RESEARCH ARTICLE

Rising Incidence of Primary Liver Cancer in Brunei Darussalam

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Abstract

Background: Primary liver cancer (PLC) is the fifth most common malignancy worldwide and is still associated with high mortality. Hepatocellular carcinoma (HCC) and cholangiocarcinoma are the two most common PLCs, and their incidence varies across regions. Currently there are no published data available on the incidence of PLC in Brunei Darussalam. Materials and Methods: All proven PLCs between 2000 and 2009 were identified from the National Cancer Registry and reviewed. Metastatic diseases were excluded. A total of 123 cases (male 65.8%, female 34.2%) were identified and their data collected for calculation of the age standardised rate (ASR). Results: The most common type of PLC was HCC (87.8%) followed by cholangiocarcinoma (10.6%). There were two cases of hepatoblastoma. The mean age at diagnosis was 63.2 years. The overall ASR of PLC was 8.2/100,000, increasing from 4.5/100,000 population in 2000 to 11.4/100,000 population in 2009. The rates were higher among males (12.0/100,000) than females (4.7/100,000). Among the ethnic groups, Chinese had the highest rates (overall 13.1/100,000 with none recorded in 2000 to 30.3/100,000 in 2009) compared to the Malays (overall 8.5/100,000 increasing from 4.5/100,000 in 2000 to 12.3/100,000 in 2009) and the indigenous groups. The incidence increased after the age of 50 and was highest among the 75-79 age groups. Increase was seen for HCC but not for cholangiocarcinoma. Conclusions: The most common type of PLC is HCC and the annual incidence of PLC is increasing in Brunei Darussalam,rates being higher in males and Chinese.

Keywords: Neoplasm - malignancy - hepatic - hepatocellular carcinoma - cholangiocarcinoma - Brunei - ethnicity

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Introduction

Cancers remain one of the world's greatest disease burdens and cause of death. In 2008, 12.7 million new cancer cases and 7.6 million cancer related deaths were recorded (Globocan, 2008; WHO, 2013). Cancers related deaths accounted for 13% of all recorded deaths. Among all the cancers, lung cancer is the most common cause of cancer deaths, followed by stomach cancer and liver cancer.

Worldwide, PLC is the fifth most common cancer in men (523,000 cases, 7.9% of the total) and the seventh in women (226,000 cases, 6.5% of the total) with 85% occurring in developing countries (Globocan, 2008). Generally, men are more affected with a ratio of 2.4 to women. Hepatocellular carcinoma (HCC) is the most common type and accounts for up to 85% of all PLC (Amon et al., 2006). The rates are highest in Eastern and South-Eastern Asia, Middle and Western Africa, but also Melanesia and Micronesia/Polynesia (particularly in men) and generally low in developed countries especially North America and Europe (Srivatanakul et al., 2004). In 2008, an estimated 694,000 deaths from liver cancer (477,000 men and 217,000 women) was reported. Liver cancer is associated with a high fatality rate (mortality to incidence of ratio of 0.93) and is ranked third most common cause of death from cancer (Globocan, 2008). The rates are similar regardless of geographic regions. In 2002, more than 377,000 people died from liver cancer in Eastern Asia, accounting for 19% of total cancer deaths. South-Eastern Asia accounted for 12%, and together they accounted for 71% of total liver cancer deaths in the world (Tsukuma et al., 2005)

In Brunei Darussalam, cancer has been the top killer from 2004 to 2007 with a mortality rate of 55.1 per 100,000 populations in 2007. Currently, there is no published data on the incidence of primary liver cancer (PLC) in Brunei Darussalam. This study assessed the incidence of PLC in Brunei Darussalam and assessing the ethnic and gender differences and the incidence among the different age groups.

Materials and Methods

Patients diagnosed with cancers are registered with Department of Pathology Register, National Cancer

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registry and also the National Cancer registry. The earlier captures all histologically proven cancers whereas the latter captures all cancer diagnosis but data capture is dependent on reporting by the clinicians involved with the patients' care. The National Cancer Registry only captures data of patients who had been referred for further management.

