EDITORIAL

LUNG CANCER : THE US PERSPECTIVE

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Lung cancer remains the leading cause of cancer deaths in the United States. Mass screening for early disease by chest radiography and sputum cytology has not been shown to be effective in reducing mortality[1]. Nevertheless, individualised screening within the framework of general health care is currently recommended for heavy smokers above 45 years of age[2]. Intensive research into early detection using photodynamic technique and trials of new approaches in surgical, radiation and chemotherapy management have yet to produce overall survival benefit.

Although advances have been made in diagnosis, staging and therapy, 5-year survival for all cases of lung cancer is only 13.4%[3]. It is the cancer accounting for the most years of life lost compared to any other cancer site[4]. The economic burden of this disease in the US is estimated at US$10 billion per annum, representing 1.5% of the annual US healthcare cost[5]. Favourable trends in smoking cessation and further advances in lung cancer biology hold the most promises toward modifying the overall dismal outcome of this disease.

Epidemiology

In the US, the incidence of lung cancer among white males has plateaued and started to decline since the mid 80's. Among males, lung cancer is estimated to be the second most common after prostate cancer in 1994 with about 100,000 new cases. Females are expected to fare slightly better with 72,000 new cases in 1994, making lung cancer the next most common cancer after breast and colorectal cancers. Most lung cancers are diagnosed in the fifth and sixth decades of life. Age-adjusted rates of lung cancer in women have surpassed that of breast cancer since 1989. It is estimated that in the year 1994, 94,000 males and 59,000 females will die from lung cancer – comparatively, 38,000 males will die from prostate cancer while 46,000 females will have similar outcome from breast cancer[6].

Death rates from lung cancer rose a precipitous 440% in three decades (1957-89)[7]. There is close correlation between the mortality from lung cancer and its incidence resulting from a low 5-year survival rate and a case-fatality of greater than 90%. This reflects the relatively poor success in the treatment of lung cancer compared to other cancers. A recent estimate suggests that even with additional interventions to reduce the number of smokers, lung cancer mortality will continue to rise within this decade before falling[8].

Pathology of Lung Cancer

In recent years, adenocarcinoma (32%) has overtaken squamous cell carcinoma (30%) as the most commonly diagnosed cell type in both sexes, followed by small-cell (24%) and large cell (14%) lung cancers[9]. Part of the increase is due to reclassification of mucin producing tumours and re-labelling of some undifferentiated large cell carcinomas as adenocarcinomas. There is also a true increase in the incidence of adenocarcinoma[10]. Increasing incidence of lung cancer among females who have higher preponderance for developing adenocarcinoma is also responsible for the trend.

Aetiology

Smoking

According to results of the American Cancer Society's Cancer Prevention Study II, a tragic 85% of lung cancer mortality (90% in men and 78% in women) can be attributed to smoking (direct and passive) and is therefore preventable[11]. Environmental tobacco smoke (ETS) has been shown in the majority of studies to produce an increase in lung cancer risk[12,13]. The odds ratio for lifetime ETS exposure is 1.3 to 2, compared to a greater than ten-fold increased risk for lifetime active smokers. Studies of the effect of ETS exposure have been complicated by the lack of a truly unexposed control group. It is suspected that approximately five thousand lung cancer deaths each year can be attributed to ETS. The effectiveness of current efforts to reduce smoking prevalence will determine the projected reductions in lung cancer mortality in the next century. Smoking cessation reduces lung cancer risk with a long latency period to risk normalisation. Efforts to prevent smoking initiation and encourage smoking cessation are currently the most effective methods to reduce lung cancer incidence and mortality. Physician counselling with assessment and documentation of smoking status as a "new vital sign" has received increasing attention over the past decade. Smoking control policies and legislation implemented in both public and private places enforce an emerging social norm that sees smoking as an undesirable behavior. Legislative efforts implemented include dissemination of information on health hazards of smoking, restriction or prevention of smoking in work and public places, protection of non-smokers from ETS (Clean Indoor Air Legislation), regulation of and limitations on advertising, sale and distribution of tobacco products and "sin" taxation to increase prices of cigarettes. Smokers are likely to suffer with double the amount of loss of work due to health reasons than non-smokers. Even with her extremely liberal society – it is legal to refuse employment to a smoker in the US. Overall cigarette consumption in the US has fallen from a high of 4,000 cigarettes per adult per year in the

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early 1960's to between 1,500-3,000 cigarettes per adult per year in 1990[8]. Despite this progress, the national goal (according to the National Cancer Institute Year 2000 Project) to reduce overall adult smoking prevalence in the US to 15% in 1990 was not achieved and strategies to control tobacco use have been revised for the 1990s[14].

