

The Burden of Cancer Attributable to Alcohol Consumption

Gianni TESTINO, MD, PhD

Department of Specialistic Medicine, S. Martino Hospital - IRCCS, Genova, Italy

ABSTRACT

Many epidemiological studies have demonstrated a correlation between alcohol intake and the occurrence of cancer in humans. All types of alcoholic beverages are associated with an increased risk which suggests that ethanol itself is the crucial compound which causes that effect.

The International Agency for Research for Cancer classified alcohol consumption and acetaldehyde associated with alcohol consumption as carcinogenic for humans (group 1): oral cavity, pharynx, larynx, esophagus, colorectal, liver and female breast.

The mechanisms by which alcohol consumption exerts its carcinogenic effect have not been defined fully, although plausible events include: a genotoxic effect of acetaldehyde; increased estrogen concentration, which is important for breast carcinogenesis; a role as solvent of tobacco carcinogens; production of reactive oxygen species and nitrogen species; and change in folate metabolism.

Most alcohol-induced diseases increases in a linear fashion as intake increases: oral, esophagus 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.

In healthy subjects, European Code Against Cancer recommends keeping daily consumption within two drinks for man and one drink for women.

In our opinion, there are not enough data to support the actually safe intake of alcohol. Any level of alcohol consumption increase the risk of developing an alcohol related cancer. The level of risk increases in line with the level consumption.

Keywords: alcohol, acetaldehyde, cancer, ethanol

The International Agency for Research on Cancer (IARC) is a specialist World Health Organization agency head-quartered in Lyon (France). Its signature production is a monograph series in which the evidence concerning the causal role of potential cancer-producing agents is reviewed exhaustively by expert committees.

In 1988 IARC had already found that alcoholic beverages are carcinogenic to humans, its highest classification of causality (Group 1) (1,2).

More recently, in October, 2009, 30 scientists from 10 countries met at the International Agency for Research on Cancer (IARC) to reassess the carcinogenicity of tobacco, *Areca nut*, alcohol, coal smoke and salt-preserved fish, and to identify additional tumor sites and mechanisms of carcinogenesis (3,4).

The IARC confirmed the causal link between alcohol consumption (Group 1) and the following malignant neoplasm categories: oral cavity, pharynx, larynx, esophagus, liver, colorectal and female breast cancer.

Address for correspondence:

Prof. Gianni Testino, Ospedale San Martino, Padiglione 10 (piano terra), Piazzale R. Benzi 10, 16132 Genova, Italy
e-mail: gianni.testino@hsanmartino.it

In June 2010 the American Institute does not identify a generally safe threshold (5).

A great number of epidemiological studies 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, esophagus, liver, colorectum, female breast) (6). 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 (7). Thygesen et al. (7) have studied a large cohort of patients with alcohol use disorders (19,000 patients, follow-up for 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 (7).

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) (8). The regional differences in the burden of alcohol-attributable cancer resulted from variations in the prevalence of drinking. Other potential sources of the regional variability are carcinogenic effect of local alcoholic beverages and the pattern of drinking.

Schutze et al. (9) evidenced how in Western Europe (Denmark, France, Germany, Greece, Italy, The Netherlands, Spain, UK), an important proportion of cases of cancer can be attributable to alcohol consumption, especially consumption higher than the recommended upper limits (> 24 g/day for men, > 12 g/day for women). In this experience, among men and women, 10% and 3% of the incidence of total cancer was attributable to former and current alcohol consumption in the selected European countries. □

CARCINOGENESIS AND ALCOHOL

The mechanisms by which alcohol consumption exerts its carcinogenic effect have not been defined fully, although plausible events include (10-12): a genotoxic effect of acetalde-

hyde, induction of cytochrome P450 2E1 (CYP2E1) (conversion of various xenobiotics), nutritional deficiencies, interactions with retinoids, changes in the degree of methylation, immune surveillance, angiogenesis, increased estrogen concentration, which is important for breast carcinogenesis.

Alcohol may be important in the initiation of cancer, either by increasing the expression of certain oncogenes or by impeding 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 carcinogenic to humans (Group 1: esophagus, head and neck) (4). It has been 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 these enzymes.

Acetaldehyde exposure in man is indisputably cumulative. This concept is also supported by a recent large-scale epidemiological survey demonstrating a supra-multiplicative combined risk for esophageal cancer among alcohol and tobacco consumers (13,14).

The total alcohol dehydrogenase activity is significantly higher in cancer tissues than in these healthy organs (e.g. liver, esophagus, 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 (10,15).

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.