For this study only histological proven PLC were included in the study and metastatic diseases were excluded. The definition of PLC followed the definition of the World Health Organisation (WHO). The two most common PLC are hepatocellular carcinoma (HCC) and intrahepatic cholangiocarcinoma. However, the relative frequency of these two types of PLC varies between countries.

Over the period, there were 123 patients with a diagnosis of PLC, 115 diagnosed by histology and eight diagnosed through laboratory markers and radiological imaging. Data was abstracted from the registries and supplemented with reviews of patients' medical record and imaging reports.

Population statistics used for calculations of the incidence rate for period 2000-2009 were obtained from Department of Economic Planning and Development, Prime Minister's Office, Brunei Darussalam. The number of death secondary to PLC was adapted from Health Indicator for Brunei Darussalam, Ministry of Health 2004 and 2009. Calculation of the crude rate was based on the number of recorded cases per year divided by the overall population and the Age Standardised Rate (ASR) was calculated based on the world population pyramid structure obtained from the WHO (Ahmad et al., 2001). The estimated Brunei population in 2005 was as follow: total 370,100; gender (male 195,300 and female 174,800), racial groups [Malays 246,900, Chinese 41,400 and others (including expatriates) 81,800] with 40.1% aged ≤19, 53.8% aged between 20 and 54, and 6.1% aged ≥55.

Statistical software, Statistical Package for the Social Sciences (SPSS) Statistic Version 16.0, was used to calculate the frequency of the difference types PLC, age, gender and ethnicity. Microsoft Office Excel 2007 was used to calculate the crude incidence, age-specific incidence and age standardised incidence for PLC. Age standardised rate were calculated using the World Health Organisation (WHO) world standard population and by direct method. The number of deaths from PLC between 2004 and 2009 were extracted from Health Information Booklet published by Ministry of Health. When comparing incidence rate, a difference greater than 0.5 was considered to be dissimilar.

Results

Over the ten year study period, there were a total of 123 cases proven PLC. The majority of the PLC was HCC. Among those tested for aetiology, 62% were found to be positive for hepatitis B infection. The breakdown of the types of PLC and the crude rate (CR) is shown in Table 1.

The median age of the patients was 63 years old (SD 20.0) with a range of 1 to 91 years old. There was a male predominance with a ratio of 86:37 (69.9%: 30.1%) and the ethnic breakdown was Malay (n=89, 72.4%), Chinese (n=30, 24.4%) followed by the others (n=4, 3.3%). There was no PLC diagnosed in the indigenous group.

Age standardized rates

The annual crude incidence rate and age standardised (ASR) for PLC the period was 3.3 and 8.2/100,000 population/year. In Brunei Darussalam, the incidence of PLC increased over the past 10 years.

Table 2 shows the ASR of PLC among men and women of different ethnic groups. Overall, men (12.0/100,000) had almost three times the rates of PLC compared to women (4.7/100,000). Among the ethnic group, Chinese (19.1/100,000) had the highest rate followed by the Malays (12.4/100,000).

Table 1. Breakdown of the Different Types and the Overall Crude Rates Primary Liver Cancer in Brunei Darussalam and the Tumour Types (2000-2009)

Types	n (%)	Male (%)	Female (%)	CR
HCC	108 (87.8)	81 (75)	27 (25)	2.9
Cholangiocarcinoma	13 (10.6)	4 (30.7)	9 (69.3)	0.35
Hepatoblastoma	2 (1.6)	1 (50)	1 (50)	0.05

*CR: Crude ratio, HCC: Hepatocellular carcinoma

Table 2. Annual Age Standardised Rate (ASR) Per 100,000 Population for Period 2000 to 2009 by Gender and Ethnicity

