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ORIGINAL PAPER

Cigarette smoking and primary liver cancer: a population-based case–control study in US men

Kangmin Zhu · Cynthia Moriarty · Lee S. Caplan · Robert S. Levine

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Abstract
Objective Using the case–control data from the Selected Cancers Study, the authors assessed whether cigarette smoking increases the risk of primary liver cancer in the US.
Methods Cases were men who were pathologically diagnosed with primary liver cancer during 1984–1988, were 31–59 years old, and lived in the areas covered by eight US cancer registries (n = 168). Controls were men without a history of primary liver cancer who were selected by random-digit telephone dialing (n = 1910).
Results Relative to non-smokers, the risks of liver cancer were 1.85 (95% confidence interval (CI), 1.05–3.25) and 1.49 (95% CI, 0.83–2.68) for former and current smokers, respectively. The adjusted odds ratio (OR) estimates were 0.96, 1.43, 1.80, and 1.87 for smoking for less than 15, 15–24, 25–34 and 35 or more years, respectively (p for trend = 0.039). The OR estimates were 1.41 (95% CI, 0.74–2.68), 1.67 (95% CI, 0.93–2.98), and 1.83 (95% CI, 0.89–3.76) for less than 1, 1–2, and 2 or more packs smoked per day (p for trend = 0.068).
Conclusions Cigarette smoking may be a factor that contributes somewhat to the occurrence of primary liver cancer among men in the United States, a country with low risk of liver cancer.

K. Zhu (✉) · C. Moriarty · L. S. Caplan · R. S. Levine
US Military Cancer Institute, Walter Reed Army Medical Center, 6900 Georgia Avenue, NW, Building 1, Suite A-109, Washington, DC 20307-5001, USA
e-mail: kangmin.zhu@na.amedd.army.mil

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Introduction

There are geographic variations in liver cancer occurrence. Eastern and South Eastern Asia, Middle Africa, and some countries of Western Africa are the areas of high risk; most parts of Europe, Central America, Western Asia, and Northern Africa are areas of intermediate risk; and Northern Europe, United States, Canada, and Australia have low risk [1–3]. Liver cancer is rare before the age of 50 years in countries at low risk, while it has high incidence at middle age in countries at high risk [1, 3], suggesting differences in exposure to etiological factors in different areas. Infectious hepatitis and dietary aflatoxin exposure are well-documented risk factors for liver cancer in high-risk areas [4]. In low-risk areas, other risk factors may play a larger role.

Several investigations have studied the question of whether cigarette smoking is a risk factor for liver cancer [5–22]. Some cohort studies in high-risk areas showed a positive association, with odds ratio (OR) estimates for cigarette smoking and primary liver cancer including 1.4 (95% confidence interval (CI), 1.3–1.6) [5] in current smoking men relative to non-smoking men, 1.50 (95% CI, 1.29–1.74), 3.3 (95% CI, 1.2–9.5), 1.55 (95% CI, 1.06–2.26), and 2.23 (95% CI, 1.53–3.23) for current smokers compared with non-smokers [6–9], and 3.14 (95% CI, 1.82–5.42) for daily smoking compared with non-smoking [10]. Some case–control studies also found an association

between cigarette smoking and liver cancer [11–15]. However, a number of cohort and case–control studies in high-risk areas were unable to demonstrate the hypothesized association [16–22] or to identify a dose-response relationship between smoking and liver cancer [13, 18, 20].

The United States is a low-risk country, where well-documented risk factors such as hepatitis virus infection and dietary aflatoxin exposure are less prevalent. It is important to study cigarette smoking in low-risk areas, not only because smoking may have larger effects on the occurrence of liver cancer in these areas, but also because it may be easier to delineate the role of cigarette smoking as a result of low ''noise'' from such factors as hepatitis infection and aflatoxin exposure. In fact, studies in the US have generated more consistent results. In contrast to case–control studies by Austin et al. and Stemhagen et al. [23, 24] in which no association between cigarette smoking and liver cancer was identified, other studies found a positive association. An early US study, a small case–control investigation in Caucasians and African Americans, showed that cases were more than twice likely to be current smokers than controls [25]. Subsequent case–control and cohort studies found OR estimates ranging from 2 to 3 [26–29] for current smoking compared with non-smoking. A recent study showed an OR estimate of about 1.6, comparing current or recent ex-smokers to non-smokers [30]. Some studies have also found that increasing smoking quantity [26] or duration [27, 31] could increase the risk of liver cancer, while some studies have found that the effects of smoking might be stronger among alcohol users [31]. However, the results on the dose-effect were not consistent [23, 30]. Also, while similar effects of smoking were found in men and women in some studies [28], an association was identified only in elderly women in others [26]. Unfortunately, many reported studies have not been able to sufficiently consider potentially confounding factors such as medical history of diseases and occupational exposures, and only a few studies in the US [28, 31] have examined possible effect modification by other risk factors such as alcohol consumption, hepatitis, or obesity.

