

Alcohol and gastrointestinal oncology

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Abstract

Results from several large epidemiological studies have firmly established that alcohol is associated with elevated cancer incidence and mortality. Recently the International Agency for Cancer Research stated that acetaldehyde associated with alcoholic beverages is carcinogenic to humans and confirmed the Group 1 classification of alcohol consumption and of ethanol in alcoholic beverages. Alcohol consumption causes cancers of the oral cavity, pharynx, larynx, oesophagus, colorectum, liver, pancreas and female breast. The frequency of 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. US Department of Health and Human Services suggest a maximum of 28 g of alcohol a day in man and half of this in women.

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The World Health Organization (WHO) has identified the consumption of alcohol as one of the top-10 risks for worldwide burden of disease^[1,2]. Recently the International Agency for Cancer Research concluded that acetaldehyde associated with alcoholic beverages is carcinogenic to humans (Group 1) and confirmed the Group 1 classification of alcohol consumption and of ethanol in alcoholic beverages^[3].

A great number of epidemiological studies have demonstrated a correlation between alcohol ingestion and the occurrence of various cancers (oral cavity, pharynx, larynx, oesophagus, liver, colorectum, female breast)^[2,4-6]. 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^[2,4-6].

More recently (June 2010) the American Institute for Cancer Research^[7] stated that current evidence does not identify a generally "safe" threshold. Evidence that alcoholic drinks of any type are a cause of various cancers of the mouth, pharynx, and larynx, oesophagus, colorectum (men), and breast is convincing. They are also probably a cause of colorectal cancer in women, and of liver cancer. It is unlikely that alcoholic drinks have a substantial adverse effect on the risk of kidney cancer^[7].

Many of these studies have been concerned with the association between alcohol intake and risk of cancer in the general population, while only a few studies have been conducted in populations with a high intake of alcohol, such as brewery workers or persons with alcohol use disorders^[8]. Thygesen *et al*^[8] have studied a large cohort of patients with alcohol use disorders (19000 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^[8].

Worldwide, 3.6% of all cancers (5.2% in men, 1.7% in women) are attributable to alcohol drinking. This proportion is particularly high among men in Central and Eastern Europe (6%-10% of all cancers)^[9]. Among women, breast cancer comprises 60% of alcohol-attributable cancers^[9].

The regional differences in the burden of alcohol-

Table 1 Alcohol and cancer: mutations and polymorphism genes

Ethanol metabolism (ADHs, ALDHs, CYP2E1, Mitochondrial Superoxide Dismutase, Myeloperoxidase)
Cytokines of inflammatory response: TNF α , TNF α promoter polymorphisms, IL1, IL10 (anti-inflammatory), TNF α type 1 receptor, CD14 receptor expression (Kupffer cell)
GABA-ergic, dopaminergic, serotonergic systems
Polymorphisms in DNA repair genes: DNA ligase III, DNA polymerase β , poly (ADP ribose) polymerase
Components of immune systems (adaptive, innate)

CYP2E1: Cytochrome P450 2E1; ADHs: alcohol dehydrogenases; ALDHs: Acetaldehyde dehydrogenases

attributable cancer result from variations in the prevalence of drinking^[9]. Other potential sources of the regional variability are the relative carcinogenic effect of local alcoholic beverages and the pattern of drinking.

The mechanisms underlying alcohol-related cancers are unclear but several factors have been suggested to play a role^[10-12]: 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 certain oncogenes or by impairing the cell's ability to repair DNA and 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 other things, affect carcinogenesis. Acetaldehyde derived from ethanol metabolism is carcinogenic to humans (Group 1: oesophagus, head and neck)^[3]. Lachenmeier and Sohnius^[10] have demonstrated 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 ADH and ALDH. The total alcohol dehydrogenase activity is significantly higher in cancer tissues than in healthy organs (e.g. liver, oesophagus, colorectum). The activity of ADH in cancer cells 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^[11,13,14].

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 pre-

dispose to certain cancers. Recently, it has been shown that the combination of a genotype of myeloperoxidase (MPO) which leads to high MPO expression and at least one Alasuperoxide dismutase 2 allele (associated with high liver iron score) markedly increases the risks of hepatocellular carcinoma (HCC) occurrence and death in patients with alcoholic cirrhosis (Table 1)^[15-17].

Alcohol may 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 CYP450 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^[12].

