MINI-REVIEW

Epidemiology of Liver Cancer: An Overview

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Abstract

The incidence of liver cancer varies widely throughout the world, with high rates in sub – Saharan Africa, eastern and southeastern Asia, and Melanesia and a low incidence in Northern and Western Europe and the Americas. Primary cancers of the liver in adults are of two main histological types: hepatocellular carcinoma, which is derived from hepatocytes, and cholangiocarcinoma, which is derived from the epithelial lining of the intrahepatic bile ducts. Hepatocellular cancer is a frequently occurring tumor in individuals in many developing countries, where several important risk factors have been demonstrated, including chronic infection with hepatitis B and C viruses and other environmental factors, such as exposure to aflatoxin, consumption of alcohol, and cigarette smoking. By contrast, cholangiocarcinoma is less common, accounting for only 7.7% of malignant tumors of the liver in the United States. However, in parts of Southeast Asia, cholangiocarcinoma occurs more frequently; it is responsible for more than 60% of liver tumors in northeastern Thailand. The geographic distribution worldwide coincides with endemic areas of the liver flukes, Opisthorchis viverrini and Clonorchis sinensis. The interaction between genes and the environment and the interplay of environmental factors, which include diet and other lifestyle parameters, illustrate the complexity underlying susceptibility.

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Introduction

There is remarkable variation in the types of cancer that predominate in different parts of the world, and especially between developed and developing countries. 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., 1999a; Parkin et al., 1999b). Of the estimated 5.2 million deaths from cancer (excluding non-melanoma skin cancer), 55% (2.8 million) occurred in developing countries. Lung cancer is still the most common cause of death from cancer worldwide with over 900,000 deaths per year, followed by gastric cancer with over 600,000 deaths and colorectal and liver cancers accounting for at least 400,000 deaths each. In men, deaths from liver cancer exceed those due to colon–rectal cancer by 38%. Over 300,000 deaths of women could be attributed to breast cancer, which remains the leading cause of death from cancer in women, followed by cancer of the stomach and lung with 230,000 annual deaths each (Pisani et al., 1999).

Definition and Classification of Liver Cancer

Most of the primary liver cancers (PLC) are of epithelial cell origin, either from hepatocytes or intrahepatic bile duct cells. Primary epithelial cancers of the liver are classified into 6 histological types as summarised in Table 1 according to their cell of origin and histological features (Hamilton and Aaltonen, 1999). Non-epithelial liver cancers are rare.

Among cancers of the hepatocyte line, hepatocellular carcinoma (HCC) is the most common type, occuring worldwide. The nomenclature of this subtype was recently revised by WHO (Hirohashi et al., 1999; Fritz et al., 2000). Cytologic features of hepatocytes and architecture of hepatic cords and sinusoids can be identified in these tumours. Grading is based upon the architectural pattern and nuclear features. Hepatoblastoma is a cancer of childhood (Stocker and Schmidt, 1999). It is a malignant embryonal tumour with divergent pattern of differentiation, ranging from cells resembling fetal epithelial hepatocytes, to embryonal cells, and differentiated mesenchymal tissues including osteoid-like material, fibrous connective tissue, and striated muscle fibers.

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Table 1. Histological Types and Subtypes of Liver Cancers

Histological type	ICD-O
Epithelial cancers	
Hepatocellular carcinoma (liver cell carcinoma)	8170/3
Trabecular pattern	
Pseudoglandular and acinar pattern	
Compact pattern	
Scirrhous pattern	
Fibrolamellar hepatocellular carcinoma	8171/3
Intrahepatic cholangiocarcinoma (peripheral bile duct carcinoma)	8160/3
Adenocarcinoma	
Adenosquamous and squamous carcinoma	
Cholangiolocellular carcinoma	
Mucinous carcinoma	
Signet-ring cell carcinoma	
Sarcomatous intrahepatic cholangiocarcinoma	
Lymphoepithelioma-like carcinoma	
Clear cell variant intrahepatic cholangiocarcinoma	
Mucoepidemoid carcinoma	
Bile duct cystadenocarcinoma	8161/3
Combined hepatocellular and cholangiocarcinoma	8180/3
Hepatoblastoma	8970/3
Pure fetal epithelial differentiation	
Combined fetal and embryonal epithelial	
Macrotrabecular	
Small cell undifferentiated	
Mixed epithelial and mesenchymal	
Mixed epithelial and mesenchymal with teratoid feature	
Undifferentiated carcinoma	8020/3
Non-epithelial cancers	
Epithelioid haemangioendothelioma	9133/1
Angiosarcoma	9120/3
Embryonal sarcoma (undifferentiated sarcoma)	8991/3
Rhabdomyosarcoma	8900/3
Others	

Cancers of the intrahepatic bile duct can be solid or cystic. Cholangiocarcinoma (CCA) is relatively rare in most populations but is second among primary cancers of the liver. It comprises cells resembling those of intrahepatic bile duct (Nakanuma et al., 1999). Bile duct cystadenocarcinoma is a cystic tumour lined by epithelium with papillary infoldings that may be mucus secreting or, less frequently, serous. Lesions arise from ducts proximal to the hilum of the liver (Wittekind et al., 1999a). Combined hepatocellular and cholangiocarcinoma is a rare tumour containing unequivocal elements of both hepatocellular and cholangiocarcinoma that are intimately admixed (Wittekind et al., 1999b).

