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Population attributable fractions of risk factors for hepatocellular carcinoma in the United States

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Abstract

Objectives—Hepatocellular carcinoma (HCC) incidence has been increasing in the United States for several decades. As the incidence of hepatitis C virus (HCV) infection declines and the prevalence of metabolic disorders rises, the proportion of HCC attributable to various risk factors may be changing.

Methods—Data from the Surveillance, Epidemiology, and End Results (SEER)-Medicare linkage were used to calculate population attributable fractions (PAFs) for each risk factor over time. HCC cases (n=10,708) diagnosed during the years 2000–2011 were compared to a 5% random sample of cancer-free persons (n=332,107) residing in the SEER areas. Adjusted odds ratios (ORs) and PAFs were calculated for hepatitis C virus (HCV), hepatitis B virus (HBV), metabolic disorders, alcohol-related disorders, smoking, and genetic disorders.

Results—Overall, the PAF was greatest for metabolic disorders (32.0%), followed by HCV (20.5%), alcohol (13.4%), smoking (9.0%), HBV (4.3%) and genetic disorders (1.5%). The PAF for all factors combined was 59.5%. PAFs differed by race/ethnicity and gender. Metabolic disorders had the largest PAF among Hispanics (39.3%, CI=31.9–46.7%) and whites (34.8%, CI=33.1–36.5%), while HCV had the largest PAF among blacks (36.1%, CI=31.8–40.4%) and Asians (29.7%, CI=25.9–33.4%). Between 2000 and 2011, the PAF of metabolic disorders increased from 25.8% (CI=22.8–28.9%) to 36.0% (CI=33.6–38.5%). In contrast, the PAFs of alcohol-related disorders and HCV remained stable.

Conclusions—Among U.S. Medicare recipients, metabolic disorders contribute more to the burden of HCC than any other risk factor and the fraction of HCC due to metabolic disorders has increased in the last decade.

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Keywords

hepatocellular carcinoma; metabolic disorders; hepatitis C virus; hepatitis B virus; population attributable fractions

INTRODUCTION

Primary liver cancer is the sixth most commonly occurring malignancy worldwide and the second leading cause of cancer mortality.[1] In the United States, the incidence of liver cancer has been increasing since 1975,[2] and liver cancer is projected to be among the top three causes of cancer mortality by 2030.[3] The predominant histologic form of primary liver cancer is hepatocellular carcinoma (HCC). In contrast to many other types of cancer, HCC frequently occurs among persons with known risk factors who have underlying liver disease.

Risk factors for HCC in the U.S. include chronic infection with either hepatitis C virus (HCV) [4] or hepatitis B virus (HBV),[5] excessive alcohol consumption,[5] cigarette smoking and rare genetic disorders (porphyrias,[6] hemochromatosis,[7] Wilson's disease,[8] alpha-1 antitrypsin deficiency,[9] glycogen storage diseases [9, 10]). Recent data suggest that a constellation of metabolic disorders, which include diabetes,[11] obesity,[12, 13] impaired glucose tolerance,[14] metabolic syndrome,[15] and non-alcoholic fatty liver disease (NAFLD),[16, 17] are also important HCC risk factors.

The extent to which each risk factor contributes to the overall HCC burden on a population level can be determined by calculation of the population attributable fraction (PAF), which is an important measure for cancer control policy development. Previous studies have examined the PAFs of HCC risk factors in the United States; [18] but relative contributions of HCC risk factors to the burden of disease may have changed over time. Recent reports have shown that the prevalence of metabolic disorders is rising: 35.4% of U.S. residents aged 60 years and older are obese,[19] 26.9% of persons 65 years and older have diabetes[20] and approximately one-fifth of the adult population have metabolic syndrome.[21] In contrast, the prevalence of HCV infection has declined due to the elimination of HCV from the nation's blood supply in the early 1990s.[22] As a result of these concurring trends PAFs may have changed in recent years. To examine this hypothesis, we estimated PAFs of the HCC risk factors for the period 2000–2011, using the SEER-Medicare Linked Database.[23, 24]