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 bases of the DNA and lead to exocyclic etheno DNA adducts which are carcinogenic. A significant correlation between CYP2E1 induction and the occurrence of exocyclic etheno DNA adducts in hepatocytes has been demonstrated clearly.

Seitz *et al.*^[11] claims that CYP2E1 activity occurs at relatively low levels of alcohol (40 g/d) and that, at these levels of intake, induction is already apparent after 1 wk, although the extent varies between individuals. 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^[11].

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. Increased retinoic acid metabolism leading to decreased retinoic acid level results in an increased expression of the AP1 gene associated with an increase in the proteins c-jun and c-fos. This finally leads to an increase in cyclin D1 which is associated with hyperproliferation, at least in liver. Thus, retinoic acid deficiency is associated with acceleration of carcinogenesis^[11,13].

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 the 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-adenosylhomocysteine level and inhibiting the activity of DNA methyltransferase enzymes. In experimental models, SAME deficiency induced by methionine-choline-deficient diet causes DNA hypomethylation and increases DNA strand breaks with DNA instability, changes associated with an increased risk for cancer. In transgenic mice lacking met

hyaladenosyltransferase II there is spontaneous development of HCC. These experimental models support a possible role for DNA methylation abnormalities in contributing to cancer in alcoholic diseases^[18].

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 result in radical related oxidative stress. Finally, alcohol consumption is associated with immunosuppression which makes chronic alcoholics more susceptible to infection and theoretically to cancer.

Chronic alcohol consumption is a strong risk factor for cancer in the upper aerodigestive tract (oral cavity, pharynx, hypopharynx, larynx, oesophagus) and alcohol also 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 alcoholic beverages is associated with an increased cancer risk and selected studies have given evidence of a dose-response trend for oral, pharyngeal, laryngeal and oesophageal cancer in never-smokers^[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^[19].

Poschl *et al*^[13] have demonstrated the following risk factors for alcohol associated carcinogenesis: (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 homozygosity, 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 homozygosity, ALDH2*2 mutation; (3) for the liver-chronic hepatopathy (i.e hemochromatosis), hepatitis B and C infection, metabolic alterations; (4) for the pancreas-chronic pancreatitis, smoking; and (5) for the breast-high oestradiol concentrations (especially in midcycle), ADH1C*1 genotype, family history. Individuals who have an increased risk of developing these cancers due to other risk factors should avoid chronic alcohol ingestion.

Alcohol, particularly when associated with tobacco use, has been recognized as an important risk factor for mouth cancer. Together, they are associated with 75% of upper aerodigestive tract cancer. The rising incidence of oral cancer has prompted a revaluation of the role of alcohol. 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 through these pathways^[20].

Alcoholics with oropharyngeal cancer have very high salivary acetaldehyde concentrations, which may be because of smoking and poor oral hygiene^[21]. 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 which can be produced by pro-carcinogens in the liver. In addition, ethanol is metabolized by bacteria in the oral cavity to acetaldehyde^[22].

Epidemiological studies have noted a response rate (RR) of 7.4 for distal colorectal cancer in individuals who consume more than 20 g of ethanol a day and consequently have low methionine and folate levels compared with occasional drinkers who have a normal methionine and folate level^[10].

Pancreatic cancer has been linked to current smoking. Increased pancreatic cancer risk has also been associated with alcohol consumption although Talamini *et al*^[23] have shown that this was significant only among heavy drinkers. Pancreatic cancer risk was 4.3-fold higher in heavy smokers (> 20 cigarettes/d) and heavy drinkers (> 21 drinks/wk) in comparison with never-smokers who drank < 7 drinks/wk.

Alcohol intake has been recognised as a definite cause of chronic liver diseases and HCC. It could be involved in the development of HCC through both direct (genotoxic) and indirect mechanisms (development of cirrhosis). 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 (50-80 g/d of ethanol), hepatitis virus infection (HBV, HCV) and metabolic alterations has recently been demonstrated. An addictive effect has been demonstrated in patients with HCV infection consuming below 50 g/d of ethanol.

Hassan *et al*^[24] have demonstrated a significant increase in the risk of cancer when alcohol intake is associated with hepatitis viruses and diabetes mellitus. A common pathway for hepatocarcinogenesis has been suggested. In case of heavy alcohol consumption (> 80 g/d) with chronic hepatitis virus infection (HBV or HCV) an OR of 53.9 (virus alone OR 19.1, alcohol alone OR 2.4) has been demonstrated 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) was found^[24,25].

