RESEARCH COMMUNICATION

Trends in Liver Cancer, Sa Kaeo Province Thailand

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Abstract

Objective: To determine liver cancer trends in Sa Kaeo Province, Thailand. Methods: Death certificate (1993-2003) and hospital records (1999-2003) were reviewed and compared to national averages and other provinces. Results: According to data from death certificates, liver cancer mortality in Sa Kaeo Province increased from 3.1 to 26.1 per 100,000 population between 1993 and 2003. In Thailand overall rates increased from 9.0 to 19.8 per 100,000 population between 1996 and 2003. According to electronic hospital records, the total number of patient encounters (in-patient admissions and out-patient visits) for liver cancer in the two main hospitals in Sa Kaeo Province increased 56% (14% annually) between 1999 and 2003. The number of cases of hepatocellular carcinoma increased from 42 in 2001 to 73 in 2003, while the number of cases of cholangiocarcinoma showed little change. Conclusions: Thailand as a whole and Sa Kaeo Province specifically have a high burden of liver cancer, which appears to have increased substantially in the past 10 years. Demonstrating the impact of ongoing strategies aimed at reducing risk factors for liver cancer, such as universal hepatitis B vaccination of infants, will require reliable data describing liver cancer disease burden and etiology. Rapid investigations using available data from death certificates, electronic admissions records, and patient charts can provide valuable insights on disease burden and trends.

Key Words: liver cancer - trends - epidemiology - hepatitis - Thailand

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Introduction

Worldwide, liver cancer is the fifth most common cancer (Parkin et al., 2001). However, rates of liver cancer and the relative frequency of the two main types (hepatocellular carcinoma and cholangiocarcinoma) vary significantly between countries, as well as in different regions of the same country (Terry, 2003). Hepatocellular carcinoma, which comprises approximately 85% of malignant hepatic tumors worldwide, has a high incidence in Sub-Saharan Africa and China, and an intermediate incidence in other parts of Asia, Latin America and Europe (Bosch et al., 1999). Cholangiocarcinoma is less common worldwide than hepatocellular carcinoma; however, in specific regions of Southeast Asia, most notably the northeast Thailand province of Khon Kaen, cholangiocarcinoma represents a majority of liver cancer cases (Haswell-Elkins, et al., 1994; Srivatanakul et al., 2004). Known risk factors for hepatocellular carcinoma and cholangiocarcinoma differ, with major risk factors for hepatocellular carcinoma including hepatitis B virus (HBV) and hepatitis C virus (HCV) infections and exposure to aflatoxin. In contrast, the main risk factor for cholangiocarcinoma is high intensity infection with the liver flukes *Opisthorchis viverrini* or *Clonorchis sinensis*. Despite the large burden of disease associated with liver cancer, surprisingly limited information is available on trends in the incidence of hepatocellular carcinoma or cholangiocarcinoma globally, or in Thailand.

Sa Kaeo Province, located in eastern Thailand along the border with Cambodia, has an overall population of approximately 600,000 (2003). In 2002, the single leading cause of death reported on death certificates in Sa Kaeo Province was cancer. Among cancer deaths, liver cancer was the leading type. In 2003, anecdotal reports from medical personnel in Sa Kaeo Province suggesting that liver cancer cases had been sharply increasing over the past few years prompted an evaluation of liver cancer cases and liver cancer trends in the province.

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Methods

To describe general trends in mortality attributed to liver cancer, death certificate records were reviewed for the period 1996 – 2003 for Thailand as a whole, as well as Sa Kaeo Province and four other provinces from different regions within the country. To further assess trends and describe the specific characteristics of liver cancer cases in Sa Kaeo Province, hospital records for liver cancer patients diagnosed between 1999 and 2003 were reviewed.

Death Certificate Review

Death certificates for the period 1993-2003 were evaluated by review of reports published by the Ministry of Interior. A case was defined as a death attributed to primary liver cancer, as indicated by an ICD10 code of C22 on the certificate of death. Crude mortality rates were calculated using provincial and national census estimates. Rates of liver cancer were compared to those for other tumors (breast, ICD10 code C50; cervix, ICD10 C53; trachea, bronchus, lung, C33-34; colon, rectum, anus, ICD10 C18-21) for which ultrasound is typically used in diagnosis.

