

# Epidemiology of hepatocellular carcinoma

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**MC Yu, J-M Yuan, S Govindarajan, RK Ross. Epidemiology of hepatocellular carcinoma. Can J Gastroenterol 2000;14(8): 703-709.** Although rare in Canada and the United States, hepatocellular carcinoma (HCC) ranks as the eighth most common cancer in the world. High-risk regions are East and Southeast Asia, and sub-Saharan Africa. Independent of race and geography, rates in men are at least two to three times those in women; this sex ratio is more pronounced in high-risk regions. Rates of HCC in the United States have increased by 70% over the past two decades. Registry data in Canada and Western Europe show similar trends. In contrast, the incidence of HCC in Singapore and Shanghai, China, both high-risk regions, has declined steadily over the past two decades. Among white and black Americans, there is an inverse relationship between social class status and HCC incidence. Chronic infection by the hepatitis B virus (HBV) is by far the most important risk factor for HCC in humans. It is estimated that 80% of HCC worldwide is etiologically associated with HBV. In the United States, although the infection rate in the general population is low, HBV is estimated to account for one in four cases of HCC among non-Asians. Chronic infection by the hepatitis C virus is another important risk factor for HCC in the United States; however, this virus is believed to play a relatively minor role in the development of HCC in Africa and Asia. Dietary aflatoxin exposure is an important codeterminant of HCC risk in Africa and parts of Asia. In Canada and the United States, excessive alcohol intake, cigarette smoking and oral contraceptive use in women also are risk factors for HCC.

**Key Words:** Alcohol; Epidemiology; Hepatocellular carcinoma; Oral contraceptives; Risk factors; Tobacco; Virus

## Épidémiologie de l'hépatocarcinome

**RÉSUMÉ :** Bien que rare au Canada et aux États-Unis, l'hépatocarcinome se classe au huitième rang parmi les cancers les plus répandus dans le monde. Les régions à haut risque sont l'Asie de l'Est et du Sud-Est et l'Afrique sub-saharienne. Indépendamment de la race et du lieu géographique, les taux sont au moins deux ou trois fois plus élevés chez l'homme que chez la femme. Cette distribution liée au sexe est plus prononcée dans les régions à risque élevé. Aux États-Unis, les taux d'hépatocarcinomes ont augmenté de 70 % au cours des deux dernières décennies. Les données tirées de registres canadiens et de l'Europe de l'Ouest révèlent une tendance similaire. En revanche, l'incidence de l'hépatocarcinome à Singapour et à Shanghai, en Chine, qui font partie des régions à haut risque, a pour sa part constamment diminué au cours des deux dernières décennies. Chez les Américains de race blanche et de race noire, on note un lien inversement proportionnel entre le statut socio-économique et l'incidence de l'hépatocarcinome. L'infection chronique par le virus de l'hépatite B (HBV) est de loin le plus important facteur de risque à l'égard de l'hépatocarcinome chez l'être humain. On estime que 80 % des hépatocarcinomes dans le monde ont un lien étiologique avec l'HBV. Aux États-Unis, bien que le taux d'infection de la population générale soit faible, l'HBV serait responsable d'un cas sur quatre chez les non-asiatiques. L'infection chronique par le virus de l'hépatite C est un autre important facteur d'hépatocarcinome aux États-Unis. Par contre, ce virus jouerait un rôle relativement mineur dans le développement de l'hépatocarcinome en Afrique et en Asie. L'exposition à l'aflatoxine alimentaire est un important codéterminant du risque d'hépatocarcinome en Afrique et dans certaines régions d'Asie. Au Canada et aux États-Unis, la consommation excessive d'alcool, le tabagisme, l'emploi de contraceptifs oraux chez les femmes constituent également des facteurs de risque d'hépatocarcinome.

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Although relatively rare in Canada and the United States, primary liver cancer is a common malignancy worldwide. It ranks as the eighth most common cancer, accounting for 4% of all newly diagnosed cancers in both sexes (1). The dominant form of primary liver cancer is hepatocellular carcinoma (HCC). Most other primary liver cancers are cholangiocarcinomas, which are histologically and etiologically distinct from HCC. In the United States, HCC constitutes 70% to 75% of cases of primary liver cancer (2,3). In most high-risk regions (East and Southeast Asia, and sub-Saharan Africa), well over 90% of primary liver cancers are HCCs (4). Exceptions are areas with high infection rates of liver flukes (*Clonorchis sinensis*, *Opisthorchis viverrini*), which are established etiological agents of cholangiocarcinoma (5). In an area in northeast Thailand where *O. viverrini* infection is endemic, 90% of primary liver cancers are cholangiocarcinomas (6).

