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Research Article

Alcohol Abuse and Hepatocellular Carcinoma: Epidemiology

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Abstract

Consumption of alcohol continues to increase in a number of countries, and is now among the most disabling habits contributing to the global burden of disease. Drinking alcohol in these amounts is linked to financial status in terms of gross domestic product, occurring most often in poor or relatively poor people and those marginalized from society. Men generally consume more alcohol than do women, have higher death rates, and die at a younger age. The proportion of alcohol-attributable deaths has increased in recent years, mainly attributable to increasing numbers of women drinking to excess. Heavy alcohol consumption is currently associated with a more than 5-fold increased cumulative probability of death, as well as a decreased mean age at the time of death. Heavy consumption over many years may also be complicated by the development of hepatocellular carcinoma [confidence interval 2.4 (95% confidence interval 1.3, 4.4)]. With the consumption of more than 60 grams of alcohol per day for more than 10 years the risk for developing the tumor approaches 1%. The risk of malignant transformation does not differ significantly between males and females, and occurs irrespective of the duration and age at the start of drinking to excess. The tumor usually, but not invariably, develops in the presence of cirrhosis.

With the emergence in recent years of obesity and the other components of the metabolic syndrome as an increasingly important cause of hepatocellular carcinoma (HCC) in resource-rich countries, and of the ability to successfully treat chronic hepatitis C virus (HCV) infections with newly available, highly effective anti-viral agents, and hence prevent the future development of HCV-induced HCC in these countries, the importance of abuse of alcohol as a cause of HCC has tended to take a 'back seat' in the recent literature. But alcohol abuse continues to increase in many countries and remains one of the major causes of HCC in both resource-rich and resource-poor regions, with no prospect of a meaningful reduction in its importance in the near future.

Keywords: Excess Alcohol; Hepatocellular Carcinoma; Increasing in Incidence; Cirrhosis; More than 60 grams per day

Introduction

Alcohol has been part of human culture since the beginning of recorded history and is consumed in almost all regions of the world [1]. Although the majority of adults world-wide either abstain from drinking alcohol altogether, or drink only very small amounts of the liquor on special occasions, consumption of alcohol in excess is common in many parts of the world, and is among the most disabling categories contributing to the global burden of disease [2]. Nationally, alcohol consumption is linked to financial status in terms of gross domestic product per adult, and is greatest in poor people and in those marginalized from society [2]. Both the industrialization of production and the promotion and globalization of marketing of alcohol have in recent times increased the amount of its consumption world-wide and hence the deleterious effects it causes [1]. Furthermore, the proportion of alcohol-attributable deaths has increased since approxi-

mately the year 2000, mainly because of increases in the number of women drinking to excess [2].

Alcohol-induced disorders, especially in men, are among the most disabling categories of the global burden of disease [2]. Excessive alcohol consumption is estimated to cause 4.6% of the global disability-adjusted life-years, 3.8% of all deaths in all age groups, and 5.3% of all deaths in individuals less than 60 years of age [2]. The costs associated with alcohol abuse amount to more than 3% of the gross national product in high- and middle-income countries [2].

Eastern European countries around Russia have the highest overall consumption of alcohol, being responsible for close to 4% of all deaths in that region (6.3% in men and 1.1% in women) [2]. In the USA 7% of the adult population (greater than 18 million individuals) meet the definition of alcohol abuse or dependence [3,4]. Abuse of alcohol is also common in Western Europe [4], and in Norwegians the cumulative actuarial mortality from heavy alcohol consumption after 1, 3, 6 and 12 months was 18%, 28%, 36% and 48%, and after 5, 10 and 15 years was 71%, 84% and 90%, respectively [5]. In the past 50 years alcohol consumption has increased by 150% in the United Kingdom [6]. Per capita alcohol consumption in Asian countries, including Korea, has increased dramatically during the past 30 to 40 years, especially in men [4,7,8]. The eastern Mediterranean region has the lowest incidence of alcohol consumption [2]. Low income-countries and poor populations have a greater disease burden per unit of alcohol consumption than do high-income countries and populations [2].

Consumption of small volumes of alcohol may contribute to a decreased incidence of a few diseases, most notably, ischemic cardiovascular disease and diabetes mellitus, but with larger volumes of consumption any beneficial effects are far outweighed by the detrimental effects.

