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HEPATOCELLULAR CARCINOMA AMONG KENTENCKY RESIDENTS FROM 1995 TO 2011: RISK FACTORS FOR LATE-STAGE DIAGNOSIS AND SURVIVABILITY

Zilahatou B. Tohon
University of Kentucky, z.tohon@uky.edu

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Zilahatou B. Tohon, Student

Dr. Wayne Sanderson, Committee Chair

Dr. Erin Abner, Director of Graduate Studies

ABSTRACT OF CAPSTONE

Student Name

Zilahatou Amadou B Tohon

The College of Public Health

University of Kentucky
2017

HEPATOCELLULAR CARCINOMA AMONG KENTENCKY RESIDENTS FROM 1995 TO 2011: RISK FACTORS FOR LATE-STAGE DIAGNOSIS AND SURVIVABILITY

ABSTRACT OF CAPSTONE

A Capstone project submitted in partial fulfillment of the requirements for the degree of Doctor of Public Health in the College of Public Health
at the University of Kentucky
By:

Zilahatou Bohari Tohon

Lexington, Kentucky

Director: (Dr. Wayne Sanderson)
Lexington, Kentucky

Co-Director: (Enter Professors Name)
Lexington, Kentucky

ABSTRACT OF CAPSTONE

HEPATOCELLULAR CARCINOMA AMONG KENTENCKY RESIDENTS FROM 1995 TO 2011: RISK FACTORS AND SURVIVABILITY

Introduction: Hepatocellular carcinoma incidence and mortality rates are the rise in the United States and in Kentucky as well. According to the National Cancer Institute, there will be an estimated 40,710 new cases of liver and intrahepatic bile duct cancer and 28,920 deaths in 2017, with than 20% of 5-years survivors [1]. The numbers of new cases expected by year 2030 is 37,574 [2]. The aim of this capstone is to assess the risk factors of late-stage diagnosis and survivability in Kentucky.

Methods: A combined dataset from the Kentucky Cancer Registry and the Behavioral Risk Factor Surveillance System was used to perform a descriptive statistics, a logistic regression and a Cox proportional-hazards regression.

Results: Of the 2,205 cases analyzed, 72.1% were males, 90.2% of white/other ethnicity, 41.1% were married and lived mostly in urban (59.5%0 and non-Appalachian region (72.1%). Their mean age at diagnosis was 64.1 years and most were diagnosed between 2005 and 2009 (81.5%) with late-stage (41.9%) and did not receive any treatment (55.3%). Our results show that black race (OR=1.5; 95% CI 1 – 2.1), gender*age interaction (male ≥ 50 years

(OR=1.3; 95% CI 1.2 – 3)), uninsured status (OR=1.6; 95% CI: 1.1 – 2.5), date of diagnosis before 2000 (O%=1.8; 95%CI: 1.3 – 2.5) and residence in counties with higher levels of binge drinking proportion (OR=1.03 (1 – 1.1) increased the risk of HCC late-stage diagnosis in this Kentucky report. Appalachia residence and single status were not associated with late-stage.

HCC mean survival time in this series was 12.4 months. The mean overall survival rates for the study period were 12.9%, 24.1% and 17.2% in men, pre- and postmenopausal women, respectively. Mean specific survival rates were 34.3%, 34.5% and 37.1% in men, pre-and postmenopausal women, respectively. Early-stage at diagnosis, treatment and younger age were associated with better overall survival. Men and postmenopausal women had 40% increased risk of all-cause mortality (p=0.06). Cause-specific survival was improved by non-smoking status, recent year of diagnosis, early stage at diagnosis and treatment. Postmenopausal women had an increased risk for both all cause (OR=2.2; 95%CI: 0.9 – 5.7) and liver cancer specific mortality (OR=1.7; 95%CI: 0.4 – 3.7), compared to premenopausal women, when parity is added to the covariates.

Conclusions: HCC Late-stage diagnosis was impacted by race, age, gender, insurance status and county-level binge drinking while non-smoking status, female gender, early stage and treatment improved survival. These results highlight the need to increase healthcare access and HCC awareness in this rural state where poverty is high and education levels are lower than average to decrease the burden of HCC and improve survival.

KEYWORDS: hepatocellular carcinoma; late-stage of diagnosis; risk factors; survival; menopausal status; gender difference; Kentucky.

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By

Zilahatou Bohari Tohon

2017

_____

Wayne T. Sanderson, PhD

(Date)_____

_____

Erin L. Abner, PhD

(Date)_____

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Zilahatou Bohari Tohon

College of Public Health

University of Kentucky

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I would like to extend my thanks to my committee members, Dr. Steven Browning and Dr. Bin Huang for their help on this capstone project. My heartfelt thanks go to my committee chair, Dr. Wayne Sanderson, for all the help and encouragement throughout all the process as well as the readiness to provide the help and guidance I needed.

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I. CHAPTER 1: INTRODUCTION

Background of the project

Hepatocellular carcinoma (HCC) is the most common primary liver cancer. Incidence and mortality rates vary according to sex and geographic areas. Worldwide, liver cancer is the fifth and seventh most common cancer in men and women respectively, while being the second and sixth leading cause of cancer death in men and women respectively[3].

Although HCC incidences and mortality rates are highest in the East and South-East Asia and in Middle and Western Africa, rates are consistently increasing in the developed countries of Europe and North America as well, raising a concern about the public health consequences of the increase[4,5]. The National Cancer Institute (NCI) estimated 35,646 new cases and 24,550 deaths from liver and intrahepatic bile duct cancer in the United States for the year 2015, and a 5-year survival rate of 17.2% for the period 2005-2011[6]. In Kentucky, both incidence and mortality rates of the cancer of the liver and bile duct significantly rose between 2008 and 2012 with an annual percentage change (APC) of 5.0% and 1.9%, respectively [7,8].

In the United States, HCC incidence rates have been steadily increasing. They tripled between 1975 and 2005 (from 1.6 per 100,000 to 4.9 per 100,000) with most of the increase occurring after 1980 and men having a steady 3-fold higher incidence compared to women[9]. Between 1992 and 2005, the increase was mostly seen in middle-aged black, Hispanic, and white males[9]. More recently, an increase of 18.5%

was observed with an APC of 3.5%, even with the histologic confirmation of HCC which likely eliminates cases counted by previous reports. The racial and age disparity is still present with larger increases in whites, black and persons aged 50-59 years with an APC of 3.8%, 4.8% and 9.1% respectively[10].

Several risk factors have been identified for HCC. Besides male gender and geographic provenance, other known risk factors are chronic hepatitis B (HBV) and hepatitis C (HCV) viral infections, alcohol consumption, tobacco smoking obesity/diabetes, and aflatoxin exposure[9,11–14].

HCC mortality rates have been increasing as well. From 1992 to 2005, HCC overall mortality rates increased with an APC of 1.6%[10]. A Surveillance, Epidemiology, and End Results (SEER) investigation found an increase in mortality rates between 1992 and 2005 rising significantly from 3.1 per 100,000 to 5.1 per 100,000 with an APC of 4.3%[9]. Between 1969 and 2011, the increase was almost twofold for males and 50% for females with all ethnic minority groups having higher rates than whites[15].

Survival rates are usually low and can be influenced by several factors. A New York City study investigating the overall survival (OS) of Hispanic patients compared to other ethnic groups found that Hispanics had an OS of 16.3 months, not significantly different from the 14 months for non-Hispanic whites and 17.3 months for non-Hispanic blacks[16]. Although the survival improves with early stage at diagnosis, Hispanic patients did not have worse survival compared to the other ethnic groups. A survival analysis of SEER data between 1973 and 2010 found that women have a better OS than men, even though the OS was still low (11 months and 10 months). Interaction between sex

and ethnicity had been investigated and women aged less than 55 years had better survival than men across all ethnic groups but Hispanic[17].

Purpose of the study

This study used secondary surveillance data routinely collected by the Kentucky Cancer Registry (KCR) and Behavioral Risk Factor Surveillance System (BRFSS) county-level data. This capstone project analyzed these data and provided the material for two papers to be submitted for publication in peer-reviewed journals. The objective of the first paper (chapter 3) was to describe risk factors of late stage HCC in Kentucky. The objective of the second paper (chapter 4) was to identify the factors associated with better long-term survival among HCC cases. The results derived from this research may be used to issue recommendations to improve the management of HCC and lessen its burden in Kentucky.

Statement of the problem

The global burden of HCC is increasing in the United States. The last four decades have seen an increase in both the incidence and mortality of HCC in the nation. An analysis of the SEER national database found a 70% increase in the incidence rate rising from 1.4 per 100,000 for the period 1976-1980 to 2.4 per 100,000 for the period 1991-1995 with a more pronounced increase among black males compared to white men[18].

The mortality rates followed a similar trend with a 41% increase from 1981 to 1995[18]. Over the last four decades, mortality rates from HCC doubled for the total population and males, while they increased by 50% for females. From 1969 to 2009,

there was a disparity by unemployment with increased mortality associated with higher unemployment levels[15]. The same disparity according to unemployment was present after adjusting for age, race and sex.

The overall 1-year cause-specific survival rates almost doubled between 1992 and 2004, explained by an increase in the number of patients diagnosed with early-stage HCC which has an improved prognosis compared to late-stage HCC. American Indians/Alaska Natives were the only racial and ethnic group who did not experience this increase in survival rates[9]. Overall median survival increased significantly from the 1970s to 2000s rising from 2 months to 8 months[19].

The prognosis of HCC depends on the etiologic factor, the genotype of HBV (if this infection is present), as well as other underlying factors. More fully understanding the risk factors for HCC and the factors determining better survival will improve the management and treatment of HCC patients and may lead to interventions to reduce its incidence and mortality and increase long-term survival and quality of life.

Overview of project processes

The data provided by the KRC is collected through the Cancer Patient Data Management System which is a reporting system from all acute care hospitals, outpatient facilities and health care facilities including treatment centers, private laboratories and physician offices in the state of Kentucky. Since 2000, the KRC is also part of the national SEER program, considered as the most accurate and complete cancer registry in the U.S. County-level population data was retrieved from the Census website and behavioral data was procured from the Kentucky BFRSS data. SAS 9.4® and IBM SPSS 22® statistical softwares were used for all the analyses. Descriptive

statistics and regression modeling were used to describe the factors associated with HCC occurrence and those which influence survival.

Scope and importance of the study

The knowledge of racial, socio-cultural, economic and lifestyle factors is necessary to assess the occurrence and prognosis of HCC. Most studies on the risk factors of HCC do not look specifically at the risk of later diagnosis nor at the geographical difference. The present capstone will increase existing knowledge about associations between various factors and risk of late-stage HCC in the Kentucky population. It will also identify the factors associated with better survival, with a particular emphasis on gender difference as well as menopausal status in female cancer patients.

II. CHAPTER 2: LITERATURE REVIEW

Several risk factors for the occurrence of HCC have been identified, from viral infections to environmental factors and lifestyle behaviors. El-Serag found a high ecologic correlation between HCC and HBV chronic infection[20]. Chronic HBV infection is the dominant risk factor of HCC in Africa and Asia, with the exception of Japan where HCV chronic infection is the most frequent risk factor. Several factors have been associated with an increased risk of HCC among HBV carriers: male sex, older age, Asian or African ancestry, family history of HCC, higher levels of HBV replication HBV genotype, longer duration of infection, co-infection with HCV, human immunodeficiency virus [HIV], or hepatitis D virus, cirrhosis, exposure to aflatoxin, and heavy intake of alcohol or tobacco[20],[21]. HCV infection is also associated with an increased risk of HCC. Risk factors among HCV carriers include any level of HCV viremia, genotype 1b, male sex, alcohol[22,23]. Although the mechanism is unknown, coffee consumption seems to have a protective effect against HCC in HCV carriers[20],[24]. HBV and HCV are likely to remain the main risk factors for HCC. It is thus important to maintain surveillance as to identify the high risk groups and target early detection and treatment.

Role of HBV genomics in the risk of HCC

Because HBV is a major risk for HCC and it is a major public health problem, it is important to investigate how HBV genotypes and its genomic variations and mutations influence HCC carcinogenesis. Different HBV genotypes and sub-genotypes have been studied to identify their association with the occurrence of HCC. The genotypes associated with an increased risk of HCC are C2, F I $_a$ and J. Genomic mutations such as PreS deletions, and precore mutations, particularly those in C1653T, T1753V, and

A1762T/G1764A increase HCC risk [25]. It is thus important to integrate the surveillance of HBV mutations as well as genetic susceptibility in the classification of HBV patients in order to determine those at higher HCC risk to provide antiviral treatment.

An updated meta-analysis of 85 case-control studies involved 16,745 HBV-infected patients, of whom 5781 had HCC. Precore mutation G1896A, G1899A and Pre-S mutation especially Pre-S1 and Pre-S2 deletion were correlated to an increased risk of HCC. Similar correlation existed between basal core promoter (BCP) double mutation A1762T/G1764A, T1753V, C1653T and HCC. Patients of Asian ethnicity, genotype C or HBeAg positive were possibly more susceptible to HCC. Besides, the mutations like G1896A and BCP double mutation may be associated with the progression of liver diseases[26].

