REGIONAL REVIEW

Cancer Epidemiology and Control in Peninsular and Island South-East Asia - Past, Present and Future

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Abstract

Malaysia, Brunei, Singapore, Indonesia, East Timor and the Philippines constitute peninsular and island South-East Asia. For reasons of largely shared ethnicity, with Chinese elements added to the basic Austromalaysian populations, as well as geographical contiguity, they can be usefully grouped together for studies of chronic disease prevalence and underlying risk factors. The fact of problems are shared in common, particularly regarding increasing cancer rates, underlines the necessity for a coordinated approach to research and development of control measures. To provide a knowledge base, the present review of available data for cancer registration, epidemiology and control was conducted. The most prevalent cancer site in males is the lung, followed by the liver, colon or the prostate in the majority of cases, while breast and cervical cancers predominate in most female populations. However, there are interesting differences among the racial groups, particularly regarding the stomach. General tendencies for increase in adenocarcinomas but decrease in squamous cell carcinomas and gastric cancer, point to change in environmental influence over time. Variation in risk factors depends to some extent on the level of economic development but overall the countries of the region face similar challenges in achieving effective cancer control. A major task is persuading the general populace of the efficacy of early detection and clinical treatment.

Asian Pacific J Cancer Prev, **10**, 81-98

Introduction

Peninsular and island South-east Asia stretches from Malaysia in the West, through the Indonesian Archipeligo to the Philippines in the East, with a total population exceeding 300 million. The majority of the populations are speakers of Austromalaysian languages, with Chinese as the main ethnic minority. Singapore is exceptional in having a Chinese majority as well as a generally high level of economic development. The variation in ethnicity and socieconomic status clearly exerts a major influence on lifestyle and beliefs, and this translates into differences in cancer incidence and mortality. For example survival rates are low because of late presentation by people of Malay or Philippino background. However, with progressive Westernization there is also a great deal of convergence.

There is a general awareness of the scope of the cancer problem faced by South-East Asia and efforts are increasing to develop and expand cancer control programs incorporating registration and screening or early detection. The present review was conducted to assess the state of cancer registration and research into underlying risk and protective factors, 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/).

Cancer Registration in Peninsular and Island South-East Asia

The well-established cancer registries within peninsular and island South-East Asia are listed in Table

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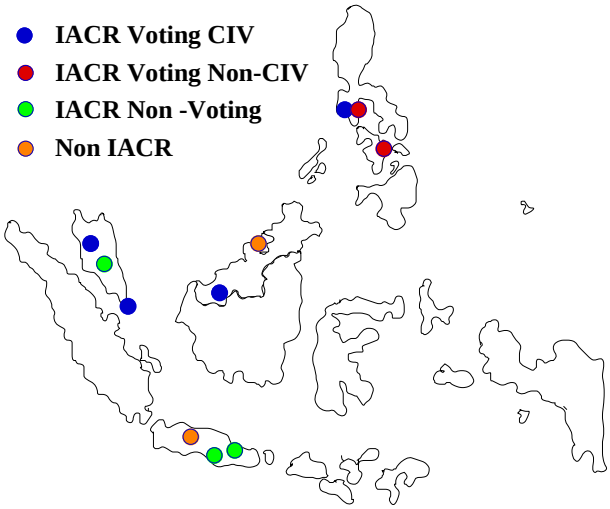

Figure 1. Cancer Registries in Peninsular and Island South East Asia

1 and shown on a map of the region in Figure 1. Singapore has long had a population-based registry providing data of a quality suitable for inclusion in the Cancer Incidence in Five Continents series of publications by IARC. Two of the registries in the Philiipines also have been active for a number of decades and the latest edition of CIV included two of the registries in Malaysia. Other registries which are primarily hospital-based are also in existence and Indonesia is now making a major effort to produce incidence data at the population level in Jakarta. Extracted data from CIV-IX are summarized in Tables 2 and 3. Percentage figures for the most prevalent cancers are

Table 1. Numbers of Peninsular and Island South-East Registries in the Series of Nine Volumes of CIV

Volume	I	II	III	IV	V	VI	VII	VIII	IX
Singapore*	1		1	1	1	1	1	1	1
Rizal					1	1		1	
Manila						1	1	1	1
Penang									1
Sarawak									1
Hawaii Filipino		1	1	1	1	1	1	1	1

*: National cancer registry

illustrated in Figure 2, with Globocan 2002 as the source for estimated population data for Malaysia, Brunei, Indonesia and the Philippines. For comparison, results for Papua New Guinea and Philippinos residing in Hawaii are included. With that latter exception, lung cancer is the most frequent neoplasm in males throughout, also being present in the first five within all sites but Sarawak. Clearly breast cancer predominates by a large margin in most female populations, but cervical cancer is also important in those countries without well-established screening programs. All of the countries are experiencing a general increase in adenocarcinomas, for example of the colorectum, prostate and breast, linked with a trend for more obesity (see Tables 4 and 5). In addition, oral, pharyngeal, oesophageal and gastric cancers appear to be on the decrease.

Other than the estimates that are given in Globocan 2002, mortality data for the region are limited, although findings for the Philippines were recently published (Redaniel et al., 2009)

Table 2. Population-based Cancer Registry Data for Peninsular and Island South-East Asia - Males*

	Malaysians		Singaporeans			Bruneiians+	Philippinos	
	Penang	Sarawak	Chinese	Malay	Indian		Manila	In Hawaii
Lip	0.2	0.1	0.0	0.0	0.0	0.0	0.0	0.0
Tongue	1.4	1.1	1.7	1.4	1.7	0.0	1.8	0.7
Mouth	1.7	1.0	1.5	0.5	2.8	0.2	1.8	1.2
Nasopharynx	9.3	15.0	12.8	5.5	1.8	13.0	5.8	3.3
Hypopharynx	1.3	0.6	1.0	0.7	1.4	0.4	0.4	0.9
Oesophagus	2.5	2.2	5.8	1.7	3.3	0.5	3.1	1.7
Stomach	12.5	12.3	21.5	6.5	7.8	14.5	7.9	8.7
Colon	13.9	7.3	26.5	10.5	7.4	15.0	14.5	20.6
Rectum	9.9	6.3	19.1	11.6	7.9	9.4	9.5	17.6
Liver	10.6	9.1	21.3	12.3	8.1	12.7	21.7	10.2
Gallbladder	1.0	0.6	2.1	1.4	2.3	0.7	1.2	2.1
Pancreas	3.4	2.3	5.4	3.9	3.1	5.5	4.3	5.9
Larynx	4.7	2.1	4.9	3.0	2.4	3.1	5.5	1.9
Trachea, lung	39.0	21.0	51.8	34.8	12.1	43.6	51.7	48.7
Penis	0.4	0.9	0.5	0.0	0.4	0.7	0.6	0.3
Prostate	11.3	5.8	18.6	16.1	11.1	18.6	25.3	78.0
Kidney	3.6	2.0	5.3	3.0	1.7	5.0	4.6	6.7
Bladder	7.3	3.1	8.0	7.9	4.6	3.3	4.7	6.5
Brain	3.5	1.6	2.3	1.4	2.7	2.2	2.8	2.7
Thyroid	1.1	1.1	2.0	2.3	1.3	2.8	2.9	5.7
Non-Hodgkin	7.0	6.6	8.1	11.9	3.3	4.7	6.8	10.9
Leukemia	6.0	4.4	5.8	6.2	4.5	4.1	4.9	6.6
Total	185	129	257	167	108	160	213	271

*Data (/100,000) from Curado et al., 2007; + Nyunt et al., personal communication

