Human carcinogenesis and alcohol in hepato-gastroenterology

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Abstract. – Alcohol consumption is one of the top-10 risks for worldwide burden of disease. The International Agency for Research for Cancer affirmed that there was evidence for the carcinogenicity of ethanol in animals and classified alcohol consumption as carcinogenic for humans.

Alcohol consumption causes cancers of the oral cavity, pharynx, larynx, oesophagus, colorectum, liver, pancreas and female breast.

Most alcohol-induced diseases increases in a linear fashion as intake increases: oral, oesophagus and colon cancer fall into this pattern: very little is known about safe margins of alcohol consumption. Given the linear dose-response relation between alcohol intake and risk of cancer, control of heavy drinking remains the main target for cancer control.

For the European Code Against Cancer the limit should not exceed between 20 g of ethanol per day and it should be as low as 10 g per day for women.

In our opinion, the analysis of the literature is unable to identify a threshold level of alcohol consumption below which no increased risk for cancer is evident.

Key Words:

Alcohol, Cancer, Carcinogenesis.

Abbreviations

CYP2E1 = Cytochrome P450 2E1,
ADH = Alcohol dehydrogenase,
ALDH = Acetaldehyde deydrogenase,
MPO = Myeloperoxidase,
SAMe = S-adenosylmethionine,
HCC = Hepatocellular carcinoma

Introduction

Alcohol consumption is a mayor correlate of health and disease, and it has been associated to cardiovascular diseases, digestive tract conditions, accidents and violence.

Alcohol drinking is one of the top-10 risks for worldwide burden of diseases[1,2]. In February 2007, the Monograph Working Group of the International Agency for Research of Cancer (IARC) concluded that there was "sufficient evidence" for the carcinogenicity of ethanol in animals and classified alcohol beverages as carcinogenic to humans[3]. The IARC confirmed the casual link between alcohol consumption and the following malignant neoplasm categories: oral cavity, pharynx, larynx, oesophagus, liver, colorectal and female breast cancer[1-3].

A great number of epidemiological investigations have demonstrated a correlation between alcohol ingestion and the occurrence of cancer. In these studies it has been demonstrated that the ingestion of all types of alcoholic beverages is associated with an increased risk which suggests that ethanol itself is the crucial compound which causes that effect (oral cavity, pharynx, larynx, oesophagus, liver, colorectum, female breast)[2,4,5]. More recently the American Institute for Cancer Research[5] stated that current evidence does not identify a generally "safe" threshold.

Many of these studies have been concerned with the association between alcohol intake and risk of cancer in the general population, while only few studies have been conducted in population with a high intake of alcohol, such as brewery workers or persons with alcohol use disorders[6]. Thygesen et al[6] have observed a large cohort of patients with alcohol use disorders (19,000 patients, follow-up of 40 years). This study confirms the well-established association between high alcohol intake and cancer of the upper digestive tract and liver, in addition the results indicate a significantly elevated occurrence of gall-bladder stomach, lung, pleura, kidney, prostate gland[6].

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3.6% of all cancers (5.2% in men, 1.7% in women) are attributable to alcohol drinking worldwide. This proportion is particularly high among men in Central and Eastern Europe (6-10% of all cancers)[7]. The regional differences in the burden of alcohol-attributable cancer resulted from variations in the prevalence of drinking[7]. Other potential sources of the regional variability are carcinogenic effect of local alcoholic beverages and the pattern of drinking.

Aim of this review is to describe the mechanisms underlying alcohol-related cancer, describe the most common cancer alcohol induced in hepato-gastroenterology, and give sensible individual recommended limits of alcohol consumption.

Alcohol and Carcinogenesis: Mechanisms

The mechanisms underlying alcohol-related cancers are unclear but several factors have been suggested to play a role[8-11]: local effect of ethanol, acetaldehyde (isoenzymes polymorphism), induction of cytochrome P450 2E1 (CYP2E1) (conversion of various xenobiotics), nutritional deficiencies, interactions with retinoids, changes in the degree of methylation, immune surveillance, angiogenesis.

Alcohol may be important in the initiation of cancer, either by increasing the expression of certains oncogenes or by impiring the cell's ability to repair DNA, thereby, increasing the likelihood that oncogenic mutations will occur.

Ethanol is metabolized to acetaldehyde by alcohol dehydrogenase (ADH), CYP2E1 and, to a much lesser extent, by catalase, and is further oxidized to acetate by acetaldehyde dehydrogenase (ALDH).

