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Mechanisms of alcohol-associated cancers: introduction and summary of the symposium

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Abstract

Chronic alcohol consumption is associated with an increased risk for cancers of many organs, such as oral cavity, pharynx, larynx, and esophagus; breast; liver; ovary; colon; rectum; stomach; and pancreas. An understanding of the underlying mechanisms by which chronic alcohol consumption promotes carcinogenesis is important for development of appropriate strategies for prevention and treatment of alcohol-associated cancers. The National Institute on Alcohol Abuse and Alcoholism, Office of Dietary Supplements, Office of Rare Diseases, National Cancer Institute, National Institute on Drug Abuse, and National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, sponsored an international symposium on Mechanisms of Alcohol-Associated Cancers in Bethesda, Maryland, USA, October 2004. The following is a summary of the symposium. Chronic ethanol consumption may promote carcinogenesis by (1) production of acetaldehyde, which is a weak mutagen and carcinogen; (2) induction of cytochrome P450 2E1 and associated oxidative stress and conversion of procarcinogens to carcinogens; (3) depletion of *S*-adenosylmethionine and, consequently, induction of global DNA hypomethylation; (4) induction of increased production of inhibitory guanine nucleotide regulatory proteins and components of extracellular signal-regulated kinase–mitogen-activated protein kinase signaling; (5) accumulation of iron and associated oxidative stress; (6) inactivation of the tumor suppressor gene *BRCA1* and increased estrogen responsiveness (primarily in breast); and (7) impairment of retinoic acid metabolism. Nicotine may promote carcinogenesis through activation of extracellular signal-regulated kinase/cyclooxygenase-2/vascular endothelial growth factor signaling pathway.

Keywords: Alcohol-associated cancer; Acetaldehyde; CYP2E1; Oxidative stress

1. Introduction

Chronic alcohol consumption is associated with an increased risk for cancers of various organs (Bagnardi et al., 2001; Longnecker, 1992; Seitz et al., 1998). The risk for development of cancer varies from low to moderate to high, depending on the type of organ affected as well as the amount of alcohol consumed. In a meta-analysis of 235 epidemiologic studies (117,471 cases), statistically significant relative risks for the development of cancers from consumption of 100 g of alcohol per day were reported for the following sites or organs: 6.01, oral cavity and pharynx; 4.23, esophagus; 3.95, larynx; 2.71, breast; 1.86, liver; 1.53, ovary; 1.38, colon and rectum; and 1.32, stomach (Bagnardi et al., 2001). In this report, significant increased risks were also found for most cancer sites with consumption of 50 g as well as 25 g of alcohol per day. The latter dose of alcohol (25 g or two drinks) is considered equivalent to moderate alcohol consumption.

Considering all organs together, as well as the number of individuals who drink moderately as well as heavily, the combined risk for the development of cancer from alcohol consumption could be an important health problem in this country. In one study, approximately 3% of all cancers in the United States were attributed to heavy drinking (Rothman, 1980). In a recent Japanese study, however, about 13% of cancers among males were found to be due to heavy alcohol drinking (Inoue & Tsugane for the JPHC Study Group, 2005).

Results of many studies support the concept that alcohol is a co-carcinogen or a tumor promoter, but not a direct carcinogen (Pöschl & Seitz, 2004). An understanding of the underlying mechanisms by which chronic alcohol

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consumption promotes carcinogenesis is important for the development of appropriate strategies for the prevention and treatment of alcohol-associated cancers.