International comparisons of cancer incidence usually do not distinguish between the two distinct types of primary liver cancer. Therefore, most available descriptive data are for primary liver cancer as a whole. However, because cholangiocarcinoma exhibits little variation overall in worldwide incidence (5), any observed racial and geographical variations in primary liver cancer are likely the result of HCC demographic variability.

#### DEMOGRAPHIC PATTERN

**International variation:** The incidence of primary liver cancer varies as much as 100-fold between high-risk and low-risk regions in the world – among the highest international variability of all major cancers. The highest rates are found in East and Southeast Asia, and sub-Saharan Africa, while the lowest rates are observed in North America and Western Europe (4). In southern Guangxi, China, a very high-risk area, the age-standardized (world population) incidence is approximately 120/100,000 person-years in men and 30/100,000 person-years in women (7) (Table 1). In contrast, corresponding rates in Danish men and women, low-risk populations, are 1.6/100,000 person-years and 0.6/100,000 person-years, respectively (4).

**North American incidence:** Incidence rates of primary liver cancer are fairly uniform across Canada. Overall, the age-standardized rate in men is approximately three/100,000 person-years; the corresponding rate in women is approximately one/100,000 person-years (4) (Table 2).

In the United States, the incidence of primary liver cancer varies five- to eightfold among major racial and ethnic groups (Table 2). The rates in non-Hispanic white men and women are similar to those in Canadian men and women. The incidence in Hispanic and black Americans is roughly two times that in white Americans. Asian Americans exhibit the highest incidence, consistent with the high rates of liver cancer seen in their countries of origin. It is interesting to note that, although Chinese, Japanese and Koreans in Asia have roughly comparable rates of liver cancer, Chinese, Japanese and Korean Americans in Los Angeles, California show a two- to fourfold difference in disease incidence. The

**TABLE 1**  
Average annual age-specific prevalence of primary liver cancer in Fusui County, Guangxi Autonomous Region, China, 1974 to 1977

Age (years)	Rate/100,000	
	Males	Females
0-9	0.0	0.0
10-19	13.7	3.7
20-29	76.7	14.1
30-39	251.6	55.7
40-49	296.9	72.6
50-59	207.4	77.0
60-69	192.0	56.3
≥70	220.9	50.5
Age-standardized (world population) rate	119.7	31.2

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**TABLE 2**  
Average annual age-standardized prevalence of primary liver cancer in Canada and the United States, 1988 to 1992

Population	Rate/100,000	
	Males	Females
Canada	3.1	1.2
Los Angeles County, California		
Nonhispanic white	2.9	1.1
Hispanic white	6.5	2.2
Black	5.1	2.2
Chinese	16.1	4.4
Japanese	5.8	3.3
Filipino	9.5	3.5
Korean	23.9	5.5

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incidence is highest in Koreans, intermediate in Chinese and lowest in Japanese, in parallel to their length of residence in the United States. Most Koreans in Los Angeles are recent immigrants; there were very few Koreans in the United States until the 1970s. On the other hand, migration from Japan to California occurred mostly from the mid-1800s to the early part of this century. Chinese Americans are mainly a mixture of recent immigrants (since the 1970s) and descendants of labourers who came to California during the 'gold rush' (mid- to late 1800s) (8,9). Alaskan natives are also known to have elevated rates of HCC (10).

**Sex and age:** HCC is a disease with a strong male dominance, which is seen across all populations. Rates in men are at least two to three times higher than the corresponding rates in women. This sex ratio is especially pronounced in high-risk regions (Tables 1, 2).

In low-risk populations, the disease is rare before age 40 years. Thereafter, incidence rates increase as a function of

approximately the fifth power of age, similar to most other epithelial cancers. In high-risk regions such as southern Guangxi, China, rates begin rising rapidly for both men and women in their 20s. For men, the rates plateau around age 40 to 49 years and decline thereafter. For women, the rates plateau a decade later than for men (ie, around age 50 to 59 years), again with lower rates in older ages (Table 1).