Hospital Record Review

Sa Kaeo Province has a total of 8 hospitals, with in-patient capacity ranging from 30-230 beds. However, the two main hospitals, Aranyaprathet (150 beds) and Crown Prince (230 beds) Hospitals, in Eastern and Western regions of the province respectively, have the most advanced staffing and diagnostic capacity (including the only ultrasound equipment), and combined see 75% of in-patients and 60% of out-patients in the province. Interviews with provincial health officers indicated that all suspect cases of liver cancer would most likely be first seen at, or referred to, Aranyaprathet or Crown Prince Hospital. Therefore, the assessment of admissions and patient records was limited to these two hospitals.

In-patient and out-patient electronic records with an ICD10 diagnostic coding of C22 (primary liver cancer) from 1999-2003 for the two hospitals in Sa Kaeo Province were reviewed. A case was defined as an in-patient or out-patient with a diagnosis of primary liver cancer and an ICD10 coding of C22. Cases were attributed to the year that a diagnosis of liver cancer was first noted. All cases were required to be residents of Sa Kaeo Province.

Patient charts were available for the period 2001-2003. Data in the medical charts of individual patients were summarized using a standardized two-page data abstraction form. The information collected included: age, sex, residence (including village, sub-district, district and province), ethnicity, smoking and alcohol use, clinical characteristics, laboratory results (including blood, stool, and ultrasound, if present), and referral information. Based on the final diagnosis (as specified on the last medical visit), each patient was classified as: 1) hepatocellular carcinoma; 2) cholangiocarcinoma; 3) liver cancer, unspecified; or 4) other. Data were analyzed using SPSS 11.0 (Chicago, IL) to examine trends over time and frequency of different case characteristics. Pearson's chi-square was used for measuring difference in frequencies, and ANOVA was used for comparing median ages.

Results

Death Certificate

The analysis of death certificate data indicated that, within Thailand as a whole, there has been a sharp increase in mortality attributed to liver cancer, with rates per 100,000 population increasing from 9.0 to 19.8 between 1996 and 2003. A similar increase was seen across five provinces, with Ranong Province in southern Thailand reporting a greater than four-fold increase (Table 1). In Sa Kaeo Province,

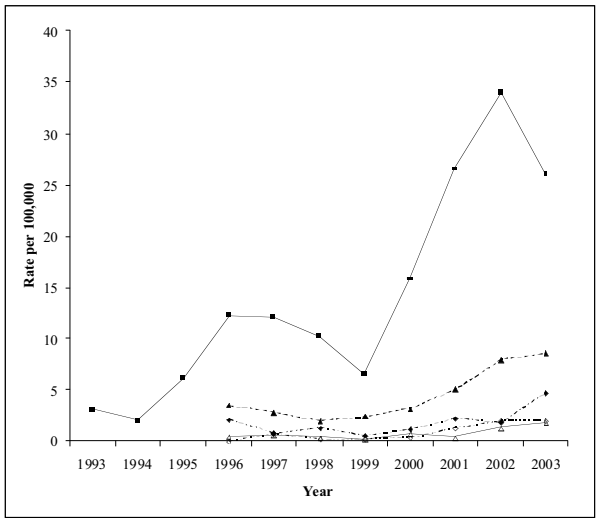

Figure 1. Cancer Mortality (rate per 100,000 population) by Type, Sa Kaeo Province, Thailand. (Legend: Solid markers: squares = liver; triangles=trachea, bronchus, lung, diamonds=colon, rectum, anus. Clear markers: triangles=breast; diamonds=cervix)

Table 1. Liver Cancer Rate per 100,000 Population, 1996 – 2003, in Provinces of Thailand

Province	1996	1997	1998	1999	2000	2001	2002	2003
Sa Kaeo	12.5	12.2	10.5	6.5	15.8	26.8	34.2	26.1
Khon Kaen	13.2	12.5	21.4	22.3	26.2	34.6	41.4	35.8
Nakhon Phanom	14.8	14.4	22.4	23.8	27.4	29.4	31.8	54.3
Chiang Rai	9.4	10.7	2.7	3.1	8.6	9.0	12.8	19.5
Ranong	2.1	1.4	1.3	1.3	4.4	9.3	4.3	9.8
National Average	9.0	9.5	12.0	12.8	14.6	16.5	17.7	19.8

greater increases were seen in liver cancer than cancers of the trachea/bronchus/lung, breast, cervix or colon/rectum/anus (Figure 1).

