Risk of liver cancer among US male veterans with cirrhosis, 1969–1996

EC Persson*,1, SM Quraishi1, TM Welzel2, JD Carreon1, G Gridley1, BI Graubard1 and KA McGlynn1

1Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, Department of Health and Human Services, Bethesda, MD 20852-7234 USA; 2Klinikum der JW Goethe-Universität Frankfurt am Main, Medizinische Klinik I, Theodor-Stern-Kai 7, 60590 Frankfurt am Main, Germany

BACKGROUND: Liver cancer incidence rates in the United States have increased for several decades for reasons that are not entirely clear. Regardless of aetiology, cirrhosis is a strong risk factor for liver cancer. As mortality from cirrhosis has been declining in recent decades, it is possible that the risk of liver cancer among persons with cirrhosis has been affected.

METHODS: Data from the US Veterans Affairs medical records database were analysed after adjustment for attained age, race, number of hospital visits, obesity, diabetes, and chronic obstructive pulmonary disease. Hazard ratio (HR) and 95% confidence interval (95% CI) were calculated using Cox proportional hazards modelling. Survival analyses were conducted using age as the time metric and incidence of cirrhosis as a time-dependent covariate.

RESULTS: Among 103,257 men with incident cirrhosis, 788 liver cancers developed. The HR of liver cancer was highest among men with viral-related cirrhosis (HR = 37.59, 95% CI: 22.57–62.61), lowest among men with alcohol-related cirrhosis (HR = 4.40–9.33) in 1969–1973 to 34.71 (95% CI: 23.10–52.16) in 1992–1996 for those with cirrhosis compared with those without. Regardless of the type, white men had higher HRs than black men. The HR of developing liver cancer increased from 6.40 (95% CI: 4.40–9.33) in 1969–1973 to 34.71 (95% CI: 23.10–52.16) in 1992–1996 for those with cirrhosis compared with those without.

CONCLUSION: In conclusion, the significantly increased HR of developing liver cancer among men with cirrhosis compared with men without cirrhosis in the United States may be contributing to the increasing incidence of liver cancer.

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Incidence rates of primary liver cancer in the United States have been increasing since 1980 (Altekruse et al, 2009). In the United States, known risk factors for liver cancer, the majority of which is hepatocellular carcinoma (HCC), include chronic infection with hepatitis B virus (HBV), chronic infection with hepatitis C virus (HCV) (Davila et al, 2004; Davila et al, 2011) and excessive alcohol consumption (Boisset et al, 2007). In addition, recent research has identified pre-existing diabetes (El-Serag et al, 2004), obesity (Neuschwander-Tetri and Caldwell, 2003) and metabolic syndrome (Welzel et al, 2011) as risk factors. Although changes in epidemiological patterns of risk factors may have influenced liver cancer incidence trends, other factors may also have contributed to the rising rates. For example, regardless of risk factor, 70–90% of liver cancers arise in livers that are affected with pre-existing cirrhosis (Schutte et al, 2009). In the United States, mortality due to cirrhosis has been declining since the early 1970s (National Center for Health Statistics (US), 2010) as treatment has improved (Kanwal et al, 2011). As cirrhosis and liver cancer are closely associated, the inverse trends in liver cancer incidence and cirrhosis mortality suggest that the two phenomena may be related. It is conceivable that as persons with cirrhosis are treated more successfully, the risk of developing liver cancer may be affected. To investigate this hypothesis, the relationship between liver cancer and cirrhosis was examined in a large cohort of US military veterans.