Variable			No.	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	Overall (2000-2009)	Relative risk
Overall			123	4.5	6.2	7.7	4.9	9.3	3.8	10.4	8.5	7.1	11.4	8.2	
Gender	Male		86	4.7	8.8	15.6	8.7	16.4	1.4	15.3	17.1	6.1	26.3	12	2.4
	Female		37	3.7	2.6	0	1	2.6	6.3	6.6	3.4	13.2	9.3	4.9	1
Ethinicity and gender															
	Male:	Chinese	21	0	0	49.8	8.4	33.8	16.6	33.6	11.9	0	53.5	19.1	1
		Malay	63	6.5	12.6	9	10.5	16.3	2.8	12.5	21.3	9.4	23.6	12.4	0.6
		Others	2	0	0	0	1.3	0	0	23.8	0	0	0	2.5	0.1
	Female:	Chinese	9	0	0	0	8.5	0	0	0	0	44.1	8.1	7.6	1
		Malay	26	6.2	2	0	0	4.5	5.3	10.1	5.8	3.8	10.3	4.8	0.6
		Others	2	0	25.3	0	0	0	0	0	0	56.9	0	8.2	1.1
Ethnicity	Chinese		30	0	0	2.5	7.9	15.1	7.8	16.1	5.2	24	30.3	13.1	1
	Malay		89	4.5	5.4	3.3	3.7	7.4	2.7	7.9	9.5	4.5	12.3	8.5	0.6
	Others		4	0	0	0	0.7	0	0	14.3	0	24.6	0	5.2	0.4

*n=Total number of cases from 2000 to 2009, RR=Relative Risk, 1=Age Standardised Rate per 100,000/year

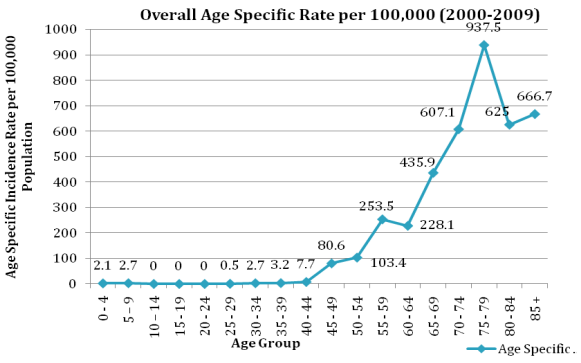

Figure 1. Age Specific Incidence Rate for PLC among Brunei Darussalam Population for the Period 2000-2009

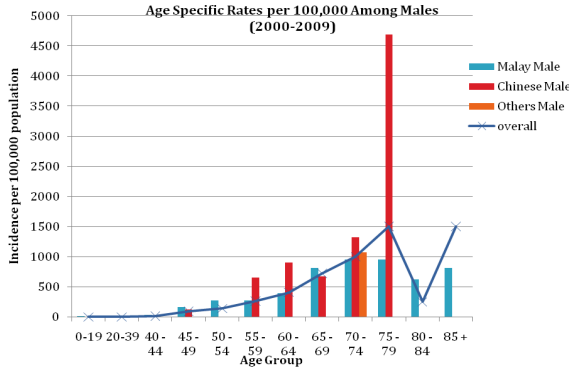

Figure 2. The Bar Graph Shows the Age Specific Incidence Rate Per 100,000 of PLC among Males of Different Races in Brunei Darussalam

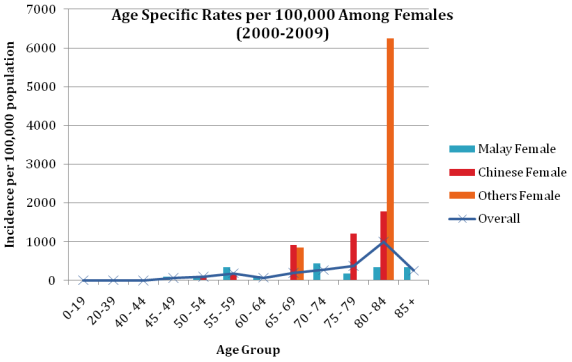

Figure 3. The Bar Graph Shows the Age Specific Incidence Rate Per 100,000 of PLC among Females of All Races in Brunei Darussalam