A model of liver carcinogenesis by alcohol intake has been proposed which 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)^[26,27]. As alcohol causes an oxidative stress, and therefore the formation of reactive oxygen species, the comparison of the frequency of DNA lesions in lymphocytes in patients with alcoholic liver disease appeared interesting. The degree of DNA fragmentation was evaluated by means of the Comet Assay which gives two indexes of the frequency of breakages of a single-stranded DNA: the length of the tail and the moment of the tail. In ALD patients, a statistically significant increase of the frequency of DNA lesions was observed. The data suggest a direct genotoxic effect

of alcohol. The close association between alcohol intake and oxidative DNA damage suggests that the free radical produced during ethanol metabolism may be the cause of DNA fragmentation in lymphocytes. Taken as a whole, these findings suggest that genotoxic mechanisms may operate in the liver in subjects who use alcohol and thus contribute to the process of hepatocarcinogenesis.

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 that HCC develops because chronic oxidative stress exerts a selection pressure that favours the outgrowth of progenitor cell clones that are most resistant to oxidative damage^[28].

Seitz *et al.*^[12] suggest that the dose-response relationship which exists between alcohol consumption and cancer risk is one of the most important reasons for the control of heavy drinking. The US Department of Agriculture and Health and Human Services suggests a low risk level of a maximum of 28 g of ethanol a day in men and half of this in women^[29].