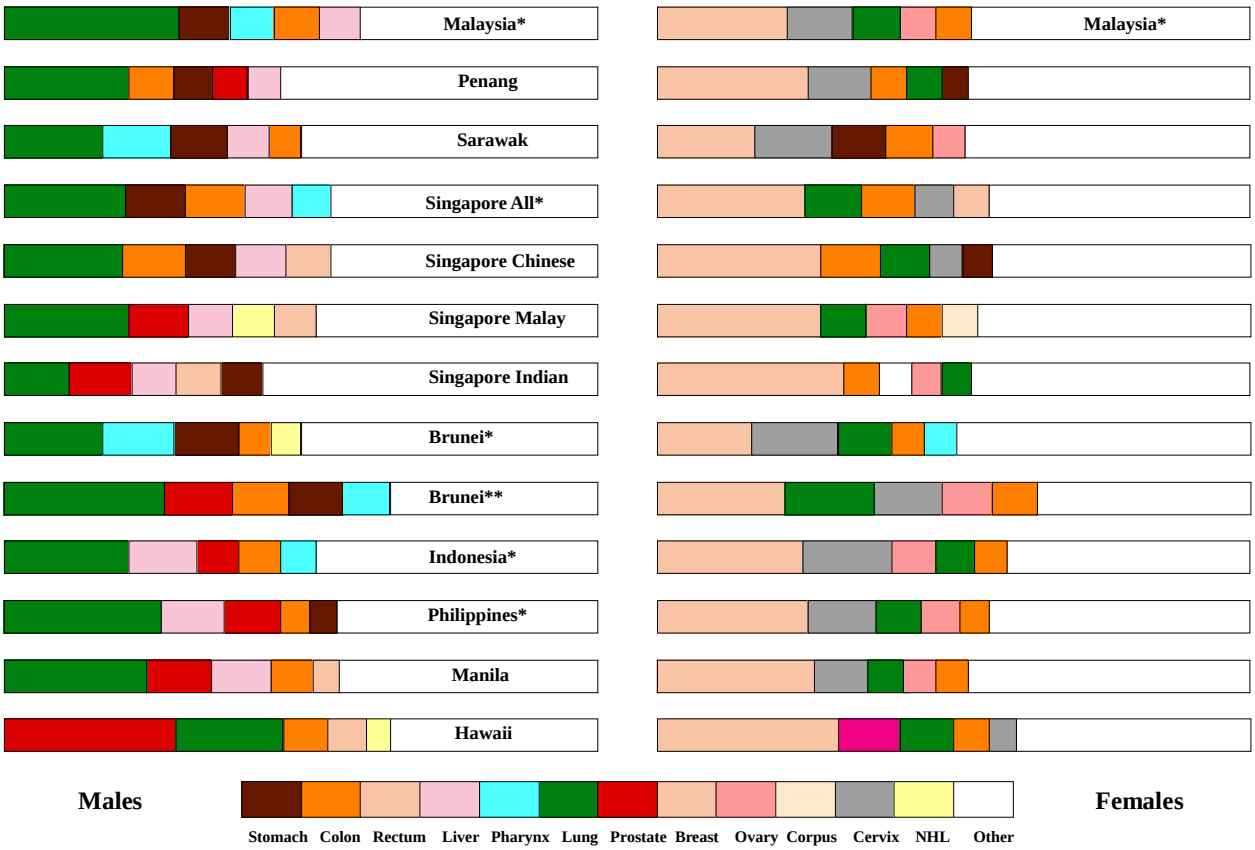

Figure 2. Percentage Data for the Five Most Prevalent Cancers in Countries of Peninsular and Island South-East Asia (*Globocan 2002, others Curado et al., 2007; **Nyunt et al., personal communication)

Table 3. Population-based Cancer Registry Data for Peninsular and Island South-East Asia - Females*

	Malaysians		Singaporeans			Bruneiians+	Philippinos	
	Penang	Sarawak	Chinese	Malay	Indian		Manila	In Hawaii
Lip	0.0	0.1	0.0	0.1	0.0	0.3	0.0	0.0
Tongue	0.8	0.9	0.7	0.4	1.4	0.0	1.1	1.0
Mouth	1.2	1.4	0.6	0.6	2.8	0.0	1.7	1.2
Nasopharynx	3.3	6.5	4.1	2.0	0.1	3.3	2.4	1.3
Hypopharynx	0.4	0.3	0.1	0.2	0.6	0.3	0.1	0.0
Oesophagus	1.7	1.7	1.2	0.6	2.5	1.5	0.8	0.9
Stomach	8.1	6.2	10.8	3.8	5.9	6.8	5.4	4.3
Colon	10.4	7.1	20.8	9.9	8.2	11.2	11.4	12.3
Rectum	6.0	5.0	10.5	7.8	5.1	5.3	7.0	6.3
Liver	3.8	3.1	5.0	3.6	3.2	4.6	7.0	2.7
Gallbladder	1.3	0.9	2.4	2.5	2.3	0.9	1.3	1.4
Pancreas	2.5	1.8	3.6	3.1	2.3	2.9	4.0	4.5
Larynx	0.5	0.5	0.3	0.2	0.4	0.8	0.8	0.0
Trachea, lung	9.9	11.2	17.5	11.8	6.8	24.0	14.8	19.1
Breast	43.9	20.5	56.4	43.5	45.0	34.1	55.2	64.3
Ovary	3.7	6.7	8.0	10.1	7.1	13.6	11.8	8.5
Corpus uteri	5.7	3.1	9.4	8.6	7.8	9.2	9.9	16.9
Cervix uteri	17.9	15.9	11.5	7.3	6.3	17.9	19.8	8.4
Kidney	1.7	0.7	2.5	2.3	1.4	1.2	2.5	3.6
Bladder	1.8	0.8	1.9	2.0	0.8	3.0	1.3	1.7
Brain	2.9	1.5	1.6	1.7	2.1	1.5	2.4	1.5
Thyroid	4.0	3.2	6.5	6.8	7.0	7.4	11.1	22.5
Non-Hodgkin	4.2	4.2	5.0	6.6	4.0	2.7	5.1	7.4
Leukemia	4.5	3.6	3.8	4.5	3.4	5.7	3.9	3.7
Total	172	124	206	158	142	158	208	210

*Data (/100,000) from Curado et al., 2007; + Nyunt et al., personal communication

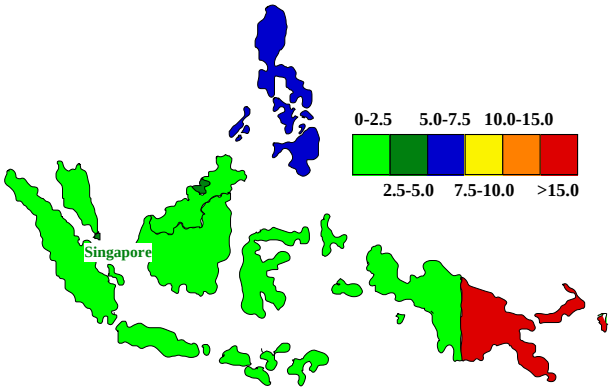

Figure 3. Male Oral Cancer Incidences/100,000 (Globocan, 2002: Ferlay et al., 2004)

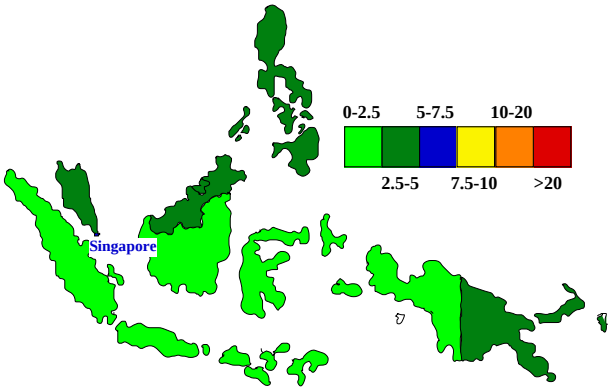

Figure 4. Male Oesophageal Cancer Incidences/100,000 (Globocan, 2002: Ferlay et al., 2004)

Organ Specific Epidemiology

Skin Cancer

Skin cancers are relative rare.

