

## ORIGINAL ARTICLES

# Association between the job types and the risk of hepatocellular carcinoma in the United States

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**Received:** April 15, 2016

**Accepted:** June 16, 2016

**Online Published:** August 9, 2016

**DOI:** 10.5430/jer.v3n1p1

**URL:** <http://dx.doi.org/10.5430/jer.v3n1p1>

## ABSTRACT

**Background:** Hepatocellular carcinoma (HCC) has many well-known predisposing factors including viral hepatitis, alcohol consumption, metabolic syndrome, and cigarette smoking. However, about 30%-40% of patients have no identifiable risk factor, indicating the presence of additional causes that are yet to be discovered. Our study aim was to evaluate the association between the risk of HCC and various occupations.

**Methods:** We conducted a hospital based case-control study that included 589 HCC patients and 1,098 healthy controls. Multivariate unconditioned logistic regression models were done to control for the confounding effects of well-known HCC risk factors.

**Results:** Female sales workers have a significantly higher risk of HCC; after adjusting for demographic factors, cigarette smoking, drinking alcohol, diabetes mellitus, viral hepatitis, and family history of cancer; the adjusted odds ratio (AOR) and 95% confidence interval (CI) was (2.8; 1.3-6.0). In contrast, there was a protective association between managers and HCC, which remained statistically significant for females after adjusting for confounding factors (OR, 0.2; CI, 0.05-0.6). With regard to the duration of occupation, sales workers had no increased risk with job duration, whereas managers working for more than 25 years were at lower risk for HCC development.

**Conclusion:** To the best of our knowledge, this is the first and largest epidemiological study to observe such associations in USA. The underlying biological explanation should be explored in future experimental studies.

**Key Words:** Occupation, Exposure, Hepatocellular carcinoma

## 1. INTRODUCTION

Hepatocellular carcinoma (HCC) is the fifth most common cancer and the second cause of cancer related mortality

worldwide.<sup>[1-3]</sup> The peculiar geographical variation in the incidence of HCC reflects the variation in the prevalence of HCC risk factors worldwide. Hepatitis B virus (HBV)

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is the main risk factor in sub-Saharan Africa and Southeast Asia, accounting for about 80% of cases, whereas hepatitis C virus (HCV) is the major cause in North America, Europe, and Japan.<sup>[1]</sup> Other risk factors include alcohol consumption, cigarette smoking, and metabolic syndrome.<sup>[2,4]</sup> In the United States, the incidence of HCC has doubled over the past three decades.<sup>[2]</sup> This dramatic increase in incidence has been attributed primarily to HCV infection.<sup>[2]</sup> However, about 30%-40% of HCC cases cannot be explained by a well-known risk factors, indicating the presence of other causes that are yet to be discovered.<sup>[3]</sup>

Given the geographical distribution of HCC, lifestyle and types of work may partially explain such variation between countries. Although large cohort studies have confirmed exposure to vinyl chloride as a risk factor for developing liver angiosarcoma, a similar occupational association has not been established for HCC.<sup>[5-7]</sup> Some studies have suggested that workers in the food preparation and serving industry, including employees in breweries, distilleries, restaurants, hotels, and bars, are at higher risk of developing HCC, which was partially explained by exposure to alcohol.<sup>[8-10]</sup> Similarly, health care professionals such as laboratory technicians, surgeons, anesthesiologists, and dialysis nurses were also found to be at higher risk of developing HCC because of their daily exposure to blood or blood products and therefore were at higher risk of acquiring HBV or HCV infections.<sup>[11,12]</sup> Accordingly, the association between these occupations and HCC is due to an established connection between the jobs and known risk factors for HCC.

Despite available reports suggesting a possible association between diverse occupational fields and primary liver cancer (PLC), only four epidemiological studies have been conducted specifically for HCC.<sup>[9,13-15]</sup>

In light of the above findings, more studies are needed to assess the actual contribution of occupational exposure as an independent risk factor for HCC development among American population. Therefore, we examine the association between various occupations and the risk of HCC among Americans after adjusting for the potentially confounding main HCC risk factors in our current large-scale case-control study.