METHODS

Data Source

The SEER-Medicare Linked Database is a linkage of cancer registry data from the National Cancer Institute's Surveillance, Epidemiology and End Results (SEER) program with the Medicare medical claims database. The SEER 18 database excluding the Alaska Native Registry covers approximately 30% of the U.S. population.[25] Medicare is the national health insurance program administered by the U.S. government that covers approximately 97% of persons aged 65 years and above.[26] Almost all Medicare beneficiaries are enrolled in Part A, which covers inpatient medical services, and 96% of Part A beneficiaries are also enrolled in Part B, which covers outpatient services. The SEER-Medicare linkage matches

approximately 93% of Medicare aged individuals in SEER cancer registries to the Medicare medical claim file.[24, 27] To identify risk factors, International Classification of Diseases, version 9 (ICD-9) codes were used to capture medical conditions and key health risk behaviors (Table 1). Because obesity, diabetes, impaired glucose metabolism (IGM), metabolic syndrome and non-alcoholic fatty liver disease (NAFLD) are highly correlated disorders, these conditions were combined into one group, referred to as 'metabolic disorders.' Rare genetic disorders (porphyrias, hemochromatosis, Wilson, alpha-1 antitrypsin deficiency and glycogen storage diseases) known to be associated with HCC were combined into a single group, referred to as 'genetic disorders.' Because the SEER-Medicare database contains limited information on alcohol consumption, a collection of alcohol-related medical conditions in addition to reported history of alcohol abuse were used as the proxy variable for heavy alcohol consumption under the variable heading 'alcohol.'[28] Similarly, the combination of chronic obstructive pulmonary disease (COPD)[29] and tobacco use were used as a proxy for heavy smoking under the variable heading 'smoking'. Thus, the following factors were analyzed for odds ratios (ORs) and PAFs: metabolic disorders, HCV, HBV, genetic disorders, alcohol, and tobacco.

Cases and Controls

HCC cases were identified using ICD for Oncology, third edition [ICD-O-3] topography code C22 and morphology codes 8170–8175. The case inclusion criteria included: diagnosis year between 2000 and 2011; age 68–100 years old; enrolled in Medicare Parts A and B continuously during the 36 months before diagnosis. A minimum age of 68 years was required to allow a 3-year Medicare history for risk factor identification. A 3-year minimum was selected in order to allow a sufficiently long interval for exposures to be identified but not so long as to limit the number of cases which could be included. Exclusion criteria included: a history of enrollment in an HMO at any time in the 36 months before diagnosis; and HCC diagnosis noted solely on autopsy or death certificate. A 5% random sample of cancer-free Medicare recipients residing in the SEER areas of the cases was used as the comparison population. Using a random number generator, index dates assigned to eligible controls based on birth year were used for PAF calculations in each of 4-year diagnosis intervals. Control selection was based on the same eligibility criteria as was case selection. The race/ethnicity variable was that used by Medicare.

Statistical Analysis

Population attributable fractions were calculated using the formula described in Bruzzi et al.[30] Multivariable logistic regression analyses that adjusted for the state buy-in-status (as an indication of lower socioeconomic status), age, gender and race/ethnicity and the other five risk factors were used to calculate ORs, PAFs and corresponding 95% confidence intervals (CI) in the overall study population; see SAS code in.[31] ORs and PAFs were also calculated by gender, race/ethnicity and diagnosis time period (2000–2003, 2004–2007, 2008–2011). Wald Chi-square tests were calculated as global tests of significance difference in ORs by year of diagnosis. Data analyses were conducted using SAS, v.9.4 (SAS, Cary, NC).

RESULTS

The analysis included 10,708 persons with HCC and 332,107 cancer-free persons. Table 2 shows that the mean age of cases was 76.9 years compared to 76.6 among controls. The majority of cases were male (66.3%), while the majority of the controls were female (61.4%). More cases were diagnosed in the most recent time period 2008–2011 (38.3%) than in the prior two. Most cases (70.9%) and controls (83.5%) were white.

Among cases, 50.1% had a history of metabolic disorders, compared to 24.8% of controls. There was evidence of HCV infection among 20.8% of cases and 0.4% of controls. Similarly, 4.5% of cases had a history of HBV, compared to 0.1% of controls. An alcohol-related condition was documented in 15.5% of cases and 1.6% of controls. A history of smoking was identified among 33.1% of cases and 18.7% of controls. Genetic disorders were found among 1.7% of cases and 0.2% of controls.