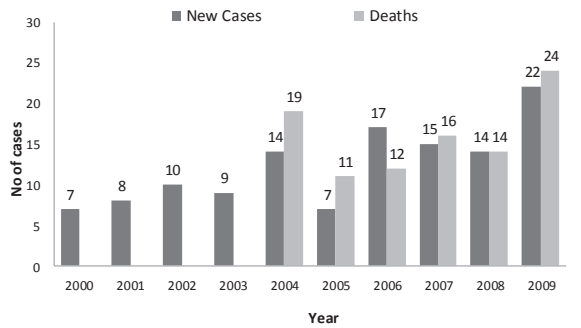

Figure 4. Bar Chat Shows the Number of New Cases Diagnosed and Number of Deaths Due to Primary Liver Cancer from Years 2004-2009. Number of deaths statistics was extracted from Health Information Booklet 2004 and 2009, published by Ministry of Health, Brunei Darussalam. Data before 2004 was not available

Age specific rates

More than 90% of the patients were above 45 years old, with the exception of two cases of hepatoblastoma which were diagnosed in children (one and six years old respectively). The age specific rate (ASR) for PLC is shown in Figure 1. The age specific rate increased as the age increases and peaked in the age 75-79 years group.

Gender age specific rate

Although the incidence increased gradually for both genders, the male incidence peaked at age 75 to 79, while the female incidence peaked later at 80-84. The incidence of liver cancer is 10 times higher in men who are above 45 than those who are below the age of 45. Figures 2 and 3 showed that the ASRs for male and female respectively.

Mortality rates

From 2004 to 2009, the number of new cases and the number of deaths due to PLC are almost very similar and in some years, there were more deaths than new cases (Figure 4).

Discussion

Among PLC, the most common type in our setting by far was HCC accounting for 87.8% of all PLC. Overall, 62% of our HCC who had testing were found to be positive for hepatitis B infection. This high proportion is not unexpected considering that chronic hepatitis B infection is prevalent in the Asia Pacific region including Brunei Darussalam. Brunei Darussalam lies in the moderate rate region with rates of between 2 and 8% of the population to be affected by hepatitis B. Given the rarity of primary sclerosing cholangitis or biliary parasite infestation, it is not unexpected that cholangiocarcinoma is less common. In contrast, cholangiocarcinoma is more common in Thailand and maybe because parasitic biliary infection is more prevalent (Kamsa-ard et al., 2011). We encountered only two cases of hepoblastoma.

From our study, the overall incidence rate of PLC increased from 4.5/100,000 in 2000 to 11.4/100,000, an almost three fold increase. The increase is mainly the result of increase in HCC. There was no change in trend of cholangiocarcinoma. The trend seen in HCC is likely due to a cohort effect of hepatitis B related HCC. The trend is likely to continue as the population age, and it is only going to decline in three to four decades after declining prevalence of hepatitis B infection. Blood donors' studies have shown a significant decline in the prevalence of hepatitis B infection in our setting (Sebastian et al., 1989; Alexander et al., 1990; Teo et al., 2011). For the moment, it is important for clinicians to be aware of the trend and pattern so that measures can be taken to prevent progression to HCC or to diagnose early in order to reduce mortality related to HCC.