The National Institute on Alcohol Abuse and Alcoholism, National Institutes of Health, sponsored an international symposium on the Mechanisms of Alcohol-Associated Cancers in Bethesda, Maryland, October 6–7, 2004. The symposium was co-sponsored by the Office of Dietary Supplements, Office of Rare Diseases, National Cancer Institute, National Institute on Drug Abuse, and National Institute of Diabetes and Digestive and Kidney Diseases. For this symposium, 16 speakers were invited to address the following issues: (1) general mechanisms of cancers; (2) epidemiology of alcohol-associated cancers; (3) alcohol and oral cancer; (4) cancers of the upper aerodigestive tract (UADT) and large intestine; (5) acetaldehyde, microbes, and cancers of the digestive tract; (6) alcohol dehydrogenase (*ADH*) and aldehyde dehydrogenase (*ALDH*) polymorphisms and cancer; (7) mechanisms of acetaldehyde-induced DNA damage; (8) alcohol and hepatocellular carcinoma (HCC); (9) alcohol and pancreatic cancer; (10) role of alcohol in breast cancer; (11) role of methionine adenosyltransferase (MAT) and *S*-adenosylmethionine (SAMe) in alcohol-associated liver cancer; (12) alcohol, folate, and cancer; (13) alcohol, iron-associated oxidative stress, and cancer; (14) alcohol, vitamin A, and cancer; (15) nicotine and gastric cancer; and (16) marijuana and cancer.

2. Summary of presentations

Dr. Linda Morris Brown summarized the results of epidemiologic studies on alcohol-associated cancers of the UADT (including oral cavity, pharynx, larynx, and esophagus), liver, breast, colorectum, and pancreas. On the basis of findings from various studies, 25% to 80% of UADT cancers are attributable to alcohol. However, there has been a decline in UADT cancers, which can be ascribed to a decrease in alcohol consumption. Individuals who consume alcohol with an empty stomach and those who consume concentrated liquor are at increased risk for the development of UADT cancers. The incidence of squamous cell carcinoma of the esophagus is several-fold higher in blacks than in whites. Chronic alcohol consumption is a risk factor for liver cancer, and the risk is dependent on the dose of alcohol consumed. In one study, the pooled risk of liver cancer associated with intake of alcohol ranged from 1.2 for 25 g per day to 1.9 for 100 g per day. The link between alcohol intake and breast cancer is dependent on the dose of alcohol consumed, whereby, according to one estimate, there is about a 10% increase in breast cancer for each 10 g of alcohol consumed. About 4% of breast cancers in developed countries may be ascribed to alcohol consumption. Whites in comparison with blacks are at an increased risk for alcohol-associated breast cancer. Alcohol consumption is a modest risk for colon cancers. According to the results of one study, the pooled alcohol-associated risk for colorectal cancer was only 1.38 for 100 g of alcohol consumed per day. Heavy, but not moderate, alcohol consumption seems to be a modest risk factor for pancreatic cancer. In a meta-analysis, the pooled risk for cancer of the pancreas was only 1.18 for intake of 100 g of alcohol per day.

Dr. Graham R. Ogden summarized the research on alcohol and oral cancer. Alcohol, in association with tobacco, is an important risk factor for oral cancer. It seems that alcoholic beverages are important factors in the etiology of oral cancer. Alcohol may promote oral cancer by reducing the cytoplasmic area of oral mucosal cells, and by enhancing the penetration of carcinogens across the oral mucosa through increasing mucosal permeability.

Dr. Helmut K. Seitz discussed possible mechanisms of cancers of the UADT and large intestine. He discussed the roles of two factors: acetaldehyde and cytochrome P450 2E1 (CYP2E1). In the gastrointestinal tract, acetaldehyde can be produced by the metabolism of ethanol, catalyzed by mucosal, salivary gland, or bacterial ADH. Acetaldehyde has been shown to have direct mutagenic and carcinogenic effects in in vitro and in vivo studies. It has been reported to cause point mutations in lymphocytes, induce sister-chromatid exchanges, impair DNA repair, induce metaplasia of tracheal epithelium, and cause nasopharyngeal and laryngeal carcinoma. Acetaldehyde may cause replication errors and/or mutations in oncogenes or tumor suppressor genes by forming adducts with DNA. Individuals homozygous for the *ADH1C*1* allele are at increased risk for the development of UADT cancers because they have increased salivary acetaldehyde levels after alcohol consumption. Individuals with the inactive form of *ALDH2* may be at increased risk for cancers of the UADT and large intestine because of higher levels of acetaldehyde after alcohol consumption. Chronic alcohol consumption is known to induce CYP2E1 in the gastrointestinal mucosa of animals and human beings. In addition to metabolizing ethanol to acetaldehyde, CYP2E1 catalyzes the conversion of various procarcinogens to carcinogens. Furthermore, CYP2E1 is known to release reactive oxygen species (ROS), which may be another mechanism by which it promotes cancer of the gastrointestinal tract.

