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Cigarette smoking and liver cancer among US veterans

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The relationship of tobacco use with risk of primary liver cancer was investigated using data from a 26-year mortality follow-up of nearly 250,000 US veterans, mostly from World War I. Significantly increased risks for liver cancer (289 deaths) were associated with most forms of tobacco use, including pipe and cigar smoking. Elevated relative risks (RRs) were seen for current cigarette smokers (RR = 2.4; 95 percent confidence interval [CI] 1.6 – 3.5) and former cigarette smokers (RR = 1.9, 1.2 – 2.9). A strong dose – response relationship ($P < 0.001$) was found for cigarette smoking, with smokers of 40 or more cigarettes per day having almost a fourfold risk (RR = 3.8, 1.9 – 8.0). Risks were also found to increase significantly with years of cigarette use and with earlier age at the start of cigarette smoking. These results are consistent with those of other cohort and case-control studies, suggesting that cigarette smoking may be related to the risk of liver cancer.

Key words: Cigarettes, liver cancer, tobacco, veterans.

Introduction

Primary liver cancer (PLC), including hepatocellular carcinoma (HCC) and cholangiocarcinoma (intrahepatic bile duct carcinoma), is one of the most common cancers in the world, accounting for a million deaths every year.[1] In high-risk areas, such as the sub-Saharan countries and Asia, liver cancer contributes up to 15 percent of all cancers, although in the United States it accounts for only 0.6 percent of all cancers.[2]

Chronic infection with hepatitis-B virus (HBV) and contamination of foods by mycotoxins, especially aflatoxin B_1, have been implicated in the etiology of PLC in high-risk countries.[3,4] However, because PLC occurs three to five times more commonly in men than in women in both high-risk and low-risk areas,[1] and because serologic markers of HBV have not been found in the majority of PLC patients in low-risk countries, additional factors—such as alcohol use, cigarette smoking, occupational exposures and, recently, hepatitis-C virus—have been suggested.[5-8]

The role of cigarette smoking in the etiology of liver cancer is not clear. Since Trichopoulous *et al.*[9] first reported a positive association of cigarette smoking with HCC among low-risk populations in 1980, several studies have examined this association in populations with a low prevalence of hepatitis-B surface antigen (HBsAg) positivity. Most have reported positive findings,[10-25] although in two recent reviews of the health consequences of smoking,[26,27] liver cancer was not considered to be tobacco-related.

We have had the opportunity to evaluate the relationship between tobacco use and primary liver cancer in a large cohort of (mostly) US World War I veterans, a population presumably with a low prevalence of HBsAg, whose mortality experience has been followed for 26 years.

Materials and methods

The study design and methods of follow-up have been described elsewhere in detail.[28,29] Briefly, 293,916

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government life-insurance policy holders, who served in the US Armed Forces during 1917 – 40, were mailed questionnaires either in 1954 or 1957, requesting information mainly about tobacco use. After the 1957 mailing, a total of 85 percent had responded. No additional information has been collected on smoking habits since this time; thus, categories of smokers are defined as reported in 1954 – 57.

The Beneficiary Identification and Record Locator Subsystem (BIRLS) of the Veterans Administration (VA) was used to follow the cohort for all causes of death from 1 January 1954 to 30 September 1980, with a 96 percent follow-up. Death certificates were obtained for 98 percent of the decedents. A total of 192,756 deaths, including 289 certificates of death from primary liver cancer, were identified after 26 years of follow-up. All deaths were coded according to the International Classification of Disease, 7th Revision (ICD-7).[30] Primary liver cancer (ICD-7 155.0) was defined as a primary malignant tumor of the hepatic cells or intrahepatic bile ducts.

The 289 PLC deaths accounted for 0.9 percent of all cancer deaths (N = 30,441) observed in this cohort during the 26-year follow-up, which is comparable to the percent of primary liver cancer among US cancer deaths in white males (1.1 pecent).[2] In addition, there were 1,037 subjects who had secondary liver cancer (ICD-7 156) mentioned on death certificates; they were not included in this analysis.