Among the types of PLC, there were gender differences. Our male population had a relative risk ratio of 2.4 times higher than the female population, consistent with what have been reported (Globocan, 2008). In our study, HCC was more common in among men whereas cholangiocarcinoma was more common in women. In the

Southeast Asia region, our PLC rates for both genders were higher than the rates reported in Peninsular Malaysia (men 4.7/100,000 and women 1.6/100,000) (Malaysia National Cancer Registry, 2007), but much lower than those reported in Singapore, especially among men (17.0/100,000) but comparable to their women (4.6/100,000) (Singapore Cancer Registry, 2006-2010). Compared to other part of Asia such as China (29.3/100,000 and women 9.1/100,000) where aflatoxin exposure is higher, our rates are much lower (Chen et al., 2011). Compared to western countries like the United Kingdom (men 6.6/100,000 and women 3.0/100,000) (Cancer Research UK, 2010) and United States of America (men 7.0/100,000 and women 2.6/100,000) (Globocan, 2008) our incidence rates were much higher. The differences are in part due to differences in the etiologies of chronic liver disease where hepatitis B is common in the East whereas hepatitis C and alcohol is more common in the West. An exception is Japan where 80% of HCC are due to chronic hepatitis C infection (Tsukuma et al., 2005).

Among the various racial groups, our Chinese had the highest rate, almost two folds higher compared to the Malays. This finding is similar to those reported from Malaysia and Singapore, which have similar population demographic. In Singapore, the rate for Chinese men (18.1/100,000) and women (4.9/100,000) were higher than the Malays (men 14/100,000 and women 4.3/100,000) and the Indians (men 10.2/100,000 and women 3.3/100,000) (Singapore Cancer Registry, 2006-2010). Similarly in Malaysia, Chinese had the highest rate (men 6.4/100,000 and women 2.0/100,000) compared to the Malays (men 3.4/100,000 and women 1.4/100,000) and Indian (men 2.2/100,000 and women 0.9/100,000) (Malaysia National Cancer Registry, 2007). Aside from PLC, other cancers such as colorectal cancers, gastric cancer and breast cancers have also been reported to be more common among the Chinese (Wang et al, 2004; Chong et al., 2009; Pathy et al., 2011). This suggests that genetic susceptibility or polymorphisms, cultural habits including diets and environmental factors such as aflatoxin are important. Importantly, chronic hepatitis B infection is more common among the Chinese compared to the other racial groups.

Not unexpectedly, the risk increases with age. This is true for most cancers (Globocan, 2008). The overall age specific incidence rate started to increase after the age of 50 and peaked at 937.5/100,000 in the 75-79 age groups. These patterns were seen in the various racial groups and gender, although the peaks were smaller for the Malays and women. Chinese men in the 75-79 age groups had rates of over 4,500/100,000 compared to the Malays (<1,000/100,000) of the same age group. This suggest that screening need to be intensified after the age of 50, and those still under follow up in the older age groups, in particular men and Chinese.

Generally, PLC is still associated with high mortality rates as most are diagnosed late and at advanced stages making treatment mainly palliative. During the ten year study period, the number of new cases and deaths were almost identical. This indicates overall poor prognoses and suggests that the survival rate of PLC was a year or less. This is similar to a European study that showed the weighted relative survival rate at one year and five years were 16% and 5% respectively (Faivre et al., 1998). The study also suggested that there was no difference in gender on survival; however, the survival rate was slightly higher in the younger age group (Pathy et al., 2011). The poor prognoses were mainly due to late detection of disease as it is asymptomatic in early stages. During the late stage, treatments are limited as the tumour might be too large to undergo resection or most of the livers are already at advanced stages of fibrosis [stage III or IV (cirrhosis)].

There are several limitations with our study. First, it is a retrospective in nature and this is inherently associated with limitations such as missing or incomplete data. Second, we only included PLC captured by the National Cancer Registry. It is possible that some patients may have been evaluated and received treatment in another country, hence not captured by the National Registry. However, the number is very small and becoming fewer in the later part as more are now seeking treatment locally. Even if patients have been treated overseas, they would still have been followed up in our clinics and eventually get registered. Third, the overall number of PLC is small compared to other countries which accounted for the fluctuations observed. However, this is reflective of the small population of the country of less 400,000 in 2005. The main strength of our study is that, the registry captured all the cases for the whole country, and as such is very representative of the country and our population.

