LIVER CANCER IN SINGAPORE: AN OVERVIEW

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GEOGRAPHY AND LOCAL DEMOGRAPHY

Singapore is the largest of several smaller islands situated south of the Malaysian Peninsula and just north of the equator. It has a land area of 584 sq. m and a resident population of 2.4 million persons (mean age 19.7 years). This consists of Chinese (76%), Malays (15%), Indians (7%) and the rest (2%). Most of the immigrant Chinese are in the older age groups, over 50 years of age and come from Fukien and Kwantung provinces of China. The proportion of Chinese dialect groups are Hokkien 42.2%, Teochew 22.3%, Cantonese 17%, Hainanese 7.3%, Hakka 7%, others 4.1%. The population is expected to grow steadily to 3 million by year 2000. Presently, the life expectancy for males is 68.6 years and 74.1 years for females.

Existent facilities are high level of education, communication and health care delivery with more than 95% of children and infants covered for primary immunisation against the more common communicable diseases, such as tuberculosis, polio, diptheria, tetanus, whooping couhg and measles. Today, hepatitis B immunoprophylaxis has alslo been introduced to children born of carrier mothers, or who have carriers in the family.

THE SINGAPORE CANCER REGISTRY

The Cancer Registry was developed as a result of joint collaboration between the University Department of Pathology, National University of Singapore and the International Agency for Research in Cancer, and World Health Organisation in 1967. Its inception, emphasised the importance of collecting accurate epidemiological data on cancer in the country. Comprehensive population-based registration of all cancers diagnosed in Singapore has been maintained since January 1968. This registry has the full support of the medical profession and through it, changing trends of cancer in the country are monitored.

LIVER CANCER

Epidemiology

Liver cancer is the third most common cancer (1). The age standardised rate per 100,000 population for period 1978-82 was 28.1 (See Table 1). In incidence, it is only superceded by lung and stomach cancers. In 1984, it was the second most common fatal malignancy in males (See Table II), second most common malignancy in Malays and third common in Indians.

TABLE 1: TEN MOST FREQUENT CANCERS AMONG MALE SINGAPORE RESIDENTS

Site	1968 — 1977			1978 — 1982		
	No.	CR[1]	ASR[2]	No.	CR[1]	ASR[2]
1. Lung	3296	30.7	54.4	2432	42.0	62.8
2. Stomach	2320	21.6	38.0	1240	21.4	31.6
3. Liver	1880	17.6	28.7	1143	19.8	28.1
4. Nasopharynx	1219	11.4	14.8	704	12.2	14.5
5. Colon	730	6.8	11.8	572	9.9	14.3
6. Rectum	692	6.4	11.3	487	8.4	12.5
7. Oesophagus	940	8.8	16.5	439	7.6	11.6
8. Skin (ex melanoma)	407	3.8	7.0	316	5.5	8.1
9. Larynx	406	3.8	6.6	287	5.0	7.2
10. Bladder	343	3.2	6.0	271	4.7	7.2
Other sites	3354	—	—	2212	—	—
ALL SITES	15595	145.3	242.6	10103	174.6	250.2

1 Crude rate per 100,000 population
2 Age-standardised rate per 100,000 population

TABLE 11

(a) Cancer Incidence in Singapore

1968—1972: 1 Lung	2 Stomach	3 Liver	4 Colorectal
1973—1977: 1 Lung	2 Stomach	3 Liver	4 Colorectal
1978—1982: 1 Lung	2 Stomach	3 Liver	4 Colorectal

(b) Male and Female Cancer Mortality for the top 3 cancers

1982

Male:	1 Lung	2 Stomach	3 Liver
Female:	1 Breast	2 Colorectal	3 Lung

1984

Male:	1 Lung	2 Liver	3 Stomach
Female;	1 Lung	2 Colorectal	3 Breast

(c) Ethnic Group Incidence

Male:	Chinese:	(1) Lung	(2) Stomach	(3) Liver
		(4) Colorectal	(5) NPC	
	Malays:	(1) Lung	(2) Liver	(3) Colorectal
	Indians:	(1) Stomach	(2) Lung	(3) Liver
Female:	Chinese:	(1) Colorectal	(2) Breast	(3) Lung
		(4) NPC		
	Malays:	(1) Breast	(2) Cervix	(3) Ovary
	Indians:	(1) Breast	(2) Cervix	)3) Colorectal

*Courtesy World Health Organisation on Cancer Epidemiology and Control, Singapore 7 to 18. October, 1985.

(a) Ethnic Differences

The age standardised incidence rates for the ethnic groups are *Males:* Chinese (40 per 100,000), Malays (20 per 100,000), Indians (15 per 100,000) and for *Females:* 6 per 100,000 for Chinese and 4 per 100,000 for Malays and Indians respectively.