REFERENCES

- 1 Boffetta P, Hashibe M. Alcohol and cancer. *Lancet Oncol* 2006; **7**: 149-156
- 2 Rehm J, Baliunas D, Borges GL, Graham K, Irving H, Kehoe T, Parry CD, Patra J, Popova S, Poznyak V, Roerecke M, Room R, Samokhvalov AV, Taylor B. The relation between different dimensions of alcohol consumption and burden of disease: an overview. *Addiction* 2010; **105**: 817-843
- 3 Béatrice Secretan, Kurt Straif, Robert Baan, Yann Grosse, Fatima El Ghissassi, Véronique Bouvard, Lamia Benbrahim-Tallaa, Neela Guha, Crystal Freeman, Laurent Galichet, Vincent Coglianò and on behalf of the WHO International Agency for Research on Cancer Monograph Working Group. A review of human carcinogens-Part E: tobacco, areca nut, alcohol, coal smoke, and salted fish. *Lancet Oncology* 2009; **10**: 1033-1034
- 4 Bagnardi V, Blangiardo M, La Vecchia C, Corrao G. A meta-analysis of alcohol drinking and cancer risk. *Br J Cancer* 2001; **85**: 1700-1705
- 5 Corrao G, Bagnardi V, Zambon A, La Vecchia C. A meta-analysis of alcohol consumption and the risk of 15 diseases. *Prev Med* 2004; **38**: 613-619
- 6 Baan R, Straif K, Grosse Y, Secretan B, El Ghissassi F, Bouvard V, Altieri A, Coglianò V. Carcinogenicity of alcoholic beverages. *Lancet Oncol* 2007; **8**: 292-293
- 7 World Cancer Research Fund. Food, nutrition, physical activity, and prevention of cancer: a global perspective. Washington (DC): AICR, 2010
- 8 Thygesen LC, Mikkelsen P, Andersen TV, Tønnesen H, Juel K, Becker U, Grønbaek M. Cancer incidence among patients with alcohol use disorders--long-term follow-up. *Alcohol Alcohol* 2009; **44**: 387-391
- 9 Boffetta P, Hashibe M, La Vecchia C, Zatonski W, Rehm J. The burden of cancer attributable to alcohol drinking. *Int J Cancer* 2006; **119**: 884-887
- 10 Lachenmeier DW, Sohnius EM. The role of acetaldehyde outside ethanol metabolism in the carcinogenicity of alcoholic beverages: evidence from a large chemical survey. *Food Chem Toxicol* 2008; **46**: 2903-2911
- 11 Seitz HK, Stickel F, Homann N. Pathogenetic mechanisms of upper aerodigestive tract cancer in alcoholics. *Int J Cancer* 2004; **108**: 483-487
- 12 Seitz HK, Stickel F. Molecular mechanisms of alcohol-mediated carcinogenesis. *Nat Rev Cancer* 2007; **7**: 599-612
- 13 Pöschl G, Seitz HK. Alcohol and cancer. *Alcohol Alcohol* 2004; **39**: 155-165
- 14 Seitz HK, Becker P. Alcohol metabolism and cancer risk. *Alcohol Res Health* 2007; **30**: 38-41, 44-47
- 15 Jelski W, Szmitkowski M. Alcohol dehydrogenase (ADH) and aldehyde dehydrogenase (ALDH) in the cancer diseases. *Clin Chim Acta* 2008; **395**: 1-5
- 16 Salaspuuro M. Acetaldehyde as a common denominator and cumulative carcinogen in digestive tract cancers. *Scand J Gastroenterol* 2009; **44**: 912-925
- 17 Nahon P, Sutton A, Rufat P, Ziøl M, Akouche H, Laguillier C, Charnaux N, Ganne-Carrié N, Grando-Lemaire V, N'Kontchou G, Trinchet JC, Gattegno L, Pessayre D, Beaugrand M. Myeloperoxidase and superoxide dismutase 2 polymorphisms modulate the risk of hepatocellular carcinoma and death in alcoholic cirrhosis. *Hepatology* 2009; **50**: 1484-1493
- 18 Morgan TR, Mandayam S, Jamal MM. Alcohol and hepatocellular carcinoma. *Gastroenterology* 2004; **127**: S87-S96
- 19 Sheron N, Olsen N, Gilmore I. An evidence-based alcohol policy. *Gut* 2008; **57**: 1341-1344
- 20 Ogden GR. Alcohol and oral cancer. *Alcohol* 2005; **35**: 169-173
- 21 Seitz HK, Meier P. The role of acetaldehyde in upper digestive tract cancer in alcoholics. *Transl Res* 2007; **149**: 293-297
- 22 Franke A, Teyssen S, Singer MV. Alcohol-related diseases of the esophagus and stomach. *Dig Dis* 2005; **23**: 204-213
- 23 Talamini R, Polesel J, Gallus S, Dal Maso L, Zucchetto A, Negri E, Bosetti C, Lucenteforte E, Boz G, Franceschi S, Serraino D, La Vecchia C. Tobacco smoking, alcohol consumption and pancreatic cancer risk: a case-control study in Italy. *Eur J Cancer* 2010; **46**: 370-376
- 24 Hassan MM, Hwang LY, Hatten CJ, Swaim M, Li D, Abbruzzese JL, Beasley P, Patt YZ. Risk factors for hepatocellular carcinoma: synergism of alcohol with viral hepatitis and diabetes mellitus. *Hepatology* 2002; **36**: 1206-1213
- 25 Testino G, Icardi G. Hepatocellular carcinoma and interferon therapy in HCV compensated cirrhosis: evaluation in relation to virological response. *Hepatogastroenterology* 2005; **52**: 4 p preceding table of contents
- 26 Testino G. Alcoholic diseases in hepato-gastroenterology: a point of view. *Hepatogastroenterology* 2008; **55**: 371-377
- 27 Grossi S, Sumberaz A, Gosmar M, Mattioli F, Testino G, Martelli A. DNA damage in peripheral blood lymphocytes of patients with cirrhosis related to alcohol abuse or to hepatitis B and C viruses. *Eur J Gastroenterol Hepatol* 2008; **20**: 22-25
- 28 Roskams T, Yang SQ, Koteish A, Durnez A, DeVos R, Huang X, Achten R, Verslype C, Diehl AM. Oxidative stress and oval cell accumulation in mice and humans with alcoholic and nonalcoholic fatty liver disease. *Am J Pathol* 2003; **163**: 1301-1311
- 29 Boyle P, Autier P, Bartelink H, Baselga J, Boffetta P, Burn J, Burns HJ, Christensen L, Denis L, Dicato M, Diehl V, Doll R, Franceschi S, Gillis CR, Gray N, Grieco L, Hackshaw A, Kasler M, Kogevinas M, Kvinnslund S, La Vecchia C, Levi F, McVie JG, Maisonneuve P, Martin-Moreno JM, Bishop JN, Oleari F, Perrin P, Quinn M, Richards M, Ringborg U, Scully C, Siracka E, Storm H, Tubiana M, Tursz T, Veronesi U, Wald N, Weber W, Zaridze DG, Zatonski W, zur Hausen H. European Code Against Cancer and scientific justification: third version (2003). *Ann Oncol* 2003; **14**: 973-1005

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