Hwai-I Yang et al. aimed to examine the prevalence of HBV genotype and precore and BCP mutants and their association with HCC risk after adjusting for well-known host and viral risk factors[27]. This study took place in Taiwan in the framework of the REVEAL-HBV cohort study, a community-based prospective cohort study which investigated the association between viral factors and the risk of liver diseases. From the cohort of 23,820 residents of seven towns free of HCC, 1,526 were tested for precore1896 and BCP 1762/1764 mutations after excluding participants with negative Hepatitis B surface antigen (HBsAg), antibodies against HCV infection, unknown anti-HCV antibody status, undetectable baseline serum HBV DNA levels, or inadequate blood sample for HBV genotyping and those with less than 10,000 copies or more of HBV DNA per milliliter. The Cox regression model allowed identifying HBV genotype C and specific alleles of BCP and precore mutants as risk factors of HCC [27]. The

prevalence of HCV genotype was constant in all age groups while the precore G1869A and the BCP A1762T/G1764A double mutation increased with age. Participants with genotype B had higher prevalence of the precore mutation while those with genotype C had higher prevalence of BCP mutation and higher viral load. HCC incidence rates per 100,000 person-years were 305.6 and 785.8 for genotypes B and C, respectively. Incidence rates were higher with the precore wild-type G1896 variant and the BCP A1762T/G1764A double mutant. Genotype C was associated with a 2.35 times increased risk of HCC while adjusting for sex, age, cigarette smoking, alcohol drinking, serum ALT level, cirrhosis at study entry, HBV DNA level, and HBV genotype. The risk was 1.76 times higher for genotype C after adjusting for sex, age, cigarette smoking, alcohol drinking, serum ALT level, cirrhosis at study entry, HBV DNA level, HBV genotype, and precore and BCP mutants. Genotype B and wild type for the precore 1896 and BCP 1762/1764 variants were associated with a decreased risk of HCC.

In another cohort study, chronic HBV patients in Hong Kong were prospectively followed to determine the independent risk factor(s) for HCC development[28]. The secondary aim was to investigate disease progression and effect on HCC development among patients infected with different HBV genotypes. An overall incidence of 1,502 cases per 100,000 person-years was estimated for the total of 426 patients (65.3% males) followed for a total of 1664 person-years. Age greater than 40 years, male sex, presence of clinical liver cirrhosis, BCP mutations, and HBV genotype C were associated with the development of HCC while HBeAg positivity and ALT levels were not associated with HCC development. A Cox proportional hazard model identified clinical liver cirrhosis and genotype C HBV infection as being independently associated

with HCC development. Clinical liver cirrhosis was the strongest predictor of HCC development with an adjusted relative risk of 10.24 (95% CI 4.39–23.89), whereas HBV genotype C had an adjusted hazard ratio of 2.84 (95% CI 1.05–7.72). The incidence of HCC development was respectively 1.1-fold and 2.3-fold higher in HBV genotype C compared to genotype B, in patients with and without clinical cirrhosis[28].

In a Taiwanese nested case-control study among participants of a large cohort of male HBV carriers, the authors examined the sequence variation in the EnhII/BCP/precore region of HBV using blood samples taken up to 14 years before diagnosis[29]. This design was chosen to counteract the lack of information on the temporal relation between nucleotide variations and HCC, the mutations possibly occurring in the course of the infection. HCC cases were confirmed either by a histological finding or elevated serum a-fetoprotein (>400 ng/ml) combined with at least one positive image on angiography, sonography and/or computed tomography, from August 1988 to December 2002. The matched controls were living members of the HBsAg carriers' cohort who had not been diagnosed with HCC throughout the follow-up period. HBV genotype, BCP double variants, anti-HBe and ALT levels were significantly associated with the risk of HCC. A significant positive association between the BCP double variants (mostly T1762/A1764) and HCC was observed even after adjusting for ALT levels and other viral factors, including genotype, viral load, HBeAg/anti-HBe status, and other sequence variants[29].

Gao et al. investigated the association between HBV preS mutations, with particular interest in preS deletion mutations, and the clinical outcome among Chinese patients with genotype C HBV infection[30]. The study included 79 HBV-infected patients-

25 asymptomatic carriers (ASC), 28 chronic hepatitis B (CHB) patients, and 26 HCC patients. The age and percentage of males significantly increased as disease severity increased. CHB patients had significantly higher levels of Serum ALT and AST levels while HCC patients had increased frequencies of *preS* deletion (38.46% versus 7.14% and 4.00% in CHB and ASC patients, respectively. P = 0.001). The HBeAg-positive rate and HBV DNA levels were comparable between patients with and without the preS mutation. Although the precise mechanism for hepatocarcinogenesis in persistent HBV infection is still imprecise, HBV genotypes may play some role in this process, and preS mutations might account for a part of the genotype difference in the development of HCC[30].

Life style factors have been associated with the occurrence of HCC. Evaluating whether these modifiable factors increase the risk of HCC is important in that it will allow the planning of targeted interventions to reduce the burden of this deadly disease.

Overweight, obesity and the risk of HCC

Obesity (body mass index > 30kg/m2) is a risk factor for several diseases, from cardiovascular to cancer. Liver cancer has the highest obesity-related excess risk[31]. The excess risk for HCC in obese and overweight patients ranges from 17% to 89%, with an average increase of 24% for each 5kg/m2 increase in BMI[32]. More than 36% of HCC cases were attributed to obesity and diabetes in an American population-based case control study (OR = 2.47, 95% CI = 2.34– 2.61) [33]. The effect of obesity on HCC risk was reviewed from thirteen studies (ten cohort studies, a nested case-control and two case-control studies). A statistically significant increased risk of HCC with increasing

BMI levels was reported by seven cohort studies (relative risk ranging from 1.4 to 4.1) while one study reported a greater risk in white USA veterans and lower risk in black veterans. The two other cohort studies did not find an association[34].

In a dose-response meta-analysis of eight articles reporting twelve studies compiling findings from 1,779, 471 individuals followed-up between 3.6 years and 19 years, Rui et al. found a significant increase of 1.02, 1.35 and 2.22-fold in the relative risk for HCC incidence when BMI was at the point of 25, 30 and 35 kg/m^2 compared with reference (the median value of the lowest category), respectively. Given the heterogeneity of the overall sample (mainly due to ethnicity), a stratified analysis was performed and still showed the increased risk of HCC with increasing BMI [35].

In a Danish cohort of 285,884 individuals followed up more than 30 years for a total of 6,963,105 person-years, a positive association between adult onset HCC and BMI z-scores at each age from 7 to 13 years in boys and girls combined was found[36]. The association was still present even after censoring patients with alcohol-related disorders, viral hepatitis, and biliary cirrhosis. The increased risk for liver cancer in adulthood was 19% and 36% higher, the HR of liver cancer per unit increase in BMI z-score at 7 and 13 years of age, respectively [HR (95% CI): 1.19 (1.04–1.38) and 1.36 (1.17–1.58)].

Metabolic disorders and HCC risk

Obesity constitutes a risk factor for diabetes mellitus (DM) and the determination of their independent and joint effects is important in the planning of HCC control interventions. Polesel et al. investigated the association between obesity, DM and HCC

risk[37]. This Italian case control study included 185 HCC patients and 404 controls. Obesity was associated with a two-fold increase in HCC risk (OR = 1.9, 95% CI 0.9–3.9) while DM was associated with nearly 4-fold increased risk (OR = 3.7, 95% CI 1.7–8.4). Furthermore, diabetic obese participants had a five-fold increased risk compared to non-obese non-diabetic. Among HBV and HCV-negative subjects, obesity and DM were both associated with a 3.5-fold increased HCC risk and the combination of these two conditions was associated with a 10-fold increase in risk (OR = 11.8 for obese diabetics compared to non-obese non-diabetic subjects) [37].

Obesity is often associated with type 2 diabetes (due to insulin resistance), metabolic syndrome (MS), and nonalcoholic fatty liver disease (NAFLD). The U.S. National Cholesterol Education Program Adult Treatment Panel III (NCEP-ATP III), defines MS as the presence of at least three of the following conditions: elevated waist circumference/central obesity, dyslipidemia (elevated triglycerides, lowered high-density lipoprotein), hypertension, and impaired fasting glucose [38]. Welzel et al. investigated the association between MS and risk of HCC and intrahepatic cholangiocarcinoma (ICC) in the general population of the United States. Impaired fasting glucose and/or DM was associated with 2.9- and 1.82-fold increased risks of HCC and ICC[39]. In addition, dyslipoproteinemia, hypertension, and obesity were each significant predictor of both HCC and ICC. Subjects with MS had a 2.58- and 2.04-fold higher risk of HCC and ICC, respectively (95% CI = 2.4-2.76 [HCC] and 1.74-2.40 [ICC]. After adjusting for demographic variables and major HCC or ICC risk factors, the increased risk associated with MS was 2.13-fold for HCC (95% CI = 1.96-2.31) and 1.56-fold for ICC (95% CI = 1.32-1.83) [39].

Smoking and HCC risk

Smoking is a known risk factor for several cancers, explained by the fact several constituents of tobacco smoke are known carcinogens in animals as well as in humans (N-nitrosodimethylamine, 4-aminobiphenyl, arsenic, vinyl chloride)[40,39,41]. Although controversial, the role of smoking in the occurrence of liver cancer has been explored by several studies. However, most of the early studies exploring this association did not account for the potential confounding by other risk factors of liver cancer[40,42].

A meta-analysis of 96 cohort and case control studies found a moderate 1.5-fold increase in HCC risk for current smokers. Ever and current smoking had an increased risk for HCC compared to never smoking with meta-relative risk (mRR) of 1.27 (1.02–1.58) and 1.51 (1.37–1.67), respectively. For high quality studies (consideration of major potential confounders and with appropriate control selections), the associations were stronger and the mRR was significant for former smoking also [1.18 (1.01–1.39)]. A dose-response was found with increased risk with increasing quantity of cigarette smoked. Despite the heterogeneity of the data, the findings support the conclusion of the International Agency for Research on Cancer (IARC) of the etiologic role of smoking in the occurrence of HCC [43].

Koh et al. examined the independent effect of smoking on HCC risk without the confounding effect of alcohol consumption in a case control study nested in a Singapore Chinese cohort[44]. Confirmed HCC cases were included in the nested study with a ratio of three controls for one case. Compared to never smokers, current smokers had an increased risk of HCC after controlling for alcohol intake and others major confounders

(HR = 1.63; 95% CI = 1.27–2.10). Furthermore, there was a significant dose-dependent association between daily number of cigarettes smoked and the risk of HCC among current smokers. In ever smokers, a significant dose response was found between HCC and duration and pack-years of smoking. When the authors restricted the analysis to participants negative for HBV and HBC who were not daily drinkers, ever smokers had a 1.85-fold increased risk compared to never smokers [44].

Alcohol and risk of HCC

Alcohol-related liver disorders accounted for 23.5% of HCC cases occurring in the United States between 1991 and 2007 (OR = 4.06, 95% CI = 3.82– 4.32) [33]. Morgan et al. examined the role of alcohol intake as primary cause or cofactor in the development of HCC. Chronic and heavy alcohol consumption was associated with an approximately 2-fold increased odds ratio for HCC. The odds ratio increases to 5- to 7-fold when ethanol use exceeded 80 g/day for more than 10 years. In the presence of HCV, HBV or diabetes, alcohol increased the risk of HCC by 2 to 5 – fold [45].

The Risk Evaluation of Viral Load Elevation and Associated Liver Disease/ Cancer–Hepatitis B Virus (REVEAL–HBV) Study Cohort investigated the joint effect of obesity and alcohol consumption on the risk of HCC[46]. The independent predictors identified by the multivariable Cox regression model were: age, alcohol use, HBeAg status, HBV-DNA levels, and cirrhosis at baseline. Increased but not significant hazard ratios were found for BMI, smoking, increased alanine aminotransferase (ALT) levels, and interaction between BMI and alcohol. Alcohol use was associated with a 54% increased risk of HCC (HR = 1.54; 95% CI: 1.04 –2.29). A 3-fold increased risk was

found among obese alcohol users compared to non-obese alcohol users (adjusted HR = 3.40; 95% CI, 1.24 –9.34). In addition, a trend was observed with increasing risk with increasing BMI. Obese individuals who had 20 years or more of alcohol use had an 8-fold increased risk compared to those with less than 20 years of alcohol use (HR = 8.2; 95% CI, 3.0 –23.0) [46].

Factors influencing HCC survival

HCC survival has been associated with female gender, early diagnosis, Child-Turcotte-Pugh class A classification for severity of cirrhosis, tumor size ≤ 2cm, initial complete response to percutaneous ablation, transplantation and resection of localized-stage tumors, screening, low serum bilirubin and alpha-fetoprotein (AFP) levels and low tumor mass[9,47–49].

The independent role of smoking in liver cancer survival has seldom been researched and the study results are ambiguous. Pre-diagnosis smoking and alcohol were inversely associated with HCC survival. Shih et al. found that cessation had a positive effect on mortality, but only after a long period (≥10 years)[50]. Siegel et al. found that younger age, lower AFP and Child-Turcotte-Pugh Class were all independently predictive of survival, but smoking was not. Neither the intensity of smoking nor smoking cessation were associated with an improved survival[51].

The American Association of the Study of Liver Diseases recommends screening for HCC by ultrasound every six months in at-risk patients with chronic HBV including Asian females over 50 years old, Asian males over 40 years old, all cirrhotic patients, and those with a family history of HCC [52]. Sarkar et al. described the evolution of

screening practice, the factors associated with it as well as its impact on patient survival in an Asian American cohort [49]. The predictors of screening were age 40–64 years, female gender, the presence of cirrhosis, liver clinic attendance, recent HBV diagnosis, and testing for HBeAg. High ALT was negatively associated with screening and high HBV viral load was independently associated with screening among cirrhotic patients. HCC survival was associated with low Model for End-Stage Liver Disease (MELD) score and curative treatment. Mean survival was significantly higher in HCC patients who had been screened, and thus were more likely to have an early diagnosis.