There are insignificant differences in the incidence rate for the different Chinese dialectial groups, although it appears that slightly more Hokkiens have Liver Cancer. This may be due to a larger proportion of Hokkiens in the country.

(b) Age of Presentation

Liver cancer seldom appears before the age of 20 years but peaks in the over 50 year age group. The youngest Liver Cancer patient is a young male child age 8 years (unpublished), who recently developed Hepatocellular Carcinoma and who was HBsAg positive. Although several members of his family were also HBsAg positive, his mother was only Anti-HBs positive.

Where familial cancers appear, a younger age of presentation occurs (e.g. early twenties and thirties) especially in other males within the HCC family where male carriers exists (2). Liver Cancer does not usually appear in females till the postmenopausal age groups, where the incidence increases but the rate does not reach the levels seen in males. The rate is 4 times more common in males than females.

Liver cancers occurring in younger females before the age of 35 years have occurred in Chinese females who were HBsAg positive and on oestrogen and progesterone oral contraceptive agents for over six months duration. In an ongoing prospective study on 236 females on such contraceptive agents, 24 carriers were identified and three have had hepatocellular carcinoma. Only one Malay female patient age 28 years with Wilson's Disease (who was only Anti-HBs positive) developed HCC, but who was not on the pill. Further field studies are needed, as hormones and other co-factors may be important in the pathogenesis of HCC.

Pathology

90% of Primary Liver Cancers are hepatocellular carcinoma, 5% cholangiocarcinoma and the rest, carcinoma of indeterminate origin. Angiosarcoma is extremely rare in the country.

(d) Risk Factors

Definite known risk factors are: chronic hepatitis B (HBV) carriage and exposure to carcinogenic material (e.g. aflatoxin and related compounds). Despite legislative control of aflatoxin content in human food material, absorbed aflatoxin B1 has been detected in normal healthy subjects by measurement of urinary aflatoxin B1 levels (3).

Alcohol consumption is high among Indians who develop Liver Cancer. Further studies on the importance of co-factors are required since there have been recent Japanese reports of a higher risk of HCC developing in carriers who smoke, drink or drink and smoke (4). Such risk factors are three, five and eight times greater for those who indulged in these practices than in the non-indulgers.

(e) Hepatitis B Transmission

Locally, perinatal transmission accounts for 1% of the carrier state, with the bulk of infection occurring horizontally. The prevalence of HBsAg in the population before the age of 20 years is 5% but this gradually rises to 10% in the age groups 40—49, 50—59 and over 60 years of age.

Transmission studies show that infection is high amongst families where there are 'e' Ag positive carriers (5). Vehicles involved in transmission were: the common sharing of tooth pricks, tooth brushes, razors, hand towels, handkerchieves, bedding and where the infected family member had impetiginous lesions or bleeding sites.

The HBsAg and 'e' Ag have also been detected within the cytosol fraction of peripheral lymphocytes of chronic carriers who were serologically negative for 'e' Ag and seronegative (all HBV markers) HCC cases (6). HBV DNA have also been detected too in the other leucocyte fraction by molecular hybridisation techniques (unpublished). The translocation of potential mutant but oncogenic DNA in primitive leucocytes circulating in the liver may be an additional mechanism of hepatocarcinogenesis.

(f) Genotype Relationship (See Figure I)

FIGURE 1
HLA HAPLOTYPE ASSOCIATION IN SINGAPORE CHINESE HCC PATIENTS

1980	(i)	HLA-B15 (R 2.9) associated AFP negative HCC (HBsAg neg.)
	(ii)	HLA-B5 with AFP positive HCC
	(iii)	HLA-B17 with Anti-HBs
1985	Family Studies B15 risk confined to	
	A2 B15 (RR 9.4)	]
	A9 B15 (RR 5.8)	] AFP neg. HCC
	A2 B5 (RR 4.6)	] AFP pos. HCC

Examination of HLA locus A and B typings in our Chinese HCC patients showed that HLA B15 was higher in the AFP negative and HBsAg negative group. This group showed a significant lack of blood Group A. A strong correlation was found between AFP and HBsAg positivities and age groups under 60 years. HLA B5 was associated with HBsAg positivity and HLA B17 with Anti-HBs positivity (7). Recent studies showed (1) that B13 was now especially in AFP positive HCC, (ii) the family risks of HCC was confined to the A2 B15 (RR = 9.4), and A9 B15 (RR = 5.8) haplotypes in AFP negative patients. The risk associated with B5 in AFP positive was due entirely to A2 B5 haplotype (RR = 4.6).

The relative risks associated with these haplotypes, particularly A2 B15 were higher than B15 alone. This is compatible with disease associated genes or chromosone 6.

