant neoplasms all over the world. It accounts for more cancer deaths than any other cancer. It is the leading cause of cancer deaths in developed countries and is also rising at alarming rates in developing countries (Jemal et al., 2010). It is increasingly being recognized in India. Lung cancer was considered to be rare in the beginning of the century (Samet et al., 2009) but has now reached almost epidemic proportions. An International standard for histological classification of lung tumors has established by World Health Organization (WHO) and the International Association for the study of Lung Cancer (IASLC) (Travis et al., 1999). There are four major types of bronchoil lung cancer. Adenocarcinoma, Squamous cell carcinoma, Small cell carcinoma and Large cell carcinoma.

These major types can be classified into more specific sub types, based on the pattern of tumor cell growth and invasion. The most important distinction is that between, small cell lung cancer (SCLC) and non small cell Lung cancer (NSCLC), because of their major clinical differences in metastatic spread and response to treatment (Ambrosini et al., 2011)

Non-small cell carcinoma (NSCLC)

Adenocarcinoma is the most frequent histopathological type of lung cancer and today it accounts for about 30-50% of all new Lung cancers (Ettinger et al., 2010). Adenocarcinoma is composed of cubodial to columnar epithelial cells and can be divided into four sub types: acinar, papillary, solid with mucous formation, and bronchoalevolar carcinoma. Most adenocarcinomas are histologically heterogenous and classified as mixed (Girard et al., 2009), and arise in the periphery of the lungs (75%). The growth rate is intermediate between that of squamous cell carcinoma and small cell carcinoma. Adenocarcinomas tend to spread early through the vascular system. Bronchoalevolar is highly differentiated form of adenocarcinoma, accounting for about 2.5% of all bronchoil carcinomas. It often presents as an infiltrate rather than as well defined tumor, or even as consolidation of an entire lobe. Multinodular lesions are uncommon (<10%), and lymph node spread is seen in 7.5% of the cases (Yamada et al., 2011).

Squamous cell carcinomas constitute approximately 20-35% of all lung cancers (Scully & Bagan, 2009) papillary, clear cell, small cell and baseloid sub types occur with polygonal or prickle type cells, stratification and intracellular bridge formation. About two third of these carcinomas are found in the central area of the lung, growing relatively slowly and tending to metastasise late. Large cell carcinomas account for about 9% of all lung cell carcinomas (Molina et al., 2008). These tumors cannot be classified either as Squamous cell carcinomas or Adenocarcinomas. They tend to spread earlier than other NSCLCs and have a poorer prognosis.

Small cell lung cancer (SCLC)

There are three sub types of small cell lung cancer; pure small cell, mixed small cell, large cell

and combined small cell carcinoma mixed with either squamous cell or adenocarcinoma (Travis, 2011). SCLC is catagorised as one of the neuro endocrine tumors of the lung, together with typical carcinoid tumor, a typical carcinoid and large cell neuro endocrine carcinoma. SCLCs constitute about 15-35% of all bronchial carcinomas (Morere et al., 2010). Small cell carcinoma is highly malignant and aggressive in nature, about two-third of these tumors presenting as a periheliar mass. Surgical treatment is not generally advisable in SCLC, mainly because of the high rate of the metastasis and invasiveness into the mediastinum at the time of diagnosis.

Epidemiology Of Lung Cancer

Half a century has passed since researchers identified the epidemic of lung cancer and the first investigations on its cause were implemented. During these 50 years, tobacco and other smoking related carcinogens have been identified as a cause of lung cancer as well as for oral and stomach cancer (Gandini et al., 2008).

Ninety percent of patients with lung cancer of all histologic types are current or former cigarette smokers. Of the annual 1, 71,600 new cases of lung cancer, -50% develop in former smokers. With increased success in smoking cessation efforts, the number of former smokers will sow, and these individuals will be important candidates for early detection and chemoprevention efforts. By far the most common form of lung cancer arising in lifetime non-smokers, in women and in young patients (< 45 years) is adenocarcinorna. The challenge for epidemiologist is to incorporate measures of genetic susceptibility into the quantitative risk assessment processes (Wild, 2009). Whether women are more susceptible than men to the carcinogenic effects of cigarettes remains controversial. Several case control studies have suggested that the association between smoking and lung cancer was considerably stronger for women than for men (Aldington et al., 2008; Olsson et al., 2011; Pesch et al., 2012).