Genetic variants have result in functional differences in enzyme activity, and lead to differences in acetaldehyde exposure among drinkers. People of Asian ethnic origin who have low or no ALDH2 activity have dysphoria, tachycardia, facial flushing, nausea, and hypotension due to acetaldehyde accumulation from drinking. An increasing number of studies suggest an interaction between genetic susceptibility and alcohol-drinking on cancer risk in human beings (16).

The increased cancer risk associated with ALDH2 deficiency has been confirmed in Japan, China and Taiwan. Salaspuro (13) evidenced how the risk of ALDH2-deficient heterozygotes was 14.5, when drinking at a low-to-moderate rate (< 30 g/day), and that of homozygotes 17.3, whereas the risk of those with the active ALDH2 genotype was 7.2. The risk of those drinking over 30 g/day was as high as 102.5.

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) (17,18).

Alcohol may act as a co-carcinogen by enhancing the effect of direct carcinogens such as those found in tobacco and 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 (11).

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 exocyclic etheno DNA adducts in hepatocytes.

CYP2E1 activity occurs at relatively low level of alcohol (40 gr/ 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 (10).

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 cyclin D1 which is associated with hyperproliferation, at least in liver. Thus, retinoic acid deficiency is associated with acceleration of carcinogenesis (10,15).

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-adenosylhomocysteine 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 (4).

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. Alcohol consumption is associated with immunosuppression which makes chronic alcoholics more susceptible to infection and theoretically to cancer.

Finally, as regard to sex young women below 50 years of age had significantly lower ADH activities in the gastric corpus and antrum when compared with age matched controls. The decrease ADH activity may result in raised ethanol blood concentrations with an increased risk of cancer. Moreover, in women there is a direct relationship between alcoholic beverage intake and circulating androgen and estrogen levels (4,11,19).

Oral cavity, pharynx and larynx

Alcohol is a major recognized risk factor for oral, pharyngeal and laryngeal cancer, and together with tobacco consumption accounts for the large majority of oral cancer in developed countries (75% of cases). The risk is strongly related to the dose of alcohol drunk, even in the absence of smoking (20). Data from several studies suggest that all types of alcoholic beverages contribute to oral, pharyngeal and laryngeal cancer risk and that ethanol is the main component of alcoholic beverages that determines the risk of this type of cancer. The most frequently consumed beverage in each area appears to be the most important determinant for these cancers. Altieri et al. (20) 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. Recently, Tramacere et al. (21) performed a dose-risk analysis using non-linear random-effects meta-regression models. The pooled relative risk (RR) was 1.21 for <1 drink per day, and rose to 5.24 for heavy alcohol drinking (>4 drinks per day). The dose-risk analysis resulted in RR of 1.29 for 10 g ethanol/day, 3.24 for 50 g ethanol/day, 8.61 for 100 g ethanol/day, and 13.02 for 125 g ethanol/day.

In oral cavity, 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 (22).

Alcoholics with oropharyngeal cancer had very high salivary acetaldehyde concentrations, which may be because smoking and poor oral hygiene (23). It has been evidenced how smoking changes oral bacterial flora rapidly from Gram-negative to Gram-positive bacteria, whi-

ch leads to acetaldehyde concentrations 50-60% higher compared with those observed without smoking.

Poor oral hygiene is a risk factor for oral cavity cancer and leads to bacterial overgrowth, periodontitis, and caries. In a study with 132 volunteers poor oral hygiene showed an approximately two fold increase in salivary acetaldehyde production, and this was confirmed after adjustment for smoking, alcohol consumption, age, and gender (24).

Esophagus

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 (25).

More than 50 prospective and case-control studies from most regions of the world found a consistent association between the risk of 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 consumption of about 50 g alcohol per day is associated with a two fold increase in risk. The increased risk for esophageal cancer was consistently observed for a range of different types of alcoholic beverage. However, the association, if any, is weak for adenocarcinoma of the esophagus (4).

It has been evidenced a strong interaction between the effects of alcohol consumption and smoking on esophageal squamous cell carcinoma among individuals with ADH1B and/or ALDH2 risk alleles (26).

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. (25) 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).

In case of patients with chronic atrophic gastritis a greatest risk for gastric carcinoma has been found in Japanese alcoholics, who are heterozygous for an inactive aldehyde dehydrogenase (ALDH2) genotype. In achlorhydric atrophic gastritis, bacterial overgrowth results in the presence of glucose in formation of minor concentrations of endogenous ethanol and acetaldehyde in the gastric juice, and after administration of a small amount of alcohol intragastric acetaldehyde production increases 6.5-fold compared to healthy controls (13,27,28).