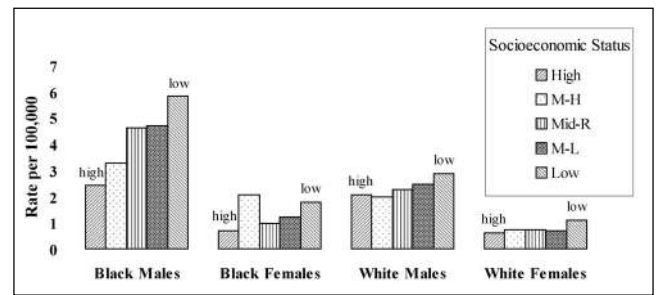
**Time trends:** In the United States, the incidence of HCC has been increasing steadily over the past two decades such that the overall age-adjusted rate during the period 1991 to 1995 is approximately 70% higher than that during the period 1976 to 1980. Rates of increase have been comparable between black and white men; these increases are more pronounced than those observed in black and white women (3). Similar time trend data have been reported for other low-risk regions, including Canada, Sweden, Norway and Germany (11). In contrast, the incidence of HCC in Singapore, a high-risk area, has declined by about one-third in both men and women over roughly the same time period (12). The incidence in Shanghai, China, another high-risk region, also has been declining, at the rate of about 1%/year (13).

A likely explanation for the rising incidence of liver cancer in the United States, Canada and Western Europe is the increased rates of hepatitis B virus (HBV) and hepatitis C virus (HCV) infections (both are major risk factors for HCC [see below]) in these population in the 1960s and 1970s. The increased infection rate is thought to have resulted from increased sexual promiscuity and needle sharing with illicit drug use during these decades. Both are risk factors for horizontal transmission of HBV and HCV. The decline in HCC incidence in East Asia may be related to the decreasing exposure to dietary aflatoxin, another major risk factor for HCC (see below) in these high-risk populations. Aflatoxin is a food contaminant arising from poor storage of grains susceptible to mold formation during spoilage. Economic development in East Asia during the past several decades has greatly diminished population exposure to this class of mycotoxins (14,15).

**Social class:** In Los Angeles, the population-based cancer registry classifies cancer patients according to social class characteristics of their places of residence. Specifically, census information on income and/or educational levels of residents in the neighbourhoods where cancer patients reside is used to rank cancer cases into one of five social class groupings. Figure 1 shows that, in general, lower social class individuals, whether white or black of either sex, have a higher risk of HCC. These results are expected because the prevalence of HBV infection and cigarette smoking, two known risk factors for HCC, are both inversely related to social class among black and white residents of Los Angeles (16,17).

### RISK FACTORS

**HBV:** HBV is a member of a family of hepatotropic DNA viruses called hepadnaviruses. HBV infection is by far the most important risk factor for HCC in humans. It is estimated that 80% of HCC worldwide is etiologically associ-



**Figure 1)** Age-adjusted (1970 United States population) incidence rates (per 100,000 person-years) in black and non-Hispanic white males and females by socioeconomic status groupings, Los Angeles County, California, 1972 to 1995. M-H Middle to high; M-L Middle to low; Mid-R Middle range

ated with chronic HBV infection (18). Among high-risk populations such as the Southern Chinese, it has been shown that the presence of hepatitis B surface antigen (HBsAg) in serum (a marker of chronicity) is the single most important predictor of HCC risk. Chinese men who are HBsAg-positive at baseline are 40 to 100 times more likely to develop HCC than are HBsAg-negative men of similar ages (7,19,20). In high-risk areas of China where the population prevalence of HBsAg positivity in men can be as high as 20% to 25%, the incidence of HCC among male HBV carriers is about 1% per year (7). Virtually all carriers acquire the infection from their carrier mothers during infancy (21).

In Canada and the United States, HBV infection is rare in the general population. Subgroups of the population known to experience increased risk of infection are those who come into frequent contact with potentially contaminated blood, such as intravenous drug users, homosexual men, patients on hemodialysis, hemophiliacs, etc (22). Although the rate of exposure is low in the general population, HBV infection is nonetheless responsible for a sizable proportion of HCC cases among non-Asians in the United States. It is estimated that one in four cases of HCC among black and white residents of Los Angeles County can be attributed to HBV (Table 3). In these low-risk populations, however, HBsAg positivity is not the sole serological marker that predicts risk. Individuals who experienced an infection that eventually resolved also have an elevated risk of HCC, although the magnitude of the increase is considerably lower than that in chronic carriers (23) (Table 3).

