RESEARCH COMMUNICATION

Patho-epidemiology of Lung Cancer in Karachi (1995-2002)

Yasmin Bhurgri[1,2]*, Asif Bhurgri[1,3] , Ahmed Usman[4], Nassar Sheikh[5], Naveen Faridi[6], Jawaid Malik[6-7], Rasheeda Ahmed[2], Naila Kayani[2], Shahid Pervez[2], Sheema H. Hasan[2]

Abstract

The objective of the study was to provide an overview of the demographics of lung cancer, the number one cancer killer of men in Karachi South (1995-2002). Lung cancer cases recorded at Karachi Cancer Registry during 1st January 1995 to 31st December 2004 were analyzed. To allow for maximum data completion, cases recorded from 1st January 1995 to 31st December 2002 were included for final analysis. Trends were studied by analyzing the age standardized incidence rates (ASR)s in 2 time periods, 1995-1997 and 1998-2002. Odds ratio for sex, age-groups, ethnicity, religion, and residence by socio-economic categories were calculated by considering all malignancies (except tobacco-associated malignancies) for each group, registered at KCR for the same period as controls. Cancer of the lung ranked the most frequent malignancy in men in Karachi in the entire 1995-2002 period, though it did not feature amongst the first 10 malignancies in the females. In the 1995-1997 period, the ASR per 100,000 population for cancer of the lung was 21.4 and 2.9 in males (M) and females (F) respectively. The mean age of the patients was 60.4 years (95% CI, 59.1-61.7) M and 53.7 years (95% CI 48.9-58.5) F. In the 1998-2002 period the incidence rate increased to 25.5 per 100,000 (M) and 4.2 per 100,000 (F). Thus between 1995 and 2002, the incidence of lung cancer registered a 19% increase in men and almost 100% in women. The component of adenocarcinoma in females remained stable during 8 years, but increased 55% in males. Histologic confirmation was 80%; majority of cancer cases presented as grade 3 and grade 4 lesions (62.3%), and were discovered at advanced stages (stage III 35.7%; stage IV 55.8%).The odds ratio (OR) in men was 4.5 (95% CI 3.7; 5.4). The risk of developing lung cancer increased with age, the highest risk being observed in the 65+ age group. A marginally higher risk was observed in the higher socio-economic categories for men and in the lower socio-economic categories for women. A higher risk was also observed for men who were residing along the coastal belt, and for ethnicities belonging to Southern Pakistan (Sindhi and Mohajir) residing in Karachi South. In conclusion, Pakistan at present falls into a low risk lung cancer region in females and a moderate risk region for males and the highest registered increase between 1995 and 2002 was observed in the older age groups (65+). It is however a cause of concern that the overall lung cancer incidence rates continue to rise. The age specific rates though stable in the younger age groups (35-49 years), are at present equivalent to contemporary rates in high- risk countries. These rates correspond with the trends of smoking prevalence in the younger age groups in the last 2 decades. Published studies have given alerts to increase in the smoking habits of the present day youngsters and with an expanding population the country can expect a substantial increase in lung cancer. This threat can only be averted by implementation of stringent anti-tobacco rules and health education; prohibition of smoking in educational institutions at all levels and a ban on the sale of cigarettes to minors.

Key Words: Lung cancer - epidemiology - Karachi, Pakistan

Asian Pacific J Cancer Prev, **7**, 60-64

Introduction

Lung cancer ICD-10 (International Classification of Diseases 10th Revision) categories C34 (WHO, 1992), is categorized as the most commonly diagnosed cancer worldwide. At the onset of the 20th century lung cancer was an unknown entity, yet by the end of the century it had acquired a status as one of the world's leading causes of preventable death (Rosen, 1993). The lung cancer pandemic of the 21st century was attributed to introduction of manufactured cigarettes (Doll and Hill, 1950; Levin et al., 1950; Wynder et al., 1950). Risk factors, other than tobacco, acting independently or synergistically can increase the individuals risk of developing lung cancer. These factors

