REGIONAL REVIEW

Cancer Epidemiology in South Asia - Past, Present and Future

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Abstract

Pakistan, India, Sri Lanka, Bangladesh, Nepal and Bhutan, with their total population of more than 1,500 million, make up the subcontinent of South Asia. Despite massive diversity across the region, there are sufficient similarities to warrant a collective approach to chronic disease control, including development of cancer control programs. Cancer is already a major problem and there are general similarities in the prevalence patterns. In males, oral and lung cancer are either number one or two, depending on the registry, with the exceptions of Quetta in the far north, Larkana and Chennai. Moderately high numbers of pharyngeal and/or laryngeal cancer are also consistently observed, with prostate cancer now becoming visible in the more developed cities. Breast and cervical cancer share first and second place except in Muslim Pakistan, where oral cancer generally follows breast. The ovary is often included in the five most prevalent types. Markedly increasing rates for breast cancer and distribution shifts in other cancers suggest that, despite improvement in cervical and oral rates, the overall burden will only become heavier over time, especially with increasing obesity and aging of what are still youthful populations. Coordination of activities within South Asia is a high priority for cancer control in the region.

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Introduction

The countries of the South Asia, whether Muslim or Hindu, Indo-European or Dravidian, share a great deal in terms of culture as well as geographical proximity. The included population is approximately 1,500 million, or almost a quarter of the total in the world. Naturally the level of economic development is very varied and this is reflected in the infrastructure for cancer control. However, given the increasing importance of neoplastic diseases, as well as the other chronic medical conditions like diabetes and circulatory problems, cooperation across the region to best marshal the available resources is a high priority. A comprehensive understanding is therefore necessary.

There is a general awareness of the scope of the cancer problem faced by South Asia and efforts are increasing to develop and expand cancer control programs incorporating registration and screening or early detection. The present review was conducted taking advantage of all of the Pubmed references covering the area, as well as the CancerMondial website of the International Agency for Research on Cancer (IARC) (www-dep.iarc.fr/) and separate publications where available.

Cancer Registration in Southern Asia

Cancer registries have been active in the region for many years, Mumbai being listed in Cancer Incidence in Five Continents from Volume II in 1972 (see Table 1),

Table 1. Numbers of South Asian Registries in the Series of Nine Volumes of CIV

Volume	I	II	III	IV	V	VI	VII	VIII	IX
Karachi								1	1
New Delhi								1	1
Ahmedabad						1		1	
Mumbai		1	1	1	1	1	1	1	1
Barshi							1		
Bangalore					1	1	1	1	
Trivandrum							1	1	1
Karunagapally							1	1	1
Chennai					1	1	1	1	1
Nagpur					1			1	1
Poona				1	1			1	1

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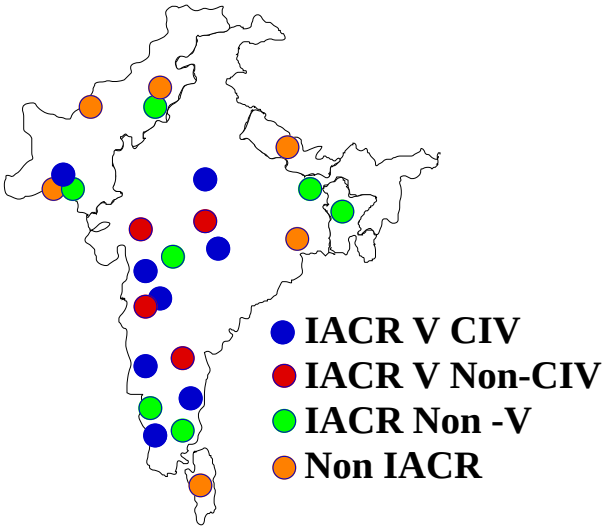

Figure 1. Cancer Registries in South Asia (V, Voting)

and there were a total of eight registries included in the last International Agency for Research on Cancer compilation, in 2002. However, all but the South Karachi registry are in India, and therefore recourse has been made in the present report to Globocan 2002 for comparisons across countries. The actual registries now in operation are illustrated in Figure 1. The available population-based data have been summarized in Tables 2 and 3, for males and females, respectively, and the overall picture in terms of the percentage s of the total burden accounted for by the five most prevalent cancers is illustrated in Figure 2. In addition to Globocan and CIV, at least partial data are available for city or region based registries in Quetta (Bhurgri et al., 2002), Larkana (Bhurgri et al., 2006), Hyderabad (Bhurgri et al., 2005) and Karachi (Bhurgri et al., 2000) in Pakistan, Allahabad (Mehrotra et al., 2008), and Kolkata (Sen et al., 2006) in India, and multiple institutes in Nepal (Pradhananga et al., 2009).

Not included in Figure 2 are Dir province, where the leading neoplasms are lymphomas and leukemia, and cancers of the digestive system, skin and breast (Zeb et al., 2006; 2008). In the Punjab, hematological malignancies are the most frequent in males followed by lung and colorectal cancer, while breast cancer is the commonest in females followed by ovarian cancer and gallbladder cancer (Aziz et al., 2003). At the Armed Forces Institute of Pathology, Rawalpindi, the most common malignant tumours in males, in order of decreasing frequency, are prostate, skin, lymph node, leukaemia, urinary bladder, colorectum, bone, lung, stomach and liver, and in females of breast carcinoma followed by skin, leukaemia, ovary, coloretum, lymph node, bone, liver, cervix and gall bladder

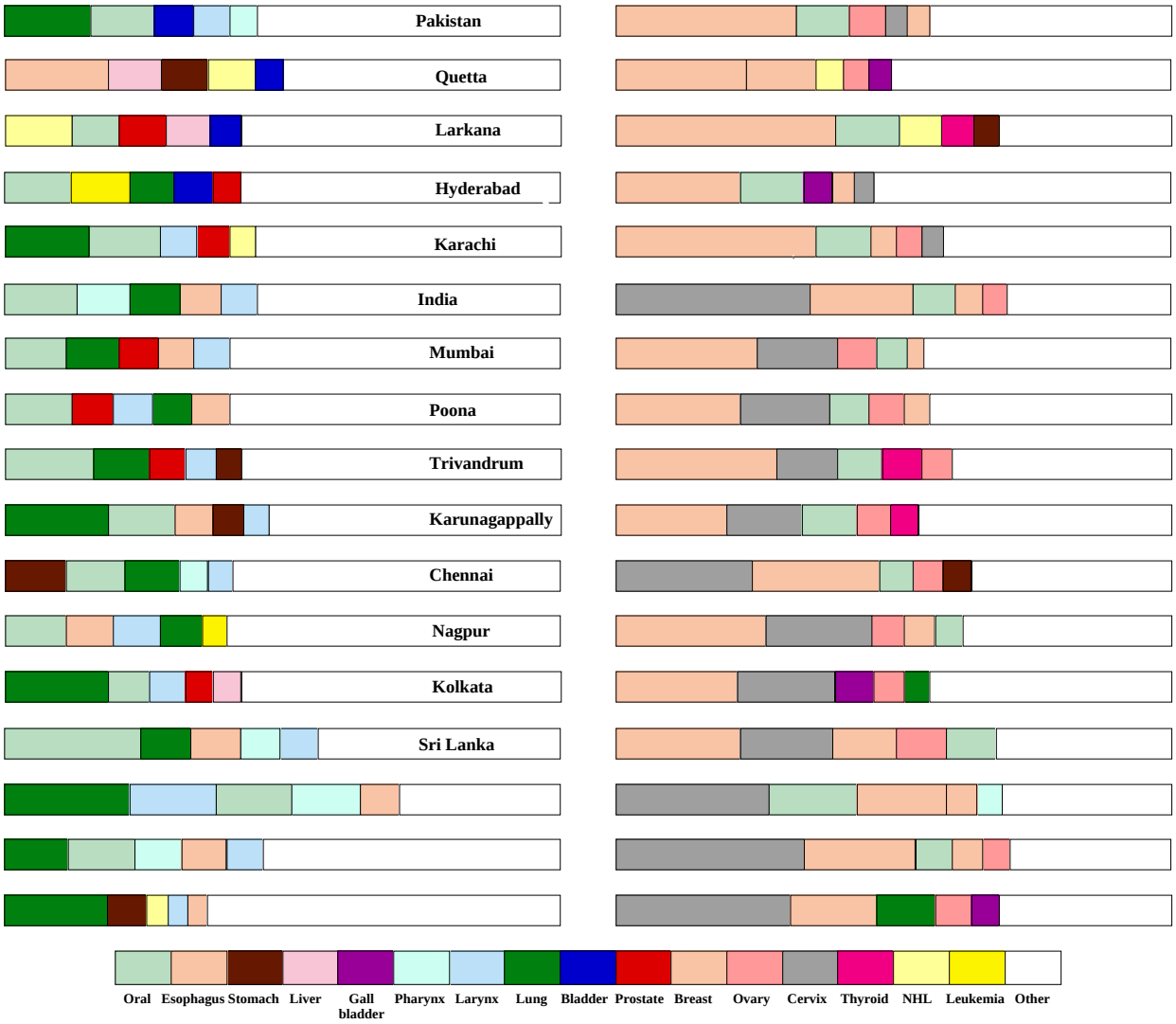

Figure 2. Percentage Data for the Five Most Prevalent Cancers in Countries of South Asia (Globocan 2002)

