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Liver and Intrahepatic Bile Ducts Cancer (ICD-10 C22) in Germany

Master Thesis

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Statutory declaration

I hereby declare that I have developed and written the enclosed Master Thesis completely by my own work and effort and that it has not been submitted anywhere for any award or evaluation. I have not used sources or means without declaration in the text. The Master Thesis was not used in the same or in a similar version to achieve an academic grading or is being published elsewhere.

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Berlin, 28th March 2012

Abstract

Background: evidence suggests that the occurrence of liver cancer has increased over the past years in Germany. Only recently, the national estimates for liver cancer incidence have been made available by Robert Koch-Institute (RKI). The aim of this study was to evaluate the development of the incidence and mortality of cancer of the liver and intrahepatic bile ducts in Germany including evaluation of regional distribution and associated risk factors.

Methods: incidence data analysis was based on data from complete population-based cancer registries that are collected annually by the German Centre for Cancer Registry data (ZfKD) at the RKI where they are pooled together in a national database. The current incidence estimates are available for the period between 1999 and 2008. The corresponding mortality data from 1980 to 2009 were obtained from official cause-of-death statistics which are published on annual basis by the German Federal Statistical Office. Joinpoint regression model was applied to evaluate changes in trends of age-standardized mortality rates over the last 30 years. Regional trends of age-standardized incidence and mortality rates were also assessed. We also collected data on the main risk factors (HBV and HCV infections, alcohol use and liver cirrhosis) from various sources to examine their time trends and regional distribution.

Results: it has been estimated that about 7600 new cases are diagnosed and 7000 people die from this cancer each year in Germany. The overall age-standardized mortality rate rose steadily since 1980 with a significant increase in men from 5.3/100,000 in 1980 to 8.1 in 2009, while in women it remained constant over this period (around 3/100,000). Similarly, estimated age-standardized incidence rate increased slightly in men from 8.7/100,000 in 1999 to 9.4 in 2008, while among women there was no change. East-west and south-north decreasing gradients in both incidence and mortality were observed. In men, increasing mortality trends since 1980 have been observed especially in the southeast and south of Germany.

Conclusion: the study suggests a steady increase in the frequency of liver cancer among German men over the last 30 years. Regional variability has also been largely demonstrated particularly among men. Reasons for the observed trends are not clear. It is likely that variations in the prevalence of HCV (and probably HBV) and alcohol consumption could have a major influence. Data on risk factors and their time trends are insufficient to draw a clear conclusion. Future studies are recommended to determine the etiologic role of both HBV/HCV infections and alcohol as well as other possible risk factors on liver cancer in Germany.

Zusammenfassung

Hintergrund: Es gibt Hinweise, dass die Häufigkeit bösartiger Tumoren der Leber in den letzten Jahren in Deutschland zugenommen hat. Erst kürzlich hat das Robert Koch-Institut hierzu erstmals nationale Inzidenzschätzungen veröffentlicht. Ziel der vorliegenden Arbeit war es, die Entwicklung von Inzidenz und Mortalität von Krebserkrankungen der Leber und der intrahepatischen Gallengänge darzustellen unter Einbeziehung regionaler Unterschiede und vorliegender Daten zu assoziierten Risikofaktoren.

Methoden: Daten der epidemiologischen Krebsregister Deutschlands, die einmal jährlich an das Zentrum für Krebsregisterdaten am Robert Koch-Institut übermittelt werden, wurden für die Schätzung der bundesweiten Inzidenz für den Zeitraum 1999 bis 2008 herangezogen. Die Mortalitätsraten wurden anhand der Todesursachenstatistik des Statistischen Bundesamtes für die Jahre 1980 bis 2009 ermittelt. Zeitliche Trends der altersstandardisierten Mortalitätsraten in diesem Zeitraum wurden mit der Methode der Joinpoint Regression untersucht. Weiterhin wurde die Entwicklung von Inzidenz und Mortalität in verschiedenen Regionen Deutschlands dargestellt. Präsentiert werden ferner Daten zur Häufigkeit der wesentlichen Risikofaktoren (HBV- and HCV-Infektionen, Alkoholkonsum und Leberzirrhose) in Deutschland aus verschiedensten Quellen.

Ergebnisse: Aktuell werden geschätzte 7.600 Fälle an Leberkrebs jährlich in Deutschland neu diagnostiziert, etwa 7.000 Menschen sterben pro Jahr an dieser Erkrankung. Die altersstandardisierte Mortalitätsrate stieg bei Männer seit 1980 kontinuierlich und signifikant von 5.3/100,000 in 1980 auf 8.1 in 2009 an, während sie bei den Frauen bei Werten um 3/100.000 annähernd konstant blieb. Auch die geschätzte altersstandardisierte Inzidenzrate stieg bei den Männern von 8.7/100,000 in 1999 auf 9.4 in 2008, bei den Frauen ergaben sich auch hier keine Veränderungen. Bei den Männer wurden höhere Inzidenz- und Mortalitätsraten im Osten und vor allem im Süden Deutschlands beobachtet, im Südosten und Süden zeigten sich hier die die deutlichsten Steigerungen bei den Mortalitätsraten.

Schlussfolgerungen: Die vorliegenden Daten weisen auf eine kontinuierliche Zunahme der Häufigkeit bösartiger Tumore der Leber unter deutschen Männern in den letzten drei Jahrzehnten hin. Auch liegen bei den Männern erhebliche regionale Unterschiede vor. Die Gründe für diese Ergebnisse sind nicht ganz klar, wahrscheinlich haben Variationen der Prävalenz von HCV- und HBV Infektionen und des Alkoholkonsums einen wesentlichen Einfluss. Daten zu zeitlichen Trends der Häufigkeiten dieser Risikofaktoren sind in Deutschland zu begrenzt vorhanden um eindeutige Schlussfolgerungen zu ziehen. Weitere Studien zur Rolle der genannten und anderer Risikofaktoren in der Ätiologie der Erkrankung werden empfohlen.

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I bear full responsibility for any unintentional errors that may remain in this work.

Nadia Baras

Table of content

List of figures

List of tables

List of abbreviations

	Acronym	Meaning
1	ZfKD	The German Center for Cancer Registry Data
2	PLC	Primary liver cancer
3	HCC	Hepatocellular carcinoma
4	CCA	Cholangiocarcinoma
5	ICC	Intrahepatic cholangiocarcinoma
6	WHO	World Health Organization
7	ICD-O-3	International Classification of Disease for Oncology third revision
8	TNM	Tumour Node Metastasis stage classification
9	CLIP	The Cancer of the Liver Italian Program staging system
10	BCLC	The Bercelona Clinic Liver Cancer staging classification
11	AASLD	The American Association for the study of Liver Disease
12	EASL	The European Association for the Study of the liver
13	UICC	Union for International Cancer Control
14	GLOBOCAN	Global Cancer Statistics of the World Health Organization
15	ASIR	Age-standardized incidence rate
16	HBV	Hepatitis B virus infection
17	HCV	Hepatitis C virus infection
18	IARC	International Agency for Research on Cancer
19	HBsAg	Hepatitis B virus surface antigen
20	ECDC	The European Centre for Disease Prevention and Control
21	EU	The European Union
22	PAT	Parenteral antischistosoma treatment
23	NASH	Non-alcoholic steatohepatitis
24	NAFLD	Non-alcoholic fatty liver disease
25	DNA virus	Deoxyribonucleic acid genome of hepatitis B virus
26	RNA virus	Ribonucleic acid genome of hepatitis C virus
27	PSC	Primary Sclerosing Cholangitis
28	AFP	Alpha-fetoprotein
29	AST	Aspartate amino transferase
30	ALT	Alanine aminotransferase
31	AP	Alkaline phosphatase
32	CT	Computed tomography
33	MRI	Magnetic resonance imaging
34	OLT	Orthotropic liver transplantation
35	PEI	Percutaneous Ethanol injection
36	RFA	Radiofrequency ablation
37	TACE	Trance arterial chemoebolisation
38	TARE	Transarterial radioembolization
39	STIKO	German Standing Committee on Immunisation (Ständige Impfkommission)
40	NORDCAN	Association of the Nordic Cancer Registries
41	SEER	Surveillance Epidemiology and End Results program of the USA

42	RKI	Robert Koch-Institute
43	GBE	Federal Health Reporting (Gesundheitsberichterstatung des Bundes)
44	GEDA	German Health Updates-Telephone Health Survey (Gesundheit in Deutschland Aktuell)
45	OECD	Organization for Economic Co-operation and Development
46	BKRG	the National Law for Cancer Registry Data (Bundeskrebsregisterdatengesetz)
47	GEKID	The Association of the Poulation-based Cancer Registries in Germany
48	DCO	Death certificate only cases
49	APC	Annual percentage change
50	SPSS	Statistical Package for the Social Sciences (Statistical software)
51	KREGIS	Cancer Registry Information system (RKI software)
52	ASMR	Age-standardized mortality rate
53	SL	Saarland cancer registry data
54	HH	Hamburg cancer registry data
55	USA	The United States of America
56	HIV/AIDS	Human Immunodeficiency Virus/ Acquired Immunodeficiency Syndrome
57	YOI	German Young Offenders Institution
58	IfSG	Infectious Disease Control Law (Infektionsschutzgesetz)

1. Introduction

Worldwide, liver cancer accounts for 5.9% of all cancer cases and 9.2% of all cancer related-death, thus ranking the third among the most leading cause of cancer mortality (1). In the year 2008, there were a total of 749,000 new cases diagnosed with this cancer around the world, of this approx. 696,000 people died (1). Generally, liver cancer is associated with a very poor prognosis. In Europe, liver cancer survival rate is among the worst survival rates observed for cancer patients, third only to cancers of the pancreas and pleura (2). The most common risk factors for liver cancer are hepatitis B and C viral infections, heavy alcohol consumption and contamination of food with aflatoxins B1. Other possible risk factors include smoking, obesity and type 2 diabetes (3,4). Liver cancer occurrence varies widely and its time trend is changing across the world which suggests variability in the distribution of the above mentioned risk factors (5,6). High incidence and mortality rates are reported in developing countries in East and Southeast Asia, and sub-Saharan Africa (1). However, declining trends were already observed mainly in Asia regions (7,8) as a result of implementation of control measures against hepatitis viruses and aflatoxins B1 which are highly prevalent among liver cancer patients in those regions (5,9,10). On the other hand, rising trends of this cancer have been observed in many developed countries where liver cancer is less frequent (11-16). Reasons for these increases are not clearly understood, however, the rising prevalence of HCV infection (5,11,17), and possibly diabetes and obesity are likely to have contributed (18).

There is some evidence suggesting that liver cancer incidence and mortality rates have also increased in Germany over the last decades (20,21,19). Very little is known about the epidemiology of liver cancer in Germany. Nationwide estimates for liver cancer incidence by Robert Koch-Institute (RKI) are only recently available (22). Therefore, we used the most recent national database collected by the German Centre for Cancer Registry data (ZfKD) at the RKI to evaluate the epidemiologic trends of liver and intrahepatic bile ducts cancers with a particular focus on regional variations and associated risk factors.

2. Literature review

Anatomy and function of the liver

The liver is the largest organ of the human body (weighting 1200-1800 g in adults) (23). It is located in the right upper part of the abdominal cavity. Anatomically, liver is divided into 4 lobes: right (the largest), left, quadrate and caudate lobes. Histologically, the liver is composed of 4 main tissue structures: the intrahepatic vascular system, hepatocytes, stroma and sinusoidal cells (23). The liver is one of the most important organs in the body because it receives blood from many organs for filtration; this makes it a target for metastatic spread from other cancers. It performs vital functions in the body including: detoxification of harmful substances either endogenous (e.g ammonia) or exogenous (e.g alcohol, drugs, other chemicals), bile acids production, cholesterol metabolism, storage function (iron, vitamins, minerals and sugars). The liver also plays a central role in carbohydrate metabolism and the maintenance of glucose levels in the blood. In addition, it is also involved in the metabolism of amino acids, protein, and hormone, as well as the formation of clotting factors and certain enzymes (24).

Definition and classification of primary liver tumours

Liver tumours can be benign or malignant. Malignant liver tumours are grouped as primary tumours (originating from the liver), and secondary tumours (metastasized to the liver from other cancers). Primary liver cancers (PLCs) are classified according to their cell of origin into two main types: epithelial and non-epithelial liver cancers (25) (Table 1). Liver cancers of epithelial cell origin are more common; they arise either from hepatocytes or the cells of the intrahepatic bile ducts. All PLCs **(liver and intrahepatic bile ducts cancers)** are coded together as C22 in the *International Classification of Disease* ICD-10 (26). Cancers of the Gallbladder and other biliary tract are coded separately (C23 and C24; respectively). Hepatocellular carcinoma (HCC) is the most common histological form (75–90% of all PLCs worldwide) (27). It is a rapidly progressing malignant tumour arising from hepatocytes (liver cells) also called hepatoma (28). Cholangiocarcinoma (CCA) is the second common form (10-25% of all PLCs) (29). It originates from cholangiocytes at any part of the intrahepatic bile ducts epithelium either from small (peripheral CCA) or large bile ducts (perihilar CCA). CCA can also arise from the right and left hepatic ducts at or near its junction (known as hilar CCA or Klatskin tumours) or distal biliary tree, these tumours are regarded as extrahepatic cholangiocarcinomas (30). Hepatoblastoma (malignant embryonal tumour)

is the most commonly occurring tumour of the liver in children representing 30-45% of all childhood primary liver tumours (28). Other forms of primary liver cancers are very rare.

Morphology of primary liver tumours

The liver is highly predisposed to reactive nodulation following repeated injury due to its regenerative ability. The most commonly observed types of primary liver tumours (mainly HCC) comprise solitary coarse-granulomatous and nodular multi-granulomatous type (especially in cirrhotic livers). A diffuse infiltrative type can also be seen however quite rare. In general, the right lobe is affected more frequently than the left lobe (28). Liver tumours are mainly supplied with arterial blood; the infiltration can occur either to the portal vein system or the hepatic veins.

Histologically, there are various subtypes for HCC (Table 1) (25). The most common is the trabecular type usually seen in highly or moderately differentiated HCCs composing of cells similar to hepatocytes (27). Other sub-types of HCC are very rare (27,28). Most of ICCs are adenocarcinomas (>90%) (28,30). Squamous cell, neuroendocrine carcinomas and sarcomas are extremely rare histological forms.

Table 1: classification of primary malignant liver tumours (ICD-10 C22) according to WHO

(excluding biliary tract NOS (C24.9) and secondary malignant neoplasm of liver (C78.7)) **(25)**

Sub-sites	**ICD-10**
Hepatocellular/HCC	C22.0
Intrahepatic bile duct carcinoma (cholangiocarcinoma)/ICC	C22.1
Hepatoblastoma	C22.2
Angiosarcoma of liver (Kupffer cell sarcoma)	C22.3
Other sarcomas of liver	C22.4
Other specified carcinomas of liver	C22.7
Liver unspecified	C22.9
Histological forms	**ICD-O-3 morphologic code**
Epithelial tumours	
Hepatocellular carcinoma **Histologic subtypes:** Trabecular type Pseudoglandular and acinar type Scirrhous type Solid type Fibrolamellar type	8170/3
Intrahepatic-cholangiocarcinoma (peripheral bile duct carcinoma) **Histologic subtypes:** Adenocarcinoma Adenosqauamous and squamous carcinoma Cholangiolocellular Carcinoma Mucinous carcinoma	8160/3

Signet-ring cell carcinoma Sarcomatous ICC Lymphoepithelioma-like carcinoma Clear cell variant Mucoepidermoid carcinoma	
Bile duct cystadenocarcinoma	8161/3
Combined hepatocellular and cholangiocarcinoma	8180/3
Hepatoblastoma	8970/3
Undifferentiated carcinoma	8020/3
Non-epithelial tumours	
Epitheliod haemangioendothelioma	9133/1
Angiosarcoma	9120/3
Embryonal sarcoma (undifferentiated sarcoma)	8991/3
Rhabdomyosarcoma	8900/3
Others	

ICD-10: International Classification of Disease tenth revision (26)*, ICD-O-3: International Classification of Disease for Oncology third revision* (31)*. The first 4 digits indicate the cell types, the last digit is behavioral code.(/1 for unspecified, borderline or uncertain behaviour, 3/ for malignant tumours)*

Staging

Determination of liver cancer stage at the time of initial diagnosis is of a great importance to determine prognosis and decide the best treatment. Various staging systems have been developed to provide a staging system that presents information on both the tumour extent and liver function. The most commonly used staging systems include the TNM (32), Okuda (33), the Child-Pugh score (34), the Cancer of the Liver Italian Program (CLIP) score (35) and the Barcelona Clinic Liver Cancer (BCLC) classification system (36). The latter is currently widely used in clinical practice in many Western countries (37). This system has been approved and recommended for HCC staging by the American Association for the study of Liver Disease (AASLD) and the European Association for the Study of the liver (EASL) (38) as the best prognostic classification system (39) that supports planning of proper treatment strategies. Although, the TNM system is considered to be less useful as it is based only on the anatomical extent of the tumour (39). However, it is still in use as a basic tool in public health surveillance to give some indications on the prognosis of cancer patients at the population level (Table 2).

Table 2: TNM staging classification of tumours of the liver and intrahepatic bile ducts (ICD-10 C22)

(according to the UICC-TNM classification, 6th edition) (40)

T-Primary Tumour	**UICC Stage group**
TX Primary tumour cannot be assessed	**Stage I = T1 N0 M0**
T0 No evidence of primary tumour	
T1 Solitary nodule without vascular invasion	**Stage II = T2 N0 M0**
T2 Solitary nodule with vascular invasion; or multiple nodules none more than 5 cm in greatest	

dimension without vascular invasion T3 Multiple tumours more than 5 cm in greatest dimension or tumour involving a major branch of the portal or hepatic vein T4 Tumour(s) with direct invasion of adjacent organs other than gallbladder; or tumour(s) with perforation of visceral peritoneum **N-Regional Lymph Nodes** NX Regional lymph nodes cannot be assessed N0 No regional lymph node metastasis N1 Regional lymph nodes metastasis **M-Distant Metastasis** MX Distant metastasis cannot be assessed M0 No distant metastasis M1 Distant metastasis	**Stage IIIA = T3 N0 M0** **Stage IIIB = T4 N0 M0** **Stage IIIC= any T N1 M0** **Stage IV = Any T Any N M1**

UICC: Union for International Cancer Control

Epidemiology

Worldwide, liver cancer is the fifth most commonly diagnosed cancer in men (7.9% of all cancers) and the seventh in women (6.5% of all cancers) (1). In the year 2008, there were a total of 749,000 new cases diagnosed and about 696,000 people died of this cancer around the world (1). The prognosis for liver cancer is generally poor, and as a result liver cancer ranked the third most leading cause of cancer mortality worldwide (1,41). Despite advancements in treatment over the last decades, survival rates after five years from diagnosis remain very low; <15% in Europe (2,42,43) and the United states (42,11,44). Marked demographic and geographic variability in incidence and mortality rates have been documented across the world (18). Globally, more than 80% of the estimated incidence occurs in the developing countries, with a great proportion in East and Southeast Asia, and sub-Saharan Africa (central and west) (1). From the 2008 WHO's GLOBOCAN statistics, the highest incidence rates were reported for Mongolia with age-standardized incidence rate (ASIR) of 116.6/100,000 men; and 74.8/100,000 women (45). Liver cancer, particularly primary malignant neoplasm, is less common in developed countries in the Americas, Australia, New Zealand and Europe (ASIRs <5/100,000) with the exception of southern Europe (ASIR 10.5/100,000 in men and 3.3/100,000 in women) and Japan (ASIR 17.6/100,000 in men and 5.8/100,000 in women)(45). Global variations in incidence rates of this cancer have been suggested to be related to a variation in exposure to risk factors (6). In most developing countries the major etiological factors include chronic infection with hepatitis viruses (particularly HBV) (7) and ingestion of food contaminated with aflatoxin B1 (a product of Aspergillus flavus fungus) (46). Whereas, HCV infection and heavy alcohol consumption are regarded as the most important risk factors in the more developed countries (47,17,48,49). Other potential risk factors include cigarette smoking, obesity, diabetes and oral contraceptive use (3). Liver cancer occurs two to four times more frequently

in men than in women (1,29) which has been related to sex-specific exposure to the above mentioned risk factors. The interactions among risk factors in the development of liver cancer have also been suggested. There is evidence that HBV infection and exposure to dietary aflatoxins can act synergistically to increase the risk of liver cancer development (46,50,51). Alcohol has also a significant synergistic effect with other risk factors, most importantly HBV and HCV, aflatoxins and diabetes mellitus (52,53).