Treatment is an influential factor in the improvement of survival, and was responsible of the dramatic change in the prognosis of HCC which was once synonymous of a death sentence with a very short survival time. In a randomized controlled trial, transarterial Lipiodol chemoembolization induced a prolonged survival in Asian patients with unresectable HCC[53]. Among HCC patients with unresectable and untransplantable tumors, patients over 55 years had an increased bilirubin and AFP levels and a decreased survival. Patients with small tumors and low typical AFP levels have longer survival compared to those with AFP levels close to 250 and relative tumor mass of about 40 have a survival of about a year[47]. A randomized, double-blind, placebo-controlled trial among naïve systemic treatment HCC patients with Child-Turcotte-Pugh class A assessed the efficacy and safety of Sorafenib (an oral multikinase inhibitor with antiproliferative and antiangiogenic effects) in the Asia-Pacific region [54]. Patients randomized to Sorafenib had 68% longer median overall survival compared to those assigned to placebo: 6.5 months versus 4.2 months (p=0.014). The 6-month overall survival was 53.3% in the Sorafenib group compared to 36.7% in the

placebo group. The hazard ratio for the time to progression, defined as from the time from randomization to disease progression or symptomatic progression, was 0.57 in favor of the Sorafenib group (p=0.0005). This study by Cheng et al. was done after the multicenter, phase 3, double-blind, placebo-controlled trial aiming to assess the Sorafenib (at a dose of 400 mg twice daily) versus placebo[52]. Llovet et al. showed that Sorafenib was efficacious and well-tolerated in patients with advanced hepatocellular carcinoma. The Sorafenib group had three months' median survival benefit compared to the placebo group.

Gender differences in HCC survival have been shown in some studies. Dohmen et al. found that survival was longer in female HCC patients. The 1-, 3-, 5- and 7-year survivals were significantly higher in females: 73.5, 50.3, 26.3 and 15.4% versus males: 67.7, 40.6, 23.8 and 8.7% (P-value: 0.0167). However, age, tumor size, number of tumors, portal thrombosis and types of follow-up were significantly different between males and females indicating that the stage at diagnosis could explain the longer survival in females[48].

Hepatitis viral infections may have a role in HCC survival as they constitute the etiology of most of the cases. A Russian study explored the influence of HBV and HVC on the survival of HCC patients. HBV and HVC infection was present in 39.9% and 17.4% of HCC patients, respectively. Although the Kaplan-Meyer estimates showed a two-fold 5-year survival for virus-free patients (22.4% for virus-free vs. 9.5% for HBV; 13.0% for HCV; 6.1% for HBV and HCV), in the adjusted model the survival was similar except for a small group with HVB/HVC co-infection[55].

A California study found that Laotian/Hmong and Cambodian HCC patients had respectively a twofold and 74% higher cause-specific mortality compared to other ethnic groups. This disparity in survival remained after adjustment for time period of diagnosis, age at diagnosis, gender, geographic region, stage at diagnosis, type of surgery, and socio-economic status (49% and 77% higher mortality for Laotian/Hmong and Cambodian, respectively)[56]. Black patients had a poorer survival compared to Hispanics and whites HCC patients[57].

Conclusion

Cancer of the liver and intrahepatic bile duct incidence and mortality were two- to three-fold higher in men compared to women, in all the trend analyses performed by SEER for the period 1975-2012. The overall delay-adjusted incidence rose from 2.64 per 100,000 in 1975 to 8.91 per 100,000 in the SEER 9 regions, with most of the increase observed in males. The same trend was observed for the age-adjusted mortality rates[58].

HBV genotype C and genetic mutations such as precore mutations, pre S deletions and BCP double mutations were associated with an increased HCC risk [25–30]. With the highest obesity-related excess risk[28], HCC risk increases with increasing BMI levels [33–35] with a 24% increase for each 5 kg/m^2 increment in BMI[31,32]. Childhood obesity accounted respectively for 19% and 36% higher HCC risk per unit increase in BMI risk at age 7 and 13 years[36].

When associated with other metabolic disorders (DM, MS, NAFLD), the role of obesity in HCC is even more prominent with up to a 10-fold increase in obese

diabetics[37–39]. Known carcinogen, smoking and its role have been investigated in the occurrence of HCC yielding results sometimes controversial or incomplete[40–42]. Smoking increases HCC risk with a positive dose-response, the risk higher when the dose or duration of smoking is higher[43,44]. Alcohol use has been associated with a 2-fold increased HCC risk. The risk is even higher in chronic and heavy alcohol use as well as when associated with smoking, diabetes, obesity and hepatitis infections[45,46].

The influence of socio-demographic and tumor-related factors as well as treatment on HCC survival are well established, with better survival associated with female gender, small tumors and curative treatments and younger age[9,47–49,51–54]. Smoking and alcohol use are inversely associated with HC survival and the positive effect of smoking cessation was seen after at least 10 years[50]. HCC risk factors and survival studies in the United States have been more focused on special groups such as immigrants or those with Asian ancestry[56,57]. The role of race and unemployment have been explored[15,16].

To date, there is no study which has explored Kentucky population, with its regional characteristics and their potential influence on the risk factors and survival of HCC.

III. CHAPTER 3: RISK FACTORS IN KENTUCKY FOR LATE-STAGE HEPATOCELLULAR CARCINOMA (HCC)

Introduction

The literature review described male gender, HBV and HVC infections, HBV genotypes and genomic mutations, obesity, alcohol consumption, diabetes and other metabolic disorders among the usual risk factors associated with HCC. The individual role of smoking has been established as well as its worsening factor when associated with others known risk factors. In this chapter, the risk factors for late stage liver cancer in incident HCC patients reported to the Kentucky Cancer Registry (KCR) are investigated. Only potential risk factors available in the KCR or county-level variables from the Behaviorial Risk Factor Surveillance System (BRFSS) are evaluated. HBV and HVC infections were not available for study. Also, this evaluation only included HCC cases and no individual data were available on the population from which the HCC cases came, and no non-case population was available for comparison. Therefore, the risk factors for developing HCC in Kentucky was not studied.

Since diagnosis of HCC in late-stage is associated with poorer prognosis and lower survivability, the focus of this chapter (paper) is an evaluation of the risk factors associated with being diagnosed with late-stage HCC in Kentucky. The initial hypotheses tested were that black race; Appalachian residence; low, county-level education level; county-level binge drinking proportions (defined as as four or more drinks for women and five or more drinks for men on any occasion during the past 30 days); and single status conferred a higher risk of being diagnosed with late-stage liver cancer.

Methodology

Data source and study population

The data used for this project were provided by KCR. Voluntary when it began in 1986, KRC was established as a population-based central cancer registry for the Commonwealth in 1990 and the reporting became requisite the following year. The Cancer Patient Data Management System is used as a reporting system by all acute care hospitals, outpatient facilities and health care facilities including treatment centers, private laboratories and physician offices. KCR maintains active surveillance of case status using linkages with state vital records and the National Death Index. The KCR collects uniform, high quality cancer data on incident cancer cases among Kentucky residents. Since 2000, KRC has been part of the national SEER program, considered as the most accurate and complete cancer registry. KCR contributes to the integrated cancer control effort led by the Markey Cancer Control Program and has received the gold certification of the North American Association of Central Cancer Registries (NAACCR) since 1999[59].

Sample

The inclusion criteria for the HCC patients in this study were:

- Invasive liver cancer cases that occurred in Kentucky from 1995 to 2011.
- First primary or only primary cancer.
- Age ≥ 20 to exclude childhood liver cancers.

Since major hypotheses studied were that black race and single status conferred higher risk for being diagnosed with HCC in late-stage, cases with missing and erroneous values for race or marriage were excluded from the analysis.

Lifestyle covariates (obesity, smoking, alcohol consumption, physical activity) and socio-economic indicators (education, income, poverty) were retrieved from the Behavioral Risk Factor Surveillance System (BFRSS) at the county level. These county level variables were merged with the individual data from KRC.

Variable definition

The potential predictors and confounders were determined according to the factors associated with HCC incidence found in the literature. The variables were defined as follow:

- Age: continuous variable, further categorized (1 = <50; 2 = 50-64; 3= 65-74; 4=≥75.
- Sex: binary variable 1 = Male; 2 = Female.
- Smoking status: this category includes all types of tobacco products including the non-smoke ones. Categorized in smokers and non-smokers. The county-level smoking variable giving the proportion of smoking proportion was not used in the analysis.
- Race: 1=white/other; 2 = black.
- Primary payer: categorical by type of insurance (not insured, private insurance, Medicaid, or Medicare).
- Marital status: categorical (single (never married), married (including common law), separated, and widowed). The observations with missing and unknown values were not analyzed. A binary variable was created with married (currently married) and single.
- Year of diagnosis: categorical 1=1995-1999; 2= 2000-2004; 3=2005-2009 and 4=2010-2011.

- Appalachia status: county-level binary variable with values as determined by the Appalachian region commission. 1=Non-Appalachian; 2 = Appalachian.
- Obesity rate: county-level continuous variable reporting the percentage age of obese in the county. Categorized in low (<25%), intermediate (25-29%) and high (≥30%).
- Metro status: binary variable with values determined using the Beale codes. 1= urban (Beale codes 1-3); 2 = rural (Beale codes 4-9).
- Poverty: percentage of the population under poverty level. Categorized in low (<15%), intermediate (15-29%) and high (≥20%)
- County-level yearly income: Average yearly income. Categorized in <15,000, 15,000-19,999 and ≥ 20,000.
- Vital status which takes the value 0=Alive (censored) and 1=dead.
- Histology: HCC (histology code 8170) and non-HCC (cholangiocarcinoma, mixed hepatocellular carcinoma and cholangiocarcinoma, cystadenocarcinoma in intrahepatic biliary ducts, undifferentiated carcinoma, epithelioid hemangioendothelioma, angiosarcoma, rhabdomyosarcoma)
- Stage: early stage (Summary stage 1 or best stage IIB) and late stage (Summary stage 2 to 5 or Best Stage IIc to IV)

Variables with more than 10% of missing value as well as erroneous values were not considered in the analysis.

Data analysis

The SAS 9.4 Software Package (Version 9.4; SAS Institute Inc, Cary, NC) was used to analyze the data. A descriptive analysis was done using the proc freq procedure.

Demographic features and preexisting medical conditions were compared using t tests for continuous variables and chi-square or Fisher's exact tests for categorical variables. A logistic regression was performed to calculate odds ratios (OR) and 95% confidence intervals (95% CI) in order to assess the potential risk factors of late stage at diagnosis HCC. The model was first run with all covariates and then variables were removed using backward elimination to find the model of best fit. Tests of statistical significance and CIs are two-sided. A p value < 0.05 is considered statistically significant.

Observations with missing values were not considered in the analyses.

Results

Table III.1 presents the characteristics of the 2,205 HCC cases reported to the KCR between 1995 and 2011. They were predominantly male (72.1%), with a mean age at diagnosis of 64.1 years, ranging from 20 to 102 years. About half the study population were smokers (53.1%), while only 21.99% never smoked. The number of pack-years ranged from 1 to 320 among smokers with a mean of 27.2 pack-years. Cases were more likely to be male (72.1%), of white or other race (90.2%), aged between 50 and 64 years (39.9%), married (41.1%), diagnosed between 2005 and 2009 (81.54%) with a late stage (41.9%) HCC (78.4%) and have Medicare (50.7%). They lived mostly in urban (59.5%) non-Appalachian area (72.1%). Female cases were

mostly post-menopausal (87.3%), with a mean number of live births of 2.7. More than half the sample did not receive any type of treatment (55.3%) and surgery was the most frequent type of treatment among those treated (50.4%).

Table III.1 : Characteristics of Incident Hepatocellular Carcinoma (HCC) Patients Reported to the Kentucky Cancer Registry – 1995-2011

Patient-Level Continuous Variables			
	# Patients	**Mean (StdDev)**	**Range**
Age at diagnosis	2205	64.08 years (12.87 years)	20-102
Survival Time	2205	12.43 months (21.82 months)	0 – 168
Number of live births (women)	206	2.7 (2.6)	0-13
Pack-years smoking	901	27.2 (33.5)	0 – 320
Patient-Level Categorical Variables			
	# Patients	**Frequency**	**percentage**
Age at Diagnosis (yrs)	2205		
<50		259	11.75
50 - 64		879	39.86
65 – 74		559	25.35
≥ 75		508	23.04
Gender			
Male	2205	1589	72.06
Female		616	27.94
Race	2202		
White/Other		1989	90.20
Black		213	9.66
Smoking Status	2205		
Non-smoker		469	21.27
Smoker		1132	51.34
Unknown		604	27.39
Marital Status	2205		
Single		751	34.06
Married		907	41.13
Unknown		547	24.81
Insurance	2205		
Not insured		124	5.62
Private insurance		548	24.85
Medicaid		221	10.02
Medicare		1117	50.66
Unknown		195	8.84
Metro Status	2205		
Urban		1312	59.50
Rural		893	40.50
Appalachian Status	2205		
Non-Appalachian		1589	72.06
Appalachian		616	27.94

Year of Diagnosis	2205		
1995 – 1999		424	19.23
2000 – 2004		559	25.35
2005 – 2009		815	36.96
2010 – 2011		407	18.46
Stage at Diagnosis	2205		
Early Stage		826	37.46
Late Stage		923	41.86
Unknown		456	20.68
Survival Duration (yrs)	2205		
≤5		2110	95.69
6 – 10		77	3.49
>10		18	0.82
Histological Type	2205		
HCC		1729	78.41
Non-HCC		476	21.59
Type of Treatment	2205		
No treatment		1224	55.51
Surgical treatment		480	21.77
Chemotherapy		411	18.64
Radiation therapy		62	2.81
Other		28	1.27
Menopausal Status at Diagnosis	616		
Pre-menopausal		58	12.66
Post-menopausal		400	87.34
Unknown		158	25.65

The county-level data associated with the 2205 cases is presented in Table III.2. At the county level, the average literacy percentage of the residents from the counties from which the HCC cases came was 74.8% (sd: 9.7%). The average percentage of binge drinking, heavy drinking, smoker and ever smoker proportions were respectively 10.1%, 3.4%, 27% and 46.6%. More than three quarters of the population had a health plan (which included Medicare or Medicaid). The mean yearly income was $18,513.6 . The median percentage of residents living under poverty level was 17.4%. Obesity and

overweight proportions were on average 27.5% and 64.9% respectively while the average exercise proportion was 67.7%.