Table 2. Age-standardized Cancer Incidence Data for South Asian Countries - Males

	Pakistan			India						
	Karachi*	Lakarna[#]	Quetta[##]	Chennai*	Mumbai*	Nagpur*	Trivandrum*	K**	Poona*	Kolkata[###]
Lip	0.9	12.0	3.8	0.2	0.4	0.5	0.4	0.9	0.6	7.6
Tongue	5.3	-	-	5.1	4.6	5.5	6.0	5.8	3.2	-
Mouth	15.3	-	-	6.0	6.1	5.5	9.2	7.1	6.7	-
Nasopharynx	1.4	-	-	0.8	0.5	0.4	0.6	2.6	2.4	-
Hypopharynx	4.6	6.6	1.0	5.1	4.1	3.1	2.0	0.6	0.4	-
Oesophagus	6.7	2.0	25.5	9.1	6.7	8.7	3.5	8.3	6.1	4.5
Stomach	6.0	2.6	11.4	12.2	4.6	4.1	4.6	6.1	4.3	5.0
Colon	3.6	6.3	8.2	1.9	3.0	2.7	2.2	2.0	2.4	2.7
Rectum	2.9	-	-	3.3	2.6	2.6	3.2	2.1	2.4	2.7
Liver	5.4	10.5	12.3	3.0	4.5	1.6	2.8	3.9	3.4	5.3
Gallbladder	1.3	0.6	2.1	1.0	1.6	0.8	0.6	0.3	0.9	1.6
Pancreas	0.9	0.5	0.6	1.4	2.2	1.3	1.7	2.5	1.9	1.6
Larynx	10.7	6.1	0.9	4.7	6.5	8.5	5.1	5.3	6.2	6.4
Trachea, lung	25.2	6.6	4.0	10.8	9.7	7.5	9.9	21.3	6.2	18.7
Penis	0.0	0.1	0.0	1.7	0.8	1.6	0.8	1.0	1.3	-
Prostate	10.1	11.1	6.9	3.9	6.9	3.0	5.6	4.4	6.4	5.3
Kidney	1.7	1.2	3.6	1.3	2.0	1.1	1.5	0.7	1.7	1.6
Bladder	9.3	9.0	7.0	2.8	3.8	2.8	1.9	4.2	2.8	4.4
Brain	3.3	3.5	2.4	3.0	3.7	3.0	2.9	3.7	3.6	2.0
Thyroid	0.7	1.7	1.8	0.8	0.7	0.4	2.0	1.7	0.7	0.7
Non-Hodgkin	7.6	15.5	2.4	4.4	4.4	4.0	3.5	3.3	3.7	3.7
Leukemia	4.3	2.0	1.0	3.7	3.8	4.5	4.4	2.7	3.6	2.7
Total	167	134	137	107	102	101	97	116	88	102

*Data from Curado et al, 2007; **Karunagapally; [#]Bhurgri et al., 2006 [##]Bhurgri et al., 2002; [###]Sen et al., 2002

Table 3. Population-based Cancer Registry Data for Pakistan and India - Females

	Pakistan			India						
	Karachi*	Lakarna[#]	Quetta[##]	Chennai*	Mumbai*	Nagpur*	Trivandrum*	K**	Poona*	Kolkata[###]
Lip	0.4	12.6	2.5	0.2	0.2	0.2	0.3	0.1	0.4	4.3
Tongue	6.6	-	-	1.6	1.9	1.7	2.6	2.4	2.0	-
Mouth	12.3	-	-	5.2	3.7	3.4	4.1	5.4	5.0	-
Nasopharynx	0.6	-	-	0.3	0.2	0.3	0.3	0.3	1.0	-
Hypopharynx	1.8	-	1.7	1.8	0.9	1.0	0.2	0.0	0.2	-
Oesophagus	8.6	2.2	23.4	5.4	3.4	5.7	0.9	2.0	5.0	3.5
Stomach	3.6	4.8	2.2	6.0	1.8	1.9	1.0	2.6	2.4	3.8
Colon	3.5	3.2	4.3	1.6	1.8	1.8	1.6	2.1	2.3	2.4
Rectum	1.3	-	-	2.2	1.4	1.8	2.2	1.4	2.4	2.0
Liver	3.7	2.0	3.1	0.9	2.2	0.9	1.0	0.8	1.4	3.9
Gallbladder	4.9	3.0	3.6	0.8	2.3	0.8	0.4	0.9	1.2	8.1
Pancreas	0.5	0.1	0.1	0.7	1.6	0.5	1.0	1.2	1.2	1.6
Larynx	1.8	0.8	0.3	0.5	0.8	1.4	0.2	0.1	1.1	0.8
Trachea, lung	3.6	0.4	0.0	2.6	3.1	2.4	1.7	2.3	3.0	4.9
Breast	69.0	20.6	11.8	26.5	26.9	27.4	24.6	16.0	24.4	25.1
Ovary	8.8	4.4	4.3	6.0	7.1	6.4	4.8	4.8	6.8	6.3
Corpus uteri	6.7	2.2	2.4	2.0	2.8	2.3	2.8	1.1	1.9	-
Cervix uteri	7.5	2.2	2.7	28.0	14.5	18.4	9.4	10.6	17.3	19.9
Kidney	0.8	1.0	1.4	0.8	0.9	0.5	0.3	0.4	0.9	0.8
Bladder	2.6	2.8	2.3	1.0	1.0	1.0	0.4	0.2	1.0	0.6
Brain	2.7	2.0	0.4	2.1	2.8	2.6	2.2	1.9	1.9	1.5
Thyroid	2.9	6.4	2.5	1.9	1.5	1.0	5.8	3.9	1.4	1.6
Non-Hodgkin	5.1	8.4	4.7	2.3	2.9	1.9	2.3	2.1	2.4	2.1
Leukemia	3.7	1.8	0.2	2.3	2.7	2.6	2.6	2.6	2.0	1.6
Total	192	110	92	115	105	103	85	80	101	114

*Data from Curado et al, 2007; **Karunagapally; [##]Bhurgri et al., 2006 [##]Bhurgri et al., 2002; [###]Sen et al., 2002

(Jamal et al., 2006). On an in-patient basis colorectal tumours were found to be most frequent, followed by stomach and esophagus malignancies (Jamal et al., 2005). In Multan, the common tumours in males, in order of decreasing frequency were leukaemia, prostate cancer, urinary bladder cancer, skin cancer and lymphomas. In females they were leukaemia, breast cancer, skin cancer, gallbladder cancer and lymphomas (Atique et al., 2008).At the Himalayan Institute of Medical Sciences (HIMS), Dehradun, situated in Uttaranchal with a low socio-economical status, the top five cancer sites are in males are lung, larynx, lymph system (non-Hodgkins lymphomas), oesophagus and stomach, while in females they are the breast, cervix, gallbladder, ovary and oesophagus (Gaur et al., 2006). In a single institution in Karachi, head and neck cancers in males and breast cancers in females were found to be most common, at rates almost highest in Asia (Hanif et al., 2009). In Nepal, for males the leading cancer sites are reported to be lung, larynx and stomach and for females lung, cervix and breast (Binu et al., 2007), with shifts noted with aging (Pradhananga et al., 2009).