*1 Karachi Cancer Registry, 2 Aga Khan University Hospital, Karachi, 3 Sindh Medical College, Karachi, 4 Jinnah Postgraduate Medical Centre, Karachi, 5 Gisborne, New Zealand, 6 Liaquat National Hospital, Karachi, 7 Ziauddin Cancer Hospital, Karachi *Correspondence: Karachi Cancer Registry, Department of Pathology, Sindh Medical College, Rafiqui Shaheed Road, Cantt, Adjacent Jinnah Postgraduate Medical Centre, Karachi, Pakistan E-mail: bhurgri@cyber.net.pk*

include occupational exposure to arsenic, asbestos, chromates, chloromethyl ethers, nickel, polycyclic aromatic hydrocarbons, radon and other agents. Outdoor and indoor air pollution, including combustion-generated carcinogens, radon, asbestos, passive cigarette smoke and fumes from cooking stoves and fires are also associated with lung cancer risk (Coultas and Samet, 1992). More than 87% of lung cancers are tobacco smoking related. Quitting smoking reduces an individual's risk significantly, although former smokers remain at greater risk for lung cancer than people who never smoked (Samet and Alberg, 2003).

A case control study conducted in Karachi had confirmed the overwhelming contribution of tobacco smoking to lung cancer in Pakistan and the evidence of carcinogenic effect of tobacco products other than cigarettes (Bhurgri et al., 2002). An increased risk for lung cancer among ever smokers [odds ratios (ORs) 22.8, 95% confidence interval [CI] 13.9-37.3], more among current smokers (OR 30.2, 95% CI 17.8-51.3) and less in ex-smokers (OR 16.7, 95% CI 9.8-28.4) was observed (Table 1). The risk appeared to be slightly higher among smokers of bidi than among smokers of cigarettes. Bidis do not burn very efficiently; and must be puffed continuously, resulting in the delivery of a higher dose of tar and nicotine (Wapiti et al., 1999). A cumulative risk was observed for tobacco consumption with both duration and amount of smoking having independent effects. Taking cigarette smokers as a baseline and adjusting for cumulative consumption, the OR estimates for subjects smoking only bidis was 1.7 (95% CI 0.5-5.0). Among women the OR for ever smoking was 10.6 (95% CI 2.5-45.3), that among men were 25.7 (95% CI 15.1-44.0); this difference might be caused by a difference in amount or duration of smoking. An increased risk was also observed for organic dust OR 2.2 (95% CI 1.2-3.8) and asbestos OR 8.0 (95% CI 1.4-44.9).

The carcinogenic effect of Environmental Tobacco Smoking (ETS) among never smokers was higher than reports from studies conducted in Europe, East Asia and North America (Hackshaw et al., 1997). Chewing was only marginally associated with increased lung cancer risk However, heavy exposure to this habit resulted in a significantly elevated odds ratio. A carcinogenic effect of snuff use on the lung was strongly suggested (Bhurgri et al., 2002).

The data of Karachi presented here is derived from the data-base of the Karachi Cancer Registry (KCR) which was established in 1995, as a collaboration of the International Agency for Research on Cancer (IARC) and has acquired 11 years stability (1995-2005) for Karachi South (KS), a sample population of Pakistan. KCR provides population-based descriptive epidemiology data of cancer incidence by age, sex, race, and time period according to site and histological characterization for various populations. Karachi South is the oldest catchment population of KCR. This is the southern-most district of Karachi with a population of 1,724,915; 929,394 (54%) males and 795,521 (46%) females; annual growth rate of 1.94% as calculated by the Federal Census Bureau. (Census, 1998). It includes all ethnicities of the country, namely Sindhi, Punjabi, Pathan, Baluch and Mohajir with a fair representation of all socio-economic categories. It comprises seven sub-divisions viz. Garden, Eidgah, City, Arambagh, Preedy, Saddar and Civil lines. The population distribution of KS is similar to the population distribution of Pakistan as regards age, gender, and religion. KS has the distinction of being the only district in the country with a representation of all ethnic and socio-economic groups of the country. It is thus a sample population of the country in the absence of other data sources.