Population-based cancer registries from many Western countries have reported rising trends in incidence and mortality rates of liver cancer over the past decades (Table 22, appendix II). Data from the United states (11,54,55), Canada (12,56), Mexico (13), Australia (14,57) and some European countries (42,58,20,15,59-61,16) including Germany (21,62) have shown changes in incidence and mortality trends. In contrast, the incidence has steadily declined in some high-incidence areas particularly in Asia including Japan (7,8). These observed changes in trends have been linked to widespread HBV vaccination programs implemented in many Asian countries since the early 1980s which effectively reduced the burden of chronic HBV infection (5,9,10). In addition, the application of screening of blood products and safe medical practice measures played a major role (18,7). On the other hand, the rising trends in liver cancer in Western countries have been linked to the increasing prevalence of HCV infection (5,11,17). It has also been proposed that increasing prevalence of diabetes and obesity are likely to have contributed (18). In recent years, declining trends in mortality from liver cancer have also been noticed in some European countries such as Italy and France (63) most probably due to changing prevalence of HCV infections and alcohol consumption which are attributed to a great proportion of liver cancer cases. A recent study suggested that the different time of spread of HCV could explain the different trends observed between countries (64). This study indicated that HCV infection epidemia occurred in some south European countries in the 1940s due to transfusion of unscreened blood, injection drug use and unsafe medical procedures during the World War II, while in the United States the spread of HCV occurred relatively later in the 1960s and 1970s due to opiate injection use (64). The situation is quite different in Japan, where in contrast to other Asian countries higher prevalence of HCV than HBV were reported among liver cancer cases (70-90% of HCC cases) (18,7). The recent declining trend is proposed to be mainly due to decreased HCV-related HCC (65). This was explained by the fact that the outbreak of HCV infection occurred much earlier in Japan (in the 1920s) because of the parenteral antischistosoma treatment (PAT) and later in the early 1940s due to intravenous amphetamine used during and after the World War II (64,66). Nevertheless, increasing trends in some parts of the world have also been described to be partly attributed to recent improvements in investigation and treatment, reporting and coding of primary tumours, screening services for at high-risk

individuals as well as changes in the treatment and prognosis of liver cirrhosis (58,5). The increased immigration of people from areas with high prevalence of hepatitis into developed countries has also been suggested to contribute to the currently rising trend of liver cancer (5,57,47,48,67).

Viral Hepatitis infections

Hepatitis virus infections are a major public health problem especially in developing countries (68). Globally, there are around 350 million people chronically infected with HBV (69) and about 130 million people are chronically infected with HCV. For HBV, the risk of developing chronic infection depends on the patient's age upon infection. About 90% of infants infected during the first year of life become chronic carriers, while the risk becomes lower (<10%) when acquiring the infection later in adulthood (70). In contrast, 75-85% of those who are infected with HCV (especially at older age) (71) will develop chronic infection. Both HBV and HCV are proved to be carcinogenic in humans based on findings from the WHO IARC Monograph evaluation (72). HBV is attributed to the great majority of liver cancer cases worldwide (around 340,000 or 54.4%), compared to HCV infection (around 195,000 or 31%) (68). The prevalence of HBV chronic carriers is over 8% in the developing world especially Asia and Sub-Saharan Africa, compared to less than 2% in the developed world in North and Central America and North and West Europe (48,72). HCV is also distributed unevenly across the world with higher prevalence rates (up to 15%) were seen in Africa and Asia including Japan and the highest (>15%) was reported in Egypt (73). A prevalence of <3% was found in most developed countries (73). However, the prevalence of HCV is much higher than HBV in developed countries and the attributable fractions for liver cancer due to HCV is higher accounting for 60% of cases compared to only 20% due to HBV (74). According to the ECDC statistics, there are around 8000 and 29000 new cases diagnosed every year with HBV and HCV infections respectively in the EU countries (69). The prevalence of hepatitis HBV (HBsAg carriage) and HCV infections is very low in Germany (0.6% and 0.4%; respectively) (75) compared to estimated numbers in Southern and Eastern Europe (76). The most common route of transmission of HBV infection in Germany is sexual exposure (reported in 41.4% of infected cases). While for HCV, infection is acquired mainly through contact with infected blood (73). In Germany, a great proportion of HCV infected individuals are found among intravenous drug users (77). It has been reported that about 45.5% of patients who have chronic hepatitis C had a history of intravenous drug use (78).

Alcohol and liver cirrhosis

Alcohol is one of the major causes of liver cirrhosis (6). It can act as an independent factor or as a cofactor in inducing hepatic carcinogenesis by accelerating cirrhosis progression (52,53). A dose-

dependent relationship was also found between alcohol drinking and liver cancer. Increasing level of alcohol intake (>60 g ethanol per day) over a long period was found to have a strong effect on liver cancer risk (53). The mechanism by which alcohol may contribute to primary liver cancer development is still not completely understood. However, it is believed that alcohol induces liver cirrhosis indirectly through causing chronic inflammation and liver cells injury. But it has also been suggested that acetaldehyde, a metabolite product of alcohol, may have a genotoxic effect (79,80).

Other causes of chronic liver diseases and cirrhosis

Inherited genetic diseases such as heamochromatosis, tyrosinemia and alpha-1-antitrypsin deficiency are also found to be associated with increased risk for liver cancer development (27). Diabetes (type 2) and obesity are found to be associated with the development of non-alcoholic steatohepatitis (NASH) which in the long run leads to HCC through progression to cirrhosis (81). NASH is the severest form of non-alcoholic fatty liver disease (NAFLD) (51). Furthermore, it has also been suggested that obesity can act as an independent risk factor for the development of HCC in patients with cryptogenic cirrhosis (neither viral nor alcoholic causes) compared to patients with other causes of cirrhosis (82).

Pathogenesis

Hepatocarcinogenesis results from an accumulation of the effect of one or an interaction of multiple risk factors (e.g viral, environmental, and host factors) (51). For the development of HCC, a multistep process must take place that involves inflammatory changes of hepatocytes triggered by carcinogens, progression to chronic hepatitis, necrosis, regeneration, fibrosis and cirrhosis. This may result in genetic alterations and finally development of HCC (83,84). Cirrhosis of any aetiology is a very important step in hepatocarcinogenesis (>80% of HCCs develop in cirrhotic livers) (28). However, HCC can also develop in non-cirrhotic liver (<10% of cases) most likely due to HBV infection which causes the viral genome to be integrated directly into the host cells genome (85). HCV RNA has not been found to have any direct oncogenic role, and in most cases cirrhosis is induced by chronic liver cell injury and inflammation (27,6). The process of hepatocarcinogensis may take 2 or 3 decades from the development of cellular lesions e.g after chronic liver infection to the development of HCC (27). Other carcinogens such as aflatoxin B1 can also induce genetic alterations such as mutation of the tumour-suppressor gene p53 leading to its inactivation and suppression of apoptosis (83). The pathogenesis of CCA is also associated with several risk factors, most commonly parasitic infestation of the bile ducts with liver flukes (Opistorchis viverrini and Chonorchis sinensis) (86) which enter the body by consumption of inadequately cooked fish. Other factors include intrahepatic cholelithiasis and primary sclerosing cholangitis (PSC) (30).

Clinical pictures

Liver cancer may cause no specific symptoms and is usually diagnosed late. In the majority of cases these include those symptoms related to the underlying chronic liver diseases. Liver cancer may be discovered incidentally during routine investigation carried out for other reasons or screening of patients at greater risk. In advanced stages, patients may present with upper abdominal pain, general malaise, anorexia or weight loss, nausea or vomiting and haematomesis due to esophagal varices. On clinical examination, signs may found such as enlarged liver or hepatomegaly (50-90%), ascites (30-60%), fever of unknown origin (10-50%), jaundice (4-35%), splenomegaly, and other signs of hepatic failure or metastasis (27,87-89).

Diagnosis

The diagnosis of liver cancer is usually established by a combination of blood tests, imaging studies and biopsy sampling of liver tissues. The most important serological tumour marker for liver cancer is alpha-fetoprotein (AFP). A significantly raised level of AFP >500ng/ml or continuously rising values even if less than 100ng/ml is considered as a strong indicator for this cancer (25). Other non-specific tests are also checked to evaluate the liver function (AST, ALT, AP, albumin and bilirubin). In addition, ultrasonography and Computed tomography (CT) of the liver help to identify the tumour and its location within the liver tissues or its extent of spread (89). The histological examination (biopsy) of liver tissue provides the definitive diagnosis of liver cancer. However, because of the high risk of bleeding and tumour cell spreading, it is not recommended for patients who have considerably high AFP levels with clear imaging findings and who are potentially eligible for curative therapy (27,89).

Treatment

The choice between treatment options for liver tumours depends on the stage of tumour, its location and other parameters of liver function according to BCLC staging (39). The AASLD and EASL treatment guidelines are now applied in most Western countries (39,89). Surgical resection and orthotropic liver transplantation (OLT) are the best curative treatment for early stage HCC and are associated with improved survival (5-years SR >50%) (39,67). OLT is regarded as the only definitive curative option to date as it is associated with lower risk of recurrence, but because of organ shortages its use is limited in many countries. Local ablations such as percutaneous ethanol injection (PEI) and radiofrequency ablation (RFA) are now considered safe and effective curative therapeutic options for early stage

tumours not eligible for resection. Transarterial chemoembolization (TACE) is now largely used for unresectable large tumours or early-stage tumour when ablative treatment cannot be applied because of tumour location. Response to systemic chemotherapy and hormone therapy is reported to be very poor and have no impact on survival. Thus, they are not recommended as a standard therapy for advanced HCC outside clinical trials (39).

Screening

There is no national screening program for liver cancer, however it is highly recommended for individual at high risk of developing liver cancer. The recommended surveillance interval is 6-12 months which has been suggested based on the tumour growth rates. The standard surveillance tests are ultrasound examination along with blood AFP (39).

The high risk groups include (39)**:**

- Cirrhosis of any etiology : HBV, HCV, alcoholic, hemochromatosis, or primary biliary cirrhosis etc
- Hepatitis B carriers (chronic infection): including those with family history of HCC, Asian males over 40 years old, Asian females over 50 years old and African men and women over 20 years old. For other patients with no cirrhosis screening is recommended for cases with high HBV DNA or those with ongoing hepatic inflammatory activity.

Prevention

Prevention of liver cancer necessitates the primary prevention of the known risk factors leading to liver cirrhosis. In developing countries, the possible primary prevention measures are vaccination programs against HBV, control of aflatoxin contamination of food, improvement of hygiene measures in health care sittings, and screening blood products and transplant organs (3). In high resources countries, in addition to application of the previously mentioned measures, avoidance of high risk practices through raising social awareness and health education (particularly for injecting drug users), reducing alcohol drinking, tobacco smoking, controlling obesity and diabetes mellitus constitute the main prevention measures (90). A Hepatitis B virus vaccine was introduced in the 1982, and since then mass-vaccination programs have been implemented in many countries worldwide, which proved to be effective in terms of reducing both the rate of chronic infection among immunized children and incidence and mortality rates of liver cancer (9). In Germany, the HBV vaccine was added to the routine childhood immunization in 1995 (91,92). Before then, the vaccine had been recommended for individuals at greater risk for HBV infection including medical staff, injecting drug users and haemodialysis patients according to the German Standing Committee on Immunisation (STIKO) (91). For the HCV, no vaccine has been available

as yet, however vaccinating HCV infected individuals against HBV and HAV is very recommended (93). Other strategies to prevent spread of other infections such as HCV or HIV among drug users include improving access to sterile injection equipments through the “syringe-exchange program” which have existed in Germany since 1984 (94). In addition, effective treatment of chronic liver diseases such as inherited metabolic diseases and antiviral treatment of chronic viral hepatitis are considered as very effective prevention measures to reduce the risk of progression to liver cirrhosis and liver cancer (95,96). As a secondary prevention, periodic screening of high-risk patients provides an effective mean for early cancer detection, thus increasing the chance for early and curative treatment.

3. Objectives

General objective:

To provide epidemiological data on liver and intrahepatic bile ducts cancer (primary liver cancer) in Germany, including evaluation of time trends of incidence and mortality rates and their regional distribution.

Specific objectives:

1. To determine the overall number of new cases and deaths of primary liver cancer.
2. To estimate incidence and mortality rates for primary liver cancer, including sex and age-specific and age-standardized rates.
3. To determine time trends in age and sex specific rates as well as age-standardized incidence and mortality rates for primary liver cancer for the available years up to the year 2008.
4. To analyze the incidence and/or mortality rates by the histological sub-sites of primary liver cancer for the available years up to the year 2008.
5. To examine stage at time of diagnosis of primary liver cancer for the years 2007/2008.
6. To examine the regional variation in the distribution of age standardized incidence and mortality rates among different federal states in Germany.
7. To compare age standardized incidence and mortality rates in Germany with other international data for the year 2008.
8. To collect published or possibly unpublished data on the prevalence of the major risk factors (such as liver cirrhosis, viral hepatitis, alcohol) across Germany and their regional distribution and time trends.
9. To correlate these data, depending on the availability of the aforementioned data (on risk factors), with incidence and mortality rates of liver cancer to explore if regional variations and time trends of primary liver cancer incidence/mortality in Germany could be explained by regional differences or changes in the prevalence of the most important risk factors.

4. Methodology:

Data sources

Mortality data sources: corresponding primary liver cancer mortality data up to 2009 coded according to the ICD-10 (C22) and ICD-9 (155) codes for causes of death and stratified by sex, 5-year age groups and period were obtained by the German Center for Cancer Registry Data (ZfKD) from *National Mortality Statistics (official cause-of death statistics*) which are published on annual basis by the *Federal Statistical Office of Germany.* The Federal Statistical Office calculates the results from all Federal German States according to 3-digits and the detailed 4-digits in the ICD (10^{th} German revision starting from 1998; and 9^{th} German revision for data from 1979 to 1997).

Incidence data sources: incidence data for all new primary liver cancer cases diagnosed up to 2008 and coded according to ICD-10 (C22) were obtained from the ZfKD which annually collects the anonymized Cancer registry data form from all German population-based cancer registries. Epidemiologic registries in Germany routinely collect demographic information on patients (sex, age, place of residence), in addition to month and year of cancer diagnosis, tumour diagnosis (ICD-10 codes), primary cancer site and morphology codes (ICD-O3), diagnosis confirmation by microscopic examination or other methods, grading, TNM stage (UICC TNM), type of primary treatment, vital status, date of death, and cause of death according to ICD-10 (97).

Population data sources: the annually updated data on the average population provided by the statistical offices cover all people who are resident in Germany, regardless of their nationality, used as reference variable for the cancer morbidity and mortality data.

International data: data from GLOBOCAN 2008 estimates (45) NORDCAN 2008 estimates (98), and SEER 2008 of the United States (99,100) were used for comparison purpose.

Data on risk factors: were obtained from *the Robert Koch institute* (RKI) survey and notification data (101) and *Federal Health Reporting* database (GBE) (102) for HBV and HCV infections, mortality from liver cirrhosis (ICD-9 571, ICD-10 K70, K73-K74) and alcoholic liver cirrhosis (ICD-9 571.2, ICD-10 K70.3). Information on alcohol consumption (in liters of pure alcohol per capita) was collected from *Organization for Economic Co-operation and Development* (OECD Health database) (103) and GBE health database (GEDA survey 2008/09) (102). In addition, a search for any published studies on any of above mentioned risk factors was performed. Data on immigrant populations were also collected from the *Federal Statistical Office* (Statistisches Bundesamt Deutschland) (104).

The German Center for Cancer Registry Data (ZfKD):

The ZfKD was established in January 2010 at the RKI after the Federal Cancer Registry Data Act (Bundeskrebsregisterdatengesetz-BKRG) came into force in August 2009, requiring that all German federal states should have a state wide cancer registration and annually transfer these data to the ZfKD (105). The ZfKD is considered as a central cancer surveillance program by which a nationwide analysis of data on cancer is carried out. For the year 2008, the center has received data from the registries of 15 out of 16 federal states (all except Baden-Württemberg) (22). Completeness of registration by register is estimated using the mortality/incidence Index of longer established reference registers (106). Based on the assumption that given the same age, gender and tumour localisation cancer survival should be more or less constant across different regions in Germany, an expected number of cases is calculated for each federal state using the incidence of the reference region and regional mortality data. If the observed incidence by sex, diagnosis and year accounts for at least 90% of the expected cases, a registry is considered 'complete'. Death certificate only cases (DCO) percentage is also calculated as a simple quality criterion to determine the completeness of the registry data. DCO refer to cases who have died of cancer but were not covered by the registry and no further information on the disease were available, these cases are added to the incidence data as DCO cases. As recently estimated by the ZfKD, more than half of the German states cancer registries are of sufficient quality and regarded as complete but also most of the remaining registries are now close to reaching the desired completeness level of 90% (105,107).

Data analysis

Estimation of incidence and mortality rates:

The age-specific and standardized incidence and mortality rates were calculated by sex for all primary liver cancers (C22). The rates are expressed per 100,000 residents per year. The age-standardized rates are calculated using the direct standardization method and adjusted to the European standard population as a reference population. Age-standardized rates adjusted to the world standard population were also calculated. To study trends in age-specific incidence rates (1999-2008) and mortality rates (1980-2009), we combined the age groups into wider intervals (45-54, 55-64, 65-74 and 75+) as very few deaths were found under the age of 40.

The recently modified method of estimating national cancer incidence is based on the assessment of completeness of registration mentioned above. For those registries considered to be 'complete' for a certain cancer type and a given year, observed cancer cases (including DCO cases) are taken into

account for the calculation of the national estimates, while for all other regions the expected number of cases (by age group and sex) is used. Finally, the national estimate is calculated by summing up either observed or estimated regional cancer incidence. Improvements in cancer registration resulted in high-quality population-based cancer registries which have contributed to form a larger pool of data with which to provide more reliable and valid estimates of cancer incidence at the national level. Therefore, the actual German incidence estimates for primary liver cancer was based on between four (1999) and eight (2008) cancer registries. As only three relatively small cancer registries in Germany were operating before 1999, this estimation could only be done for the years 1999 to 2008.

To evaluate the long-term trends of the age-adjusted incidence rates for Germany, results from Saarland (from 1980) and Hamburg (from 1985) cancer registries that are known to be complete and have been collecting data continuously over many year, were presented in addition.

We also investigated changes in trends of mortality from all primary liver cancers using the 3-digits (ICD-10 C22 and ICD-9 155) data available over the period from 1980 through 2009. We calculated the Annual Percent Change (APC) to estimate changes in trends of mortality rates over the last 30 years. A linear regression model was applied with maximum of 4 joinpoints, 95% confidence interval (CI) and a significance level at $P < 0.05$ which indicates that the APC is significantly greater than zero (108).

We examined also the selected 4-digits ICD-9 (155.0, 155.1, 155.2) and ICD-10 (C22.0-C22.9) mortality data to evaluate trends in mortality by liver cancer subsites for the period from and 1980-1997 and 1998 to 2009, respectively.

Regional distribution and regional trends in age-adjusted incidence and mortality rates:

The division of "Nielsen areas" of Germany has been adopted from the *Nielsen company* (109) to examine the regional trends and distribution of age-standardized mortality rates from 1980 through 2009. As shown in (Figure 1) there are 7 regions according to the Nielsen classification, however for our analysis we grouped 2 separate regions (Baden-Württemberg and Bayern) to represent the 'South' region making up all together 6 regions (region 1=North-west, 2=West, 3a=South-west, 3b+4= south, 5+6=North-east, 7=South-east). However, evaluation of regional trends was not possible for incidence rates because of variations in the registration years among cancer registries.

Risk factor data analysis:

Age-standardized mortality rates per 100,000 (German standard population 1987) were calculated for chronic liver cirrhosis and alcoholic liver cirrhosis for both sex and by region according to the 'Nielsen areas of Germany' for the time period from 1980-2010 (102).