Oral Cancer

Oral cancer is rare except the Philippines (and in Papua New Guinea, included for reference but clearly differing from the other populations in peninsular and island South-East Asia) (see Figure 3). In Indians, oral mucosal lesions are associated with betel quid, areca nut and tobacco chewing habits (Zain et al., 1999; Ali et al., 1996-1997). Non-Malay Bumiputras (the indigenous people of Sabah and Sarawak) have an intermediate prevalence while the lowest incidences are amongst the Chinese (Zain et al., 1997). The habit of reverse smoking was once quite common in the Philippines, this being associated with palatal mucosal changes (Mercado-Ortiz et al., 1996).

In Malaysia, there is now a focus on interdisciplinary oral cancer research, with establishment of a partnership (Zain et al., 2009). This is now being extended to include Indonesia, it recently being found that genetic polymorphisms of GSTM1, GSTT1 and CYP1A1 may not be risk factors for oral cancer in the Jakarta population (Amtha et al., 2009).

Adult patients attending the School of Dental Sciences, Universiti Sains Malaysi, demonstrated a moderate level of awareness regarding oral cancer risk factors, complications, signs and symptoms, and prevention of oral cancer (Saini et al., 2006). Most people realise that the betel quid habit is harmful (Tan et al., 2001).

Nasopharyngeal Cancer

In Indonesia and Malaysia, and particularly Sarawak and Brunei, nasopharyngeal carcinoma is very prevalent. Indeed, the Bidayuh native people of Borneo Island appear to have the highest incidence recorded anywhere in the world (Devi et al., 2004). Patients generally present with cervical lymphadenopathy (Tiong and Selva, 2005). Long-term smoking is a risk factor, but alcohol consumption is not, in contrast to the case with oropharyngeal cancer (Friborg et al., 2007). Herbal medicines among subjects testing strongly positive for anti-EBNA antibodies caused a 49-fold excess risk of NPC in one earlier study (Hildesheim et al., 1992). In predominantly non-Chinese cases, smoking, again herbal medicine use, and burning of anti-mosquito coils were found to be independently associated with risk (West et al., 1993). Diet is a major influence and change in this and other lifestyle elements appears to be behind the declining incidence over time (Luo et al., 2007). There is also a genetic predisposition and the presence of a LMP1 30-bp deletion or XhoI-loss is associated with Chinese race and type III nasopharyngeal cancer (See et al., 2008).

Table 4. Oesophageal Cancer Histopathology: SCC-AC Percentages

	Male			Female		
	SCC	AC	Ratio	SCC	AC	Ratio
Penang	52	33	1.6:1	75	11	6.8:1
Sarawak	69	26	2.7:1	78	16	4.9:1
Singapore C	82	10	8.2:1	75	14	5.4:1
Singapore M	15	54	0.3:1	60	40	1.5:1
Singapore I	79	17	4.6:1	91	9	10.1:1
Manila	64	24	2.7:1	64	22	2.9:1

Data from Curado et al., 2007

Oesophageal Cancer

Oesophageal cancer incidences are low throughout the region (see Figure 4). In males, the ratio of squamous cell carcinomas to adenocarcinomas is around 2:1, except in Singapore Malays which have a predominance of the latter and Singapore Chinese who mostly have SCCs (see Table 4). A similar situation exists for females except that the general preponderance of SCCs is more pronounced (Curado et al., 2007).

Stomach Cancer

Stomach cancer is of middle ranking incidence in

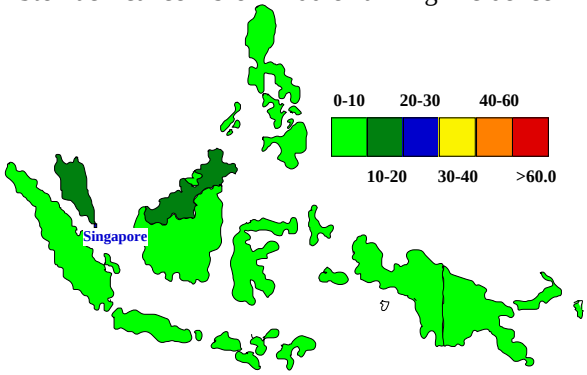

Figure 5. Male Gastric Cancer Incidences/100,000 (Globocan, 2002: Ferlay et al., 2004)

Malaysia and Singapore Chinese but is exceedingly rare in Indonesia (see Figure 5). This is related to the relative lack of infection with *H.pylori*, for example in Yogyakarta (Tokudome et al., 2005) and Semarang (Tokudome et al., 2006). Similar results have been reported in Malaysia, whereby the incidence of gastric carcinoma was found to be much higher in Chinese in Penang compared to Malays in Kelantan, where *H. pylori* infection is exceptionally rare (Gurjeet et al., 2005). Malays in fact have consistently low prevalence rates (Goh and Parasakthi, 2001). Many patients present with very late stage disease (Kandasami et al., 2003) but *H pylori* screening was not found to be a cost-effective strategy, even in Chinese at the age of 40 years (Xie et al., 2008).

Risk factors identified by multiple logistic regression analysis in Singapore are Chinese race, *H. pylori*, low level of education, smoking, and high intake of salted fish and vegetables, while high intake of fresh fruits and vegetables is protective. Chili intake is not a significant protective factor. Despite a high prevalence of *H. pylori*, the incidence of gastric cancer among Indians is low and this paradox has been termed the "Indian enigma" (Goh et al., 2007).

Colorectal Cancer

Colon and rectal cancers are relatively important in the entire region (see Figure 6), but demonstrate ethnic and gender variation (see Table 5), with marked colon preponderance in Chinese and females (de Kok et al., 2008). Rates appear to be slightly increasing (see Figure 7). A high ratio between rectal and colon cancer in correlation with the food consumption was earlier noted in Indonesia (Soeripto et al., 2003)

A number of papers have been published regarding risk factors, particularly in Singapore. Meat intake

Table 5. Colorectal Cancer Site: Colon and Rectal Relative Ratios

	Male			Female		
	Colon	Rectum	Ratio	Colon	Rectum	Ratio
Penang	13.9	9.9	1.4:1	10.4	6.0	1.7:1
Sarawak	7.3	6.3	1.2:1	7.1	5.0	1.4:1
Singapore C	26.5	19.1	1.4:1	20.8	10.8	2.0:1
Singapore M	10.5	11.6	0.9:1	9.9	7.8	1.3:1
Singapore I	7.4	7.9	0.9:1	8.2	5.1	1.6:1
Manila	14.5	9.5	1.5:1	11.4	7.4	1.5:1

Data from Curado et al., 2007

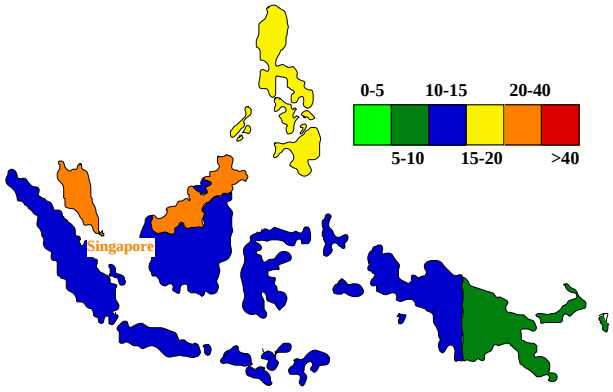

Figure 6. Male Colorectal Cancer Incidences/100,000 (Globocan, 2002: Ferlay et al., 2004)

increased and and vegetable intake significantly decreased risk of colorectal carcinoma (Seow et al., 2002b), compatible with the hypothesis that isothiocyanates from cruciferous vegetables modify risk of colorectal cancer in individuals with low glutathione S-transferase activity (Seow et al., 2002a). However, more recently, no association with either meat-dim sum or vegetable-fruit-soy patterns of nutrition was reported (Butler et al., 2008b). Subtypes of fatty acids may differentially influence risk of colorectal cancer of a specified stage and marine n-3 polyunsaturated fatty acid intake may be positively associated with advanced disease (Butler et al., 2008a). Diet and lifestyle intervention among patients with colorectal adenomas is under investigation in Malaysia (Kandiah et al., 2005). A high proportion of metabolic diseases, hypertension and diabetes type 2 among colorectal carcinomas seen in Kelantan population (Othman and Zin, 2008). Hyperinsulinemia may play a role in colorectal carcinogenesis, even in a relatively lean population (Seow et al., 2006) and circulating IGF-I concentrations may be important (Probst-Hensch et al., 2003) with an influence of genetically inherited variation in expression (Wong et al., 2008). PPARgamma2 and PPARgamma3 genotypes could also be significantly associated with risk (Koh et al., 2006). Green but not black tea is a possible risk factor for advanced cancers (Sun et al., 2007) and cigarette smoking and alcohol use have been found to interact in the Chinese in an additive manner with regard to rectal cancer (Tsong et al., 2007).