Table III.2: County-Level Characteristics of Incident Hepatocellular Carcinoma (HCC) Patients Reported to the Kentucky Cancer Registry – 1995-2011 – Data from the Behavioral Risk Factor Surveillance System (BRFSS)

Variable	Median Value (StdError)	Range
% Ever smoke cigarettes	46.47 (0.09)	32.13 – 64.08
% Currently smoke cigarettes	27.13 (0.09)	15.4 – 46.9
% Binge drinking	10.48 (0.07)	1.4 – 18.03
% Heavy drinkers	3.19 (0.03)	0.2 – 6.5
% Overweight	64.17 (0.07)	51.7 – 75.3
% Obese	27.31 (0.09)	19.3 – 41.6
% Physically active	69.61 (0.13)	49.7 – 81.1
% Literate	79.0 (0.21)	49.4 – 86.5
% With health insurance	88.11 (0.12)	66.3 – 93.96
% Live in poverty	15.4 (0.13)	5.8 – 38.3
Household yearly income	$18,339 ($85.40)	$9,716 – 25,374

Table III.3 shows bivariate analyses by stage at diagnosis (excluding unknown stage) for selected variables. The county-level variables percentage of ever smokers, current smokers, health insurance were not included in this analysis as the individual corresponding variables are available. The percentage of binge drinking was preferred to the heavy drinking that is less frequent and percentage of obese was used instead of percentage of overweight because obesity has a higher increased risk of death[60].

Male gender, older age , black race, lack of insurance, year of diagnosis before 2000 HCC histology were statistically significant. White/other male aged 50-64, diagnosed between 2005 and 2009 with HCC were more likely to be seen with a late stage. Marital status, residence (metro or appalachia), smoking, binge drinking, physical

activity, obesity, literacy, poverty and yearly income were not associated with stage at diagnosis.

Table III.3: Bivariate analysis of Liver Cancer Cases in Kentucky by Stage at Diagnosis, 1995-2011

Variable		**Stage at diagnosis**		***P* value**
	N	Early stage N=826	Late stage N=923	
Sex				**0.02**
Male	1279	70.6	75.4	
Female	470	29.4	24.6	
Race				**0.02**
White/Other	1564	91.3	87.9	
Black	184	8.7	12.1	
Age				**0.02**
20-49	213	13.0	11.5	
50-64	711	42.6	38.9	
65-74	455	22.6	29.0	
75+	370	21.8	20.6	
Marital status				0.7
Single	621	44.2	45.2	
Married	768	55.8	54.8	
Appalachian Status				0.1
Non-Appalachia	1283	71.6	75.0	
Appalachia	466	28. 5	25.0	
Metro Status				0.6
Rural	675	39.2	38.0	
Urban	1074	60.8	62.0	
Insurance				**0.01**
Not Insured	112	5.4	7.6	
Insured	490	30.0	27.2	
Medicaid	197	13.3	9.8	
Medicare	919	51.3	55.5	
Year of diagnosis				**0.001**
1995-1999	263	11.6	18.1	
2000-2004	418	23.9	23.9	
2005-2009	714	43.0	38. 9	
2010-2011	354	21.5	19.1	
Smoking Status				0.4
Non-Smoker	395	29.3	27.4	
Smoker	1002	70.7	72.6	

Histology				**0.004**
Non-HCC	304	14.7	19.8	
HCC	1445	85.3	80.2	
Binge drinking proportion				0.08
<10%	824	49.3	45.2	
≥10%	925	50.7	54.8	
Physical activity proportion				0.7
<65%	474	28.1	26.2	
65-69.9%	435	24.3	25.4	
≥70%	840	47.6	48.4	
Obesity proportion				0.25
<25%	385	23.1	21.0	
25-29%	1000	55.1	59.1	
≥30%	364	21.8	19.9	
Literacy proportion				0.4
<80%	855	49.9	48.0	
≥80%	894	50.1	52.0	
Yearly household income				0.5
<15,000	397	23.8	21. 7	
15,000 -19,999	559	32.0	32.0	
≥20,000	793	44.2	46.4	
Poverty proportion				0.3
<15%	860	47.7	50.5	
15-19%	484	27.6	27.7	
≥20%	405	24.7	21.8	

The full model for the logistic regression evaluating the risk of late stage at diagnosis is presented in table III.4. In addition to the variables in our hypotheses (race, Appalachian residence, county-level education, county-level binge drinking, and marital status), other variables were included, whether to account for potential confounding or because they are known risk factors: age, gender, insurance status, smoking status, county-level percentage of exercise, county-level yearly income, and year of diagnosis.

Compared to the uninsured, those with private insurance and Medicaid had respectively 41% and 46% less risk of being diagnosed with late stage (p=0.03 and p=0.02). Medicare was close to being signifcant with a p-value of 0.08, showing that

having any healthcare plan was protective for not being diagnosed with late-stage HCC. Of the orginal hypotheses evaluated, black race had an odds ratio of 1.32 for being late-stage with a p-value of 0.18. County-level percentage of binge drinking is significantly associated with late stage diagnosis. With each increase of 1%, the odds of being diagnosed late increased by 1.1-fold (p=0.03).

There was no evidence that being single imparted an increased risk for being diagnosed with late-stage HCC. Appalachian residence, smoking status and county-level low education do not appear to have any effect on late stage diagnosis.

Patients from counties with high literacy level (≥ 80%), moderate physical activity (65-70%), moderate and high obesity percentage have a non-statistically significant higher risk of late-stage diagnosis.

A significant interaction was found in the univariate logistic regression between gender and age as well as between alcohol and gender (data not shown). Male cases from counties with high percentage of binge drinking had a 1.3-fold higher odds (95% CI: 1.05 – 1-71) of being diagnosed with late stage HCC compared to female from counties with low percentage of binge drinking. Male cases aged 65-74 have almost a two-fold higher odds of being diagnosed with late-stage (OR: 1.99; 95% CI 1.4 – 2.84) compared to females aged 20-49. Although the males have higher odds in the other age groups, the differences were not statistically significant. The only significant interaction terms in the logistic regression was between gender and age and were thus kept in the final model. Compared to females aged 20-49, males aged 65 to 74 years old had a significant two-fold higher risk of late-stage diagnosis. At any age, males had a higher

risk of late-stage diagnosis. In both males and females, the risk of late-stage diagnosis increased with increasing age.

Table III.4: Logistic Regression for the Risk Factors of Late Stage at Diagnosis (Full Complete Model), Kentucky Residents, 1995-2011

Variables	**OR**	**95% CI**	***p***
Race			
White/Other	Ref		
Black	1.32	0.88 – 1.98	*0.6*
Age * Gender			
20-49, Female	Ref		
20-49, male	0.75	0.39 – 1.44	*0.6*
50-64, male	1.16	0.73 – 1.83	*0.3*
65-74, male	2.0	1.16 – 3.48	*0.05*
≥75, male	1.14	0.63 – 2.07	*0.2*
50-64, female	0.73	0.32 – 1.64	*0.4*
65-74, female	0.74	0.3 – 1.79	*0.5*
≥75, female	0.62	0.26 – 1.49	*0.2*
Appalachia residence			
Non appalachia	Ref		
Appalachia	0.83	0.55 – 1.26	*0.4*
Marital status			
Single	Ref		
Married	0.97	0.74 – 1.26	*0.8*
Insurance			
Not insured	Ref		
Insured	0.54	0.32 – 0.91	***0.02***
Medicaid	0.49	0.28 - 0.86	***0.02***
Medicare	0.61	0.35 – 1.06	*0.08*
Smoking			
Smoker	Ref		
Non-smoker	1.12	0.84 – 1.49	*0.4*
Physical activity			
Low	Ref		
Moderate	0.97	0.63 – 1.49	*0.8*
High	0.92	0.53 – 1.6	*0.4*
% Binge drinking	1.1	1.0 – 1.12	***0.05***
Literacy			
Low	Ref		
High	1.07	0.67 – 1.72	*0.8*
Obesity			
Low	Ref		
Moderate	1.3	0.96 – 1.82	*0.2*
High	1.23	0.78 – 1.95	*0.4*

The covariates retained in the final fitted model (see table III.5) after a backward elimination of non-significant variables are the gender-age categories, insurance status, race, year of diagnosis and county level % binge drinking. Although Appalachian residence, county-level education and marital status were part of our initial hypotheses, we chose to exclude them because they had high p-values and decreased the goodness of fit.

Compared to females aged 20-49, the odds of late stage diagnosis in males increased by 1.2-fold, 1.9-fold and 1.3-fold in ages 50-64, 64-74 and ≥75 respectively. Compared to males, females had a decreased risk of 20% although the difference was not significant.

The ininsured patients had an increased odds of 1.6-fold compared to those with private insurance while Medicaid patients had a non significant decreased odd of 0.8-fold and Medicare patients are not statistically different from the referent group.

Blacks had an increased odd of 1.5-fold compared to the white/other group. The period 1995-1999 has a 1.8-fold increased odds of late diagnosis compared to the years 2010-2011 while the increased odds were not significant for the periods 2000-2004 and 2005-2009.

the county-level proportion of binge drinking was significantly associated with a higher risk. Each 1% increase was associated with a 1.03-fold increased odds of late diagnosis.

Table III.4: Final model for the OR of late stage at diagnosis among Kentucky liver cancer patients, 1995-2011

Covariates	Late-stage OR (95%CI)	*P* value
Age*Gender		*0.07*
20-49, Female	Referent	
20-49, male	0.8 (0.4 – 1.5)	*0.6*
50-64, male	1.2 (0.8 – 1.7)	*0.4*
65-74, male	1.9 (1.2 – 3.0)	*0.02*
≥75, male	1.3 (0.8 – 2.03)	*0.2*
50-64, female	0.8 (0.4 – 1.6)	*0.5*
65-74, female	0.8 (0.4 – 1.5)	*0.5*
≥75, female	0.8 (0.4 – 1.5)	*0.3*
Race		**0.02**
White/Other	Referent	
Black	1.48 (1.0 – 2.1)*	0.01
Insurance		0.05
Insured	Referent	
Medicaid	0.8 (0.59 – 1.56)	0.3
Medicare	1.1 (0.83 – 1.46)	0.5
Not insured	1.6 (1.1 – 2.5)*	**0.03**
Year of diagnosis		0.003
1995-1999	1.8 (1.27 – 2.5)*	0.0009
2000-2004	1.2 (0.86 – 1.55)	0.3
2005-2009	1.04 (0.80 – 1.35)	0.8
2010-2011	Referent	
%Binge drinking	1.04 (1.03 – 1.1)	**0.03**

*Statistically significant

Discussion

This study was conducted in a rural state with high poverty rates, high overweight and obesity rates, low physical activity as well as low education level. The demographic characteristics of Kentucky HCC patients are similar to HCC patients profile in the country. Consistent with national reports[9,61], our sample was mostly male, of white or other race ethnicity and aged 50-64 years.

We did not find evidence that physical activity, marital status, literacy proportion and Appalachia residence were associated with late-stage diagnosis of HCC. However, our analysis confirms previous findings that gender, race, age, and insurance status as factors impacting late-stage diagnosis[15,33,62–65]. Patients residing in counties with higher levels of binge dirinking had a higher risk of late-stage diagnosis. We also found a decreasing trend over time in the odds of HCC cases with late-stage diagnoses, with diagnosis before 2000 having almost twice the risk of being late-stage. Thus, the population with highest late stage HCC risk in this Kentucky sample are the blacks, uninsured males aged 50 and older, living in counties with high proportion of binge drinking and diagnosed before the year 2000.

Similar to national trends, HCC cases steadily increased between 1995 and 2009 with a higher proportion of the HCC cases being diagnosed with late-stage between 1995 and 1999[18,19]. This trend may be due to an update in the management of HCC with a better compliance to screening recommendation as well as the increasing age of the population[47,66].

Without surprise, our cancer cases were mostly males with a similar mean age at diagnosis of 64 years as their national counterparts[10]. The male to female ratio of 2:1 supports the global trend of HCC incidence according to gender, with an increasing risk

with increasing age. Access to care is highly correlated to the existence of insurance plans and thus it is plausible that patients without insurance status have a higher risk of late diagnosis as confirmed by previous research[9,19,67,68].

Late-stage HCC diagnosis may be caused or worsened by diagnostic delays. A Texan study found that almost 20% of HCC patients experienced delayed diagnostic of more than three months, which can lead to an increase in tumor size [69]. HCC is a highly lethal disease making surveillance a primordial part of its management. Results from the Hepatitis C Antiviral Long-Term Treatment against Cirrhosis Trial (HALT-C) suggest that despite consistent surveillance, a third of patients are diagnosed with late-stage HCC [70]. This situation calls for an increase in provider awaressness to improve surveillance and thus reduce the incidence of late-stage HCC.