Incidence of Liver Cancer

The Worldwide Pattern

Cancer of the liver is the fifth most common cancer in the world. In 1990, an estimated 437,000 new cases were diagnosed worldwide, accounting for 5.4% of all new cancers. Mortality attributable to liver cancer was estimated at 427,000 people, 8.2% of all cancer deaths.

The geographical distribution of liver cancer varies greatly worldwide, perhaps more than any other major tumour site (Ferlay et al., 1998). The disease is relatively uncommon in developed countries. In the developing world, in contrast, liver cancer is very common, accounting for more than 80% of the global liver cancer cases with high rates in Sub-Saharan Africa, East and Southeast Asia, and Melanesia; China alone accounts for 55% of the worldwide incidence. The incidence among men is over twice that among women.

HCC accounts for the greatest portion of PLC (Hirohashi et al., 1999). The male:female ratio is approximately 4:1 (Akriviadis et al., 1998). The incidence of PLC which is mainly HCC is increasing in developed countries whereas it is declining in the developing world (McGlynn et al., 2001). Although reasons for the trends are not entirely clear, partly they are the result of better diagnosis, coding, and classification (Sharp et al., 2001). The phenomenon has been

linked to the increased seroprevalence of HCV in the developed world and the elimination of HBV-cofactors in developing countries. The decline may become very pronounced when the HBV-vaccinated segment of population in developing countries reaches adulthood.

CCA accounts for an estimated 15% of liver cancers worldwide (Nakanuma et al., 1999) and 7.7% of malignant tumours of the liver in the United States. The variation in geographical distribution of this cancer is marked. It accounts for a considerable fraction in Indochina countries such as Thailand, an endemic area for Opisthorchis viverrini, and Far East Asia, an endemic area for Clonorchis sinensis (Parkin et al., 1993). A relatively high percentage of CCA is also seen in Hong Kong and Italy. The male:female ratio ranges from 1.1:1 to 2.2:1 (Parkin et al., 1997). An increasing trend for mortality from CCA in non-endemic areas for liver flukes has been noted in all regions of the world (Patel, 2002). Though advances in diagnostic tools, coding, and classification might have contributed to this trend (Sharp et al., 2001), an increase in incidence of this cancer following more and longer exposure to intrahepatic bile duct inflammatory disease might also be a real factor.

Incidence of Cancer in Asia

Leading cancers in different regions of Asia vary greatly in relative order (Ferlay et al., 1998). In East Asia, the first five leading cancers are cancer of stomach, liver, lung, esophageal, and colorectal cancers in males and that of stomach, breast, lung, colorectum, and liver cancers in females. Stomach cancer is less in Southeast than in East Asia as the five leading cancers are that of lung, liver, colorectum, stomach and esophagus in males and that of breast, cervix, lung, colorectum, and ovary in females. In South Central Asia, cancers of the lung and upper digestive tract are prevalent and the five leading primary cancer sites in males are lung, oral cavity, esophagus, pharynx, and stomach and cervix, breast, oral cavity, esophagus, and ovary in females. In West Asia, lung cancer is the leading malignancy in males followed by urinary bladder, stomach, colorectum, and larynx cancers whereas the most common cancer in females is breast cancer followed by colorectum, ovary, stomach, and esophagus cancers. Liver cancer is among the five leading cancers in East and Southeast Asia while the incidence of this malignant tumour is low in South, Central and West Asia.

Incidence of Liver Cancer in Asia

In Asia, the incidence of PLC is high in East and Southeast Asia and in Arab countries while the incidence is low in South Asia. In males, the age-standardized incidence rate (ASR), estimated for 1990, varies from 0.7 in Sri Lanka to 40.1 in Thailand (Vatanasapt et al., 1993). The distribution is similar in females while the ASR ranges from 0.4 in Sri Lanka to 16.3 in Thailand.

High incidences of HCC are related to HBV infection in most places, except in Japan where HCV is the major risk factor. Aflatoxin also plays a significant role in some areas of China. CCA is prevalent in endemic areas of liver fluke infestation such as the Indochina region in South-east Asia and some areas of China, Korea, and, in the past, Japan in the North-east of the continent.

Incidence of Liver Cancer in Thailand

PLC is the most frequent malignancy in Thailand with an estimated 11,581 new cases (ASR=40.5 per 100,000 population 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). It is the leading cancer in males and the 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. The incidence rate reported from registries in Thailand ranged between 6.4 (Songkhla) and 87.5 (Khon Kaen) in males, and from 1.4 (Songkhla) to 37.2 (Khon Kaen) in females. The age distribution of liver cancer patients is similar in reports from all centers in Thailand. The age–specific incidence rates of liver cancer increase at older ages and reach the peak around the age of 65. The ratio of male to female in CCA ranges from 1.1:1 to 2.2:1.

