LUNG CANCER IN INDIA

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D Behera, *New Delhi*

LUNG CANCER - WORLD SCENARIO

In the beginning of the century, lung cancer was considered to be rare.[1] But now it has reached epidemic proportions. This is the leading cause of cancer death in developed countries and is rising in alarming rates in developing countries.[2] Estimates of the worldwide incidence and mortality from 27 cancers in 2008 have been prepared for 182 countries as part of the GLOBOCAN series published by the International Agency for Research on Cancer recent. Results for 20 world regions, summarizing the global patterns for the eight most common cancers have been made in this report. Overall, an estimated 12.7 million new cancer cases and 7.6 million cancer deaths occurred in 2008, with 56% of new cancer cases and 63% of the cancer deaths occurring in the less developed regions of the world. The most commonly diagnosed cancers worldwide are lung (1.61 million, 12.7% of the total), breast (1.38 million, 10.9%) and colorectal cancers (1.23 million, 9.7%). The most common causes of cancer death are lung cancer (1.38 million, 18.2% of the total), stomach cancer (738,000 deaths, 9.7%) and liver cancer (696,000 deaths, 9.2%). Cancer is neither rare anywhere in the world, nor mainly confined to high-resource countries. Striking differences in the patterns of cancer from region to region are observed.[3] 5-year survival rate for lung cancer has improved only marginally from 5% in the late 1950s to 14% by 1994. This is in contrast to the 5 years survival of 52% in other cancers.[4,5]

LUNG CANCER IN INDIA

In India Lung cancer was initially thought to be extremely rare.[1] Few attempts were made to know the exact frequency. Lung cancer constituted 14.4% of all cancers in a review of 9210 consecutive autopsies by Banker in 1957.[4] Sirsat (1958) reported that lung cancer formed one percent of all cancers in Tata Cancer Hospital.[5] Viswanathan and Sengupta (1961) collected information from different hospitals of the country and found that the incidence of lung cancer in hospital population was 27.4 per million in 1950 and in 1959 it was 78.6 per million.[8] They also found an increase in the incidence of bronchogenic carcinoma following analysis of the records of 15 teaching institutions in India over a period of 10 years. From 16.1 in 1950, it had increased to 26.9 in 1961 per 1000 malignancies. According to Wig et al. (1961), lung carcinoma is a frequent finding amongst all the chest diseases.[9] The survey conducted in Uttar Pradesh in 1966 by Misra and others showed that the incidence was 4.2 per 10,000 hospital admissions and 2.1 per cent al all malignancies.

The National Cancer Registry Programme of the Indian Council of Medical Research, which collected data from six different parts of the country, both rural and urban areas, showed varying figures at different areas.[10] While cancer of the trachea, bronchus and lungs was the most common form of malignancy in males in 1989 from Bombay, Delhi, and Bhopal, it was the second most common in Madras and third in Bangalore, and was most unusual in Barshi, a rural area. The disease was most uncommon in females and only in Bombay it was the sixth common malignancy and Bhopal it was the seventh in rank.

Hospital data from different parts of the country also showed different patterns. Behera and Kashyap analysed the pattern of malignancy in patients admitted in PGIMER, Chandigarh from 1973 to 1982.[11] They found that of the 223930 hospital admissions there were 863 lung cancer cases (0.38%).

Table 1: The worldwide distribution of Lung Cancer

GLOBOCAN - 2008						
Estimated numbers (thousands)	Men		Women		Both sexes	
	Cases	Deaths	Cases	Deaths	Cases	Deaths
World	1095	951	513	427	1608	1378
More developed regions	482	411	241	188	723	599
Less developed regions	612	539	271	239	883	778
WHO Africa region (AFRO)	12	11	4	4	16	15
WHO Americas region (PAHO)	172	144	134	101	306	245
WHO East Mediterranean region (EMRO)	21	19	5	4	26	23
WHO Europe region (EURO)	313	278	104	91	417	369
WHO South-East Asia region (SEARO)	108	97	42	37	150	134
WHO Western Pacific region (WPRO)	465	397	222	187	687	584
IARC membership (21 countries)	456	386	233	180	689	566
United States of America	114	90	100	71	214	161
China	351	304	170	148	521	452
India	47	41	11	10	58	51
European Union (EU-27)	207	182	80	70	287	252