The ORs associated with each of the six risk factors, adjusted for sex, age at diagnosis, race/ethnicity, state buy-in status and other risk factors are shown in Table 3. The risk of developing HCC was highest in association with HCV (OR=59.9, 95%CI=55.1–65.1), followed by HBV (OR=21.6, 95%CI=17.9–26.0), alcohol (OR=7.3, 95%CI=6.8–7.8), genetic disorders (OR=7.3, 95%CI=6.0–8.9), metabolic disorders (OR=2.8, 95%CI=2.7–2.9) and finally, smoking (OR=1.4, 95%CI=1.3–1.4). The OR associated with HCV was approximately twice as high among women (OR=81.8 95%CI=72.9–91.9) than men (OR=42.1, 95%CI=37.6 – 47.3). In contrast, the OR associated with HBV was more than twice as high among men (OR=28.2, 95%CI=22.3–35.6) as women (OR=13.2, 95%CI=9.5–18.3) and the OR associated with genetic disorders was three times higher among men (OR=9.7, 95%, 95%CI=7.7–12.3) than women (OR=3.2, 95%CI=2.0–5.1). The ORs associated with metabolic conditions, alcohol and smoking did not vary greatly by gender.

The ethnic/racial examination of risk factors is shown in Table 4. As with the gender-specific analyses, risks were ordered in roughly the same way as in the overall analysis. In all four groups, the ORs were highest in association with HCV and lowest in association with smoking. The ORs associated with HBV were the second highest in all groups except Hispanics and varied widely, with Asians having the greatest risk (OR=31.2, 95%CI=23.2–42.2) and Hispanics having the lowest risk, which did not attain statistical significance (OR=2.5, 95%CI=0.4–15.5). The ORs associated with alcohol-related conditions also varied widely, with Hispanics having the highest risk (OR=9.5, 95%CI=6.8–13.2) and blacks having the lowest risk (OR=3.6, 95%CI=2.7–4.7). Increased risk associated with metabolic disorders was found in all racial/ethnic groups with the greatest ORs found among whites (OR=3.1, 95%CI 2.9–3.3) and Hispanics (OR=2.8, 95%CI=2.2–3.5). The OR associated with genetic conditions was statically significant only among whites (OR=8.2, 95%CI=6.7–10.2, $p<0.001$). The HCC risk associated with smoking was similar among whites, blacks and Asians. Among Hispanics, there was no significant association between smoking and risk.

The risks associated with each factor by period of diagnosis (2000–2003, 2004–2007, 2008–2011) are shown in Table 5. Global tests of the odds ratios associated with HCV ($p<0.0001$),

genetic conditions (p=0.002), alcohol (p=0.04), and smoking (p<0.0001) found significant differences by time interval. In contrast, global tests of the odds ratios associated with HBV (p=0.26) and metabolic disorders (p=0.17) found no significant differences by time interval.

The overall and gender-specific PAFs of each factor are shown in Table 6. Overall, the greatest PAF was for metabolic disorders (PAF=32.0%, 95%CI=30.5–33.5), followed by HCV (PAF=20.5%, 95% CI=19.0–22.0), alcohol (PAF=13.4%, 95% CI=11.7–15.0), smoking (PAF=9.0% for 95% CI= 6.9–11.1), HBV (PAF= 4.3%, 95%CI 2.5–6.1) and genetic disorders (PAF=1.5%, 95% CI=−0.4–3.3). The PAF of all six factors combined was 59.5% (95%, CI=58.5–60.5). Metabolic disorders were associated with the greatest PAFs among both genders (men: PAF 32.5%, 95%CI=30.7–34.4; women: PAF 30.8%, 95%CI=28.1–33.4). The PAFs of HCV and alcohol-related disorders differed by gender. The PAF of HCV was higher among women (PAF=26.2, 95%CI =23.8–28.6) than men (PAF=17.5, 95%CI=15.7–19.4), while the PAF of alcohol-related disorders was higher among men (PAF=17.0%; 95%CI=15.1–18.9) than women (PAF=6.2%; 95%CI=3.2–9.3). There was no significant difference in the PAFs by gender for smoking, HBV or genetic disorders.