The prevalence of smoking in women up to the present day however has not declined as rapidly as in men after the landmark 1964 US Surgeon General's First Report linking smoking to ill health effects. This is in part due to targeted advertising by tobacco companies and correlates with the higher rate of increase in lung cancer mortality for females in the US. Although the prevalence of smoking among females has declined from 31.9% in 1965 to about 23.5% in 1991, it may surpass that of males by the Year 2000 if current trends persist. In the 21st century, it is possible that lung cancer may become a Woman's disease in the US[15].

Asbestos

Past exposure to asbestos is the most frequent occupational cause of lung cancer in the US – accounting for about 5% of all US lung cancers in 1981. The US Occupational Safety and Health Administration (OSHA) recommended Threshold Limit Value for asbestos is less than 0.2 fibers/mL air[16]. Risk of indoor exposure in buildings have been found to be negligible and currently the EPA requires asbestos removal from buildings only before demolition activities[17]. It is estimated that a heavy smoker who also has heavy exposure to asbestos on a daily basis has 50 times more chances of developing lung cancer than the non-smoking, non-asbestos-exposed male population.

Ionising Radiation

The magnitude of lung cancer risk from indoor radon exposure ("radon daughters") in homes is currently being studied intensively. Several reports have associated a small predominance of small-cell carcinomas with radon exposure. It is estimated that radon exposure may be responsible for between 5% to 10% of new lung cancer cases[18].

Other documented carcinogens include arsenic, bischloromethyl ether, chromium, ionizing radiation, certain man-made mineral fibres, mustard gas, nickel, soots, tars, mineral oils and vinyl chloride[19].

Increased intake of fruits, vegetables and higher serum beta-carotene levels have been associated with lower lung cancer risk. A multicentre study of active dietary supplementation in those at high risk for lung cancer, the National Cancer Institute's Beta-Carotene and Retinol Efficacy Trial (CARET), is in progress[20].

Molecular genetics and Lung Cancer

Significant progress has been made in deciphering the molecular defects present in lung cancer cells. Research suggests that genetic characteristics modify an individual's risk for smoking and environmentally related lung cancers. Six families of activated oncogenes are known to be associated with lung cancer. They are present in 86% of non-small-cell lung carcinoma DNA from smokers. The *ras* and *myc* oncogene families are most important, being associated with morphological/behavioural changes and continuous division/immortality respectively. No *ras* mutations have been observed in non-smokers. Strong expression of particular *ras* oncogene products have been associated with poorer prognosis and survival. Mutations with loss of function of tumour suppressor gene p53 are present in almost all small-cell lung cancers and half of non-small-cell lung cancers[21].

The ability to metabolise carcinogens, determined genetically, has also been found to affect lung cancer risk. Two inherited variants which are part of the cytochrome P450 system, the aryl hydrocarbon hydroxylase system and the debrisoquine metabolic phenotype have been associated with lung cancer risk. Enzymes of the aryl hydrocarbon hydroxylase system can activate polycyclic aromatic hydrocarbons and arylamines into potent carcinogens[22].

Treatment of Lung Cancer

Despite aggressive research effort there has not been significant change in the treatment of lung cancer. Surgery remains the only hope for the patients with limited non-small cell bronchogenic carcinoma – unfortunately only 25% of the patients have resectable disease at the time of diagnosis[23]. In recent years, efforts are being made to extend the benefits of surgery to patients with N2 disease. Surgery can still be performed in selected patients with squamous cell carcinoma and ipsilateral paratracheal lymph node involvement. Even in the 1990s, chemotherapy plays a limited role in the management of non-small-cell lung cancer[24]. On the contrary, chemotherapy has improved the outcome of patients with small-cell lung cancer. Today, 2-year survival from limited-stage small-cell lung cancer with chemotherapy is up to 25% – up significantly from 15 years ago when life expectancy of these patients ranged from weeks to 3 months[25]. Combined-modality therapy for limited small-cell lung cancer has produced 2-year survival rates of over 40%[26].

Future Directions

The preliminary findings in the areas of lung cancer biology and genetics require further confirmation and refinement before translation to clinical practice. Possible applications include detection of gene mutation markers in premalignant tissues (sputum or lavage cells) to identify individuals at risk, who can then be counselled to avoid or stop smoking. Molecular tumour markers may also aid in differential diagnoses, staging, prognostication, and improvements in therapeutic strategies[27]. Alterations of tumour growth with gene therapy and selective targeting of malignant cells by immunotherapy may herald novel approaches to lung cancer treatment and survival optimisation[28].

Although lung cancer incidence in males is approaching a peak in the United States, it is expected to remain high for the next 3 decades. The rate of decline will be dependent primarily on current and future smoking trends, although modification of environmental exposures may have an effect. Increasing taxation of cigarettes sales and banning subsidies for tobacco production will be necessary to effectively limit tobacco consumption. As US domestic tobacco consumption declines, increasing tobacco exports will be sought by tobacco companies to maintain current production levels. Thus, tobacco exports to countries with rising smoking-rates can be expected to result in similar lung cancer epidemics in the near future.

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