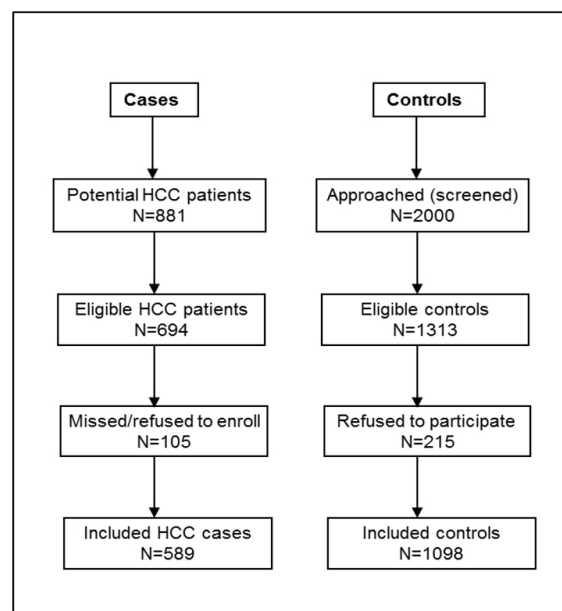
## 2. MATERIALS AND METHODS

### 2.1 Study design and population

This study is part of an active case-control study at The University of Texas M.D. Anderson Cancer Center. The study was approved by the Institutional Review Board.<sup>[4,16-18]</sup> Case patient was pathologically or radiologically diagnosed with HCC who were referred for treatment at gastrointestinal med-

ical oncology and surgical oncology outpatient clinics at MD Anderson. All case patients were resided in U.S with no history of other cancers.

The healthy control individuals are defined as healthy subjects without past medical history of malignancy selected from among individuals who accompanied patients with different cancers at The University of Texas M. D. Anderson Cancer Center. To ensure that these individuals had accompanied patients with a variety of cancer types, we approached individuals at the endoscopy, chemotherapy, and diagnostic imaging clinics (computed tomography, magnetic resonance, and tomography imaging). These clinic locations were used for recruitment because they see a large pool of patients with different cancers. All controls included in the study are genetically unrelated family members (such as spouses) of cancer patients who had cancers other than liver, gastrointestinal, lung, or head and neck cancer. Family members and spouses of patients with these cancers were excluded as controls to avoid selection bias due to sharing a common genetic and environmental factors including alcohol consumption, cigarette smoking, viral hepatitis, and family history of cancer. So, the included controls were spouses of patients with breast, prostate, skin, renal, bladder, and gynecological cancers. All controls were healthy and cancer free at time of recruitment. Controls were frequency matched to HCC case patients by age ( $\pm 5$  years). We aimed at including all eligible controls who agreed to participate in the study to facilitate stratified analysis by sex.



**Figure 1.** Ascertainment of cases and controls

A short structured questionnaire was used to screen for poten-

tial controls based on the eligibility criteria. We found that 83.6% of the eligible control subjects agreed to participate in our risk assessment study (see Figure 1). A comparison between control individuals who agreed to participate in our research and those who refused revealed no significant differences in demographic characteristics and cancer type of their accompanied patients.