A Poisson regression model[31] was used to calculate relative risks (RR) and confidence intervals (CI) for various categories of tobacco use. Unless otherwise specified, all figures following RR estimates in the text are 95 percent CI. Five-year age intervals and calendar time periods were used for age and time adjustments.

Results

Table 1 shows that RRs were significantly elevated among current cigar or pipe smokers (RR = 3.1, 2.0 – 4.8), former cigarette smokers (RR = 1.9, 1.2 – 2.9), and current cigarette smokers (RR = 2.4, 1.6 – 3.5). A significant dose-response relationship ($P < 0.001$) was observed for number of cigarettes smoked, with smokers of 40 or more cigarettes per day having a 3.8-fold increased risk. In addition, risks of liver cancer increased significantly with both an earlier age at the start of cigarette smoking ($P < 0.001$) and number of years of smoking ($P < 0.01$) (Table 2).

Although information on alcohol intake was not available, we attempted to assess this variable indirectly by excluding the 61 liver-cancer subjects with any mention of liver cirrhosis (ICD-7 581) on the death certificate. There was little effect on the results: the RR for current cigarette smokers was 2.5 (1.6 – 3.8); for former smokers, 2.3 (1.5 – 3.7); and for pipe or cigar smokers, 3.0 (1.8 – 4.9). None of the 289 liver cancer subjects had mention of infectious hepatitis (ICD-7 092), alcoholism (ICD-7 322), or alcoholic psychosis (ICD-7 307), on the death certificate. Compared to US white males,[32] this cohort of veterans had a standardized mortality ratio (SMR) for cirrhosis of the liver of 0.53 (0.50 – 0.56).

Table 1. Relative risks, with 95% confidence intervals (CI), of primary liver cancer by tobacco use among US veterans, 1954 – 80

Smoking category	No. of deaths	Relative risk[a]	CI
Total number of cases	289		
Nonsmokers[b]	37	1.0	
Current cigar/pipe	47	3.1	2.0 – 4.8
Former cigarette smokers, not current cigar/pipe	48	1.9	1.2 – 2.9
Other	43	1.8	1.2 – 2.8
Current cigarette smokers[c]	114	2.4	1.6 – 3.5
< 10/day	18	2.2[d]	1.2 – 3.8
10 – 20/day	48	2.0	1.3 – 3.0
21 – 39/day	39	2.9	1.8 – 4.5
> 39/day	9	3.8	1.9 – 8.0

[a]Adjusted for age and calendar time period.
[b]Includes two nonsmokers who used smokeless tobacco.
[c]Includes cigarette smokers who also used pipes, cigars, or smokeless tobacco.
[d]Linear trend with amount smoked, $P < 0.001$.

Discussion

Our results support the hypothesis first proposed in 1980[9] that cigarette smoking plays a role in the etiology of liver cancer. Since then, 12 case-control studies[10 – 21] and four cohort studies[22 – 25] have examined the role of cigarette smoking, with six of the case-control[10 – 15] and all of the cohort studies[22 – 25] reporting a significant positive association. In addition, two[18,20] of the six case-control studies reporting no association with smoking actually had positive findings, although they were not statistically significant. Earlier cohort studies either did not report on PLC or combined it with biliary tract cancers.

The type of liver cancer associated with cigarette smoking in the literature has been primarily hepatocellular carcinoma (ICD-9 155.0). In our survey of US veterans, the cause of death was coded using ICD-7, which combines HCC with intrahepatic bile duct cancer. Nevertheless, the observed smoking effect likely reflects an association with HCC, which comprises at least 80 percent of PLC.[2]

We were unable to evaluate the effect of smoking

Table 2. Relative risks, with 95% confidence interval (CI), of primary liver cancer by age started cigarette smoking and duration of smoking among US veterans, 1954 – 80

Smoking variables	No. of deaths	Relative risk[a]	CI
Nonsmoker	37	1.0	
Age of first cigarette use[b]			
<20	72	2.9[c]	1.6 – 5.3
20 – 24	32	2.3	1.2 – 4.3
>24	9	1.0	0.4 – 2.3
Number of years smoked cigarettes[b]			
<35	18	0.9[c]	0.4 – 2.1
35 – 39	35	2.6	1.4 – 4.9
>39	60	2.7	1.5 – 4.9