Acetaldehyde is highly toxic and carcinogenic. The amount of acetaldehyde to which cells or tissues are exposed after alcohol ingestion may be of great importance and may, among others, affects carcinogenesis.

Acetaldehyde outside ethanol metabolism is carcinogenetic to humans (Group 1: oesophagus, head and neck)[3]. It has been demonstrated[8] that if the acetaldehyde concentrations are calculated for a "standard drink" of each beverage it appears that the major exposure would derive from wine and to a lesser degree from beer and spirits.

The enzyme responsible for oxidation of acetaldehyde is ALDH. Both formation and degradation of acetaldehyde depends on the activity of these enzymes. The total ADH activity is significantly higher in cancer tissues than in this healthy organs (e.g. liver, oesophagus, colorectum). The activity of ADH is much higher than the activity of ALDH. This suggests that cancer cells have a greater capability for ethanol oxidation but less ability to remove acetaldehyde than normal tissues[9,12].

Functional variants in genes involved in alcohol metabolism result in differences between individuals in exposure to carcinogenic acetaldehyde, suggesting a possible interaction of genetic susceptibility and alcohol exposure in cancer[13].

ADH and ALDH are encoded by multiple genes. Because some of these genes exist in several variants and the enzymes encoded by certain variants may result in elevated acetaldehyde levels, the presence of these variants may predispose to certain cancers. Recently, it has been evidenced how the combination of a genotype of myeloperoxidase (MPO) leading to high MPO expression and at least one Ala-superoxide dismutase 2 allele (associated with high liver iron score) markedly increased the risks of HCC occurrence and death in patients with alcoholic cirrhosis (Table I)[14-17].

In relation with the direct genotoxic effect of alcohol we have investigated the occurrence of DNA fragmentation (Comet assay)[18] in peripheral blood lymphocytes from "social drinkers". Three groups of subjects with mild liver function alterations. Group 1: ingestion of less than 20 g/die (10

Table I. Human carcinogenesis and alcohol: mutations and polymorphism genes.

- Cytokines of inflammatory response: TNF alpha, TNF alpha promoter polymorphisms, IL1, IL10 (anti-inflammatory), TNF alpha type 1 receptor, CD14 receptor expression (Kupffer cell)
- GABA-ergic, dopaminergic, serotoninergic systems
- Polymorphisms in DNA repair genes: DNA ligase III, DNA polymerase b, poly (ADP ribose) polymerase
- Ethanol metabolism (ADHs, ALDHs, CYP2E1, mitochondrial superoxide dismutase, myeloperoxidase)
- Genes involved in estrogen synthesis and metabolism (CYP17, CYP19, CYP1B1, catechol-0-methyltransferase)
- Polymorphisms in methylenetetrahydrofolate reductase
- Components of immune systems (adaptive, innate)

subjects, mean age 48), group 2: ingestion of 21-40 g/die (14 subjects, mean age 49), group 3: ingestion of 41-60 g/die (12 subjects, mean 48.5). Smokers in the group 1: 7 (70%), in the group 2: 10 (83%), in the group 3: 9 (75%). Alcohol intake was evaluated by using standardized questionnaires. DNA fragmentation was evaluated by the alkaline Comet Assay as described previously. Extent of DNA damage was quantified by measuring the tail length with computerized image analysis (Sarin System, Florence, Italy). Statistical analysis: Wilcoxon/Kruskal-Wallis. Group 1: 1.05 (0.9-1.3), group 2: 1.35 (1.07-1.93), group 3: 1.8 (1.32-2.88) ($p < 0.001$). From these preliminary results it emerges a significant DNA fragmentation in subjects drinking more than 20 g/die. These results, if confirmed by wider casuistry, support the hypothesis of a direct genotoxic effect of alcohol consumption.

Alcohol may be act as a co-carcinogen by enhancing the effect of direct carcinogens such as those found in tobacco and the diet. This effect of alcohol is at least in part via induction of the CYPP450 family of enzymes that are found in the liver, lung and intestine and are capable of metabolizing various tobacco and dietary constituents into cancer promoting free radicals[10].

It has been shown that in the liver the concentration of CYP2E1 can be correlated with the generation of hydroxyethyl radicals and thus with lipid peroxidation. Lipid peroxidation leads to the generation of 4-hydroxy nonenal which may bind to pyrimidine and purine based of the DNA and lead to exocyclic etheno DNA adducts which are carcinogenic. It has clearly demonstrated a significant correlation between CYP2E1 induction and the occurrence of esocyclic etheno DNA adducts in hepatocytes.

