# Chapter 1

# Introduction

## 1.1 Background

Liver cancer is a significant causes of morbidity and mortality worldwide, with an estimated half a million new cases per year. Because of its high fatality (overall ratio of mortality to incidence of 0.93), there were an estimated 694,000 deaths from liver cancer in 2008 (477,000 in men, 217,000 in women). It is the third most common cause of death from cancer (El-Serag 2001, Ferlay et al. 2010).

There are two kinds of liver cancer: hepatocellular carcinoma (HCC) and cholangiocarcinoma (CCA). HCC, associated with hepatitist B virus, is a major problem in all regions of Thailand, with the exception of the Northeast. CCA is accounted for 89% of all liver cancer in Khon Kaen, which has the highest incidence rate in the world (Jemal et al. 2010, Llovet 2005, Vatanasapt et al. 2002). CCA is a rare tumor in other western countries. High rates in the Northeast of Thailand have been found related to the habit of eating uncooked cyprinoid fish (Viratroumanee et al. 2009, Ahmed et al. 2008, Vatanasapt et al. 2002).

Another study conducted by Sripa et al. (2007) suggested that the cause is eating uncooked fish infected by fecal parasites carried by snails that proliferate in unsanitary water. Fluke-infected fish are plentiful in the local rivers such as the Chi River in Khon Kaen province, Thailand. Local people catch the fish in nets and prepare the fish-based meals with local herbs, spices, and condiments. The finished dish of *koi-pla* is a dietary staple of many northeastern Thai villagers and is a common source of infection with O. *viverrini*. It is known that liver fluke infection caused by *O. viverrini*, *O. felineus* and *C. sinensis*. The Life Cycle of *O. viverrini* and *C. sinensis* is shown in Figure 1.1.