In all geographical regions men consume more alcohol than do women, although the exact ratio varies [2,3]. Women in high-income countries consume more alcohol than do those in low-income countries [2,3]. In regard to both the age at which the alcohol abuse commences and the duration of the abuse, uncertainty exists as to whether or not substantial differences exist between men and women in these respects [6]. Nevertheless, more deaths overall are attributable to alcohol abuse in men (6.3%), although premature deaths are relatively more common in women (1.1%) [6]. Heavy alcohol consumption is also responsible for a younger mean age at the time of death in men [6]. No known substantial dose-effect difference between men and women has been recognised [9-16], even though, given similar exposure levels, alcohol abuse has more detrimental effects on the progression of liver disease in women [12].

The risk of hepatocellular carcinoma (HCC) development with a consumption of alcohol of greater than 80g per day is increased 5-fold compared to non-drinkers [4]. The likelihood of malignant transformation in the presence of alcohol-induced cirrhosis approaches 1% per year, and does not decrease with subsequent abstinence [4]. HCC may also supervene in a non-cirrhotic liver [4]. Alcohol abuse in patients with chronic hepatitis doubles the risk of HCC developing [4]. Once cirrhosis is established, abstinence does not decrease the risk of malignant transformation [4].

A number of mechanisms have been suggested to explain why women appear to be more vulnerable than men to the many adverse consequences of alcohol abuse [17-19]. These include attaining higher concentrations of alcohol in blood after drinking equivalent amounts of alcohol because of less body water [17-19], having almost complete loss of first-pass protection to prevent excess alcohol from being absorbed [17-19], having a lower level of gastric alcohol dehydrogenase and thus a weaker first-pass barrier [17-19], and because of their higher liver volume per unit of lean body mass they eliminate alcohol from the blood more rapidly [17-19]. These mechanisms result in higher concentrations in the liver of acetaldehyde, a toxic product of alcohol [17-19].

Independent predictors of a poor prognosis for individuals with alcohol abuse are continuous consumption of greater than 50 grams of ethanol per day and an advanced age [4]. Common causes of death are hepatic failure or hemorrhage, or a combination of these [4]. HCC is one of the major malignant tumors in the world today, affecting close to one-half a million people and being the third leading cause of cancer deaths world-wide, and with mortality rates increasing more rapidly than any other leading cause of cancer [3]. In the USA age-adjusted incidences of HCC trebled between 1975 and 2005, with an overall percentage change of 4.3% [4,9-14]. Alcohol abuse accounts for between 32 and 45% of these tumors, although the carcinogenic mechanisms responsible are incompletely understood [4,9-14]. The rate of increase of alcohol-induced HCC in the USA exceeds that of any other leading cause of cancer [12,13]. These prevalence's are also five times higher than that of chronic HCV infection [14]. Alcohol abuse may be the cause as much as 45% of the HCCs in Japan [4,8] and 20.5% of those in Taiwanese men [15]. An increased incidence has also been reported in Korea [4].

The risk of developing alcohol-induced HCC at present, and in the foreseeable future, is determined by the amount of alcohol consumed and the time over which it is consumed, starting at a daily consumption of more than 50 grams of alcohol for at least 10 years, increasing progressively with more than 60 grams, with more than 70 grams, and, most frequently and severely, with more than 80 grams of alcohol over the same time-span. Compared with non-drinkers those who drank alcohol to excess had an adjusted odds ratio for HCC development of 2.4 (95% confidence interval 1.3 - 4.4) [4]. Other studies showed a 4.4- to 7-fold increased risk of HCC supervention [12,13]. The risk of HCC developing increases with the rising level of alcohol intake, with no substantial difference between males and females and irrespective of the duration or age at the start [4,12,13]. The chance of HCC developing in decompensated alcohol-induced cirrhosis approaches 1% per year [4,12,13], and the risk does not decrease with subsequent abstinence of alcohol.