The cancer profile (ICD-10 categories) in Karachi South (WHO, 1992; Bhurgri, 2004) males is lung (C33-C34 - 11.7%; Age Standardized Incidence Rates- ASR 25.5), oral cavity (C00-C06 - 13.1%; ASR 22.5), larynx (C32 - 6.1%; ASR 11.8), urinary bladder (C67 - 4.8%; ASR 9.9), prostate (C61 - 4.1%; ASR 9.8), lymphoma (C81-85;96 - 7.0%; ASR 9.6), pharynx (C09-14 - 4.3%; ASR 8.2), and colo-rectum (C18-21 - 4.4%; ASR 7.8). In females the commonest cancers are breast (C50 - 34.6%; ASR 69.1), oral cavity (C00-C06 - 8.9%; ASR 8.9), cervix (C53 - 4.1% ASR 8.6), oesophagus (C15 - 3.7%, ASR 8.6), ovary (C56 - 4.2%; ASR 7.8), lymphoma (C81-85;96 - 3.5%; ASR 7.2), gall bladder (C23-C24 - 2.6%; ASR 5.8), and skin (C43-44 - 2.6%; ASR

Table 1. Odds Ratios of Lung Cancer for Tobacco Smoking

	OR* (95% CI)	OR** (95% CI)
Type of tobacco product		
Never smoker	1.0# -	-
Cigarette only	20.1 (12.0-33.5)	1.0# -
Bidi only	18.3 (6.6-50.9)	1.7 (0.6-5.1)
Cigarette + bidi	53.7 (26.1-110.6)	1.6 (0.8-3.1)
Cigarette + bidi + others	71.0 (13.8-365.2)	1.7 (0.3-8.7)
Other combinations	12.8 (4.5-36.4)	0.2 (0.07-0.7)
Years of smoking		
Never smoker	1.0# -	-
1-19	8.4 (3.8-18.5)	1.0# -
20-29	10.1 (5.0-20.1)	1.3 (0.5-3.4)
30-39	20.7 (11.5-37.2)	2.4 (0.9-5.9)
40+	53.2 (29.4-96.2)	6.0 (2.4-14.8)
Average daily amount (cigarette-equivalents)		
Never smoker	1.0#-	-
1-9	4.1 (1.8-9.2)	1.0# -
10-19	14.5 (8.0-26.3)	3.2 (1.4-7.5)
20-29	36.7 (20.1-67.0)	6.9 (3.0-16.2)
30+	85.9 (43.9-168.3)	16.1 (6.5-39.7)
Cumulative consumption (cigarette-equivalents/day x years)		
Never smoker	1.0#-	
1-99	4.3 (1.9-9.7)	1.0#
200-399	7.8 (3.8-16.2)	1.9
400-599	18.1 (8.5-38.5)	4.5
600-799	26.8 (13.2-54.5)	6.4
800+	71.3 (39.4-129.3)	20.2

Reference: Bhurgri et al 2002
* Odds ratio adjusted for sex, age and hospital
** Odds ratio adjusted also for supplementary confounding factor # Reference category

5.6).

This present study was conducted with the objective of examining descriptive epidemiological characteristics, incidence and time trends of lung cancer in Karachi (1995-2002).

Materials and Methods

Incident cases of lung cancer, ICD-10 categories C34 registered at the KCR (1995-2004) were reviewed. The cases were categorized by tumour site and the age and sex of the patient. Trends were studied by grouping cases into two periods: period 1 (1995-1997), and period 2 (1998-2002). All morphological types were included, epithelial malignancies, lymphoma, and sarcoma.

The reported cancer data were rechecked, and residency status re-ascertained. People residing in the specified geographical regions for more than six months were considered residents. The cases were categorized by tumour site, age and sex of the patient. Variables recorded were the hospital patient-number, date of incidence, name, age, sex, address, ethnicity, topography, morphology, grading and staging. The data were classified using ICD-O3 (International Classification of Diseases-Oncology, 3rd edition) and computerized using a customized version of CANREG-3 software (WHO, 1990).

