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March 2006

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Recommended Citation

Bhurgri, Y., Bhurgri, A., Nishter, S., Ahmed, A., Usman, A., Pervez, S., Kayani, N., Ahmed, R., Hassan, S. H., Riaz, A., Bhurgri, H., Bashir, I. (2006). Pakistan - Country Profile of Cancer and Cancer Control 1995-2004. *Journal of the Pakistan Medical Association*, 56(3), 124-130.

Available at: http://ecommons.aku.edu/pakistan_fhs_mc_pathol_microbiol/232

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**Pakistan - Country Profile of Cancer and Cancer Control
1995-2004**

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Pakistan is an Islamic Republic in Southern Asia, bordering the Arabian Sea (30 00 N, 70 00 E). It is situated between India on the east, Iran and Afghanistan on the west and China in the north. The total area of Pakistan is 803,940 sq km, 778,720 sq km of land and 25,220 sq km of water. Largely an agricultural country the arable land constitutes 27.87% of the total land area. The climate is mostly hot, dry desert, becomes temperate in northwest and arctic in the north. The terrain is flat Indus plain in the east; mountains in north and northwest; and the Baluchistan plateau in the west. The administrative divisions of the country are 4 provinces (Sindh, Punjab, Baluchistan and North-West Frontier Province), a territory (Federally Administered Tribal Area), 1 capital territory (Islamabad), and the Pakistani administered portion of the disputed Jammu and Kashmir region (Azad Kashmir and the Northern Areas).¹

The estimated population of Pakistan is 162,419,946, with an annual population growth rate of 2.03% (July 2005). The population is young, the median age being 19.44 years in males and 19.74 years in females. The age structure is a typical developing country pyramid with the 0-14 years constituting 39.6% of the population (male 3,104,311/female 31,244,297); the 15-64 years group forming the bulk i.e. 56.3% (male 46,759,333/female 44,685,828) and the 65+ years comprising 4.1% (male 3,189,122/ female 3,437,055) of the population. The major ethnic groups in the country are Punjabi, Sindhi, Pashtun (pathan), Baloch, Muhajir (immigrants from India at the time of partition and their descendants). Muslims comprise 97% of the population with the Christians, Hindus, and other religions comprising 3% of the population.¹

Pakistan is a developing country, which falls into the

low to medium resource category by WHO classification. Since 2001, it has had a bolstered economy and renewed access to global markets. Despite a positive outlook, the inflation rate is 4.8% (FY03/04 estimate), purchasing power parity is \$347.3 billion (2004 estimate) and present exchange rates Pakistani rupees per US dollar are 60.0. Islamabad raised the development spending from about 2% of GDP in the 1990s to 4% in 2003, and foreign exchange reserves continued to reach new levels in 2004, supported by robust export growth and steady worker remittances. This is a positive outlook for Pakistan, though there is skepticism regarding long-term developmental prospects, given Pakistan's low level of development. Medium-term prospects for all development projects including health related ones are the best in nearly a decade. The world health report 2005² on Pakistan indicates a GDP per capita (2002) of \$1,920. The total health expenditure per capita (HE/GDP) in 2002 was \$62, which is 3.2% of GDP and less than the 2001 HE/GDP which was \$85. Life expectancy at birth for males and females is 62.0 years and adult mortality male/female (per 1000) is 225/199.^{1,2}

The Federal Government of Pakistan in Islamabad and the Provincial Health Governments share the responsibilities of health coverage, with a rapidly increasing private health sector. The Government health coverage is limited to subsidized in-patient and out-patient care, but is not adequate to give cover to the thirty two percent of the population which remains below poverty line (FY00/01 estimate). Health insurance coverage and employer benefits are negligible. Free immunization coverage is restricted to EPI and selective communicable diseases like polio. Free cancer screening, old age benefits and health care, concept of Medicare and Medicaid-like programmes, and subsidized pharmaceutical drug programmes have not been implemented. The majority of population (approximately 70%) is responsible for their own and their extended families' health expenditures. In this background the National Cancer Control Program (NCCP) evolved as part of the National Action Plan using evidence-based strategies for prevention, early detection, treatment, and palliation as advised by WHO.³⁻⁷ The magnitude of cancer burden was assessed with the help of the sample data of Karachi South (1995-1997), as published in Cancer Incidence in the Five Continents (CIV) volume VIII, and cancer estimates for Pakistan in Globocan.⁸⁻¹¹ Time trends in cancer were measured in 2 periods, 1995-1997 and 1998-2002. Geographical variations were analyzed on the basis of the joint Karachi Cancer Registry (KCR) and Aga Khan University Cancer Surveillance for Pakistan (ACSP), data.