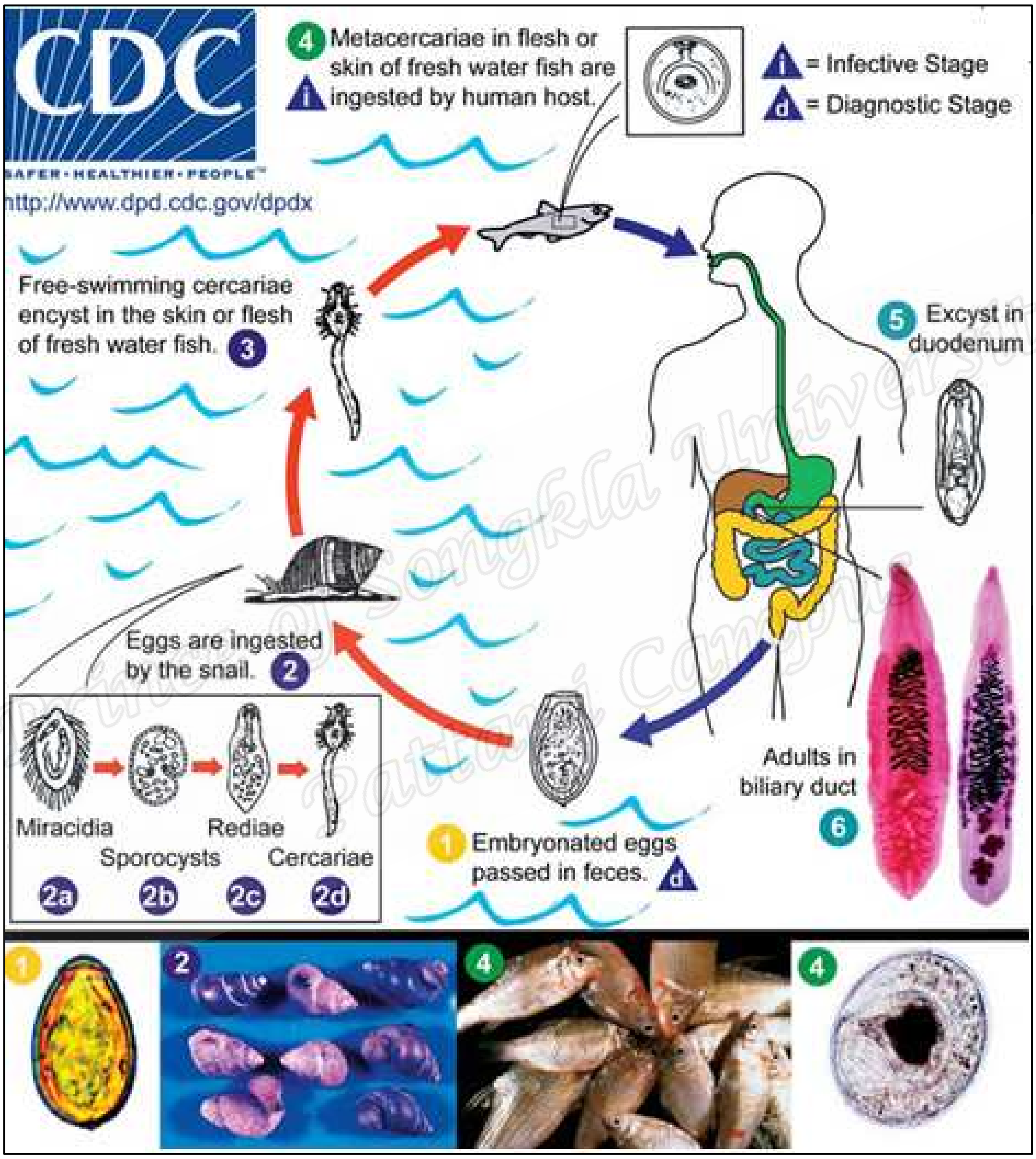


Figure 1.1: Life Cycles of *O. viverrini* and *C. sinensis*

sources: Sripa et al. (2007)

Causes of deaths for liver cancer have been coded according to the World Health Organization’s International statistical classification of diseases (ICD). For HCC, the

ICD-10 code is C22.0 and for CCA, the ICD10-code is C22.1. HCC and CCA have different etiology but Thai death certificates code both as C22.9 (unspecified liver cancer).

Mortality of liver cancer in Thailand is high. A 2004 report by WHO gives age-standardised Thai liver cancer mortality as 29.1 per 100,000 population compared with 13.6 for Japan. However, such comparison is complicated by the fact that these countries have quite different age distributions. In 2006 only 4.4% of the Thai population was aged 70 or more, compared with 15.0% in Japan.

Nearly 40% of death certificates in Thailand give the ICD-code cause as R00-99 "ill-defined", and thus many specific causes, including liver cancer, go largely under-reported, whereas less than 4% of Japan deaths are ill-defined.

To validate vital registration reported data (VR), a verbal autopsy (VA) study was carried out in 2005 based on a sample of 3,316 in-hospital and 6,328 outside-hospital deaths from 28 selected districts in 9 provinces (Rao et al. 2010, Pattaraarchachai et al. 2010, Polprasert et al. 2010, Porapakkham et al. 2010). Byass (2010) concluded that there are still some uncertainties in these revised estimates.

This study aims to use appropriate statistical methods to estimate the number of liver cancer deaths based on the 2005 VA study and to examine trend and geographical patterns of liver cancer mortality in Thailand in the period 2000 to 2009. The geographical distributions of the mortality rates can be used as an important indicator for public health professionals to identify high risk area where limited resources can be directed to improve health services related to liver cancer treatments to achieve earlier diagnosis and to reduce mortality.

## 1.2 Objectives

The objectives of this study were as follows:

1. To use appropriate statistical methods to estimate number of liver cancer deaths based on the VA study.
2. To examine trend and geographical patterns of liver cancer mortality in Thailand in the period 2000-2009.

## 1.3 Rationale

Mortality statistics by age and gender are important for epidemiological research and health policy. Annual national mortality statistics from vital registration systems in Thailand are of limited utility because about 40% of deaths are registered with unknown or ill-defined. The Thai Ministry of Public Health proposed a VA study to improve specific cause of death. Using the VA data the reported number of deaths can be improved. The estimated numbers of deaths from analysis of the VA data have been published (Rao et al. 2010, Pattaraarchachai et al. 2010, Polprasert et al. 2010, Porapakkham et al. 2010). However, Byass (2010) concluded that there are still some uncertainties in these revised estimates. Therefore, the appropriate statistical model for analysis of the VA data is essential. Since liver cancer is still the public health problem in Thailand research focusing on liver cancer mortality is also important.

## 1.4 Expected advantages

1. Liver cancer mortality rate in Thailand will perceive and clearly review by using graphical method and map.
2. The result of this study will provide useful information about the factors that associate with liver cancer on the burden of liver cancer mortality rate in each gender, year and age-group.
3. The finding will be useful for health planning and recommendation to reduce mortality from liver cancer.

## 1.5 Literature reviews

Reliable national vital registration statistics are essential to guide priorities for resource allocation within the health sector in order to improve quality of life. Liver cancer is an important disease, and we must be able to monitor mortality as well as incidence with equivalence rubrics in all parts of the world.

Liver cancer is a malignant tumour in the liver. There are two different types of liver cancer (primary and secondary liver cancer). Primary liver cancer is cancer that starts in the liver. There are two main types of primary liver cancer which are hepatocellular carcinoma (HCC) and cholangiocarcinoma (CCA). HCC starts from the main cells in the liver, which are called hepatocytes. This is the most common type of primary liver cancer and occurs most frequently in people with a liver disease called cirrhosis. CCA starts in the cells lining the bile duct. Secondary liver cancer is cancer that starts in another part of the body and spreads (metastasises) to the liver. Most cancers can spread to the liver but the most common types of secondary cancer start in the bowel, breast, pancreas, stomach, oesophagus, ovary or lung. These liver cancers are named after the primary cancer. For example, bowel cancer that has spread to the liver is called metastatic bowel cancer. Secondary liver cancer may be found at the same time that the primary cancer is diagnosed. However, this is not always the case. It can also be diagnosed before or after the primary cancer (The Cancer Council, 2007).