An estimated 221,200 new cases of lung cancer are expected in 2015, accounting for about 13% of all cancer diagnoses. The incidence rate has been declining since the mid-1980s in men, but only since the mid-2000s in women. From 2007 to 2011, lung cancer incidence rates decreased by 3.0% per year in men and by 2.2% per year in women. Lung cancer accounts for more deaths than any other cancer in both men and women. An estimated 158,040 deaths are expected to occur in 2015, accounting for about 27% of all cancer deaths (American Cancer Society, 2015). Death rates began declining in 1991 in men and in 2003 in women. From 2007 to 2011, rates decreased by 2.9% per year in men and by 1.9% per year in women. Gender differences in lung cancer mortality reflect historical differences in patterns of smoking uptake and cessation over the past several decades.

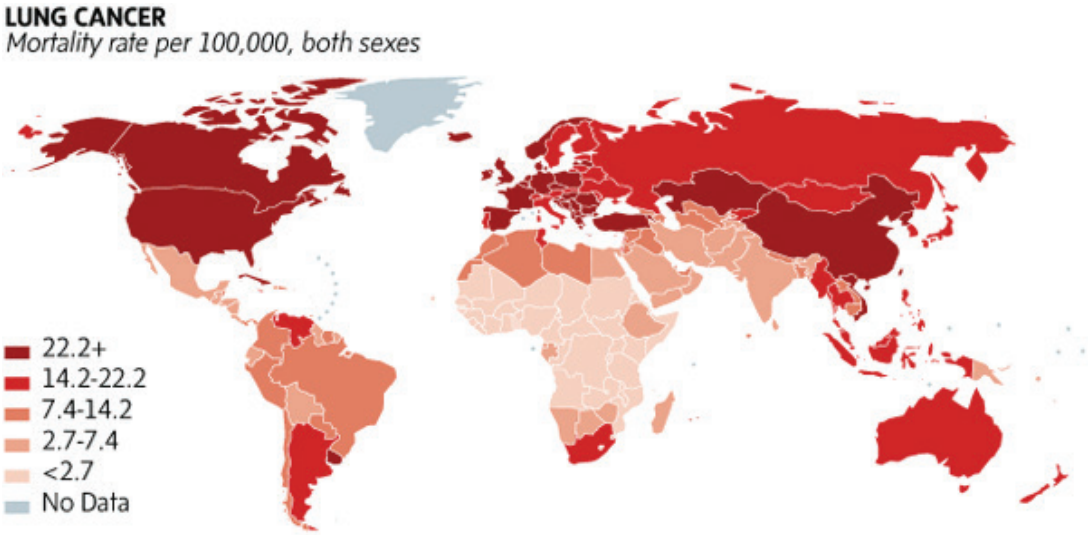

Fig 1: Lung cancer Mortality rate worldwide
Source: Globocan 2012 (International Agency for Research on

Etiologic Factors For Lung Cancer

Tobacco smoke

The IARC monograph entitled 'Tobacco Smoke and Involuntary Smoking', published in 2004, and concluded the following based on an evaluation of the world's literature (IARC, 2004). Cigarette smoking increases the risk of all histological types of lung cancer. It causes cancer of the oral cavity and this risk is greatly increased by the use of smokeless tobacco or by alcohol consumption in combination with smoking. Cigarette smoking is also causally associated with laryngeal, oropharyngeal and hypopharyngeal cancer, and increases the risks for sinonasal and nasopharyngeal cancer (Jha, 2009). Tobacco products contain a diverse array of chemical carcinogens.

