
MINI-REVIEW

Epidemiology of Liver Cancer in Thailand

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Abstract

The cancer registry is an essential part of any rational programme of cancer control. The information is the primary resource for epidemiological research and for planning and evaluating health services for the prevention, diagnosis and treatment of cancer. Epidemiological research, based on comprehensive cancer registration, remains the most valid and efficient way to plan and evaluate all aspects of cancer control.

The estimated incidence of primary liver cancer in Thailand is very high, Liver cancer is the leading cancer in males and third in frequency in females. There is a very marked regional variation, with the highest incidence in the northeast, the age – standardized incidence rate of liver cancer in Khon Kaen is highest in the world. The percentage of hepatocellular carcinoma (HCC) and cholangiocarcinoma (CCA) varies greatly between regions. In Thailand, chronic infections with hepatitis B virus and the liver fluke, *Opisthorchis viverrini* are the major risk factors for the development of HCC and CCA, respectively. Primary prevention is an important approach for prevention and control of liver cancer.

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Introduction

During the last 20 years, the leading cause of death in Thailand has changed from infectious diseases to non-communicable diseases. These comprise diseases of heart (including “heart failure”), malignant neoplasms, and accidents and poisonings. Their rates have gradually increased over the past decade.

Cancer registries document cases of cancer within a particular region, providing information on how often cancers occur, and on how many people survive their disease. These data are needed for planning and monitoring cancer control strategies and for identifying priorities in public health.

The population – based cancer registry records all new cases in a defined population (most frequently a geographical area) with the emphasis on epidemiology and public health. The hospital – based cancer registry records all cases in a given hospital, usually without knowledge of the background population, the emphasis is on clinical care and hospital administration. The cancer registry is an essential part of any rational programme of cancer control (Muir et al, 1985). The registry analyses provides information on the incidence and characteristics of specific cancers in the resident population and on temporal variations in incidence. The information is the primary resource for epidemiological

research and for planning and evaluating health services for the prevention, diagnosis and treatment of cancer. The values of a cancer registry depends on the quality of its data. Epidemiological research, based on comprehensive cancer registration, remains the most valid and efficient way to plan and evaluate all aspects of cancer control.

Cancer in Thailand

The National Estimates

The incidence rates from five cancer registries in Thailand, according to site of cancer, classified by the International Classification of Diseases Vol. 9., in addition, an estimate of the incidence for the whole country in 1993 are shown (Deerasamee et al, 1999).

The estimated numbers of new cancer cases in Thailand in the year 1993 was 32 801 in men and 30 940 in women. These correspond to age-standardized rates of 151.3 per 100 000 for men and 123.8 per 100 000 in women.

Liver cancer is the most common cancer in males (ASR=37.4), followed by lung cancer (ASR=26.5), colon & rectum cancer (ASR=10.4) and oral cancer (ASR=5.4). In women, cervix cancer is the most common (ASR=20.9), followed by breast cancer (ASR=16.3), liver cancer (ASR=15.5) and lung cancer (ASR=11.1).

The very high incidence of liver cancer in the Northeastern region means that liver cancer is the major cancer of men in the whole country, with an estimated 8 189 new cases in 1993. Lung cancer is second in importance (5 500 new cases); taken together, these two sites are responsible for 42.2% of all cancers in men.

In women, cervix cancer is the most important (5 462 new cases), followed by breast cancer (4 223 new cases), liver cancer (3 679 new cases) and lung cancer (2 608 new cases), these four sites being responsible for 51.6% of all cancers in women.

The Geographical Distribution of Cancer

Of the 8.1 million new cancer cases diagnosed worldwide in 1990, the most common was lung cancer, which accounted for 12.8% of the total. This was followed by cancers of the stomach, breast, colon and rectum, liver, prostate and uterine cervix (Parkin et al 1999). There is remarkable variation in the types of cancer that predominate in different parts of the world, and especially between developed and developing countries.

In Thailand in 1993, the age-standardized incidence rates (ASR) of cancer at all sites ranged from 99.0 per 100 000 (M) and 79.0 per 100 000 (F) in Songkhla to 173.8 per 100 000 (M) in Khon Kaen and 156.4 per 100 000 (F) in Chiang Mai (Srivatanakul et al, 1999b).