The Selected Cancers Study was a large case–control study conducted in US men in which information on smoking and many potential confounders was available. Using the data from this study, we examined the cigarette smoking-liver cancer relationship in US men. In particular, we assessed the smoking-liver cancer relation by smoking quantity and duration, controlling for potential confounders and taking into account effect modification by other risk factors.

Methods

Details of the Selected Cancers Study have been described elsewhere [32]. The cancers investigated in the study included lymphoma, primary liver cancer, nasal cancer, nasopharyngeal cancer, and sarcoma. Men diagnosed with these cancers during 1984–1988 were included if they were 31–59 years old and lived in the areas covered by eight cancer registries in the US. Controls were men who were frequency matched to lymphoma cases by geographic area covered by cancer registry and 5-year date-of-birth intervals, and were selected through random-digit telephone dialing.

A total of 310 men were reported with liver cancer during the study period. Among these patients, 263 were interviewed and 233 had a specimen available for diagnosis. A total of 168 patients were confirmed to have primary liver cancer by a pathology review panel. Of the 168 patients, 123 were ''definite'' primary liver cancer cases and 45 were ''probable'' cases. A total of 138 cases had hepatocellular carcinoma and 30 cases had other histologic types. A total of 2,299 men were identified to be eligible as controls through random-digit-dialing, among whom 83.1% completed the interview (n=1910) and were used in the analysis. Informed consent was obtained from each study subject in the original study and the ethical guidelines were conformed.

Surviving cases and controls were interviewed on the phone by trained personnel. In-person interviews were performed only when necessary to ensure subject's participation (8.3% of cases and 1.9% of controls). About 109 of the cases were deceased at the time of interview. Proxy interviews were done for the deceased cases (64.9%). The information collected primarily included demographic characteristics (date of birth, ethnic background, education level, marital status, religion preference, and family income), relevant medical history (malaria, mononucleosis, systemic lupus erythematosis, allergy, tonsillectomy, appendectomy, immunodeficiency, hepatitis, cirrhosis, multiple sclerosis, chicken pox, arthritis, and so on), occupations (working with or around chemical solvents, wood, asbestos, or dust), exposure to radiation, exposure to pesticides, chemotherapy, personal habits (smoking and alcohol consumption), drug abuse, and military service history.

Logistic regression analysis [33] was used to analyze the relationship between cigarette smoking and primary liver cancer. We first analyzed whether a subject had ever smoked is related to primary liver cancer. In the analysis, matching variables (age and resident area in terms of cancer registry) and the presence of a

phone in the home four months prior to interview were always included in the models because of their possible complex effects on study results. Other variables were selected as potential confounders if they were significantly ($p < 0.05$) associated with the risk of liver cancer in the data or could logically be thought to confound the smoking-liver cancer relationship. We then examined the smoking-liver cancer relationship in terms of current/past smoking status, years for which a subject smoked, packs that a subject smoked per day, and pack-years (daily number of packs of cigarettes smoked multiplied by the number of years the subject smoked). Furthermore, we assessed whether the possible effects of smoking could be modified by age, ethnicity (Asian versus other ethnic groups), alcohol consumption, and history of hepatitis and cirrhosis diagnosed three years prior to the reference date. Since risk factor profiles may differ between different histological types of cancer, we repeated the analyses for hepatocellular carcinoma in order to minimize the potential effects due to the mixture of various histological types. Other histological types were not analyzed because of the small number of cases.

Results

Demographic characteristics of the cases and controls are presented in Table 1. Cases tended to be older. While about 22% and 38% of control men were in the age groups of younger than 40 years and older than 50 years respectively, the corresponding proportions were about 13% and 57% among men with primary liver cancer. The ethnic distributions of the cases and controls were strikingly different, with cases being much less likely to be White (48.2 vs. 81.5%), much more likely to be Asian (25.6 vs. 3.5%) and more likely to be Black (15.5% vs. 7.8%) than controls. While the proportion of never-married men was similar between the two groups, men with liver cancer tended to have a lower education level and annual household income than controls.