Chemical class	No. of compounds	Representative carcinogens
PAH	14	B(a)P, dibenz[a,h]anthracene
Nitrosamines	8	NNK, NNN
Aromatic amines	12	4-Aminobiphenyl, 2-naphthylamine
Aldehydes	2	Formaldehyde, acetaldehyde
Phenols	2	Catechol
Volatile hydrocarbons	3	Benzene, 1,3-butadiene
Nitro compounds	3	Nitromethane
Other organics	8	Ethylene oxide, acrylonitrile
Inorganic compounds	9	Cadmium
Total	61	

Table 1 Carcinogens present in tobacco smoke (Adapted from Gerald et al., 2004)

Table 1 presents an overview of carcinogens in tobacco products. More than 60 known carcinogens have been detected in cigarette smoke. Several carcinogens listed in Table 1 have been detected only sporadically, but most are routinely found. All of the carcinogens in Table 1 have been formally evaluated by the IARC, and in each case, studies in either laboratory animals or in humans have provided sufficient evidence of carcinogenicity. There is a large range of potencies and concentrations among these carcinogens. In general, the stronger carcinogens such as polycyclic aromatic hydrocarbons (PAHs), nitrosamines, and aromatic amines occur in lower amounts in cigarette smoke (1–200 ng per cigarette) than the weaker carcinogens such as acetaldehyde (nearly 1mg per cigarette). The total amount of carcinogens in cigarette smoke add up to 1–3 mg per cigarette (similar to the amount of nicotine, 0.5–1.5 mg per cigarette), although most of this total is comprised of weaker carcinogens such as acetaldehyde, catechol, and isoprene (Gerald et al., 2004). Tobacco carcinogens and their DNA adducts are absolutely central to cancer induction by tobacco products. The contribution of specific tobacco carcinogens to tobacco-induced cancer can be evaluated by a weight of the evidence approach (Rengarajan et al., 2015). Examples were given for various carcinogens and tobacco related cancers, e.g. the role of PAH and Nitrosamines 4- (methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) in lung cancer.

Factors considered in this approach include the presence of the compound in tobacco products, its carcinogenicity in laboratory animals(Rajendran et al., 2014), its human uptake, and metabolism and adduct formation, it's possible role in causing molecular changes in oncogenes or suppressor genes, and other relevant data (Gerald et al., 2004).

Asbestos

Asbestos is the name of' a group of minerals that occur naturally as fibres and are used in certain industries. Asbestos fibres tend to break easily into particles that can float in the air and stick to clothes. When the particles are inhaled, they can lodge in the lungs, damaging cells increasing the risk for lung cancer (Berman & Crump, 2008).

Radiation

Epidemiologic studies of populations that have been exposed to high doses of radiation show that lung cancer is one of the cancers associated with exposure to ionizing radiation. However, the risks of low-dose radiation, which are more relevant to contemporary workers and the general population, have proven difficult to characterize. Assessing the cancer risk that is associated with exposure to low dose radiation among humans is methodologically difficult because the signal-to-noise ratio is highly unfavorable. The following two types of radiation, which are classified by the rate of energy transfer to the tissue, are relevant to lung cancer low linear energy transfer (LET) radiation (eg, x-rays and gamma rays); and high-LET radiation (eg, neutrons and radon)(Ghissassi et al.,2009).

Air Pollution

During a typical day, the average adult inhales about 10,000 L of air (NRC, 1985). Consequently, even the carcinogens that are present in the air at low concentrations are of concern as a risk factor for lung cancer. Extrapolation of the risks associated with occupational exposures to the lower concentration of carcinogens in polluted ambient air leads to the conclusion that a small proportion of lung cancer cases could be due to air pollution (Kampa & Castanas, 2008).

Other Diseases that Increases the risk of lung cancer

Smokers with emphysema or chronic inflammatory lung diseases, such as asthma, are at increased risk for lung cancer. Both smokers and nonsmokers whose lungs are scarred from recurrent lung diseases, such as pneumonia or tuberculosis, are also at increased risk, particularly for bronchoalveolar lung cancer.