We personally interviewed HCC cases and controls for 25-30 minutes using a validated structured study questionnaire to collect detailed information about patients' demographics and HCC predisposing factors including viral hepatitis, diabetes mellitus, family history of liver cancer or other cancers, cigarette smoking, and alcohol drinking. Participants considered to be cigarette smokers if they had smoked  $\geq 100$  cigarettes during their lifetimes, and former smokers if they stopped smoking with  $\geq 1$  year before study enrollment. Participants considered to be heavy smokers when they had smoked  $> 20$  pack-years.<sup>[4]</sup> Also, participants considered to be alcohol drinkers if they had consumed each month at least four alcoholic drinks of beer, wine, or hard liquor for up to 6 months during their lifetimes. Then, we classified

drinkers into mild to heavy alcohol drinkers according to the amount of ethanol they consumed in milliliters during their lifetime.<sup>[4]</sup> Written informed consents from study participants were obtained. For the purpose of the current study we collected detailed histories of occupations and job exposures. Between January 2004 and December 2011, 589 HCC patients and 1,098 healthy controls were eligible and participated in the current investigation. Figure 1 shows ascertainment of eligible cases and controls.

Questions associated with work history included a list of current and prior occupations with duration of each job; job title; job description; and types of tools, equipment, and/or chemicals used. Information regarding previous substance exposure was also collected, including the type of substance and duration of exposure. Finally, all subjects were asked about their site of residence. Those who lived in a highly industrialized area were asked about their duration of residence. For the purposes of this analysis, we included only the occupation of the longest duration, regardless of whether it was the current or previous job.

**Table 1.** Association between types of occupation and risk of HCC

SOC	Occupation Classification	Cases	Controls	Univariate	Adjusted*	HCV-/HBV-#
		N = 589	N = 1,098	OR (95% CI)	OR (95% CI)	OR (95% CI)
SOC-11	Management	54	170	0.6 (0.4-0.8)	0.5 (0.3-0.8)	0.6 (0.4-0.9)
SOC-13	Business and financial operations	29	69	0.8 (0.5-1.2)	0.8 (0.5-1.5)	0.7 (0.4-1.4)
SOC-15	Computer and mathematical	6	11	1.0 (0.4-2.8)	0.6 (0.1-2.8)	0.9 (0.2-4.3)
SOC-17	Architecture and engineering	34	54	1.2 (0.8-1.8)	1 (0.7-1.8)	0.9 (0.5-1.9)
SOC-19	Life, physical, and social science	6	16	0.7 (0.3-1.8)	1 (0.3-3.3)	1.3 (0.4-4.1)
SOC-21	Community and social service	11	16	1.3 (0.6-2.8)	1.7 (0.6-4.6)	3.1 (0.9-9.0)
SOC-23	Legal occupations	12	22	1.0 (0.5-2.1)	1.7 (0.7-4.2)	1.5 (0.6-3.9)
SOC-25	Education, training, and library	28	101	0.5 (0.3-0.8)	0.9 (0.6-1.7)	1.0 (0.6-1.7)
SOC-27	Arts, design, entertainment, sports, and media	13	19	1.3 (0.6-2.6)	1.1 (0.4-3.0)	1.0 (0.3-2.9)
SOC-29	Healthcare practitioners and technical	24	64	0.7 (0.4-1.1)	1.02 (0.6-1.9)	0.9 (0.4-1.7)
SOC-31	Healthcare support occupations	6	6	1.9 (0.6-5.8)	3.1 (0.7-13.3)	3.1 (0.7-13.5)
SOC-33	Protective service occupations	14	27	1.0 (0.5-1.9)	1.2 (0.5-2.7)	1.2 (0.5-2.8)
SOC-35	Food preparation/serving related	11	12	1.7 (0.8-3.9)	0.7 (0.2-2.4)	1.2 (0.2-5.6)
SOC-37	Building/grounds cleaning/maintenance	31	69	0.8 (0.5-1.3)	1.1 (0.6-2)	0.9 (0.5-1.7)
SOC-39	Personal care and service	4	11	0.7 (0.2-2.1)	1.7 (0.5-6.2)	1.5 (0.4-6.2)
SOC-41	Sales and related	47	66	1.4 (1.1-1.9)	1.9 (1.2-3.1)	1.9 (1.1-3.0)
SOC-43	Office and administrative support	50	136	0.7 (0.5-0.9)	0.9 (0.6-1.4)	0.9 (0.5-1.4)
SOC-45	Farming, fishing, and forestry	8	18	0.8 (0.4-1.9)	0.9 (0.3-2.6)	1.0 (0.3-3.0)
SOC-47	Construction and extraction occupations	67	62	2.1 (1.5-3.1)	1 (0.6-1.8)	1.1 (0.6-2.0)
SOC-49	Installation, maintenance, and repair	40	45	1.7 (1.1-2.6)	0.8 (0.4-1.6)	0.7 (0.4-1.5)
SOC-51	Production occupations	40	62	1.2 (0.8-1.8)	0.9 (0.5-1.6)	0.8 (0.4-1.5)
SOC-53	Transportation and material moving	39	26	2.9 (1.8-4.9)	1.4 (0.7-2.8)	1.8 (0.8-4.0)
SOC-55	Military specific occupations	15	16	1.8 (1.1-3.6)	1.8 (0.7-4.5)	1.5 (0.5-4.6)