Seitz et al[9] affirms that CYP2E1 activity occurs at relatively low level of alcohol (40 g/day) and at these levels of intake, induction is already apparent after one week, although the extent varies interindividually. Some individuals exhibit a very low extent of induction of CYP2E1 activity, whereas others show a high extent of induction. Thus, it could well be that the variation in extent of induction of CYP2E1 activity may modulate alcohol-associated carcinogenesis in man.

Chronic alcohol consumption also leads to decreased retinoic acid levels. This is predominantly due to the induction of CYP2E1 which is responsible for the degradation of retinol and retinoic acid to polar metabolites such as 4-oxo- and 18-hydroxy retinoic acid. This increased retinoic acid metabolism decreases retinoic acid which by itself results in an increased expression of the AP1 gene associated with an increase in their proteins c-jun and c-fos, finally leading to an increase in cycline D1 which is associated with hyperproliferation, at least in liver. Thus, retinoic acid deficiency is associated with acceleration of carcinogenesis[9,12].

DNA methylation is an important regulator of gene expression: decreased methylation is associated with increased gene expression. In particular, decreased methylation of tumor promoter genes has been proposed as a possible mechanism for development of cancers. The hepatic enzyme methyladenosyltransferase II is decreased in alcoholic diseases. This results in decreased production of S-adenosylmethionine (SAMe), the methyl donor for DNA methylation reactions. Furthermore, homocysteine levels are increased in alcoholic diseases, increasing the S-adenosyl-homocysteine level and inhibiting the activity of DNA methyltransferase enzymes. In experimental models, SAMe deficiency induced by methionine-choline-deficient diet caused DNA hypomethylation and increased DNA strand breaks with DNA instability, changes associated with an increased risk for cancer. In transgenic mice lacking methyladenosyltransferase II there is spontaneous development of HCC. These experimental models support a possible role for DNA methylation abnormalities contributing to cancer in alcoholic diseases[19].

Since reduced levels of iron, zinc and vitamins A, B and E have been experimentally associated with some cancers, the nutritional deficiencies associated with chronic alcohol intake may also radical related oxidative stress. Finally, alcohol consumption is associated with immunosuppression which makes chronic alcoholics more susceptible to infection and theoretically to cancer.

Alcohol and Cancer in Gastroenterology

Chronic alcohol consumption is a strong risk factor for cancer in the upper aerodigestive tract (oral cavity, pharynx, hypopharynx, larynx, oesophagus) and also alcohol increases the risk for cancer of the colorectum and the breast.

A great number of epidemiological studies have demonstrated that the ingestion of all types of alcoholics beverages is associated with an increased cancer risk and selected studies have evidenced a dose-response trends for oral, pharyngeal, laryngeal and oesophageal cancer for never-smoking[1].

Most alcohol-induced disease increases in a linear fashion as intake increases: oral, oesophagus, breast and colon cancer fall into this pattern, with no "safe level" of consumption[20].

Cancers of the Oral Cavity and Pharynx

Alcohol is a major recognized risk factor for oral and pharyngeal cancer, and together with tobacco consumption accounts for the large majority of oral cancer in developed countries (75% of cases). The risk in strongly related to the dose of alcohol drunk, even in the absence of smoking[21]. Data from several studies suggest that all types of alcoholic beverages contribute to oral and pharyngeal cancer risk and that ethanol is the main component of alcoholic beverages that determines the risk of these type of cancer. The most frequently consumed beverage in each area appears to be the most important determinant for these cancers. Altieri et al[21] evidenced a significant trends in risk with increasing total alcohol intake, with multivariate OR of 2.1 for drinkers of 3-4 drinks/day, as compared to abstainers or light drinkers, 5 for 5-7, 12.2 for 8-11 and 21.1 for >12 drinks/day.

Alcohol may influence the proliferative cells by both intracellular and intercellular pathways. The carcinogenic exposure of the proliferating stem cells in the basal layer may be regulated throught these pathways[22].

Alcoholics with oropharyngeal cancer had very high salivary acetaldehyde concentrations, which may be because smoking and poor oral hygiene[23].

Some data were available on the cessation of consumption and the risk for oral and pharyngeal cancer. The available evidence suggests that former drinkers have lower risks for oral and pharyngeal cancer than current drinkers of alcoholic beverages.