**HCV:** HCV is a member of the Flaviviridae family of hepatotropic RNA viruses. Epidemiological studies in diverse populations have established chronic HCV infection as a major cause of HCC in humans (24). However, there is considerable variation worldwide in its contribution to local HCC burden. In high-risk areas such as China and sub-Saharan Africa, HCV plays a relatively minor role in HCC development (25-27). On the other hand, in intermediate-risk regions such as Japan and southern Europe, and low-risk regions such as the United States, HCV is responsible for a substantial proportion of total HCC cases (24). In Los Angeles, one-third of HCC cases in black and white residents are

**TABLE 3**  
**Relative risk of hepatocellular carcinoma by hepatitis B virus (HBV) and hepatitis C virus (HCV) serological status in non-Asians of Los Angeles County, California, 1984 to 1996**

	Patients (with HCC)	Controls	Relative risk (95% CI)
<b>HBV markers</b>			
HBV negative	93	238	1.0
HBV positive*	57	23	5.1 (2.9 to 9.1)
HBsAg positive	11	0	– (6.9 to –) <sup>†</sup>
HBsAg negative and antihepatitis B core positive	46	23	3.6 (2.0 to 6.4)
<b>HCV markers</b>			
HCV negative	98	255	1.0
HCV positive <sup>‡</sup>	52	6	22.3 (9.2 to 53.9)
HCV RNA negative <sup>§</sup>	11	5	4.7 (1.5 to 14.3)
HCV RNA positive	35	0	– (23.4 to –) <sup>†</sup>
<b>HBV and HCV markers</b>			
HCV negative and HBV negative	68	233	1.0
HCV negative and HBV positive	30	22	4.5 (2.4 to 8.6)
HCV positive <sup>‡</sup> and HBV negative	25	5	17.5 (6.3 to 48.3)
HCV positive <sup>‡</sup> and HBV positive	27	1	56.2 (7.3 to 430.8)

Population-attributable risks were prior HCV infection alone (21%), prior HBV infection alone (13%) and prior co-infections of HCV and HBV (12%). \*Hepatitis B surface antigen (HBsAg) positive and/or antihepatitis B core positive; <sup>†</sup>There were no controls in this category, thus no finite estimate for the relative risk or its upper CI could be calculated; <sup>‡</sup>Anti-HCV positive; <sup>§</sup>Due to insufficient serum, six patients with HCC and one control subject had unknown HCV RNA status. Adapted with permission from reference 34

HCV-related. Among chronic HCV carriers, there is a tremendous difference in HCC risk between those with and those without the presence of HCV RNA in serum (a marker of active viral replication) (Table 3).

There is some evidence that HCV infection is playing an increasingly important role in HCC development among non-Asian Americans. In Los Angeles, the proportion of patients with HCC who are positive for HBV and/or HCV infections remained fairly constant – around 50% to 55% – during the period 1984 to 1996. However, there was a noticeable change in the relative contributions of HBV and HCV to viral hepatitis-related HCC cases between the first and second half of this 13-year period. The proportion of HCV-related cases increased from 29% to 37%, while that of HBV-related cases decreased from 43% to 35% (Table 4).

**Other hepatitis viruses:** The recently discovered hepatitis G virus (HGV) is an RNA virus belonging to the Flaviviridae family. Chronic viremia may develop after infection. Exposure to blood products is a recognized route of transmission in humans (28-30). In most populations (East Asia, Australia, Western Europe, United States), the prevalence rate of chronic HGV infection in the general population is relatively low, in the range of 1% to 3%. Exceptions exist, in-

**TABLE 4**  
**Proportion of hepatitis B virus (HBV)- and hepatitis C virus (HCV) -related cases of hepatocellular carcinoma among non-Asians of Los Angeles County, California, 1984 to 1996**

	1984-1989 n (%)	1990-1996 n (%)
HCV positive*	15 (29)	37 (37)
HBV positive <sup>†</sup>	22 (43)	35 (35)
HCV positive* and/or HBV positive <sup>†</sup>	27 (53)	55 (55)
Total	51 (100)	99 (100)

\*Anti-HCV positive; <sup>†</sup>Hepatitis B antigen positive and/or antihepatitis core positive. Data from references 16 and 34

cluding the populations of São Paulo, Brazil and the black population of South Africa, where rates are estimated at 10% to 12% (31,32). Although two case-control studies (33,34) reported a statistically significant association between HGV and HCC that was unrelated to HBV and HCV, the total body of clinical and epidemiological evidence, including the latest prospective cohort investigation in Shanghai, China, strongly suggests that HGV is not oncogenic (29,30,32,35, 36).