\*Adjusted for age, sex, race, education level, cigarette smoking. Alcohol drinking, diabetes mellitus, family history of cancer, HCV, HBV in all;

#Adjusted for age, sex, race, education level, cigarette smoking. Alcohol drinking, diabetes mellitus, family history of cancer in absence of chronic HCV or HBV infection.

**Table 2.** Participants' characteristics

	Cases	Controls	P value
	N = 589 (%)	N = 1,098 (%)	
<b>Age (years)</b>			
≤ 40	20 (3.4)	50 (4.6)	≤ .0001
41-50	54 (9.2)	179 (16.3)	
51-60	180 (30.6)	335 (30.5)	
61-70	174 (29.5)	356 (32.4)	
> 70	161 (27.3)	178 (16.2)	
<b>Sex</b>			
Male	435 (73.9)	631(57.5)	≤ .0001
Female	154 (26.1)	467 (42.5)	
<b>Ethnicity</b>			
White	412 (69.9)	967 (88.1)	≤ .0001
Hispanic	79 (13.4)	84 (7.7)	
African American	66 (11.2)	39 (3.6)	
Asian	32 (5.4)	8 (0.7)	
<b>Educational level</b>			
≤ High school	34 (5.8)	8 (0.7)	≤ .0001
Some college	233 (39.6)	305 (27.8)	
≥ College degree	318 (54.0)	785 (71.5)	
Missing	4 (0.7)	0 (0.0)	
<b>Hepatitis virus</b>			
HCV-/HBV-	310 (52.6)	1,057 (96.3)	≤ .0001
HCV+/HBV-	151 (25.6)	7 (0.6)	
HCV-/HBV+	70 (11.9)	31 (2.8)	
HCV+/HBV+	58 (9.8)	3 (0.3)	
<b>Cigarette smoking</b>			
No	183 (31.2)	580 (52.8)	≤ .0001
≤ 20 pack/year	168 (28.6)	256 (23.3)	

All of the job titles were coded according to the 2010 Stan-

standard Occupational Classification (SOC), which was developed by the Office of Management and Budget.<sup>[19]</sup> The structure of the SOC is comprehensive and designed to incorporate all occupations in the United States economy, including occupations in the public, private, and military sectors. The SOC classifies occupations at four distinct levels: major groups, minor groups, broad occupation, and detailed occupation. The 23 major groups (see Table 1) are divided into 97 minor groups, which in turn are divided into 461 broad occupations. These broad occupations are further divided into 840 detailed occupations. Each job title in the SOC is identified by a six-digit code. The first two digits represent the major group. The third digit represents the minor group. The fourth and fifth digits represent the broad occupation and the sixth digit represents the detailed occupation. For example, 13(-0000) stands for Business and Financial Operations Occupations (major group) and 13-2(000) is equivalent to Financial Specialists (minor group). Inclusion of the fourth and fifth digits signifies the broad occupation, which in this case can be Financial Analysts and Advisors (13-205[0]). The addition of the sixth digit identifies the detailed occupation, which can be Insurance Underwriters (13-2053). In the current study, however, the statistical analysis for job titles was conducted at the two-digit level (*i.e.*, major groups).