MATERIALS AND METHODS

Study cohort

The study utilised hospital discharge diagnoses that occurred between 1 July, 1969 and 30 September, 1996 at 142 US Veterans Affairs (VA) hospitals. This inpatient-only study population included all black (N = 816,395) and white (N = 3,599,650) male veterans between the ages of 18 and 100 years who were hospitalised at least once during the study period. Men belonging to ethnic/racial groups other than black or white were excluded from the study because of small numbers. Females were also excluded because of small numbers. Almost 26 million hospital discharge records were included. Hospital discharge diagnoses from 5,790,493 male veterans were identified. Persons were excluded (N = 917,867) for a number of reasons: non-veterans, age <18 years or >100 years, died at the first hospital admission, developed cancer during the first year of study entry or had prevalent cancer on first admission. In addition, 371,129 men were excluded because of failure to survive 1 year after diagnosis and 85,452 men were excluded who had a diagnosis of cirrhosis before or at the day of entry. In total, hospital discharge diagnoses of 4,416,045 male
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The study included 4,416,045 study participants, of whom 103,257 were diagnosed with cirrhosis after at least one cirrhosis-free hospitalisation (Table 1). The most common type of cirrhosis was alcoholic cirrhosis (N = 92,208), followed by viral hepatitis-related cirrhosis (N = 779). The remaining cirrhosis diagnoses (idiopathic cirrhosis) were unrelated to either alcohol or viral hepatitis (N = 10,270). Among the 103,257 men who were diagnosed with cirrhosis, 788 subsequently developed liver cancer during follow-up (Table 2). In contrast, of the 4,312,788 men without cirrhosis, 3,620 subsequently developed liver cancer. The mean follow-up time among men with cirrhosis was 9.8 years among white men and 11.2 years among black men. In men with cirrhosis who developed liver cancer, the mean length of follow-up was 6.8 years for white men and 7.7 years for black men (data not shown).

### Table 1  Characteristics of the study population, US Veterans Affairs inpatient hospitalisation database, 1969–1996

|                | No cirrhosis | All cirrhosis | Alcoholic cirrhosis | Viral cirrhosis | Idiopathic cirrhosis |
|----------------|--------------|---------------|---------------------|----------------|----------------------|
| **All men**    |              |               |                     |                |                      |
| No.            | 4,312,788    | 103,257       | 92,208              | 779            | 10,270               |
| Person-years   | 50,541,819   | 1,032,636     | 916,591.7           | 933,72         | 106,707.4           |
| Mean years follow-up | 11.7        | 10.0         | 9.9                 | 12.0           | 10.4                 |
| Mean no. of hospital visits | 4.4         | 5.6         | 5.7                 | 7.9            | 4.7                  |
| Median age     |              |              |                     |                |                      |
| Study entry    | 52.6         | 52.6         | 52.4                | 41.2           | 54.6                 |
| Study exit     | 64.7         | 62.8         | 62.7                | 50.1           | 64.3                 |
| No. COPD       | 711,897      | 22,869       | 20,789              | 92             | 1998                 |
| No. diabetes   | 558,076      | 17,708       | 15,375              | 153            | 2180                 |
| No. obesity    | 241,322      | 7031         | 6245                | 36             | 750                  |
| No. who develop liver cancer | 3620       | 788          | 678                 | 15            | 95                   |
| **White men**  |              |               |                     |                |                      |
| No.            | 3,512,949    | 86,701       | 77,299              | 649            | 8,753                |
| Person-years   | 41,052,131   | 847,307      | 750,830.3           | 74,50          | 8,903.1              |
| Mean years follow-up | 11.7        | 9.8         | 9.7                 | 11.5           | 10.2                 |
| Mean no. of hospital visits | 4.4         | 5.6         | 6.8                 | 7.8            | 4.6                  |
| Median age     |              |              |                     |                |                      |
| Study entry    | 53.6         | 53.2         | 53.0                | 42.3           | 55.3                 |
| Study exit     | 65.3         | 63.2         | 63.0                | 50.4           | 64.9                 |
| No. COPD       | 624,153      | 20,566       | 18,690              | 77             | 1799                 |
| No. diabetes   | 441,813      | 14,732       | 12,728              | 18             | 1886                 |
| No. obesity    | 206,455      | 6476         | 5758                | 34             | 684                  |
| No. who develop liver cancer | 2677       | 662          | 569                 | 11            | 82                   |
| **Black men**  |              |               |                     |                |                      |
| No.            | 799,839      | 15,556       | 14,909              | 130            | 1,517                |
| Person-years   | 9,489,687.8  | 185,329.3    | 165,761.4           | 1892.2         | 17,675.7            |
| Mean years follow-up | 11.9        | 11.2         | 11.1                | 14.6           | 11.7                 |
| Mean No. of hospital visits | 4.5         | 5.7         | 5.7                 | 8.2            | 5.0                  |
| Median age     |              |              |                     |                |                      |
| Study entry    | 47.8         | 49.0         | 49.0                | 36.1           | 50.6                 |
| Study exit     | 60.2         | 60.3         | 60.3                | 49.6           | 61.1                 |
| No. COPD       | 87,744       | 2303         | 2099                | 15             | 189                  |
| No. diabetes   | 116,263      | 2976         | 2647                | 35             | 294                  |
| No. obesity    | 34,867       | 555          | 487                 | 2              | 66                   |
| No. who develop liver cancer | 943         | 126          | 109                 | 4              | 13                   |