There is information about ethnic and social variation (Zeb et al., 2006). For example, cancers of the buccal cavity, pharynx, larynx, oesophagus and cervix uteri are more frequently seen in non-Parsi than Parsi populations in Mumbai, while breast and endometrial cancers, as well as lymphomas and leukaemias, are more common in the latter (Yeole et al., 2001). Considerable variation is also evident with different religious faiths (Yeole et al., 2006). The registered numbers of overall cancer cases in Bangalore, Chennai, Delhi, Bhopal and Mumbai are rising (Marimuthu, 2008), although an earlier study found no increase in Delhi (Tyagi et al., 2001). Yeole has recently published a series of papers on trends over time. Age-adjusted incidence rates for cancers of the stomach and esophagus are generally decreasing, while colon and rectum and liver cancers are on the rise in most registries (Yeole, 2008a). Bhurgri et al (2006) have focused on the upper aerodigestive tract.

Organ Specific Epidemiology

Skin Cancer

Skin cancers are rare.

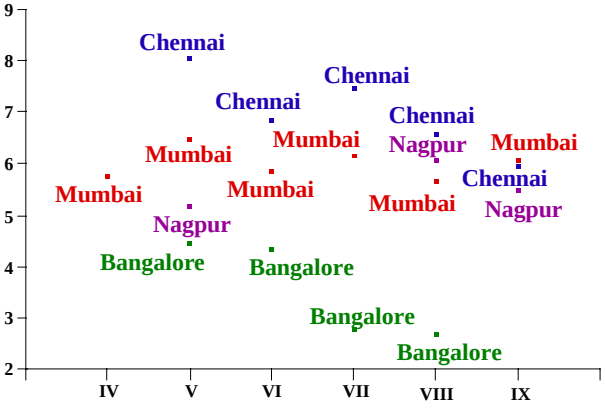

Figure 4. Male Mouth Cancer Incidences/100,000 over Time (Waterhouse et al., 1982; Muir et al., 1987; Parkin et al., 1992; 1997; 2002; Curado et al., 2007)

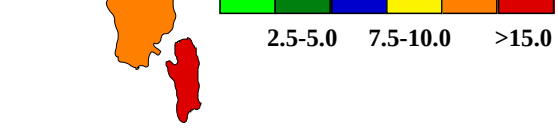

Figure 3. Male Oral Cancer Incidences/100,000 (Globocan, 2002: Ferlay et al., 2004)

Oral Cancer

In half of the registries from the region, oral cavity cancer is number one in males, and in almost all of the remainder is number two in frequency (see Figure 3). High rates have been reported in Nepal (Baskota et al., 2005) and in Indian tea estate labourers in Sri Lanka (Ariyawardana et al., 2007). Similarly, in females it is generally number two or three and often the absolute numbers are equivalent to those in men, which may reflect the pattern of exposure to known risk factors such as betal quid, arecanut, with or without *Aspergillus* contamination, and chewing or other forms of tobacco (Bhurgri et al., 2003b; Patel et al., 2007; Basu et al., 2008). In some situations alcohol might play a role, rather than smoking (Thomas et al., 2003). A history of diabetes mellitus might also predispose (Dikshit et al., 2006) while high socioeconomic status is protective (Hashibe et al., 2003). Gas-affected regions of Bhopal in the year 1992 have subsequently shown an elevated risk (adjusted for tobacco chewing) (Dikshit and Kanhere, 1999).

Generally, in India incidences of both mouth and tongue cancers are decreasing although apparently independently of one another (see Figures 4 and 5). In

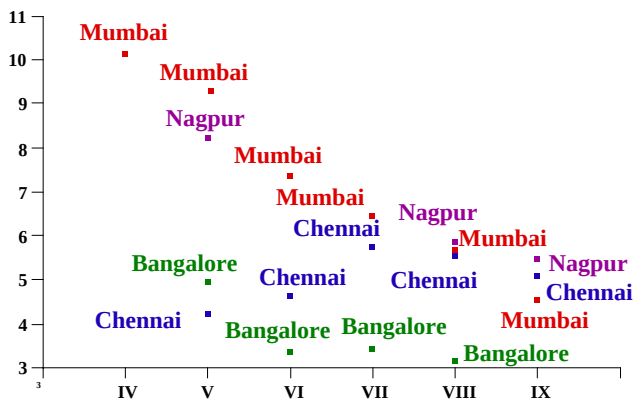

Figure 5. Male Tongue Cancer Incidences/100,000 over Time (Waterhouse et al., 1982; Muir et al., 1987; Parkin et al., 1992; 1997; 2002; Curado et al., 2007)

Pakistan, sub-categories of oral cancer also show variation in trend, with lip cancer in men decreasing, and tongue increasing, but the most dramatic is rise in the cheek in both sexes, a strong socio-economic factor with a poorer, low literacy profile being apparent (Bhurgri, 2005). Sub-site specific risk factors need to be elucidated by analytical epidemiological assessment (Yeole, 2007). Decreasing trends in oral cancers in Indian men may be attributed to a decrease in the usage of pan and tobacco (Sunny et al., 2004b) , although the tongue is exceptional (Elango et al., 2006). Use of smokeless tobacco (Pan masala, Zarda etc.) is on the increase in North India, especially in Uttar Pradesh, and is responsible for the large majority of these tumours (Mehrotra et al., 2005), the tongue being the most frequently involved site (Mehrotra et al., 2003). People of Mohajir ethnicity generally have a higher prevalence of paan, gutka and tumbaku use while Pathans are more exposed to niswar (Mazahir et al., 2006). One reported male/female ratio was 3.7:1 (de Silva et al., 1995). Many cancers in the young do not have a readily recognizable etiology, especially tongue lesions (Siriwardena et al., 2006; 2007). The fact that deficient CYP2A6 activity due to genetic polymorphism reduces oral cancer risk in betel quid chewers suggest involvement of particular carcinogens (Topcu et al., 2002). Hypermethylation may also contribute to pathogenesis (Takeshima et al., 2008).

As expected, 5-year survival for localized cancers depends on the subsite, with a poorer prognosis for less readily observable locations (Yeole et al., 2000). The low rate points to need for early detection (Yeole et al., 2003).

Regarding screening, it has been suggested that adequate coverage can be obtained in population-based oral screening in developing countries (Warnakulasuriya and Pindborg, 1990; Ramadas et al., 2008), but good patient-provider communication is essential to assure high compliance with referral (Warnakulasuriya et al., 1988; Warnakulasuriya and Nanayakkara, 1991; Sankaranarayanan et al., 2000; Ramadas et al., 2008). Importantly, after surgical excision of non-homogeneous oral leukoplakia in a screening intervention trial, Kerala, almost three quarters of patients remained disease free with no evidence of recurrent/new lesions during follow-up (Pandey et al., 2001). Urinary nicotine, cotinine, and NO2+NO3 could be helpful as adhunct parameters for screening programs for oral cancer (Patel et al., 2007).

Awareness of risk factors is a problem (Khawaja et al., 2006; Ariyawardana and Ekanayake, 2008) and knowledge about the causal relationships with tobacco smoking and use of alcohol is lower than for betel chewing (Ariyawardana and Vithanaarachchi, 2005). In the absence of state-sponsored preventive activities, it is necessary to improve the capacity of individual health practitioners and medical centres to participate in oral health promotion and oral pre-cancer screening (Ariyawardana et al., 2007).

Regarding molecular mechanisms underlying oral cancer development, overexpression of p63 in oral precancerous lesions and SCC in betel-quid chewers in Sri Lanka may be a useful marker for oral precancerous lesions (Haniffaet al., 2007). Molecular biomarkers may find use for early detection (Suhr et al., 2007).