Our analysis did not show our initial hypotheses that Appalachian residence, low county-level education or single status provided a higher risk of late-stage HCC diagnosis. County level literacy and poverty proportions, and average income were used to assess socioeconomic level and were not associated with late-stage HCC. Similar to our findings, a Canadian retrospective cohort exploring the risk factors of HCC in the Ontario Cancer Registry data did not observe any association between stage at diagnosis and SES [71]. Ford et al., however, found that increased HCC rates in New York city were associated with neighborhoods highly infected with HBV and HCV, poorer, and inhabited by a high proportion of uninsured persons [72].

This study has several limitations. We lacked individual values for alcohol use, education level, overweigh, obesity and physical activity. These variables would have been more associated with personal risk if they were not simply at the county level. The

lack of racial diversity of our series may impede the generalization of our findings. Furthermore, our sample did not include information on HBV and HCV status, which are known HCC risk factors. The missing values in some of our covariates of interest was important. Stage of diagnosis, smoking status at diagnosis and marital status were unkown in 20%, 27% and 25% of the sample, respectively. The observations with unkown values were excluded from the logistic regression, which could have contributed to the non significant findings for these variables.

Despite these limitations, this study is the first to our knowlegde exploring the risk factors of late-stage HCC diagnosis in Kentucky. With the increasing incidence of HCC in Kentucky, our findings suggest that the State's efforts toward the control of HCC should focus on implementing recommendations directed to uninsured males residents aged 50 to 64 years. Moreover, further investigation is warranted to document the effect of lifestyle (physical activity, smoking, alcohol use) on the risk of late stage HCC. With evidence of a geographic variation in the epidemiology of HCC, it is paramount to study the effect of socioeconomic status on the incidence of late-stage HCC for better tailored interventions.

IV. CHAPTER 4: FACTORS ASSOCIATED WITH HCC SURVIVAL IN KENTUCKY

Introduction

Factors associated with increased HCC survival include female gender, early diagnosis, a class A Child-Turcotte-Pugh cirrhosis score, tumor size ≤ 2cm, initial complete response to percutaneous ablation, transplantation and resection of localized-stage tumors, screening, low serum bilirubin and alpha-fetoprotein (AFP) levels and low tumor mass [9,47–52]. The present study evaluates factors associated with longer survival among Kentucky HCC patients who were diagnosed between 1995 and 2011 and entered into the KCR. We examined both overall and specific survival with respect to hormonal status, which has been found to be predictive of liver cancer incidence in women. Furthermore, studies have shown that women have longer survival than men.

Our research hypothesis is that early stage diagnosis, female gender and non-smoking status will be associated with a better HCC survival.

Methods

Data source and study population

Sample

The same data set described in chapter 3 was used for this part of the project. Cases extracted from death certificate or autopsy only were excluded.

Variable definitions

In addition to those described in chapter 3, we considered the following variables:

- Vital status which takes the value 0=alive (censored) and 1=dead.
- Year of survival: continuous, used to compute the survival time in years. It was categorized in three categories: ≤ 5 years, 6-10 years and >10 years.

- Histologic type: HCC and non-HCC.
- Live births: number of live births at diagnosis. Categorized in 1=0; 2=1-2 and 3=>2.
- Hormonal status: modified gender variable with 3 categories: men, postmenopausal women and premenopausal women.

Data analysis

The primary end point is the overall survival and thus the outcome variable is the time to event, a continuous variable calculated in days, computed by subtracting the date of diagnosis from the date of death or last contact. Follow-up time for those still alive at the time of the linkage with the National Death Index was calculated using the date of diagnosis and date of last follow-up.

A descriptive analysis by hormonal status was performed in order to select the variables that will be included in the survival analysis. A cross-tabulation of all the variables of interest with overall and specific mortality was also performed for the selection of the variables to be included in the Cox regression.

The 5-, 10- and 15-years survival rates were estimated using the Proc Lifetest procedure. Both actuarial and Kaplan-Meyer methods were used. The mean overall survival was calculated by hormonal status to assess whether the overall survival is different across groups. A Cox proportional hazard model was fitted to determine the effect of gender with both overall and specific survival. A subset of the data comprised of female patients with available information on live births was used to further assess the effect of menopausal status on both type of survival, adjusting for parity.

The final survival model was selected using a backward elimination procedure. The full complete model included all the independent variables and the interactions, as reported in the literature or identified during the bivariate analysis. A two-way interaction between treatment and stage at diagnosis was evaluated given that stage at diagnosis determines the type of treatment available to patients.

Results

Table IV.1 presents the characteristics of the sample by hormonal status. This bivariate analysis shows age, race, insurance status, smoking status, treatment, metropolitan status, histological type, stage, marital status, and survival were associated with hormonal status. County-level poverty, physical activity, binge drinking, literacy proportions were significantly associated to hormonal status as well. Both overall and specific mean survival were similar (9.8 %) in men and post menopausal women and were significantly higher in premenopausal women (24.1 %).

Both overall and liver cancer specific survival rates were low. The 5-years overall survival rates were 10.3%, 8.3% and 26% in men, post and pre-menaupausal women, respectivelely while the 5-years specific survival rates were 19.3%, 19.3% and 30.3% (data not shown). Mean overall survival for the study period was 9.8 % in men and 11.4% in females while mean specific survival was 29.5 % and 30.7 % and men and women, respectively (data not shown).

Table IV.1: Stratified Analysis by Hormonal Status, Kentucky Residents, 1995-2011

Variables	#	%Men N = 1589	%Postmenopausal women	%Premenopausal women	*P*

			N = 400	N = 58	
Age					***<.0001***
<50	244	81.2	3.7	15.2	
50-64	828	85.4	12.1	2.5	
65-74	512	74.4	25.6	0	
≥75	463	65.4	34.6	0	
Race					***0.04***
Black	196	79.6	15.3	5.1	
White/Other	1850	77.4	20.0	2.6	
Treatment					***0.002***
No treatment	1125	78.4	19.8	1.8	
Surgical treatment	447	72.5	22.6	4.9	
Chemotherapy	389	80.7	15.2	4.1	
Radiation therapy	59	78.0	22.0	0	
Other	27	85.2	14.8	0	
Appalachian Status					***0.11***
Non-Appalachia	1439	78.8	18.5	2.7	
Appalachia	578	74.6	22.2	3.3	
Metro Status					***0.02***
Urban	1215	79.7	17.5	2.9	
Rural	832	74.6	22.6	2.8	
Smoking Status					***<.0001***
Non-Smoker	443	56.4	39.1	4.5	
Smoker	1083	83.8	13.3	2.9	
Insurance					***<.0001***
Not insured	116	88.0	6.0	6.0	
Insured	515	79.6	14.4	6.0	
Medicaid	206	84.5	9.2	6.3	
Medicare	1052	72.5	27	0.5	
Stage at Diagnosis					***0.08***
Early Stage	774	75.3	21.5	3.2	
Late Stage	872	79.8	17.3	2.9	
Histological Type					***<.0001***
HCC	1625	80.3	16.9	2.8	
Non-HCC	422	67.5	29.6	2.8	
Marital Status at Diagnosis					***<.0001***
Single (never married)	225	89.3	6.2	4.4	
Married	857	83.1	14.2	2.8	
Separated/ Divorced	262	80.2	16.0	3.1	
Widowed	203	44.3	55.7	0	
Mortality rates					***0.0033****
≤5 years	1961	78.0	19.4	2.6	
6 – 10 years	69	71.0	20.3	8.7	
>10 years	17	58.8	29.4	11.8	

Mean overall survival[$] (%)	208	9.8	9.8	24.1	***0.0005****
Mean specific survival[$] (%)	611	29.5	30.5	34.5	***0.03****
Year diagnosed					***0.04***
1995-1999	388	74.5	21.9	3.6	
2000-2004	523	74.2	22.8	3.1	
2005-2009	755	79.2	18.5	2.3	
2010-2011	381	82.4	14.7	2.9	
County-level %Literacy					***0.5***
Low	1053	76.5	20.6	2.9	
Moderate	994	78.8	18.4	2.8	
County-level yearly income					***0.1***
<15,000	490	74.1	23.3	2.7	
15,000 – 20,000	677	77.4	19.4	2.7	
≥ 20,000	880	79.8	17.2	3.1	
County-level %Binge drinking					***0.3***
<10%	985	76.4	20.9	2.7	
≥ 10%	1062	78.1	18.3	2.9	
County-level %physical exercise					***0.03***
<70%	1109	75.5	21.6	2.9	
≥ 70%	938	80.2	17.1	2.8	
County-level %obesity					***0.6***
<30%	1610	78.1	19.1	2.7	
≥ 30%	437	75.7	21.1	3.2	
County-level % under poverty					***0.03***
<20%	1544	78.9	18.2	2.9	
≥ 20%	503	73.8	23.7	2.6	

**Chi-square may be invalid **Log-Rank [$]Survival analysis, life table method*

Table IV.2 shows the unadjusted overall and specific survival rates for the covariates selected after the bivariate analysis. The covariates associated with overall survival were hormonal status, age at diagnosis, marital status, insurance status, year of diagnosis, smoking, stage at diagnosis, treatment, histology and county-level proverty proportion.

Unadjusted survival rates were significantly higer in premenopausal women, women with children, younger patients (<65 years), married patients, those insured, those diagnosed in 2010-2011. As expected, non-smokers, patients with early stage HCC, those having had a surgical treatment had higher survival rates. Cases from and with a poverty proportion < 20% had also higher survival rates. Year of diagnosis was significantly associated with survival. Survival rates increased from 2.12% in 1995-1999 to 23.6% in 2010-2011.

Married cancer patients had longer survival compared to single. Survival rates were shorter in smokers, in those diagnosed late, in those diagnosed between 1995 and 2004, with an almost two-fold increase in survival after 2005 and in non-HCC histological cancer.

Survival was significantly different according to insurance status, with privately insured having the highest survival and Medicare the lowest. Surgical treatment has the highest survival rates while those who didn’t receive any treatment and those treated with radiation have similar, much lower survival rates. Poverty proportion was associated with overall survival but not with specific survial.

Gender, race and metro/rural residence were not different in survival. Likewise, our analysis did not find any association between both overall and specific survivals and county level physical activity proportion.

Mean overall survival rates were 12.88%, 17.24 % and 24.14 % in men, post and pre-menopausal women, respectively. The mean specific survival probabilities were higher and the same trend is seen, with pre-menopausal women having a longer survival than post-menopausal women and men (p-value for log-rank = 0.02).

The adjusted Kaplan-Meyer survival curves were significantly different according to hormonal status, with pre-menopausal women having a better survival compared to both men and postmenaupausal women (figure IV.1 and IV.2). Furthermore, premenopausal women had better overall and cause-specific survival than their postmenopausal counterparts (figures IV.3 and IV.4).

Both men and post-menopausal women have similar survival rates that are significantly lower than pre-menopausal women. Of the 551 women with live births data, 3.99% without any live births have the same rate (4.55%) whether overall or specific survival is considered. Survival rates increased with increasing number of live births, the increase being more pronounced in specific survival. Unsurprisingly, increasing age is associated with decreasing survival.

Table IV.2: Unadjusted Overall and Specific Survival Rates by Covariate, Kentucky Residents, 1995-2011

Covariates	Overall survival rate	Log-rank p value	Specific survival rate	Log-rank p value
Gender		0.09		0.2
Male	9.75		29.52	
Female	11.36		30.68	
Hormonal status		**0.0005**		**0.02**
Men	9.75		29.52	
Post-menopausal women	9.75		30.5	
Pre-menopausal women	24.14		34.48	
Live births		**0.01**		**0.0005**
0	4.55		4.55	
1-2	12.5		25	
>2	12.27		31.7	
Race		0.25		0.38
Black	9.39		29.11	
White/Other	10.26		29.86	
Age at diagnosis		**<0.0001**		**<0.0001**
20-49	16.22		36.29	
50-64	14.33		35.61	
65-75	7.51		25.40	
≥75	2.95		21.46	
Marital status		**0.0004**		**0.006**
Single	9.85		31.82	
Married	14.44		34.84	
Insurance status		**<0.0001**		**<0.0001**
Not insured	16.13		42.74	
Insured	18.43		36.50	
Medicaid	12.67		38.91	
Medicare	6.62		27.04	
Smoking status		**0.02**		**0.01**
Non-smoker	12.37		33.9	
smoker	9.54		29.15	
Residence		0.05		0.15
Rural	8.40		28.67	
urban	11.43		30.64	
Year of diagnosis				
1995-1999	2.12	**<0.0001**	13.92	**<0.0001**
2000-2004	5.55		28.26	
2005-2009	10.92		32.27	
2010-2011	23.59		43.73	
State at diagnosis		**<0.0001**		**<0.0001**
Early stage	20.22		47.70	
Late stage	4.55		21.02	

Histology		**<0.0001**		**<0.0001**
HCC	11.28		31.98	
Non-HCC	6.3		22.06	
Treatment		**<.0001**		**<0.0001**
No treatment	1.80		18.06	
Chemotherapy	7.54		27.25	
Radiation therapy	1.61		27.42	
Surgery	35.42		62.08	
other	3.57		35.71	
Poverty proportion		**0.04**		0.18
Low to intermediate	11.4		30.32	
High	6.94		28.33	
Physical activity		0.07		0.29
Low to moderate	9.06		29.45	
high	11.55		30.31	