PLC comprises both hepatocellular carcinoma (HCC) and cholangiocarcinoma (CCA). There is considerable geographic variation, as a result of the very striking pattern of occurrence of cholangiocarcinoma, which varies more than 12 folds 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 regions. In Khon Kaen in 1993 (Deerasamee et al., 1999), 82% of PLC cases are cholangiocarcinoma. The percentage is estimated based on 4.6–5.4 percent of histologically verified cases in males and females. The proportion of CCA among PLC cases is also relatively high in Chiang Mai (38.2%) and Lampang (46.2%) in the north. The proportion is lower in Bangkok (22.1%) and the cases may be mainly migrants from the northeast and north. Cholangiocarcinomas are, in contrast, quite rare in Songkhla (4%) in the south. The geographical variation corresponds with the distribution of Opisthorchis viverrini which is densely endemic in the northeastern region and very rare in the southern region (Harinasuta and Harinasuta, 1984).

From the incidence rates of liver cancer and the percentage of CCA in different registries in Thailand (Deerasamee et al., 1999), the incidence rates of CCA and HCC can be estimated as shown in table 2. Though the accuracy of the estimates are limited by the degree of under-registration and percentage of histological verification which varies from 50% in Bangkok and Songkhla to 5% in Khon Kaen, the trend of higher incidence rate of HCC in the north than in other regions is demonstrated. The incidence rates of CCA in males and are similar to those in females in all registries except Khon Kaen. The rates of HCC are

Table 2. ASRs for CCAs and HCCs in Population-based Cancer Registries in Thailand

Registry	Males			Females		
	Total	CCA	HCC	Total	CCA	HCC
Chiang Mai	19.3	7.2	11.6	10.5	7.1	3.0
Lampang	23.4	10.4	11.0	11.9	6.1	4.3
Khon Kaen	87.5	67.5	12.5	37.2	33.5	0.6
Bangkok	11.0	2.2	8.3	3.4	1.7	1.7
Songkhla	6.4	0.3	5.9	1.4	0.4	1.0

consistently higher in males than in females and, excluding the estimates for Khon Kaen, the male:female ratio for HCC varies from 3-4:1 in the northern to 5-6:1 in the central and southern Thailand. Considering all PLC, the male:female ratio is as low as 2:1 in Chiang Mai, Lampang, and Khon Kaen while it is around 3:1 in Bangkok and as high as 4.6:1 in Songkhla. The male:female ratio for all PLC varies from 1.3:1 to 4:1 in different parts of the world (Ferlay et al., 1998). The ratio is particularly high in Asia Pacific countries such as Thailand, Vietnam (4.1:1), and Hong Kong (3.7:1).

Mortality and Survival Rates

Both CCA and HCC are highly fatal diseases. The late presentation and the difficulty of a surgical approach mean that the overall survival is poor. The mortality rate is high in Asia and Africa and low in America and Europe (Ferlay et al., 1998). The worldwide pattern of the mortality rate of PLC is almost the same as that of the incidence rate. About 400,000 deaths from liver cancer are expected in a year worldwide.

The five-year relative survival rate in Khon Kaen is 8.5% in males and 8.3% in females (Vatanasapt et al., 1998). In Chiang Mai, the five-year relative survival rate was zero in males and only 1.1% in females (Martin et al., 1998). The difference between the two regions may be partly due to the difference in proportion of the two main histological types, CCA and HCC. The better prognosis of PLC observed in Khon Kaen might be explained by a high proportion of CCA patients naturally presenting with obstructive jaundice in a somewhat earlier stage of disease.

Though the mortality from liver cancers is not routinely reported from population–based cancer registries in Thailand, it can be estimated from the incidence rate and 5–year survival rate (Parkin and Hakulinen, 1991). The estimated mortality rate from liver cancer for both sexes is 15 per 100,000 in Chiang Mai and it is as high as 56 in Khon Kaen.

Etiology

Hepatocellular Carcinoma

Hepatitis Viruses

The role of chronic infection with hepatitis B virus (HBV) in the aetiology of HCC is well established. The IARC Monograph (IARC, 1994a) provides an extensive summary of the results of some 15 cohort studies and 65 case–control studies worldwide examining the association between seropositivity for hepatitis B surface antigen (HBsAg) and the risk of HCC. The cohort studies yield relative risk estimates between 3 and 30. Some of these studies were able to address potential confounding by aflatoxin, HCV infection, alcohol consumption and tobacco consumption, and the IARC overall evaluation assessed HBV as carcinogenic to humans (IARC, 1994). The declining HCC incidence following HBV vaccination clearly supports the etiological contribution (Chang et al., 1997; Lee et al., 1998). HCV has a lower global prevalence than HBV. HBV appears to be responsible for many of HCC occurring in Africa and China and HCV for HCC occurring in Japan (Parkin et al., 1999c). HCV causes the most HCC in Europe, North America and Japan. Chronic infection with HBV, HCV or both is the most common cause of HCC worldwide. HBV–HCV co-infection also seems to carry a higher risk for HCC development than either infection alone. Chronic hepatitis D virus (HDV) infection does not increase the risk of HCC development over that of HBV infection alone, but the latency period between HDV infection and HCC development is 30–40 years, compared with 30–60 years for HBV infection alone.