Table 2: Lung Cancer in India

INDIA	Male	Female	Both sexes
Population (thousands)	610618	570793	1181412
Number of new cancer cases (thousands)	430.1	518.8	948.9
Age-standardised rate (W)	92.9	105.5	98.5
Risk of getting cancer before age 75 (%)	10.2	10.8	10.4
Number of cancer deaths (thousands)	321.4	312.1	633.5
Age-standardised rate (W)	71.2	65.5	68.0
Risk of dying from cancer before age 75 (%)	8.0	7.1	7.5
5 most frequent cancers			
	Lung	Cervix uteri	Cervix uteri
	Lip, oral cavity	Breast	Breast
	Other pharynx	Ovary	Lip, oral cavity
	Oesophagus	Lip, oral cavity	Lung
	Stomach	Oesophagus	Oesophagus

Lung cancer was the fifth common cancer after lympho-reticular malignancy, carcinoma cervix, oropharyngeal cancer and carcinoma of breast. The total number of lung cancer admissions steadily rose from 1973.

As of 1st July 2002 a total of 41,000 lung cancer cases would have been diagnosed as per data from the ICMR Cancer Registry. Males predominate with a M:F ration of 4.5:1 and this ratio varies with age and smoking status. The ratio increased progressively upto 51-60 years and then remained same. The smoker to non-smoker ratio is high up to 20:1 in various studies. Upto 40 years of age small cell type predominates and has less association with smoking. After the age of 40 years squamous cell type is commonest in smokers and adenocarcinoma in non-smokers. The demographic pattern of lung cancer in India is similar to those of Western countries 40 years ago. The regional burden of lung cancer in the world is shown in Table 1.[3]

The burden of lung cancer in India as reported in the Globocan Report is shown in Table 2.

The distribution of different cancers and the mortality are depicted in Figures 1 & 2.

Table 3 shows demographic data of lung cancer patients in the Indian studies, divided broadly into two groups, studies before and after 1985. The mean age was 52.16 years before 1985 and 54.6 years after 1985 which is not significant different.

The smoker: non-smoker ratios have been lower in most of the Indian studies compared to those in the West. 40% of