Dr. Mikko Salaspuro presented data on acetaldehyde, microbes, and cancers of the digestive tract. Acetaldehyde seems to be a major causal factor responsible for increased incidence of cancers of the oral cavity and large intestine in alcoholics. In the oral cavity, acetaldehyde can be formed locally by the metabolism of alcohol, catalyzed by ADH of mucosa, salivary glands, or some microbes. Because of the poor ability of microbes and mucosa to detoxify acetaldehyde, high concentrations of acetaldehyde may be attained in the gastrointestinal tract after alcohol consumption. Indeed, marked amounts of acetaldehyde are detected in the saliva of healthy volunteers after ingestion of ethanol. These levels are reduced considerably after the use of an antiseptic mouthwash, supporting the suggestion of a role

of oral microbes in the production of salivary acetaldehyde. Findings of studies done with in vitro experiments show that aerobic bacteria and yeasts are primarily responsible for increased acetaldehyde production. Poor hygiene is a risk factor for oral cavity cancer, and this may be due to increased microbial acetaldehyde production. Results of studies done in vitro and in vivo show that microbial acetaldehyde production is significantly associated with ethanol concentration and is pH dependent. Acetaldehyde present in the saliva can reach the esophagus and stomach after being swallowed, rendering these organs susceptible to the carcinogenic effect of acetaldehyde. In the large intestine, acetaldehyde can be formed by the metabolism of ethanol catalyzed by the ADH of mucosa or microbes. Human colonic contents or some microbes representing normal colon flora have been shown to metabolize ethanol to acetaldehyde. On the other hand, antibiotic treatment has been shown to significantly reduce fecal ADH activity and acetaldehyde production in colon from ethanol. In conclusion, a significant amount of acetaldehyde can be produced by microbes in the oral cavity and large intestine after alcohol consumption. This acetaldehyde may contribute to the incidence of cancers observed in alcoholics.

Dr. Akira Yokoyama evaluated an association between *ADH* and *ALDH* polymorphisms and aerodigestive tract cancers in the Japanese population and noted the following. Ethanol is first oxidized to acetaldehyde by ADH and then to acetate by ALDH. Homozygous inactive *ALDH2* encoded by the mutant allele *ALDH2*2* is present in 42% of Japanese, whereas heterozygous inactive *ALDH2* encoded by *ALDH2*1/2*2* is present in 13% of Japanese alcoholics. People with homozygous inactive *ALDH2* experience flushing response after alcohol consumption, which prevents them from further drinking. The flushing response is due to an excess accumulation of acetaldehyde in the blood. On the other hand, people with heterozygous inactive *ALDH2* do not experience flushing response after alcohol consumption, thereby permitting them to drink more despite acetaldehyde accumulation. There is a strong association between inactive heterozygous *ALDH2* and the risk of squamous cell carcinoma of the esophagus in East Asian drinkers, which seems to be due to accumulation of acetaldehyde, a known animal carcinogen. Inactive heterozygous *ALDH2* also increases the risk of oropharyngolaryngeal, gastric, and colorectal cancers, but not of liver cancer. Superactive *ADH1B* (*ADH2*, old nomenclature) encoded by *ADH1B*2* (*ADH2*2*, old nomenclature) is found in 93% of the Japanese population, whereas less active *ADH1B* (a risk factor for alcoholism in East Asians) encoded by *ADH1B*1* is found in 31% of Japanese alcoholics. The less active *ADH1B* is another risk for squamous cell carcinoma of the esophagus. Individuals with both less active heterozygous *ADH1B* and inactive heterozygous *ALDH2*, in comparison with individuals with only one of these, are at greater risk for the development of cancers. The combination of two enzymes prevents alcohol-induced flushing, thereby permitting individuals to drink more, and resulting in a higher level of acetaldehyde exposure to the tissues.