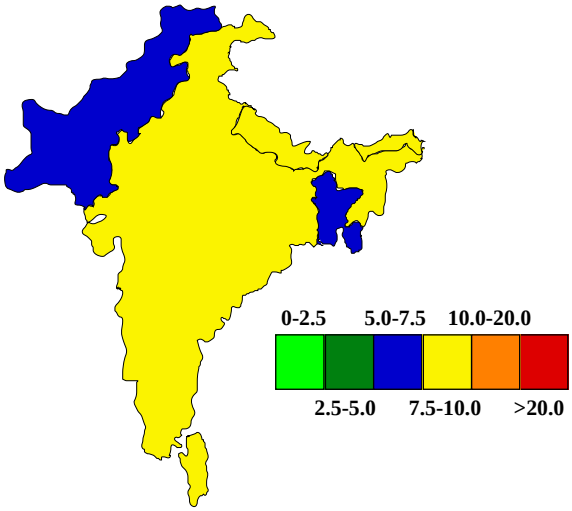

Figure 6. Male Oesophageal Cancer Incidences/100,000 (Globocan, 2002; Ferlay et al., 2004)

Pharyngeal Cancer

High rates of nasopharyngeal cancer are found in the northeastern states of India (Nandakumar et al., 2005).

Oesophageal Cancer

Oesophageal cancer is relatively common in India, and in the Baluchistan province of Pakistan, where it is the commonest malignancy in both genders (Bhurgri et al., 2003a). Rates are also high in India, Sri Lanka and Nepal (see Figure 6), but appear to be falling (Figure 7). An excessive likelihood of development of squamous cell carcinoma (SCC) versus adenocarcinoma, and in the upper-third of the esophagus relative to the lower-third of the organ has been reported in Pakistan (Badar et al., 2005).

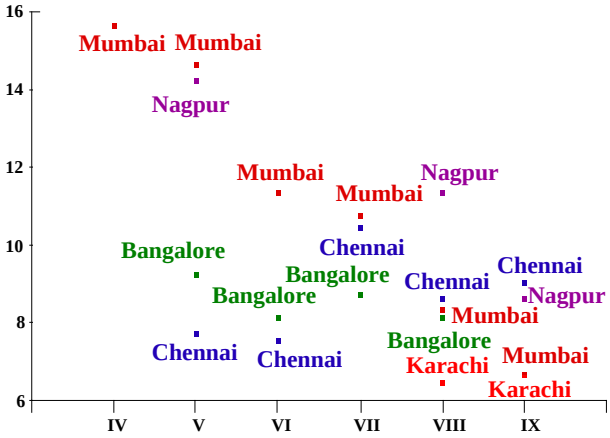

Figure 7. Male Oesophageal Cancer Incidences/100,000 over Time (Waterhouse et al., 1982; Muir et al., 1987; Parkin et al., 1992; 1997; 2002; Curado et al., 2007)

Table 4. Oesophageal Cancer Histopathology: SCC-Adenocarcinoma Ratios

	Male			Female		
	SCC	AC	Ratio	SCC	AC	Ratio
Karachi	81.3	15.7	5.2:1	92.2	4.3	21.4:1
New Delhi	50.1	10.9	4.6:1	57.0	5.0	11.4:1
Mumbai	86.6	10.3	8.4:1	90.6	6.8	13.3:1
Nagpur	95.5	1.0	95.5:1	95.5	0.0	------
Karunagapally	73.2	16.1	4.5:1	88.2	5.9	14.9:1
Trivandrum	71.1	22.4	3.2:1	69.2	19.2	3.6:1
Chennai	87.9	6.6	13.3:1	91.5	5.2	17,6:1

Data from Curado et al, 2007

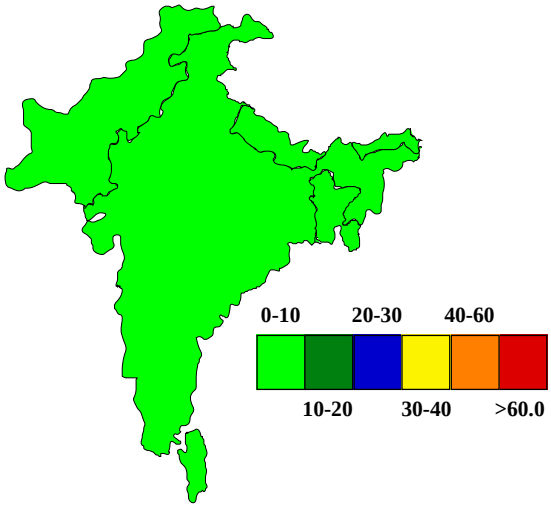

Figure 8. Male Stomach and Colon Cancer Incidences/ 100,000 (Globocan, 2002: Ferlay et al., 2004)

In India overall, SCCs predominate, although there is some variation and both sexes in Trivandrum have relatively large proportions of ACs (see Table 4).

Potential risk factors in Karachi are use of all forms of tobacco, areca nut, infrequent consumption of raw fruits and vegetables and diet deficiencies, with slightly higher incidences for females than males (Bhurgri et al., 2004). The same appears to be the case for Sri Lanka, where pathological changes such as acanthosis, basal cell hyperplasia, intra epithelial neoplasia, chronic oesophagitis koilocytosis and papillomatosis occur in the oral hypopharyngeal and other areas of the oesophageal squamous mucosa, in association with squamous carcinoma of the oesophagus (Ratnatunga and Edussuriya 1997). Generally lesions are locally advanced (Alidina et al., 2004).

Stomach Cancer

Stomach cancer is relatively rare (see Figure 8) except in particular registries like Chennai, and in Mizoram, in the north-eastern state of India, where it is associated with tobacco use (Phukan et al., 2005). It is generally on the decrease (see Figure 9) (Sunny et al., 2004a; Yeole, 2008a), although Pakistan may be an exception in this regard (Bhurgri et al., 2009a). While the stomach cancer incidence is very low, a PCR-based study revealed very high positive

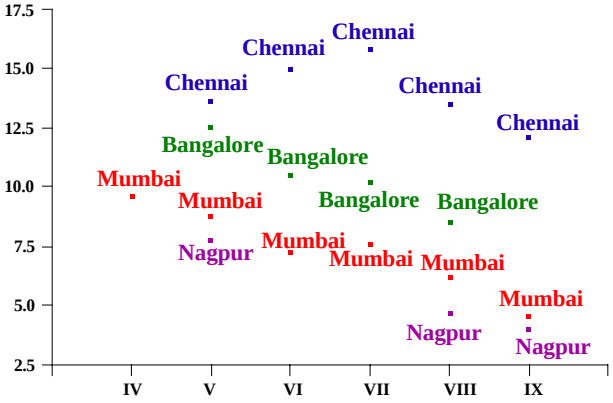

Figure 9. Male Gastric Cancer Incidences/100,000 over Time (Waterhouse et al., 1982; Muir et al., 1987; Parkin et al., 1992; 1997; 2002; Curado et al., 2007)

rates for *Helicobacter pylori* infection and cagA (Fernando et al., 2002). Itself not sufficient to cause cancer, *H. pylori* infection may interact with consumption of saum or smoked dried meat or soda (alkali), used as a food additive (Phukan et al., 2006). In one study, tobacco chewing, bidi or cigarette smoking and alcohol drinking did not emerge as major risk factors for stomach cancer, but consumption of dry fish at least once a week 12-fold excess risk , while tea consumption was protective (Rao et al., 2002). Both intestinal and diffuse types of gastric carcinoma showed strong association with H. pylori, chronic gastritis being the background lesion, while atrophy and intestinal metaplasia indicate long term infection (Arif and Syed, 2007).

Gastric carcinoma in the region carries a bad prognosis, with a 5-year survival rate of only 13.3% in one series (Khan et al., 2005), most patients presenting with unresectable disease (Mohammad and Makaju, 2006b; Siriwardana and Pathirana, 2007).

Colorectal Cancer

While colorectal cancers are still consistently rare across countries (see Figure 8), they appear to be very slightly on the increase (Yeole, 2008a), the majority being found in the rectosigmoid region (Perera et al., 2008). Rates of rectal cancer were earlier found to be steady (Mohandas and Desai,1999). Generally numbers in both colon and rectum sites are about equal, but rectal cancers are more frequent in some registries. Young age and delayed presentation are typical (Singh et al., 2002b), with left-sided tumors (Pal, 2006; Anwar et al., 2008). Disease is usually very advanced with 5-year relative survival of less than 40% overall (Ahmad et al., 2005). Age, site of cancer and clinical stage of disease are independent predictors of survival (Yeole et al., 2001).