Plasma samples were available for only 889 control subjects who were tested, along with all HCC patients, for the presence of HCV antibodies (anti-HCV), HBV surface antigen (HBsAg), and HBV core antibody (anti-HBc).

## 2.2 Statistical methods

We used Microsoft Access to enter and manage the collected information of study participants. Data were analyzed using Stata software (Stata, College Station, TX). The significance of differences in the distributions of categorical variables between cases and healthy controls was determined by Chi-square test. Logistic regression analyses were done to estimate the marginal effects of each work category using maximum-likelihood estimation. All significant risk or protective factors at  $p < .05$  from Univariate analyses were taken into consideration to adjust for their confounding effects using multivariate logistic regression analyses. The multivariate adjusted OR (AOR) and 95% Confidence In-

terval (CI) were estimated after controlling for the potential confounding of age, sex, race, education level, and other significant HCC risk factors. Our results were also stratified by sex.

## 3. RESULT

Table 2 shows the demographic characteristics of the 589 patients with HCC and the 1,098 healthy controls. In respect to age distribution, 87.4% of cases and 79.1% of controls were older than 50 years. Most of the subjects were Caucasians. Cases were slightly older than controls, with a mean age  $\pm$  standard error (*SE*) of  $3.6 \pm 0.5$  years. The overall mean age ( $\pm$  *SE*) for HCC cases was  $63 \pm 4$  years and for controls was  $60 \pm 3$  years. Because we choose frequency matching, not pair matching, we were able to include age in the logistic model to adjust for the slight variation in age distribution that could confound the results.

Education ( $\geq$  college degree) was more frequent among controls (71.5%) compared to HCC cases (54.0%) ( $P \leq .0001$ ). Compared with cases (47.4%), only 3.7% of controls were infected with HBV or HCV. Heavy alcohol consumption ( $> 60$  g/day) and longstanding diabetes ( $> 1$  year) were four times more common in HCC cases than in controls. Similarly, cases were almost twice likely to have a history of extensive cigarette smoking ( $> 20$  pack years) compared with controls. Family history of cancer was comparable for both cases and controls. However, the prevalence of family history of liver cancer was significantly higher in cases than in controls.

Table 1 demonstrates the association between various occupations and risk of HCC in all subjects. A positive association was observed between sales workers and HCC, which remained significant after adjusting for other confounding factors and excluding patients with viral hepatitis (1.9 [1.1-3.0]). A separate analysis of the sexes showed that only female sales workers had a statistically significant risk of HCC (AOR = 2.8 [1.3-6.0]). Of interest, there was a protective association between managers and HCC, which remained statistically significant for females in multivariate analysis (OR, 0.2; 95% CI, 0.05-0.6). The remaining occupations did not have a significant association with HCC after adjusting the OR in all and in men and women separately.

**Table 3.** Duration of occupation (years) in HCC patients and controls: association with risk of HCC multivariable logistic regression