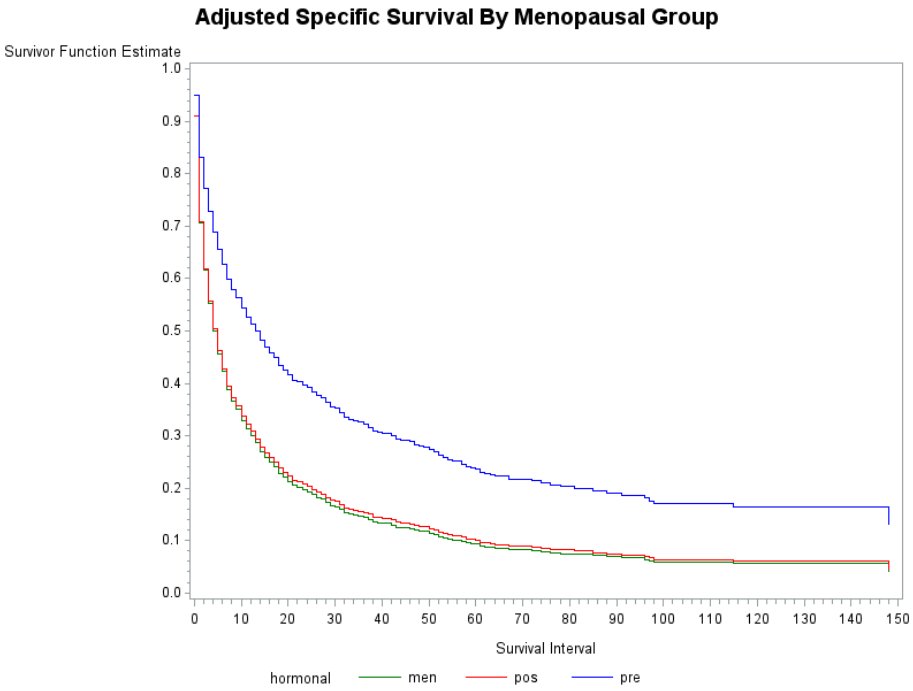

Figure IV-1: Kaplan Meier Curve for All-Cause Survival by Hormonal Status at Diagnosis, Adjusted for Age, Stage and Treatment in Kentucky Residents, 1995-2011

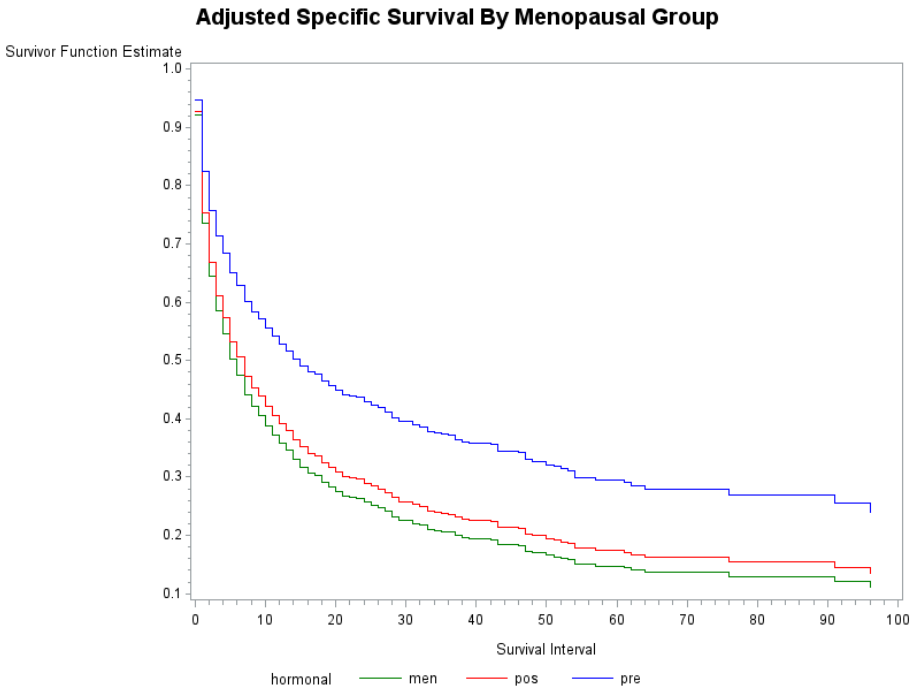

Figure IV-2: Kaplan Meier Curve for Specific Survival by Hormonal Status at Diagnosis in Kentucky Residents, Adjusted for Age, Smoking, Year Diagnosed, Treatment, County-level % Binge Drinking, 1995-2011

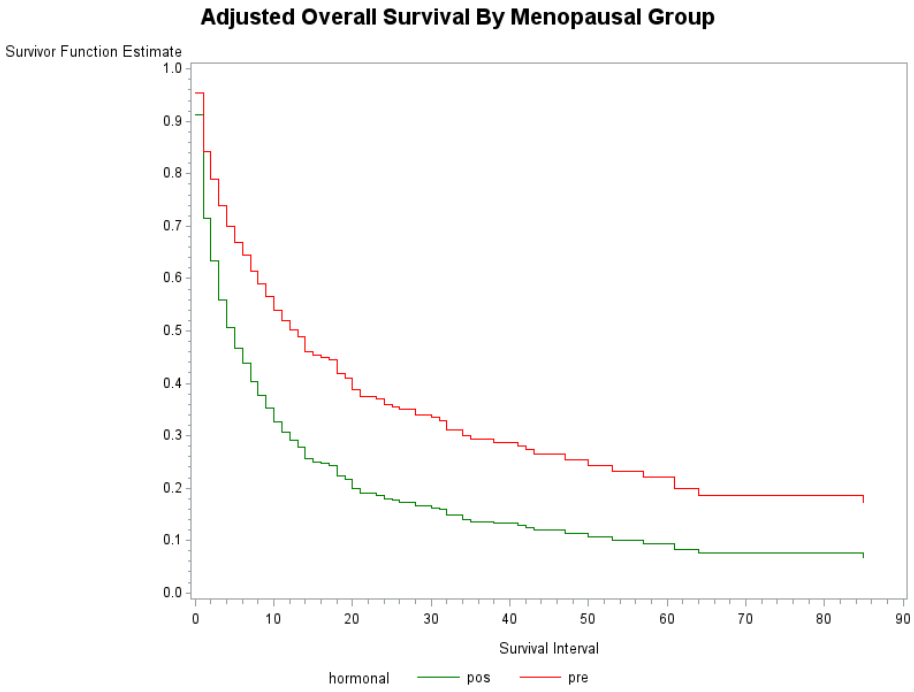

Figure IV-3: Kaplan Meier Curve for All-Cause Survival by Menopausal Status at Diagnosis, Adjusted for Age, Stage and Treatment in Female Kentucky Residents, 1995-2011

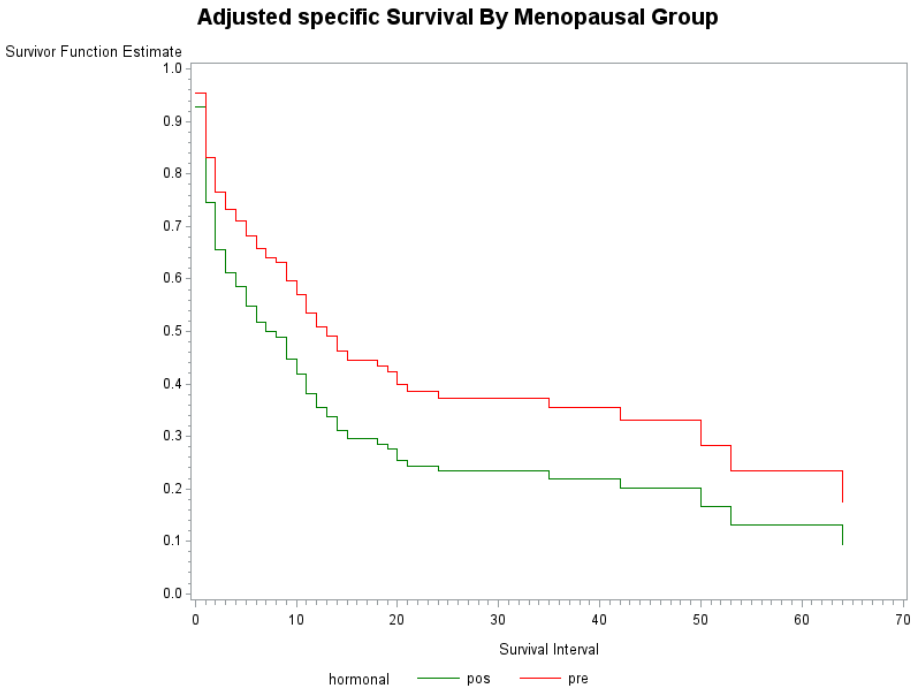

Figure IV-4: Kaplan Meier Curve for Specific Survival by Menopausal Status at Diagnosis in Female Kentucky Residents, Adjusted for Age, Smoking, Year Diagnosed, Treatment, County-level % Binge Drinking, 1995-2011

Men and post-menopausal women had a 1.75-fold and 1.7-fold higher hazard of dying no matter the cause, compared to pre-menopausal women (Table IV.3). In unadjusted specific survival, men and post-menopausal women had a significant 1.5-fold increased risk of cause-specific mortality, compared to pre-menopausal women.

Table IV.3: Adjusted and Unadjusted Hazards Ratios for Overall and Cause Specific Mortality among Kentucky Cancer Cases, 1995-2011

	Unadjusted HR & (95% CI)	Adjusted HR & (95% CI)
All-cause survival		
Men	1.75 (1.3 – 2.36); p=0.0003	1.38 (0.98 – 1.96)*
Post-menopausal women	1.70 (1.24 – 2.32); p=0.0009	1.38 (0.96 – 2.0)*
Liver-cancer specific survival		
Men	1.5 (1.1 – 2.1); p=0.01	1.63 (0.78 – 1.74)#
Post-menopausal women	1.45 (1.03 – 2.04); p=0.03	1.19 (0.78 – 1.83)#

*Adjusting for age, treatment, stage, and two-way interaction between treatment and stage
#Adjusting for age, smoking, year diagnosed, treatment, stage, and two-way interaction between treatment and stage

The full complete model for the Cox regression included all the covariates that were found statistically significant in the overall and specific survival analysis by covariate (see Table IV.2).

In the final adjusted model, the covariates that were predictive of a better overall survival were being a premenopausal woman, diagnosed at an early stage and having been treated. Both men and post-menaupausal women had a 1.38-fold increase in the risk of dying no matter the cause compared to pre-menopausal women. Compared to those diagnosed early, late stage cancer patients had an average 1.5-fold increase in the risk of dying from all causes with radiation patients having the higest increase (2.2-fold). As expected, patients without any treatment had the highest risk of death, with a

5.3-fold and 4.9-fold increased risk of all cause death, for early and late stages, respectively when compared to their counterparts who had surgery. In early stages, the risk of death increased 3.1-fold, 2.9-fold, 2.8-fold in other treatment, radiation and chemotherapy , respectively compared to surgery. In late stage, the risk of death increased 3.3-fold, 2.7-fold and 2.2-fold in radiation therapy, other treatment and chemotherapy compared to surgery. Although the hazard of dying increased with increasing age, the difference was not significant.

Table IV.4: Adjusted Hazard Ratios for Liver Cancer-Overall Survival in Kentucky Residents, N=1646, 1995-2011 (Fitted, Reduced Model)

Parameter	Hazard Ratio	95% Hazard Ratio Confidence Limits	P value
Hormonal status			0.16
Pre-menopausal women	Referent		
Men	1.38	0.98 – 1.96	0.06
Post-menopausal women	1.38	0.96 – 2.0	0.08
Age			0.09
20-49	Referent		
50-64	1.04	0.87 – 1.25	0.6
65-74	1.18	0.97 – 1.43	0.09
≥75	1.19	0.98 – 1.46	0.08
Stage at diagnosis			<.0001
Early stage	Referent		
Late stage, chemotherapy	1.45	1.15 – 1.82	
Late stage, no treament	1.76	1.52 – 2.04	
Late stage, other	1.64	0.67 – 4.06	
Late stage, radiation therapy	2.20	1.15 – 2.20	
Late stage, surgery	1.90	1.47 – 2.47	
Treatment			<0.0001
Surgical treatment	Referent		
Chemotherapy, early stage	2.88	2.25 – 3.68	
No treatment, early stage	5.30	4.37 – 6.42	
Other, early stage	3.14	1.66 – 5.96	
Radiation therapy, early stage	2.91	1.62 – 5.24	
Chemotherapy, late stage	2.19	1.69 – 2.83	
No treatment, late stage	4.89	3.84 – 6.24	
Other, late stage	2.72	1.36 – 5.43	
Radiation therapy, late stage	3.36	2.29 – 4.93	

Specific survival was associated with smoking status, year diagnosed, treatment and stage (Table IV.5). Smokers had a 1.2-fold increased risk compared to non-smokers after adjusting for hormonal status, age at diagnosis, year diagnosed, treatment and stage at diagnosis. Compared to those diagnosed in 2010-2011, patients diagnosed in 1995-1999 and 2004-2009 had both a 1.3-fold increased risk of liver cancer specific death, after adjusting for age, hormonal status, smoking, treatment and stage while those diagnosed in 2000-2004 were not different from the referent group.

Compared to surgical treatment, those without any treatment had an average 6-fold increased liver cancer specifc risk of death in early and late stages, respectively after adjusting for age, hormonal status, smoking, year diagnosed and stage. In early stage, the specific risk of death increased from other treatment to radiation and chemotherapy while the increase rose from chemotherapy to other treatment, and radiation therapy in late stage.

Compared to the early diagnosis, late stage liver cancer cases have a risk of death that increases from those with chemotherapy (1.6-fold) to no treatment (1.9-fold), surgery (2-fold), other treatment (2.3-fold) and radiation (2.9-fold).