Dr. Philip J. Brooks described the formation of DNA adducts with acetaldehyde and discussed their significance in alcohol-related carcinogenesis. Acetaldehyde can react with DNA to form an adduct known as N^2-ethyl-2′-deoxyguanosine (N^2-ethyl-dG). For the stabilization of this adduct, a subsequent reduction step is required that can be carried out by vitamin C and reduced glutathione (GSH). This adduct has been detected in DNA from liver in rats exposed to 10% ethanol in drinking water, as well as in DNA obtained from white blood cells of human alcoholics. This adduct has been found to be mutagenic in *Escherichia coli*, but not in mammalian cells. Thus, its carcinogenic relevance in human beings is not clear. Acetaldehyde can react with DNA to form another adduct, 1,N^2-propano-2′-deoxyguanosine (PdG). This reaction is facilitated by histones and polyamines, such as spermine, spermidine, and putrescine. PdG has been shown to be responsible for the genotoxic, mutagenic, and carcinogenic effects of crotonaldehyde. The PdG adduct can exist in a ring-closed form or a ring-open aldehyde form. The ring-closed form is likely to be mutagenic owing to its effect on base pairing of deoxyguanosine with deoxycytosine. On the other hand, the ring-open aldehyde form can participate in the formation of secondary adducts, including DNA–protein cross-links and DNA interstrand cross-links. Formation of these secondary adducts may explain many of the genotoxic effects of acetaldehyde.

Dr. Iain H. McKillop discussed the role of alcohol consumption in the development of HCC. Chronic alcohol consumption is a major cause of cirrhosis, which is a risk factor for HCC. Ethanol is metabolized primarily in the liver by ADH and CYP2E1, leading to the production of acetaldehyde, which has been found to be mutagenic and carcinogenic in animal studies. CYP2E1 can also catalyze conversion of various procarcinogens to carcinogens. Chronic ethanol consumption is associated with oxidative stress, which has been linked to carcinogenesis. In the liver, oxidative stress may arise through CYP2E1 induction, lipid peroxidation, and GSH depletion. The presence of HCC is associated with increased expression and function of inhibitory guanine nucleotide regulatory proteins (Gi proteins) and components of an extracellular signal-regulated kinase–mitogen-activated protein kinase (ERK–MAPK) cascade. Stimulation of Gi proteins activates the ERK–MAPK cascade, leading to enhanced cell mitogenesis. Furthermore, ethanol has been shown to increase the expression of Gi proteins and enhance ERK–MAPK signaling and cell growth. This effect of ethanol was mediated through acetaldehyde because it was abrogated by 4-methylpyrazole, an ADH inhibitor. Taken together, these findings indicate that ethanol may promote the development of HCC by (1) producing acetaldehyde, (2) inducing CYP2E1 activity, (3) inducing oxidative stress, and (4) up-regulating Gi proteins and ERK–MAPK signaling.

Dr. Vay Liang W. Go discussed the role of alcohol and alcoholic pancreatitis in the development of pancreatic cancer. Long-term heavy alcohol consumption is a major factor associated with chronic pancreatitis, which has been linked to pancreatic cancer. Alcohol may contribute to the development of pancreatic cancer in many ways. Alcohol can be metabolized in the pancreas by ADH and CYP2E1 to acetaldehyde, which may injure pancreatic tissues through its genotoxicity and DNA adduct formation. Alcohol-induced up-regulation of CYP2E1 may convert some of the dietary procarcinogens to ultimate carcinogens. CYP2E1 may also contribute to pancreatic cancer through generation of ROS, which are known to cause oxidative DNA damage. Alcoholic chronic pancreatitis is characterized by inflammation and fibrosis. Chronic inflammation is known to play a key role in carcinogenesis and can accelerate the oncogenic process. The duration of inflammation seems to be the major factor involved in the transition of benign to malignant condition.