Cancer of the Oesophagus

Up to 50-75% of cases of esophageal cancer in both men and women are attributable to the consumption of alcohol. Chronic alcohol consumption is frequently associated with secondary motility disorders and lower esophageal sphincter tone alteration. These effects predispose to gastroesophageal reflux, esophagitis and intestinal metaplasia. The mucosa becomes more susceptible to carcinogens, such as polycyclic aromatic carbohydrates or can be produced by pro-carcinogens in the liver. In addition, ethanol is metabolized by bacteria in the oral cavity to acetaldehyde[24].

More than 50 prospective and case-control investigations from most regions of the world found a consistent association between the risk for oesophageal cancer (squamous-cell carcinoma) and the consumption of alcoholic beverages. The risk increases with increasing amounts of alcoholic beverages consumed and, compared with non-drinkers, regular use of about 50 g/day is associated with an approximately twofold increase in risk. The association is weak for adenocarcinoma of the oesophagus.

Of 13 cohort researches among the general population, ten reported a statistically significant association between alcoholic beverage consumption and the risk for oesophageal cancer when controlled for tobacco smoking.

The effects of smoking and consumption of alcoholic beverages appear to be multiplicative and the largest relative risks are seen in smokers who also consume alcoholic beverages. The available data from molecular-genetic epidemiological studies provide ample evidence that the heterozygous aldehyde dehydrogenase two genotype contributes to the development of squamous-cell carcinomas that are related to the use of alcohol[25].

There is uncertainty about the effects of cessation of alcohol beverage intake and the duration of consumption on the risk for oesophageal cancer. The available evidence suggests that former drinkers have lower risks for oesophageal cancer than current drinkers.

Cancer of the Stomach

In the stomach ethanol directly and dose-dependently impairs the gastric mucosal barrier. Both acidification of the mucosal cells and ethanol itself induce release of inflammatory and vasoactive substances. Inflammation and vasoconstriction lead to ischemia and mucosal damage. However, Franke et al[24] reported that in more than 40 epidemiological studies no association between gastric cancer and chronic alcohol consumption was found. This is also valid for consumption of large amounts of alcohol. Recently, this data has been confirmed by Boffetta and Hashibe[1].

Colorectal Cancer

Several meta-analyses observed a positive linear relation between alcohol consumption and colorectal cancer. These studies provide evidence for an increased RR of approximately 10-20% for colorectal cancer with regular consumption of

approximately 50 g of alcohol/day, compared with abstainers. This association is similar for both colon cancer and rectal cancer.

Seitz and Stichel[10] have noted a RR of 7.4 for distal colorectal cancer in individuals who consume more than 20 g of ethanol a day in association with low methionine and folate levels compared with occasional drinkers who have a normal methionine and folate level[10].

There is no consistent evidence that the association of colorectal cancer with the consumption of alcoholic beverages is modified by gender or by tobacco smoking.

The data on the effects of duration and cessation of consumption of alcoholic beverages on the risk for colorectal cancre are inadequate[25].

Cancer of the Pancreas

Pancreatic cancer was associated to current smoking. Alcohol consumption was associated to increased pancreatic cancer risk, but Talamini et al[26] have evidenced that ORs were significant only among heavy drinkers. Pancreatic cancer risk was 4.3-fold higher in heavy smokers (> 20 cigarettes/day) and heavy drinkers (> 21 drinks/week) in comparison with never smokers who drunk < 7 drinks/week. If, such an association exists, a probable mechanism is throught development of chronic pancreatitis as a result of drinking alcohol (> 80 g/day for 10-12 years).

Alcohol and Hepatocellular Carcinoma

A large body of data derives from cohort studies, including cohorts of heavy drinkers, and case-control studies from most regions of the world, many of which were carried out in China. These studies provide firm evidence that the consumption of alcoholic beverages is an independent risk factor for primary liver cancer. Various types of alcoholic beverages consumed do not have substantially different effect on liver cancer[25].

Alcohol intake could be involved in the development of HCC through both direct (genotoxic) and indirect mechanisms (development of cirrhosis). Alcohol associated liver cirrhosis is probably the most important risk factor for HCC in populations with low prevalence of infection with hepatitis B virus and hepatitis C virus such as the USA and northern Europe.

Studies in the USA and in Italy suggest that alcohol is the most common cause of HCC (accounting for 32-45% of HCC).

A significant synergy between alcohol consumption, hepatitis virus infection (HBV, HCV) and metabolic alterations has recently been demonstrated.

A number of studies have demonstrated a high prevalence of antibodies to HCV among alcoholics with liver disease, ranging from 11% to 46%[27].