[a]Adjusted for age, calendar time period, and number of cigarettes smoked.
[b]For smokers, only current cigarette smokers (1954 – 57) were included.
[c]Linear trend $P < 0.001$ (test of linear trend performed for smokers only).

independent of chronic HBV-infection and alcohol use, which were not asked for in the questionnaire. However, since the chronic HBV-carrier rate in the US is relatively low, ranging from 0.26 to two percent[33,34] compared to 25 percent in hyperendemic areas of the world,[35] chronic HBV-infection is unlikely to account for PLC in this cohort. Heavy exposure to mycotoxins, a reported risk factor in high-risk areas, also is uncommon in the US.[36]

Prolonged and excessive use of alcohol is a risk factor for PLC, especially in the aftermath of alcoholic hepatitis and cirrhosis.[37] Since drinking and smoking habits are correlated with one another, it is important to consider possible confounding of the smoking-related risks by alcohol intake.

Although veterans of World War II, Korea, and Vietnam have more drinking problems and alcohol-related diseases than the rest of the US population,[38,39] the prevalence of alcohol use in this cohort of mostly World War I veterans is unknown. However, it may not be high, since the death rate from liver cirrhosis was actually well below US norms. Excluding those PLC subjects with accompanying liver cirrhosis mentioned on the death certificates had virtually no effect on the risks for cigarette smoking. Moreover, the SMRs for alcohol-related cancer sites such as the oral cavity, larynx, and esophagus in this cohort were 0.53 (0.48 – 0.57), 0.43 (0.37 – 0.49) and 0.57 (0.52 – 0.62), respectively, suggesting that these veterans experienced fewer alcohol-related cancer deaths than the US white male population. In addition, the prevalence of ever-smoking in this cohort (57 percent) was considerably lower than that of US white males (74 percent) of the same age,[40] and the SMR for lung cancer was 0.62 (0.61 – 0.64)—indicating that, as a group, members of this cohort have lower rates of smoking-induced cancer. Thus, drinking and smoking patterns of these World War I veterans may not resemble those of other veterans, perhaps because of selection criteria for this cohort, which was chosen based on continued payments for life insurance benefits after discharge from the service.[28] The cohort members were better educated and more likely to hold management and skilled-worker positions than US white males of the same age.[28]

Earlier reports on this cohort combined deaths from cancers of the liver and biliary tract.[28,29] In the 16-year follow-up, a 2.3-fold risk was associated with cigarette smoking for the combined sites.[29] In our 26-year follow-up, we found a 2.4-fold risk for liver cancer alone; in a separate analysis of biliary tract cancer, the risk from cigarette smoking was 1.4, with no dose – response relationship for amount smoked.

Misclassification of smoking exposure is likely to have occurred in this study, since no additional information on smoking was obtained after 1954 – 57. However, if the quitting patterns among veterans resemble those of other American men, more than 40 percent may have quit smoking in the ensuing 26 years since they reported themselves as smokers.[40] Hence, risk ratios for current smokers are likely to have been underestimated.

We used only subjects with mention of primary liver cancer on the death certificate for analysis. However, since the liver is a common site for metastasis, some cases of secondary liver cancer are likely to be misclassified and reported as PLC. One study compared the diagnoses of PLC recorded on death certificates to those on hospital records and found that only 72 percent of the death certificate diagnoses of PLC were confirmed by hospital records.[41] If a similar proportion of liver cancer deaths among this cohort were misclassified, and if an increased proportion of these were smokers, the association with smoking would be overestimated, but such an effect is likely to be negligible.

Despite the limitations of this study, our results are

consistent with most other epidemiologic studies, and indicate that smoking is a risk factor for primary liver cancer in low-risk areas such as the US.