Symptoms

Frequent bouts of pneumonia or an episode that does not clear up in a normal period of time. Weight loss, Fever, Chest pain and Coughing. Shortness of breath from cancer that has spread to the pleura, the membrane covering the lung is common. In some cases, tumour growth or metastasis presses against the superior venu cava, a large vein that returns blood from the upper part of the body to the heart. When this happens, a condition called superior vena cava syndrome may occur, leading to obvious swelling in the upper extremities and face (Peake, 2008). The cancer may spread to or press against the oesophagus, interfering with swallowing and nutrition. The nerves that control the larynx can be damaged, causing hoarseness. Damage to the brachial plexus, a group of naves branching from the neck, can cause pain, weakness or numbness in the arm or hand (Pancoast's syndrome). Bronchoalveolar lung cancer may produce very large amounts of mucus. Some lung cancers give out substances that remove calcium from bone and release it into the blood stream, causing a condition called hypcrcalcemin. Patients with this disorder can experience nausea, vomiting, constipation, weakness and fatigue. Other lung cancers (usually small cell cancer) cause the body to retain water, lowering the bloods sodium levels (Molina et al., 2008). This condition, called hyponatremia can produce confusion, weakness and even seizures.

Early Detection

Screening with spiral CT has been shown to reduce lung cancer deaths by 16% to 20% compared to standard chest x-ray among adults with a 30 pack-year smoking history who were current smokers or had quit within 15 years. In January 2013, the American Cancer Society issued guidelines for the early detection of lung cancer based on a systematic review of the evidence. These guidelines endorse a process of shared decision making be-

tween clinicians who have access to high-volume, high-quality lung cancer screening programs and current or former smokers who are 55 to 74 years of age, in good health, and with at least a 30 pack-year history of smoking. Shared decision making should include a discussion of the benefits, uncertainties, and harms associated with lung cancer screening.

Treatment

While the best treatment is early detection, conventional cancer treatment usually includes a combination of surgery, chemotherapy and radiation therapy. Chemotherapy is the use of anti-cancer drugs to kill cancer cells and also disrupts the growth of cancer cells. Chemotherapy is sometimes the first choice for treating many cancers. It differs from surgery or radiation in that it is almost always used as a systemic treatment (Gadgeel et al., 2012). Chemotherapy involves treating the patient with antitumour drugs, which destroy cells during the process of cell division and DNA replication.

Chemotherapy for Lung Cancer

Chemotherapy is the ease of drugs to kill cancer cells. Most chemotherapeutic drugs are cytotoxic - they work by killing cells. They do this by preventing the formation of new DNA or by blocking some other essential functions in the cells. Some drugs work by causing cell to commit biochemical suicide, a process known as apoptosis (Kepp et al., 2011). Chemotherapy can be used to: Attempt a cure, Slow the cancer growth, Prevent the earner from spreading, Relieve symptoms that may be caused by cancer by shrinking the tumour. Chemotherapy is most effective against tumours with rapidly dividing cells such as oat cell cancer and large cell carcinoma. By comparison, the cells of solid tumors divide relatively slow and chemotherapy is often less effective against them. In addition, chemotherapy kills only a certain fraction of cells growing in a lung tumour at any one time - cells that are at a certain stage in the cel1 cycle (Lapenna & Giordano, 2009).

Chemoprevention

Chemoprevention defined as the use of naturally occurring or synthetic agents to prevent, inhibit or reverse the process of carcinogenesis, is a relatively new approach to cancer prevention that has a precedence in other areas of medicine such as cardiology, in which cholesterol-lowering and platelet anti-aggregating agents are administered to prevent coronary heart disease in individuals with elevated risk. Chemoprevention also offers a novel approach to control the incidence of lung cancer (Mehta, et al., 2010).

Conclusion

Cancer continues to be a leading cause of death around the world. In the spectrum of cancer, Lung cancer is the most prevalent cancer in the world that represents a major public health problem worldwide and it accounts for 1.18 million cancer-related deaths in both men and women. Tobacco smoking is well established as the major etiological risk factor for lung cancer, contributing to a tenfold increase in risk in long-term smokers compared with non-smokers. The key to successful management of lung cancer is awareness, screening and early detection. This review presented essential facts regarding lung cancer, which could help for its management and treatment.

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