SOC	Occupation Classification	Mean ( $\pm$ SE)		P	$\leq$ Mean Value (controls)		$>$ Mean Value (controls)	
		Case	Controls		N* OR (95% CI) <sup>#1</sup>	N <sup>#2</sup> OR (95% CI) <sup>#1</sup>		
SOC-11	Management	21.96 $\pm$ 1.45	25.15 $\pm$ 0.81	.06	33/82	0.7 (0.4-1.2)	21/88	0.3 (0.2-0.7)
SOC-13	Business and financial operations	25.21 $\pm$ 2.48	25.36 $\pm$ 1.28	.95	15/37	0.7 (0.3-1.6)	13/32	0.8 (0.4-1.9)
SOC-15	Computer and mathematical	22.25 $\pm$ 12.39	22.09 $\pm$ 3.76	.99	3/6	0.2 (0.002-1.4)	1/5	0.1 (0.001-10.1)
SOC-17	Architecture and engineering	29.12 $\pm$ 1.87	28.20 $\pm$ 1.39	.69	16/28	0.9 (0.4-2.1)	17/26	0.9 (0.4-1.9)
SOC-19	Life, physical, and social science	18.67 $\pm$ 6.45	27.56 $\pm$ 3.57	.22	4/6	2.3 (0.5-11.2)	2/10	0.4 (0.05-2.8)
SOC-21	Community and social service	21.40 $\pm$ 4.49	26.06 $\pm$ 3.00	.38	7/8	1.9 (0.5-7.8)	3/8	0.9 (0.2-4.0)
SOC-23	Legal occupations	26.55 $\pm$ 2.47	22.64 $\pm$ 2.53	.34	5/13	2.1 (0.6-6.7)	6/9	1.2 (0.3-4.5)
SOC-25	Education, training, and library	29.81 $\pm$ 2.24	26.83 $\pm$ 1.14	.24	11/45	1.0 (0.4-2.2)	15/56	0.8 (0.4-1.6)
SOC-27	Arts, design, entertainment, sports, media	27.00 $\pm$ 4.76	23.84 $\pm$ 2.12	.50	6/9	1.6 (0.4-6.7)	6/10	0.9 (0.2-3.4)
SOC-29	Healthcare practitioners and technical	28.55 $\pm$ 2.39	24.86 $\pm$ 1.57	.22	10/37	0.9 (0.4-2.3)	12/26	0.8 (0.3-1.9)
SOC-31	Healthcare support occupations	17.33 $\pm$ 3.77	15.00 $\pm$ 4.03	.68	3/4	3.5 (0.6-20.6)	3/2	2.4 (0.2-31.6)
SOC-33	Protective service occupations	23.31 $\pm$ 3.09	24.22 $\pm$ 1.66	.78	8/13	1.7 (0.6-5.0)	5/14	0.8 (0.3-2.7)
SOC-35	Food preparation/serving related	15.91 $\pm$ 1.88	18.75 $\pm$ 4.55	.58	6/8	1.5 (0.3-7.2)	5/4	0.4 (0.05-2.3)
SOC-37	Building /grounds Cleaning/maintenance	33.10 $\pm$ 2.56	32.54 $\pm$ 1.79	.86	15/35	1.7 (0.8-3.7)	16/32	1.1 (0.5-2.5)
SOC-39	Personal care and service	24.00 $\pm$ 5.58	23.18 $\pm$ 3.72	.91	3/6	2.6 (0.5-14.0)	1/5	1.2 (0.1-11.0)
SOC-41	Sales and related	24.09 $\pm$ 1.85	22.70 $\pm$ 1.22	.51	22/34	2.4 (1.2-4.7)	23/32	1.4 (0.7-2.8)
SOC-43	Office and administrative support	24.00 $\pm$ 1.81	22.26 $\pm$ 0.94	.37	25/73	1.0 (0.6-1.9)	21/63	0.8 (0.4-1.4)
SOC-45	Farming, fishing, and forestry	35.75 $\pm$ 5.65	35.11 $\pm$ 3.18	.92	4/10	1.3 (0.3-5.2)	4/8	0.5 (0.1-2.8)
SOC-47	Construction and extraction occupations	25.98 $\pm$ 11.94	26.15 $\pm$ 9.20	.93	25/32	1.1 (0.5-2.4)	38/30	1.4 (0.7-2.8)
SOC-49	Installation, maintenance, and repair	23.69 $\pm$ 11.02	28.11 $\pm$ 9.96	.06	25/24	1.0 (0.4-2.4)	14/21	0.9 (0.3-2.3)
SOC-51	Production occupations	26.92 $\pm$ 13.44	26.45 $\pm$ 11.05	.85	15/30	0.8 (0.3-1.9)	23/32	1.3 (0.7-2.5)
SOC-53	Transportation and material moving	26.08 $\pm$ 19.16	22.46 $\pm$ 12.88	.40	19/14	1.6 (0.5- 4.7)	20/12	1.5 (0.6-3.6)
SOC-55	Military specific occupations	20.93 $\pm$ 8.02	24.56 $\pm$ 5.27	.15	1/7	0.1 (0.01- 2.2)	14/9	3.1 (1.1-8.9)