Rectocolonic

Several meta-analyses observed a positive linear relation between alcohol consumption and rectocolonic. These studies provide evidence for an increased RR of approximately 10-20% for colorectal cancer with regular consumption of approximately 50 gr of alcohol/day, compared with abstainers. This association is similar for both colon cancer and rectal cancer (2).

Seitz and Stichel (11) have noted a RR of 7.4 for distal rectocolonic cancer in individuals who consume more than 20 gr of ethanol a day in association with low methionine and folate levels compared with occasional drinkers who have a normal methionine and folate level.

It is important the presence of putative precancerous lesions such as aberrant crypt foci (11).

Pancreas

Pancreatic cancer was associated to current smoking. Alcohol consumption was associated to increased pancreatic cancer risk, but Talamini et al. (27) 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.

The biologic mechanism underlying an association between alcohol consumption and

pancreatic cancer is not fully understood. If such an association exists, a probable mechanism is through development of chronic pancreatitis as a result of drinking alcohol (>80 gr/day for 10-12 years) (28,29).

In addition, ethanol is metabolized in the pancreas via oxidative and nonoxidative pathways. Several mechanisms have been hypothesized: activation of nuclear transcription factors, increased production of reactive oxygen species, and dysregulation of cell proliferation and apoptosis (30).

Liver

Alcohol intake has been definitely recognized as a cause of chronic liver diseases and hepatocellular carcinoma (HCC). It 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 (50-80 gr/day of ethanol), hepatitis virus infection (HBV, HCV) and metabolic alterations has recently been demonstrated (29).

Below 50 gr/day it has been demonstrated an addictive effect in patients with HCV infection.

Hassan et al. have 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 (31-33).

In case of heavy alcohol consumption (>80 gr/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) (31-33).

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 af-

ected by chronic alcoholic liver disease (ALD) (29,34).

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 has been considered interesting. The degree of DNA fragmentation has been 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 has been noticed. 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 the subjects who use alcohol and thus contribute to the process of hepatocarcinogenesis (31,32).

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 (29).

Breast

Alcohol consumption is an established risk factor for breast cancer and increases breast cancer risk in a dose-dependent manner: risk increases by 10% for each drink consumed per day. Not only does alcohol increase the risk of developing breast cancer but it may also increase the risk of breast cancer recurrence and death following breast cancer (35-42).

Increased estrogen and androgen levels in women consuming alcohol appear to be important mechanisms underlying the association. Other plausible mechanisms include enhanced mammary gland susceptibility to carcinogenesis, increased mammary carcinogen DNA damage and greater metastatic potential of breast cancer cells. Susceptibility to the breast cancer-enhancing effect of alcohol may also be affected by other dietary factors

(low folate intake), lifestyle habits (use of hormone replacement therapy) or tumor hormone receptor status (43).

There are several polymorphisms, involved in estrogen synthesis and metabolism, such as in CYP17, CYP19, CYP1B1, and the catechol-O-methyltransferase, which have been associated with breast cancer risk (44).

Recently, Kwan et al. (45) have examined the association of alcohol consumption after breast cancer diagnosis with recurrence and mortality among early-stage breast cancer survivors. Drinking 6 or more grams of alcohol per day compared with no drinking was possibly associated with an increased risk of breast cancer recurrence and death from breast cancer. Regular drinking equivalent to two to four standard drinks or more per week was associated with 1.3-fold and 1.5-fold increased risk of breast cancer recurrence and breast cancer death respectively. The associations appeared stronger among postmenopausal women and overweight/obese women separately. In addition to the effects of alcohol, obesity can elevate circulating sex hormones and insulin levels, thereby promoting estrogen production and breast cell proliferation, particularly among postmenopausal women (45).

Alcohol intake is one of the few modifiable breast cancer risk factors yet identified (43). □

CONCLUSIONS

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

Chronic alcohol consumption is a strong risk factor for cancer in the upper aerodigestive tract (oral cavity, pharynx, hypopharynx, larynx, esophagus) 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 alcoholic beverages is associated with an increased cancer risk and selected studies have evidenced a dose-response trends for oral, pharyngeal, laryngeal and esophageal cancer for never-smoking.

For the healthy subjects, European Code Against Cancer recommends keeping daily

consumption within two drinks (20-30 gr of alcohol/day) for man and one drink for women and the US Department of Agriculture and Health and Human Services suggest as a low risk, a maximum of 28 gr of ethanol a day in men and half of this in women.

The relationship between alcohol consumption and cancer support current political efforts

to reduce or to abstain from alcohol consumption to reduce the incidence of cancer.

In our opinion, current evidence does not identify a generally safe threshold. Any level of alcohol consumption increase the risk of developing an alcohol related cancer. The level of risk increase in line with the level of consumption.

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