Alcohol

Alcohol–induced liver injury is a leading cause of liver cirrhosis and HCC among Western population (Donato et al., 1997). Alcoholic cirrhosis is perceived to be less associated with HCC than is cirrhosis secondary to HBV or HCV. HCV infections and heavy alcohol consumption are considered to be the major risk factors of liver cancer deaths in Japan (Corrao and Arico, 1998). Alcohol consumption is more important than HCV infections as a major cause of liver cancer in Japanese men (Makimoto and Higuchi, 1999) and the most important risk factor for hepatocarcinogenesis in areas with low hepatitis virus prevalence (Hellerbrand et al., 2001).

Aflatoxin

Aftatoxin, a fungal toxin of Aspergillus flavus and Aspergillus parasiticus, is an important factor for HCC carcinogenesis particularly in individuals chronically infected with HBV (IARC, 1993; Montesano et al., 1997) in Southern China and Sub–Saharan Africa. Which leads to a more than 50–fold increase in the risk of developing

HCC. HCC risk is increased if aetiological risk factors exist in combination, e.g. HBV infection and exposure to aflatoxin (Sun et al., 1999). Using biomarkers to assess aflatoxin exposure in a case–control study failed to identify an aflatoxin–associated risk of HCC in Thailand (Srivatanakul et al., 1991b). The data on p53 mutations and liver DNA adduct levels are consistent with the low exposure to aflatoxin observed to data using the aflatoxin–albumin adduct (Hollstein et al., 1992). The foods most commonly contaminated, peanuts and maize, are not the dietary staples in Thailand.

Other Causes of Chronic Liver Diseases

Iron overload (Mandishona et al., 1998), long–term use of oral contraceptives (Mant and Vessey, 1995; Waetjen and Grimes, 1996) and high dose anabolic steroids increase risk for HCC. The development of liver cirrhosis, particularly in association with inherited genetic diseases such as alpha–1–antitrypsin deficiency or haemochromatosis, place the individual at a greatly increased risk of HCC development.

Hemochromatosis: Genetic hemochromatosis has been found to be due to constitutive iron uptake from a mutated iron transporter now termed the HFE protein. It has been suggested that heterozygotes for HFE mutations exposed to hepatitis virus infections or who had been alcohol abusers could have an increased risk of developing cirrhosis and later liver cancer than people without the mutations exposed to the same risk factors (Lauret et al., 2002). The iron overload state may be more linked to HCC than HBV and HCV, with a lifetime risk of death due to HCC rising to 45% in some series (Fargion et al., 1992).

Tyrosinemia: Autosomal–recessive disorder is due to deficiency of fumarylacetoacetase, which is the last enzyme in the biochemical pathway to degrade the amino acid tyrosine. The accumulation of upstream products leads to severe liver disease and HCC in childhood. HCC occurs in 37% of patients who survive to 2 years of age, and may occur in patients who have undergone liver transplantation (Schafer and Sorrell, 1999).

Alpha–1–antitrypsin deficiency: It is an autosomal–recessive disorder leading to increased activity of the enzyme trypsin, and may lead to cirrhosis (Smanadhikorn et al., 1995) and development of HCC (Zhou et al., 2000).

Oral Contraceptives

The risk for HCC among oral contraceptive users was significantly increased and had a dose–response relationship (Henderson et al., 1983) with duration of exposure in women with HCC either positive or negative for HBV markers (Forman et al., 1986; Neuberger et al., 1986).

Occupational Exposure

With the exception of the well established association between occupational exposure to vinyl chloride monomer and liver angiosarcoma (Blair and Kazerouni, 1997), the role of occupational exposures in liver carcinogenesis is limited. However, prolonged exposure to organic solvents such as toluene and xylene may represent a risk factor for liver cancer (Porru et al., 2001).

Cigarette Smoking

There is a statistically significant and dose dependent association between tobacco smoking and HBsAg negative HCC (Trichopoulos et al., 1987). There has been a prospective study on the relationship of cigarette smoking and liver cancer in an endemic region in Japan. The result indicates that smoking is a risk factor of liver and stomach cancer in a population with a high background risk for these cancers. However, causal inferences should be made cautiously due to a lack of information on known risk factors (Mizoue et al., 2000). Polycyclic aromatic hydrocarbon may also play a role in human hepatocarcinogenesis (Chen et al., 2002).