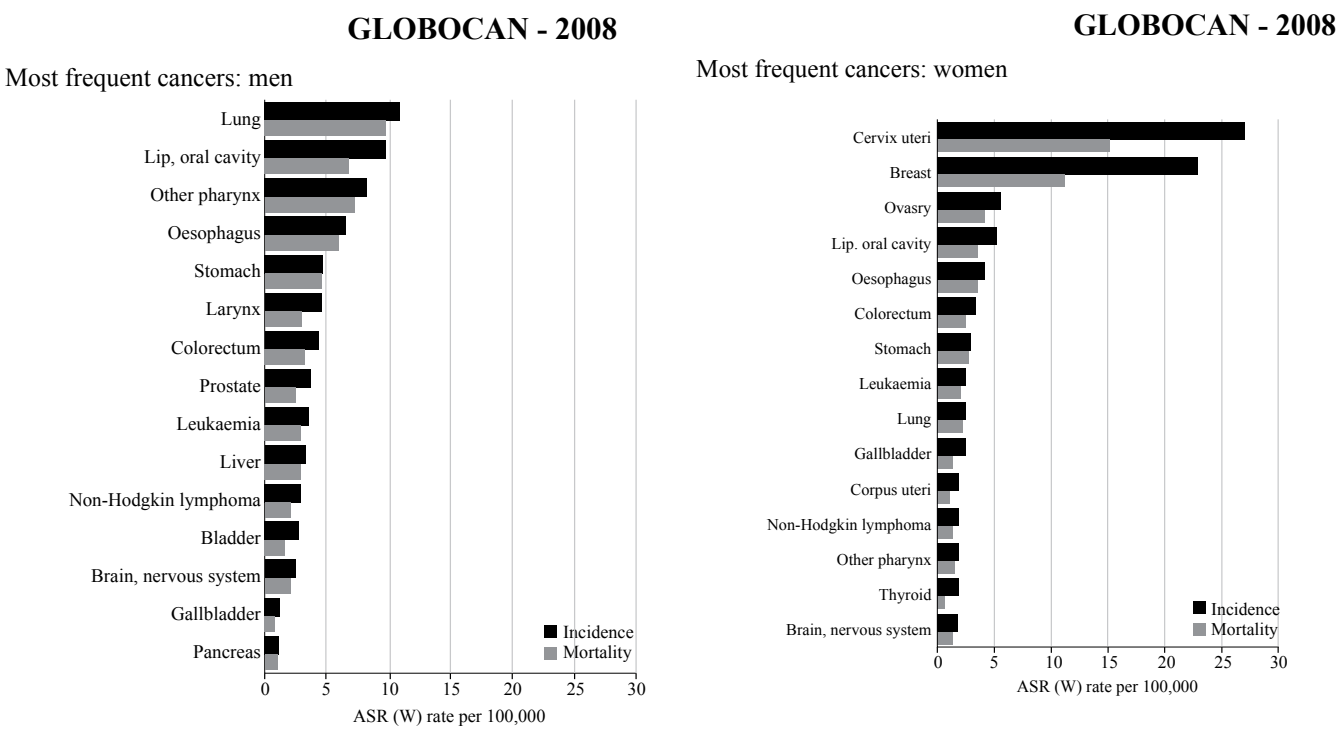

Fig. 1:

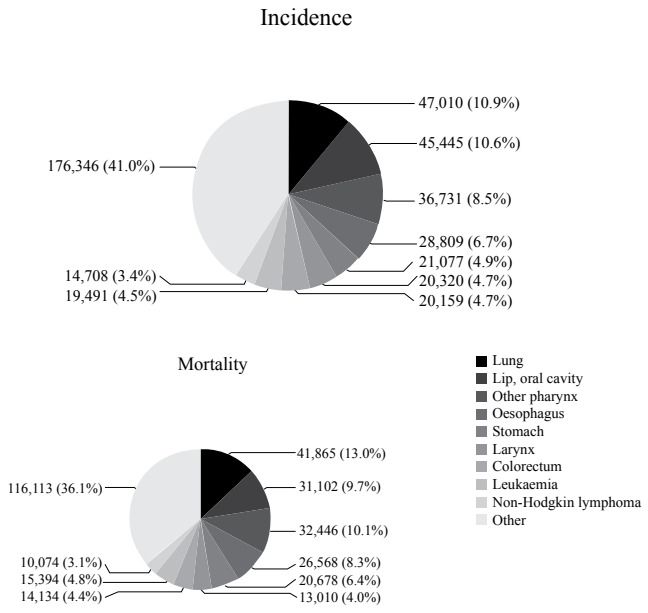

Fig. 2:

patients of lung cancer are less than 50 years of age and 11% are less than 40 years. In younger age group it is lung cancer is commonly misdiagnosed as tuberculosis.

Non small cell lung cancer constitutes 75-80% of lung cancers. More than 70 % of them are in Stages III and IV

Table 3 : Demographic data of Lung Cancer from Indian studies (12*)*

	Details		1958-1985	1986-2001
1.	Total cases		1735	2973
2.	M:F		6.67:1	5.76:1
3.	Mean age (yrs)		52.16	54.6
4.	SM:NS		2.5:1	2.7:1
5.	Urban:Rural		19.6 – 81.6	18.4 – 80.4
6.	Occupation	Farmer		13.9-48%
		Laborer		21.0 – 27.3%
		Clerk/teachers		16.7%
		Business		21.3%
		Housewives		8.0-14.7%
		Others		23%
7.	Religion	Hindus		75.1%
		Muslims		18.9%
		Christian		5.9%

when diagnosed making curative surgery difficult. The 5 year survival is only 14% and it has not changed dramatically in last two decades. Small cell lung carcinoma which constitutes 20% is in the extensive stage when diagnosed in 70% of patients.