Manual and computerized validity checks for the cancer data were performed as per recommendations of International Agency for Research on Cancer (IARC) and International Association of Cancer Registries (IACR), (Parkin et al., 1994). This involved factors influencing comparability i.e. classification and coding. All cases whether clinically diagnosed or histologically verified, were included in the study. The residency status of cases was re-ascertained and rechecked. People residing in the specified geographical regions for more than six months were considered residents. Demographical variables recorded were the hospital patient-number, date of incidence, name, age, sex, address, ethnicity, topography, morphology, grading and staging. Tumours were categorized according to the UICC, TNM staging system, to standardize with the staging systems in other parts of the world.

Crude, age-adjusted, and age-specific incidence rates were calculated based on the 1998 census for Karachi South (population of 1,724,915; males 929,394 and females 795,521), annual growth rate 1.94% (Census 1998). The growth rates were based on the inter-census growth-rate and measures for inflow and outflow of population, calculated by the Federal Bureau of Statistics. Standardized incidence rate was calculated with an external reference population (Segi M, 1960). The methodology applied was direct standardization, using 5-year age groups. The rates given are the annual incidence per 100,000 population, averaged over the number of years for which data are presented. Trends were studied by analyzing the ASR for 2 time periods, 1995-1997 and 1998-2002.

To determine the socio-economic profile, the district was divided into 3 subcategories based on the income of approximately 70% of the resident population. The categories ranged from 1 to 3 in an ascending income strata (table 1). Category I was composed of the predominantly financially deprived class with an annual income of less than $2000, and a low literacy level. Residents of category II had an annual income range of $2001-$20,000 with a moderately high literacy. Category III was largely made up of educated professionals, with an annual income of more than $20,000 (Table 1). A sample survey was conducted to categorize the financial status of the population.

Odds Ratio for sex, age-groups, ethnicity, religion, and subdivision by socio-economic categories were calculated by considering all malignancies (except tobacco associated malignancies) for each group, registered at KCR for the same period (1st January 1995 to 31st December 2002) as controls. The malignancies considered were ICD-O3, morphological categories, M-8000 to M-8991 (Fritz et al., 2000). All specimens for 1998-2002 were initially evaluated on H&E stained sections and subsequently when required immunohistochemical analysis was performed by employing envision technique. The data were analyzed using SPSS 13.0.

Results

Cancer of the lung ranked the most frequent malignancy in men in Karachi in the entire 1995-2002 period, though it did not feature amongst the first 10 malignancies in the females. The age standardized incidence rates (ASR) per 100,000 population for cancer of the lung was 21.4 and 2.9 in males and females respectively in 1995-1997. The mean age of the patients was 59.7 years (95% CI, 58.4-59.7), males 60.4 years (95% CI, 59.1-61.7), and females 53.7 years (95% CI 48.9-58.5). In 1998-2002 the ASR was 25.5 and 4.2 per 100,000 in males and females respectively. The mean age of the patients was 60.0 years (95% CI, 58.9-61.1), males 60.0 years (95% CI, 58.9-61.3), and females 59.9 years (95% CI 56.2-63.7) (Table 2).

The gender ratio remained approximately 8.0 in the entire period (1995-2002). About 80% of the malignancies were histologically confirmed. Majority of the cancer cases presented as grade 3 and 4 lesions (62.3%), and were discovered at advanced stages (stage III 35.7%; stage IV 55.8%). The proportion of squamous cell carcinoma, small cell carcinoma and large cell carcinoma were 61% and 58.8% in males and females in 1995-1997. The reciprocal rates in 1998-2002 were 34.8 and 33.3%. The component of adenocarcinoma in females had remained stable in 8 years, but increased 55% in males (Table 3).

The age specific incidence rates (ASIR) in males show a gradual rise from 35 to 65 years of age. Subsequently an apparent decrease in the risk was observed. The ASIR showed an earlier onset of disease in period two and a continuous increase in the older age groups.