Cholangiocarcinoma

Liver Flukes

The evidence for an association between chronic infection with liver flukes and the risk of cholangiocarcinoma of the liver has been evaluated (IARC, 1994b). Opisthorchis viverrini, endemic in South East Asia, was considered definitely carcinogenic. Two studies (in Thailand) allow estimates of the relative risk associated with infection; Parkin et al (Parkin et al., 1991) found an OR of 5.0 for subjects with raised antibody titres, Haswell–Elkins et al (Haswell – Elkins et al., 1994) an OR of about 4 for early cancer with the presence of O. viverrini eggs in faeces.

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 (Jones, 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.

Exogenous and Endogenous Nitrosamines

The preserved protein foodstuffs, such as Pla–ra (a fermented fish product) dried fish, sausage, dried shrimps, cured pork, and salty meat, as well as the common salts and ground water consumed by northeastern Thai people, contain high levels of either nitrosating agents and nitrosatable substances or nitrosating agents alone (Migasena and

Changbumrung, 1974; Migasena et al., 1980). Nitrosamines were detected in low concentrations in many locally preserved Thai foods containing protein, especially fermented fish (Pla–ra) which is consumed daily by most people in the northeast. Some vegetables commonly consumed in the northeast contain high concentrations of nitrate (Migasena et al., 1989).

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. 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. 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). The interaction between nitrosamines and O. viverrini infestation may play an important role in the development of CCA in the northeast of Thailand.

Hepatitis Viruses

CCA appears to be related to hepatitis viral infections especially HCV, and could be detected at an early stage, similar to HCC, by following up cases of chronic hepatitis and cirrhosis (Yamamoto et al., 1998; Tomimatsu et al., 1993). HCV–related cirrhosis is a major risk factor for CCA in Japanese patients (Kobayashi et al., 2000).

Hepatolithiasis

Hepatolithiasis (recurrent pyogenic cholongitis), which is not uncommon in the Far East, is also associated with CCA (Ugihara and Kojiro, 1987; Nakanuma and Ohta, 1982).

Inflammatory Bowel Disease and Primary Sclerosing Cholangitis

Patients with primary sclerosing cholangitis and ulcerative colitis have a predisposition to develop colorectal neoplasia and also bile duct carcinoma, including CCA (Harrison , 1999; van Leeuwen and Reeders, 1999; Broome et al., 1995; Wee et al., 1985).

Deposition of Thorotrast

There have been reports of thorotrast (thorium dioxide) –related hepatic malignancies. A review in 1988 by Ito (Ito et al., 1988) demonstrated the evidences that Th influences were more carcinogenic to epithelial cells of the bile duct and sinusoidal lining cells than hepatocytes.

Biliary Malformation and Other Lesions

CCA may arise rarely in solitary unilocular or multiple liver cysts, congenital segmental or multiple dilatation of the bile ducts (Caroli disease), congenital hepatic fibrosis, and von Meyenburg complexes of the liver (Honda et al., 1986; Yamato et al., 1998).

Conclusion

The large differences in the pattern of liver cancer incidence between developed and developing countries imply different priorities for prevention. About 80% of liver cancers worldwide are caused by HBV, HCV, and liver flukes (Jones, 1997). Most of HCC cases in the high risk areas (Sub – Saharan and South Africa, East Asia and Melanesia) chronic infection with HBV is the principal underlying cause, with the exception of Japan which has high prevalence of HCV infection. HBV vaccination has become a powerful tool in reducing cirrhosis and HCC. In western countries, the low risk areas (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 the northeastern Thailand. It is caused by chronic infection with the liver fluke, Opisthorchis viverrini, which is ingested through infected raw cyprinoid fish.

People vary greatly in their response to certain environmental carcinogens to develop particular cancers. 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. Individuals who inherit polymorphic susceptibility alleles involving in response to environmental carcinogens will have an increased risk of developing cancer when they are exposed to specific carcinogens.

References

Akriviadis E, Llovet JM, Efremidis SC, et al (1998). Hepatocellular carcinoma, *Br J Surg*, **85**, 1319-31.

Bartsch H, Frank N (1996). Blocking the endogenous formation of N-nitroso compounds and related carcinogens, In: Principles of Chemoprevention, Stewart BW, McGregor D, Kleihues P (eds.). IARC Scientific Publications, No.139, International Agency for Research on Cancer, Lyon, 189-201.

Blair A, Kazerouni N (1997). Reactive chemicals and cancer, *Cancer Causes Control*, **8**, 473-90.

Broome U, Lofberg R, Veress B, et al (1995). Primary sclerosing cholangitis and ulcerative colitis: evidence for increased neoplastic potential. *Hepatology*, **22**, 1404-8.

Chang MH, Chen CJ, Lai MS, et al (1997). Universal hepatitis B vaccination in Taiwan and the incidence of hepatocellular carcinoma in children, Taiwan Childhood Hepatoma Study Group. *N Engl J Med*, **336**, 1855-9.