Liver Cancer

Liver cancer is generally relatively rare, only being included in the first five cancers in Larkana and Kolkata males. Most patients present with large, multifocal tumours, with evidence of prior infection with hepatitis B or C (Yusuf et al., 2007). There is a possibility that the recent documented increase in non-alcoholic steatohepatitis (NASH), with clinical, biochemical and histological features similar to those reported in western countries, might indicate an elevated risk in the future (De Hewavisenthi et al., 2005).

Gallbladder Cancer

In females in the North-east of India and possibly Nepal, gallbladder cancers are relatively frequent (Nandakumar et al., 2005). Risk factors are gallstones, low age at menarche, high parity, young age at first delivery, low fiber and vitamin A intake, high fat intake, fasting, a habit of missing dinner and tobacco chewing (Rizvi and Zuberi, 2003; Dutta et al., 2005; Shukla et al., 2008).

Low zinc levels may promote (Gupta et al., 2005), while vegetables protect (Rai et al., 2006). Most of the studies have shown a good association with Salmonella, especially in the area of high endemicity of typhoid, and bacterial degradation of bile and chronic inflammation may

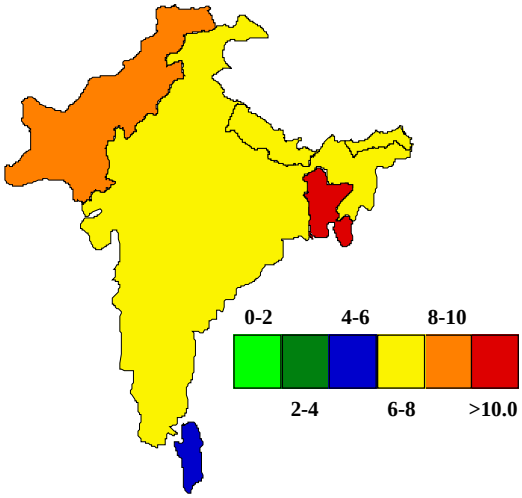

Figure 10. Male Laryngeal Cancer Incidences/100.000 (Globocan, 2002: Ferlay et al., 2004)

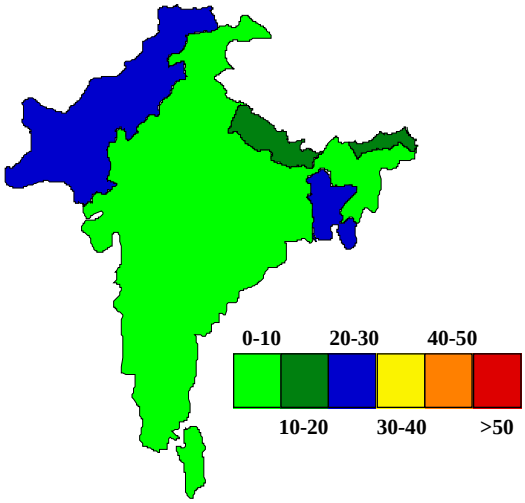

Figure 11. Male Lung Cancer Incidences/100.000 (Globocan, 2002: Ferlay et al., 2004)

also play some role (Kumar et al., 2006). *Helicobacter hepaticus* infection may also be important (Pradhan and Dali, 2004).

Pancreatic Cancer

Pancreatic cancer rates are generally low. Studies are required to confirm the associated risk factors such as *Manihot esculenta* and foods with a high content of chilli (de Silva et al., 2005).

Pharyngeal Cancer

Cancer of the pharynx, other than the nasopharynx, is relatively comon in males of Pakistan, some Indian registries, Sri Lanka and Bangladesh. Smoking bidi is even more hazardous than cigarette smoking in the development of lung and oropharyngeal cancer (Dikshit and Kanhere , 2000). Rates rise with age but starting at 25+, a decade and a half after the oral cancer rise (Bhurgri et al., 2006a).Gas-affected regions of Bhopalin the year 1992 in comparison to gas-unaffected regions and the year 1987-1990 combined were estimated. In a case-control study the RRs of 0.9, 1.4 and 1.2 for lung, oropharynx (adjusted for smoking) and oral cavity cancer, respectively, (adjusted for tobacco chewing) were estimated as the effect of the gas accident.(Dikshit and Kanhere, 1999)

Laryngeal Cancer

Laryngeal cancer is moderately frequent in males in all registries and appears particularly common in Bangladesh (see Figure 10). After adjusting for education, years of use of alcohol, smoking, chewing of betel leaf with tobacco in the model, low green leafy vegetables and preference for spicy foods were found to be positively related to risk of laryngeal cancer (Kapil et al., 2005).

Lung Cancer

Overall, cancer of the lung in males is number one or two in the majority of registries, but frequencies are low at the country level (see Figure 11) and may be decreasing (see Figure 12). In females it is very rare but appears to be on the increase (Agarwal et al., 2009). There is major variation in the proportions of different histopathological types (see Table 8), adenocarcinomas predominating in Mumbai and Trivandrum, but SCCs elsewhere (Behera and Balamugesh, 2004). In Pakistan, in contrast, SCCs are the most common in both sexes. In Kashmir, most cancers are smoking related SCCs, with a very poor prognosis (Kan et al., 2006). The risk of developing lung cancer increases with age, with a marginally higher risk 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 (Bhurgri et al., 2006b). Lung cancer incidence increases with the number of bidi smoked a day, the duration of

Table 8. Lung Cancer Histopathology: SCC-Adenocarcinoma Ratios

	Male			Female		
	SCC	AC	Ratio	SCC	AC	Ratio
Karachi	40.2	8.3	4.8:1	38.3	14.9	2.6:1
New Delhi	24.0	9.6	2.5:1	15.0	22.2	0.7:1
Mumbai	29.8	41.4	0.7:1	14.9	56.4	0.3:1
Nagpur	45.1	29.8	1.5:1	36.1	42.1	0.9:1
Karunagapally	22.8	21.9	1.0:1	26.7	46.7	0.6:1
Trivandrum	14.7	28.4	0.5:1	11.9	35.7	0.3:1
Chennai	41.9	26.2	1.6:1	31.3	37.4	0.8:1

Data from Curado et al, 2007

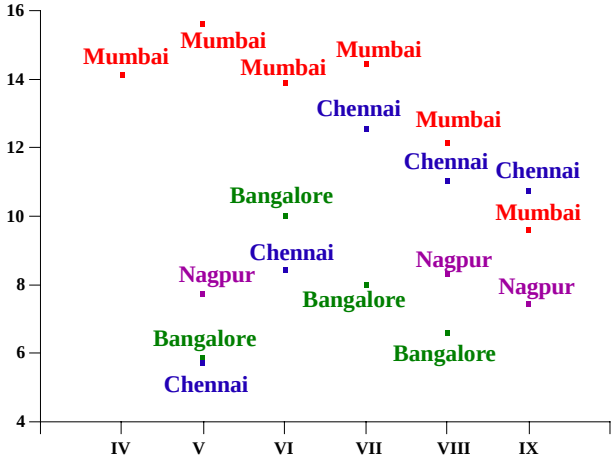

Figure 12. Male Lung Cancer Incidences/100,000 over Time (Waterhouse et al., 1982; Muir et al., 1987; Parkin et al., 1992; 1997; 2002; Curado et al., 2007)

exposure and the younger the age of starting, with risk not returning to the level of non-smokers within 10 years after cessation (Jayalekshmy et al, 2008). In addition to smoking, occupational exposure to carcinogens, indoor air pollution and dietary factors have also been implicated (Joshi, 2003; Behera and Balamugesh, 2004).

In Pakistan, significant differences were found in the average age at diagnosis between males (60.1 years) and females (57.5 years) and, in the distributions of non-smokers, current smokers, and ex-smokers, but none for histology (Badar et al., 2006). Overall 5-year observed and relative survival rates for lung cancers were 12.5% and 15.9% respectively (Yeole, 2005). Most cancers are late stage and there may furthermore be delays during the diagnostic evaluation and treatment (Chandra et al., 2009). One complicating factor is the high prevalence of tuberculosis and radiological similarities lead to a large number of lung cancer patients initially receiving the wrong treatment (Singh et al., 2009). Management of lung cancer must include strategies to improve various aspects of QOL and the nutritional status (Mohan et al., 2008).