While in many Western countries adenocarcinoma has become the commonest histological type of lung cancer in India it is still squamous cell carcinoma in both males and females. Compared to data before 1985 the series after 1985

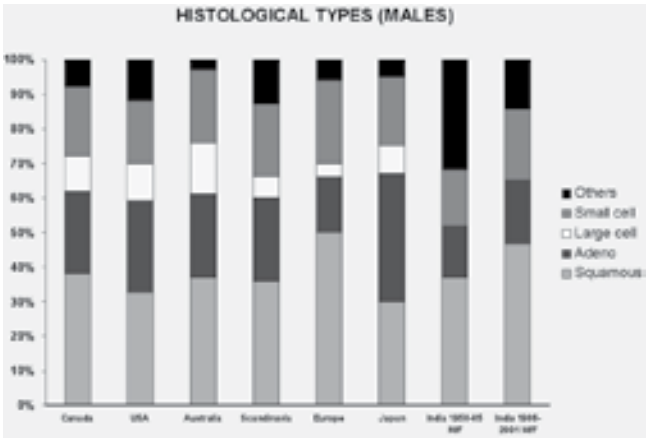

Fig. 3 : Showing histological types of lung cancers in Males in different countries including India.

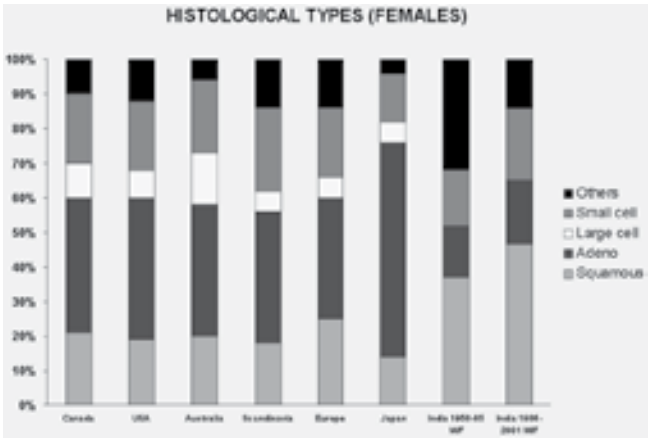

Fig. 4 : Showing histological types of lung cancers in Females in different countries including India.

show a marginal increase in percentage of adenocarcinoma. (Figure 3,4,5)

SMOKING AND LUNG CANCER IN INDIA

In patients with lung cancer, history of active tobacco smoking was found in 87% of males and 85% of females. History of passive tobacco exposure is found in 3%. So, 90% of all cases result from tobacco exposure.

The percentage of tobacco related products smoked in India are Bidi (28.4-79%), Cigarettes (9.0-53.7), Hooka (3.4- 77.3) and mixed (7.5 - 13.6).[13]

The relative risk of developing lung cancer is 2.64 for bidi smokers and 2.23 for cigarette smokers with 2.45 as the overall RR (Notani and Singvi, Bombay, 1974).[13] Bidi is more carcinogenic has been shown by other studies by Jussawalla & Jain (1979)[14] and Pakhala et al (1990).[15] Hooka smoking has been associated with lung cancer by Nafae et al (1973).[16]

In a recent study by Gupta D et al eighty nine per cent of men and 33 per cent of women among the patients were ever-

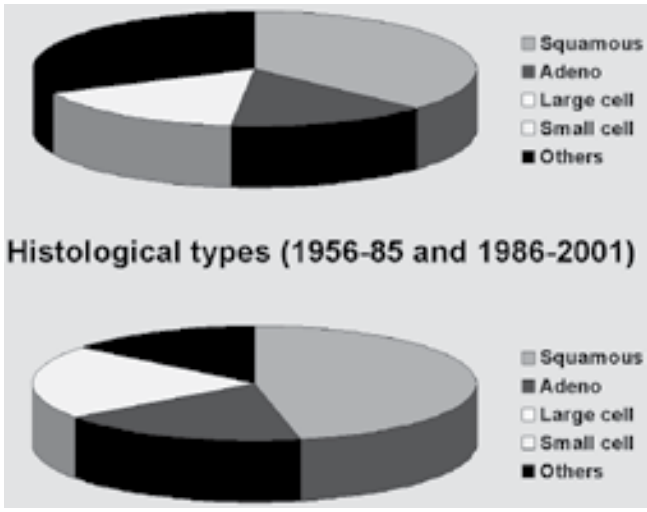

Fig. 5 : Distribution of histological types in different periods in India

smokers as compared to 60 per cent of men and 20 per cent of women among controls. The Odds Ratio (OR) for ever-smoking was 5.0 (CI 3.11-8.04) among men and 2.47 (CI 0.79-7.75) among women. Smoking of bidi and hooka as well as cigarettes had similar ORs for cumulative consumption.[17]