Clinical Features

In a study on 2,000 patients collected between 1977 and 1985, 85% of HCC presentd with hepatic enlargement and pain (9,10). Pulmonary metastases (20%), bone metastases (20%), lymph node (10%), brain cranial nerve and spinal cord (5%), cardiac (10), ascites (60%) (See Table III).

Patients who were AFP negative had better prognosis than those who were positive.

Unresected, the 1 year survival is less than 20%, with hardly any 5 year survivals.

TABLE III
PRESENTING FEATURES OF PRIMARY HEPATOCELLULAR CARCINOMA ANALYSIS OF 2000 CASES BETWEEN 1977—85

1. Liver mass	95%
2. Abdominal pain	80%
3. IVC Obstruction	60%
4. Ascites	60%
5. Dysphagia	50%
6. Fever (septicaemias rigors)	40%
7. Hepatorenal syndrome	40%
8. Diarrhoea (mucoid)	40%
9. Encephalopathy	20%
10. Haematemesis and malaena	20%
11. Pulmonary metastases/dyspnoea	10%
12. Intestinal obstruction	5%
13. Skeletal metastases	5%
14. Polycythaemia	5%
15. Haemophilia	5%
16. Thrombocytosis (greater than 5×10^6 per mm^3	1%
17. Haematuria	1%
Others	
Collapsing pulse	95%
Liver bruit	60%
Hepatic rub	65%
Associated polycystic liver	1 case
Associated Wilson's disease	1 case

TREATMENT

Early diagnosis of subclinical HCC

Earlier diagnosis through selective screening of high risk groups have identified asymptomatic tumours. These groups are: (1) HBsAg positive male carriers in Liver Cancer families (2) Males over the age of 40 years who are carriers.

However, planning and coordination is required for such large scale screening programmes of carriers.

Investigations here show that lipoidal and CATS, used to identify satellite nodules is a useful method for further determining suitability of surgery. Ultrasound scanning of the liver complements AFP detection, and the latter can identify 90% of HCC clinically. However, problems arise when hyperplastic nodules, which produce positive AFP too are also identified. Such lesions may be regarded as pre-malignant. Surgical resection is possible in only 15% of our patients because in many instances, the associated abnormal hepatic dysfunction is high. In spite of effective surgery, recurrences at one year are high and nearly 50% recur within the first six months.

Chemotherapy using various agents have been extensively explored (11,12). One of the most effective agents is the anthracycline Adriamycin, which produced 50% response when given intravenously. Significant effects were seen in 10% of patients when Adriamycin was used as a radiosensitiser (13). However, its value was limited to patients with uncompromised liver function. Irradiation therapy in more advanced disease have led to irreversible hepatic failure and radiation colitis. Other drugs such as Cisplatin, VP16213, CCNU and antithyroid drugs (carbimazole), even orchidectomy to remove testosterone dependence (14), and hormonal manipulations with Tamoxifen or Aminoglutemide have been tried but have not arrested the rapid growth rate of these tumours.

More recently, new approaches have been used in targeting anticancer agents using lipoidal, a radiocontrast material. Eight months follow up of patients with advanced irresectible HCC (two with recurrences after hemihepatectomy) have shown unexpected survival in 3 with impressive regression of tumour (15).

Such selective targeting using other anticancer agents and/or monoclonal antibodies, against HCC in the future would open up further opportunities for treatment.

RESEARCH PROGRAMMES

(a) Extension of HB immunisation are now being carried to reduce the carrier state. Such vaccinations in males in the older age groups (over 18 years) in whom liver cancer rates are higher and horizontal transmissions are known to occur. It has been crudely estimated that nearly 60% of lives can be saved from Liver Cancer by elimination of HBV (See Table IV).

TABLE IV
ESTIMATE ON LIVES SAVED FROM LIVER CANCER BY HEPATITIS B VACCINATION OF SUSCEPTABLES

Attributable Risk Formula (AR) $= \dfrac{P(R-1)}{PR+1-P}$

Where P = Proportion of population at risk
and R = Relation risk

For Liver Cancer: P = 8% (prevalence)
RR = 20

$$AR = \frac{0.08 \times (20 - 1)}{(0.08 \times 20) + (1 - 0.08)}$$

$= 60\%$

Assumption: All carriers developed Liver Cancer.
Based upon trends: 60% of lives can be saved by elimination of carrier state from 1985 — 2000

(b) Treatment of HBV carriers using prednisolone and adenosine arabinoside and interferons.

(c) Selective screening of carriers to determine frequency and selectivity of screening agents for early HCC.

(d) Cell cultures of human leucocytes and liver cancer cells to determine the relationship between HBV ingested carcinogens and oncogenes.

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