Table 7 presents PAFs by racial/ethnic group. While metabolic disorders had the greatest PAF among Hispanics (39.3%, 95%CI=31.9–46.7) and whites (34.8%, 95%CI= 33.1–36.5), HCV had the greatest PAF among blacks (36.1%, 95%CI=31.8–40.4) and Asians (29.7%, 95%CI=25.9–33.4). The third greatest contributor to HCC among all groups except Asians was alcohol-related disorders, while the third greatest contributor among Asians was HBV (17.8%, 95%CI=13.4–22.2). The PAF of smoking was similar in whites (10.5%, 95%CI=8.0–13.0) and blacks (10.6%, 95%CI=2.8–18.5), but was lower among Asians (5.2%, 95%CI=−0.7–11.1) and Hispanics (1.1, 95%CI=−11.1–13.2).

Between 2000–2003 and 2008–2011, the PAF of all risk factors combined increased from 52.2 to 63.7% (Table 8). Increases in PAF were most evident in association with metabolic disorders (25.8% to 36.0%) and smoking (5.1% to 12.2%). The PAF associated with HCV modestly increased until 2004–2007, but was then stable. In contrast, the PAFs of HBV (3.9% to 4.7%), alcohol (12.3% to 13.8%) and genetic disorders (1.9% to 1.1%) were fairly stable over time.

DISCUSSION

The current U.S. study found that 59.5% of HCC diagnosed between 2000 and 2011 can be attributed to six known HCC risk factors. One factor alone, metabolic disorders, accounted for 32% of the total HCC burden, increasing from 26% to 36% over the period of study. In contrast, the attributable fraction associated with HCV remained stable throughout at approximately 20%. The attributable fraction of the various factors differed by racial/ethnic group and by gender. While metabolic disorders were the greatest contributor to HCC among whites and Hispanics, HCV was the greatest contributor among blacks and Asians. By gender, the contribution of HCV was higher among women than men, but the contribution of alcohol was higher among men than women.

The 32% PAF associated with metabolic disorders in the present study is similar to that reported for obesity/diabetes (PAF=37%) in a prior SEER-Medicare study that covered the years 1973–2007.[18] Other studies of HCC attributable risks[5, 32–35] have not reported the contribution of more than one metabolic disorder at a time. Examinations of obesity alone have reported PAFs of 7.0% in Italy [35] and 16.1% in a large European cohort from several countries.[5] Examinations of diabetes alone have reported PAFs ranging from 8% to 14% in Italy,[32, 35] 20% in Texas,[33] and between 6% and 27% in Hawaii, depending on racial/ethnic group.[34] Comparison of the current results with those of other studies, however, must await the reporting of PAF results for metabolic disorders as a group.

In the present study, HCV had the second highest PAF (20.5%) of any factor after metabolic disorders. This PAF is consistent with most prior estimates, both from the U.S.[18, 33] and Europe,[5, 36] but notably lower than a prior estimate from Italy (PAF=65%).[35] Females had a higher PAF (26.2%) than males (17.5%). Although the reason for this is unclear, it may be related to higher HCV-related mortality among men at younger ages. Among the racial/ethnic groups in the current study, blacks had the highest PAF associated with HCV (36.1%), while Asians had the second highest (29.7%). Among black persons, the high burden of HCV-related HCC is consistent with race-specific HCV prevalence estimates from U.S. surveys.[37] The large fraction of HCV-related HCC cases among Asians in the current analysis may be due to the high percentage of persons of Japanese ancestry in SEER catchment areas (i.e., Hawaii and California). Although HBV is the dominant HCC-related virus in most Asian countries, an HCV epidemic after World War II in Japan resulted in an epidemic of HCV-related HCC in the ensuing decades.[38]