Stage at the time of diagnosis: because of the high proportion of missing values (cases with unknown T,N or M stage) we were unable to produce the UICC stage group. Therefore, only T stage results are presented here to give some overview on stage of liver cancer in Germany. T stage refers to the size and the extent of tumour spread usually within 4 months after the diagnosis. The T stage was based on the clinical evaluation by the treating physician.

Analysis tools:

All statistical analysis was carried out using spreadsheet Excel tools, SPSS software and the RKI-KREGIS software to calculate age-specific and adjusted rates. A Joinpoint regression analysis was applied by using a program provided by the U.S National Cancer Institute (the *Joinpoint Regression Program*, version 3.5, 2011) (108).

Figure 1: The 'Nielsen-Regions' of Germany

Source: The Nielsen Company (109)

Ethical and political contexts:

Epidemiological cancer registration in Germany is regulated by law in each federal states, with case notification being mandatory in most states. Data transmission for the German Center for Cancer Registry Data is regulated by the National Law for Cancer Registry Data [Bundeskrebsregisterdatengesetz, BKRG]. The BKRG provides for all analyses to be conducted as part of this thesis. No individual patient was identified or contacted nor individual data were directly linked to other data sources. The analyses follows the German guidelines for Good Epidemiological Practice and Good Practice for Analysis of Secondary Data.

5. Results

Primary liver cancer mortality

Summary statistics

It has been estimated that about 7000 people die each year from cancer of the liver and intrahepatic bile ducts in Germany. Due to the poor prognosis, this cancer was responsible for 4.1% of all cancer-related deaths in men and 2.5% in women, thus it ranked 7th among the most common cause of death from cancer in men and 11th in women in the year 2009 (Table 8, appendix I). The estimated overall age-standardized mortality rate (ASMR, European standard) in 2009 was 5.3 per 100,000 populations (8.1/100,000 among men and 3.0/100,000 among women), almost similar to the previous year 2008 (Table 3). Men are nearly 2 times more likely to die from liver cancer than women.

Table 3: mortality from primary liver cancer (ICD-10 C22) in Germany, 2008-2009

Deaths 2009	**Men**	**Women**	**Overall**
Number of death	4738	2493	7231
Crude mortality rate/100,000	11.8	6.0	8.8
Standardized mortality rate/100,000*	8.1	3.0	5.3
Standardized mortality rate/100,000**	5.3	2.0	3.5
Deaths 2008			
Number of death	4523	2539	7062
Crude mortality rate/100,000	11.2	6.1	8.6
Standardized mortality rate/100,000*	7.9	3.1	5.3
Standardized mortality rate/100,000**	5.2	2.0	3.5

**European Standard*
***World Standard*

Age-specific mortality rates

The age-specific mortality rates increase steadily with age in both sexes, with males having higher mortality rates than females (Figure 2). The median age of death in 2009 for men is 72 years old and for women it is approx. 77 years old. Figure 3, shows trends in age-specific mortality rates over the period analyzed (1980-2009) in both men and women. There was no apparent change in trends in women especially among the younger age group throughout the study period; however, there were very slight increases among the older age group (75 and older). In men, a slight increase among the younger age group (55-64 years) and a more notable increase among the older age group (65-74 and 75+) were observed (Table 10, appendix I).

Figure 2: age-specific mortality rates (5-years age group) of primary liver cancer (ICD-10 C22) by sex, Germany, 2009

(Deaths per 100,000)

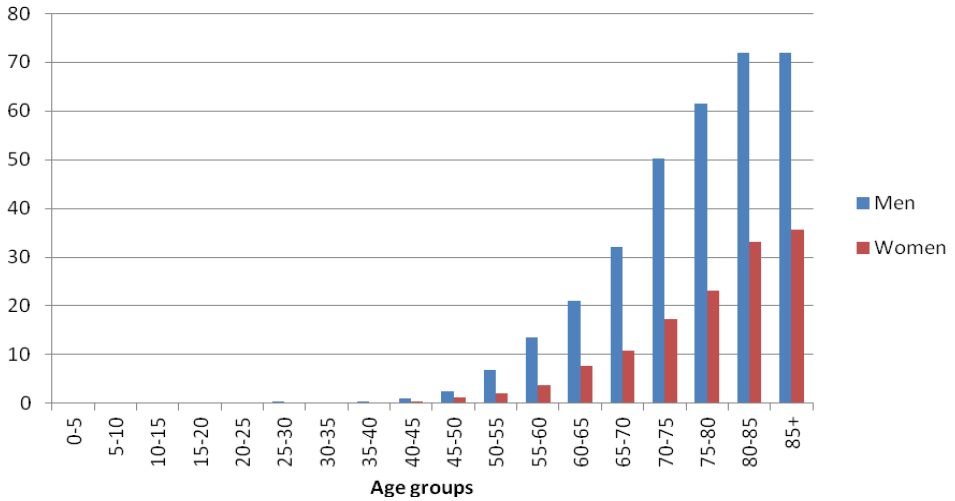
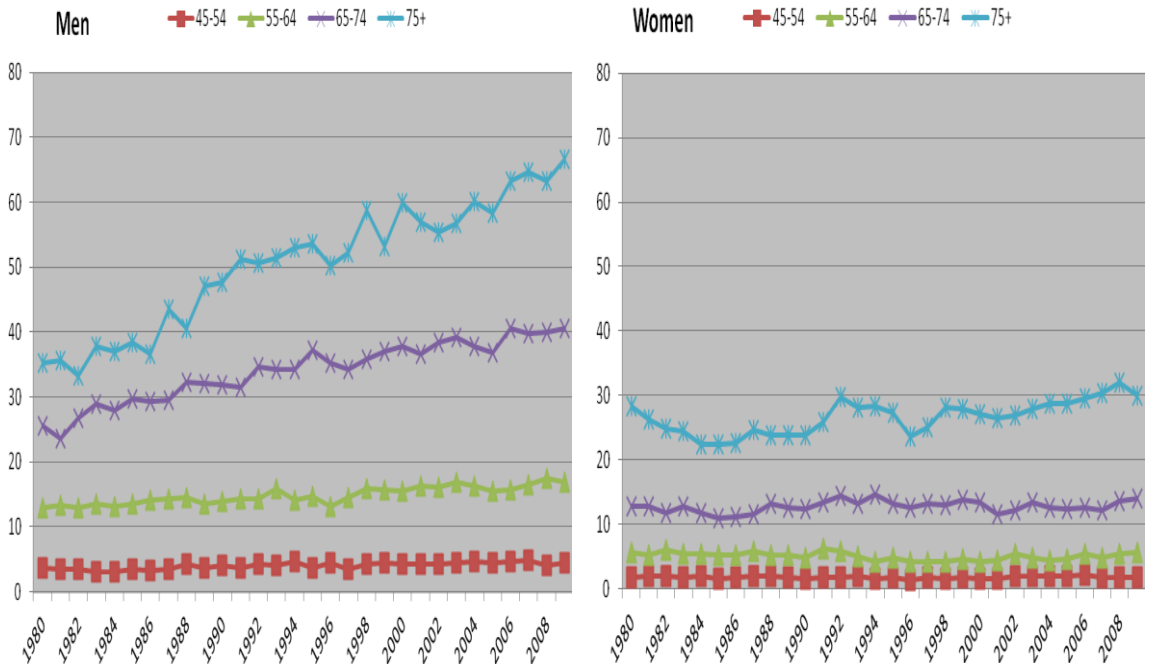


Figure 3: trends in age-specific mortality rates of primary liver cancer (ICD-10 C22, ICD-9 155) by age group and sex, Germany, 1980-2009

(Deaths per 100,000)



Trends in mortality from primary liver cancer

The ASMRs for primary liver cancer increased steadily during the last 3 decades with a noticeable increase among men from 5.3/100,000 in 1980 to 8.1/100,000 in 2009 (an increase of 52.3%). ASMRs among women remained unchanged over the same time period (3.1/100,000 in 1980 and 3.0/100,000 in 2009) (Figure 5, Table 11, appendix I). The total absolute number of deaths also increased from 3741 (1876 men and 1865 women) in 1980 to 7231 (4738 men and 2493 women) in 2009 (Figure 4). By applying a log-linear regression model, a statistically significant increasing trend was found in men with APC of ASMR (per 100,000) of 2.12% (CI: 1.3,2.9) for the period from 1980-1988 and 0.88% for the period 1988-2009 (CI: 0.71,1.0) (Figure 6). The magnitude of the increase in slope for the period before 1988 was higher than that observed from 1988 to 2009. On the other hand, among women the trend was not interpretable, although the resulted 3 segments from the model were significant except for the period 1992 to 1996 the decline was not significant (Table 4). However, the changes in trend were not substantial as the rates remained around 3.0/100,000 women.

Figure 4: trends in number of deaths for primary liver cancer (ICD-10 C22, ICD-9 155) by sex, Germany, 1980-2009

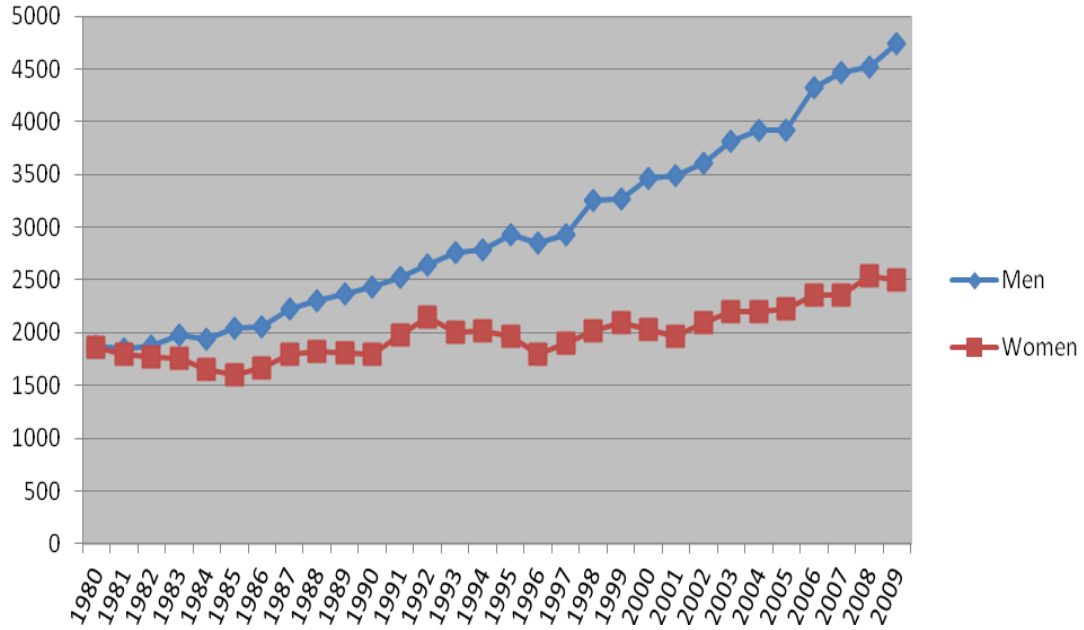


Figure 5: long-term trends in age-standardized mortality rates for primary liver cancer (ICD-10 C22, ICD-9 155) by sex, Germany, 1980-2009

(Deaths per 100,000 to European standard population)

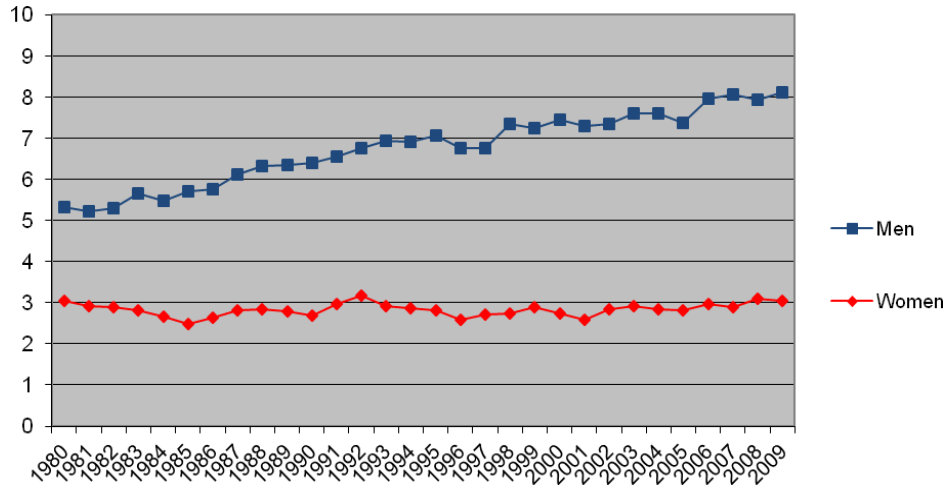
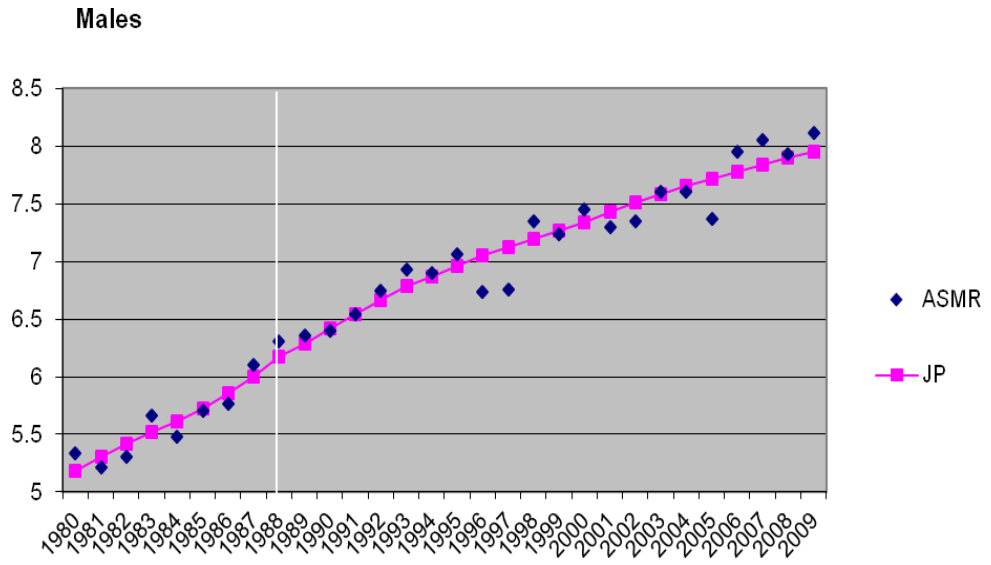
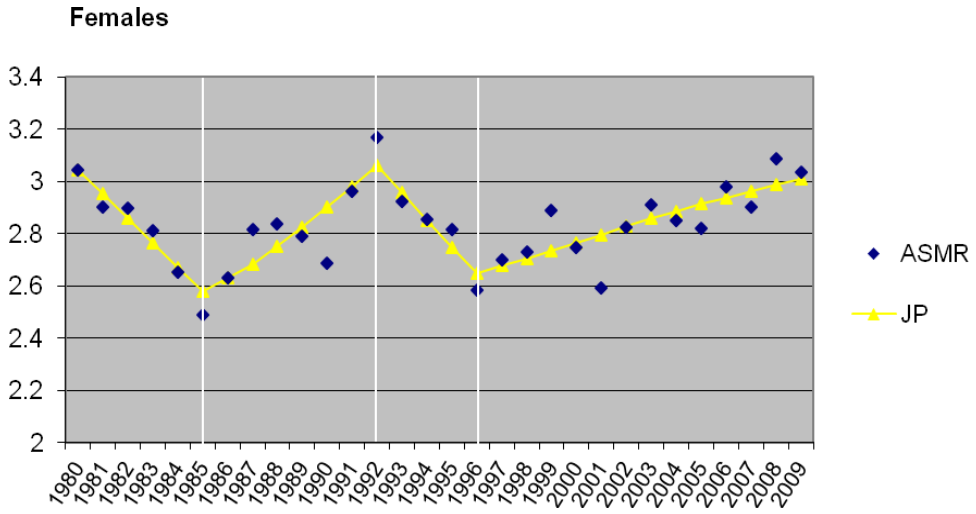


Figure 6: age-standardized mortality rates with log-linear model adjustment for primary liver cancer (ICD-10 C22, ICD-9 155), Germany, 1980-2009

(Deaths per 100,000 to European standard population)



ASMR: age-standardized mortality rates , JP: the best fitted joinpoint model



ASMR: age-standardized mortality rates , JP: the best fitted joinpoint model

Table 4: age-standardized mortality rates with log-linear model adjustment for primary liver cancer (ICD-10 C22, ICD-9 155), Germany, 1980-2009

(Deaths per 100,000 to European standard population)

Males				Females			
Trend	Years	APC	95% CI	Trend	Years	APC	95% CI
1	**1980-1988**	2.12	(1.3,2.9)*	1	**1980-1985**	-3.09	(-5.1,-1.1)*
2	**1988-2009**	0.88	(0.7,1.0)*	2	**1985-1992**	2.11	(0.6,3.6)*
				3	**1992-1996**	-3.89	(-8.3,0.6)
				4	**1996-2009**	1.03	(0.6,1.5)*

* P<0.05

APC: annual percent change, CI: confidence interval

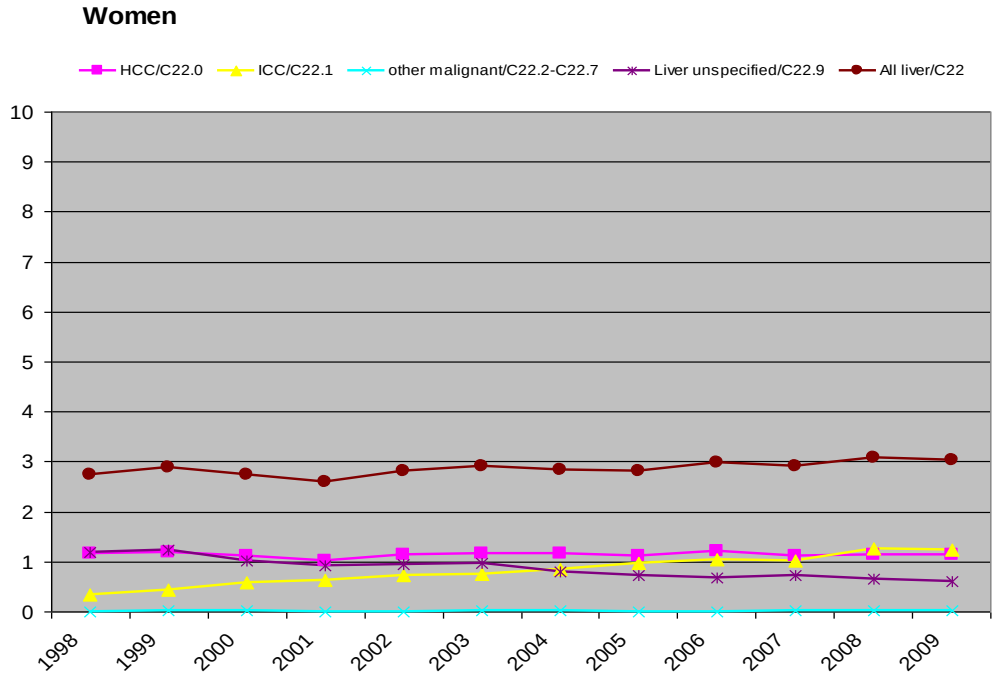
Trends in mortality by primary liver cancer sub-sites