\*N: Number of cases/Number of controls with duration of occupation  $\leq$  the mean value of the duration (years) for each occupation among control subjects. For example 32 cases and 82 controls worked in management  $\leq$  25.15 years;

<sup>#1</sup>Adjusted for age, sex, race, education level, cigarette smoking. Alcohol drinking, diabetes mellitus, family history of cancer, HCV, HBV in all;

<sup>#2</sup>N: Number of cases/Number of controls with duration of occupation  $>$  mean value of the duration (years) for each occupation among control subjects. For example 21 cases and 88 controls worked in management for  $>$  25.15 years.

The relationship between the duration of occupation and risk of HCC is demonstrated in Table 3. The mean value of working years for each job among controls was used as the cut off value for the association between the job duration and HCC (see Table 3). Multivariate logistic regression analysis showed a significant association between HCC and sales workers employed for  $\leq$  22.70 years (OR, 2.4; 95% CI, 1.2-4.7), while, a significant negative association was observed between HCC and managers employed for  $>$  25.15 years (OR, 0.3; 95% CI, 0.2-0.7). Interestingly, our results showed that military personnel employed for  $>$  24.56 years have a higher risk for HCC development (OR, 3.1; 95% CI, 1.1-8.9).

We found no significant association between HCC and occupational exposure to various chemical agents as asbestos,

arsenic, chromium, solvent, glue, paint, pesticides, herbicides, fertilizers, motor oil, gasoline, car or truck exhaust, diesel, dust, fibers, radioactive materials, dry cleaning agents, Polychlorinated Biphen, or plastic exposure.

#### 4. DISCUSSION

The results of this investigation showed increased risk for HCC development among sales workers, whereas managers and executives were protected from HCC development. Up to our knowledge, this is the first study to find an association between the occupations of sales workers and managers and risk of HCC development.

Unlike previous studies, we found no significant association between HCC and employees of the food industry, farmers, painters, automobile repairers, plumbers, machinery

fitters, dry cleaners, printers, and health care professionals.<sup>[8, 11, 13, 14, 20]</sup> This major discrepancy in results can be attributed to numerous limitations in these studies such as small sample sizes; lack of confirmed pathological diagnosis of HCC or pooled analysis for all primary liver cancers including cholangiocarcinoma and angiosarcoma; variation in job stratification; inadequacy of collected data with reliance on death certificates, medical records, tumor registries, and surrogate interviews; and failure to adjust for potential confounding factors such as viral hepatitis, diabetes mellitus, cigarette smoking, and alcohol consumption. We do not know whether strict regulation by Occupational Safety and Health Administration (OSHA) and American National Standards Institute (ANSI) standards in the United States could have any effect on the lack of association between the occupations mentioned earlier and HCC in the U.S. population.

Similarly, sales workers were found to be at high risk of other cancers. Previous studies showed a statistically significant associations between sales workers and both bladder and colon cancers. For example, three studies have suggested that reduced physical activity may explain the increased risk of bladder cancer in sales workers.<sup>[21–23]</sup> Of note, a study by Chow *et al.* found a small yet statistically significant risk of colon cancer among sedentary occupations, including administrators, professionals, clerical workers, and sales workers, thereby supporting the proposed inverse relationship between physical activity and colon cancer.<sup>[24]</sup>