In 1997, a novel DNA virus was identified in a Japanese patient with post-transfusion non-A, non-B, non-C hepatitis; the virus was named TT virus after the index case (37). Available evidence indicates that TT virus infection, which has a worldwide distribution, is unlikely to be related to HCC development (38-40).

**Dietary aflatoxin:** Aflatoxins can induce HCC in a variety of animal species (41). Humans are exposed to these mycotoxins through ingestion of moldy foods, a consequence of poor storage of susceptible grains. Although descriptive studies comparing dietary aflatoxin levels and HCC rates across populations have shown a remarkably linear relationship between exposure level and disease incidence (7,42,43), definitive data linking dietary aflatoxin to HCC in humans became available only recently, after the development of assays to measure aflatoxin metabolites in bodily fluids (urine, blood). Using urinary aflatoxin metabolites as markers of exposure, studies (44,45) have shown that Chinese men with detectable aflatoxin DNA adducts in urine were nine times more likely to develop HCC than those without such urinary adducts. Moreover, a powerful interaction between chronic HBV infection and aflatoxin exposure in HCC development has been shown; HBV carriers positive for urinary aflatoxin metabolites possessed 60 times the risk of HCC relative to noncarriers negative for urinary aflatoxin metabolites (Table 5).

Aflatoxins require metabolic activation to achieve their full carcinogenic potential. Thus, polymorphic genes that participate in aflatoxin metabolism may be part of the reason for the interindividual variability in HCC risk among HBV-infected subjects residing in high aflatoxin exposure areas. McGlynn and colleagues (46) examined two such genes, ep-

oxide hydrolase (EPHX) and glutathione S-transferase M1 (GSTM1), both of which are involved in aflatoxin detoxification in hepatocytes, in a case-control study of HCC in Shanghai, China. GSTM1-null subjects showed an almost twofold risk of HCC compared with non-null subjects, while subjects homozygous for the EPHX mutant allele (which is associated with an approximately 40% decrease in enzymatic activity) exhibited a fourfold higher risk relative to wild-type homozygotes. Chen et al (47) examined aflatoxin-albumin adduct levels in relation to HCC risk in a cohort of chronic HBV carriers in Taiwan and noted that adduct level was a predictor of risk only in subjects who were GSTM1 and/or GSTT1 null (ie, those relatively deficient in aflatoxin detoxification). The overall evidence, therefore, indicates that the genetically determined ability to metabolize aflatoxin is an important risk factor for HCC in aflatoxin-exposed populations.

**Alcohol/tobacco:** Clinical studies strongly suggested that excessive alcohol intake was an important contributor to HCC in North America long before epidemiological data confirmed this exposure-disease relationship. A clear excess risk exists, however, only among heavy, long term drinkers (60 drink-years or more); there is no evidence that moderate drinking (one to three drinks a day) is related to increased HCC risk (17,48,49).

Multiple chemical components of cigarette smoke are hepatic carcinogens in animals (50). A number of case-control and cohort studies have investigated cigarette smoking in relation to HCC risk. Evidence seems to suggest that smoking interacts with viral factors in an additive (as opposed to multiplicative) manner in affecting HCC development (17,51-53). This may explain the negative findings of studies conducted in HBV endemic regions, which generally lack sufficient sample sizes to examine this association between exposure and disease within the subset of HBsAg-negative subjects. The positive correlation between alcohol and tobacco use in most populations, especially in the West, hampers studies of the association between smoking and HCC. Nonetheless, there is growing epidemiological support for cigarette smoking as an independent risk factor for HCC (54). A recent molecular epidemiological study compared DNA adduct levels of 4-aminobiphenyl, an ingredient of cigarette smoke, in liver tissues of histologically confirmed HCC cases with those of patients with metastatic liver tumours or intrahepatic stones. A statistically significant, dose-response relationship was observed between DNA adduct levels and HCC risk (55).