Chen SY, Wang LY, Lunn RM, et al (2002). Polycyclic aromatic hydrocarbon-DNA adducts in liver tissues of hepatocellular carcinoma patients and controls. *Int J Cancer*, **99**, 14-21.

Corrao G, Arico S (1998). Independent and combined action of hepatitis C virus infection and alcohol consumption on the risk of symptomatic liver cirrhosis. *Hepatology*, **27**, 914-9.

Deerasamee S, Martin N, Sontipong S, et al (1999). Cancer in Thailand Vol.II, 1992-1994, IARC Technical Report No.34, International Agency for Research on Cancer, Lyon.

Donato F, Tagger A, Chiesa R, et al (1997). Brescia HCC Study, Hepatitis B and C virus infection, alcohol drinking, and hepatocellular carcinoma: a case – control study in Italy. *Hepatology*, **26**, 579-84.

Fargion S, Mandelli C, Piperno A, et al (1992). Survival and prognostic factors in 212 Italian patients with genetic hemochromatosis. *Hepatology*, **15**, 655-9.

Ferlay J, Parkin DM, Pisani P (1998). GLOBOCAN 1: Cancer Incidence and Mortality Worldwide, International Agency for Research on Cancer, Lyon.

Forman D, Vincent TJ, Doll R (1986). Cancer of the liver and the use of oral contraceptives. *Br Med J*, **292**, 1357-61.

Fritz A, et al, eds.(2000). World Health Organisation, International Classification of Disease for Oncology, 3rd. ed., World Health Organization, Geneva.

Hamilton SR, Aaltonen LA, eds (1999). Pathology and Genetics of Tumours of the Digestive System, International Agency for Research on Cancer, Lyon, 158.

Harinasuta C, Harinasuta T (1984). Opisthorchis viverrini: life cycle, intermediate hosts, transmission to man and geographical distribution in Thailand. *Arzneimittelforschung*, **34**, 1164-7.

Harrison PM (1999). Prevention of bile duct cancer in primary sclerosing cholangitis. *Ann Oncol*, **10**, 208-11.

Haswell-Elkins MR, Mairiang E, Mairiang P, et al (1994). Cross-sectional study of Opisthorchis viverrini infection and cholangiocarcinoma in communities within a high-risk area in northeast Thailand. *Int J Cancer*, **59**, 505-9.

Hellerbrand C, Hartmann A, Richter G, et al (2001). Hepatocellular carcinoma in southern Germany: epidemiological and clinicopathological characteristics and risk factors. *Dig Dis*, **19**, 345-51.

Henderson BE, Preston-Martin S, Edmondson HA, et al (1983). Hepatocellular carcinoma and oral contraceptives. *Br J Cancer*, **48**, 437-40.

Hirohashi S, Ishak KG, Kojiro M, et al (1999). Hepatocellular carcinoma in: Hamilton SR, Aaltonen LA, eds. Pathology and Genetics of Tumours of the Digestive System, International Agency for Research on Cancer, Lyon, 159-172.

Hollstein MC, Wild CP, Bleicher F, et al (1992). p53 mutations and aflatonin B1 exposure in hepatocellular carcinoma patients from Thailand. *Int J Cancer*, **53**, 1-5.

Honda N, Cobb C, Lechago J (1986). Bile duct carcinoma associated with multiple von Meyenburg complexes in the liver, Hum. *Pathol*, **17**, 1287-90.

IARC (1993). Some naturally occurring substances: Food items and constituents, heterocyclic aromatic amines and mycotoxins, IARC Monographs on the evaluation of carcinogenic risks to humans, Vol. 56, International Agency for Research on Cancer, Lyon.

IARC (1994a). Hepatitis Viruses, IARC Monographs on the evaluation of carcinogenic risks to humans, Vol. 59, International Agency for Research on Cancer, Lyon,

IARC (1994b). Schistosomes, Liver Flukes and Helicobacter pylori, IARC Monographs on the evaluation of carcinogenic risks to humans, Vol. 61, International Agency for Research on Cancer, Lyon, 121-175.

Ito Y, Kojiro M, Nakashima T, et al (1988). Pathomorphologic characteristics of 102 cases of thorotrast-related hepatocellular carcinoma, cholangiocarcinoma, and hepatic angiosarcoma. *Cancer*, **62**, 1153-62.

Jones S ed. (1997). IARC / WHO, Cancer research for cancer control, 18-19.

Kobayashi M, Ikeda K, Saitoh S, et al (2000). Incidence of primary cholangiocellular carcimoma of the liver in Japanese patients with hepatitis C virus related cirrhosis. *Cancer*, **88**, 2471-7.

Lauret E, Rodriguez M, Gonzalez S, et al (2002). HFE gene mutations in alcoholic and virus-related cirrhotic patients with hepatocellular carcinoma. *Am J Gastroenterol*, **97**, 1016-21.