PASSIVE SMOKING AND LUNG CANCER

Environmental tobacco smoke is a known lung carcinogen. A meta-analysis of 41 studies showed that environmental tobacco exposure carries a Relative Risk of developing lung cancer of 1.48 (1.13-1.92) in males and 1.2 in females (1.12-1.29). Risk increases with increase in exposure. Exposure at work place results in relative risk of 1.16. In a study on non-smoking lung cancer patient's Environmental tobacco exposure during childhood carries a OR of 3.9 (95% CI 1.9-8.2). There is increasing risk with increase in number of smokers in the house and duration of exposure. Women had high OR of 5.1. Work places and vehicular pollutant exposure had weak association.

Another study by Rapiti et al has shown that environmental tobacco smoke exposure during childhood is strongly associated with the risk of developing lung cancer. (OR 3.9, CI 95% 1.9-8.2). The harmful effect was found mostly with cigarette smoking and there was increased risk with increased number of smokers and with increasing duration of smoking. Women had a high odds ratio of 5.1.

OCCUPATIONAL RISK OF LUNG CANCER[18,19]

Definitely known

I. Asbestos: Insulation workers and shipyard workers are exposed to asbestos. There is some increase in risk of lung cancer after 10 years of exposure, substantial risk after 20 years of exposure. Concurrent smoking increases the risk to 90 fold.

II. Arsenic: Smelter workers and Vineyard workers are exposed to arsenic. The risk is dose related. Lung cancers have upper lobe predominance and there may be multiple primaries.

III. Nickel Refinery workers: Squamous cell carcinoma is more common

IV. Radiation: Uranium mining. Oat cell carcinoma is more common.

V. Haematie mining: Due to radon exposure.

VI. Hard rock mining:

VII. Chromium exposure in ore mining and pigment manufacturing: squamous cell is most common.

VIII. Chloromethyl exposure in workers in industries: oat cell carcinoma is most common.

IX. Ethers and mustard gas: squamous and undifferentiated carcinomas most common.

X. Soots, tars exposure in coke oven workers.

XI. Oils and coke exposure in Gas house workers, roofers and rubber workers.

2. Suspected causes.

Acrylonitrite, berrylium, and dimethyl sulphate

GENETICS OF LUNG CANCER[20,21]

Cytogenetic studies have identified many chromosomal changes in lung cancer with numerical abnormalities, and structural aberrations including deletions and transolocations. These mutations include activation of the dominant cellular protooncogenes (which promote oncogenesis) of the ras and myc family and inactivation of the recessive or tumor suppressor genes (these genes help suppression of tumor development). Small cell Lung cancer is associated with oncogenes like c-myc, L-myc, N-myc, c-raf and tumor suppressor genes like p53 and Rh. Non small cell lung cancer is associated with K-ras, N-ras, H-ras, c-myc, c-raf and tumor suppressor genes like p16 and Rh.

DIET AND LUNG CANCER

There is increasing evidence that some dietary factors may be protective for lung cancer, and some may increase the risk. β-carotene was hypothesized to have a protective role. In the Western Electric study it was shown that persons with the lowest intake of foods rich in beta-carotene had the highest risk for lung cancer.[22] Smoking with deficiency of Vit A increases the chance of developing squamous cell carcinoma. Deficiency of retinoids leads to squamous cell transformation and there is increased B(a)-P DNA adduct formation. This is reversed by adding retinoids. However none of the three large subsequent trials showed a chemoprotective effect from beta-carotene or vitamins A or E dietary supplements.[23-26] Two of the trials (ATBC trial and CARET trial) showed an increased risk for lung cancer in the study participants who received beta-carotene.