There has been, during recent years, a steady linear increase in the odds ratio of HCC developing in certain regions of the world. This phenomenon has been, in addition to other increasing causes of the tumor, a consequence of increased alcohol intake at or above a level of 60 grams per day for more than 10 years in White, Black and Hispanic males, with the odds ratio increasing to the greatest extent when alcohol abuse exceeds 80 grams per day for more than 10 years [4,8,11,12,20-31]. In a study in Northern Europe, alcohol-induced cirrhosis was present in 76% of the patients at necropsy, and 10% of these died as a result of the development of HCC [5].

Alcohol in excess may have a direct genotoxic effect or it may function indirectly by a mechanism involving the development of cirrhosis [4,12,13]. The chances of HCC intervening by either mechanism rises with high levels of alcohol intake and the age at which they commenced. Moreover, no conclusive data are available on either a "safe" level of alcohol intake [4] or a decline in the risk of HCC development for up to 10 years after abstinence is begun [4].

Heavy consumption of alcohol is associated with a more than 5-fold increased accumulative probability of death, as well as a decreased mean age at death across racial/ethnic groups in both sexes [4-8,10]. Before the age of 45 years the cumulative probabilities of death remain low and are similar in the sexes. However, after this age, men show faster increases in cumulative probabilities of death than do women; for example, male decedents with heavy alcohol use have died 4.2 years younger than female decedents [4]. No substantial differences in the incidence of alcohol-induced HCC between males and females were recorded in some populations [11,26], although increased incidences in southern African Black males [22] and in male patients from southern Germany (3.2:1.0) have been recorded [23].

In the USA and Italy alcohol abuse is the most common cause of HCC, accounting for 32 to 45% of the patients, respectively [7]. In the former country between 1996 and 1998, age-adjusted hospitalization rates for HCC attributed to alcohol-induced cirrhosis were more than 70% higher than that for HCV infection [7]. Epidemiological studies have also suggested that heavy alcohol abuse, the metabolic syndrome, and HBV- and HCV-induced HCC may exert synergistic effects that are more than additive, but less than multiplicative, in explaining the increasing incidence of HCC in the USA and other countries during the past 2 decades [11,22-25]. The odds ratio for the development of HCC remained high even 10 years after a patient had stopped drinking alcohol [22]. In fact, the risk was highest in those who stopped drinking at that time [9,11], with a steady increase in the odds ratio of HCC with a history of heavy alcohol intake during the previous 14 years [14]. Those who had stopped drinking less than 10 years previously were at a higher risk of developing the tumor than were current drinkers [8], because the odds ratio for the development HCC does not decrease until the abstinence has persisted for more than 10 years [11].

Overall, 15% of alcoholic cirrhotics are reported to develop HCC, and the great majority of the tumors, although not all, develop in a cirrhotic liver [15]. In a number of case-series in Northern Europe, alcohol-induced cirrhosis accounted for one-third to one-half of the patients. In high-income countries there is a strong relation between economic wealth and alcohol consumption: the higher the gross domestic product, the greater the overall volume of consumption of alcohol and the lower the proportion of abstainers [8]. In these countries disorders induced by alcohol are, especially for men, among the most disabling disease categories [6].

Individuals who stop drinking one to 10 years after being heavy drinkers for a prolonged period remain at high risk of developing HCC. In addition, a threshold value of alcohol consumption, below which no increased risk of cancer is evident, has not been identified [23].

A multiplicative synergistic interaction between alcohol and obesity in causing HCC has been documented in both men and women [20]. The precise mechanisms underlying this interaction remain to be elucidated. Chronic HCV infection is present in 10 to 40% of patients with alcohol-induced cirrhosis [11], the prevalence of the infection being significantly higher than that in the general population [24]. Synergism between alcohol abuse and chronic HCV (or HBV) infections for drinkers of more than 60 grams of alcohol per day increase the odds for HCC development, with a more than additive but less than multiplicative effect (6.3% in men and 1.1% in women) [4,7]. The prevalence of HCV infection is 3- to 30-fold higher in alcoholics compared with the general population. Patients with both HCV infection and alcohol abuse develop severe hepatic fibrosis and a higher rate of cirrhosis and HCC compared with non-drinkers, and they may develop HCC at a younger age [7,11].

Conclusion

In conclusion, alcohol abuse persists or is increasing in both men and women in many countries. It carries a poor prognosis in its own right, and has become an increasingly important cause of HCC with its grave prognosis.

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