The frequency distribution by ethnicity was Sindhi (17.9% M; 30.9% F), Punjabi (14.6% M; 30.9% F), Pathan (8.4% M; 7.1% F), Baluch (7.8% M; 4.8% F), Urdu speaking

Table 2. Frequency and Odds Ratios of Cases on the Basis of Age-groups, Residence, and Religion

Frequencies	Male (%)	Female	Odds Ratio (95% CI)	
Age groups				
0-14	0.5	0.0	0.01	(0.07-1.5)
15-24	0.5	3.7	0.01	(0.07-1.5)
25-34	0.5	3.7	0.01	(0.07-1.5)
35-44	5.2	3.7	0.12	(0.07-0.2)
45-54	19.0	18.5	0.36	(0.2-0.47)
55-64	26.2	37.0	0.38	(0.3-0.49)
65-74	36.6	33.3	0.60	(0.5-0.74)
75+	11.4	0.0	0.60	(0.5-0.83)
Subdivisions				
Category I	%	%	†	
City	28.5	21.8	1.02	(0.87-1.2)
Category II				
Garden	17.2	19.2	1.08	(0.89-1.30)
Eidgah	7.8	6.4	0.89	(0.79-1.60)
Arambagh	9.0	6.4	1.00	(2.13-3.47)
Preedy	6.0	2.6	0.87	(0.76-1.36)
Category III				
Saddar	21.2	30.8	0.85	(0.18-5.7)
Civil Lines	10.3	12.8	1.26	(1.1-1.58)
Religion				
Muslim	95.8	93.6	1.04	(0.71-1.52)
Christian	1.3	3.8	0.66	(0.62-1.75)
Hindus	2.5	2.6	1.26	(0.84-1.88)

CI- Confidence Intervals

Mohijirs (28.6% M; 14.2% F), Gujrati speaking Mohajirs (5.3% M; 2.4% F), Memon Mohajirs (14.0% M; 4.8% F) and others (2.5% M; 4.8% F).

The odds ratio (OR) in men was 4.5 (95% CI 3.7-5.4). The risk of developing lung cancer increased with age, with the highest risk being observed in the 65+ age group. The odds ratio for socio-economic residential gender stratified categories remained between 0.85 and 1.26 with a slightly higher risk in the higher socio-economic categories (Table 1). A marginally higher risk was observed for the men residing in higher socio-economic areas [Civil Lines, OR 1.26 (95% CI 1.1-1.58)] and for women residing in lower socio-economic areas [City, OR 2.4 (95% CI 1.9-2.9)]. A higher risk was also observed for men residing along the coastal belt, and for ethnicities belonging to Southern Pakistan (Sindhi and Mohajir) residing in Karachi South.

Table 3. Relative Frequencies of Histological Subtypes by Site: Karachi and the IARC Database

Morphology	% (Total) Karachi 1995-1997		1998-2002		% (Total) IARC
	Male	Female	Male	Female	
Squamous Cell Carc	61.0	58.8	34.8	33.3	27.2
Adenocarcinoma	6.9	17.6	10.7	17.7	17.2
Small Cell Carc	12.8	5.9	16.2	4.4	12.4
Large and undifferentiated cell carcinoma	11.6	8.8	14.0	11.1	6.5
Other carcinomas	-	-	-	-	0.6
Unspecified carc	7.6	8.8	23.3	24.4	21.6
Sarcomas	-	-	0.3	-	0.1
Other specified	-	-	0.8	2.2	0.1
Unspecified	-	-	-	6.7	14.3

Discussion

Lung cancer has ranked the most frequent malignancy in men in Karachi during the entire 1995-2002 period, though it does not feature amongst the first 10 malignancies in females. Lung cancer is more common in developed countries and less common in developing countries (Parkin et al., 1994) with a rising epidemic in the developing world predicted by Parkin and Boffetta a decade ago in 1994.

Pakistan falls into a low risk region in females and a moderate risk region for males. This supports the observation of Alberg and Samet , in 2003 that 'international rankings of lung cancer incidence for men and women from the same countries tend to differ only slightly, so that the highest rates of lung cancer occur in the same regions of the world for both sexes'.