Case control studies from China have shown that vegetable intake is a protective factor for lung cancer.[27] Shankaranarayanan et al found that green vegetable and bananas have protective effect on development of lung cancer.[28] Pumpkins and onions have most consistent protective effect. Animal food products and dairy products have a predisposing effect on lung cancer. Dietary cholesterol and animal fat increases the risk of lung cancer. Behera et al found that β-carotene and Vit A levels are reduced and vit C levels increased in patients with lung cancer compared to healthy controls but this is not statistically significant.[29] (Table No). Plant carotenoids alpha-carotene (found in carrots and tomatoes) and lycopene (found in tomatoes) are associated with 20-25% lower risk of lung cancer.[30] Flavonoids (found in apples) and isothiocyanates (found in cruciferous vegetables) has also been found to reduce the risk for lung cancer.[31]

AIR POLLUTION AND LUNG CANCER

Urban air contains many known carcinogens and exposure to this have been known to predispose to lung cancer mortality in U.K and U.S. Lung cancer is more frequent in subjects residing in neighborhoods where outdoor air is smoky.[32,33]

Studies from China have shown that coal burning at home is a significant risk factor for development of lung cancer in non-smoking females.[34] Coal smoke contains many potential carcinogens like SO2, CO, TSP, B(a)P, radon, thoron. Use of kerosene for cooking has also been seen associated with development of lung cancer but not in all studies. Incense smoke is suggested as a carcinogen since it contains high levels of benzpyrene.

In a study by Gupta D et al on risk factors of lung cancer cumulative exposure of > 45 yr in women to indoor air pollution from use of coal or wood for cooking or heating showed an OR of 1.43 (CI 0.33-6.30).[17] Residence in urban areas did not entail an increased risk for developing lung cancer.

REACTIVE OXYGEN SPECIES AND ANTIOXIDANT DEFENSE SYSTEM IN LUNG CANCER.

Studies by Sharma RN et al have shown that there is significant increase in vitro superoxide anion and hydrogen peroxide formation in alveolar macrophages from malignant lobe and neutrophils of lung cancer patients.[35] On the other hand activities of catalase and glutathione peroxidase were found to be decreased. The assays of antioxidant vitamins such as retinal and α-tocopherol revealed that their levels in alveolar macrophages from malignant lobe were found to be significantly decreased. This oxidant/antioxidant imbalance

in the malignant lobe of lung cancer patients could potentially enhance the neoplastic behaviour by augmenting both genetic instability of a tumor and its capacity to injure and penetrate the host tissues.

CLINICAL SPECTRUM OF PRIMARY LUNG CANCER IN INDIA

Jindal and Behera (1990) found in a series of 1009 lung cancer cases that both the mean and peak ages of lung cancer were lower compared to the West(54.3 years).[12] The smoker to non-smoker ratio was 2.7:1. Most of the patients had advanced disease and 51.8% had evidence of metastases. The commonest presentation was mass lesion with or without collapsein 68%, 25% had pleural effusion and 16.7% superior venacaval compression syndrome. Squamous cell carcinoma is found in 34.3%, anaplastic in 27.6%, adenocarcinoma in 25.9% and unclassified in 12.2%.

DIAGNOSIS OF LUNG CANCER

Clinical

The symptoms like fever, cough, expectoration, hemoptysis, fever, weight loss and anorexia are common to both tuberculosis and lung cancer and in India since tuberculosis is rampant it is not uncommon to find a lung cancer being treated as tuberculosis initially. But age of the patient, smoking history, mediastinal symptoms like hoarseness of voice, SVC obstruction and dysphagia etc. will favor lung cancer. Physical examination should look for signs of collapse or mass, clubbing, metastatic and non-metastatic complications of lung cancer.

The duration of symptoms before lung cancer is diagnosed are <3 months in 32.6 – 44% cases, 3-6 months in 16.0-34.3% and >6 months in 21.0 – 24.0%. Most cases were treated as tuberculosis for varying periods of time before a diagnosis is made.

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