A screening program is in place in Singapore and participation in fecal occult blood testing is associated with

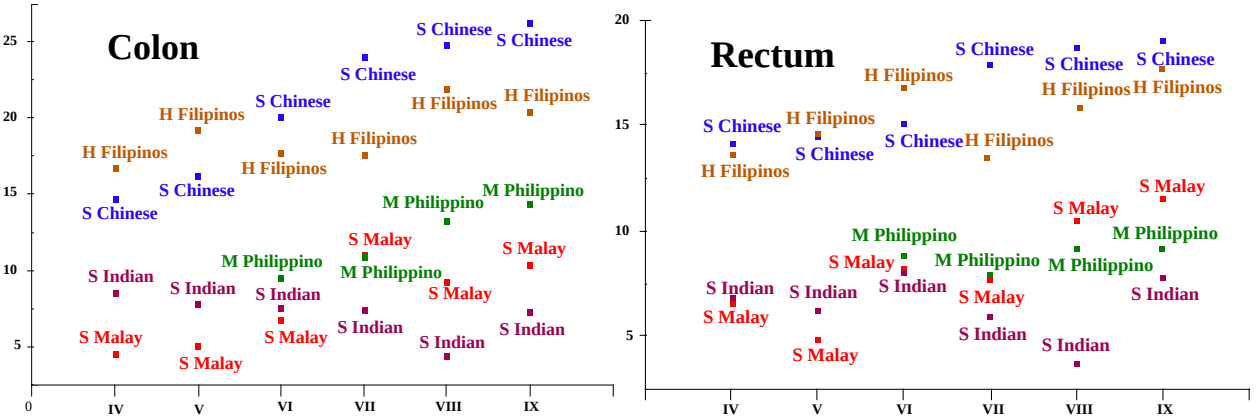

Figure 7. Population-based CIV Incidence Rates over Time (Waterhouse et al., 1982; Muir et al., 1987; Parkin et al., 1992; 1997; 2002; Curado et al., 2007)

specific areas of knowledge and perception among Singaporean-Chinese (Ng et al., 2007). Despite the dramatic increase in incidence of colorectal cancer in Singapore, there has also been significant progress in survival of patients with localized disease (limited to large bowel) (Wong et al., 2007). However, in Malaysia, colorectal cancer presents at an advanced stage in the majority of patients (Goh et al., 2005). A massive screening program was earlier launched in the Philippines (Cajucom et al., 1992), but the present status is unclear. A significant proportion of colonic adenomas in Malaysian patients appear as small flat lesions, which could easily be missed during endoscopy (Rajendra et al., 2003). Thus the American Society of Gastrointestinal Endoscopy guidelines would need to be modified for Asia to be of practical use (Chan and Goh, 2006).

Liver Cancer

Liver cancer is a relatively important neoplasm in males (see Figure 8), especially in the Philippines and Indonesia, although rates are generally falling (see Figure 9). In males the hepatocellular carcinoma (HCC) massively predominates in most population-based registries, except in Penang (see Table 6), although cholangiocellular carcinomas (CCCs) are relatively more frequent in females.

In the past the great majority of HCC in the Philippines were presumed due to chronic hepatiti B virus (HBV) infection (Lingao, 1989). Patterns of familial transmission of HBV and the risk of developing liver cancer: a case-control study in the Philippines, the fact of having a mother or father who has been infected in the past with HBV increases the risk of developing HCC (Munoz et al., 1989).The HBV was found to be the major viral etiological agent in 75% of chronic liver disease, while in 10% of cases both HCV and HBV were detected. HCV was implicated as the sole viral agent in only a small proportion (1.5%) of patients with chronic liver disease (Sinniah and Ooi, 1993).

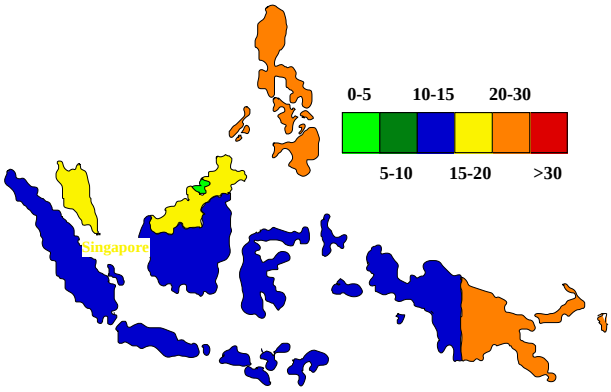

Figure 8. Male Liver Cancer Incidences/100,000 (Globocan, 2002: Ferlay et al., 2004)

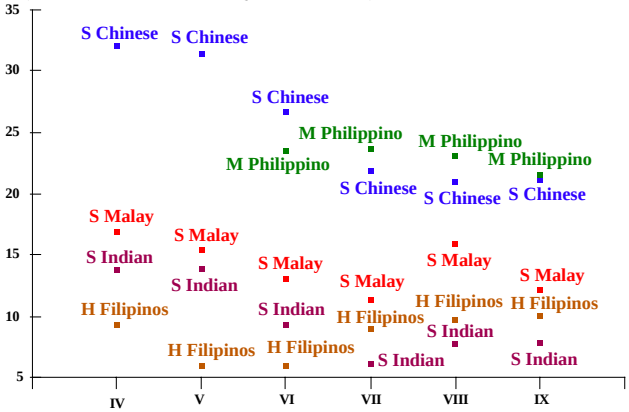

Figure 9. Population-based CIV Liver Cancer Incidence Rates over Time (Waterhouse et al., 1982; Muir et al., 1987; Parkin et al., 1992; 1997; 2002; Curado et al., 2007)

Table 7. Liver Cancer Histopathology: Hepatocellular and Cholangiocellular Cancer Ratios

	Male			Female		
	HCC	CCC	Ratio	HCC	CCC	Ratio
Penang	62.6	16.5	3.8:1	45.0	37.5	1.2:1
Sarawak	91.4	4.0	22.9:1	60.6	22.5	2.7:1
Singapore C	89.3	5.5	16.2:1	72.7	19.0	2.0:1
Singapore M	84.6	3.8	22.3:1	75.0	12.5	6.0:1
Singapore I	69.2	7.7	9.0:1	50.0	0.0	------
Manila	75.9	9.9	7.7:1	63.1	22.9	2.8:1

Data from Curado et al., 2007

Gallbladder Cancer

Gallbladder cancers are relatively rare, including in Singapore Indians.

Pancreatic Cancer

Rates for pancreatic cancers are below 5 per 100,000, except in Singapore, with some variation cross the region (see Figure 10).

Laryngeal Cancer

Laryngeal cancers are relatively rare (see Figure 11), the highest rates being about 5 per 100,000 in Singapore Indians and Manila Philippinos, with a tendency for decrease apparent in some populations.