Table IV.5: Adjusted Hazard Ratios for Liver Cancer -Specific Survival for Kentucky Residents, N=1333, 1995-2011 (Fitted, Reduced Model)

Parameter	Hazard Ratio	95% Hazard Ratio Confidence Limits	P value
Hormonal status			0.70
Pre-menopausal women	Referent		
Men	1.12	0.78 – 1.74	0.46
Post-menopausal women	1.20	0.78– 1.83	0.66
Age at diagnosis			0.43
20-49	Referent		
50-64	0.98	0.78 – 1.24	0.88
65-74	1.13	0.86 – 1.43	0.33
≥75	1.07	0.83 – 1.38	0.60
Smoking			0.059
Non-smoker	Referent		
Smoker	1.2	1.0 – 1.4	
Year diagnosed			0.01
1995-1999	1.32	1.05 – 1.65	0.02
2000-2004	1.02	0.83 – 1.27	0.84
2005-2009	1.25	1.03 – 1.51	0.03
2010-2011	Referent		
Treatment			<0.0001
Surgical treatment	Referent		
Chemotherapy, early stage	3.36	2.38 – 4.73	
No treatment, early stage	6.47	4.90 – 8.54	
Other, early stage	2.51	0.79 – 8.03	
Radiation therapy, early stage	2.81	1.29 – 6.12	
Chemotherapy, late stage	2.54	1.82 – 3.56	
No treatment, late stage	5.88	4.25 – 8.12	
Other, late stage	2.75	1.16 – 6.53	
Radiation therapy, late stage	3.84	2.33 – 6.34	
Stage at diagnosis			<0.0001
Early stage	referent		
Late stage, chemotherapy	1.60	1.19 – 2.16	
Late stage, no treament	1.93	1.60 – 2.32	
Late stage, other	2.32	0.58 – 9.35	
Late stage, radiation therapy	2.90	1.24 –6.76	
Late stage, surgery	2.12	1.47 – 3.06	

To consider the role of childbearing on the effect of menopausal status in liver cancer survival, we performed a proportional hazard Cox regression on a sub-sample of women with available childbearing data. Table IV.7 presents the hazards ratios generated for both overall and specific survival.

Postmenopausal women had a non significant 2.2-fold increase in the risk of all-cause death compared to premenopausal women, after adjusting for the number of live births age at diagnosis, stage, treatment received and county-level % of physical activity. The specific liver cancer risk of death is increased by 30% in postmenopausal women compared to their premenopausal counterparts, after adjusting for childbearing, age, stage, treatment and county-level physical exercise. These differences were not statistically significant.

The adjusted risk of all-cause mortality and liver cancer specific mortality decreased with increasing number of live births although the difference was not significant. Compared to childless women, the adjusted risk of all-cause death increased by 80% and 50% in women with 1-2 live births and ≥2 live births, respectively while the risk of liver cancer mortality decreased by 10% in women with more than two live births.

Age at diagnosis is associated with both all-cause and liver cancer specific mortality, which increased with increasing age, with hazard ratios close to the significance level. Early-stage at diagnosis, surgical type of treatment, residence in county with ≥70% of people exercising were predictive of better survival. Late-stage diagnosis increased by 70% the risk of all-cause death, compared to early stage, after adjusting for age, menopausal status, childbearing, treatment and county level % of

exercise. Compared to surgical treatment, patients whithout any treatment regimen had an almost 5-fold increased risk of all-cause mortality, while radiation therapy and chemotherapy had a 2.5-fold and 2-fold increase, respectively after adjusting for age, menopausal status, childbearing, stage and county level % of exercise. Other treatment was not significantly different from surgery for both all-cause and liver cancer mortality.

Liver cancer specific mortality is associated with late stage diagnosis (2.2-fold increased mortality), treatment and county-level yearly income. The increased risk of liver cancer mortality was respectiveley 6-fold, 3.5-fold and 3.2-fold in patients with no treatment, radiation therapy and chemotherapy. Surprisingly, patient from county with yearly household income ≥$20,000 had 60% more risk than their counterparts residing in counties with yearly income <$15,000.

Table IV.6: Hazard Ratios for Liver Cancer Survival in Kentucky Female Residents, 1995-2011

Covariates	Overall survival N=409			Specific survival N=413		
	Hazard Ratio	95% HR CL	P value	Hazard Ratio	95% HR CL	P value
Menopausal status			*0.09*			*0.7*
Pre-menopausal	Referent	1		Referent		
Post-menopausal	2.2	0.9 – 5.7		1.3	0.4 – 3.7	
Live births			*0.3*			*0.9*
0	Referent			Referent		
1-2	1.8	0.8 – 4.0	*0.2*	1.0	0.4 – 2.4	*1*
>2	1.5	0.7 – 3.2	*0.4*	0.9	0.4 – 2.2	*0.9*
Age at diagnosis			*0.08*			*0.07*
20-49	Referent			Referent		
50-64	0.4	0.2 – 1.0	*0.05*	0.4	0.1 - 1.2	*0.2*
65-74	0.7	0.3 – 1.9	*0.5*	0.9	0.3 – 3.0	*0.8*
≥75	0.8	0.3 – 2.1	*0.6*	0.9	0.3 – 2.9	*0.9*
Stage at diagnosis			*0.01*			*0.001*
Early stage	Referent			Referent		
Late stage	1.7	1.1 – 2.5		2.2	1.4 – 3.4	
Treatment			*<0.0001*			*<.0001*
Surgical treatment	Referent			Referent		
Chemotherapy	2.0	1.1 – 3.7	*0.02*	3.2	1.6 – 6.4	*0.001*
No treatment	4.6	2.7 – 7.9	*<.0001*	6.0	3.1 – 11.7	*<.0001*
Other	0.9	0.1 – 7.5	*1*	1.4	0.2 – 11.4	*0.9*
Radiation therapy	2.5	1.0 – 6.1	*0.05*	3.5	1.3 – 9.6	*0.005*
Physical activity			*0.005*			
Low to moderate	Referent					
High proportion	1.7	1.2 – 2.5				
County-level county-level yearly income						*0.04*
				Referent		
<15,000				0.8	0.5 – 1.5	*0.5*
15,000-20,000				1.6	1.0 – 2.7	*0.07*
≥20,000						

Discussion

Our main findings from this large population-based study which adjusted for age and menopausal status in particular, show that early stage at diagnosis and treatment are predictive of better overall survival while early stage at diagnosis, year of diagnosis, non-smoking status and treatment regimen were predictors for a better specific survival.

Menopausal status and age were not significantly associated with survival. However, our gender difference in all-cause and liver cancer specific survival, is close to statistical significance, hinting to an effect of gender on survival, which is consistent with the published literature. Indeed, an improved survival in female has been reported by Dohmen et al.[48] who hypothesied that the difference may be due to the lead-time bias. Beal et al. have also reported increased mortality rates in males [73]. A review by Cook found a 17% increased risk in males compared to females, with a steadily increasing male to female mortality rate ratio of 2.03, 2.18 and 2.33 for the periods 1977-1986, 1987-1996 and 1997-2006, respectively [74].

Our results show that premenopausal women had better five years survival than both men and postmenopausal women, which corroborates the increased risk in males found in other studies.

We found a 20% increased risk of cause-specific deaths in smokers, which has also been reported by Siegel et al. and Shih et al. [50,51]. However, the magnitude of the difference they found is bigger (60% and 70% increased mortality) and may be attributed to the fact they investigated the joint effect of smoking and drinking on liver cancer survival. Evans et al. found that smoking was associated with a decreased survival in female only [75]. Jee et al. also found a 40% increased risk of death in current

smokers compared to never smokers [11]. The observed increased mortality in smokers may be attributed to the presence of toxic metabolites from smoking able to increase cancer aggressiveness or the presence of comorbidities that will prevent smokers from benefiting from treatment.

Year of diagnosis was another predictor of survival. Patients diagnosed before 2000 and between 2005 and 2009 had 32% and 25% increased risk for cause-specific mortality than those diagnosed after 2010. This decrease in the risk of death with time has also been observed by Beal et al. in recent birth cohorts [73] as did Altekruse et al. [9,61]. As expected, early stage diagnosis and treatment were associated with an improved survival rate. Patients diagnosed late and did not receive any treatment had an increased risk of cause-specific death of 93% compared to those who were diagnosed early and had surgery. Similar to our results, several authors have found an improved survival in early stage patients, which is understandable given the wider treatment range available to them [76–78]. Surveillance allowed the detection of early cases and increased by two-fold the receipt of curative treatment [76].

To our knowledge, this study is the first to investigate liver cancer mortality in Kentucky. The major strength if this study is that the data was provided by KRC, which is a reliable and complete source for cancer incidence and mortality data for the state. The use of the Cox multivariable regression method allowed to control for risk factors as well as possible confounders as well as deal with censoring and delayed entry, as patients are included at the time of cancer diagnosis that is different for each participant.

Our study has several limitations however. Hepatitis virus infections (B, C), screening practice, intensity or duration of smoking and alcohol consumption have been

associated with survival but we have not been able to explore those variables in our analysis. More than 20% of our study sample has an unknown smoking status; this could have underestimated the hazard ratio associated with smoking. Our analysis used county-level obesity proprotion and county-level variables for assessing socioeconomic status. Furture use of individual-level variables may allow a clearer picture of the predictors of HCC survival. Finally, Kentucky has a very homogenous ethnic distribution which limits the generalization of this study to other populations.

Our findings confirm the role of smoking status, as well as stage at diagnosis, year of diagnosis and treatment on the survival rates of liver cancer patients. The impact of screening, gender differences and the conjoining role of smoking and drinking (highly correlated) need to be further investigated.

V. CHAPTER 5: CONCLUSION

This capstone project aimed to identify and describe the risk factors of late-stage HCC diagnosis in Kentucky residents between 1995 and 2011 as well as identify the factors predicting better survival. Our findings can be used to increase HCC awareness within both the public and health care providers given the increasing HCC incidence in the state and its high lethality. These results can be used for planning of interventions to better target the highest risk population. They offer also an orientation on future research.

Summary of Findings

Our working hypothesis for the investigation on the risk factors of late-stage liver cancer was that a higher risk of being diagnosed with late-stage liver cancer will be seen with black race; Appalachian residence; low county-level education level; county-level binge drinking and single status. Our analysis of the 2,205 liver cancer cases that occurred between 1995 and 2011 and retrieved from KCR did not show that Appalachian residence, low county-level education level and single status conferred a higher risk of late-stage liver cancer diagnosis. Nevertheless, our analysis confirms previous studies that race and county-level proportion of binge drinking (as continious variable) increased the risk of late-stage diagnosis[15,33,62–65]. Our results also concurred with other authors that racial and ethnic differences are an important risk factor. Wong found that blacks had more than double the incidence in Caucasians[79].

In addition to the covariates in our hypothesis, our results found male gender, age between 65 and 74 years, lack of insurance and diagnosis before 2000 to give higher risk of HCC late diagnosis. Male gender is a known risk factor of both incidence

and mortality of HCC as is evidenced in numerous studies [21,62,71] the mechanisms for the increased risk may be through the absence of estrogen as has been shown by McGlynn et al. who found that surgical menopause by bilateral oophorectomy increased HCC risk in women[80]. Older age has been observed to increase the risk of HCC [21,71]. We also found a decreasing trend over time in the risk of HCC late-stage diagnoses, which correspond to the global trend in liver cancer incidence [4,6,7,59]. Our report showed that county-level binge drinking increased the risk of late-stage HCC, as did Jee et al. in Korea with individual alcohol intake ≥100g confering a 1.4-fold higher risk of HCC [11] and Chuang et al. who reported 19%, 40% and 81% higher risk of HCC for 25, 50 and 100 g of daily alcohol intake and believed there is no safe alcohol threshold for risk of developing liver cancer [81]. Consequently, the population with the highest late-stage HCC risk in this Kentucky sample are the black, uninsured males aged 50 and older, diagnosed before the year 2000 and living in counties with higher proportions of binge drinking.

For the second paper (chapter 4), we hypothesied that early-stage diagnosis, female gender and non-smoking status would confer a better liver cancer survival. Our results showed that early stage at diagnosis and treatment were predictive of better overall survival while early stage at diagnosis, year of diagnosis, non-smoking status and treatment regimen were predictors for a better specific survival.

We did not find evidence that females had significantly lower mortality whether all-cause or cause-specific than males, although we found that men and post-menopausal women had a similar risk, hinting at a possible role of sex hormones. A protective effect of female gender on liver cancer all-cause mortality was found by

Artinyan et al., women having 8% less risk than men [82]; Dong et al. showed that females had lower risk of cause-specific mortality compared to men in a study of the effect of alcohol use on HCC mortality [83].

Early-stage at diagnostic was a strong predictor of better all-cause and cause-specific survival, reducing by more than half the risk of death. This finding is comparable to the worsening survival of uninsured HCC cases diagnosed late in Tennessee found by Zaydfudim et al. [78]. Treatment regimen was strongly associated with survival. HCC cases who recieved any type of treatment had better survival than their counterparts with no treatment with surgical patients having a six-fold risk reduction. Other authors have shown better HCC survival in patients eligible for surgery and chemotherapy compared to other regimens [53,54,84]. Our analysis shows a 20% increased risk of cause-specific mortality in smokers. The role of smoking has been intensely investigated with disimilar results. Our finding confirms that of Mangus et al. that smoking has a worsening effect on HCC survival, with the risk increasing with increasing intake [85]. On the other hand, Raffetti et al. found that although smoking was associated with some features predicting better survival, it did not have an effect on survival when also considering the number of cigarettes smoked daily or the cumulative pack-year [86]. Finally, we showed that survival increased with time of diagnosis, confirming previous findings of increasing survival rates attributed to earlier diagnosis and more eligibilty for treatment [9,15,61,87].