Kidney Cancer

Renal cell carcinoma rates are generally very low, although a link with obesity might suggest increase in the future (Ildaphonse et al., 2009; Mathew et al., 2009). Alteration in interleukin-4-receptor alpha gene expression may be associated with risk (Mohan et al., 2009)

Urinary Bladder Cancer

Urinary bladder cancers are within the first five most common neoplasms in Pakistan but elsewhere they are rare. There is a clear male predominance, with some linkage to tobacco, and possibly also to employment as a motor vehicle driver or railroad worker (Manju et al., 2009). Patterns of urological malignancies have been described for Sri Lanka (Goonewardena and de Silva, 1999) and Pakistan (Badar et al., 2009). Around 90% of primary bladder tumors are transitional cell, with nearly half the patients having muscle-invasive disease on initial presentation (Goonewardena et al., 2004).

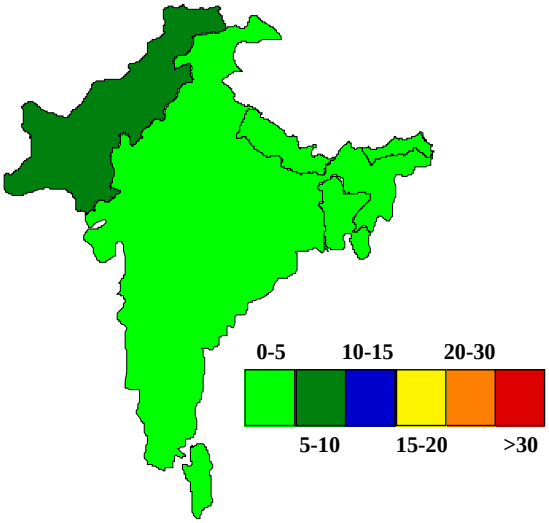

Figure 13. Prostate Cancer Incidences/100,000 (Globocan, 2002: Ferlay et al., 2004)

Prostate Cancer

Prostate cancer is relatively common in some of the Indian registries, but at the country level absolute incidences are very low (see Figure 13). Earlier, stability in age adjusted-incidence rates was considered to reflect no changes in the etiological factors for prostate cancer in Mumbai (Sunny et al., 2004c). However, more recently, increasing trends in the age adjusted incidence rates throughout a 25 year period of observation were noted for most of the registries, especially in Chennai and Bhopal and to the least extent in Mumbai (Yeole, 2008c). Recent publications suggest that a major problem with prostate cancer in Pakistan (Bhurgri et al., 2008; Ahmad et al., 2009). In Sri Lanka also, the real incidence of prostate cancer was earlier questioned (de Silva et al., 1999). A low fat diet rich in fruits and vegetables may reduce the risk of developing prostate cancer (Sunny, 2005)

There has been interest in outcome of elevated prostate specific antigen and transrectal ultrasound guided prostatic biopsy for detection (Samarasinghe et al., 2004). Survival in one Indian series was 49.2% for localised disease, 23.5% for direct extension and regional node involvement and 12.7% for distant metastatis patients (Yeole and Sunny, 2001),

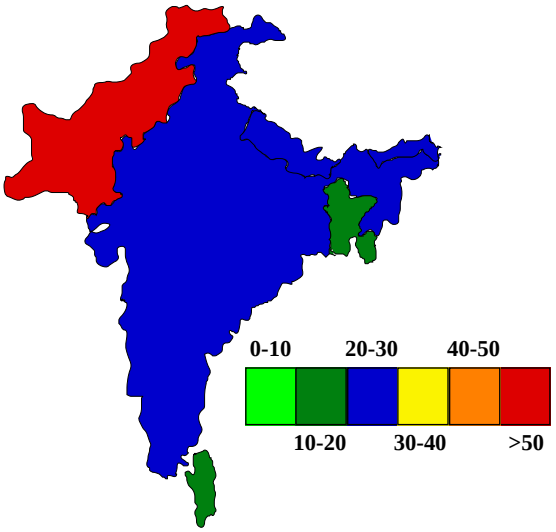

Figure 14. Female Breast Cancer Incidences/100.000 (Globocan, 2002: Ferlay et al., 2004)

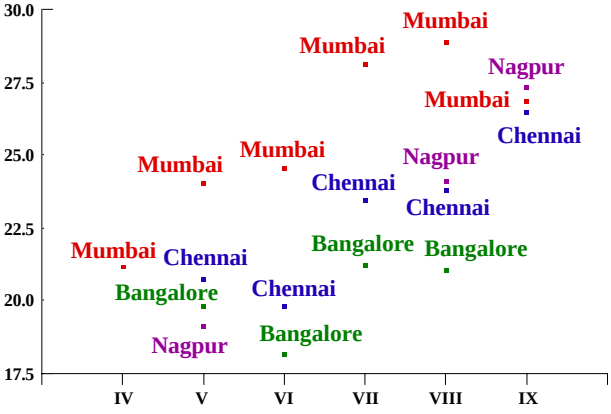

Figure 15. Female Breast Cancer Incidences/100,000 over Time (Waterhouse et al., 1982; Muir et al., 1987; Parkin et al., 1992; 1997; 2002; Curado et al., 2007)

Breast Cancer

While still relatively infrequent as compared to the Western world, breast cancer is already a major problem throughout the region (see Figure 14) and there is strong evidence that continued rapid rise can be expected in the future (see Figure 15) (Takiar and Srivastav, 2008; Yeole, 2008b). Intermediate breast cancer trends exhibited by Indian immigrants in the US may help predict future incidence trends amongst Indian (particularly urban) residents (Ghumare and Cunningham, 2007). However, the incidence of breast cancer in Karachi South (KS) for the period 1995-1997 was already the third highest in Asia (Bhurgri et al., 2007).

No history of breast-feeding, lower parity, smoking, postmenopausal status, family history of breast cancer, unmarried status, and use of contraceptive pill are risk factors (Faheem et al., 2007). In Kolkata a positive correlation has been found with a higher standard of living, higher educational status, and higher intake of animal protein, fat and deep fried foods (Datta et al., 2009).Christians in India have the greatest risk of breast risk and Muslims have the lowest, but in all the populations breast cancer was found to be less prevalent at the lower education level (Yeole and Kurkure, 2003). Increased anthropometric values, like BMI, are risk factors of postmenopausal BC in India (Mathew et al., 2008). Nepalese breast cancer cases, particularly premenopausal, have unexpectedly been seen at a relatively young age with late menarche, early first full-term pregnancy, long duration of lactation and a large number of children (Singh et al., 2002a). Diet is also important and mean vitamin C, vitamin E and selenium levels were found to be lower in patients as compared to the controls (Singh et al., 2005). Recently, plasma beta-carotene, vitamin E and vitamin C were also significantly associated with decreased risk of breast cancer, whereas increased risk was linked to plasma vitamin A (Shah et al., 2009). In South India, tapioca was found to be protective and chicken consumption a risk factor in one study (Jayalekshmi et al., 2009). The CYP17 TT/CC genotype is associated with decreased risk for breast cancer, especially in post menopausal women (Samson et al., 2009).