Hospital Records

According to electronic hospital admissions records, the total number of patient encounters (in-patient and out-patient) for liver cancer in Crown Prince and Aranyaprathet Hospitals increased 56% (14% annually), from 174 to 271 cases, between 1999 and 2003 (Table 2). The increase was somewhat greater at Crown Prince Hospital (15% annually), which also reported 69% of the overall number of cases over the time period, than at Aranyaprathet Hospital (12% annually). Little difference was seen in liver cancer admission rates according to district of residence within the province (data not shown).

Patient medical charts were available for 95% of the 719 patients who were identified by electronic record review as having been diagnosed with liver cancer during the years 2001-2003 (Table 2). Twenty-three percent (23%) of the records located were found to have a diagnosis other than liver cancer and had been miscoded as C22; these were excluded from further analysis.

Among the 521 patients diagnosed with liver cancer during 2001-2003, the number of cases attributed to hepatocellular carcinoma increased from 42 in 2001 to 73 in 2003. During the same period, the number of individuals diagnosed with cholangiocarcinoma remained approximately constant, accounting for 40 cases in 2001 and 44 cases in 2003. The number of cases with a diagnosis of ' liver cancer, unspecified' or 'other' also remained approximately constant (Table 2).

Comparing the characteristics of patients classified with hepatocellular carcinoma (n=167) and cholangiocarcinoma (n=143), patients with a diagnosis of hepatocellular carcinoma were slightly younger (median age of 55 vs. 60 years, p=.05), more likely to be male (78% vs. 62%, p=.005), and more likely to frequently consume alcohol (19% vs. 10%, p=.02). The two groups of patients had a similar prevalence of abdominal pain, hepatomegaly, and abdominal mass.

Limited laboratory data were available to suggest etiologies. Among individuals diagnosed with hepatocellular carcinoma with serological testing results for HBV or HCV markers, 46% (6 of 13) were hepatitis B surface antigen (HBsAg) positive and 40% (2 of 5) were antibody to hepatitis B core antigen (anti-HBc) positive. Among individuals diagnosed with cholangiocarcinoma, 13% (1 of 8) were HBsAg positive and 0% (0 of 2) were anti-HBc positive. Thirteen percent (1 of 8) of hepatocellular carcinoma patients had antibody to HCV (anti-HCV) compared to 0% (0 of 1) of cholangiocarcinoma patients. Stool examination was also done on a limited number of patients. Among individuals diagnosed with hepatocellular carcinoma, 7% (1 of 15) had a positive result on stool examination (for *Strongyloidies sp*.), while the only positive result among the stool examinations (1 of 13, or 8%) among cholangiocarcinoma patients was due to the presence of *Opisthorchis* eggs. Of the limited number of biopsy reports available, most (11 of 14) were inconclusive.

Discussion

Liver cancer is an important public health problem in many parts of the world, but details of disease burden, temporal trends, and the factors underlying these trends are not well documented. Using death certificate data and hospital records we conducted a rapid examination of trends in liver cancer rates in Sa Kaeo Province, Thailand, and found evidence that one type of liver cancer in particular, hepatocellular carcinoma, was increasing. The investigation demonstrated that available data sources can provide valuable information on liver cancer trends and underlying etiologies. Improving the quality and availability of this type of data, and conducting periodic follow-up analyses can further increase our understanding of the burden and epidemiology of liver cancer in high disease areas, and help assess the impact of primary prevention strategies.