Assessment of cancer burden

Pakistan has been historically unsuccessful in sustaining the

numerous population-based registries established in the past. In the first 5 decades published data of a few sporadic institution-based registries, and the Pakistan Medical Research Council (PMRC) provided the country with its only cancer database.¹² This data had limited value as the demographic details of the patients were partially recorded; there was associated selection bias of different hospitals, lack of continuity and geographical variations within the country could not be clearly determined. The Karachi Cancer Registry (KCR) was established in 1995. The registry was developed with the perspective of measuring the cancer burden through a sample population of the country. KCR, the first population-based cancer registry of Pakistan has acquired 11 years stability (1995-2005) for the data of Karachi South (KS), the sample population of Pakistan. At present KCR is a voting member of International Association of Cancer Registries (IACR).

The Aga Khan University Cancer Surveillance for Pakistan (ACSP), was established in 2000 at the Aga Khan University Pathology-based Cancer Registry (APCR), and covers a large geographical area and population of Pakistan, through 64 centers. This coverage is likely to increase at the rate of a minimum of 10 new centers annually in the future. This data has been of immense value in determining the geographical variation of malignancies in Pakistan and as a strong prop for KCR. APCR is an associate member of the IACR. KCR with the help of ACSP has calculated the incidence of Karachi Division (1998-2002), population of 9,802,134; 5,261,712 males and 4,540,422 females, annual growth rate 3.52, Quetta population 759,245 [56% males (M) and 44% females (F)], annual growth rate 4.13; Hyderabad population 2,840,653 (52.2% M, 47.8% F) annual growth rate 1.13; Larkana, population 4,169,488 (51.8% M, 48.2% F) annual growth rate 2.49 and Peshawar population 3,880,989 (52.2% M, 47.8% F) annual growth rate 3.17. There is a variable degree (30-40%) of incompleteness in these data, however this is the nearest Pakistan has gone towards assessment of individual cancer burden and the data is fast acquiring completion.¹³⁻¹⁵

The age-standardized rates (ASR) for cancer (all sites), 1995 to 1997 in KS were 139.11/100000 in males and 169.5/100000 in females. Corresponding rates for 1998 to 2002 were 179.0/100000 in males and 204.1/100000 in females. In the 1995-1997 data, the most common malignancies (ASR per 100,000) in males were lung (21.3), oral cavity (14.2), urinary bladder (9.0), and larynx (8.8). The cancers in females were breast (53.1), oral cavity (14.5), and ovary (10.9). The data 1998 to 2002 showed a rising incidence for lung (25.5), larynx (11.8), and urinary bladder (9.9) in males and breast (69.1), esophagus (8.6), and cervix (8.6) in females. The mean age of cancer all sites was 51.2 years (95% CI 49.4; 53.1) male; 50.0 years (95%

CI 48.2; 52.4) females in 1995-1997. Corresponding rates for 1998-2002 were 49.5 years (95%CI 47.5; 51.4) in males and 53.7 years (95% CI 51.5; 55.6) in females. Histological confirmation remained 97%, with 47.1% presenting in grade II or I; 65.0% presenting as stage III and IV.

KCR has registered an increase in the incidence of cancers during the last decade, more apparent in females. This could be attributed to a better coverage over a decade, however this dramatic increase was not observed uniformly for all cancer sites. A rising incidence of breast cancer, with the highest recorded rates for reproductive age breast cancer remains a salient feature of KCR data. A cohort shift was observed in the first generation of female Karachiites born in Pakistan. This was also associated with a marginal down staging of breast cancer despite the lack of intervention and absence of cancer control measures at an official level. The most striking increase however was observed in oral cavity cancer in both genders.

The cancer burden of Karachi South is primarily due to:

1. Tobacco associated Cancers

Tobacco-associated cancers are responsible for approximately half the tumors in males and a quarter in females. Eight of the ten most frequent cancers in men (lung, oral cavity, larynx, urinary bladder, pharynx, esophagus and prostate) and two of ten most common cancers in females (oral cavity and esophagus) are associated with tobacco use. All these cancers have registered a dramatic increases.