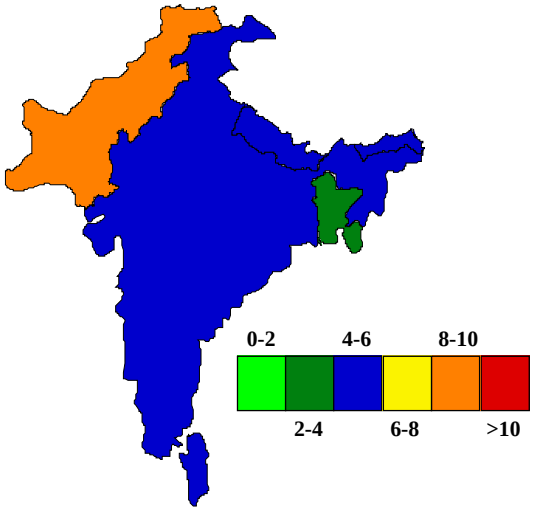

Figure 16. Ovarian Cancer Incidences/100.000
(Globocan, 2002: Ferlay et al., 2004)

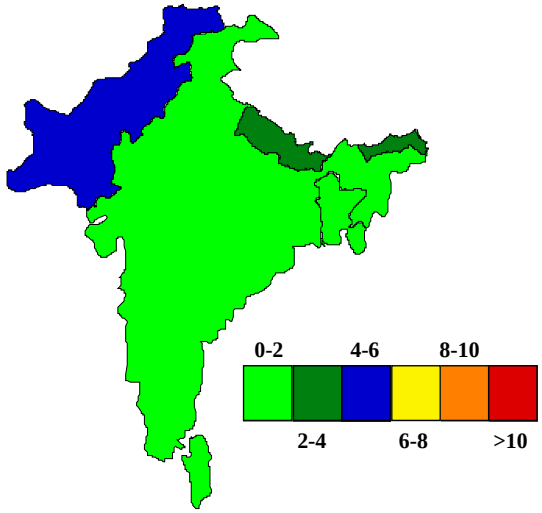

Figure 17. Endometrial Cancer Incidences/100.000
(Globocan, 2002: Ferlay et al., 2004)

Most cases present late and survival is poor (Nandakumar et al., 1995a; Gilani et al., 2003; Sharma et al., 2005; Bhattacharya and Adhikary, 2006; Mohammad and Makaju, 2006a). Elevated risks for late stage reporting were observed for women who were unmarried, widowed/ divorced and with lower education (Ali et al., 2008). Strong associations have similalry been noted between low socioeconomic status and advanced disease, delay in diagnosis, limited access to minimal expected treatment and inferior disease free and overall survival (Aziz et al., 2004). Substantial differences were found between groups of patients stratified according to tumor diameter and nodal involvement, but none for ER status (Badar et al., 2005b)

Practice and knowledge of breast self-examination is low, even among Indian teachers (Khokar, 2009a) although short text email messages may be an effective aid ibn this regard (Khokar , 2009b). With breast self-examination, size of the breasts and lumps had significant relation to performance and a Kappa test showed 68% agreement between findings of examinations done by the experts and respondents (Tara et al., 2008). International cost-effectiveness of clinical breast screening for breast cancer in India compares favorably with that of mammography (Okonkwo et al., 2008). With outreach compliance is good (Dinshaw et al., 2007a). However, most patients receive their first mammograms when they already have clearly palpable disease (Badar et al., 2007b) and an objective grading system is necessary (de Silva et al., 1998) with international collaboration (Perera et al., 2004).

The prevalence or ER, PR and Her/2neu amplification in carcinoma of breast among Sri Lankans is similar to that described internationally (Ratnatunga and Liyanapathirana, 2007).

Ovarian Cancer

Ovarian cancers are relatively frequent, particularly in Pakistan (see Figure 16). Stage at presentation in the majority of ovarian cases is advanced, with Cancer Antigen-125 elevated in 70% of one series (Sarwar et al., 2006).

Corpus uteri

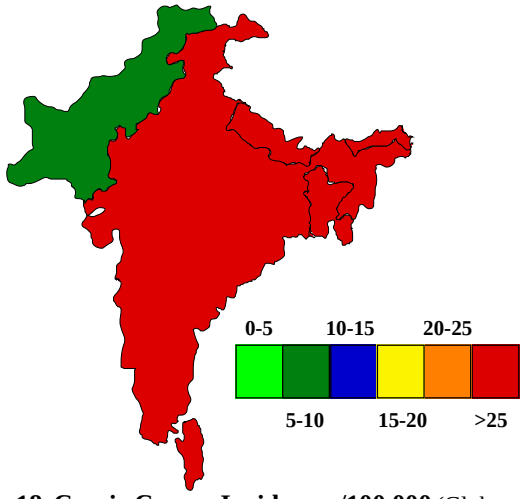

Figure 18. Cervix Cancer Incidences/100.000 (Globocan, 2002: Ferlay et al., 2004)

Cancer corpus uteri is generally rare, for example in Nepal (Mohammad and Makaju, 2006a), with the possible exception of Pakistan (see Figure 17). In Karachi South the population is moderate risk, tumours predominantly occurring in middle-aged individuals with a higher socio-economic status (Bhurgri et al., 2007a). On the average the malignancy is observed a decade earlier then reported in the West.

Cervix uteri

Cervical cancer is very common throughout South Asia except for muslim Pakistan (see Figure 18). However, the trend is for decrease in incidence rates in most registries (see Figure 18) (Murthy et al., 2005; Takiar and Srivastav, 2008; Yeole, 2008b). The major risk factor is clearly the high risk HPV, together with an importance for genital hygiene in the fight against infections that have a role in the development of cervical dysplasia and cancer (Varghese et al., 1999). Risk factors thus mainly pertain to early sexual debut, multiple sexual partners, menstrual hygiene and unprotected sex conducive to the transmission of an etiological agent (Juneja et al., 2003; de Silva et al., 2006). In Darjeeling, low socioeconomic status, having the first coitus before age 17, and low literacy are established factors (Bhattacharyya et al., 2000). A large proportion of cervical cancer patients in Pakistan (67%) present in stages II to IV and only few presented early at

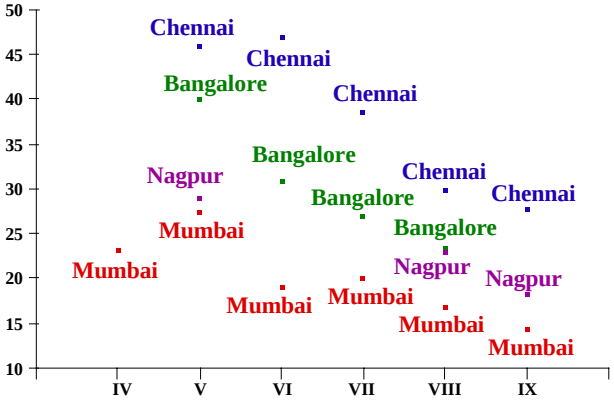

Figure 19. Cervical Cancer Incidences/100,000 over Time(Waterhouse et al., 1982; Muir et al., 1987; Parkin et al., 1992; 1997; 2002; Curado et al., 2007)

stages 0 or I, emphasizing the need for early detection (Badar et al., 2007; Bhurgri et al., 2007b). Good participation levels for cervical cancer screening can be achieved in rural areas of developing countries by using appropriate strategies to deliver services (Basu et al., 2007). Communication methods and delivery strategies must be aimed at encouraging older, less-educated women (Nene et al., 2007).

On approach considered appropriate for rural India is visual inspection with acetic acid (VAI) or Lugols iodine (VILI) which can be performed reliably by trained paramedical workers or doctors, with no significant difference between the two, and is an effective screening option in low resource settings (Bhatla et al., 2004; Sankaranarayanan et al., 2007). In some situations, VIA may be more sensitive and have a higher accuracy than the Pap smear (Tayyeb et al., 2003), although it requires careful monitoring (Sankaranarayanan et al., 2005) and it has been argued that unaided visual inspection or "downstaging" is not suitable as an independent primary screening modality (Basu et al., 2002). In Nepal, VIA as a screening test for cervical neoplasia did not miss any lesion detected by Pap smear and confirmed by cervical biopsy (Dhaubhadel et al., 2008). A consistently higher sensitivity but equal specificity of VILI compared with VIA has been reported (Arbyn et al., 2008). 'See and treat' with cryotherapy by nurses under medical supervision is acceptable, safe and effective for cervical cancer prevention in low-resource settings (Sankaranarayanan et al., 2007). Detection rates obtained by HPV testing were similar to cytology, despite higher investments (Sankaranarayanan et al., 2005). The main utility of hybrid capture-II is in the triage of patients with cytology smear diagnosis of ASC-US, ASC-H or L-SIL, for referral to colposcopic examination. HC-II alone has the best diagnostic accuracy but owing to high cost it is unsuitable for general screening (Legood et al., 2006; Kumar et al., 2007). Affordability has also been stressed for Sri Lanka (Kumarasinghe et al., 1999; Sirisena, 1999).