Lee MS, Kim DH, Kim H, et al (1998). Hepatitis B vaccination and reduced risk of primary liver cancer among male adults: a cohort study in Korea. *Int J Epidemiol*, **27**, 316-9.

Makimoto K, Higuchi S (1999). Alcohol consumption as a major risk factor for the rise in liver cancer mortality rates in Japanese men. *Int J Epidemiol*, **28**, 30-4.

Mandishona E, MacPhail AP, Gordeuk VR, et al (1998). Dietary iron overload as a risk factor for hepatocellular carcinoma in Black Africans. *Hepatology*, **27**, 1563-6.

Mant JW, Vessey MP (1995). Trends in mortality from primary liver cancer in England and Wales 1975-92: influence of oral contraceptives. *Br J Cancer*, **72**, 800-3.

Martin N, srisukho S, Kunpradist O, et al (1998). Survival from Cancer in Chiang Mai, Thailand, In: Sankaranarayanan R, Black RJ, and Parkin DM, eds., Cancer survival in Developing Countries, IARC Scientific Publications No.145, International Agency for Research on Cancer, Lyon, 109-121.

McGlynn KA, Tsao L, Hsing AW, et al (2001). International trends and patterns of primary liver cancer. *Int J Cancer*, **94**, 290-6.

Migasena P, Changbumrung S (1974). The role of nitrosamines in the causation of primary carcinoma. *J Med Assoc Thai*, **57**, 175-8.

Migasena P, Reaunsuwan W, Changbumrung S (1980). Nitrates and nitrites in local preserved protein foods. *J Med Assoc Thai*, **63**, 500-5.

Migasena P, Changbumrung S, Tungtrongchitr R (1989). Evidence of chemical initiators and promoters in Thailand. In: Sornmani S, Bunnag T (eds.). Proceedings of the workshop in development of early diagnosis and management of cholangiocarcinoma associated with opisthorchiasis Faculty of Tropical Medicine, Mahidol University, Bangkok, 103-125.

Mizoue T, Tokui N, Nishisaka K, et al (2000). Prospective study on the relation of cigarette smoking with cancer of the liver and stomach in an endemic region. *Int J Epidemiol*, **29**, 232-7.

Montesano R, Hainaut P, Wild CP (1997). Hepatocellular carcinoma: from gene to public health. *J Natl Cancer Inst*, **89**, 1844-51.

Nakanuma Y, Ohta G (1982). Pathological study of hepatolithiasis associated with intrahepatic cholangiocarcinoma, Annual