Lung Cancer

Lung cancer (see Figure 12) is still very much the leading cancer in males, but is also important in most of the female populations. Even in most male populations, adenocarcinomas are more frequent than SCCs, and these constitute a very clear majority in females (see Table 7). Rates are decreasing or steady (see Figure 12) and the decline in the incidence of SCC is likely to be associated

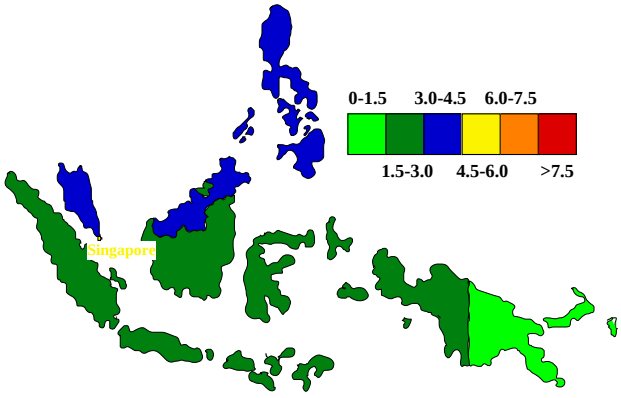

Figure 10. Male Pancreatic Cancer Incidences/100,000 (Globocan, 2002: Ferlay et al., 2004)

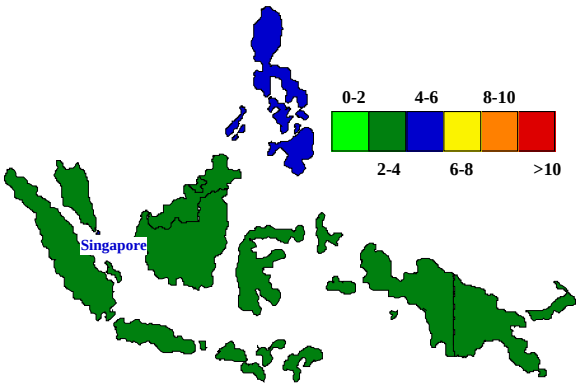

Figure 11. Male Laryngeal Cancer Incidences/100,000 (Globocan, 2002: Ferlay et al., 2004)

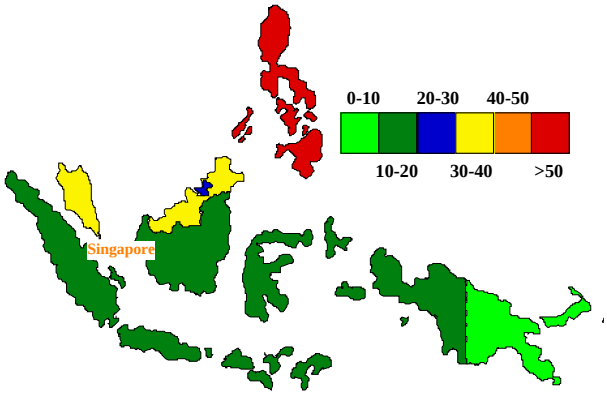

Figure 12. Male Lung Cancer Incidences/100,000 (Globocan, 2002: Ferlay et al., 2004)

with the known decrease in the frequency of smoking among Singaporeans (Fernandes et al., 2006). In contrast, there appears to be a trend toward an increase in the incidence of adenocarcinoma in Singapore, although the absolute incidence remains relatively low, associated with a rise in the frequency of reflux esophagitis and obesity (Fernandes et al., 2006). In Kelantan, the commonest histological type was earlier found to be squamous cell carcinoma in men, significantly linked with smoking, and adenocarcinoma in women (Yaacob et al., 1990). In the period 1991-1999 in Malaysia, adenocarcinoma was the commonest cell type in both men and women as well as in smokers and never smokers (Liam et al., 2006). Young lung cancer patients are more likely to have never smoked, to have adenocarcinoma, and to present with poorer performance status (Liam et al., 2000). Definite epidemiologic differences exist between never-smoker and smoker non-small cell lung cancer in Singapore, linked to survival outcome (Toh et al., 2006).

Table 7. Lung Cancer Histopathology: SCC-Adenocarcinoma Ratios

	Male			Female		
	SCC	AC	Ratio	SCC	AC	Ratio
Penang	31.0	25.0	1.2:1	18.3	47.3	0.4:1
Sarawak	36.1	21.2	1.7:1	18.2	39.0	0.5:1
Singapore C	27.6	37.7	0.7:1	12.5	59.0	0.2:1
Singapore M	15.2	39.5	0.4:1	7.8	54.9	0.1:1
Singapore I	20.8	35.1	0.6:1	10.7	60.7	0.2:1
Manila	23.1	28.0	0.8:1	12.3	46.9	0.3:1

Data from Curado et al., 2007

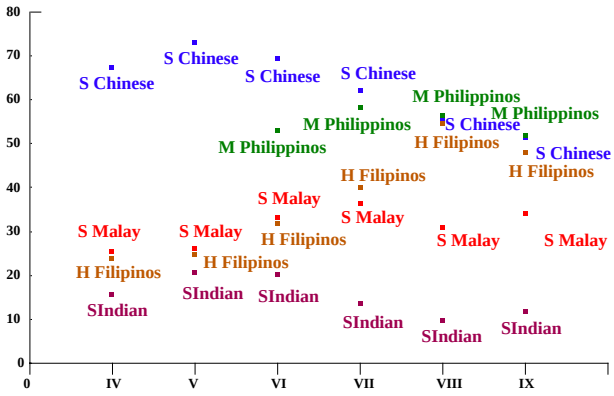

Figure 13. Population-based CIV Lung Cancer Incidence Rates over Time (Waterhouse et al., 1982; Muir et al., 1987; Parkin et al., 1992; 1997; 2002; Curado et al., 2007)

Clearly smoking is the major risk factor for male SCC. It is less important in females (Tan et al., 2003). A lack of any association has been reproted between chronic *Chlamydophila pneumoniae* infection and lung cancer among non-smoking Chinese women in Singapore (Koh et al., 2005). While, a history of asthma, hay fever, allergic dermatitis, food allergy or other allergic conditions was also not found related to lung cancer risk, chronic rhinosinusitis is associated, providing evidence linking inflammation to lung carcinogenesis, especially among women (Koh et al., 2008). This is also supported by protection by dietary beta-cryptoxanthin (Yuan et al., 2003), as well as the relation between isothiocyanates and cancer, and its modification by GST status (Seow et al., 2005). CYP1A1 appears to be a susceptibility gene for lung cancer among non-smoking Asian women, possibly influenced by sidestream smoke (Ng et al., 2005).

Kidney Cancer

Low rates prevail, as compared with Western populations, although a slight rise is apparent with some CIV data.

Urinary Bladder Cancer

Urinary bladder cancer incidence rates vary from only 4.7 to 8.0 per 100,000 (see Figure 14), and in none of the registries surveyed is it included in the first five ranking neoplasms. Therefore it is unclear what might be the significance of the finding that soy protein and isoflavone intake is associated with increase in bladder cancer risk, after adjustment for cigarette smoking and level of

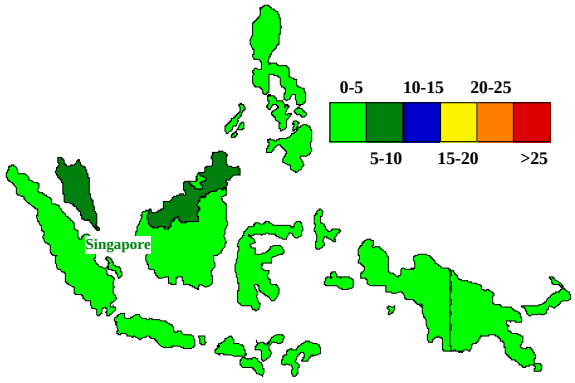

Figure 14. Urinary Bladder Cancer Incidences/100,000 (Globocan, 2002: Ferlay et al., 2004)

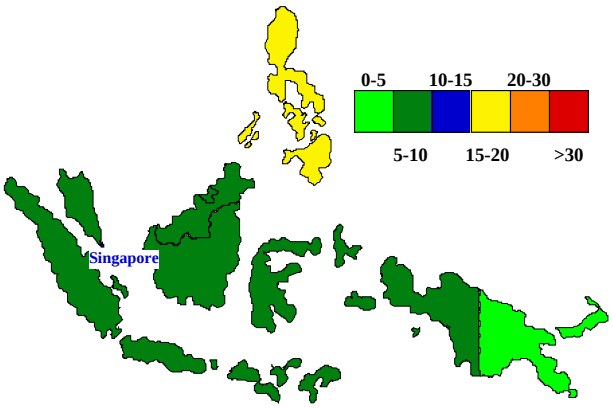

Figure 15. Prostate Cancer Incidences/100,000 (Globocan, 2002: Ferlay et al., 2004)