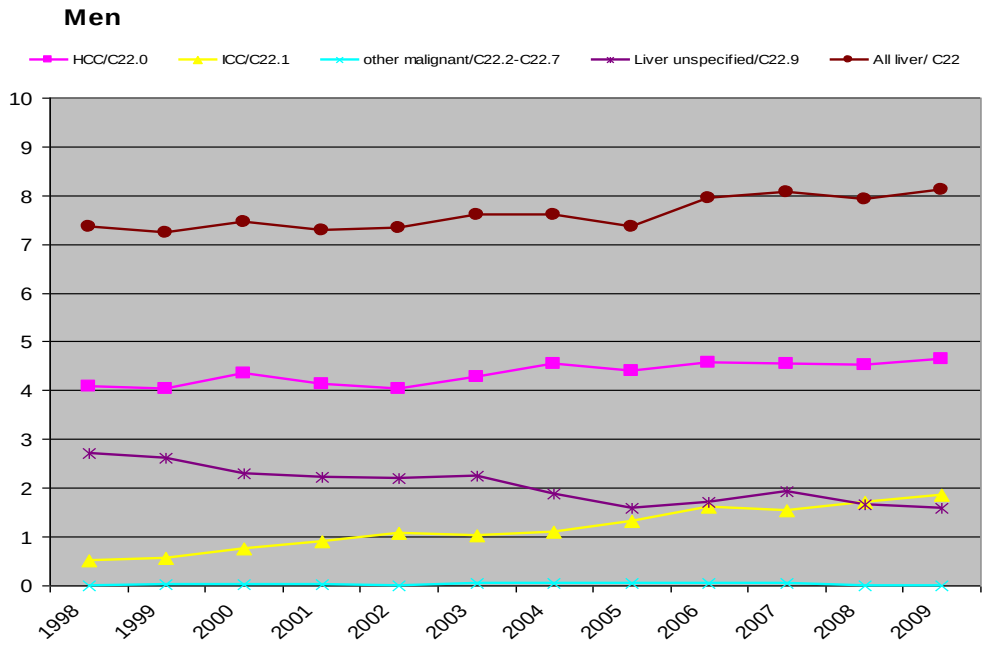
In 2009, Hepatocellular carcinoma (C22.0) was responsible for 50.4% of all deaths from primary liver cancer in both sexes and intraheaptic cholangiocarcinoma (C22.1) was responsible for about 29%. Other sub-sites of primary liver cancer account for the remaining proportion (including unspecified liver cancers). Some differences in trends between men and women were found (Figure 7). Among men, ASMRs of HCC increased slightly from the year 1998 (4.1 per 100,000 men; 1814 deaths) to the year 2009 (4.6 per 100,000 men; 2711 deaths), compared to women whose rates remained more or less stable throughout the time period 1998-2009 (1.2 to 1.1/100,000, 843 to 932 deaths) (Table 12, appendix I). Interestingly, ASMRs for ICC increased in both sexes. Among women, rates increased from

0.3 per 100,000 in 1998 to 1.2 per 100,000 in 2009. Similarly ASMRs for ICC increased in men from 0.5 to 1.9 per 100,000 over the same time period. The absolute number of deaths also increased from 247 in 1998 to 999 in 2009 in women and from 231 in 1998 to 1078 in 2009 in men (Table 13, appendix II). Among men, the ASMRs for HCC were higher than ICC over the studied period, while among women the HCC and ICC ASMRs have appeared similar since the early 2000s. ASMRs for Unspecified tumours of the liver (C22.9) showed a clear decline among both sexes from 1998 to 2009. Data before 1998 according to the ICD-9 codes, showed also a continuous decrease in mortality due to unspecified liver cancers since the 1980 and increases in both liver cancer primary (mainly HCC) and ICC sub-sites among both sexes since then. For ICC (155.1), ASMRs have increased similarly in both women and men from almost zero in 1980 to 0.2/100,000 in 1997 (Figure 8). However, there were a more noticeable increase in ASMRs of primary liver tumours (155.0) until 1997, ASMRS increased from 1.8/100,000 in 1980 to 4.3/100,000 in 1997 among men and from 0.8/100,000 in 1980 to 1.6/100,000 in 1997 among women.

Figure 7: age-standardized mortality rates for primary liver cancer by sub-sites (ICD-10 C22.0-C22.9), Germany, 1998-2009

(Deaths per 100,000 to European standard population)

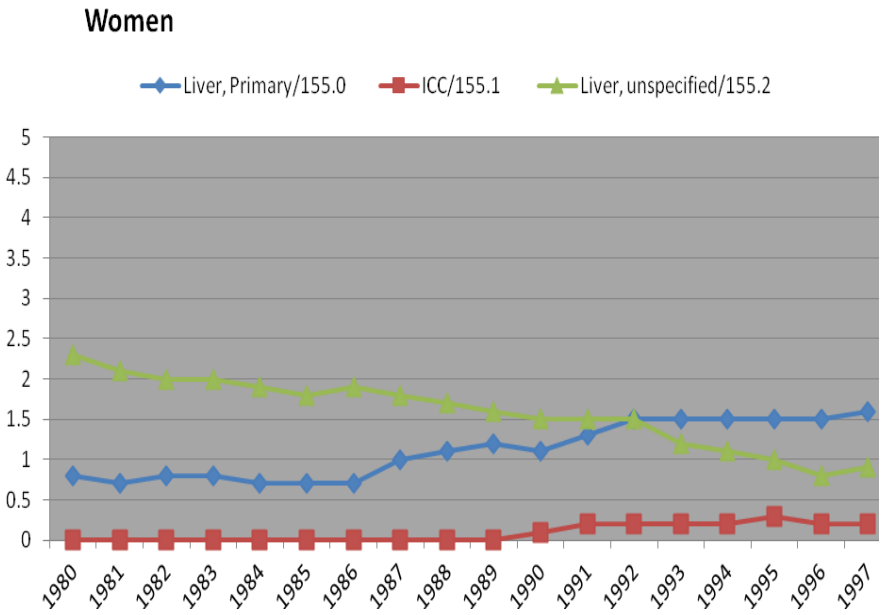


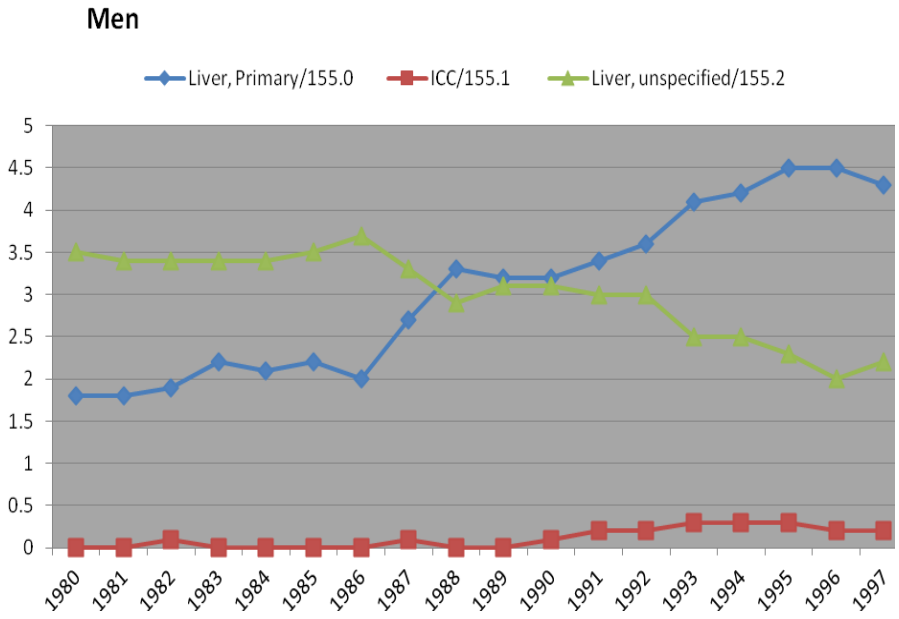


HCC: hepatocellular carcinoma C22.0, ICC: intrahepatic cholangiocarcinoma C22.1, Other malignant tumours of the liver include: hepatoblastoma C22.2, angiosarcoma C22.3, other sarcoma of the liver C22.4 and other specified carcinoma of the liver C22.7. Liver unspecified C22.9, all liver: all primary liver cancer sub-sites C22

Figure 8: age-standardized mortality rates for primary liver cancer (ICD-9, 155.0-155.2) by sub-sites, Germany, 1980-1997

(Deaths per 100,000 to European standard population)





Liver primary (155.0) include: HCC and hepatoblastoma. ICC (155.1): intrahepatic cholangiocarcinoma. Liver unspecified (155.2): not specified whether primary or secondary

Regional trends in age-standardized mortality rates of primary liver cancer

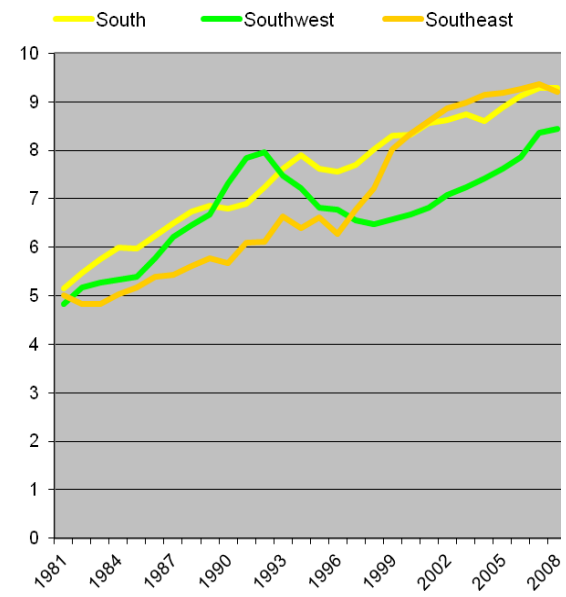
The ASMRs showed large variations between different German regions especially among men. Among men, increasing trends were seen in several regions since 1980. Surprisingly, Southern regions have demonstrated a larger increase in mortality than other regions (Figure 9) (Table 15, appendix I). The highest increase was observed in the Southeast (84%), followed by South (80%) and Southwest (75%). In the North and West slight increases have been observed, the lowest change was seen in the Northwest (11%). In women, regional trends remained constant throughout the study period with very small variations among the different regions. However, generally the rates seemed to be lowest in the Northwest.

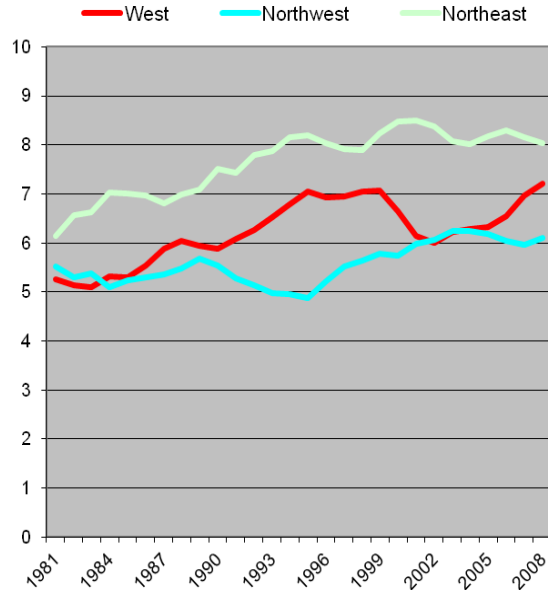
In general, East and West variations in ASMRs of primary liver cancer have been found. It appears that Eastern states have higher mortality rates (8.8/100,000 men, 3.2/100,000 women) than Western states (7.9/100,000 men, 3.0/100,000) especially observed in men than in women (Figure 10). However, the variations in ASMRs were much larger between the South (9.2/100,000 men, 3.1/100,000 women) and the North (6.2/100,000 men, 2.8/100,000 women), Figure 10.

Figure 9: long-term trend in age-standardized mortality rates of primary liver cancer (ICD-10 C22, ICD-9 155) by regions of Germany, 1981-2008, Nielsen-regions (moving 3 years average)

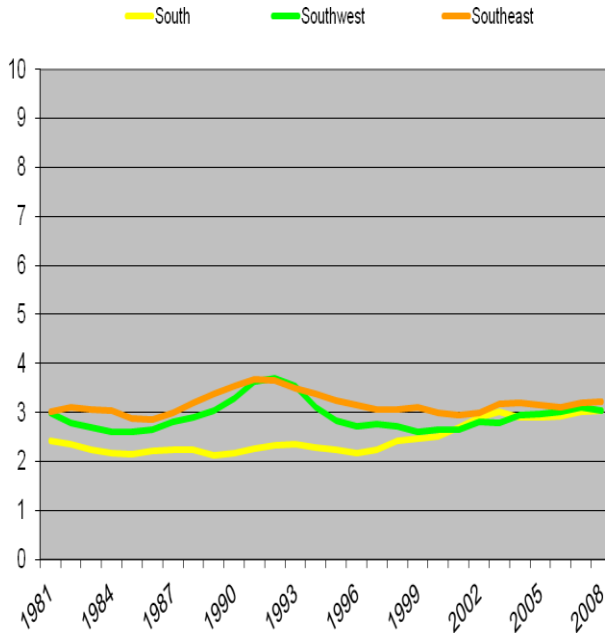
(Deaths per 100,000 to European standard population)

Men:





Women:



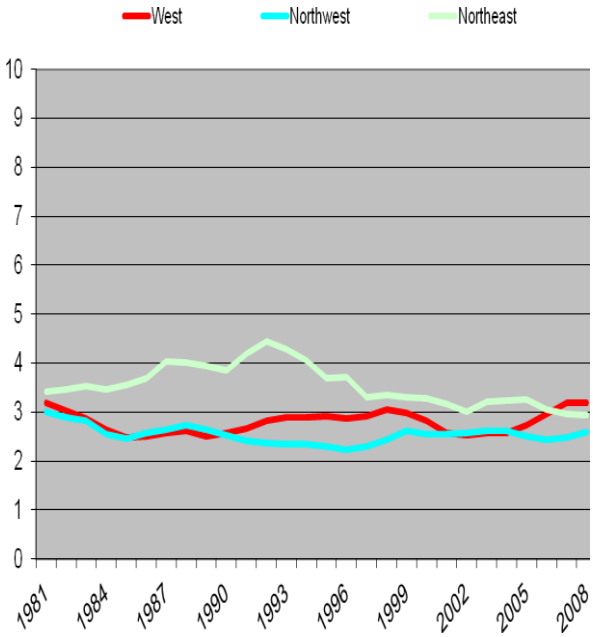
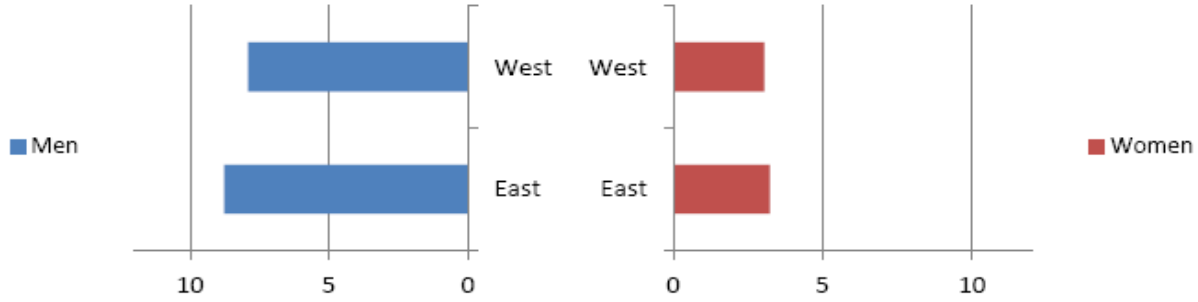


Figure 10: regional distribution of age-standardized mortality rates of primary liver cancer (ICD-10 C22), Germany, 2008/2009

(Deaths per 100,000 to European standard population)



East : includes Thüringen, Sachsen, Sachsen Anhalt, Brandenburg and Mecklenburg-Vorpommern. West: include all other states . Berlin has been excluded from both the East and West.

Primary liver cancer incidence

Summary statistics

In Germany, an estimated number of 7615 (5270 men and 2345 women) new cases were diagnosed with primary liver cancer in 2008 (Table 5) which is very close to the number of deaths that occurred in the same year (7062). Primary malignant liver cancer accounts for about 1.6% of all cancer cases (2.1% for men and 1.1% for women) in Germany. It is a relatively rare cancer in Germany ranking the 12th among the most commonly diagnosed cancers in men and 19th in women (Table 16, appendix I). Men develop liver cancer more frequently than women (male: female ratio of 2.2:1). The age-standardized incidence rate (ASIR, to European standard) in 2008 was 6.0/100,000 people (9.4/100,000 in men and 3.2/100,000 in women). As estimated by the ZfKD, one in 92 men and one in 210 women will develop liver cancer in the course of their lives in Germany (22).

Table 5: primary liver cancer incidence (ICD-10 C22) in Germany, 2008

New cases 2008	Men	Women	Overall
Number of new cases	5270	2345	7615
Crude incidence rate/100,000	13.1	5.6	9.3
Standardized incidence rate/100,000*	9.4	3.2	6.0
Standardized incidence rate/100,000**	6.3	2.2	4.1

**European Standard*
*** World Standard*

Age-specific incidence rates

Liver cancer develops very rarely before the age of 50 (only 4% of cases diagnosed with primary liver cancer in 2008 were younger than 50 years) (**Figure 11**). The median age of onset is nearly 70 years old for men and 74 years old for women. Over the last ten years, a slightly increasing trend in age-specific incidence rates was seen among men particularly among the 55-64 and 65-74 years age groups. At the same time, rates remained more or less stable among women, however, a small decline was found in the age group of 65-74 years old (Figure 12) (Table 18, appendix I).

Figure 11: age-specific incidence rates (5-years age group) of primary liver cancer patients (ICD-10 C22) by sex, Germany, 2008

(Cases per 100,000)

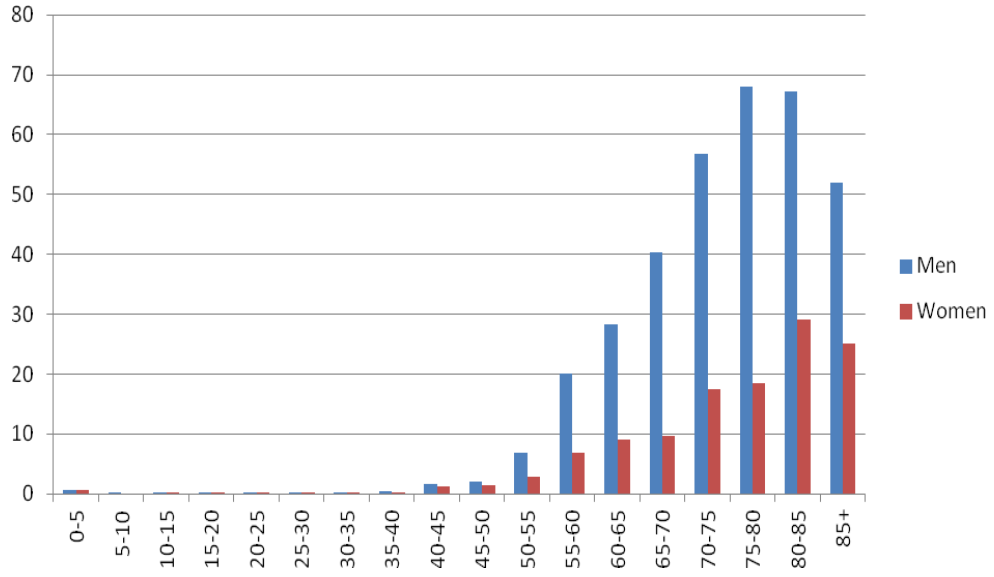
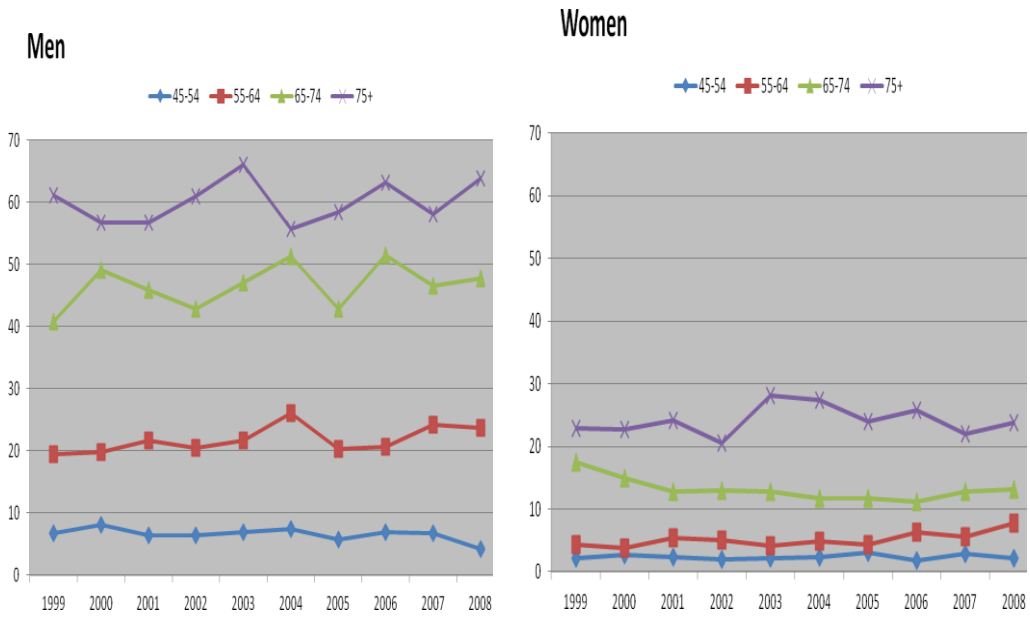


Figure 12: trends in age-specific incidence rates of primary liver cancer (ICD-10 C22) by age group and sex, Germany, 1999-2008

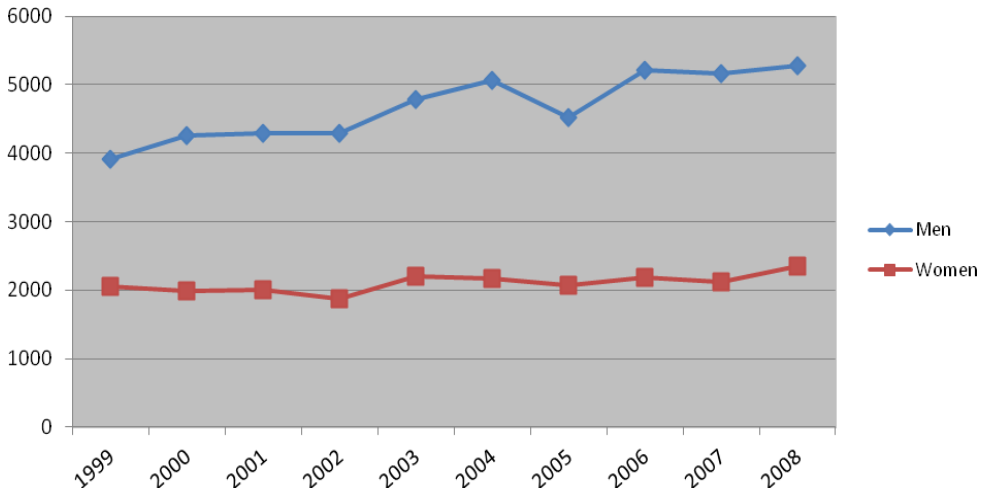
(Cases per 100,000)



Trends in incidence of primary liver cancer

In Germany, there were an estimated number of 67838 (46796 males and 21043 females) new cases diagnosed with primary liver cancer over the period from 1999 to 2008 (Table 19, appendix I). The number of incident cases had slightly increased since the last 10 years, however the increase was more prominent among men than women (Figure 13).