Oral cavity cancer in Karachi South ranks second in both genders with similar rates in both. The incidence is the highest reported worldwide. The age standardized incidence rates (ASRs) per 100,000, 1st January 1998 to 31st December 2002 in Karachi South were 22.5 in males and 20.4 in females whereas the ASRs per 100,000 for 1st January 1995 to 31st December 1997 were 14.2 and 14.5 in males and females, respectively. A progressive increase in the incidence rate has been observed in both genders, more apparent in males. Sub categories of oral cancer show a variation in trends over the last decade. Lip cancer in males decreased and the age-standardized incidence rate fell from 0.9 to 0.7 per 100,000 from period 1 (1995-1997) to period 2 (1998-2002). The rates remained leveled at 0.4 in females. An increased incidence is observed for tongue, the ASR per 100,000 increased from 4.2 to 5.3 in males from 4.9 to 6.6 in females. The highest increase was observed in cancers of the mouth. The ASR per 100,000 in males increased from 9.1 during 1995-1997 to 15.3 in 1998-2002; whereas in females the rates increased from 9.3 to 12.3. The major risk factors of oral cancer in Pakistan are smoking, areca nut, betal quid or paan and tobacco chewing, naswar, paan masala, gutka and poor nutrition. Alcohol consumption is not a prevalent habit in Karachi, therefore not a major risk

factor. Smoking is considered an inappropriate hobby socially for females; however the practice of chewing rates are high in all socio-economic circles. A survey in Karachi indicated that 36% of the males and 44% females in Karachi chew pan or pan with tobacco. The age specific rates show a gradual rise to a maximum in the 7th decade. in both sexes.^{16,17}

Lung cancer remains the leading malignancy amongst males in Karachi South. The ASR is moderately high for males, which is a seven times higher risk as compared with females in Karachi. This ratio is the highest in the world region. The major risk factor for lung cancer i.e. tobacco smoking is practiced by 36% of the males and 9% of the females in Karachi. Squamous cell carcinoma, with a lesser percentage of small cell and large cell carcinoma is the predominant morphology, with a small percent of adenocarcinomas observed in females. The age specific rates show a gradual rise from the 4th to 6th decade with a sharp ascent in the 7th decade. The stage at diagnosis is usually very advanced, vast majority being diagnosed with a stage 4 disease. Late presentation and lack of facilities for thoracic surgery make the prognosis very poor. The 5-year survival for lung cancer (1995 cases) was 1%.¹⁸ As for other tobacco-related cancers the age-standardized incidence rates for pharynx are high in Karachi. The risk is two-fold in the males. The age specific rates show a gradual rise to a maximum in the 6th decade in males and 7th decade in females. Hypopharynx is the most common site for cancer in the pharynx, a pattern observed elsewhere in the subcontinent. The ASR of cancer oesophagus, predominantly squamous cell carcinoma was seen to be marginally higher in the females. The male:female ratio remains equal, whereas most other world regions show a greater risk in males. The age specific rates show a gradual rise to a maximum in the 7th decade, in both sexes.¹⁹⁻²² Tobacco chewing, undernourishment, and lower socio-economic status appear to be risk factors. The highest recorded rate for larynx cancer for males in Asia is seen in Karachi, with the males exhibiting a six times higher risk than the females. The age specific rates show a gradual rise to a maximum in the 7th decade, in males and 8th decade in females.

There was an apparent lower risk for prostate cancer in 1995-1997, which may be an indicator of 'missing cancers' diagnosed on the basis of clinical investigations or a lack of use of clinical investigations and biochemical markers for confirmatory diagnosis. The lower life expectancy in Pakistan and also the lack of post-mortems substantially contributed to the low age-standardized incidence rates for prostate cancer in comparison to the developed countries. However in the 1998-2002 data the incidence had increased, nearly doubled. The age specific rates show a gradual rise from the 5th to 7th decade with a sharp ascent in the 8th decade. The incidence rates for urinary bladder cancer

registered a marginal increase. The age specific rates show a gradual rise from the 4th to 6th decade with a sharp ascent in the 7th and 8th decade in males and the 8th decade in females.

2. Cancer of the breast

This is the most frequent cancer of women in Karachi, accounting for one-third of the cancers in the females. The incidence of breast cancer is very high in Karachi; the highest in Asia, except for the Jews in Israel. The incidence of reproductive age breast cancer is the highest reported globally. The age-specific curves show a gradual increase in risk up to the 7th decade, followed by a flattening or an actual apparent decrease in risk. Reproductive factors cannot be considered major risk factors as early marriages, multiple births and prolonged breast-feeding are the norm. Early menarche, late menopause and thus the prolonged effect of reproductive hormones could be the other possible risk factors along with dietary factors and obesity. The roles of BRCA1, BRCA2 and other genetic factors have not been adequately studied in this population. A family history of breast cancer is noted in approximately 3% of the cases registered. The predominant histological type is duct cell carcinoma. Prognosis is fair and the 5-year survival for breast cancer (1995 cases) was 53%. A pronounced increase in the incidence of breast cancer has been observed in the last 5 years. The incidence rate of breast cancer and the rise in incidence in Karachi South are comparable to the highest risk regions of the world. This reflects a genuine continuous increase in incidence though a percentage of it could be attributed to a literate, urban area awareness of breast cancer, a response to non-government early detection initiatives and ready availability of mammography and breast screening clinics.