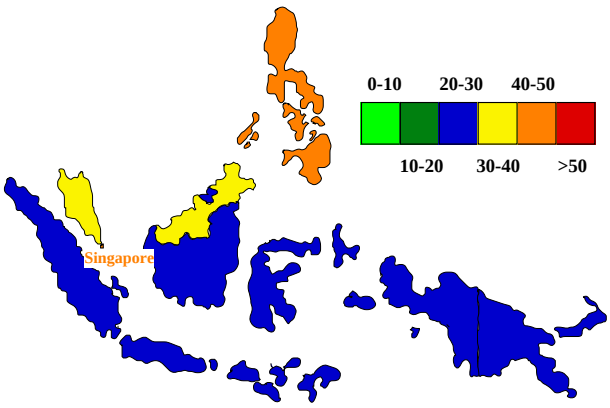

Figure 17. Female Breast Cancer Incidences/100,000 (Globocan, 2002: Ferlay et al., 2004)

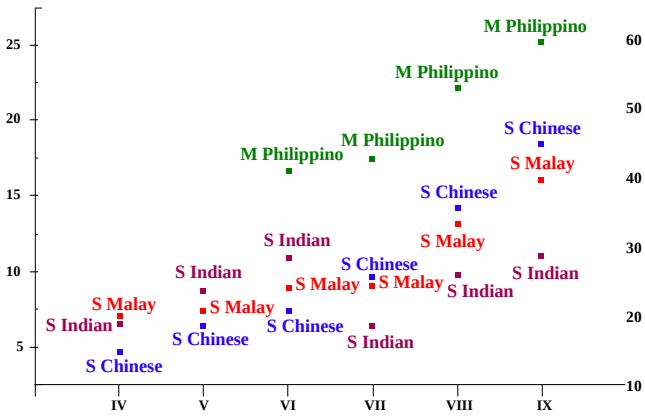

Figure 16. Population-based CIV Prostate Cancer Incidence Rates over Time (Waterhouse et al., 1982; Muir et al., 1987; Parkin et al., 1992; 1997; 2002; Curado et al., 2007)

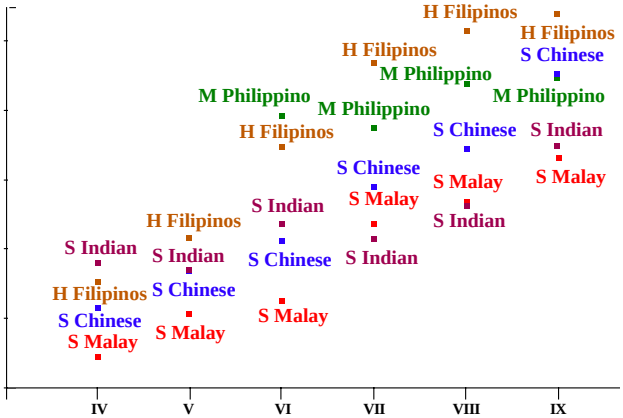

Figure 18. Population-based CIV Breast Cancer Incidence Rates over Time (Waterhouse et al., 1982; Muir et al., 1987; Parkin et al., 1992; 1997; 2002; Curado et al., 2007)

education (Sun et al., 2002).

Prostate Cancer

While relatively rare (see Figure 15) prostate cancer is on the increase across the region (see Figure 16), independent of ethnicity. Change in lifestyle is presumably involved but sporadic PSA testing may be exerting an influence. One problem is that serum values are lower than in the US in Chinese, Malays and Indians (Chia et al., 2007). Application of commonly accepted values for PSA levels were concluded to have resulted in many unnecessary biopsies in Indonesian patients (Rahardjo et al., 2000).

Breast Cancer

Without exception, the breast is the most prevalent cancer site in females of peninsular and island South-East Asia (see Figure 17). Where data for trends are available, the direction is rapidly upwards (see Figure 18). The incidence rate in Metro Manila and Rizal province doubled in the 13-year period between 1980 and 1992 (Laudico et al., 1998), although the rate of change has now slowed. Rates were found to be significantly higher in Metro Manila than in municipalities mostly in Rizal Province (Laudico et al., 2008; 2009; Redaniel et al., 2008). In the 1970s, Indian women had the highest age-standardized breast cancer but by the mid-1980s the highest rates were seen among the Chinese. Remarkable differences are evident in the age-specific incidence rates by ethnic groups. While there is some evidence that an age-drift model describes the trend seen in the Indians, age-period-cohort and age-cohort models have the best fit for the Chinese and Malays, respectively (Sim et al., 2006). A larger cohort effect seen in Singaporean as compared with Swedish women could be attributed to more rapid changes in reproduction and lifestyle patterns and suggest continued increase to European levels in the future (Chia et al., 2005). Generally, the age distribution is younger than in the Western world, with the peak in the 50s, although a shift from premenopausal to postmenopausal was noted over the period from 1993-1999 (Chia et al., 2002). At the population level, younger women (< 45 years) with breast cancer in Singapore have higher relative survival rates (Chia et al., 2004)

Regarding risk factors, it has been estimated that the prevalence of BRCA mutations among unselected breast cancer cases in the Philippines is 5.1% (De Leon Matsuda et al., 2002). However, as in the Western world, environmental and particularly reproductive factors must account for most of the burden. These include nulliparity, family history of breast cancer and previous use of oral contraceptives, ages at menopause and menarche (Morabia et al., 2000; Purwanto et al., 2000; Parkin et al., 2002; Norsa'adah et al., 2005). Significant protective effects have been noted for lactation (Purwanto et al., 2000; Hejar et al., 2004; Kamarudin et al., 2006). There may be ethnicity-dependent variation, however (Verkooijen et al., 2008). Whether this is due to differences in expression of CYP17

and HSD17B1 genes, both possible determinants on risk (Wu et al., 2003), is unclear. Evidence from the Philippines points to an importance for the androgen receptor gene (Liede et al., 2003).

Dietary macro/micro-nutrients also affect breast cancer risk (Ohno et al., 2000), with fat intake as an important determinant (Wakai et al., 2000). A good antioxidant status by consuming diet rich in vitamin A, E and selenium is protective (Shahar et al., 2008). Soy could clearly also be playing a role and intake is significantly associated with decrease in plasma estrogen levels (Wu et al., 2002) as well as percentage mammographic density (Ursin et al., 2006). This parameter is linked to breast cancer in Singapore Chinese (Heng et al., 2004). Possible protective agents in the region include green tea (Yuan et al., 2005), tocotrienols (Nesaretnam et al., 2007), and high levels of dietary n-3 fatty acids from fish/shellfish (Gago-Dominguez et al., 2003; 2004). Longer sleep duration may reduce breast cancer risk, possibly via its effect on melatonin levels (Wu et al., 2008). Circulating IGF-I concentrations increase the risk of breast (Probst-Hensch et al., 2003).

A major problem in Malaysia, Indonesia and the Philippines is late presentation at hospital for treatment. For example, between 1993 and 1996, 35% of the breast cancer cases in the University of Malaya presented at stage 3 or 4, and 93% of these women had a lump of a mean size of 5.3 cm (Yip et al., 2007). Rates of screening are low, for example in Malaysia (Parsa et al., 2008). Therefore the finding that a low cost 'Early Cancer Surveillance Program', started in 1994 in Sarawak, could result in downstaging of both breast and cervical cancers is of particular importance. The program consisted of (i) training health staff in hospital and rural clinics to improve their skills in early cancer detection, (ii) raising public awareness through pamphlets, posters and sensitization by health staff and resulted in a having of the alte stage III and IV breast cancer cases (Devi et al., 2007). Education may be especially necessary for poor, non-educated people from rural areas (Leong et al., 2007). Delays in presentation can also be attributed to strong beliefs in traditional medicine, coupled with fear and denial (Hisham and Yip, 2004). Acceptance of medical treatment and provision of appropriate resources is imperative to ensure that health behaviour exhibited by women is not self-destructive but self-preserving (Taib et al., 2007). Cultural taboos prevent women from examining their own bodies, and women fear their husbands will leave them if they have a mastectomy, reconstruction being relatively rare (Shameem et al., 2008). Recognizing factors that affect prognosis of breast cancer patients in Malaysia may improve delivery of health care to at-risk groups by strategizing interventions as survival depends on early detection and effective treatment (Taib et al., 2008). Training and practice of skills among health center workers should be a focus (Ngelangel et al., 1997). Having a family history of breast cancer does not appear to have much impact on the health-seeking behavior of women in Malaysia. Public education should target women at risk because of a family history, to encourage them to present earlier and to undergo screening for breast cancer (Yip et al., 2008).