In Karachi, the highest registered increase in the incidence of lung cancer, was observed in the older age groups (65+). The rates though stable in the younger age groups (35-49 years), are equivalent to the rates of contemporary individuals in the developed countries like US. As these are younger birth cohorts, this pattern should translate into a substantial increase in the incidence and occurrence of lung cancer in Pakistan, parallel to rates in the high risk zones. These trends provide clues about the determinants of lung cancer and complements data published on smoking habits of the population.

One out of every two to three middle-aged men in Pakistan smoke cigarettes (Ahmad et al., 2005). The overall smoking prevalence has not changed in the last decade. In 1998 a nation-wide survey in Pakistan had found that 21.6% of the subjects aged 15 or above were smokers with a higher proportion among men (36%) than women (9%), (Alam, 1998), whereas a cross-sectional survey in 2004, reported an overall 34% prevalence of current smokers (Khuwaja et al., 2004), with increased rates due to the earlier age of onset (15-29 years) (OR=4.2, 95% CI 2.1-7.3), unmarried (OR=3.1, 95% CI 1.9-5.4), educated (OR=2.0, 95% CI 1.2-3.3), and being student (OR=3.2, 95% CI 1.8-5.4). The majority (55%) began smoking when younger than 25 years and 42% used tobacco in other forms as well.

Several studies have reported a high prevalence of smoking in educational institutions. Rozi et al in 2005 reported a 13.7% prevalence of smoking amongst high school students. The lack of awareness of the risk factors of smoking may not be very clearly elucidated, as young medical students and doctors have a higher prevalence of tobacco use, in comparison to the general population. Omair et al in 2002 reported a higher prevalence of smoking among male students of medical colleges; Piryani and Rizvi in 2004, reported a higher frequency of smoking among young doctors. This is the birth cohort which may be responsible for higher lung cancer rates in the country in the future. However these are the groups of educated, professionals who may migrate out of the country, and may register as lung

cancer cases elsewhere. They may thus not have a strong impact on cancer rates in Pakistan in the future.

It is a global observation within all countries that lung cancer in men outpaces that in women (Alberg and Samet , 2003). The gender ratio of 8, observed in Karachi, is one of highest in the world, corresponding with the smoking habits of the population. The highest risk of lung cancer remains in the women of lower socio-economic background and may be associated with the prevalence of huqqa and bidi use. Nisar et al in 2005 surveyed adult women of low socio-economic group and concluded that huqqa use was prevalent in 79%, with either an early onset of the habit, usually in childhood or after marriage by peer pressure especially in joint families.

Notable shifts have taken place in the incidence rates of lung cancer by histologic type in men. There was an increase in adenocarcinoma lung in males, though the rates remained stable for women. The rates of adenocarcinoma lung despite the increasing rates in men remain below the rates in women. The proportion of squamous cell carcinoma, small cell carcinoma and large cell carcinoma were 61% and 58.8% in males and females in 1995-1997. The reciprocal rates in 1998-2002 were 34.8 and 33.3%.†The apparent fall in the frequency of squamous cell carcinoma in the 1998-2002 period, can be explained by the increase in the diagnosis of advanced lung cancer cases on the basis of clinical investigations like CT scan and MRI, where the malignancy was reported as an unspecified carcinoma/malignancy.

A warning and a cause of concern are the rising incidence rates of lung cancer apparent for both genders. If the 18% increase in the incidence rates in men and the 100% increase in women over the last 8 years, continues unabated, the country will over the next 5-10 years move into the high risk zone. The countries in South Central Asian Region, in the immediate neighbourhood of Pakistan (Iran and India) show a much lower incidence (Sadjadi et al, 2005; Ferlay et al, 2004) and stable or decreasing trends. This regional distribution provides clues to the prevalence of risk factors of lung cancer in this geographical area and can be interpreted as better awareness of tobacco as a carcinogen.

References

Ahmad K, Jafary F, Jehan I, et al (2005). Prevalence and predictors of smoking in Pakistan: results of the National Health Survey of Pakistan. *Eur J Cardiovasc Prev Rehabil*, **12**, 203-8.