In light of the above associations, reduced physical activity may also be the cause of increased risk of HCC in sales workers. A study conducted in Japan showed that the prevalence of obesity and fatty liver was higher among sales workers.<sup>[25]</sup> Sedentary lifestyle is strongly associated with obesity, which is a major risk factor of metabolic syndrome and its hepatic component, non-alcoholic fatty liver disease (NAFLD). In fact, 75% of obese individuals experience NAFLD.<sup>[26]</sup> Non-alcoholic steatohepatitis (NASH), a severe form of NAFLD, can progress to fibrosis, cirrhosis, and eventually to HCC. Preclinical studies have demonstrated that mutated tumor suppressor genes play an important role in the development of steatosis and progression to HCC in NAFLD.<sup>[27–29]</sup> There is also growing evidence that vascular endothelial growth factor and adipokines secreted by visceral adipose tissue facilitate progression of NASH to HCC by enhancing angiogenesis and upregulating various signal transduction pathways.<sup>[30]</sup>

In our study, managers were at lower risk for developing HCC despite leading sedentary lives, in contrast to the above association. This discrepancy can be attributed to excess

coffee consumption among managers. Numerous studies have shown an inverse relationship between coffee consumption and HCC development.<sup>[31–37]</sup> The exact mechanism by which coffee inhibits HCC development remains unclear. Animal studies have shown that coffee induces liver enzymes involved in the detoxification and cellular antioxidant defenses, thereby exerting its protective effect.<sup>[38]</sup> Potential compounds responsible for the chemoprotective effects of coffee include caffeine, diterpenes (such as cafestol and kahweol), and chlorogenic acid.<sup>[37, 39–41]</sup> Despite being a possible explanation for our observation, we have no data regarding coffee consumption among patients to support this hypothesis.

Furthermore, our study showed that military personnel who were employed for more than 25 years had a 3 times higher risk of developing HCC. This finding was also observed in previous studies but was attributed to the increased rates of HCV in these patients.<sup>[42, 43]</sup> This is not applicable to our study since we adjusted our results for viral hepatitis, suggesting the presence of other contributing factors. Potential causes may include extensive use of dietary supplements<sup>[44]</sup> and higher rates of human immunodeficiency virus (HIV) infection in this population.<sup>[45, 46]</sup> Preclinical studies have shown that the HIV Tat gene plays a central role in liver carcinogenesis because of its antiapoptotic properties.<sup>[46]</sup> Whether these are the actual causes for our observation remains unclear.

Our study had numerous strengths. First, we had a large patient population. Second, the data were collected via meticulous interviews with subjects, increasing the accuracy of the gathered information and enabling us to obtain details regarding the occupational exposure and degree of alcohol and tobacco consumption. Third, we were able to adjust for most potential confounding factors associated with HCC including viral hepatitis. Fourth, all of the cases had confirmed diagnosis of HCC. Finally, we used a highly stratified occupation classification system, thereby accentuating important associations. Our study also had a number of limitations. Although the patients were prospectively enrolled, data were retrospectively collected via interviews, increasing the possibility of recall bias. Furthermore, to simplify data analysis, we included only the occupation of longest duration. This elimination may have had a negative effect on our results. In this study, we did not consider the effects of physical activity, body mass index, and dietary factors such as coffee consumption, on the incidence of HCC and therefore cannot validate our hypotheses. To confirm our hypotheses and prove the association between the occupations of sales workers and managers and risk of HCC, we need to conduct a larger study to collect detailed information regarding lifestyle and

physical activity.

## 5. CONCLUSION

In conclusion, the impact of occupational exposures and job types on the risk of HCC development is not well studied. The current investigation yielded significant association between specific occupations and HCC development especially among females. Future investigations are warranted to highlight the biological plausibility for the observed association

and to assess whether genetic susceptibility to HCC may explain the variation in the risk magnitude between men and women.

## ACKNOWLEDGEMENTS

Supported by: National Institutes of Health grants R03 ES11481 (to M.H.) and CA106458-01 (to M.H.)

## CONFLICTS OF INTEREST DISCLOSURE

The authors have declared no conflicts of interest.

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