In Chiang Mai, lung cancer is the most important site in both men and women. Liver cancer is in second place in men, and cervix cancer in women. The incidence of cervix cancer in women is the highest amongst the five registries.

In Lampang, the profile is similar to that in Chiang Mai, except that the incidence of lung cancer in men is even higher than in Chiang Mai. (age standardized rate 54.6 per 100 000).

In Khon Kaen, the picture is dominated by liver cancer, by far the most common cancer in men (50% of all cancers) and women (28% of cancers). Cervix cancer is second in frequency in women.

Recently, the results from population – based cancer registry in Nakornpanom Province in the northeastern region of Thailand (unpublished results) are shown that in 1998 (1997 – 1999), liver cancer is the most common cancer in both males (ASR=69.1, 53.6% of all cancers) and in females (ASR=35.7, 31.4% of all cancers). The profile of cancer is similar to that in Khon Kaen. There is also remarkable variation in the incidence of liver cancer in different areas of Nakornpanom.

In Bangkok, lung cancer is the most important tumour of men, followed by cancers of the colon-rectum, and then liver. In women breast cancer is now the leading cancer, ahead of cervix cancer (in contrast to the other four registries), and colorectal cancer is third in frequency.

In Songkhla, the leading site in men is lung cancer, followed by oral cavity and oesophagus, for which rates are higher than elsewhere, followed by liver cancer, with an incidence much lower than in the other registries. In females, cervix and breast cancers predominate, with thyroid cancer

in third place; liver cancer is not even in the first ten cancers.

Liver Cancer

Primary liver cancer (PLC) is a major public health problem worldwide. In 1990, the global number of new cases was estimated at 316,3000 for males and 121,1000 for females, accounting for 7.4% (males) and 3.2% (females) of all malignancies, excluding skin cancer (Parkin et al, 1999).

The geographical distribution of liver cancer varies greatly worldwide, perhaps more so than any other major tumor site (Srivatanakul et al, 1999a). The disease is relatively uncommon in developed countries. In the developing world, liver cancer is very common, accounting for more than 80% of the global liver cancer cases with high rates in sub-Saharan Africa, Eastern and Southeastern Asia, and Melanesia; China alone accounts for 55% of the worldwide incidence. Incidence among men is over twice that among women.

The estimated incidence of PLC in Thailand is very high. It is the most frequent malignancy in Thailand with an estimated 11,581 new cases (ASR=40.5 in males, ASR=16.3 in females) in 1990 (Vatanasapt et al, 1993). and 11,868 new cases (ASR = 37.4 in males, ASR=15.5 in females) in 1993 (Deerasamee et al, 1999). PLC is the leading cancer in males and third in frequency in females. There is a very marked regional variation, with the highest incidence in the northeast, the age – standardized incidence rate (ASR) of liver cancer in Khon Kaen is the highest in the world (Parkin and Muir 1992,) The over all incidence rate ranged between 6.4 and 87.5 per 100,000 in males, and 1.4 to 37.2 in females (Vatanasapt and Sriamporn, 1999)

Histological types

Primary cancer of the liver, which comprises both hepatocellular carcinoma (HCC) and cholangiocarcinoma (CCA), is the leading cancer of males and third in frequency in females. There is considerable geographic variation, as a result of the very striking pattern of occurrence of cholangiocarcinoma which varies more than 12-fold between regions, while the frequency of hepatocellular cancer is more or less constant in different parts of the country. (Srivatanakul et al, 1988).

The percentage of different histological types of liver cancer varies greatly between the regions of Thailand, (Srivatanakul et al, 1991b; Parkin et al, 1993; Vatanasapt and Sriamporn, 1999). In Khon Kaen in 1993, 82% of cases are cholangiocarcinoma. It is based on 4.6 – 5.4 per cent of histologically verified cases in males and females. The proportion of liver cancer cases which are CCA is also relatively high in Chiangmai (38.2%) and Lampang (46.2%), but is lower in Bangkok (22.1%) and these may be mainly migrants from the northeast and north. Cholangiocarcinomas are, in contrast, quite rare in Songkhla (4%). Cholangiocarcinoma is a relatively rare cancer; worldwide

it accounts for an estimated 15% of liver cancers. A very high incidence is estimated for Khon Kaen in Northeast Thailand.