Yamauchi et al[28] showed that the cumulative incidence of HCC after 3, 5, and ten years in cirrhotic HCV infected patients with an average daily alcohol consumption of 120 g was 13.3%, 41.3%, and 80.7% versus 0%, 8.3%, and 18.5%, respectively, compared with alcoholic cirrhotics without HCV infection.

A case control study by Corrao et al[29] in 115 patients with alcoholic liver disease and chronic HCV demonstrated a clear dose dependency between long term alcohol consumption and the development of cirrhosis, a necessary precondition of HCC development in chronic HCV. The Authors concluded that as little as 20 g/day was detrimental[27].

The mechanism by which alcohol interacts with HCV in causing increased severity of liver disease and HCC is not clear and several possibilities have been examined[27]:

- Chronic alcohol consumption and HCV infection synergistically aggravate histological damage resulting in faster progression,
- Alcohol may compromise the host's immune response to HCV infection,
- Alcohol appears to enhance HCV replication with subsequent direct cytopathic damage,
- Alcoholic patients with HCV infection show higher hepatic iron levels than patients with HCV infection alone and iron excess is an important factor in liver damage and may increase HCV replication,
- More recently a correlation among toll-like receptor (TLRs), alcohol, HCV and tumorigenesis has been evidenced. Synergism between alcohol and HCV may lead to liver tumorigenesis through TLR signalling[30].

In the report of Hassan et al[31] it has been demonstrated a significant increase of the risk when alcohol intake is associated with hepatitis viruses and diabetes mellitus. It has been suggested a common pathway for hepatocarcinogenesis.

In case of heavy alcohol consumption (>80 g/day) with chronic hepatitis virus infection

(HBV or HCV) it has been evidenced an OR of 53.9 (virus alone OR 19.1, alcohol alone OR 2.4) and in case of heavy alcohol consumption with diabetes (insulin-dependent, non-insulin-dependent) it has been evidenced an OR of 9.9 (diabetes alone 2.4)[31,32].

A model of liver carcinogenesis by alcohol intake has been proposed. It shows both its early (initiation) and late effects (promotion/ progression). We have recently evaluated the possible mechanism of initiation in patients affected by chronic alcoholic liver disease (ALD)[16,33].

In the late phase (promotion/ progression) the hyperproliferation may cause hepatocyte DNA to become susceptible to mutagenesis, resulting in gene instability. In fact, it has been demonstrated how HCC develops because chronic oxidative stress exert a selection pressure that favors the outgrowth of progenitor cell clones that are most resistant to oxidant damage[34,35,36].

Finally, a substantial amount of epidemiological studies indicate that alcohol is an independent and strong risk factor for HCC.

Quantification of the association is not possible based on epidemiological and case-control studies, because cirrhosis and other liver conditions antedating HCC invariably leads to a substantial decrease in alcohol drinking. Consequently, the risk is grossly elevated in the years after stopping drinking. Validity of information on alcohol drinking in the distant past remains open to discussion[37,38].

Conclusions

Consumption of alcoholic beverages is one of the most important known causes of human cancer after tobacco smoking, chronic infection and obesity[30]. Despite its importance in human carcinogenesis, research on alcohol and cancer remains limited in terms of clinical, epidemiological, and experimental settings[1].

The following risk factors for alcohol associated carcinogenesis have been evidenced[12]:

1. For the upper aerodigestive tract: smoking, poor oral hygiene and poor dental status, highly concentrated alcoholic beverages, alterations in assumption of vitamin A and beta-carotene, ADH1C*1.1 homozygocity, ALDH 2*2.2 mutation, precancerous conditions such as Barrett's oesophagus and gastro-oesophageal reflux;

2. For the colorectum: chronic inflammatory bowel disease, polyps, deficiency of folate, ADH1C*1 homozygocity, ALDH2*2 mutation;

3. For the liver: chronic hepatopathy (i.e, emochromatosis), hepatitis B and C infection, metabolic alterations;

4. For the pancreas: chronic pancreatitis, smoking;

5. For the breast: high oestradiol concentrations (especially in midcycle), ADH1C*1 genotype?, family history.

Individuals who have an increased risk of developing those cancers due to other risk factors should avoid chronic alcohol ingestion[12].

Seitz and Stickel[10] affirm as a dose-response relationship between alcohol consumption and cancer risk exists, one of the most important aspects is the control of heavy drinking.

For the European Code Against Cancer, in healthy subjects, the limit should not exceed between 20 g of ethanol per day and it should be as low as 10 g per day for women[39].

However, the analysis of the literature is unable to identify a threshold level of alcohol consumption below which no increased risk for cancer is evident.

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