The PAF associated with HBV (4.3%) was similar to the report of the prior SEER-Medicare study, but lower than the PAFs reported from Europe (7.9–16.0%) [5, 35, 36] and from a Texas case-control study (16.0%).[33] The differences in PAF between the U.S. and Europe are not unexpected as the U.S. is a low-endemicity region for HBV, while some European countries are of intermediate endemicity.[39] The difference between the current study and the U.S. case-control study may be related to the difference in ascertainment methods of the populations. The case-control study used hospital controls with cancer, thus their exposures may have differed from those of the general population.[33] In the current study, the highest PAF for HBV was observed among Asians (17.8%), with PAFs of less than 3% seen among all other groups. As chronic HBV infection is more common among Asians than among other racial/ethnic groups, particularly Asians not born in the U.S., the higher PAF among Asians is in line with expectations.[40] The prevalence of HBV is declining in most Asian countries, however, because HBV vaccination of neonates is now widespread.[41, 42] As a result, the PAF associated with HBV will almost certainly decline in coming generations.

The PAF associated with smoking (9%) was similar to the PAF of 12% reported from Italy,[35] but strikingly lower than two estimates from a European multi-country cohort study (34.9–47.6%).[5, 43] The large difference in PAF associated with smoking may be due to the unusually low prevalence of smokers in the European cohort comparison group.[35, 44] In the current study, the PAF for smoking increased over time, although not significantly so, from 5.1% to 12.2%. Whether this indicates a real increase in the contribution of smoking to HCC risk, however, is not clear. The variable used in the current study was a combination of codes

for COPD and tobacco use. If physicians were more likely over time to indicate that HCC cases were smokers, a larger proportion of HCC cases would appear to be attributable to smoking.

The PAF due to alcohol (13.4%) in the current study was similar to that of a large European cohort (10.2%), but lower than PAFs of 18–33% reported by other European studies and by one hospital-based U.S. case-control study (PAF=32%).[33] As the alcohol variable in the current study was based on codes for alcohol abuse and alcohol-related conditions, it is likely that only persons who consumed large quantities of alcohol were identified. Thus the PAF of the current study may only reflect the contribution of excessive alcohol consumption to HCC risk. The difference between the current study and the U.S. study could have been due to the use of hospitalized controls with cancer in the case-control study.[33]

The small fraction of HCC cases attributable to genetic disorders (PAF=1.5%) in the current study was consistent with the prior SEER-Medicare analysis.[18] As the HCC-related genetic disorders are more common among persons of European ancestry, the PAF among whites (1.9%) was considerably higher than the PAFs among other racial/ethnic groups. Other studies have yet to report PAFs due to genetic disorders, although the rarity of the disorders among all populations indicates that the PAFs will be small.

Our findings challenge assumptions that HCV is the primary factor responsible for the rising incidence of HCC in the U.S.[45] In persons of age 68 years and greater, metabolic disease was responsible for an increasing and greater fraction of HCC cases than was HCV infection, which was stable over time. These PAFs could change in the future, however, as the individuals most likely to be infected with HCV are members of the 1945–1965 birth cohort,[46] which was still too young to be included in the current analysis. Although some persons in this birth cohort would have become eligible for Medicare in 2010, they would not have reached the minimum age (68 years) for study inclusion. As members of the 1945–1965 birth cohort age, however, a larger proportion of cases could be attributable to HCV if the use of effective anti-HCV drugs does not become widespread.

The current study had strengths and limitations. A major strength was that the SEER-18 registries included over 30% of the population, allowing robust analyses within population strata and across time periods. Furthermore the study population is comprised of members of the age group with the highest incidence rates of HCC.[47] In addition, cancer case ascertainment in SEER areas is estimated to be 98% [24] and Medicare covers up to 97% of persons aged 65 years old and older.[26] Limitations include that the results of the current analysis may not be generalizable to persons younger than 68 years of age. The identification of risk factors using medical claims data also has a potential for underreporting of behavioral risk factors such as smoking and alcohol [48] and underreporting of conditions that are only ascertained based on medical indication (i.e., HBV and HCV). Obesity is likely underreported as well.[48]

In conclusion, the finding that metabolic disorders have the highest PAF of all HCC risk factors in the U.S., and that their PAF has been increasing, suggests that these conditions should receive more attention as modifiable risk factors for HCC.