Improving our Understanding of Liver Cancer Trends and Causes

In Thailand, death certificate data indicated that mortality from reported liver cancer has increased between 1996 and 2003, and in Sa Kaeo Province increases were seen since 1993. Similar increases were not seen for other major cancer types. Hospital records from Sa Kaeo Province provided

Table 2. Trends in Diagnosis of Liver Cancer, by Hospital and Specific Type, Sa Kaeo Province, Thailand, 1999 - 2003

Variable	Year 1999	2000	2001	2002	2003
# Liver Cancer Admissions (from electronic hospital records)	174	206	205	243	271
# (%) Patient Records Found			196 (96%)	229 (94%)	255 (94%)
# (%) Patient Records Eligible			148 (76%)	187 (82%)	186 (73%)
Patient Classification					
Hepatocellular carcinoma			42 (28%)	52 (28%)	73 (40%)
Cholangiocarcinoma			40 (27%)	59 (32%)	44 (24%)
Liver Cancer, unspecified			59 (40%)	63 (34%)	58 (31%)
Other			7 (5%)	10 (5%)	10 (5%)

additional evidence for an increase in the number of liver cancer cases, however, this increase was substantially smaller than death records indicated.

The specific nature of the increase and the underlying factors are unclear. Primary liver cancer is difficult to diagnose, and limited information on case-patients was available – few patients were referred for liver biopsy, and few had complete laboratory information. While changes in diagnostic equipment, staffing or protocols, or in patient utilization of health care services or demographics might theoretically account for the observed trends, there was no evidence that these changes occurred in Sa Kaeo Province. The absence of similar increases for other types of cancer in Sa Kaeo Province also suggests that the increase in hospital admissions for liver cancer represents a true increase in primary liver cancer incidence.

The term liver cancer encompasses a heterogeneous group of specific diagnoses reflecting different etiologic factors. Improvements in diagnostic accuracy could help to focus prevention strategies on relevant risk factors. While definitive diagnosis of liver cancer usually relies on histologic examination, in high-incidence regions of the world, the differentiation of hepatocellular carcinoma and cholangiocarcinoma can be made with a high degree of accuracy based on a combination of imaging and laboratory measures (Kew, 1997). For example, a high or rising serum alpha-fetoprotein (AFP) level (greater than 400 ng/ml), and a hypervascular hepatic mass (>2 cm) on radiographic imaging studies is characteristic of hepatocellular carcinoma (Bruix et al., 2001). In contrast, patients with cholangiocarcinoma typically have normal serum AFP levels, elevated serum alkaline phosphatase levels, and more frequently present with jaundice (Ahrendt et al., 2001; Zhou et al., 2000). In these patients, ultrasound typically shows dilated intrahepatic ducts and normal extrahepatic ducts.

Despite limitations in accurately distinguishing hepatocellular carcinoma from cholangiocarcinoma in our data, it appears that the majority of the increase in liver cancer mortality can be attributed to a rise in hepatocellular carcinoma. HBV infection is the most frequent underlying cause of hepatocellular carcinoma worldwide, and in Thailand between 8-10% of males and 6-8% of females are estimated to be HBsAg positive (Merican et al., 2000). HBV prevalence in Sa Kaeo appears to be similar: among antenatal clinic attendees at one hospital in 2002, 6% were HBsAg positive. However, without more detailed information on trends in HBV prevalence, or on age-specific HBV prevalence, understanding the underlying dynamics driving increasing rates of hepatocellular carcinoma changes is difficult. Consequently, it is also difficult to predict whether the current increase will continue, and if so, for how long.

In addition to HBV infection, other factors may also be contributing to the high burden of hepatocellular carcinoma in Sa Kaeo Province, although most likely to a smaller extent. HCV infection is another underlying cause of hepatocellular carcinoma, and is found in between 1.5% and 3% of adults in Thailand (Nantachit et al., 2003). In Sa Kaeo Province, just less than one percent (0.9%) of blood donors were anti-HCV positive. Information on aflatoxin exposure, another important cause of hepatocellular carcinoma, is not available in Sa Kaeo Province, although a number of studies conducted in other parts of Thailand have failed to find an important role for aflatoxin exposure in local cases of hepatocellular carcinoma (Srivatanakul et al., 1991a; Srivatanakul et al., 1991b; Wild et al., 1990).