Figure 13: trends in number of new cases for primary liver cancer (ICD-10 C22) by sex, Germany, 1999-2008

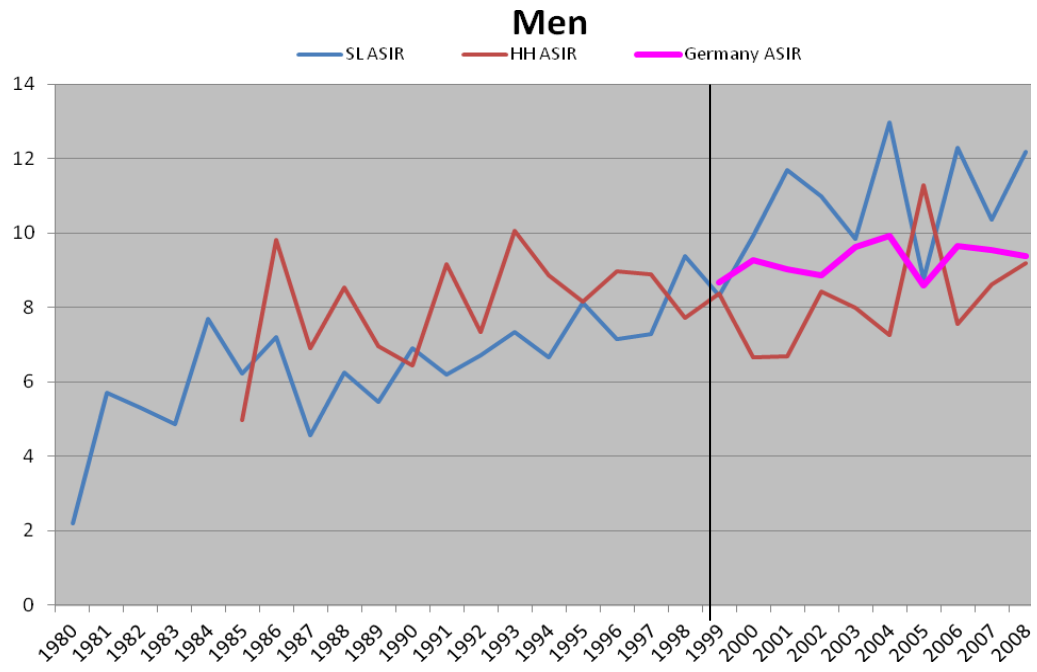


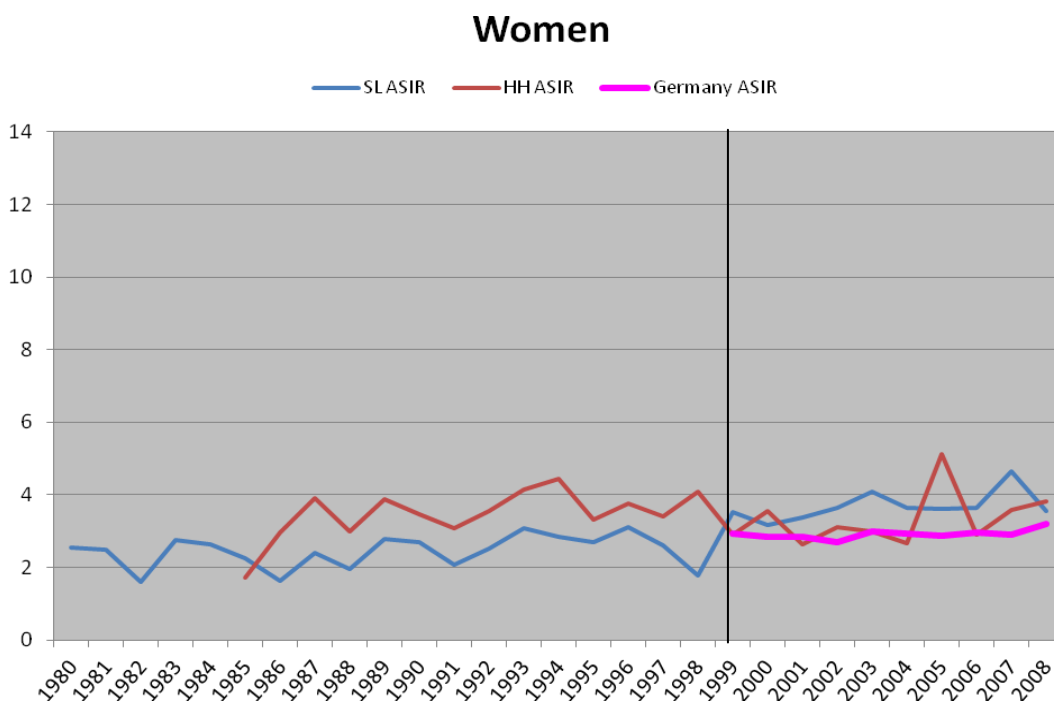
Long term trends in age-standardized incidence rates of primary liver cancer in Germany:

Similar to mortality trends, the estimated ASIRs have slightly increased among men over the periods under investigation (Figure 14) (Table 20, appendix I). However, long-term data from Saarland cancer registry showed more notable increases in incidence of this cancer where ASIRs rose from 2.2/100,000 men in 1980 to 12.7/100,000 men in 2008, a 6-fold increase. Data from Hamburg cancer registry showed very slight changes where ASIRs were fluctuating between 6 and 9/100,000 men since 1985. The overall German incidence estimates showed also a slight increase in ASIRs among men from 1999 to 2008 (from 8.6 to 9.3/100,000 men; respectively). Among women, ASIRs remained stable over the same time period, except a very slight increase in ASIRs in Saarland from 2.5/100,000 in 1980 to 3.5/100,000 in 2008; respectively.

Figure 14: long-term trends in age-standardized incidence rates for primary liver cancer (ICD-10 C22) by sex, Germany, 1980-2008

(cases per 100,000 to European standard population)





ASIR: age-standardized incidence rates, SL: Saarland cancer registry, HH: Hamburg cancer registry, Germany: the overall German incidence estimate by the ZfKD at RKI

Incidence by primary liver cancer sub-sites

According to the ZfKD estimates for the year 2008, about 58% of all primary liver cancers were Hepatocellular carcinomas (C22.0) and approximately 22% were intrahepatic cholangiocarcinomas (C22.1). Hepatoblastoma (C22.2) is a very rare sub-site (accounting only for 0.4% of all primary liver cancers) (22). Hepatocellular carcinoma was more frequent in men than women, while no sex differences were observed for ICC.

Among men, >70% of all primary liver tumours were histologicaly verified hepatocellular carcinomas and about 13% were cholangiocarcinoma. Among women approximately half of the diagnosed liver tumours were histologically verified hepatocellular carcinomas and about 29% were cholangiocarcinomas. Other histological form including other adenocarcinoma (8% of all incident cases) and mixed hepatocellular and cholangiocarcinoma (2% of all incident cases). By examining the number of new cases diagnosed by histological verification between two time period 1999-2000 and 2007-2008, we have found no significant changes in trends of histlogically verified HCCs and ICCs (data not shown).

Liver cancer stage at the time of diagnosis

In Germany, nearly more than 3 quarter of cases diagnosed with liver cancer have no complete information on TNM stage at the time of diagnosis. Therefore, we presented only T stage category of the TNM. Nevertheless, T staging data are found to be missing in about 80% of cases (including the DCO cases). However, among both men and women with complete T stage nearly one half are diagnosed with advanced stage T3 and T4 at the time of diagnosis when the tumour(s) are of considerable size with invasion of major vessels and/or adjacent organs. There is no difference between males and females in the T stages (Table 6). However, this data should be interpreted with care because of high number of cases with no or unknown stage information who could also have poor stages at the time of presentation.

Table 6: T stage of the TNM classification for primary liver cancer in Germany, 2007/2008

T stage	Men		women	
	n	%	n	%
T0	3	0.0	1	0.0
T1	474	5.8	179	5.0
T2	441	5.4	152	4.3
T3	540	6.6	225	6.3
T4	263	3.2	111	3.1
TX/unknown	3995	49.1	1625	45.6
DCO	2421	29.8	1267	35.6
Total	**8137**	**100.0**	**3560**	**100.0**

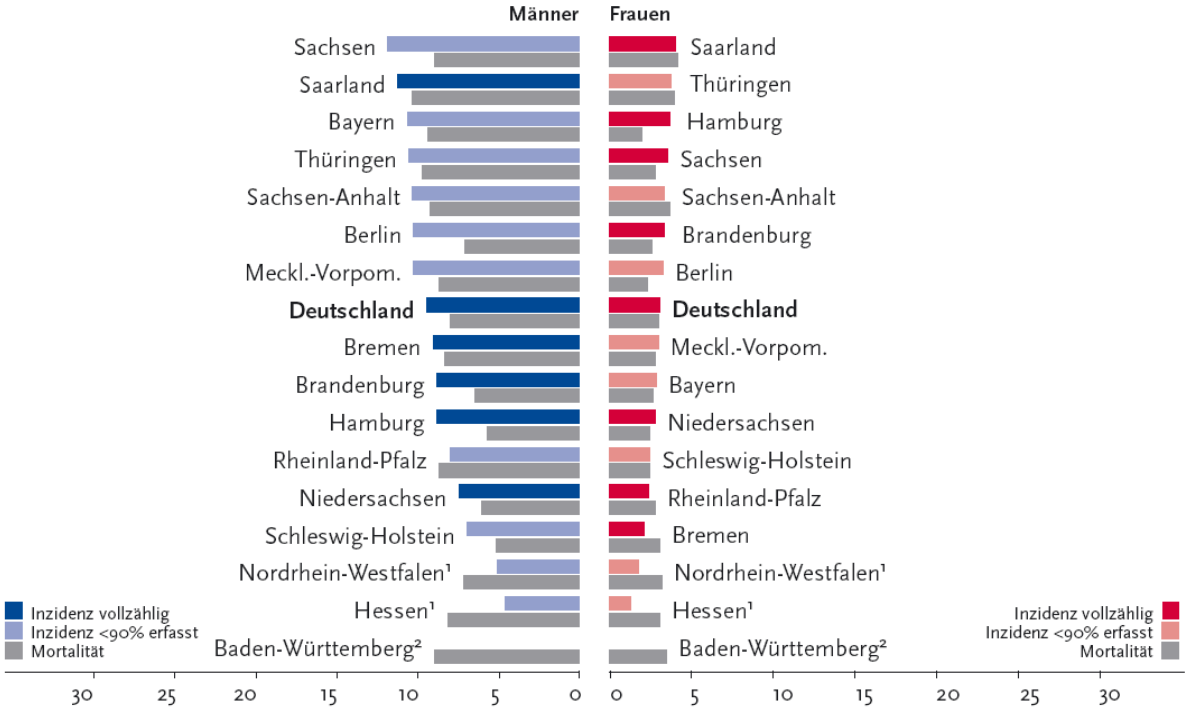
Regional distribution of age-standardized incidence and mortality rates

The ASIRs and ASMRs vary obviously across different federal states in Germany. ASIRs ranged from 5 to 12/100,000 among men and from 1.3 to 4/100,000 among women across all German federal states in the year 2007/2008 (Figure 15) (22). ASMRs ranged from 5.2 to 10.4/100,000 in men and 2.0 to 4.2/100,000 in women. In both sexes, lower incidence and mortality rates were observed in the Northwestern federal states than other states. Figure 15 also shows the degree of completeness of incidence data for liver cancer in different epidemiologic cancer registries. Cancer registry data from Saarland, Hamburg, Niedersachsen, Bremen and Brandenburg are considered complete (>90%) in terms of capturing all cancer incident cases in the region under the registry coverage. However, the higher mortality rates than incidence observed in Nordrhine-Westfalen and Hessen cancer registries do not mean that the registration is not complete in this area, but it is due to the fact that some new cancer

registries have been recently established in these states and therefore the DCO cases has not yet been added to the incidence data.

Figure 15: regional distribution of age-standardized incidence and mortality rates of primary liver cancer (ICD-10 C22), Germany, 2007-2008

(Cases/deaths per 100,000 to European standard population)



[1]*without DCO cases* [2]*no incidence data available*

Source: Cancer in Germany 2007/2008 (22)

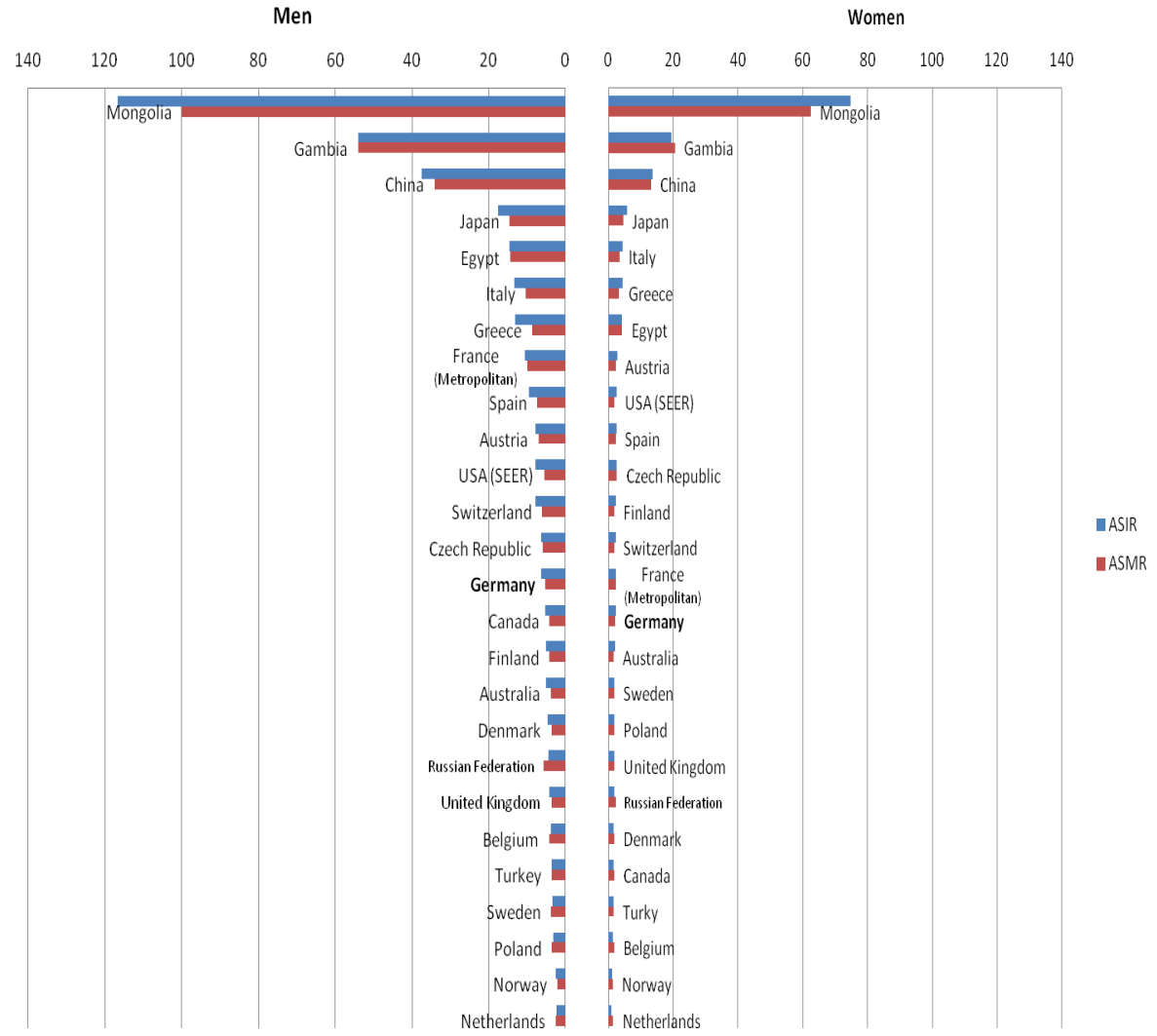
International comparison

Figure 16, shows the geographical variation in age-standardized incidence and mortality rates (world standard) for selected countries in different parts of the world in the year 2008. Highest ASIR and ASMR in our analysis were found in Mongolia in both sexes (116.6 and 99.9/100,000 men, 74.8 and 62.5/100,000 women; respectively). Generally, higher mortality rates were observed in East and Southeast Asia (Mongolia, China and Japan) and Africa (the Gambia and Egypt). Within Europe rates also varied, restricted to men, highest ASIR and ASMR (per 100,000) were found in Southern Europe (13.4 and 10.4 in Italy, 10.5 and 10 in France, 9.6 and 7.4 in Spain) and lowest rates were found in Northern Europe (2.5 and 2/100,000 in Norway as well as 2.4 and 2.6/100,000 in the Netherlands). For both sexes, ASIR and ASMR in Germany (6.3 and 5.2/100,000 men, 2.2 and 2/100,000 women; respectively) were

located in the middle among European countries and quite similar to that of Finland (5.1 and 4.3/100,000 men, 2.3 and 2.0/100,000 women; respectively) and Czech (6.4 and 5.9/100,000 men, 2.5 and 2.4/100,000 women; respectively). The rates in the USA were relatively comparable (7.9 and 5.2/100,000 men, 2.6 and 2.0/100,000).