References

1. Waterhouse J, Shanmugarathnam K, Muir C, Powell J, eds. *Cancer Incidence in Five Continents. Volume IV.* Lyon: International Agency for Research on Cancer, 1982; IARC Sci. Pub. No. 42.
2. Young JL, Percy CL, Asire AJ. *Surveillance, Epidemiology, and End Results Program: Incidence and Mortality Data: 1973 – 1977.* Natl Cancer Inst Monogr 1981; **57:** 50 – 1, 144 – 5.
3. Beasley RP, Hwang L, Lin C, Chien C. Hepatocellular carcinoma and hepatitis B virus: a prospective study of 22,707 men in Taiwan. *Lancet* 1981; **II:** 1129 – 33.
4. Enwonwu, CO. The role of dietary aflatoxin in the genesis of hepatocellular cancer in developing countries. *Lancet* 1984; **II:** 956 – 8.
5. Tabor E, Gerety RJ, Vogel CL, *et al.* Hepatitis B virus infection and primary hepatocellular carcinoma. *JNCI* 1977; **58:** 1197 – 200.
6. Tabor E. Hepatocellular carcinoma: possible etiologies in patients without serologic evidence of hepatitis B virus infection. *J Med Virology* 1989; **27:** 1 – 6.
7. Editorial. Hepatocellular cancer: differences between high and low incidence regions. *Lancet* 1987; **II:** 1183 – 4.
8. Yu MC, Tong MJ, Coursaget P, Ross RK, Govindarajan S, Henderson BE. Prevalence of hepatitis B and C viral markers in black and white patients with hepatocellular carcinoma in the United States. *JNCI* 1990; **82:** 1038 – 41.
9. Trichopoulos D, MacMahon B, Sparros L, Merikas G. Smoking and hepatitis B-negative primary hepatocellular carcinoma. *JNCI* 1980; **65:** 111 – 4.
10. Lam KC, Yu MC, Leung JW, Henderson B. Hepatitis B virus and cigarette smoking: risk factors for hepatocellular carcinoma in Hong Kong. *Cancer Res* 1982; **42:** 5246 – 8.
11. Yu MC, Mack T, Hanisch R, Peters RL, Henderson BE, Pike MC. Hepatitis, alcohol consumption, cigarette smoking, and hepatocellular carcinoma in Los Angeles. *Cancer Res* 1983; **43:** 6077 – 9.
12. Trichopoulos D, Day NE, Kaklamani E, *et al.* Hepatitis B virus, tobacco smoking and ethanol consumption in the etiology of hepatocellular carcinoma. *Int J Cancer* 1987; **39:** 45 – 9.
13. Tanaka K, Hirohata T, Takashita S. Blood transfusion, alcohol consumption, and cigarette smoking in causation of hepatocellular carcinoma: a case-control study in Fukuoka, Japan. *Jpn J Cancer Res* 1988; **79:** 1075 – 82.
14. Yu HE, Harris RE, Kabat GC, Wynder EL. Cigarette smoking, alcohol consumption and primary liver cancer: a case-control study in the USA. *Int J Cancer* 1988; **42:** 325 – 8.
15. Tsukuma H, Hiyama T, Oshima A, *et al.* A case-control study of hepatocellular carcinoma in Osaka, Japan. *Int J Cancer* 1990; **45:** 231 – 6.
16. Stemhagen A, Slade J, Altman R, Bill J. Occupational risk factors and liver cancer. *Am J Epidemiol* 1983; **117:** 443 – 54.
17. Hardell L, Bengtsson NO, Jonsson U, Eriksson S, Larsson LG. Aetiological aspects on primary liver cancer with special regard to alcohol, organic solvents and acute intermittent prophyria—an epidemiological investigation. *Br J Cancer* 1984; **50:** 389 – 97.
18. Kew MC, DiBisceglie AM, Paterson A. Smoking as a risk factor for hepatocellular carcinoma. A case-control study in southern African blacks. *Cancer* 1985; **56:** 2135 – 7.
19. Austin H, Delzell E, Grufferman S, *et al.* A case-control study of hepatocellular carcinoma and the hepatitis B virus, cigarette smoking and alcohol consumption. *Cancer Res* 1986; **46:** 962 – 6.
20. Lu SN, Lin TM, Chen CJ, *et al.* A case-control study of primary hepatocellular carcinoma in Taiwan. *Cancer* 1988; **62:** 2051 – 5.
21. La Vecchia C, Negri E, Decarli A, D'Avanzo B, Franceschi S. Risk factors for hepatocellular carcinoma in northern Italy. *Int J Cancer* 1988; **42:** 872 – 6.
22. Oshima A, Tsukuma H, Hiyama T, Fujimoto I, Yamano H, Tanaka M. Follow-up study of HBsAg-positive blood donors with special reference to effect of drinking and smoking on development of liver cancer. *Int J Cancer* 1984; **34:** 775 – 9.
23. Tu J, Gao R, Zhang D, Gu B. *Hepatitis B Virus and Primary Liver Cancer on Chongming Island, People's Republic of China.* Natl Cancer Inst Monogr 1985; **69:** 213 – 5.
24. Shibata A, Hirohata T, Toshima H, Tashiro H. The role of drinking and cigarette smoking in the excess deaths from liver cancer. *Jpn J Cancer Res* 1986; **77:** 287 – 95.
25. Hirayama T. A large-scale cohort study on risk factors for primary liver cancer, with special reference to the role of cigarette smoking. *Cancer Chemother Pharmacol* 1989; **23:** S114 – 7.
26. International Agency for Research on Cancer. *Tobacco Smoking.* Lyon: IARC, 1986; Monogr Eval Carcinog Risk Chem Man, **38:** 199 – 298.
27. A Report of the Surgeon General. *The Health Consequences of Smoking: Cancer.* Rockville, MD: US Department of Health and Human Services, Public Health Service, Office on Smoking and Health, 1982; DHHS Pub. No. 82-50179.
28. Kahn HA. *The Dorn Study of Smoking and Mortality among US Veterans: Report on Eight and One-half Years of Observation.* Natl Cancer Inst Monogr 1966; **19:** 1 – 125.
29. Rogot E, Murray JL. Smoking and causes of death among US veterans: 16 years of observation. *Public Health Rep* 1980; **95:** 213 – 22.
30. World Health Organization. *Manual of the Classification of Diseases, Injuries, and Causes of Death. 7th Revision.* Geneva: WHO, 1957.
31. Breslow NE, Day NE. *Statistical Methods in Cancer Research, Vol 2. The Design and Analysis of Cohort Studies.* Lyon International Agency for Research on Cancer, 1987; IARC Sci. Pub. No. 82, 120 – 76.
32. Monson RR. Analysis of relative survival and proportionate mortality. *Comput Biomed Res* 1974; **7:** 325 – 32.
33. Seeff LB, Beebe GW, Hoofnagle JH, *et al.* A serologic follow-up of the 1942 epidemic of post-vaccination hepatitis in the United States Army. *N Engl J Med* 1987; **316:** 965 – 70.
34. McQuillan GM, Townsend TR, Field HA, Carroll M, Leahy M, Polk BF. Seroepidemiology of hepatitis B virus infection in the United States 1976 to 1980. *Am J Med* 1989; **87** (Suppl 3A): 5 – 10.