**Abbreviation:** COPD = chronic obstructive pulmonary disease.
The results of the survival analysis by calendar year, in which cirrhosis was treated as a time-dependent variable, are displayed in Table 3. The analysis revealed a statistically significant increase (P\text{trend}=0.016) in liver cancer HRs for cirrhosis compared with veterans without any cirrhosis over time: 1969–1973: HR = 6.40 (95% CI: 4.40–9.33); 1974–1979: HR = 8.86 (95% CI: 6.47–12.14); 1980–1985: HR = 15.72 (95% CI: 11.30–21.86); 1986–1991: HR = 15.81 (95% CI: 10.86–23.03) and 1992–1996: HR = 34.71 (95% CI: 23.10–52.16). An examination of alcohol-related cirrhosis alone found very similar results (P\text{trend}=0.011) for: 1969–1973: HR = 6.92 (95% CI: 4.70–10.19); 1974–1979: HR = 8.42 (95% CI: 6.01–11.80); 1980–1985: HR = 12.78 (95% CI: 8.65–18.88); 1986–1991: HR = 14.77 (95% CI: 9.68–22.54) and 1992–1996: HR = 32.49 (95% CI: 20.35–51.86). The numbers of liver cancers associated with other types of cirrhosis were too small for calculation of the HRs by time period.

Liver cancer incidence rate between 1969 and 1996

Overall, the incidence rate of liver cancer increased from 1969 to 1996, from 8.1 out of 100 000 to 9.1 out of 100 000 person-years. Among white men, the incidence increased from 7.6 in 1969 to 8.5 out of 100 000 person-years in 1996, whereas among black men the incidence increased from 10.3 in 1969 to 11.5 out of 100 000 person-years in 1996 (data not shown). Further, the incidence rate of liver cancer among men with and without cirrhosis shown in Figure 1 is analogous to Table 3 over time. Between 1969 and 1996 the incidence of liver cancer among men with cirrhosis increased from 36.1 to 247.3 out of 100 000 person-years, whereas the incidence among men without cirrhosis only slightly increased from 6.5 to 7.9 out of 100 000 person-years. The incidence of liver cancer by race in men with cirrhosis increased from 31.5 to 256.0 out of 100 000 person-years among white men, and from 56.9 to 180.0 out of 100 000 person-years among black men. Men among without cirrhosis, a slightly increased incidence was evident among both white (from 6.2 in 1969 to 7.3 out of 100 000 person-years in 1996) and black men (from 7.6 to 10.6 out of 100 000 person-years, data not shown).