Figure 16: age-standardized incidence and mortality rates of liver cancer (ICD-10 C22) in Germany in 2008 compared internationally

(Cases/deaths per 100,000 to World Standard population)



ASIR: age-standardized incidence rates, ASMR: age-standardized mortality rates

Data sources: GLOBOCAN 2008 and NORDCAN 2008, and the USA data from SEER data 2008. German ZfKD 2008 incidence and mortality estimates.

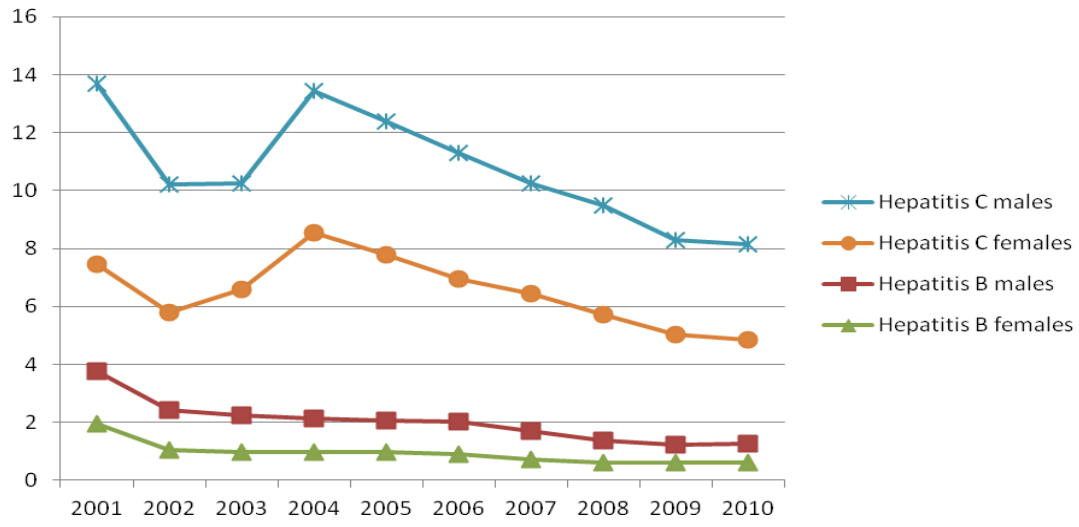
Risk factor data

Hepatitis B and C virus infections

According to the recent RKI notification data, a downward trends in both acute HBV and first-diagnosed HCV infections were seen in both gender since 2001 (Figure 17). Incidence rates of HCV is higher than HBV in both sexes. Men are more frequently infected with hepatitis viruses than women (Table 25, appendix III). The change in the notification system in 2001 has limited the comparability of these data with the earlier data. In 2001, the Infectious Disease Control Law (IfSG) was introduced which required that all laboratories in Germany are obliged to report confirmed viral hepatitis cases to the RKI (77). Regionally, incidence rates of HBV infection vary among the federal states, ranging from 0.4 per 100,000 in Niedersachsen to 2.1 per 100,000 in Hamburg in 2009. For HCV infection incidence rates ranged from 3.0 per 100,000 in Brandenburg to 18.6 in Berlin. This variation is proposed to be related to regional differences in risk factors for HBV and HCV infections (e.g intravenous drug users in big cities like Berlin), distribution of immigrant population from endemic areas or differences in case reporting across states (110).

Figure 17: incidence of viral hepatitis B and C infection in Germany, 2001-2010

(Cases per 100,000 population)



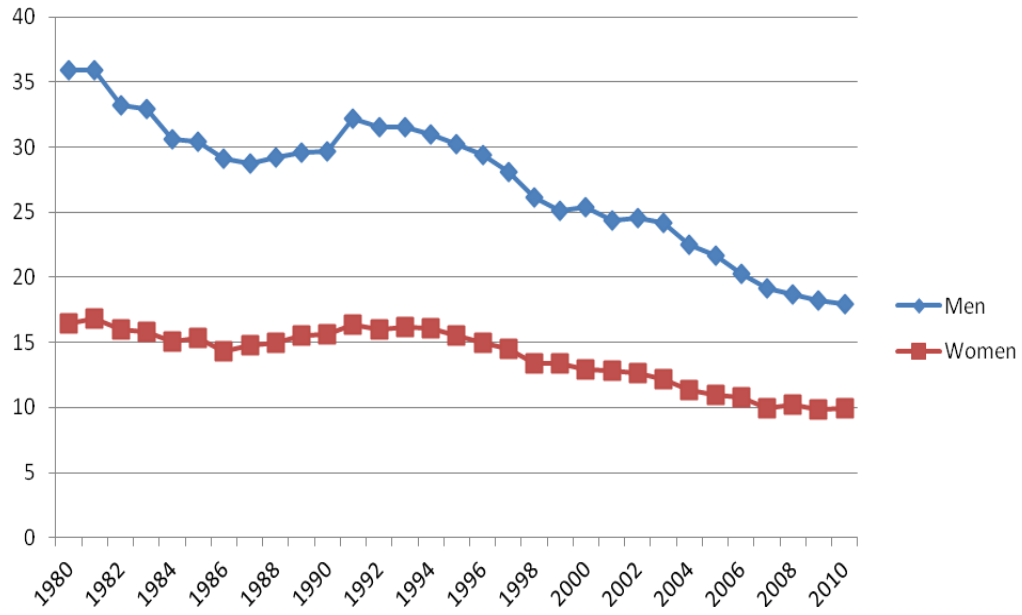
Source: RKI notification data (101)

Liver cirrhosis

As it can be clearly seen, mortality from liver cirrhosis has steadily declined in both men and women since 1980 (Figure 18). Mortality from alcoholic liver cirrhosis has shown a downward trend, however, only in some regions. Men have higher mortality rates than women. Higher mortality rates from alcoholic cirrhosis were found in the southeast and northeast (Figure 19). The difference between regions is more notable among men. It should be mentioned, however, that evaluation of data before 1990 was difficult because of the changes made in coding practices and death certifications after the unification of Germany (Table 23 and Table 24, appendix III).

Figure 18: trends in age-standardized mortality rates from chronic liver diseases and liver cirrhosis (ICD-9 571, ICD-10 K70,K73-K74) by sex in Germany, 1980-2010

(Deaths per 100,000 to the standard German population 1987)

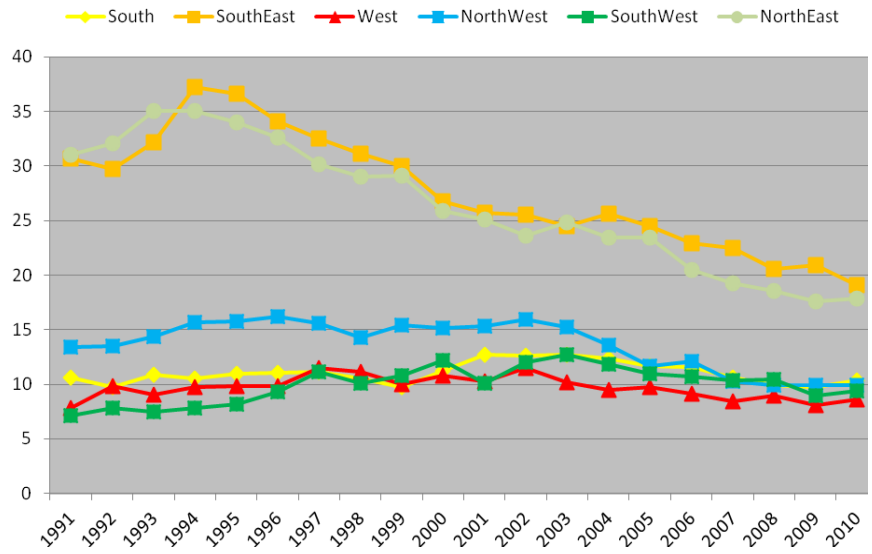


Source: GBE Health data (102)

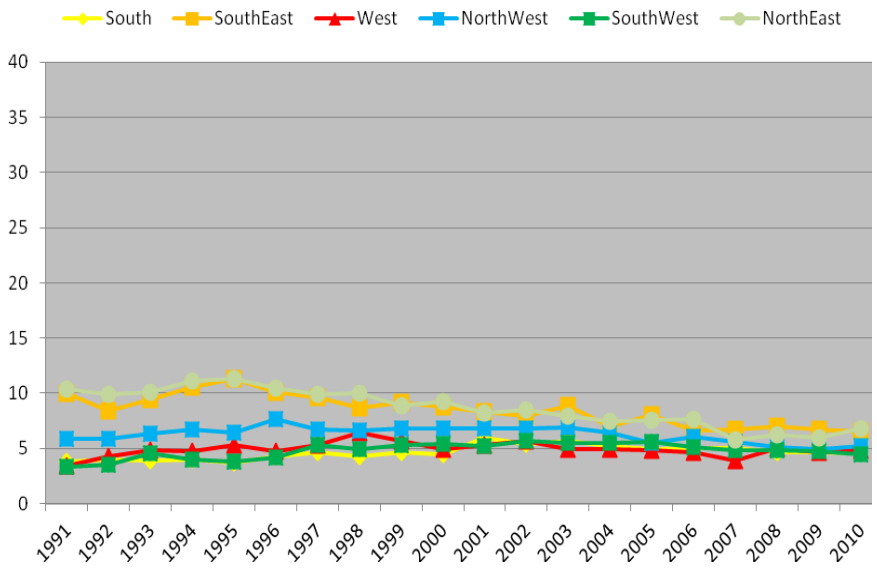
Figure 19: trends in age-standardized mortality rates from alcoholic liver cirrhosis (ICD-9 571.2, ICD-10 K70.3) by region in Germany, 1991-2010

(Deaths per 100,000 to the standard German population 1987)

Men:



Women:



Source: to calcualate age-standardized mortality rates by region for the time period 1991-2010, data on the number of deaths of alcoholic liver cirhosis and population by sex, age groups and region were obtained from GBE Health data (102).

Published studies

We have identified 6 retrospective studies conducted in different time periods and regions (Table 7). Most of these studies were carried out in the west of Germany and only one in the south. So far, no case-control or prospective cohort studies were found in Germany. Among all studies, hepatitis viral infections and chronic alcohol consumption constitute the main risk factors for liver cancer among cases diagnosed. However, both HBV and HCV infections were found in more than two-thirds of cases except data from the southern study showed the opposite where alcohol was responsible for >50% of liver cancer cases (Figure 20). Less than one quarter of cases in these studies had cryptogenic cirrhosis (neither viral nor alcohol causes).

Figure 20: the prevalence (in percentage) of the most common risk factors among cases diagnosed with liver cancer in Germany

(Data are derived from selected studies [see table 7], the numbers are referred for both sexes)

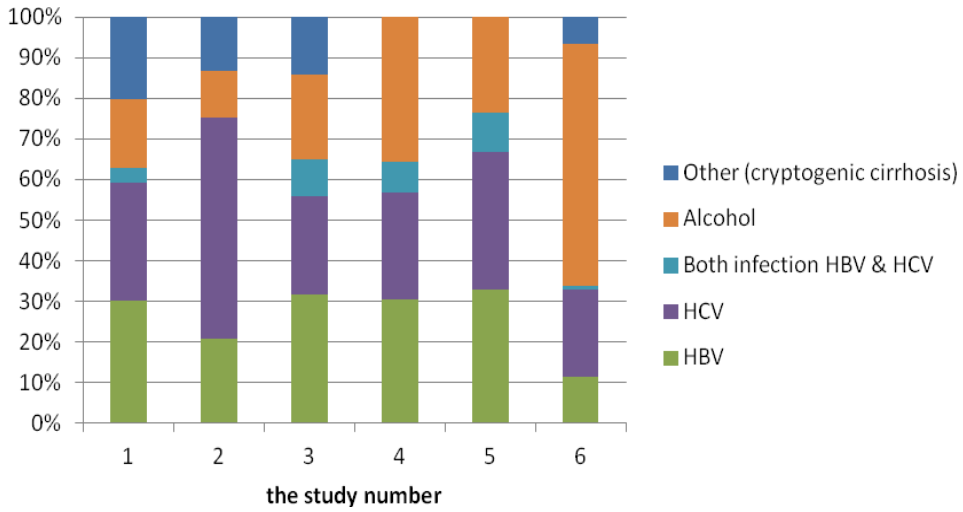


Table 7: Studies investigated the prevalence of the most common risk factors in cases diagnosed with liver cancer in Germany

No	Reference	Region	Study design	Sample size	Study period	HBV	HCV	Both infection HBV & HCV	Alcohol	Other (cryptogenic cirrhosis)	Cirrhosis
1	Goeser T, 1994 (111)	Heidelberg (west)	Retrospective (no controls)	n=81	1986-1992	26%	25%	3%	14.8%	17.3%	NA

2	Petry W, et al; 1997 (112)	Düsseldorf (West) Only Abstract	Retrospective (no controls)	n=100	----------	20%	53%	0	11%	13%	90%
3	Kubica S, et al; 2000 (113)	Hannover (north west)	Retrospective (no controls)	n=268	1993-1997	35.1%	26.9 %	10%	23.1%	15.7%	74.6%
4	Rabe C, et al; 2001 (114)	Bonn (west)	Retrospective (no controls)	n=95	1997-1999	29%	25%	7%	34%	NA	84%
5	A.Erhardt, et al; 2002 (19)	Düsseldorf (west)	Retrospective (no controls)	n=205	1988-2001	36.6%	37.6 %	10.8%	26.4%	NA	NA
6	Kirchner G, et al; 2010 (115)	Regensburg (south)	Retrospective (no controls)	n=458	1994-2008	10.9%	20.5 %	1%	57.2%	6.2%	85.2%

6. Discussion

This study presents a nationwide analysis of data on the incidence and mortality of primary liver cancer in Germany. As in other Western countries, this cancer is relatively rare in Germany. However, due to its unfavourable prognosis, it is one of the ten most common causes of death from cancer in both sexes. Our investigation revealed a steady increase in the overall age-standardized mortality rates over the last 30 years with a significant increase among men but not among women. The estimated age-standardized incidence rates have also similarly increased only in men. Regional variations in both age-standardized incidence and mortality rates have also been observed particularly among men.

Our findings confirmed other studies reported recently from the Northeast and West of Germany (21,62) that were also based on data from the respective cancer registries. Similar trends were also reported from the United States (11,54,55), Canada (12,56), Mexico (13), Australia (14,57) and some European countries (42,58,20,15,59-61,16). In fact, the increase in trend of liver cancer in Germany was less marked compared to that observed in the USA and Australia where rates have more than doubled (11,14). In most developed countries, reasons underlying these increases are not completely known. The most important risk factors in these countries are HCV and alcoholic cirrhosis, as the prevalence of HBV is very low compared to developing countries (48,116). The rising trends in liver cancer have been linked mainly to increasing prevalence of HCV infection (5,11,17), and possibly growing prevalence of diabetes and obesity (18). In Europe, differences in incidence and mortality rates have been noticed as well as different patterns in trends were reported (63). As in some high-incidence areas in Asia particularly Japan (7,8), declining trends in mortality from liver cancer have also been observed in recent years in some European countries with relatively high mortality rates such as Italy and France which have experienced increasing trends in mortality until the mid 1990s (63). It has been suggested that the different time of spread of HCV could explain the different trends observed between countries (64). HCV infection epidemia occurred in some Southern European countries in the early 1940s due to transfusion of unscreened blood, injection drug use and unsafe medical procedures during the World War II, whereas in the USA the spread of HCV occurred relatively later in the 1960s and 1970s due to opiate injection use (64). In Japan, the outbreak of HCV infection occurred much earlier (in the early 1920s) because of the parenteral antischistosoma treatment (PAT) and intravenous amphetamine used during and after the World War II in the 1940s (64,66).

Worldwide, many studies showed that age-standardized incidence and mortality rates in women expressed minimal changes or remained stable compared to men (Table 22, appendix II). Similarly, we have found no increase in the trend among women. Our study showed that men were nearly two times

more likely to develop and die from liver cancer (M: F ratio about 2:1). Similar ratios were also found in the USA, Australia and other European countries. However, higher ratios were found in areas with medium to high incidence rates for liver cancer as in south Europe (e.g France with a ratio of 5:1) and some Asian countries (e.g Indonesia with a ratio of 4.3:1) (57,117). Higher risk in men is strongly related to the higher prevalence of risk factors in men such as viral hepatitis infections, alcohol use, intravenous drug abuse, smoking and obesity than in women (117).

In Germany, reasons for the observed rising trends are as yet not clear. In Europe, it has been reported that more than 60% of liver cancer cases are mainly attributable to HBV and HCV (18% and 44%; respectively) (118), and about 30% are attributable to heavy alcohol consumption (119). Liver cirrhosis is the major risk factor for liver cancer in Germany as in many other Western countries (75-90% of cases diagnosed with liver cancer had cirrhosis) (see Table 7 above). However, the main etiology of liver cirrhosis in Germany is not entirely known. Cancer registry data do not contain information on risk factors in patients diagnosed with cancer, as these data are not routinely collected by cancer registries in Germany. Therefore, epidemiological studies that evaluate the prevalence of possible risk factors among liver cancer cases are very important source of information to determine the main etiologies of liver cancer. However, we have found very scant and heterogeneous studies that had been conducted among liver cancer patients in Germany. Nevertheless, the majority of reviewed studies reported viral hepatitis as the main etiology (HBV was found in 11-37%, HCV in 21-53%, and coinfection with both HBV/HCV 0-11% of diagnosed cases). Alcohol was also found in 11-57% of liver cancer cases and about 6-17% of cases had cryptogenic cirrhosis (neither viral nor alcohol causes) (Figure 20). However, it should be noted that this strikingly high proportion of >50 for alcohol was only reported from one study in the South of Germany while all other studies were conducted in the West. This could be related to regional differences in the levels and pattern of alcohol drinking, but also to the methods used to measure the quantity of alcohol intake in patients included in these studies. Nevertheless, it appears that both hepatitis viral causes and alcohol use are responsible for a great proportion of liver cancer cases investigated in different time periods. However, it seems that the prevalence of both HBV and HCV infections (>60%) is greater than alcohol among the studied liver cancer cases. To our knowledge, only one study had evaluated trends in risk factors among cases diagnosed with liver cancer in Germany (19). The authors suggested that HCV is the main etiology driving the rise in HCC incidence where they found that the proportion of HCV-related HCC had significantly increased during the study period from 31% in 1990-1995 to 44.6% in 1996-2001, whereas the proportion of HBV-related HCC declined and alcohol-related HCC remained unchanged.

However, historical data on hepatitis virus B and C infections are very limited in Germany due to a 2001 change in the notification system which made it difficult to compare the recent data to the earlier one to determine if there is a change in trends of both viruses (77). According to the recent RKI notification statistics (101) (Figure 17), the incidence of both acute HBV and first-diagnosed HCV infections have steadily declined since 2001 in both sexes. It has also been reported that HBV incidence has already declined since the early 1990s, possibly as a result of the implementation of HBs-Ag screening of blood products in 1970 and the introduction of HBV vaccination in the routine childhood immunization program in 1995 (110,77). For the HCV infection, increases in incidence was reported in the early 1990s , however, due to blood testing for HCV which became available in 1990 immediately after the discovery of the virus. This resulted in the detection of many chronic HCV infections in the high risk groups or individuals with suspected liver diseases (77).

In Germany, the main route of HCV transmission is intravenous drug abuse found in 45.5% of cases with chronic HCV infection particularly among men (78). A prevalence of 50-90% of HCV infection was found among injection drug users. The most commonly abused intravenous drug is heroin (120). The prevalence of injection drug users (heroin) is estimated to be ranged between 78,000 to 184,000 persons (1.4-3.4 per 1000 population) aged 15-64 years (120). The problem of opiate drug use in Germany is thought to be dated back before the 1960s. It has been reported that the number of heroin users had greatly increased during the 1970s and continued to increase until the 1990s after which a declining trend has been reported (121). One can assume that HCV spread occurred before the 1990s, but it is difficult to make such assumption due to the lack of data on HCV during that time period. However, a downward trend of HCV infection among drug users has also been reported over the recent years (110).

A substantial decline in chronic liver cirrhosis mortality has been observed in both sexes since 1980 in Germany (Figure 18) as well as in several countries worldwide (122) most possibly as a result of improved management of liver cirrhosis over the last decades. The improved survival of patients with chronic cirrhosis could increase their risk to develop liver cancer, and this could have led to a slight increase in the overall liver cancer incidence and mortality rates. However, it is believed that improvements in diagnostic techniques, coding of primary tumours, and better management of liver cirrhosis cannot explain the gender and regional differences in trends we have observed although they could have a minor influence on the overall rising trends.