Studies on liver cancer mortality trends have been used mortality data with causes of death had been coded according to the World Health Organization's International classification of diseases (ICD). There are several categories of liver cancer in the ICD and confusion in studying mortality from the liver arises. For example, a study on mortality trends from hepatocellular carcinoma (HCC) in Japan used ICD-10 code C22.0 (Shibuya and Yano 2005). A study on mortality trends from primary liver cancer in Europe used ICD-9 code 155.0 (Vecchia et al. 2000). Another study on mortality trends for liver cancer in Mexico used ICD-10 codes C22.0-C22.9 (Mendeez-Sanchez 2008). Therefore, liver cancer mortality rates and its comparison between studies have to be interpreted with the caution.

It is well known that liver cancer mortality and incidence rates vary with gender, age, geographic region, and ethnicity. The numbers of cases worldwide in 2008 occur in men is more than double compared to women. The overall ratio of mortality to incidence is almost one.

Liver cancer occurs more frequently in some part of the world as well as in different ethnic groups. The geographical distribution of the mortality rates is similar to that observed for incidence. Geographical inequalities in liver cancer mortality have been evaluated in terms of magnitude and pattern (Faramnuayphol et al. 2008, Pearce 2006, Vecchia et al. 2000). The regions of high incidence are found in West, Eastern and South-East Asia, Middle and Western Africa, Melanesia and Micronesia/Polynesia. Low rates are estimated in developed regions, with the exception of Southern Europe. International variation in the availability of diagnostic testing as well as in the coding and registration practices for liver cancer makes the interpretation of long-term time trends difficult. Although it is difficult to accurately predict future changes in disease epidemiology, some experts have suggested that the overall global incidence of liver cancer will continue to rise in the next few years until a plateau is reached in 2015-2020 (Llovet 2005).

In recent years, a number of epidemiologic studies have highlighted how liver cancer incidence rates may change over time; for example, analysis of data from cancer registries demonstrated that liver cancer incidence rates tripled in the U.S. between 1975 and 2005 (Altekruse 2009). This growth in liver cancer incidence was particularly notable in Hispanic, black, and white middle-aged men and may have been partially attributable to an epidemic of hepatitis C viruses infection in the U.S. during the 1960s (Altekruse 2009, Armstrong 2006). Epidemiological studies have shown that risk factors of liver cancer are related to familial history, environmental factors (e.g., alcohol, hepatitis B and/or C virus, and aflatoxin B1 exposure) and genetic variations (Viratroumanee et al. 2009, Covolo et al. 2005, Sun et al. 2001).

The burden of liver cancer is also growing in Latin America, which was previously known for low rates of liver cancer (Méndez-Sánchez 2008, Bray 2005). In Mexico, for example, general mortality rates for liver cancer increased from 4.1 per 100,000 in 2000 to 4.7 per 100,000 in 2006, with the impact of liver cancer on morbidity and mortality predicted to increase further in the future (Méndez-Sánchez 2008).

International trends in mortality have also been evaluated in 22 populations for the period 1979–1998. Among men, increases in mortality from liver cancer have been reported in the United States, Japan, Australia, Scotland, France, and Italy, whereas decreasing trends have been reported in the United Kingdom. Trends among women were similar. Increases in the rates of cholangiocarcinoma have also been reported in the United States, Japan, Australia, Scotland, England, and Wales and among women in the United States, Australia, England, and Wales (Vecchia et al. 2000).

Simple vital statistics for describing liver cancer incidence and mortality are age-specific death rates. It can be classified by other factors contributing in the study such as age- and sex-specific mortality rates (Bosh 2004).



Several statistical models have been used for analyzing liver cancer mortality trends. A log-linear model was used to derive the percent annual change in mortality rates in Europe (Vecchia et al. 2000). The "joinpoint regression analysis" was used to estimate the expected annual percent changes for describing linear mortality trends by period in Italy (Stracci 2007). A Poisson regression model was used to estimate of trends in cancer incidence among Singapore Malays, which is a low-risk population, across individual calendar years to obtain average annual percent changes (Wang et al. 2004).

For countries with low quality of VR data, the VA study is necessary to improve the quality of vital statistics based on the VR data. The standard verbal autopsy procedures to verify register cause of death have been successfully applied in China and the Islamic Republic of Iran (Rao et al. 2007, Khosravi et al. 2008).