Report of Japanese Hepatolithiasis Study Group, 208-216.
Nakanuma Y, Sripa B, Vatanasapt V, et al (1999). Intrahepatic cholangiocarcinoma in: Hamilton SR, Aaltonen LA, eds. Pathology and Genetics of Tumours of the Digestive System, International Agency for Research on Cancer, Lyon, 173-180.
Neuberger J, Forman D, Doll R, et al (1986). Oral contraceptives and hepatocellular carcinoma. *Br Med J*, **292**, 1355-7.
Ohshima H, Bartsch H (1994). Chronic infections and inflammatory process as cancer risk factors: possible role of nitric oxide in carcinogenesis. *Mutat Res*, **305**, 253-64.
Parkin DM, Hakulinen T (1991). Analysis of Survival in: Jensen OM, Parkin DM, MacLennan R, Muir CS, Skeet RG, Cancer Registration Principles and Methods, International Agency for Research on Cancer, Lyon, 159-176.
Parkin DM, Srivatanakul P, Khlat M, et al (1991). Liver cancer in Thailand, I. A. case-control study of cholangiocarcinoma. *Int J Cancer*, **48**, 323-8.
Parkin DM, Ohshima H, Srivatanakul P, et al (1993). Cholangiocarcinoma: epidemiology, mechanisms of carcinogenesis and prevention, Cancer Epidemiol. *Biomarkers Prevention*, **2**, 537-44.
Parkin DM, Whelan SL, Ferlay J, et al (1997). Cancer incidence in Five Continents Vol.VII. *IARC Sci Publ*, **143**, 45-173.
Parkin DM, Pisani P, Ferlay J (1999). Estimates of the worldwide incidence of twenty-five major cancers in 1990. *Int J Cancer*, 827-841.
Parkin DM, Pisani P, Ferlay J (1999a). Global cancer statistics. *CA Cancer J Clin*, **49**, 33-64.
Parkin DM, Pisani P, Munoz N, et al (1999b). The Global health burden of infection associated cancers. *Cancer Surv*, **33**, 5-33.
Patel T (2002). Worldwide trends in mortality from biliary tract malignancies, *BMC Cancer*, **2**, 10.
Pisani P, Parkin DM, Bray F, et al (1999c). Estimates of the worldwide mortality from 25 cancers in 1990. *Int J Cancer*, **83**, 18-29.
Porru S, Placidi D, Carta A, et al (2001). Primary liver cancer and occupation in men: a case-control study in a high-incidence area in Northern Italy. *Int J Cancer*, **94**, 878-83.
Schafer DF, Sorrell MF (1999). Hepatocellular carcinoma. *Lancet*, **353**, 1253-7.
Sharp GB, Cologne JB, Fukuhara T, et al (2001). Temporal changes in liver cancer incidence rates in Japan, accounting for death certificate inaccuracies and improving diagnostic techniques. *Int J Cancer*, **93**, 751-8.
Smanadhikorn P, Pongpaew P, Srivatanakul P, et al (1995). Alpha 1-antitrypsin phenotype PiMZ, a risk factor for liver cirrhosis but not for liver cancers in Thailand. *Southeast Asian J Trop Med Public Health*, **26**, 240-2.
Srivatanakul P, Sontipong S, Chotiwan P, et al (1988). Liver cancer in Thailand: temporal and geographic variations, J. Gastroenterol. *Hepatol*, **3**, 413-20.
Srivatanakul P, Ohshima H, Khlat M, et al (1991a). Opisthorchis viverrini infestation and endogenous nitrosamines as risk factors for cholangiocarcinoma in Thailand. *Int J Cancer*, **48**, 821-5.
Srivatanakul P, Parkin DM, Khlat M, et al (1991b). Liver cancer in Thailand, II A case-control study of Hepatocellular carcinoma. *Int J Cancer*, **48**, 329-32.
Stocker JT, Schmidt D (1999). Hepatoblastoma in: Hamilton SR, Aaltonen LA, eds. Pathology and Genetics of Tumours of the Digestive System, International Agency for Research on Cancer, Lyon, 184-189.
Sun Z, Lu P, Gail MH, et al (1999). Increased risk of hepatocellular carcinoma in male hepatitis B surface antigen carriers with chronic hepatitis who have detectable urinary aflatoxin metabolite M1, *Hepatology*, **30**, 379-83.
Tomimatsu M, Ishiguro N, Taniai M, et al (1993). Hepatitis C virus antibody in patients with primary liver cancer (hepatocellular carcinoma, cholangiocarcinoma, and combined hepatocellular – cholangiocarcinoma) in Japan. *Cancer*, **72**, 683-8.
Trichopoulos D, Day NE, Kaklamani E, et al (1987). Hepatitis B virus, tobacco smoking and ethanol comsumption in the etiology of hepatocellular carcinoma. *Int J Cancer*, **39**, 45-9.
Ugihara S, Kojiro M (1987). Pathology of cholangiocarcinoma, In: Neoplasms of the Liver, Okuda K, Ishak KG, eds., Springer -Verlag, Tokyo, 143-158.
van Leeuwen DJ, Reeders JW (1999). Primary sclerosing cholangitis and cholangiocarcinoma as a diagnostic and therapeutic dilemma. *Ann Oncol*, **10**, 89-93.
Vatanasapt V, Martin N, Sriplung H, et al (1993). Cancer in Thailand (1988-1991), IARC Technical Report No.16, International Agency for Research on Cancer, Lyon.
Vatanasapt V, Sriamporn S, Kamsaard S, et al (1998). Survival from Cancer in Khon Kaen, Thailand. In: Sankaranarayanan R, Black RJ, and Parkin DM, eds, Cancer survival in Developing Countries, IARC Scientific Publications No.145, International Agency for Research on Cancer, Lyon, 123-134.
Waetjen LE, Grimes DA (1996). Oral contraceptives and primary liver cancer: temporal trends in three countries. *Obstet Gynecol*, **88**, 945- 9.
Wee A, Ludwig J, Coffey Jr RJ, et al (1985). Hepatobiliary carcinoma associated with primary sclerosing cholangitis and chronic ulcerative colitis. *Hum Pathol*, **16**, 719-26.
Wittekind C, Fischer HP, Ponchon T (1999a). Bile Duct Cystadenoma and Cystadenocarcinoma in: Hamilton SR, Aaltonen LA, eds. Pathology and Genetics of Tumours of the Digestive System, International Agency for Research on Cancer, Lyon, 182-183.
Wittekind C, Fischer HP, Ponchon T (1999b). Combined hepatocellular and cholangiocarcinoma in: Hamilton SR, Aaltonen LA, eds. Pathology and Genetics of Tumours of the Digestive System, International Agency for Research on Cancer, Lyon, 181.
Yamamoto M, Takasaki K, Nakano M, et al (1998). Minute nodular intrahepatic cholangiocarcinoma, Cancer, 82, 2145 – 2149.
Yamato T, Sasaki M, Hoso M, et al (1998). Intrahepatic cholangiocarcinoma arising in congenital hepatic fibrosis: report of an autopsy case. *J Hepatol*, **28**, 717- 22.
Zhou H, Ortiz- Pallardo ME, Ko Y, et al (2000). Is heterozygous alpha – 1 – antitrypsin deficiency type PIZ a risk factor for primary liver carcinoma? *Cancer*, **88**, 2668-76.