The case and control groups also differed with respect to smoking. About 79% of the cases had ever smoked cigarettes regularly while about 67% of the controls had done so. The proportions of ex-smokers and current smokers were 40.6 and 39.4 among cases and 38.5 and 28.2 among controls, respectively.

The results from logistic regression are shown in Table 2 for all liver cancers. After adjustment for potential confounders, cases were about 1.7 times more likely to have regularly smoked cigarettes than controls (95% CI, 0.99–2.82). The corresponding estimates were 1.49 (95% CI, 0.83–2.68) and 1.85 (95% CI, 1.05–3.25) for current smokers and ex-smokers. In terms of dose, there appeared to be a dose-response relationship between liver cancer and quantity smoked with adjusted OR estimates of 0.96, 1.43, 1.80, and 1.87 for smoking

Table 1 Demographic characteristics of primary liver cancer cases and controls, the Selected Cancers Study, 1984–1988

Variable		Cases		Controls	
		n	%	*n*	%
Age at interview (year)	<40	21	12.5	428	22.4
	40–44	22	13.1	394	20.6
	45–49	29	17.3	364	19.1
	>=50	96	57.1	724	37.9
Ethnic background	White	81	48.2	1,557	81.5
	Black	26	15.5	149	7.8
	Asian	43	25.6	67	3.5
	Hispanic	17	10.1	131	6.9
	Other or unknown	1	0.6	6	0.3
Never being married	Yes	17	10.1	135	7.1
	No	151	89.9	1,775	92.9
Education level	<High school	39	23.2	221	11.6
	High school to technical school	58	34.5	548	28.7
	1–3 years of college	29	17.3	394	20.7
	College degree or postgraduate	34	20.2	745	39.0
	Unknown	8	4.8	2	0.1
Annual household income	<$20,000	44	26.2	236	12.4
	$20,000–<$30,000	24	14.3	290	15.2
	$30,000–<$40,000	21	12.5	333	17.4
	$40,000–<$50,000	18	10.7	268	14.0
	>=$50,000	23	13.7	722	37.8
	Unknown	38	22.6	61	3.2

Table 2 The relationship between smoking and primary liver cancer, the Selected Cancers Study, 1984–1988

Variable		Number of cases	Number of controls	OR[a]	95% CI
Ever smoking	No	31	630	Reference	
	Yes	123	1,267	1.68	0.99–2.82
Current smoking	Non-smoker	31	630	Reference	
	Ex-smoker	62	732	1.85	1.05–3.25
	Current-smoker	61	535	1.49	0.83–2.68
Number of years smoked	None	31	630	Reference	
	>0 to <15	14	374	0.96	0.45–2.06
	15 to <25	31	429	1.43	0.76–2.70
	25 to <35	35	301	1.80	0.94–3.48
	>=35	31	161	1.87	0.89–3.94
				p for trend = 0.039	
Number of packs smoked per day	None	31	630	Reference	
	>0 to <1	32	335	1.41	0.74–2.68
	1 to <2	58	676	1.67	0.93–2.98
	>=2	27	251	1.83	0.89–3.76
				p for trend = 0.068	
Number of pack-years[b]	None	31	630	Reference	
	>0 to <15	23	424	1.07	0.55–2.10
	15 to <30	28	376	1.51	0.79–2.90
	30 to <45	29	246	1.74	0.88–3.43
	>=45	28	215	1.58	0.74–3.33
				p for trend = 0.101	

[a] Adjusted for year of birth, cancer registry, existence of home phone, education level, ethnic background, marital status, number of siblings lived with when growing up, growing up in an urban/suburban environment, medical history (mononucleosis, hepatitis, cirrhosis, systemic lupus erythematosis, chicken pox, allergy, appendectomy, tonsillectomy, having received blood products other than a transfusion), radiation exposure in either an occupational or a medical setting, having lived or worked on a farm/ranch, exposures to pesticides/asbestos/nickel, having worked in a pulp mill/saw mill/planning mill, having worked with or around wood preservatives or wood treating chemicals, having worked around cutting oils, and alcohol consumption. The subjects with ''unknown'' on any of these variables were excluded