Although there does not appear to be a sharply increasing trend in cases of cholangiocarcinoma in Sa Kaeo Province, the finding of 24%-32% of cases being due to cholangiocarcinoma is higher than expected for this region of Thailand, given the low frequency of *O. viverrini* infection reported. Limited information on trends of *Opisthorchis* infection in Sa Kaeo Province, and limited diagnostic testing of liver cancer patients for the presence of *O. viverrini* infection, make it difficult to understand possible trends in risk factors associated with cholangiocarcinoma, and to estimate the possible future burden of cholangiocarcinoma in the province.

In addition to improving the availability and use of specific diagnostic tools to more accurately classify liver cancer as hepatocellular or cholangiocarcinoma, efforts to improve the quality of death certificate reports and hospital record coding can greatly improve the ability to conduct rapid assessments of liver cancer of trends. Specific studies to assess diagnostic accuracy (for example using post-mortem autopsy) and the establishment of cancer registries can provide further, and more detailed, information to complement death certificate and hospital record-based data.

Implementing Effective Strategies for Primary Prevention of Liver Cancer

Despite uncertainties about the trend and underlying causes of liver cancer in Sa Kaeo Province, prevention measures are needed to address the undisputedly high rates of liver disease. Because treatments options are limited, and median survival short, primary prevention strategies, that is, prevention aimed at eliminating or reducing exposure to those factors that cause liver cancer, represent the best opportunity to alter the natural history of liver cancer.

In Sa Kaeo Province, the majority of liver cancer cases were due to hepatocellular carcinoma, and the majority of these cases were likely due to HBV infection. Hepatitis B vaccination is the most effective means of HBV infection prevention. Because the virus is often transmitted from mother to child, and the risk of chronic infection is greatest for newborns and young children, vaccination at an early age is necessary. Hepatitis B vaccination has been integrated into Thailand's expanded program on immunization since 1992, and the effect of vaccination on reducing chronic HBV infection has already been demonstrated (Poovorawan et al., 2000). In order for Thailand to demonstrate the impact of reduced infection on liver cancer rates (something Taiwan, with twenty years of vaccination efforts has demonstrated among children (Chang et al., 1997; Chang, 2003; Huang et al., 2000)), improved data and repeated assessments are

needed.

However, recognizing that current newborn vaccination campaigns in Thailand will take decades to impact upon liver cancer rates, other primary prevention measures directed at older persons should not be forgotten. Both HBV and HCV transmission can be reduced by ensuring effective blood screening and proper sterilization and safe needle use. Because of the lack of a hepatitis C vaccine, this approach is particularly important in preventing HCV infection.

In addition to targeting hepatocellular carcinoma, primary prevention strategies can address causes of cholangiocarcinoma. To reduce the burden of cholangiocarcinoma, public health education campaigns can spread messages to reduce the consumption of raw fish, and sanitation efforts can be conducted to reduce fecal contamination of water sources.

Although the extent to which alcohol and other hepatoxic exposures (such as herbal remedies) influence the burden of liver cancer in Sa Kaeo Province is uncertain, primary prevention campaigns can also include education to limit these factors, which can have an additive impact on hepatocarcinogenesis (Larrey, 1997) .

Conclusion

Liver cancer has increased substantially in Sa Kaeo Province, Thailand, in the past 10 years. Both hepatocellular carcinoma and cholangiocarcinoma were important causes of liver cancer, however our data indicated that the increase was most likely due to increases in the number of cases of hepatocellular carcinoma. Using readily available data, it was possible to demonstrate both a high burden of disease due to liver cancer in Sa Kaeo Province, and an increasing trend. Given the high rates of HBV infection prevalence in other regions of Thailand, similar increases may be occurring elsewhere. However, this analysis also shows the limitations inherent in documenting and understanding the dynamics underlying liver cancer burden in high prevalence areas of the world given the limited available data. Improving our understanding of the burden of disease and changing trends in liver cancer in areas of high prevalence can help in the design of effective prevention efforts, and provide evidence of their value and impact.

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