In Singapore, 5-year overall survival rates are equivalent to published results from the West (Lim et al., 2007), presumably due, at least in part to a programme, launched in January 2002, adopting international standards of breast screening practice and breast cancer detection (Wang, 2003). However, to achieve decrease in incidence it should be carried out every 2 years (Gao et al., 2002). Although a trial of clinical breast examination was carried out in the Philippines, the attitude of the population was markedly refractory with respect to clinical follow-up and the program was discontinued after the completion of the first screening round (Pisani et al., 2006).

Regarding prognostic factors, CA15-3 (Velaiutham et al., 2008) may be important but not c-erbB-2 (Sharifah et al., 2008). The hormonal receptor status (estrogen/progesterone) is a necessary starting point for treatment decision-making (Laudico et al., 2004; 2006), but standardized processing is essential (Uy et al, 2007a;2007b). It should be borne in mind that he biopsy method used to confirm the diagnosis is influenced by where the patient first presents, and by the size of the tumour (Tham et al., 2009).

Ovarian Cancer

Ovarian cancer rates vary from 7.1-11.8 per 100,000 (see Figure 19), with particularly high incidences in Malaysia and the Philippines, and levels appear to have remained relatively stable over the last 30 years.

Corpus uteri

Endometrial cancers (see Figure 20) appear to be on

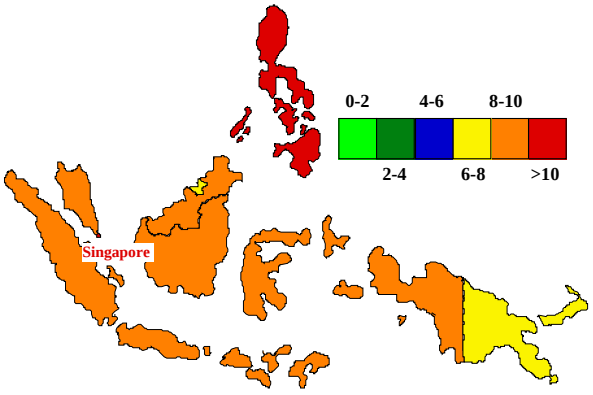

Figure 19. Ovarian Cancer Incidences/100,000 (Globocan, 2002: Ferlay et al., 2004)

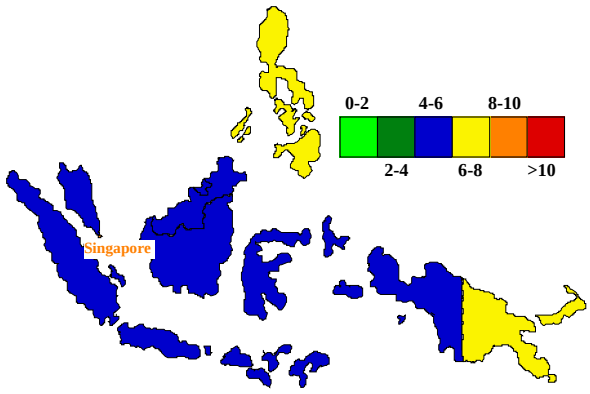

Figure 20. Corpus Uteri Cancer Incidences/100,000 (Globocan, 2002: Ferlay et al., 2004)

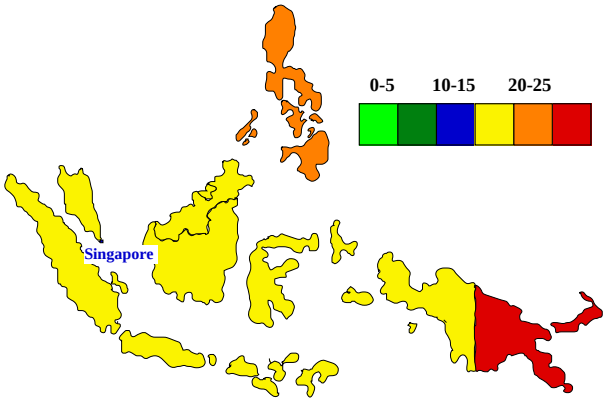

Figure 21. Cervical Cancer Incidences/100,000 (Globocan, 2002: Ferlay et al., 2004)

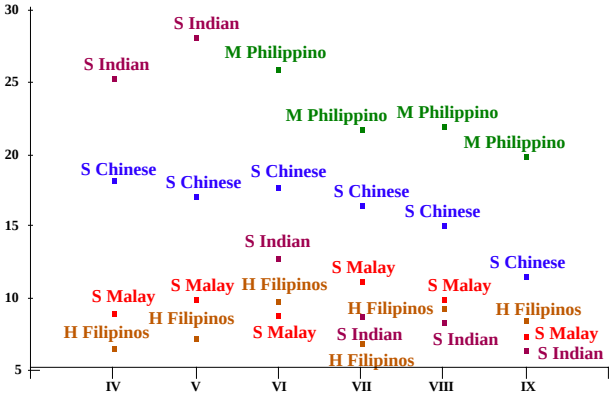

Figure 22. Population-based CIV Cervical Cancer Incidence Rates over Time (Waterhouse et al., 1982; Muir et al., 1987; Parkin et al., 1992; 1997; 2002; Curado et al., 2007)

the increase, except in Hawaiin Filipinos. whose incidence rate is already at 16.5 per 100.000.

Cervix uteri

With the exception of Singapore, where there is a screening program in place, cervical cancer is in second place in all the countries of the region (see Figure 21). Rates are decreasing in Singapore, but less rapidly in Chinese than the other populations (see Figure 22), and a worrying increasing trend of adenocarcinoma has been observed (Chea et al., 1999). These latter now account for 10-20% of the total lesions.

As elsewhere, human papilloma virus (HPV) infection is the major risk factor. HPV 16 is the most prevalent HPV genotype present in abnormal cervical smears in Malaysian patients (Sharifah et al., 2009), whereas a particularly prominent role for HPV 18 has been reported in Indonesia. As has been shown for squamous cell carcinoma, HPV is also the central cause of adenocarcinoma/adenosquamous carcinoma of the uterine cervix in the Philippines (Ngelangel et al., 1998). The high amount of multiple HPV infections found in adenosquamous carcinomas may prompt further research on the pathogenesis of this type of cervical tumours (Schellekens et al., 2004).

There is also evidence for *Chlamydia trachomatis* as a human papillomavirus cofactor in the etiology of invasive cervical cancer in the Philippines, possibly mediated by chronic inflammation (Smith et al., 2002). In addition, smoking is a risk, passive as well as active , the likelihood

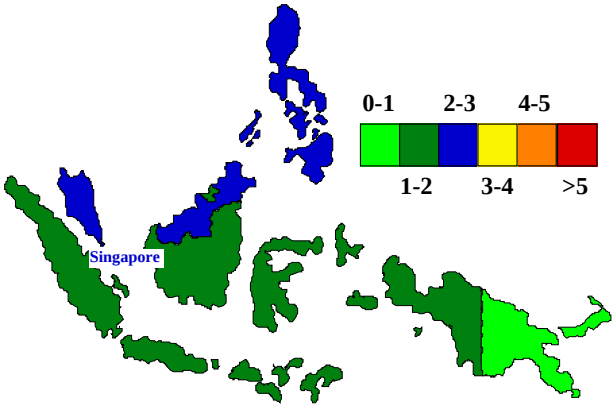

Figure 23. Male Brain Cancer Incidences/100,000 (Globocan, 2002: Ferlay et al., 2004)

of detection of early lesions increasing by 4.6% with every cigarette smoked daily by the spouse (Tay and Tay, 2004).