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Table 1

International Classification of Diseases, Ninth Edition Codes for Hepatocellular Carcinoma Risk Factors

Hepatitis C virus	070.41, 070.44, 070.51, 070.54, 070.70, V02.62
Hepatitis B virus	070.22, 070.23, 070.32, 070.33, V02.61
Alcohol-related disorders	291, 291.0–291.5, 291.8, 291.81, 291.82, 291.89, 291.9, 303, 303.0, 303.00–303.03, 303.9, 303.90–303.93, 305.0, 305.00–305.03, 357.5, 425.5, 535.3, 535.30, 535.31, 571.0–571.3, 790.3, 980, 980.0, 980.8, 980.9, E86.0, E86.00, E86.01, E86.08, E86.09, V11.3
Genetic disorders	
Porphyrias	277.1
Hemochromatosis	275.0, 275.01
Wilson's disease	275.1
Alpha-1 antitrypsin deficiency	273.4
Glycogen storage disease	271
Metabolic disorders	
NAFLD	571.8
IGM	790.2, 790.21, 790.22, 790.29
Diabetes	250.00–250.93
Obesity	277.7, 278, 278.0, 278.1, 278.8, 278.00–278.02, 278.03, 783.1, V45.86, V85.4, V85.30–V85.45
Metabolic syndrome	277.7
Smoking	
Smoking	305.1, V15.82
COPD*	491, 491.0, 491.1, 491.8, 491.9, 491.2, 491.20–491.22, 492, 492.0, 492.8, 494, 494.0,494.1, 496

Abbreviations: COPD, chronic obstructive pulmonary disease; HCC, hepatocellular carcinoma: ICD-9, International Classification of Diseases, ninth edition; IGM, impaired glucose metabolism; NAFLD, nonalcoholic fatty liver disease

Table 2

Distribution of Demographic and Risk Factors in Patients With Hepatocellular Carcinoma (Cases) and Controls, Surveillance, Epidemiology, and End Results-Medicare, 2000–2011

	HCC n (%)	Controls n (%)
	n=10,708	n=332,107
Mean Age (Years)	76.9	76.6
Gender		
Male	7,098 (66.3)	128,259 (38.6)
Female	3,610 (33.7)	203,848 (61.4)
Year of diagnosis		
2000–2003	2,971 (27.7)	110,338 (33.2)
2004–2007	3,639 (34.0)	88,217 (26.6)
2008–2011	4,098 (38.3)	133,552 (40.2)
State buy-in support	3,358 (31.4)	83,424 (25.1)
Race/ethnicity		
White	7,594 (70.9)	277,404 (83.5)
Black	826 (7.7)	26,756 (8.1)
Asian	1,213 (11.3)	11,278 (3.4)
Hispanic	443 (4.1)	7,512 (2.3)
Other/unknown	632 (5.9)	9,157 (2.8)
Metabolic disorders	5,362 (50.1)	82,425 (24.8)
Diabetes	4,867 (45.5)	69,624 (21.0)
Obesity	712 (6.6)	16,995 (5.1)
NAFLD*	563 (5.3)	1,827 (0.6)
Impaired fasting glucose	267 (2.5)	7,185 (2.2)
Metabolic syndrome	31 (0.3)	747 (0.2)
Hepatitis C virus	2,231 (20.8)	1,270 (0.4)
Hepatitis B virus	479 (4.5)	271 (0.1)
Alcohol	1,660 (15.5)	5,322 (1.6)
Smoking	3,548 (33.1)	62,025 (18.7)
Genetic disorders	184 (1.7)	572 (0.2)
Porphyrias	14 (0.1)	43 (0.0)
Hemochromatosis	153 (1.4)	470 (0.1)
Wilson’s disease	4 (0.0)	27 (0.0)
Alpha-1 antitrypsin deficiency	8 (0.1)	19 (0.0)
Glycogen storage disease	7 (0.1)	21 (0.0)

Abbreviations: HCC, hepatocellular carcinoma; NAFLD, nonalcoholic fatty liver disease.