35. Chung D, Ko Y, Chen C, *et al.* Seroepidemiological studies on hepatitis B and D viruses infection among five ethnic groups in southern Taiwan. *J Med Virology* 1988; **26:** 411 – 8.
36. Rodricks J, Hesseltine C, Mehlman M. *Mycotoxins in Human and Animal Health.* Park Forest South, Illinois: Pathotox Publishers, Inc., 1977: 7 – 28.
37. International Agency for Research on Cancer. *Alcohol Drinking.* Lyon: IARC, 1988; Monogr Eval Carcinog Risk Chem Man, **44:** 208 – 12.
38. Remer SG. The prevalence of alcoholism in a veterans administration medical center. *Military Medicine* 1983; **148:** 735 – 9.
39. Richard MS, Goldberg J, Rodin MB, Anderson RJ. Alcohol consumption and problem drinking in white male veterans and non-veterans. *Am J Public Health* 1989; **79:** 1011 – 15.
40. A Report of the Surgeon General. *Reducing the Health Consequences of Smoking: 25 Years of Progress.* Rockville, MD: US Department of Human Services, Public Health Service, Office on Smoking and Health 1989; DHHS Pub. No. 89-8411.
41. Percy C, Stanek E, Gloeckler L. Accuracy of cancer death certificates and its effect on cancer mortality statistics. *Am J Public Health* 1981; **71:** 242 – 50.