HR of liver cancer within calendar year by cirrhosis status

The results of the survival analysis by calendar year, in which cirrhosis was treated as a time-dependent variable, are displayed in Table 3. The analysis revealed a statistically significant increase (P\text{trend}=0.016) in liver cancer HRs for cirrhosis compared with veterans without any cirrhosis over time: 1969–1973: HR = 6.40 (95% CI: 4.40–9.33); 1974–1979: HR = 8.86 (95% CI: 6.47–12.14); 1980–1985: HR = 15.72 (95% CI: 11.30–21.86); 1986–1991: HR = 15.81 (95% CI: 10.86–23.03) and 1992–1996: HR = 34.71 (95% CI: 23.10–52.16). An examination of alcohol-related cirrhosis alone found very similar results (P\text{trend}=0.011) for: 1969–1973: HR = 6.92 (95% CI: 4.70–10.19); 1974–1979: HR = 8.42 (95% CI: 6.01–11.80); 1980–1985: HR = 12.78 (95% CI: 8.65–18.88); 1986–1991: HR = 14.77 (95% CI: 9.68–22.54) and 1992–1996: HR = 32.49 (95% CI: 20.35–51.86). The numbers of liver cancers associated with other types of cirrhosis were too small for calculation of the HRs by time period.

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such as ultrasound and CT/MRI, has occurred in the last several decades. Arguably, before the advent of advanced imaging, cirrhosis patients might have died of hepatic decompensation before a nascent liver cancer could be detected. Another possibility is that the aetiology of the underlying cirrhosis may have changed over time. For example, if the proportion of viral-related cirrhosis and alcohol-related cirrhosis varied, the risk of developing liver cancer might appear to vary also, as viral-related cirrhosis has been reported to carry a higher risk than alcohol-related cirrhosis (Morgan et al, 2004; Bialecki and Di Bisceglie, 2005; Kanwal et al, 2011). Prior reports have suggested that the risk of liver cancer among persons with HBV-related cirrhosis is ~2–3%, whereas the comparable risks for HCV-related and alcohol-related cirrhosis are 1–7% and 1%, respectively (Morgan et al, 2004; Bialecki and Di Bisceglie, 2005). Consistent with these reports are the findings of the current study. Although the risk of liver cancer varied by type of cirrhosis, however, the HR of liver cancer associated with each type of cirrhosis was increased compared to no cirrhosis, suggesting that a shift in underlying aetiology does not completely account for the increased HRs over time.

Another possible explanation for increasing risk of liver cancer would be better screening for liver cancer over time. There is scant evidence, however, that screening for liver cancer in the United States has improved. For example, a recent report revealed that <20% of US patients with cirrhosis who later developed liver cancer received regular screening in the 1990s (Davila et al, 2010). In the current analysis, HRs of liver cancer were notably higher in white men than black men with most types of cirrhosis, and the exception of viral-related cirrhosis. This racial difference in liver cancer risk is not fully understood, but previous studies have noted that health care and survival trends vary by race, ethnic group and socioeconomic status (Artinyan et al, 2010). In regard to liver cancer, it has been reported that black persons are diagnosed at more advanced stages and experience a poorer survival than white persons (Davila and El-Serag, 2006). Our findings may suggest that white men with cirrhosis also receive better treatment, or treatment at an earlier stage of cirrhosis, and therefore are more likely to survive long enough to develop liver cancer. Mortality rates of cirrhosis support this suggestion. Between 1970 and 2006, the mortality rate of cirrhosis per 100 000 persons declined from 16.6 to 7.0 among white persons and from 88.1 to 9.1 among black persons. Although black persons experienced a greater percentage decline in cirrhosis mortality, rates among black persons have remained steadily higher than rates among white persons.

This investigation had a number of strengths, including a very large size of ~4.5 million persons with 26 million associated records. The study also had a long period of follow-up of almost three decades, which enabled a sufficient number of cancer outcomes to develop at different periods of follow-up. Clinical diagnoses were obtained from medical records and thus were not subject to recall bias. In addition, because minority populations tend to be overrepresented in the VA population, the study was large enough to examine the HRs separately in white and black men. Morgan et al (2010) noted that the potential for confounding by socioeconomic status may be limited because patients within the VA system are more likely to be similar socioeconomically than are persons who do not use the VA system (Randall et al, 1987). In addition, previous VA studies have shown similar health care utilisation and outcomes for black and white people (Deswal et al, 2004; Giordano et al, 2006).