Age and sex distribution

The age distribution of liver cancer patients is similar in all centers in Thailand.

The age – specific incidence rates of liver cancer increase at older ages and show relatively high rates over age 55 – 59. Males are always more frequently affected than females (Vatanasapt and Sriamporn, 1999)

The ratio of male to female in CCA ranges from 1.1 to 2.2. (Parkin et al, 1997)

Aetiology

It has been reviewed (Hamilton and Aaltonen, 2000) that HCC in the high – risk areas with ASR more than 20.1 per 100,000 for males (Sub – Saharan and South Africa, East Asia, and Melanesia), chronic infection with hepatitis B virus (HBV) is the principal underlying cause, with the exception of Japan which has high prevalence of hepatitis C infection. HBV vaccination has become a powerful tool in reducing cirrhosis and HCC, but implementation is still suboptimal in several high risk regions. In western countries, the low – risk areas with ASR < 3.2 (North and South America, South – Central Asia, Northern Europe, Australia and New Zealand), chronic alcohol abuse is a major aetiological factor. Cholangiocarcinoma has a different geographical distribution, with highest incidence in northeastern Thailand. It is caused by chronic infection with the liver fluke. *Opisthorchis viverrini* which is ingested through infected raw fish.

In Thailand, chronic infections with hepatitis B virus (HBV) and the liver fluke, *Opisthorchis viverrini* (OV) are the major risk factors for the development of hepatocellular carcinoma (HCC) and cholangiocarcinoma (CCA), respectively (Srivatanakul et al, 1991c; Parkin et al, 1991; IARC, 1994). Using biomarkers to assess aflatoxin exposure in a correlation study (Srivatanakul et al, 1991b) and a case – control study (Srivatanakul et al 1991c) and failed to identify an aflatoxin – associated risk of HCC, as well as the cohort study of HBsAg carriers in Bangkok, organized by the IARC and the National Cancer Institute, Bangkok, Thailand (unpublished results) involving longitudinal collection of blood samples for the measurement of aflatoxin – albumin adducts. The data obtained in Thailand with respect to aflatoxin exposure using aflatoxin – albumin adducts are compared with data from other countries in Africa and South – east Asia (Wild et al, 1990; 1992), they indicate a relatively low level of exposure in Thailand. The low aflatoxin exposure in Thailand initially appears to contradict earlier reports of contamination of local foods but the foods most commonly contaminated, peanuts and maize, are not the dietary staples in Thailand. The use of biological markers of exposure provides a more reliable

assessment of exposure resulting from these different dietary practices at the level of the individual. This is consistent with the data from liver tissue and the low prevalence of G to T mutations in codon 249 of the p53 gene in HCC patients from Thailand (Hollstein et al, 1993).

Prolonged inflammation, induced by infection, causes the continued production of molecules that combat infection, but that also act as carcinogens within the body. Such chronic inflammation plays a crucial role in certain cancers, in particular, those of the liver and stomach. (IARC/WHO, 1997).

During inflammation, specialized cells produce several different oxygen and nitrogen species. These free radicals are highly reactive and kill the infectious agent. However, they may also harm normal tissues: they can damage DNA, causing mutations, breaks and chromosomal aberrations. The tissue injury they induce is accompanied by an increased rate of cell division, and a decreased efficiency of DNA repair. Prolonged exposure of the cell's genetic material to these agents can result in the accumulation of harmful mutations.

Reactive oxygen and nitrogen species also alter the physiological functions of normal cells. They may modulate the activities of proteins and genes that regulate cell proliferation, differentiation and death, and can cause metabolic enzymes to produce active carcinogens rather than detoxified metabolites. Enzymes involved in tumor growth may also become activated.