Alam SE (1998), Prevalence and pattern of smoking in Pakistan. *J Pak Med Assoc*, **48**, 64-6.

Alberg AJ, Samet JM (2003) Epidemiology of lung cancer Chest, 123, 21S-49S

Bhurgri Y (2004). Karachi Cancer Registry Data, Implications in NCCP Pakistan. *Asian Pac J Cancer Prev*, **5**, 86-91.

Bhurgri Y, Decullier, E, Bhurgri A, et al (2002). A case-control study of lung cancer in Karachi. *Int J Cancer*, **98**, 952-5

Boffetta P, Parkin DM (1994) Cancer in developing countries. *Cancer J Clin*, **44**, 81-91

Coultas DB and Samet JM (1992) Occupational lung cancer. *Clin Chest Med*, **13**, 341-54

Doll R, Hill AB (1950). Smoking and carcinoma of the lung. *BMJ*, **2**, 739-48

Ferlay J, Bray F, Pisani P and Parkin DM (2004) Globocan 2002: Cancer Incidence, Mortality and Prevalence Worldwide IARC CancerBase No. 5. version 2.0, IARCPress, Lyon.

Fritz A, Percy C, Jack A, et al (editors) (2000) International classification of diseases for oncology. 3rd ed. Geneva (Switzerland), World Health Organization.

Hackshaw AK, Law MR, Wald NJ (1997) The accumulated evidence on lung cancer and environmental tobacco smoke. *BMJ*, **315**, 980-8.

Khuwaja AK, Kadir MM (2004) Smoking among adult males in an urban community of Karachi, Pakistan. *Southeast Asian J Trop Med Public Health*, **35**, 999-1004.

Levin ML, Goldstein H and Gerhardt PR (1950). Cancer and tobacco smoking: a preliminary report. *JAMA*, **143**, 336-8.

Nisar N, Billoo N, Gadit AA (2005). Pattern of tobacco consumption among adult women of low socio-economic community Karachi, Pakistan. *J Pak Med Assoc*, **55**, 111-4.

Omair A, Kazmi T, Alam SE (2002). Smoking prevalence and awareness about tobacco related diseases among medical students of Ziauddin Medical University. *J Pak Med Assoc*, **52**, 389-92.

Parkin DM, Pisani P, Lopez AD, et al. (1994) At least one in seven cases of cancer is caused by smoking: global estimates for 1995. *Int J Cancer*, **59**, 494-504.

Parkin DM, Chen VW and Ferley J (eds.) (1994). Comparability and Quality Control in Cancer Registration, IARC Technical Report No.19 International Agency for Research on Cancer Lyon.

Piryani RM, Rizvi N (2004). Smoking habits amongst house physicians working at Jinnah Postgraduate Medical Centre, Karachi, Pakistan. *Trop Duct*, **34**, 44-5.

Rosen G. A History of Public Health. Baltimore, MD: The Johns Hopkins University Press, 1993

Rozi S, Akhtar S, Ali S, Khan J (2005). Prevalence and factors associated with current smoking among high school adolescents in Karachi, Pakistan. *Southeast Asian J Trop Med Public Health*, **36**, 498-504.

Sadjadi A, Nouraie M, Mohagheghi MA, Mousavi-Jarrahi A, Malekezadeh R, and Parkin DM (2005). Cancer occurrence in Iran in 2002, an international perspective. *Asian Pac J Cancer Prev*, **6**, 359-63.

Segi M (1960). Cancer Mortality in Selected Sites -in 24 Countries (1950-57), Sendai, Tohoku University School of Public Health.

Wapiti E, Kendal SK, Gupta D, and Boffetta P (1999). Passive smoking and lung cancer in Chandigarh, India. *Lung Cancer*, **23**, 183-9.

WHO (1992) International Statistical Classification of Diseases and Health Related Problems 10th Revision, Geneva, World Health Organisation.

Wynder EL, Graham EA (1950). Tobacco smoking as a possible etiologic factor in bronchiogenic carcinoma: a study of six hundred and eighty-four proved cases. *JAMA*, **143**, 329-36