Germany is among countries with high prevalence of alcohol consumption. However, alcohol intake levels have slightly declined since the early 1990s (103). In addition, it appears that mortality from

alcoholic cirrhosis is also declining, however this trend was seen in some regions while in others it has not markedly changed (Figure 19). It seems that alcohol use may not be the main contributor to the observed increase in the frequency of liver cancer.

We have found east-west and south-north decreasing gradient in incidence and mortality of liver cancer particularly among men. In men, higher increases in mortality rates were found in the Southeast and South, while lower increases were found in the Northwest. We do not have a clear explanation of the regional variability in incidence and mortality rates of liver cancer across the regions of Germany. However, these variations are more likely to be related to regional differences in the prevalence of alcohol intake and HBV/HCV infections, as well as risk factors predisposing to HBV or HCV infection such as high risk sexual behavior, intravenous drug use, or other life style related risk factors, and distribution of immigrant populations from endemic areas.

The highest incidence and mortality of liver cancer in the East and particularly in the Southeast, where the prevalence of HBV and HCV is very low (75,110), could be related to higher prevalence of alcohol drinking (123) and higher mortality from alcoholic cirrhosis (Figure 19). However, alcohol consumption cannot explain the large variations in liver cancer mortality rates seen between South and North because the level of alcohol consumption don not seem to vary greatly between the Southern and Northern part of Germany (123). In addition, the Northeast has not shown marked increases in liver cancer mortality rates compared to that observed in the Southeast which has similarly high prevalence of alcohol and low prevalence of viral hepatitis. This suggests that other factors besides alcohol and hepatitis viruses could also be associated with these observed variations and need to be explored.

Immigrants from high-prevalence areas for hepatitis viruses could also account for these observed variations. Several lines of evidence support the fact that the prevalence of viral hepatitis in Germany is higher among immigrants. One study has indicated that a great proportion of people who have chronic HBV infection in Germany had a migration background with much higher risk among immigrants from the former Soviet Union and Eastern Europe (124). Accordingly, another study has reported that although hepatitis B infection is rare among children and adolescent in Germany, children with immigrant backgrounds have a greater risk for HBV infection (125). In addition, another study has investigated the prevalence of HCV among young men offenders in the German prison (Young Offenders Institution-YOI) (126). This study has indicated that the prevalence of HCV was significantly higher among men who had immigrated from the former Soviet Union (31.1%) than among men of German origin (6.2%), and a great proportion of those tested positive for HCV in this study reported a history of

intravenous drug use (>90%). There are around 15 million people with migration background in Germany (about 19% of the total population) (104) with the great majority of Turkish and Eastern European origin. These areas are probably endemic to HBV infection. In Turkey, HBV infection is more prevalent than HCV (6-7% vs 1-<2%) (76). Most immigrants live in large cities particularly in the Western and Southern states as well as Berlin, as opposed to the Eastern states (104). Thus it is very possible that immigration contributes to the observed regional variation in the prevalence of hepatitis B and C viruses, and consequently the distribution of liver cancer incidence and mortality. Unfortunately, the cancer registry data do not permit analysis of incidence and mortality by nationality or race/ethnicity. It would be very important to address this issue in additional studies which evaluate risks of liver cancer among different ethnic groups.

7. Limitations and strengths

Our study has some limitations that should be considered when interpreting the results. First, long-term national incidence estimates could not be provided because of limited incidence data for the period before 1999. Nevertheless, the short-term incidence estimates showed also an upward trend in incidence among men which was also demonstrated from Saarland and Hamburg cancer registry data since 1980. In addition, long-term trends in incidence rates by regions could not be completely evaluated because of different years of registration of the regional cancer registries. Second, there was limited information on the prevalence and long-term trends of the most important risk factors especially hepatitis virus infections before 2000. Finally, we found very few and heterogeneous studies that assessed the potential role of the most important risk factors among liver cancer patients in Germany.

The major strengths in this study is the high quality of the cancer registry database in Germany in terms of completeness that provides more reliable national incidence estimates. In addition, this is the first study that examined the regional trends and distribution of incidence and mortality rates in Germany. Further, the long-term and detailed mortality data analysis for a cancer with very poor prognosis like liver cancer provided very important information on its burden which is very necessary for planning of effective prevention and control programs. Moreover, we made efforts to collect all available data on the major risk factors from different sources to evaluate their association to the observed liver cancer incidence and mortality rates trends and their regional variations.

8. Conclusion

Liver cancer is one of the most significant causes of death from cancer in Germany. We have found a steady increase in mortality rates from cancer of the liver and intrahepatic bile ducts over the last 30 years with more pronounced increase among men which has also been found in the incidence estimates. Regional variability has also been largely demonstrated particularly among men. East-west and south-north decreasing gradients in incidence and mortality were observed. Among men, increasing trends in mortality were seen in many regions with highest increase observed in the Southeast and South since 1980.

The reasons for these observed trends are as yet not clear. It is likely that variations in the prevalence of HCV (and probably HBV) and alcohol consumption could have a major influence. However, data on risk factors (especially HBV and HCV) and their time trends are insufficient to draw a clear conclusion. It seems that alcohol is the most possible explanation for the difference between the East and West, however, it is less likely to explain the differences between the South and North and also less likely to explain the rising trends in incidence and mortality rates because the data suggest that trends in alcohol consumption and mortality from alcohol cirrhosis have very slightly changed or declined.

Immigrants from high-prevalence areas for hepatitis viruses form a group of population at increased risk for liver cancer and may also contribute to the rising liver cancer trends observed in Germany. Despite the great achievements made by prevention programs to reduce the incidence of viral hepatitis infections that has been observed over the last few years, however these programs should also reach this group of people to prevent new infections and provide appropriate treatment to those already infected.

Recommendations:

Epidemiological studies such as case-control or prospective cohort studies are highly needed to determine the contribution of viral hepatitis, alcohol and other possible risk factors including NAFLD, obesity and diabetes mellitus, and to evaluate their role in the future trends of liver cancer in Germany.

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Appendix I

Table 8: number of cancer-related deaths and age-standardized mortality rates for selected cancers in Germany, 2009

(Deaths per 100,000 to European Standard population)

Cancer sites	ICD-10 codes	Men		women	
		Deaths	ASMR	Deaths	ASMR
Oral cavity and pharynx	C00-14	3813	7.4	1169	1.8
Oesophagus	C15	3776	6.8	1161	1.6
Stomach	C16	5783	10.0	4461	5.4
Colon and rectum	C18-21	13572	23.2	12504	14.2
Liver	C22	4738	8.1	2493	3.0
Gallbladder and extrahepatic bile ducts	C23-24	1190	2	2035	2.1
Pancreas	C25	7410	12.9	7749	9.4
Larynx	C32	1215	2.2	162	0.3
Lung	C33, C34	29158	50.6	13103	19.3
Malignant melanoma of the skin	C43	1454	2.6	1203	1.7
Breast	C50	131	0.2	17066	24.0
Cervix	C53			1581	2.6
Uterus (corpus uteri)	C54, C55			2360	2.9
Ovaries	C56			5623	7.7
Prostate	C61	12217	20.0		
Testis	C62	170	0.4		
Kidney an efferent urinary tract	C64-66, C68	4807	8.2	2908	3.5
Bladder*	C67	3587	6.0	1766	1.8
Nervous system	C70-72	3130	6.0	2609	4.1
Thyroid gland	C73	262	0.5	429	0.5
Hodgkin's lymphoma	C81	173	0.3	139	0.2
Non-Hodgkin lymphoma	C82-85	2999	5.1	2658	3.1
Plasmacytoma/multiple myeloma	C90	1809	3.0	1828	2.1
Leukaemia's	C91-95	3799	6.5	3308	4.1
All malignant neoplasms**	C00-97	116383	201.4	99155	128.6

**not include malignant neoplasms in situ and neoplasms of uncertain behaviour*
***not include non-melanoma skin cancer (C44)*
ASMR: age-standardized mortality rates

Table 9: age-specific mortality rates (5-years age group) of primary liver cancer patients (ICD-10 C22) by sex, 2009

(Deaths per 100,000)

Age group	Men	Women	Both sexes
0-5	0.0	0.1	0.0
5-10	0.0	0.1	0.0
10-15	0.0	0.0	0.0
15-20	0.1	0.1	0.1
20-25	0.1	0.0	0.0

25-30	0.4	0.2	0.3
30-35	0.1	0.2	0.2
35-40	0.3	0.2	0.3
40-45	1.0	0.4	0.7
45-50	2.4	1.2	1.8
50-55	6.8	2.1	4.5
55-60	13.6	3.8	8.7
60-65	21.0	7.7	14.2
65-70	32.2	10.9	21.1
70-75	50.2	17.2	32.4
75-80	61.4	23.2	39.5
80-85	72.0	33.1	47.0
85+	72.0	35.7	45.2

Table 10: trends in age-specific mortality rates of primary liver cancer (ICD-10 C22, ICD-9 155) by age group and sex, 1980-2009

(Deaths per 100,000)

Age-group	**Women**				**Men**			
	45-54	**55-64**	**65-74**	**75+**	**45-54**	**55-64**	**65-74**	**75+**
1980	1.7	5.7	12.8	28.2	3.6	13.0	25.6	35.2
1981	2.0	5.2	12.8	26.2	3.5	13.3	23.7	35.7
1982	2.0	6.1	11.8	24.9	3.4	13.0	26.8	33.3
1983	1.7	5.5	12.8	24.5	3.0	13.6	28.8	37.9
1984	1.9	5.4	11.8	22.3	3.1	13.1	28.0	37.0
1985	1.4	5.2	11.0	22.4	3.4	13.6	29.7	38.4
1986	1.8	5.3	11.1	22.6	3.3	14.1	29.4	36.7
1987	1.9	5.8	11.6	24.6	3.5	14.4	29.5	43.5
1988	1.9	5.3	13.1	23.8	4.2	14.5	32.3	40.7
1989	1.8	5.2	12.5	23.9	3.6	13.6	32.2	47.0
1990	1.6	4.8	12.3	23.8	4.0	14.0	31.8	47.7
1991	1.7	6.2	13.3	26.0	3.7	14.4	31.4	51.1
1992	1.8	5.8	14.5	29.7	4.2	14.2	34.7	50.7
1993	2.0	5.0	13.2	28.0	4.1	15.9	34.2	51.4
1994	1.5	4.2	14.7	28.4	4.6	14.2	34.2	53.0
1995	1.8	4.8	13.1	27.3	3.7	14.6	37.2	53.5
1996	1.4	4.3	12.6	23.5	4.4	13.2	35.2	50.2
1997	1.7	4.2	13.2	25.1	3.5	14.4	34.2	52.2
1998	1.5	4.3	13.0	28.0	4.2	15.9	35.8	58.7
1999	1.8	4.6	13.7	27.8	4.4	15.7	36.9	53.2
2000	1.6	4.2	13.4	27.0	4.2	15.4	37.8	60.0
2001	1.5	4.5	11.6	26.6	4.2	16.4	36.6	57.0
2002	1.9	5.3	12.1	26.9	4.3	16.1	38.5	55.3
2003	1.9	4.8	13.5	27.9	4.5	17.0	39.2	56.7
2004	2.0	4.5	12.5	28.7	4.7	16.3	37.7	60.1
2005	1.9	4.6	12.3	28.8	4.4	15.5	36.9	58.4
2006	2.1	5.4	12.7	29.5	4.7	15.6	40.6	63.3
2007	1.7	4.7	12.2	30.4	4.8	16.5	39.8	64.6

2008	1.7	5.4	13.7	31.9	4.0	17.5	40.0	63.2
2009	1.6	5.5	14.0	30.0	4.4	16.9	40.7	66.7

Table 11: trends in age-standardized mortality rates (and number of deaths) of all primary liver cancer (ICD-10 C22, ICD-9 155) by sex, Germany, 1980-2009

(Deaths per 100,000 to European standard population)

Year	Men (deaths)	Women (deaths)	Both sexes (deaths)
1980	5.3 (1876)	3.1 (1865)	3.9 (3741)
1981	5.2 (1845)	2.9 (1798)	3.8 (3643)
1982	5.3 (1875)	2.9 (1765)	3.8 (3640)
1983	5.7 (1981)	2.8 (1750)	3.9 (3731)
1984	5.5 (1942)	2.7 (1646)	3.7 (3588)
1985	5.7 (2047)	2.5 (1598)	3.7 (3645)
1986	5.8 (2061)	2.6 (1666)	3.9 (3727)
1987	6.1 (2232)	2.8 (1799)	4.1 (4031)
1988	6.3 (2299)	2.8 (1821)	4.2 (4120)
1989	6.4 (2365)	2.8 (1813)	4.2 (4178)
1990	6.4 (2431)	2.7 (1791)	4.1 (4222)
1991	6.5 (2526)	2.9 (1972)	4.5 (4498)
1992	6.7 (2639)	3.2 (2147)	4.6 (4786)
1993	6.9 (2766)	2.9 (2009)	4.6 (4775)
1994	6.9 (2791)	2.9 (2016)	4.5 (4807)
1995	7.1(2928)	2.8(1967)	4.5 (4895)
1996	6.7(2848)	2.6(1801)	4.3 (4649)
1997	6.8 (2925)	2.7(1903)	4.4 (4828)
1998	7.3 (3252)	2.7 (2011)	4.7 (5263)
1999	7.2 (3274)	2.9 (2089)	4.8 (5363)
2000	7.5 (3460)	2.7 (2029)	4.7 (5489)
2001	7.3 (3485)	2.6 (1961)	4.6 (5446)
2002	7.3 (3604)	2.8 (2101)	4.8 (5705)
2003	7.6 (3819)	2.9 (2197)	5.0 (6016)
2004	7.6 (3923)	2.8 (2202)	4.9 (6125
2005	7.4 (3917)	2.8 (2225)	4.8 (6142)
2006	7.9 (4329)	3.0 (2351)	5.2 (6680)
2007	8 1(4469)	2.9 (2358)	5.2 (6827)
2008	7.9 (4523)	3.1 (2539)	5.3 (7062)
2009	8.1 (4738)	3.0 (2493)	5.3 (7231)

Table 12: age-standardized mortality rates of primary liver cancer by sub-sites (ICD-10 C22.0-C22.99), Germany, 1998-2009

(Deaths per 100,000 to European standard population)

Men:

Year	HCC (C22.0)	ICC (C22.1)	Other malignant (C22.2-C22.7)	Liver unspecified (C22.9)	All liver (C22)
1998	4.1	0.5	0	2.7	7.3

1999	4.0	0.6	0.0	2.6	7.2
2000	4.4	0.8	0.0	2.3	7.5
2001	4.1	0.9	0.0	2.2	7.3
2002	4.0	1.1	0	2.2	7.3
2003	4.3	1.0	0.1	2.3	7.6
2004	4.6	1.1	0.1	1.9	7.6
2005	4.4	1.3	0.1	1.6	7.4
2006	4.6	1.6	0.1	1.7	7.9
2007	4.5	1.5	0.0	1.9	8.1
2008	4.5	1.7	0	1.7	7.9
2009	4.6	1.9	0	1.6	8.1

Women:

Year	HCC (C22.0)	ICC (C22.1)	Other malignant (C22.2-C22.7)	Liver unspecified (C22.9)	All liver (C22)
1998	1.2	0.3	0	1.2	2.7
1999	1.2	0.4	0.0	1.2	2.9
2000	1.1	0.6	0.0	1.0	2.7
2001	1.0	0.6	0	0.9	2.6
2002	1.1	0.7	0	0.9	2.8
2003	1.2	0.8	0.0	1.0	2.9
2004	1.2	0.9	0.0	0.8	2.8
2005	1.1	1.0	0	0.7	2.8
2006	1.2	1.0	0	0.7	3.0
2007	1.1	1.0	0.0	0.7	2.9
2008	1.1	1.3	0.0	0.7	3.1
2009	1.1	1.2	0.0	0.6	3.0

Table 13: number of deaths of primary liver cancer by sub-sites (ICD-10 C22.0-C22.99), Germany, 1998-2009

Men:

Year	HCC C22.0	ICC C22.1	Other malignant C22.2-C22.7	Liver unspecified C22.9	All liver C22
1998	1814	231	0	1200	3252
1999	1836	251	10	1177	3274
2000	2037	350	12	1061	3460
2001	1979	427	15	1064	3485
2002	2000	515	0	1080	3604
2003	2164	504	20	1131	3819
2004	2367	559	25	972	3923
2005	2357	686	25	849	3917
2006	2501	869	23	936	4329
2007	2527	860	21	1061	4469
2008	2574	971	0	959	4523
2009	2711	1078	0	933	4738
Total	**26867**	**7301**	**151**	**12423**	**46793**

Women

Year	HCC C22.0	ICC C22.1	Other malignant C22.2-C22.7	Liver unspecified C22.9	All liver C22
1998	843	247	0	903	2011
1999	847	303	18	921	2089
2000	813	424	15	777	2029
2001	751	458	0	738	1961
2002	832	519	0	733	2101
2003	854	561	17	765	2197
2004	884	638	8	672	2202
2005	874	738	0	603	2225
2006	940	816	0	578	2351
2007	888	820	10	640	2358
2008	936	1003	22	578	2539
2009	932	999	22	540	2493
Total	**10394**	**7526**	**112**	**8448**	**26556**

Table 14: age-standardized mortality rates of primary liver cancer by sub-sites (ICD-9, 155.0-155.2), Germany, 1980-1997

	Men			Women		
	Liver, Primary 155.0	ICC 155.1	Liver, unspecified 155.2	Liver, Primary 155.0	ICC 155.1	Liver, unspecified 155.2
1980	1.8	0	3.5	0.8	0	2.3
1981	1.8	0	3.4	0.7	0	2.1
1982	1.9	0.1	3.4	0.8	0	2
1983	2.2	0	3.4	0.8	0	2
1984	2.1	0	3.4	0.7	0	1.9
1985	2.2	0	3.5	0.7	0	1.8
1986	2	0	3.7	0.7	0	1.9
1987	2.7	0.1	3.3	1	0	1.8
1988	3.3	0	2.9	1.1	0	1.7
1989	3.2	0	3.1	1.2	0	1.6
1990	3.2	0.1	3.1	1.1	0.1	1.5
1991	3.4	0.2	3	1.3	0.2	1.5
1992	3.6	0.2	3	1.5	0.2	1.5
1993	4.1	0.3	2.5	1.5	0.2	1.2
1994	4.2	0.3	2.5	1.5	0.2	1.1
1995	4.5	0.3	2.3	1.5	0.3	1
1996	4.5	0.2	2	1.5	0.2	0.8
1997	4.3	0.2	2.2	1.6	0.2	0.9

Table 15: long-term trend in age-standardized mortality rates of primary liver cancer (ICD-10 C22, ICD-9 155) by regions of Germany, 1981-2008, Nielsen-regions

(moving 3 years average)

(Deaths per 100,000 to European standard population)
Men:

	West	South	Southwest	Northwest	Southeast	Northeast
1981	5.3	5.2	4.8	5.5	5.0	6.1
1982	5.1	5.5	5.2	5.3	4.8	6.6
1983	5.1	5.7	5.3	5.4	4.8	6.6
1984	5.3	6.0	5.3	5.1	5.0	7.0
1985	5.3	6.0	5.4	5.2	5.2	7.0
1986	5.5	6.2	5.8	5.3	5.4	7.0
1987	5.9	6.5	6.2	5.4	5.4	6.8
1988	6.0	6.7	6.5	5.5	5.6	7.0
1989	5.9	6.9	6.7	5.7	5.8	7.1
1990	5.9	6.8	7.3	5.5	5.7	7.5
1991	6.1	6.9	7.8	5.3	6.1	7.4
1992	6.3	7.2	8.0	5.1	6.1	7.8
1993	6.5	7.6	7.5	5.0	6.6	7.9
1994	6.8	7.9	7.2	5.0	6.4	8.2
1995	7.1	7.6	6.8	4.9	6.6	8.2
1996	6.9	7.6	6.8	5.2	6.3	8.0
1997	6.9	7.7	6.5	5.5	6.8	7.9
1998	7.0	8.0	6.5	5.6	7.2	7.9
1999	7.1	8.3	6.6	5.8	8.0	8.2
2000	6.7	8.3	6.7	5.7	8.3	8.5
2001	6.2	8.6	6.8	6.0	8.6	8.5
2002	6.0	8.6	7.1	6.1	8.9	8.4
2003	6.2	8.7	7.2	6.2	9.0	8.1
2004	6.3	8.6	7.4	6.2	9.2	8.0
2005	6.3	8.9	7.6	6.2	9.2	8.2
2006	6.6	9.1	7.9	6.0	9.3	8.3
2007	7.0	9.3	8.4	6.0	9.4	8.2
2008	7.2	9.3	8.4	6.1	9.2	8.0