3. Gastrointestinal malignancies

The lower incidence of stomach cancer and lymphoma in comparison to the developing countries of Asia and Africa indicates that the high *Helicobacter pylori* (*H. pylori*) prevalence²³ is neutralized to some extent by protective influences, yet to be studied. The age specific rates for gastric adenocarcinoma show a gradual rise to a maximum in the 7th decade, in both sexes. There is an identical risk for both sexes, the male:female ratio being 1. A progressive rise in the incidence rate has been observed in the females over the past 5 years. The incidence of colo-rectal carcinoma is similar to Asian countries, but much lower than in the developed countries. The risk is equal in both sexes at present. However a 41 % rise in incidence was noted in the males between 1995 to 1999, which may indicate a higher risk in the males in future. The incidence for liver cancer is lower than Eastern Asia, but higher than the Sub-continent and the

West. The risk is equal in both sexes. The age specific rates show a gradual rise to a maximum in the 7th decade, in males and 8th decade in females. Morphologically hepatocellular carcinoma predominated with a much smaller percentage of cholangiocarcinoma. The low incidence of liver cancer correlates well with the prevalence of HBV infection.²⁴ A seroprevalence of HBV sAb of 3.0% and HCV Ab of 4.0% has been observed in healthy children and HbsAg 2.3% with HCV 1.2% in healthy blood donors.²⁵ The highest incidence for gall bladder cancer in the world region for females is seen in Karachi. The age specific rates show a gradual rise to a maximum in the 7th decade, in both sexes. Females show a four times higher risk than males. A steady rise in incidence has been observed in the females. The higher prevalence of gallstones could be the major etiological determinant with dietic, hormonal, genetic and biological pathogens (*H. pylori*, viruses and parasites) as co-determinants.

4. Female genital tract

Malignancies of the female genital tract i.e. cervix, ovary and uterus (body) comprises 13.1% of the total cancers in the females. A progressive incidence rate has been recorded for all in the last 10 years. At present cancer cervix is rated the third most frequent malignancy in females, it replaces cancer of the ovary in this position in the 1995-1997 data

5. Lymphoma

The incidence of lymphoma is increasing largely contributed by non-Hodgkin's lymphoma. A 19% increase in the males and a 23% increase in females have been observed during 1995 to 2002. The incidence rates of NHL registered in Karachi South are likely to be a reflection of non-AIDS-associated NHL. HIV / AIDS incidence was too low during the study period in this population to have an impact on NHL incidence. The preponderance of low- and intermediate-grade lymphomas, paucity of central nervous system NHL and a higher childhood NHL component supports this hypothesis.²⁶

Geographical variations in Pakistan

The global variation in the incidence of cancers is strongly reflected in the epidemiological pattern of cancers in Pakistan. The predominant effect of tobacco associated malignancies is visible in the entire country however the type of tobacco, the dose and mode of its use determine the site of tobacco-related cancers. Oral cavity and lung cancer are the most important cancers in the Indus Plain, a reflection of tobacco and areca nut chewing and smoking. There is a high incidence zone of cancer esophagus in the Baluchistan Plateau where the malignancy is the commonest cancer in both males and females. This preponderance

may be an indicator of environmental carcinogens, of probable dietary type, acting equally on both sexes, the gender ratio being equal. The oral use of 'naswar', associated with drinking hot salted tea 'kahwa', exposure to dietary amines and nitrate, and pickled or smoked red meat are implicated as probable risk factors. Amongst the females, breast cancer is the most frequent malignancy reported from all regions of Pakistan, from the Arabian Sea upto the Himalayas, except for the esophageal cancer belt in the Baluchistan Plateau, in the northwest of Pakistan. The incidence of lymphoma and colorectal cancer increases as we proceed northwards, from Karachi to become the most frequent malignancy in Peshawar. The incidence rates calculated for different regions of Pakistan (except KS) have an estimated 50-80% data completion. Nonetheless the data is reliable, reflects a plausible cancer pattern and is gradually but persistently acquiring better coverage and completion.²⁷⁻³⁰

Cancer control measures advocated for the next 2 decades

A cost-effective NCCP can be effectively implemented in all countries if the planning takes into critical consideration the limitations in the political, social, economic and organizational factors of every country on an individual basis, especially the developing countries. Though collectively all developing countries have similar problems, the realistic assessment of the limitations will prevent overenthusiastic siphoning of finances into poor risk ventures.