Humans with chronic infections and associated inflammatory conditions excrete high levels of nitrate and certain nitrosamino acids in the urine, indicating increased nitric oxides and N – nitroso compounds synthesis (Ohshima and Bartsch, 1994). For example, subjects in Thailand infested with the liver fluke *Opisthorchis viverrini*, as identified by the presence of *O. viverrini* eggs faeces or positivity for *O. viverrini* antibody, excreted significantly more NPRO after proline ingestion than did controls, indicating elevated endogenous nitrosation potential (Srivatanakul et al, 1991a). After ingestion of ascorbic acid, the positive subjects had significantly reduced NPRO levels, implying that endogenous nitrosation of proline was inhibited. Epidemiological studies have shown that infestation with the liver fluke is associated with an increased risk of cholangiocarcinoma in south – east Asia, especially in north – east Thailand, and other countries (Parkin et al, 1991; Haswell – Elkins et al, 1992). Similarly, subjects with liver cirrhosis excreted in their urine significantly increased levels of nitrate and the sum of four major nitrosamino acids including NPRO compared with healthy control subjects (Bartsch et al., 1989). These results support the notion that nitrosamines formed endogenously from ingested precursors could be a risk factor for the development of cholangiocarcinoma in *O. viverrini* – infested subjects as well as for the development of hepatocellular carcinoma in cirrhosis patients. (Bartsch and Frank, 1996)

People vary greatly in their likelihood of developing particular cancers and in their response to certain

environmental carcinogens. A large number of interacting factors contribute to an individual's risk for cancer: these include environmental exposures, genetic factors, diet, lifestyle, age, and gender. The intrinsic susceptibility of an individual is altered by inherited mutations in genes involved in predisposition to specific cancers, genes involved in the metabolic activation or detoxification of carcinogens, and genes controlling the repair of DNA or cellular damage.

The interaction between genes and the environment and the interplay of environmental factors, which include diet and lifestyle, illustrate the complexity in understanding the susceptibility to environmental exposures.

Individuals who inherit polymorphic susceptibility alleles involved in response to environmental carcinogens will have an increased risk of developing cancer when they are exposed to specific carcinogens. Therefore, risk to these people is influenced by gene-environment interaction.

The availability of biological markers of exposure and an understanding of their role in the etiopathogenesis of liver cancer has a direct bearing on the implementation of measures for primary prevention.

The studies on molecular epidemiology of liver cancer (both HCC and CCA) are under investigations in Nakornpanom Province.

Liver Cancer Control

The aim of cancer control is a reduction in both the incidence of the disease and the associated morbidity and mortality. Its achievement requires not only a knowledge of the disease process, but also an understanding of the social and economic factors which govern how that knowledge can be put to effective use. The Committee of National Cancer Control Programme (NCCP) of Thailand have set up the four principal approaches to cancer control, being incorporated into the NCCP of Thailand (Deerasamee and Srivatanakul, 1999) defined by the World Health Organization (WHO, 1995). Primary Prevention is the important approach for prevention and control of liver cancer.

Primary prevention means minimizing or eliminating exposure to carcinogenic agents, and includes reducing individual susceptibility to the effect of such agents. It is this approach that offers the greatest chance of successful long-term cancer control.

Strategies for primary prevention of liver cancer in Thailand :

- ◆ vaccination against hepatitis B virus infection
- ◆ prevention and control of *Opisthorchis viverrini* infection
 - ◆ public education
 - ◆ chemoprevention
 - the use of chemopreventive agents should be limited to persons at very high risk.
 - ◆ behavioral interventions
 - having important advantages for population – level prevention, a low risk of side – effects

- modification in lifestyle exposures
- controlling alcohol consumption
- eat more vegetables and fruits (400 – 500 gm/day)
- do not eat raw fish
- drink a lot of water (more than 11 glasses/day)
- preventing tobacco smoking
- exercise

- ◆ promoting dietary modification to achieve a healthier diet
 - (or preventing change of diet to more hazardous pattern).
 - dietary modification should take into consideration local cultures, customs, culinary styles, availability of dietary items, seasonality, and cost.
 - prevention of contamination of foods by carcinogens e.g. pesticides, and avoid adding to food substances such as nitrites and nitrates
 - encouraging change in dietary patterns, particularly to decrease salting and pickling for food preservation (nitrates, nitrite and salt)

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