Women:

	West	South	Southwest	Northwest	Southeast	Northeast
1981	3.2	2.4	3.0	3.0	3.0	3.4
1982	3.0	2.4	2.8	2.9	3.1	3.5
1983	2.9	2.2	2.7	2.8	3.1	3.5
1984	2.6	2.2	2.6	2.5	3.0	3.5
1985	2.5	2.2	2.6	2.5	2.9	3.5
1986	2.5	2.2	2.6	2.6	2.8	3.7
1987	2.6	2.2	2.8	2.6	3.0	4.0
1988	2.6	2.2	2.9	2.7	3.2	4.0
1989	2.5	2.1	3.0	2.6	3.4	3.9

1990	2.6	2.2	3.3	2.5	3.5	3.8
1991	2.7	2.3	3.6	2.4	3.7	4.2
1992	2.8	2.3	3.7	2.4	3.7	4.4
1993	2.9	2.3	3.5	2.3	3.5	4.3
1994	2.9	2.3	3.1	2.3	3.4	4.1
1995	2.9	2.2	2.8	2.3	3.3	3.7
1996	2.9	2.2	2.7	2.2	3.2	3.7
1997	2.9	2.2	2.8	2.3	3.1	3.3
1998	3.1	2.4	2.7	2.4	3.1	3.3
1999	3.0	2.5	2.6	2.6	3.1	3.3
2000	2.8	2.5	2.6	2.5	3.0	3.3
2001	2.6	2.7	2.7	2.5	3.0	3.2
2002	2.5	2.9	2.8	2.6	3.0	3.0
2003	2.6	3.0	2.8	2.6	3.2	3.2
2004	2.6	2.9	2.9	2.6	3.2	3.2
2005	2.7	2.9	3.0	2.5	3.2	3.3
2006	3.0	2.9	3.0	2.4	3.1	3.1
2007	3.2	3.0	3.1	2.5	3.2	3.0
2008	3.2	3.1	3.0	2.6	3.2	2.9

Table 16: most frequently diagnosed cancers in Germany, 2008

(Cases per 100,000 to European standard population)

Source: Cancer in Germany 2007/2008 (22)

	ICD-10 codes	Men		women	
		new cases	ASIR	new cases	ASIR
Oral cavity and pharynx	C00-14	9520	19.1	3490	5.9
Oesophagus	C15	4800	9.0	1380	2.1
Stomach	C16	9210	16.8	6660	8.6
Colon and rectum	C18-21	35350	63.0	30040	39.4
Liver	C22	5270	9.4	2345	3.2
Gallbladder and extrahepatic bile ducts	C23-24	2270	4.0	2890	3.6
Pancreas	C25	7390	13.4	7570	9.8
Larynx	C32	3610	6.9	510	0.9
Lung	C33, C34	33960	60.6	15570	24.3
Malignant melanoma of the skin	C43	8910	17.1	8890	16.6
Breast	C50	520	1.0	71660	123.1
Cervix	C53			4880	9.5
Uterus (corpus uteri)	C54, C55			11280	17.2
Ovaries	C56			7790	12.2
Prostate	C61	63440	110.9		
Testis	C62	3970	9.5		
Kidney an efferent urinary tract	C64-66, C68	8960	16.5	5540	8.2
Bladder*	C67	11460	20.1	4510	5.6
Nervous system	C70-72	3810	7.7	2990	5.3
Thyroid gland	C73	1710	3.5	4160	8.6
Hodgkin's lymphoma	C81	1160	2.7	920	2.0
Non-Hodgkin lymphoma	C82-85	7270	13.7	6430	9.8

Plasmacytoma/multiple myeloma	C90	2980	5.3	2650	3.6
Leukaemia's	C91-95	6340	12.4	5080	7.9
All malignant neoplasms**	C00-97, excl. C44	**246700**	**450.0**	**223100**	**349.9**

**not include carcinoma in situ and neoplasms of uncertain behaviour*
***not include non-melanoma skin cancer (C44)*
ASIR: age-standardized incidence rate

Table 17 : age-specific incidence rates (5-years age group) of primary liver cancer patients (ICD-10 C22) by sex, 2008

(Cases per 100,000)

Age-group	Men	Women	Both sexes
0-5	0.7	0.6	0.6
5-10	0.1	0.0	0.0
10-15	0.2	0.2	0.2
15-20	0.1	0.2	0.2
20-25	0.2	0.2	0.2
25-30	0.1	0.2	0.1
30-35	0.3	0.2	0.3
35-40	0.5	0.2	0.3
40-45	1.5	1.2	1.4
45-50	2.0	1.5	1.8
50-55	6.9	2.9	4.9
55-60	20.0	6.8	13.3
60-65	28.3	9.1	18.5
65-70	40.4	9.6	24.4
70-75	56.9	17.4	35.5
75-80	68.1	18.6	39.5
80-85	67.1	29.1	42.1
85+	51.9	25.1	32.1

Table 18: trends in age-specific incidence rates of primary liver cancer (ICD-10 C22) by age group and sex, 1999-2009

(Cases per 100,000)

	Women				Men			
Age-group	**45-54**	**55-64**	**65-74**	**75+**	**45-54**	**55-64**	**65-74**	**75+**
1999	2.1	4.2	17.5	22.9	6.8	19.4	40.8	61.1
2000	2.7	3.7	15.0	22.7	8.1	19.7	49.2	56.7
2001	2.4	5.4	12.7	24.1	6.4	21.7	46.0	56.8
2002	2.0	5.1	12.9	20.5	6.4	20.4	42.9	61.0
2003	2.1	4.2	12.8	28.1	6.9	21.7	47.2	66.1
2004	2.4	4.9	11.8	27.4	7.4	26.1	51.3	55.8
2005	3.0	4.3	11.8	23.9	5.7	20.3	42.9	58.5
2006	1.8	6.3	11.2	25.8	6.9	20.7	51.5	63.3
2007	2.9	5.6	12.8	22.0	6.8	24.2	46.6	58.1
2008	2.2	7.8	13.2	23.9	4.3	23.7	47.7	63.8

Table 19: trends in age-standardized incidence rates (and number of new cases) of all primary liver cancer (ICD-10 C22) by sex, Germany, 1999-2009

(cases per 100,000 to European standard population)

	Men (new cases)	Women (new cases)	Both sexes (new cases)
1999	8.7 (3906)	2.9 (2051)	5.4 (5958)
2000	9.3 (4266)	2.9 (1989)	5.7 (6254)
2001	9.0 (4289)	2.8 (2010)	5.6 (6299)
2002	8.9 (4299)	2.7 (1875)	5.4 (6174)
2003	9.6 (4792)	3.0 (2203)	6.0 (6995)
2004	9.9 (5071)	2.9 (2175)	6.1 (7246)
2005	8.6 (4516)	2.9 (2075)	5.4 (6591)
2006	9.6 (5221)	3.0 (2192)	6.0 (7413)
2007	9.5 (5166)	2.9 (2126)	5.9 (7292)
2008	9.4 (5270)	3.2 (2345)	6.0 (7615)

Table 20: long-term trends in age-standardized incidence rates for primary liver cancer (ICD-10 C22) by sex, Germany, 1980-2008

(Cases per 100,000 to European standard population)

	Men			Women		
Year	**SL ASIR**	**HH ASIR**	**Germany ASIR**	**SL ASIR**	**HH ASIR**	**Germany ASIR**
1980	2.2			2.5		
1981	5.7			2.5		
1982	5.3			1.6		
1983	4.9			2.7		
1984	7.7			2.6		
1985	6.2	5.0		2.2	1.7	
1986	7.2	9.8		1.6	3.0	
1987	4.6	6.9		2.4	3.9	
1988	6.2	8.5		2.0	3.0	
1989	5.5	7.0		2.8	3.9	
1990	6.9	6.4		2.7	3.5	
1991	6.2	9.2		2.1	3.1	
1992	6.7	7.3		2.5	3.5	
1993	7.3	10.0		3.1	4.1	
1994	6.7	8.9		2.8	4.4	
1995	8.1	8.2		2.7	3.3	
1996	7.1	9.0		3.1	3.8	
1997	7.3	8.9		2.6	3.4	
1998	9.4	7.7		1.8	4.1	
1999	8.3	8.4	8.7	3.5	2.9	2.9
2000	9.9	6.6	9.3	3.2	3.6	2.9
2001	11.7	6.7	9.0	3.4	2.6	2.8
2002	11.0	8.4	8.9	3.6	3.1	2.7

2003	9.8	8.0	9.6	4.1	3.0	3.0
2004	13.0	7.3	9.9	3.6	2.7	2.9
2005	8.7	11.3	8.6	3.6	5.1	2.9
2006	12.3	7.6	9.6	3.6	2.9	3.0
2007	10.4	8.6	9.5	4.7	3.6	2.9
2008	12.2	9.2	9.4	3.5	3.8	3.2

ASIR: age-standardized incidence rate, SL: Saarland cancer registry, HH: Hamburg cancer registry, Germany: the overall incidence estimate for Germany

Table 21: age-standardized incidence and mortality rates of liver cancer (ICD-10 C22) in Germany in 2008 compared internationally

(Cases/deaths per 100,000 to World Standard population)

	Males		Females	
Country	**ASIR**	**ASMR**	**ASIR**	**ASMR**
Mongolia	116.6	99.9	74.8	62.5
The Gambia	53.9	54	19.5	20.5
China	37.4	34.1	13.7	13.1
Japan	17.6	14.5	5.8	4.7
Egypt	14.6	14.4	4.2	4.2
Italy	13.4	10.4	4.4	3.5
Greece	13.2	8.6	4.3	3.3
France (Metropolitan)	10.5	10	2.2	2.3
Spain	9.6	7.4	2.5	2.3
Austria	7.9	7	2.7	2.2
USA (SEER)	7.9	5.5	2.6	1.9
Switzerland	7.8	6.1	2.3	1.9
Czech Republic	6.4	5.9	2.5	2.4
Germany	6.2	5.2	2.2	2.0
Canada	5.3	4.2	1.6	1.7
Finland	5.1	4.3	2.3	1.9
Australia	5	3.8	2	1.6
Denmark	4.6	3.6	1.5	1.7
Russian Federation	4.4	5.6	1.9	2.3
United Kingdom	4.2	3.6	1.9	1.7
Belgium	3.8	4.3	1.4	1.9
Turkey	3.6	3.5	1.5	1.5
Sweden	3.4	3.7	1.9	1.8
Poland	3.2	3.6	1.9	1.8
Norway	2.6	2	1.2	1.3
The Netherlands	2.4	2.6	0.8	1.3

Data sources: GLOBOCAN 2008, NORDCAN 2008, the USA SEER data 2008, and the ZfKD 2008 estimates for Germany.

Appendix II

Table 22: trends of liver cancer incidence and mortality world-wide

(studies reported from population-based cancer registries)

(rates per 100,000)

Study	Country	Study period	Incidence rates (IR)		Mortality rates (MR)	
			M	F	M	F
(61)	Italy	1988-1992 to 1998-2002 (HCC and unspecified)	17.8→19.3	4.9→5.6		
(59)	France	1980-2000*	4.4→11	0.8→1.5		
(16)	Switzerland	1975-1994*			3.9→5.2	1.2→1.1
(60)	UK	1968-1996*			2.56→3.7	1.29→1.9
(15)	UK	1971-1973 and 1999-2001**	3.9→6.1	3.1→3.9		
(57)	Australia	1972-2005*	2.0→8.3	0.5→3.3	2.1→5.9	0.5→2.2
(14)	Australia	1977-1982 to 2003-2007*	2.9→7.12	1.0→2.3	2.5→5.3	0.8→1.7
(56)	Canada	1984-2000 (HCC-IR)	3.98→5.5	1.6→2.2		
		1984-2001 (HCC-MR)			4.1→5.8	1.8→2.5
(12)	Canada	1976-1980 to 1996-2000 (HCC)	3.1→6.0	1.4→2.0		
(55)	USA	1976-1980 to 1996-2000*	2.4→4.7 (Both sexes)			
(54)	USA	1998-2003 (HCC)	5.0→6.2	1.3→1.7		
(11)	USA	1975-2005 (HCC-IR)	2.6→7.9			
		1980-2005 (HCC-IR)		0.8→2.3		
		1992-2005 (HCC-MR)			3.3→4.0 (both sexes)	
(13)	Mexico	2000-2006 (HCC)			4.5→5.1	3.8→4.4
(8)	Japan	1981-2003 (HCC)	29.2→24.0	6.6→7.3		
		1990-2003 (HCV-HCC)***	218→92	47→34		

*all primary liver cancers

**including liver, gallbladder and biliary tract C22-C24

*** only among patients aged 60-69 years old

Appendix III

Risk factors data:

Table 23: trends in age-standardized mortality rates from liver cirrhosis and alcoholic liver cirrhosis by sex in Germany, 1980-2010

(Deaths per 100,000 to the standard German population 1987)

	Men		Women	
	Liver cirrhosis	Alcoholic liver Cirrhosis	Liver cirrhosis	Alcoholic liver Cirrhosis
1980	35.9	7.9	16.5	2.5
1981	35.9	9.1	16.8	2.6
1982	33.2	8.3	16	2.7
1983	32.9	8.5	15.8	2.7
1984	30.6	8.4	15.1	2.8
1985	30.4	8.6	15.3	2.9
1986	29.1	8.5	14.3	2.8
1987	28.7	9.2	14.8	3.2
1988	29.2	10	15	3.4
1989	29.6	10.3	15.5	3.8
1990	29.7	11.6	15.6	4.3
1991	32.2	14.4	16.4	5.4
1992	31.5	14.7	16	5.5
1993	31.5	15.5	16.2	5.9
1994	31	16.3	16.1	6.1
1995	30.2	16.3	15.5	6.2
1996	29.4	16.2	15	6.2
1997	28.1	16.2	14.5	6.4
1998	26.1	15.4	13.4	6.4
1999	25.1	15.1	13.4	6.2
2000	25.4	15.1	12.9	6.1
2001	24.4	15.0	12.8	6.3
2002	24.6	15.4	12.6	6.3
2003	24.2	15.1	12.2	6.2
2004	22.5	14.4	11.3	5.8
2005	21.7	13.8	11	5.7
2006	20.3	13.1	10.8	5.6
2007	19.2	12.2	9.9	5.1
2008	18.7	11.8	10.2	5.2
2009	18.2	11.3	9.8	5.0
2010	17.9	11.5	9.9	5.1

Source: GBE health data (102)

Table 24: trends in age-standardized mortality rates from alcoholic liver cirrhosis in Germany by region 1980-2010

(Deaths per 100,000 to the standard German population 1987)

Men:

	South	Southeast	West	Northwest	Southwest	Northeast
1980	7.7	-	5.8	9.3	3.9	-
1981	8.4	-	6.0	10.3	6.4	-
1982	8.3	-	5.2	9.1	5.8	-
1983	8.2	-	5.8	9.9	6.7	-
1984	8.6	-	5.3	9.9	5.6	-
1985	9.3	-	5.8	8.3	6.3	-
1986	8.5	-	5.0	8.0	6.1	-
1987	8.7	-	6.6	9.3	6.9	-
1988	8.1	-	7.3	9.7	7.5	-
1989	9.2	-	6.3	10.0	8.0	-
1990	9.8	-	6.7	12.0	7.7	-
1991	10.6	30.7	7.8	13.4	7.1	31.0
1992	9.7	29.7	9.8	13.5	7.8	32.1
1993	10.8	32.2	9.0	14.4	7.5	35.0
1994	10.5	37.2	9.8	15.7	7.8	35.0
1995	10.9	36.6	9.8	15.8	8.2	34.0
1996	11.1	34.1	9.9	16.2	9.3	32.6
1997	11.1	32.5	11.4	15.6	11.1	30.1
1998	10.5	31.1	11.1	14.3	10.1	29.0
1999	9.8	30.0	10.0	15.4	10.8	29.1
2000	11.3	26.7	10.8	15.2	12.2	25.9
2001	12.7	25.8	10.3	15.3	10.1	25.1
2002	12.6	25.5	11.5	15.9	12.0	23.7
2003	12.7	24.5	10.2	15.2	12.7	24.9
2004	12.3	25.6	9.5	13.6	11.8	23.5
2005	11.7	24.5	9.7	11.7	11.0	23.5
2006	11.6	22.9	9.2	12.1	10.7	20.5
2007	10.6	22.5	8.4	10.2	10.4	19.3
2008	9.9	20.6	8.9	9.9	10.5	18.5
2009	9.7	20.9	8.1	9.9	9.0	17.6
2010	10.3	19.1	8.6	9.9	9.4	17.9

Women:

	South	Southeast	West	Northwest	Southwest	Northeast
1980	2.2	-	1.9	3.4	1.4	-
1981	2.4	-	2.2	3.2	2.2	-
1982	2.4	-	2.2	3.2	2.5	-
1983	2.3	-	2.5	3.2	2.2	-
1984	2.4	-	2.0	3.6	1.9	-

1985	2.7	-	2.2	3.1	2.1	-
1986	2.5	-	1.9	3.3	2.1	-
1987	2.7	-	2.6	4.1	2.4	-
1988	2.8	-	2.5	3.9	2.7	-
1989	3.3	-	2.8	4.2	3.0	-
1990	3.2	-	2.9	5.2	3.8	-
1991	3.8	10.0	3.4	5.9	3.3	10.4
1992	4.0	8.4	4.3	5.9	3.5	9.9
1993	3.9	9.4	4.8	6.3	4.6	10.1
1994	4.0	10.5	4.7	6.7	4.0	11.1
1995	3.7	11.3	5.3	6.4	3.8	11.3
1996	4.2	10.1	4.7	7.7	4.2	10.5
1997	4.7	9.6	5.3	6.7	5.3	9.9
1998	4.2	8.7	6.5	6.6	4.9	10.0
1999	4.6	9.1	5.7	6.9	5.3	8.8
2000	4.4	8.8	5.0	6.8	5.4	9.2
2001	5.9	8.3	5.3	6.8	5.2	8.2
2002	5.4	8.0	5.7	6.8	5.7	8.5
2003	5.6	8.9	4.9	6.9	5.5	7.9
2004	5.2	7.0	4.9	6.5	5.5	7.5
2005	5.0	8.0	4.9	5.5	5.6	7.6
2006	5.0	6.6	4.6	6.0	5.1	7.6
2007	5.0	6.7	3.9	5.6	4.9	5.8
2008	4.7	7.0	5.0	5.2	4.9	6.2
2009	4.6	6.7	4.6	4.9	4.7	6.0
2010	4.5	6.5	4.8	5.2	4.5	6.8

Source: GBE health data (102)

Table 25: incidence of hepatitis B and C virus, Germany, 2001-2010

(Cases per 100,000)

	Hepatitis B			**Hepatitis C**		
Year	**Men**	**Women**	**Both sexes**	**Men**	**Women**	**Both sexes**
2001	3.8	2.0	2.8	13.7	7.5	10.5
2002	2.4	1.1	1.7	10.2	5.8	8.0
2003	2.3	1.0	1.6	10.2	6.6	8.4
2004	2.1	1.0	1.5	13.5	8.5	11.0
2005	2.1	1.0	1.5	12.4	7.8	10.0
2006	2.0	0.9	1.4	11.3	7.0	9.1
2007	1.7	0.7	1.2	10.2	6.4	8.4

2008	1.4	0.6	1.0	9.5	5.7	7.6
2009	1.2	0.6	0.9	8.3	5.1	6.7
2010	1.3	0.6	0.9	8.1	4.8	6.5

Source: RKI notification data (101)