Pakistan has a significant cancer burden and rising trends of risk factors, it is a country in dire need of Cancer Control. The primary recommended strategy for 'National Cancer Control Program' (NCCP), Pakistan based on the assessment of eight common cancers in Karachi and the WHO estimates would remain identical. Assessing the magnitude of the cancer problem is an initial step, in the development of NCCP. The categories of information needed for the initial analysis are demographic data, risk factor data, data on other diseases and capacity assessment have been provided by KCR. This data is substantiated by the data of the ACSP which provides the geographical variation. KCR data along with WHO estimates can form the initial framework of NCCP in Pakistan, the lack of a national cancer registration should not deter initiatives.

It is recommended that with this backbone data available for planning, assessment and evaluation, NCCP Pakistan can be implemented and monitored. Intervention in the form of primary and secondary cancer prevention, if associated with careful planning can stretch restricted resources available for cancer control to be used efficiently. Benefits of an immediate, prompt and targeted implementation established today will be realized after 20-30 years' however the earliest benefits to the population can be real-

ized within the first 2 years in the form of down staging of malignancies.

The following strategies should be followed for success of NCCP Pakistan with stringent annual evaluation.

Legislation

Implementation of anti-tobacco legislation in the form of taxation, ban on public smoking or chewing and ban on advertising and enforcement A curb on the epidemic levels of tobacco and areca nut use would reduce 43.7% of the malignancies in males and 17.8% in females.

Establishment of equitable pain control and a palliative care network is an urgent and essential necessity as more than 70% of cancer patients report in very advanced stages of malignancy.

Public Health Education

Cancer trends are interplay of prevalent risk factors, the level of prevalence, preventive education and intervention. A cost effective and efficient cancer control focused around the target populations would be beneficial for Pakistan with assistance of audio-visual media, in view of the literacy status.

Primary Prevention

In the form of tobacco and areca nut control, diet control (colon, breast, gastric cancers), checks on preservatives, dyes, and pesticides; protection from occupational hazards (lung, pleural, peritoneum, skin, eye, scrotum, liver, lymphatic, haematopoietic malignancies), control of biological agents (hepatitis B vaccination - liver cancer, H.pylori treatment - gastric cancer and MALTOMA, avoidance of aspergillus contamination - oral cavity and liver) and solar UV protection (eye and skin cancers) will help in the control of half the malignancies.

Public health education, especially of school children, adolescents, healthcare providers by mass education and media influence.

Capacity Building

This is required by the Government to increase the availability of professionals, technical help and technology, and equipment.

Counselling

In developing countries like Pakistan, the biggest financial and psychological drain is the element of false hope, futile frantic searches for miracle treatments, and collaborative faith healing by quacks and physicians alike.

Population Screening

Resource restrictions put high technology methods beyond the scope of Pakistan today. Early detection of cancers of

accessible sites as an urgent requirement would be warranted for oral, cervical and breast cancer, after sufficient capacity building, initially in the high-risk groups. In females, this could help target 47.6% (approximately half) of the malignancies and in men 13% of the total.

Oral cancer and cancer cervix

A cost effective and reliable community-based screening program could be successfully implemented. Self-examination of the oral cavity, and cytology-based screening for high-risk cervical cancer populations should be established. This will reduce the incidence of oral cancer, but requires careful planning, and extensive financial resources. Therefore mobilization of general practitioners, health visitors, volunteer organizations and medical students for early detection of oral cancer is the essential need of today.

Breast cancer

There is an intense need for a well-directed cancer control program focusing on population screening and control of breast cancer. The justification would be a target of a third (35.5%) of the cancers in females. The primary recommended strategy for breast cancer screening in Pakistan, based on the assessment of the disease in Karachi would be regular breast examinations of all females in the reproductive age group by trained healthcare workers. This associated with health education for the population and training of health providers is essential for early diagnosis. Healthcare planning should focus on capacity building over the next 2 decades for a more aggressive breast screening.

Pitfalls

Two thirds of the breast cancers are reproductive age malignancies. Thus mammography, which benefits women aged 50-69 years, would have limited effectiveness in these patients diagnosed before 50 years of age. The cost effectiveness at a national level would be questionable, as the cost of a reliable mammography in the country is \$50-100. The annual cost for breast cancer for screening the high-risk population of Pakistan, in the first year would run into approximately \$400,000,000. The minimal annual increase in the number of females which would require screening cases 3039179 (2001 estimate). The maintenance cost each year subsequently would be approximately \$200,000,000. These estimates have not included the cost of capacity building, structural or, human.

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