The results from both papers should be beneficial to health care professionals in the management of HCC in the state, whether in the design of targetted interventions to

increase prevention or survival by increasing the number of early-stage diagnoses which are eligible for more treatment options.

Implications for Public Health

According to the Center for Disease Control and Prevention, the public health system is defined as “all public, private, and voluntary entities that contribute to the delivery of essential public health services within a jurisdiction”[88]. In order to deliver services of quality, public health professionals need to know all the determinants that may influence a particular health problem within a particular population, that is at higher risk. A population’s health is controlled by the five determinants of health that are biological, socioeconomic, psychosocial, behavioral, or social in nature [89].

Through this capstone project, we endeavored to define the most sucesptible population by assessing the influence of biology, behavior and socieconomic environment on liver cancer in Kentucky. Liver cancer incidence and mortality rates have been increaseing over the last two decades in the United States, with a significant average annual percentage change of 2.7% (incidence) and 2.5% (mortality) [58,90]. HCC occurs mostly in older males with limited access to healthcare and low SES [47,68,78]. This capstone upholds previous findings and confim that the intervention efforts should be targeted towards older black men, without health insurance and living in counties with heavy alcohol use. Health professionals should focus screening efforts for an effective surveillance to reduce late-stage diagnosis that may be beyond any therapeutic reach. Furthermore, we must advocate for an universal health coverage to increase acces to healthcare through policy change.

More than 50% of patients in our series did not receive treatment and only 40% had access to potentially curative treatment (surgery and chemotherapy). Previous sudies have established how critical treatment is to the survival of HCC patients [52–54,84,91]. With a mean survival time of only one year and less than 5% of patients surviving after 5 years, epidemiologists should focus on studying the factors delaying both early diagnosis and treatment in Kentuckians. The factors worsening the survival of HCC patients should be made public so that awareness is raised among both the public and health professions. Concurrently, to reverse the current trend of increasing HCC, public health leaders should provide policy makers with results that trigger changes leading to increased health coverage within the state and increased access to healthcare for vulnerable populations.

Strenghts and limitations

This capstone has several strenghts. It is the first to assess the risk factors of late-stage HCC and its survavibilty in Kentucky. Another strength is our data source. The KCR is undeniably an excellent source of reliable and comprehensive data of HCC cases in the State. While papers have explored extensively the risk of HCC incidence and mortality, few investigated determining factors of late-stage diagnosis. Moreover, survival studies have seldom researched the independent role of sex hormones on HCC survival. This capstone aspired to fill the gap in knowledge.

Several limitations may impede the results of our research. The major limitation is the lack of individual-level data concerning key covariates. SES was estimated through county-level data of income, education and poverty level. With 120 counties in the state, the results reported may have accounted for a lack of precision. Future

studies should estimate at narrower level or better have access to individual data. Likewise, alcohol intake, obesity and overweight status was evaluated at the county-level, but their impact would have been more pertinent if these variables were associated with individuals.

Viral hepatitis is a critical predictor of HCC and the fact that our series lacked data on the infectious status of our cases was another limitation.

Recommendations

The state of Kentucky has a relatively homogenous racial and ethnic population with most of the black population living in only two counties, Jefferson and Christian. Therefore in this study it was difficult to assess the affect of race on HCC survival, unlike the reports by other authors. Future research should explore HCC survival in more heterogenous study populations.

SES has an important role in health and well-being of population, and its interpretation is conditioned by the way it is defined. It is important to understand the importance of SES and its interaction with race and ethnicity as well as its impact on HCC risk. Future studies should design suitable measurement to account for all social determinants of health.

With the continued increase in the incidence and mortality of HCC and given the uncertainty around healthcare access, it is imperative to for researchers to study the cost-effectiveness of care for the procurement of the best quality of HCC management for Kentuckians.

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ce_options=&search_stat_list=s10&search_site_list=c14&search_race_list=&Mid=884&Mid=885&Mid=886&Mid=889&Mid=895#results. Accessed December 6, 2017.

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VITA

Zilahatou Bahari-Tohon

Date of birth: February 19, 1970

Place of birth: Dan Issa, Maradi (Republic of Niger)

EDUCATION

MPH: Epidemiology and biostatistics, Victor Segalen Bordeaux II University, Bordeaux, France, 2007

MD: Abdou Moumouni Niamey University, Niamey, Niger, 1999

ADDITIONAL PROFESSIONAL EDUCATION AND TRAINING

Intensive course on multivariate analysis applied to epidemiology: Free University of Brussels, Brussels, Belgium 2005

Regional training workshop in ultrasonography for the evaluation of morbidity due to schistosomiasis: Niger Ministry of Health, Niamey, Niger 2004

Inter University Diploma CESAM: Pierre & Marie Curie University, Paris, France 2004.

Clinical trials and tropical and infectious diseases Diploma: Pasteur Institute Infectiology School, Paris, France 2003

Training on Abdominal and Obstetrical ultrasonography: Anvers University/MoH, Niamey, Niger, 2002

WHO Course on Transmissible Diseases Surveillance: Swiss Tropical Institute, Lausanne, Switzerland, 2001.

PROFESSIONAL EXPERIENCE

April 2017 to present: **Independent Consultant,** Reseau International Schistosomoses, Environnement, Amenagement et Lutte (RISEAL) Niamey, Niger

Participation in surveys and studies (drafting of protocols, supervision of data collection, data analysis, report writing, participation in the writing of articles).

2012-2015 : DrPH Practicum experiences

2012: Clark County local health department: secondary collection of health data, analysis of community survey and writing of the report.

2015: Kentucky Cancer Consortium: literature review, writing of a white paper and development of an infograph on obesity and skin cancer; review of new evidence on skin cancer.

Centre de Recherches Médicales et Sanitaires (CERMES), Niamey, Niger: 2000–2011.

Epidemiology unit: research assistant, investigator, medical office

January 2006 – June 2011: **Research Assistant at the Epidemiology unit**

Responsible of meningococcal carriage cohort study in the framework of the introduction of an anti-meningococcus A conjugate vaccine: participation in protocol writing, public explanations, inclusion of participants, home visits, interviews, pharyngeal sample collections.

Coverage surveys after mass drug administration: led field teams, made interviews, analysed data and wrote reports.

Principal investigator of a study on the “Evolution of the health of schoolchildren after implementation of sanitary facilities in schools:” led field team, interviews, ultrasound examination, data analysis and reports.

Investigator in the carriage study of meningococcus X serogroup: field team leader, public explanations, active search of cases, home interviews, sample collections, data entry supervision, data analysis, study report.

Principal investigator of a preliminary study on the nature and the frequency of bacterial meningitis sequelae in Niger: wrote research protocol, field work (active search of cases, interviews, clinical and audiometric examinations), data analysis and study report.

Responsible of field studies in the framework of the monitoring and evaluation of the schistosomiasis and soil-transmitted helminths national control programme: field team leader, performed ultrasounds, data analysis and reports and articles writing.

Co-investigator of a HIV seroprevalence study among pregnant women and prostitutes: field team, data analysis and wrote study report and article.

2003-2005: **Research Intern and responsible of the medical office**

Principal investigator of the survey “Comparison of the vitro sensibility to anti-malarial drugs of *P.falciparum* in pregnant women during pregnancy and in the placentas of the same women after deliverance”: inclusion of study participants, supervision of medical doctoral student.

Organisation and conduct of field studies in the framework of the monitoring of the Schistosomiasis National Programme.

2000-2002: **Investigator**

Co-investigator in the HIV seroprevalence survey in pregnant women in 2002: interviews, sample collections, data analysis.

Co-investigator in the BILVHAX clinical trial: clinical examination of participants, interviews, field ultrasounds, vaccine administration with post-vaccine surveillance, home visits.

Responsible of the medical office: medical consults, drug management.

CONSULTATION WORK

Niger's Neglected Tropical Diseases Program, 2008-2009: Coverage survey after mass drug administration. Team leader for field missions. Planning, budgeting, data entry supervision, data analysis and report

WHO Regional Office for Africa, 2010-2011: Epidemiologist on the multi-country study exploring Community Perceptions and Perspectives about Health Systems in Africa. Participated in protocol writing, budgeting, field agents training, supervision and data analysis.

PUBLICATIONS

Boubacar Mainassara H, Tohon Z. Assessing the Health Impact of the following Measures in Schools in Maradi (Niger): Construction of Latrines, Clean Water Supply, Establishment of Hand Washing Stations, and Health Education. *Journal of parasitology research*. 2014; 2014:190451.

Jusot JF, Tohon Z, Yazi AA, Collard JM. Significant sequelae after bacterial meningitis in Niger: a cohort study. *BMC infectious diseases*. 2013; 13:228.

Garba A, Toure S, Dembele R, et al. Present and future schistosomiasis control activities with support from the Schistosomiasis Control Initiative in West Africa. *Parasitology*. Nov 2009; 136(13):1731-1737.

Tohon ZB, Mainassara HB, Garba A, et al. Controlling schistosomiasis: significant decrease of anaemia prevalence one year after a single dose of praziquantel in Nigerian schoolchildren. *PLoS neglected tropical diseases*. 2008; 2(5):e241.

Tohon Z, Mamadou S, Mainassara HB, et al. HIV seroprevalence surveys in Nigerien pregnant women: a comparison between 2002 and 2006. *Transactions of the Royal Society of Tropical Medicine and Hygiene.* Nov 2007; 101(11):1101-1105.

Tohon Z, Garba A, Amadou Hamidou A, et al. [Behaviour and HIV seroprevalence investigation in sex workers of Dirkou, Niger, 2002]. *Bulletin de la Societe de pathologie exotique.* Mar 2006; 99(1):49-51.

Garba A, Labbo R, Tohon Z, Sidiki A, Djibrilla A. Emergence of Schistosoma mansoni in the Niger River valley, Niger. *Transactions of the Royal Society of Tropical Medicine and Hygiene.* May 2004; 98(5):296-298.

Garba A, Tohon Z, Sidiki A, Chippaux JP, de Chabalier F. [Efficacity of praziquantel in school-aged children in a hyperendemic zone for Schistoma haematobium (Niger, 1999)]. *Bulletin de la Societe de pathologie exotique.* Mar 2001; 94(1):42-45.

AWARDS AND GRANTS

2011-2014: Fulbright scholarship, Institute of International Education (IIE), 1400 K Street NW, Suite 700, Washington, DC 20005

2011-2012: World Fellowship, The Delta Kappa Gamma Society International. P.O. Box 1589 Austin, TX 78767-1589

2010 : Travel grant, Institut Pasteur International Network (RIIP), Institut Pasteur, 25-28 Rue Du Docteur Roux, 75015 Paris, France.

2006-2007: Study grant, Institut Pasteur International Network (RIIP) Institut Pasteur, 25-28 Rue Du Docteur Roux, 75015 Paris, France.

2005: Study grant, Belgium Development Agency, Boulevard Mali Bero, Avenue du Mounio BP 12987, Niamey Niger

2001: Study grant, World Health Organization, Avenue Appia 20, 1211 Geneva 27, Switzerland

CONFERENCES ACTIVITY/PARTICIPATION

Z Tohon, H Boubacar, R Yahaya, B Abdou, P Boisier. Five years follow-up of schoolchildren infected with schistosomiasis in Niger: evidence of the benefit of a regular praziquantel administration on the reinfection. Scientific Conference of the International Network of Pasteur Institutes, Hong-Kong November 2010. Poster.

Tohon Z, Boubacar Mainassara H, Garba A, Elhaj Mahamane A, Bosqué-Oliva E, Ibrahim ML, Duchemin JB, Chanteau S, Boisier P. The burden of parasitic infections in the anaemia of schoolchildren in Niger. Scientific Conference of the International Network of Pasteur Institutes, Paris June 2008. Poster.

Impact of praziquantel on schistosomiasis related morbidity in Niger from 2004 to 2007. Regional workshop on Overview on research and control of schistosomiasis and STH in Africa. Bamako, Mali July 2007. Oral communication.

Z Tohon, H Boubacar Mainassara, A Elhaj Mahamane, A Garba, E Bosque-Oliva, S Chanteau, P Boisier. Impact of a praziquantel single dose treatment on the morbidity due to S. haematobium in school children in Niger. 11th International Congress of Parasitology, August 2006 Glasgow, Scotland. Poster.

Z Tohon, A ElHaj Mahamane, A Garba, S Chanteau, P Boisier. Relationship between Schistosoma haematobium infection and anaemia in Nigerien children: not so simple.

Congress Medicine and Health in the Tropics: September 2005, Le Pharo, Marseilles. Poster.

HIV/AIDS seroprevalence survey in pregnant women of sanitary districts of Loga, Arlit and Mirriah and prostitutes of Dirkou. Workshop of restitution to Government. Niamey, April 2003. Oral communication

LANGUAGE SKILLS

Language	Reading	Speaking	Writing
French	Excellent	Excellent	Excellent
English	Excellent	Excellent	Excellent
Hausa	Good	Excellent	No
Zarma	No	Excellent	No

MEMBERSHIP OF PROFESSIONAL BODIES:

Member of the Niger National Order of physicians, pharmacists and dentists

Founding member of AIRSE (Association Intervention en Recherche, Santé et Environnement)

Member of Réseau International Schistosomoses, Environnement, Aménagement et Lutte (RISEAL, International Network for Schistosomiasis, Environment, Planning and Control)

Member of Société de Pathologie Exotique (SPE).

Member of the Royal Society of Tropical Medicine and Hygiene

Founding member of Réseau Femmes, Sciences et Technologies du Niger (Network of Nigerien women in sciences and technologies)

OTHER SKILLS:

Software: SAS, SPSS, EpiInfo, Microsoft office (Word, Excel, Power Point, …), EndNote, Zotero