Table 3

Odds Ratios and 95% Confidence Intervals for Hepatocellular Carcinoma Risk Factors, Surveillance, Epidemiology, and End Results-Medicare, 2000–2011

	All		Male				Female			
	OR[a]	95% CI	Cases	Controls	OR[a]	95% CI	Cases	Controls	OR[a]	95% CI
Hepatitis C virus	59.9	55.1, 65.1	1274	557	42.1	37.6–47.3	957	713	81.8	72.9, 91.9
Hepatitis B virus	21.6	17.9, 26.0	343	136	28.2	22.3, 35.6	136	135	13.2	9.5, 18.3
Alcohol	7.3	6.8, 7.8	1394	3560	7.5	6.9, 8.1	266	1762	6.4	5.4, 7.6
Genetic disorders	7.3	6.0, 8.9	155	258	9.7	7.7, 12.3	29	326	3.2	2.0, 5.1
Metabolic disorders	2.8	2.7, 2.9	3600	32806	2.8	2.6, 2.9	1762	49619	2.7	2.5, 2.9
Smoking	1.4	1.3, 1.4	2631	28127	1.4	1.3, 1.4	917	33898	1.4	1.3, 1.5

Abbreviations: CI, confidence interval; OR, odds ratio

[a]adjusted for race/ethnicity, socioeconomic status, age at diagnosis, and other risk factors

Table 4

Odds Ratios and 95% Confidence Intervals for Hepatocellular Carcinoma Risk Factors by Race/Ethnicity, Surveillance, Epidemiology, and End Results-Medicare, 2000–2011

	White		Black		Asian		Hispanic	
	OR[a]	95% CI	OR[a]	95% CI	OR[a]	95% CI	OR[a]	95% CI
Hepatitis C virus	60.9	54.9, 67.5	63.8	51.3, 79.3	57.8	44.4, 75.2	40.2	26.9, 59.9
Hepatitis B virus	14.4	10.5, 19.8	4.9	2.2, 11.0	31.2	23.2, 42.2	2.5	0.4, 15.5
Alcohol	7.9	7.3, 8.6	3.6	2.7, 4.6	6.2	4.0, 9.7	9.5	6.8, 13.2
Genetic disorders	8.2	6.7, 10.2	2.5	0.7, 9.2	1.2	0.2, 5.9	2.6	0.3, 24.3
Metabolic disorders	3.1	2.9, 3.3	1.4	1.2, 1.7	2.0	1.8, 2.4	2.8	2.2, 3.5
Smoking	1.4	1.3, 1.5	1.4	1.2, 1.7	1.3	1.1, 1.6	1.0	0.8, 1.3

Abbreviations: CI, confidence interval; OR, odds ratio

[a]adjusted for race/ethnicity, socioeconomic status, age at diagnosis, and other risk factors

Table 5

Odd ratios and 95% Confidence Intervals for Hepatocellular Carcinoma Risk Factors by Years of Diagnosis, Surveillance, Epidemiology, and End Results-Medicare, 2000–2011

	2000–2003				2004–2007				2008–2011			
	Cases	Controls	OR[a]	95% CI	Cases	Controls	OR[a]	95% CI	Cases	Controls	OR[a]	95% CI
Hepatitis C virus	541	323	57.3	48.6, 67.4	800	343	65.4	56.3, 76.1	890	604	53.3	46.8, 60.6
Hepatitis B virus	121	68	19.3	13.3, 28.0	158	76	17.5	12.5, 24.6	200	127	26.3	19.8, 34.9
Alcohol	439	1851	6.1	5.3, 7.0	574	1352	8.2	7.2, 9.3	647	2119	7.4	6.5, 8.3
Genetic disorders	64	167	10.2	7.3, 14.3	62	151	7.5	5.2, 10.7	58	266	4.8	3.3, 6.8
Metabolic disorders	1288	23794	2.5	2.3, 2.7	1799	21163	2.9	2.7, 3.1	2275	37468	2.9	2.7, 3.1
Smoking	893	21593	1.2	1.1, 1.3	1195	16105	1.4	1.3, 1.5	1460	24327	1.5	1.4, 1.6

Abbreviations: CI, confidence interval; OR, odds ratio

[a]adjusted for race/ethnicity, socioeconomic status, age at diagnosis, and other risk factors