In the longer term the alternative is vaccination, especially if costs can be brought down drastically (Das et al., 2008; Diaz et al., 2008). A wide spectrum of HPV types is seen in Indian and Sri Lankan women, but the most frequent is HPV-16 in all grades of histology (de Silva et al., 2006). A vaccine against HPV-16 and HPV-18 could prevent two thirds of cases of high-grade cervical neoplasia (Bhatla et al., 2008; Basu et al., 2009). Integration sites may not have prognostic significance (Nambaru et al., 2009)Of 59/60 HPV positive samples in Pakistan, 56 showed the presence of HPV16 and one sample was positive for HPV18 (Khan et al., 2007).

Late stage reporting is also a problem, especially in the absence of bleeding (Kaku et al., 2008).

Brain and Nervous Tissue

There is some variation in incidences across South Asia (see Figure 20). An increasing trend in cancers of nervous system in both sexes has been noted for almost all registries in India (Yeole 2008d).

Thyroid cancer

South Asia is a low to intermediate incidence area for thyroid cancer (see Figure 20). However, there is a relatively high incidence belt in females in southwest coastal districts of India (Nandakumar et al., 2005). A trend towards more differentiated thyroid cancer with lesser degree of spread was observed in recent years, possibly due to the iodination programme implemented in 1995 (Ratnatunga et al., 2003). Because many patients have multifocal disease, aggressive surgery is generally recommended (Amarasinghe et al., 2007).

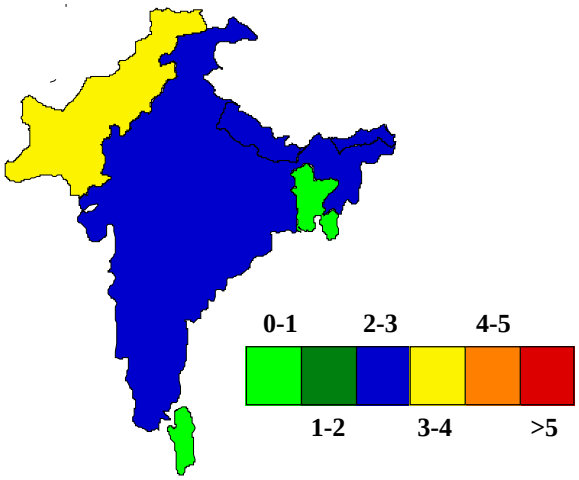

Figure 20. Male Brain and Nervous Tissue Cancer Incidences/100.000 (Globocan, 2002: Ferlay et al., 2004)

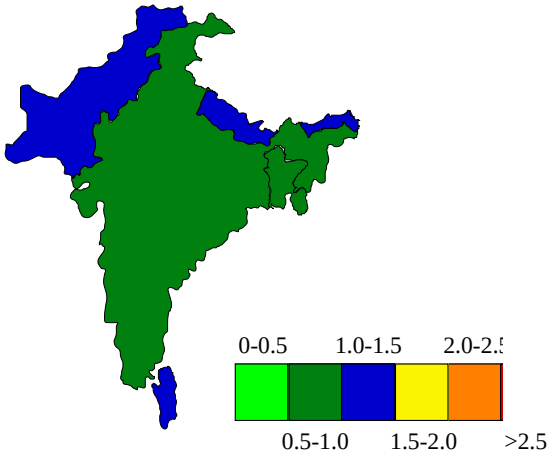

Figure 20. Male Thyroid Cancer Incidences/100.000 (Globocan, 2002: Ferlay et al., 2004)

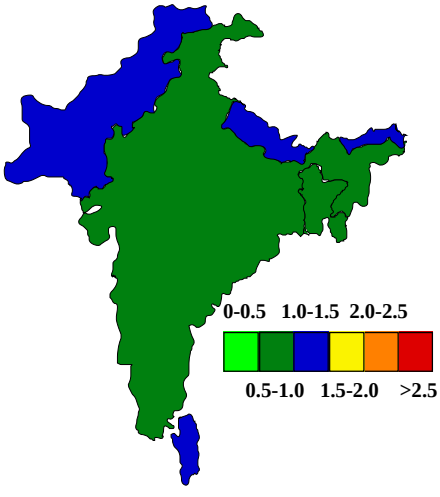

Figure 20. Male Non-Hodgkin Lymphoma Incidences/ 100.000 (Globocan, 2002: Ferlay et al., 2004)

Leukemias and Lymphomas

For both lymphomas and leukaemias, South Asia is a low incidence region, with slightly higher rates in Pakistan than elsewhere. In India, in general there has been a tendency for increase in NHLs but they constitute a wide group of cancers (including entities such as Burkitt's lymphoma and diffuse large B-cell lymphoma), each with a distinct development path, age profile and prognosis (Yeole, 2008f). There are notable differences in the specific subtypes between different geographic regions in India, T-cell NHLs constituting only 12.5% of NHLs at Barshi, but accounting for 31 and 27.5% at Pondicherry and Jaipur, respectively (Naresh et al., 2002). Diffuse large B-cell lymphomas are common in NWFP (Khurshed et al., 2007). In Pakistan, Hodgkin's lymphoma, Burkitt's lymphoma and lymphoblastic lymphoma are higher amongst the children, whereas follicular lymphomas, mantle cell lymphoma and CLL/SLL are more frequently reported in 5th, 6th and 7th decades (Mushtaq et al., 2008).The main bulk are childhood cancers, with malignancies being twice more common in males than females (Jamal et al., 2006).

Regarding risk factors, the significantly higher risk associated with the GSTM1 (null/null) and GSTP1 [(Ile/ Val)/ (Val/Val)] genotype suggest an environmental carcinogen role for lymphoblastic leukemia (Suneetha et al., 2008).

In Bangalore, the overall observed 5-year survival for lymphoid and haemopoietic malignancies (both sexes) was 26%, lower in all the individual lymphomas and leukaemias as compared with similar reports from the developed countries (Nandakumar et al., 1995)

Future Perspectives

While infection, betel and tobacco associated cancers continue to be important, the future will see continuing

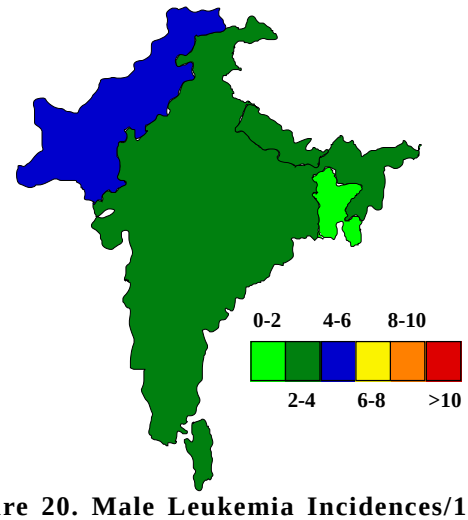

Figure 20. Male Leukemia Incidences/100.000 (Globocan, 2002: Ferlay et al., 2004)

increase in at least breast cancer as a reflection of change in metabolic disease. Chronic diseases are on the increase and already account for more deaths than all communicable diseases combined. In particular, the metabolic syndrome and diabetes is becoming rapidly more prevalent in Pakistan (Basit and Shera, 2008; Hydrie et al., 2009), India (Siegel et al., 2008), Sri Lanka (Illangasekera et al., 2004; Wijewardene et al., 2005), Bangladesh (Sayeed et al., 2003) and Nepal (Ono et al., 2007). Serious metabolic abnormalities are now evident in obese chldren (de Silva et al., 2006; Bhardwaj et al., 2008).

In terms of epidemiological research, the risk factors for the major cancers are already well established. What is not known is how to translate the information into effective cancer control policies. Lack of awareness is a key factor underlying late presentation and non-compliance with screening guidelines, where they exist.

Thus the need for early diagnosis for a possible curative treatment needs more stress (Bhatt et al., 2009). In India, and presumably most of the remainderof the subcontinent, the existing treatment facilities for cancer control in-terms of radiotherapy and financial allocation are woefully inadequate to take care of even the present load (Murthy et al., 2008). The only way to fight this scourge under such circumstances is to have pragmatic programmes and policies based on currently available scientific information and sound public health principles. Clearly, tobacco control needs to receive more stress as part of a comprehenisve approach (Jandoo and Mehrotra, 2008).

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