Despite its notable strengths, the study also had some limitations. Persons who use the VA health care system are not restricted from using other health care systems. For example, as the VA system does not have many emergency rooms, VA patients who require acute care, might not present at a VA hospital. It is likely, however, that persons with chronic conditions, such as cirrhosis, would continue their care at the VA as the care would be

**DISCUSSION**

In the present study, the HR of developing liver cancer among men with cirrhosis compared with men without cirrhosis increased steadily between 1969 and 1996. Recent progress understanding the pathophysiology of cirrhosis and management of the complications of cirrhosis has resulted in reduced mortality rates among persons with end-stage liver disease in the United States (Grattagliano et al, 2011). Thus, it is possible that with improved survival among men with cirrhosis the risk of being diagnosed with other sequel is affected.

The development and overall availability of tools to manage cirrhosis complications has greatly improved in the United States in recent decades, although further improvement is certainly warranted (Kanwal et al, 2011). Since the early 1980s, these tools have included therapeutic options for the prevention of oesophageal varices and recurrent variceal haemorrhage (i.e., drug and endoscopic therapy, transjugular intrahepatic porto-systemic shunt); a lower threshold for diagnostic paracentesis in conjunction with earlier detection and treatment of infectious complications; the availability of treatment options for HBV- and HCV-infected patients with compensated cirrhosis; a rising awareness of the importance of renal function monitoring for the earlier diagnosis and management of hepatorenal syndrome; and liver transplantation (Hoefs and Runyon, 1985; Grossmann et al, 1990; Sabha et al, 1990; The Veterans Affairs Cooperative Variceal Sclerotherapy Group, 1991; Poynard et al, 1991; Rossie et al, 1997; Sharara and Rockey, 2001). The use of these and other options have almost certainly had an effect on cirrhosis mortality rates. Whether therapy of cirrhosis inadvertently leads to increases in the risk of liver cancer is not clear, although previous studies suggest that the risk of liver cancer increases linearly from the time of first diagnosis of cirrhosis. In addition, a recent report of an HCV-infected cohort in the VA system found that the incidence of HCC rose more dramatically than previously predicted (Kanwal et al, 2011). Although the cohort described by Kanwal et al (2011) was an HCV-infected cohort rather than a cirrhosis cohort, the majority of HCCs develop among persons with cirrhosis, thus supporting the findings of the current study.

Other possible explanations for the increased HR of liver cancer among men with cirrhosis are several. Better diagnostic detection of liver cancer through a wider application of imaging methods,
given without charge. Similarly, if an individual reported to an emergency room owing to their cancer, they would likely be referred back to the VA system. The current study was restricted to black and white males as there were too few females and non-white/non-black males to include. This study was also limited by little information on relevant covariates, such as cigarette smoking, alcohol consumption, diet, physical activity, and body mass. The use of medical conditions as proxy variables, such as COPD for smoking, cannot guarantee that the covariate effect is captured entirely. As such, adjustments for lifestyle variables were likely incomplete. Surrogate variables tend to be conservative estimates of true variables, and thus would be likely to underestimate the association rather than overestimate it. Other covariates, such as obesity, are almost certainly underascertained in the data, as medical records have much more complete information on conditions that are under treatment rather than conditions that are simply present. The ascertainment of infection with HBV and/or HCV was also incomplete. Blood tests to detect chronic infection with HBV were not available until the early 1970s, whereas tests for HCV were not available until the early 1990s. Other clinical data, laboratory data, and medical records were not available to verify diagnoses, diagnostic tests or treatment.

Finally, our study included only hospitalised veterans; persons who utilise the VA medical system have been reported to be of lower socioeconomic status and in poorer health compared with the general population (Agha et al, 2000), suggesting that caution should be exercised when extrapolating results to the general population.

In conclusion, the current study shows that the hazard of developing liver cancer among men with cirrhosis in the VA health care system significantly increased between 1969 and 1996. Although the increased hazard is compatible with numerous explanations, it is possible that better treatment of cirrhosis has resulted in higher hazards of liver cancer diagnoses over time. Further study of this question in other populations is warranted.

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Conflict of interest

The authors declare no conflict of interest.

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