Table 6

Overall and Sex-Specific Hepatocellular Carcinoma Population Attributable Fractions, Surveillance, Epidemiology, and End Results-Medicare, 2000–2011

	All		Male		Female	
	PAF[a]	95% CI	PAF[a]	95% CI	PAF[a]	95% CI
Metabolic disorders	32.0	30.5, 33.5	32.5	30.7, 34.4	30.8	28.1, 33.4
Hepatitis C virus	20.5	19.0, 22.0	17.5	15.7, 19.4	26.2	23.8, 28.6
Alcohol	13.4	11.7, 15.0	17.0	15.1, 18.9	6.2	3.2, 9.3
Smoking	9.0	6.9, 11.1	9.9	7.2, 12.5	7.2	3.8, 10.6
Hepatitis B virus	4.3	2.5, 6.1	4.7	2.5, 6.8	3.5	0.4, 6.6
Genetic disorders	1.5	−0.4, 3.3	2.0	−0.3, 4.2	0.6	−2.7, 3.8
Total	59.5	58.5, 60.5	60.6	59.4, 61.8	57.1	55.4, 58.9

Abbreviations: CI, confidence interval; PAF, population attributable fraction

[a]adjusted for race/ethnicity, socioeconomic status, age at diagnosis, and other risk factors

Table 7

Race and Ethnicity-Specific Hepatocellular Carcinoma Population Attributable Fractions, Surveillance, Epidemiology, and End Results-Medicare, 2000–2011

	White		Black		Asian		Hispanic	
	PAF[a]	95% CI	PAF[a]	95% CI	PAF	95% CI	PAF[a]	95% CI
Metabolic disorders	34.8	33.1, 36.5	14.4	6.4, 22.3	21.8	16.5, 27.1	39.3	31.9, 46.7
Hepatitis C virus	16.9	15.1, 18.8	36.1	31.8, 40.4	29.7	25.9, 33.4	21.1	14.0, 28.3
Alcohol	14.9	13.0, 16.8	12.4	6.2, 18.5	5.0	−0.1, 10.1	20.0	12.7, 27.3
Smoking	10.5	8.0, 13.0	10.6	2.8, 18.5	5.2	−0.7, 11.1	1.1	−11.0, 13.2
Hepatitis B virus	1.7	−0.5, 3.9	2.7	−3.9, 9.3	17.8	13.4, 22.2	1.1	−8.3, 10.5
Genetic disorders	1.9	−0.3, 4.1	0.4	−6.3, 7.1	0.1	−5.3, 5.5	0.3	−8.8, 9.3
Total	59.8	58.7, 61.0	56.2	52.1, 60.4	58.8	55.9, 61.6	63.1	58.3, 68.0

Abbreviations: CI, confidence interval; PAF, population attributable fraction

[a]adjusted for race/ethnicity, socioeconomic status, age at diagnosis, other risk factors

Table 8

Hepatocellular Carcinoma Population Attributable Fractions by Years of Diagnosis, Surveillance, Epidemiology, and End Results-Medicare, 2000–2011

	2000–2003		2004–2007		2008–2011	
	PAF[a]	95% CI	PAF[a]	95% CI	PAF[a]	95% CI
Metabolic disorders	25.8	22.8, 28.9	32.2	29.6, 34.8	36.0	33.6, 38.5
Hepatitis C virus	17.9	15.0, 20.8	21.6	19.2, 24.1	21.3	18.9, 23.7
Alcohol	12.3	9.2, 15.5	13.8	11.1, 16.6	13.6	11.0, 16.3
Smoking	5.1	0.9, 9.2	9.1	5.5, 12.7	12.2	8.9, 15.4
Hepatitis B virus	3.9	0.4, 7.3	4.1	1.0, 7.2	4.7	1.8, 7.6
Genetic disorders	1.9	−1.5, 5.4	1.5	−1.7, 4.6	1.1	−1.9, 4.1
Total	52.2	50.1, 54.4	60.2	58.6, 61.9	63.7	62.3, 65.2

Abbreviations: CI, confidence interval; PAF, population attributable fraction

[a]adjusted for race/ethnicity, socioeconomic status, age at diagnosis, other risk factors