In conclusion, PLC has increased significantly in Brunei Darussalam in the past 10 years and is largely due to the increase in number of HCC cases. This may be due to the cohort effect of chronic hepatitis B infection which is still common in our setting. Similar to what have been shown in other countries, men have higher rate than women and among the difference racial groups, Chinese has higher rate compared to the other racial groups.

References

Ahmad OB, Boschi-Pinto C, Lopez AD, et al (2001). Age standardization of rates: a new who standard', GPE Discussion Paper Series: No.31, no. EIP/GPE/EBD World Health Organization 2001.

Alexander MJ, Sinnatamby AS, Rohaimah MJ, et al (1990). Incidence of hepatitis B infection in Brunei Darussalam-analysis of racial distribution. *Ann Acad Med Singapore*, **19**, 344-6.

Amon JJ, Nedsuwan S, Chantra S, et al (2006). Trends in liver cancer, Sa Kaeo Province Thailand. *Asian Pac J Cancer Prev*, **6**, 382-6.

Cancer research UK. Liver cancer incidence statistics 2010. Available from http://www.cancerresearchuk.org/cancer-info/cancerstats/types/liver/incidence/ (Accessed 6th December 2012).

Chen JG, Zhang SW (2011). Liver cancer epidemic in China: past, present and future. *Semin Cancer Biol*, **21**, 59-69.

Chong VH, Abdullah MS, Telisinghe PU, et al (2009). Colorectal cancer: incidence and trend in Brunei Darussalam. *Singapore Med J*, **50**, 1085-9.

Faivre J, Forman D, Esteve J, et al (1998). Survival of patients with primary liver cancer, pancreatic cancer and biliary tract cancer in Europe. *Euro J Cancer*, **34**, 2184-90.

International Agency for Research on Cancer. GLOBOCAN 2008 Fact Stats. Available from http://globocan.iarc.fr/

factsheet.asp (Accessed 14th February 2013).
Kamsa-ard S, Wiangnon S, Suwanrungruang K, et al (2011). Trends in liver cancer incidence between 1985 and 2009, Khon Kean, Thailand: cholangiocarcinoma. *Asian Pac J Cancer Prev*, **12**, 2209-13.
National Cancer Registry Report. Malaysia Cancer Statistics-Data and Figure 2007. Available from http://www.makna.org.my/PDF/MalaysiaCancerStatistics2007.pdf (Accessed 6th December 2012).
Pathy NB, Yip CH, Taib NA, et al (2011). Breast cancer in a multi-ethnic Asian setting: results from the Singapore-Malaysia hospital-based breast cancer registry. *Breast*, **20**, 75-80.
Sebastian VJ, Bhattacharya S, Ray S, et al (1989). Hepatitis-B surface antigen and VDRL in healthy blood donors of Brunei Darussalam. *Singapore Med J*, **30**, 568-70.
Singapore Cancer Registry Interim Annual registry Report. Trends in cancer incidence in Singapore 2006-2010. Available from http://www.nrdo.gov.sg/uploadedFiles/NRDO/Cancer_Trends_Report_06-10_final2.pdf (Accessed 6th December 2012).
Srivatanakul P, Sriplug H, Deerasamee S (2004). Epidemiology of liver cancer: an overview. *Asia Pac J Cancer Prev*, **5**, 118-25.
Teo KS, Saparudin MS, Zaini Z, et al (2011). Transfusion transmissible infections in Brunei Darussalam: a blood donor study. *Brunei Int Med J*, **7**, 321-7.
Tsukuma H, Tanaka H, Ajiki W, et al (2005). Liver cancer and its prevention. *Asia Pac J Cancer Prev*, **6**, 244-50.
Wang H, Seow A, Lee HP (2004). Trends in cancer incidence among Singapore Malays: a low-risk population. *Ann Acad Med Singapore*, **33**, 57-62.
World Health Organization: WHO (2013). Cancer Fact Sheet N*297 Reviewed January 2013. Available from http://www.who.int/mediacentre/factsheets/fs297/en/ (Accessed 14th February 2013).