[b] Daily number of packs of cigarettes smoked multiplied by the number of years the subject smoked

less than 15, 15–24, 25–34, and 35 or more years (p for trend = 0.039), respectively, and 1.41, 1.67, and 1.83 for smoking less than one pack, 1–1.9 packs, and 2 or more packs per day (p for trend = 0.068), respectively. When pack-years were used as a measure, the odds ratio estimates were 1.07, 1.51, 1.74, and 1.58 for smoking less than 15, 15–29, 30–44, and 45 or more pack-years (p for trend = 0.101), respectively. The effects of smoking were not significantly modified by age, ethnicity, alcohol consumption, hepatitis diagnosed three years before the reference date, and cirrhosis diagnosed three years prior to the reference date (data not shown).

Table 3 shows the results of the logistic regression limited to the hepatocellular carcinoma cases. The odds ratios for hepatocellular carcinoma in relation to smoking status, number of years, number of packs, and pack-years tended to be lower than those in Table 2.

Discussion

This study found that cigarette smoking might be weakly associated with liver cancer in US men, especially with increasing duration of smoking and probably with increasing number packs smoked. However, the estimates of the association tended to be lower, and the dose-effect relationship tended to be less obvious when the analysis was restricted to hepatocellular carcinoma cases only. This may be related to the sampling variation due to a smaller sample size when hepatocellular carcinoma was analyzed alone. Another possibility is that cigarette smoking might be more of a risk factor for other histologic types of primary liver cancer than for hepatocellular carcinoma.

There are two major concerns in the evaluation of the study findings: the inclusion of some probable (rather than confirmed) liver cancer patients, and the use of some proxy interviews in the case group. If probable cases were not liver cancer patients, an association between cigarette smoking and liver cancer might be under- or over-estimated, depending upon the relation between smoking and the medical conditions that appeared as liver cancer. Since a substantial proportion of cases were deceased at the time of study, and data were therefore collected on them through proxy interviews with next of kin, data quality might differ between cases and controls, biassing the study results. To evaluate the potential impacts of these two

Table 3 The relationship between smoking and hepatocellular carcinoma, the Selected Cancers Study, 1984–1988

Variable		Number of cases	Number of controls	OR[a]	95% CI
Ever smoking	No	22	630	Reference	
	Yes	74	1,267	1.59	0.83–3.03
Current smoking	Non-smoker	22	630	Reference	
	Ex-smoker	35	732	1.77	0.88–3.58
	Current-smoker	39	535	1.41	0.68–2.91
Number of years smoked	None	22	630	Reference	
	>0 to <15	7	374	0.89	0.34–2.36
	15 to <25	22	429	1.48	0.68–3.22
	25 to <35	19	301	1.55	0.67–3.58
	>=35	19	161	1.47	0.57–3.77
				p for trend = 0.252	
Number of packs smoked per day	None	22	630	Reference	
	>0 to <1	16	335	1.00	0.44–2.30
	1 to <2	38	676	1.78	0.87–3.68
	>=2	15	251	1.78	0.70–4.57
				p for trend = 0.098	
Number of pack-years[b]	None	22	630	Reference	
	>0 to <15	13	424	0.85	0.36–2.01
	15 to <30	21	376	1.95	0.88–4.31
	30 to <45	16	246	1.28	0.52–3.10
	>=45	15	215	1.25	0.46–3.40
				p for trend = 0.434	

[a] Adjusted for year of birth, cancer registry, existence of home phone, education level, ethnic background, marital status, number of siblings lived with when growing up, growing up in an urban/suburban environment, medical history (mononucleosis, hepatitis, cirrhosis, systemic lupus erythematosis, chicken pox, allergy, appendectomy, tonsillectomy, having received blood products other than a transfusion), radiation exposure in either an occupational or a medical setting, having lived or worked on a farm/ranch, exposures to pesticides/asbestos/nickel, having worked in a pulp mill/saw mill/planning mill, having worked with or around wood preservatives or wood treating chemicals, having worked around cutting oils, and alcohol consumption. The subjects with ''unknown'' on any of these variables were excluded

[b] Daily number of packs of cigarettes smoked multiplied by the number of years the subject smoked

factors, we repeated analyses using only confirmed cases and excluding proxy interviews. In these analyses, the directions of the odds ratios remained the same, but none of the confidence intervals excluded unity, primarily because the sample size was smaller. However, almost all odds ratio point estimates tended to be higher when data from proxy interviews were excluded, suggesting that next of kin might underreport smoking habits of the deceased cases. Hence, the association between smoking and primary liver cancer in this study might be somewhat underestimated in the group as a whole.