**Estrogen:** In the 1970s, a series of case reports followed by case-control studies established oral contraceptives as causal agents of benign liver tumours (hepatocellular adenomas, focal nodular hyperplasias) (56,57). Case reports of hepatocellular carcinoma developing in relatively young women using oral contraceptives also began to surface during that time (58,59). Estrogens, including those in oral contraceptive formulations, are powerful promoters of hepatocarcinogenesis in animals (60,61). The uncontrolled observations linking oral contraceptive use to HCC development were subse-

**TABLE 5**  
**Combined effects of hepatitis B surface antigen (HBsAg) positivity and the presence of urinary aflatoxin metabolites on risk of hepatocellular carcinoma in men in Shanghai, China**

HBsAg	Aflatoxin negative			Aflatoxin positive*		
	Cases	Controls	RR <sup>†</sup> (95% CI)	Cases	Controls	RR <sup>†</sup> (95% CI)
Negative	5	134	1.0	13	102	3.4 (1.1-10.0)
Positive	9	24	7.3 (2.2-24.4)	23	7	59.4 (16.6-212.0)

\*Presence of aflatoxin B<sub>1</sub>, aflatoxin P<sub>1</sub> or aflatoxin B<sub>1</sub>-N<sup>7</sup>-Gua; <sup>†</sup>Adjusted for cigarette smoking. RR Relative risk Reproduced with permission from reference 44

quently confirmed by a number of case-control studies conducted in Western populations. These studies consistently demonstrated a strong association between exposure, especially long term use, and risk (17,62-68). However, two studies conducted among women in areas where HBV infection is endemic failed to show any increase in HCC risk among users of oral contraceptives (69,70). Yu et al (17) pointed out that these seemingly disparate observations could be explained by an additive (rather than multiplicative) model of viral (HBV)-hormonal (estrogen) interaction in HCC development. Under the assumption of additive risks, a sample size many times larger than those used in the two latter studies would be required to detect the additional risk in oral contraceptive users against the very high background risk in HBV carriers.

Data are sparse on the possible risk of HCC in users of menopausal estrogen replacement therapy. Yu et al (17) noted a statistically nonsignificant 50% increase in risk among users of conjugated equine estrogen, but the excess risk disappeared after adjustment for use of oral contraceptives.

**Androgens:** A series of case reports documented the occurrence of HCC in relatively young men who had been long term users of androgenic steroids (71-73). These clinical observations are consistent with experimental findings showing male animals to be more susceptible to chemically induced HCC than their female counterparts. This sex difference disappears in castrated male animals, but is restored when testosterone is administered to castrated immature male or immature female animals (41,74).

HBV-infected men appear to be more likely than HBV-infected women to progress to the chronic carrier state (75,76). Therefore, testosterone may indirectly contribute to the development of HCC by promoting progression to chronicity after primary HBV infection.

**Iron:** Primary hemochromatosis is an autosomal recessive disease that is characterized by excessive iron absorption in the gut and storage in multiple organs including the liver. These patients are at extremely high risk for HCC (over 200-fold compared with the general population) (77). By screen-

ing populations in the United States with the use of serum iron measures, a prevalence of one in 200 to one in 400 persons, and a carrier rate of 10% have been suggested for this disorder (78). One clinical complication of primary hemochromatosis is diabetes mellitus, which may partly explain the observed high risk of HCC among patients with diabetes mellitus (17,79,80).

Black residents of South Africa are potentially exposed to high levels of dietary iron through the intake of home-

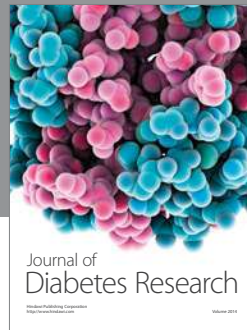
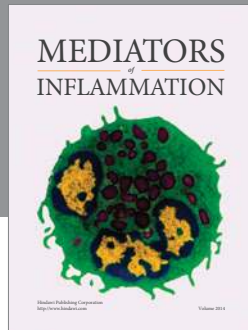
brewed beer that is prepared in nongalvanized iron drums and has been shown to have a high iron content (81). Mandishona et al (82) measured serum ferritin and transferrin saturation in 24 black South African HCC patients and 48 race-, sex- and age-matched control subjects. Five (21%) patients with HCC versus three (6%) control subjects exhibited iron overload (defined as concurrent elevation of serum ferritin and transferrin saturation), a difference that was statistically significant.

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