Available cytology-based screening appears appropriate for early detection (Wang et al., 2003), but in one study one third of women did not return for regular screening (Lee et al., 2002). Mass approaches have been adopted, for example in Brunei (Affandi et al., 1993), but awareness is a problem. For example, less than 50% of Hong Kong's Filipino domestic workers reported having had a cervical smear taken (Holroyd et al., 2003). The acetic-acid visualization method has also been recommended for initial cervical cancer screening in the Philippines, rather than the Pap smear on the basis of results for sensitivity (Ngelangel et al., 2003). The alternative is HPV detection (Saini et al., 2007). At the same time, prophylactic HPV vaccines have been licensed in Malaysia and the Philippines and also the bivalent vaccine in the latter, but no national or government vaccination policy has been implemented (Domingo et al., 2008). In Malaysia, a routine comprehensive public vaccination programme for adolescent girls has yet to be adopted by the government, despite an affirmative recommendation by medical professional bodies (Tay et al., 2008).

Brain and Nervous Tissue Cancer

Brain cancer is relatively infrequent, except in Malaysia and the Philippines (see Figure 23).

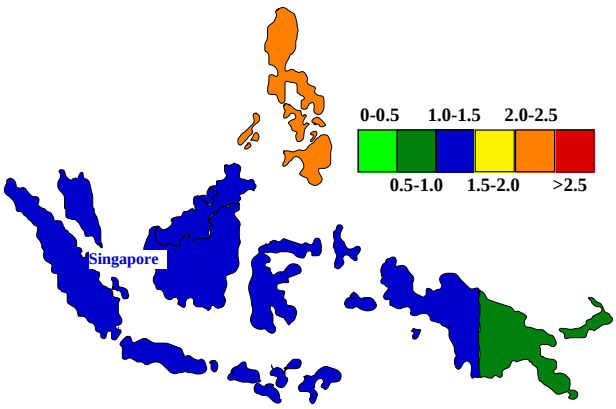

Figure 24. Male Thyroid Cancer Incidences/100,000 (Globocan, 2002: Ferlay et al., 2004)

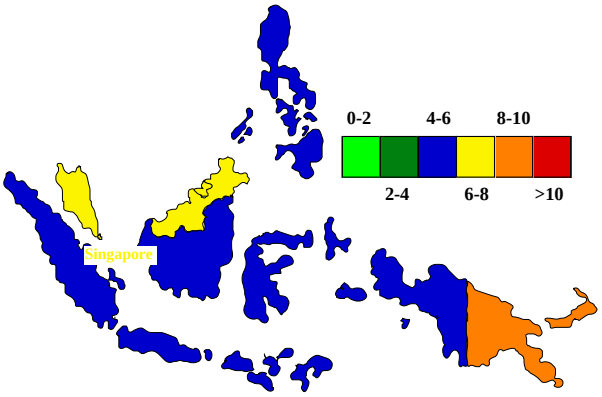

Figure 25. Male Non-Hodgkin Lymphoma Incidences/ 100,000 (Globocan, 2002: Ferlay et al., 2004)

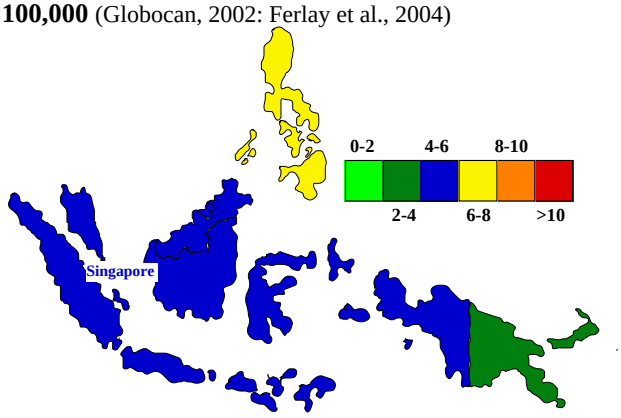

Figure 26. Male Leukemia Incidences/100,000(Globocan, 2002: Ferlay et al., 2004)

Thyroid Cancer

Thyroid cancer is quite frequent in the Philippines (see Figure 24). Malignant thyroid lesions arising from multi-nodular goitre are also common in a population living in an iodine-deficiency area in kelantan (Othman et al., 2009). Well-differentiated thyroid cancer predominates in the Malay population (Abdullah, 2002). Patients generally present very late (Khoo et al., 1998) and significant prognostic factors are age, tumour size, regional recurrence and stage (Voralu et al., 2006).

Leukemias and Lymphomas

Both Non-Hodgkins lymphomas (NHL) and leukemias are relatively common (see Figures 25 and 26). In the Klang valley, malaysia, there is some evidence of environmental factors playing a role, particularly living proximity to power lines (Rahman et al., 2008). An association may exist between HBV infection and NHL (Lim et al., 2007).

Childhood Cancers

There are significant and important racial differences in the frequency of subtypes of childhood ALL in Malaysia (Ariffin et al., 2007). In Sabah, there is a higher prevalence of diffuse large cell lymphoma and lower incidence of follicular lymphoma and Hodgkins lymphoma (Peh et al., 2003), as seen elsewhere in Asia. The reason remains unclear (Hjalgrim et al., 2008). There was an overall increase in the number of cases of NHL in the 1990s (Peh et al., 2003)

Future Perspectives

Clearly there is a need to increase the capacity for cancer registration, especially in those locations without population-based registries at present. At the same time it is important that the data that are available in hospital-based registries are integrated in the most effective fashion. In the future it is to be expected that the trends for increase in breast, colorectal and prostate cancers will continue. Obesity and diabetes mellitus are now common in the region (Mohamad et al., 1996; Mafauzy et al., 1999; Lantion-Ang, 2000; Dhanjal et al., 2001; Ismail et al., 2002; Baltazar et al., 2004) and circulatory problems are becoming more acute (Singh et al., 2000; Nawawi et al., 2002), for example with over 20% of all deaths are now caused by cardiovascular disease in the Philippines (Khor, 2001).

Cigarette smoking is an important determinant of acute coronary events (Quek et al., 1989) and is positively associated with overall cancer incidence, including cancers at specific sites like the head and neck region, upper gastrointestinal tract, pancreas , lung and bladder (Shankar et al., 2008). How to counteract the deleterious effects of a non-healthy lifestyle is thus a major challenge. It is of the essence that tobacco control be taken seriously (Alechnowicz and Chapman, 2004). It has also been argued that more stress needs to be placed on effective management and parameters for assessment of management success (Latiff, 2008).

One focus must be on the diet, including the influence of salt and heavy metal contamination (Sharif et al., 2007). Whether this might interact with ethnic variation in genotype needs to be analysed (Nurfadhlina et al 2006).

With the exception of Singapore (Yeoh et al., 2006), the countries in the region do not have population-based screening programs in place and research should be focused on the likely benefits and relative burden of particular approaches to early detection and down-staging. From the evidence obtained in the Philippines and Malaysia on breast cancer, it would appear that community-based education programs should be given a high priority. Advocacy can play a role here so that galvanizing the political will to meet this challenge needs more emphasis (Yip et al., 2006).

In conclusion, building on cancer control efforts in the past (Lim, 2002; Ngelangel and Wang, 2002), from the present overview it appears that more emphasis needs to be placed on research into the Western lifestyle-related cancers of the colon and breast, while continuing to concentrate attention on reducing cervical cancer by screening and liver cancer by vaccination and education. The burden of other chronic disease is also on the increase and a coordinated approach to prevention would target the causes of well over half of the mortality in the region.

Acknowledgment

Malcolm Moore thanks the Japanese Foundation for Promotion of Cancer Research for financial support during the drafting of this review.

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