There was a possibility of residual confounding. In the data analysis, we were unable to control for some risk factors of liver cancer, such as exposure to aflatoxin and family history of primary liver cancer. Lack of adjustment for aflatoxin exposure might not have substantially affected our results, because this factor is less prevalent in the US. Men with Asian background, who were over-represented in the case group, might be exposed to aflatoxin and cigarette smoking to a greater extent than men of other ethnic backgrounds. However, ethnic background was adjusted for in our analyses, thus nullifying this concern. Family history of primary liver cancer may be associated with liver cancer and with smoking. Thus, the possibility of residual confounding by family history of primary liver cancer cannot be excluded. The effective control of the possible confounding effects of family history of liver cancer requires large numbers of liver cancer cases and controls.

Previous studies in the US have been relatively consistent in finding an association between cigarette smoking and primary liver cancer. However, potential confounding was often insufficiently controlled for in these studies, as only demographic variables [26, 27] or a few additional variables (hepatitis/cirrhosis [25, 28], diabetes (28, 30) or alcohol consumption [23, 25, 26, 28, 30, 31]) were considered in them. Our study controlled for additional potential confounders, including medical history of more diseases, occupational exposures and radiation exposure, and this may be partly responsible for our association appearing weaker than those in most previous studies. This may suggest the importance of controlling for potential confounders in discerning the smoking-liver cancer relationship,

although the true association in our study might have been stronger if only direct interviews were used for all cases. Our study also examined whether other risk factors might modify the smoking-liver cancer relationship. As suggested in some previous studies [34, 35], the smoking-liver cancer relationship may differ depending upon other factors such as alcohol consumption and hepatitis. However, we found no effect modification by age, race, alcohol consumption, and histories of hepatitis and cirrhosis. This differs from results from a few US studies which identified effect modification by age [26], alcohol consumption [31], viral hepatitis [28], or obesity [31], but agrees with a few other US studies that did not find effect modification by alcohol consumption [23, 30]. Both men and women were included in some of these studies [26, 28].

Several possibilities may account for a higher risk among former smokers than current smokers in our study. If current smoking cases were less likely to respond to the study compared with current smoking controls, current smokers might be more underrepresented in the case group, leading to a diluted measure of association. On the other hand, a diluted measure of association might also result if current smokers were more likely to smoke filter cigarettes than former smokers and the risk of cancer associated with filter cigarettes is lower than that with nonfilter cigarettes as shown in some studies [36–38]. Also, former smokers might have quit as a result of health problems that might be associated with higher exposure to smoking or decreased resistance to the effects of tobacco. In addition, potential differences between current and former smokers with respect to other risk factors for liver cancer cannot be excluded.

The association between cigarette smoking and liver cancer has been considered as a causal one in a recent publication by the International Agency for Research on Cancer [39] and may be biologically plausible. Liver is a major organ that metabolizes and transforms many chemicals in the body. Tobacco smoke contains more than 40 chemical compounds that are biologically active and often metabolized in the liver [8]. For example, polycyclic aromatic hydrocarbons, nitrosamines and aromatic amines, all of which are carcinogenic [40], are processed by hepatic enzymes [8]. Therefore, the liver may be a target of many chemical materials included in tobacco smoke. Animal experiments have shown that when rodents are exposed to smoke or its components, the occurrence of primary liver cancer increases [41] and that cigarette smoke can enhance the intensity of metabolic activation of the carcinogenic material, 2-amino-3,8-dimethylimidazo [4,5-f] quinoxaline [42]. In human studies, cigarette smoke was related to increasing serum α-1-antitrypsin [43, 44], which is linked to increased risk of heptocellular carcinoma [45, 46]. This may explain the smoking-liver cancer association. Experimental studies have shown that cigarette smoke may modify the risk of hepatocellular carcinoma related to tumor-suppressor gene, such as p53 [47], and increase the expression of oncogenes such as neu [48]. The results of these studies suggest the possibility that cigarette smoking may induce or promote carcinogenic changes of liver cancer. Epidemiological studies with the use of biomarkers are warranted for further clarifying the smoking-liver cancer relationship.

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