Dr. Peter G. Shields discussed possible mechanisms by which alcohol consumption may promote breast cancer. Alcohol consumption is associated with increased risk for breast cancer in both premenopausal and postmenopausal women. Breast tissue may metabolize alcohol to acetaldehyde, catalyzed by ADH and CYP2E1. Acetaldehyde can be metabolized further to acetate by means of ALDH or xanthine oxidoreductase (XOR) in the breast tissue. Metabolism of alcohol by CYP2E1 and of acetaldehyde by XOR can result in ROS generation. Both acetaldehyde and ROS have been implicated in the initiation and progression of cancer. Alcohol has been shown to down-regulate the expression of the tumor suppressor gene *BRCA1* and increase the transcriptional activity of estrogen receptor alpha. Thus, alcohol may contribute to breast cancer by inactivation of *BRCA1* and increasing estrogen responsiveness. In experimental studies with animals, alcohol has been shown to initiate as well as promote dimethylbenzathracene-initiated mammary tumors. Alcohol seems to render rodent mammary gland susceptible to carcinogen-induced damage by altering mammary gland structural development and stimulating cell proliferation in the terminal end buds of the mammary gland. Alcohol consumption is associated with increased breast mammographic density, which is a risk factor for the development of breast cancer in human beings. Chronic alcohol consumption is associated with folate deficiency, which may increase the risk of breast cancer by causing DNA hypomethylation and/or inducing uracil misincorporation during DNA synthesis.

Dr. Shelly C. Lu summarized the role of SAMe and MAT in the development of alcohol-associated liver cancers. She described the role of endogenous SAMe deficiency as well as exogenous SAMe administration on liver cancer. Ethanol administration to rats for 9 weeks resulted in a relative switch in hepatic MAT expression, decreased SAMe levels, hypomethylation of c-*myc*, increased c-*myc* expression, and increased DNA strand breaks, supporting the suggestion of an association between reduced SAMe levels and malignant degeneration. *MAT1A* knockout mice, which are deficient in hepatic SAMe (76% lower), develop hepatic hyperplasia by 3 months, spontaneous steatohepatitis by 8 months, and HCC by 18 months, further supporting the suggestion of a link between SAMe deficiency and malignant transformation. Patients with alcoholic liver disease have decreased MAT activity that results in reduced SAMe levels. Thus, these patients may be susceptible to the development of HCC. Taken together, findings of these studies seem to indicate that chronic deficiency of SAMe predisposes liver to malignant transformation. Exogenous SAMe inhibits the growth of hepatoma cells in culture and prevents development of HCC in rats treated with hepatocarcinogens. These results support the idea that SAMe plays an important role in rescuing the liver from the development of spontaneous or chemical-induced HCC. *S*-Adenosylmethionine is antiapoptotic in normal hepatocytes but proapoptotic in liver cancer cells, further suggesting that SAMe may be used for the prevention and treatment of HCC.

Dr. Joel B. Mason summarized the effect of alcohol on folate metabolism and discussed its connection with carcinogenesis. Folate deficiency has been linked to an increased risk of cancers for several organs, such as colorectum, lung, breast, and cervix. In addition, chronic ethanol intake is known to impede the normal bioavailability and metabolism of folate. Thus, alcohol intake and folate deficiency may act synergistically in promoting carcinogenesis. Excessive alcohol intake may impair the bioavailability of folate by diminishing its intestinal absorption, increasing its urinary excretion, and inducing cleavage of its molecule. Alcohol can impair folate metabolism in many ways. Both acute and chronic ethanol ingestion are known to inhibit the activity of methionine synthase, which catalyzes the transfer of a methyl group from folate to homocysteine, leading to methionine reformation. The decreased methionine synthase activity can result in decreased production of SAMe and increased accumulation of homocysteine and *S*-adenosylhomocysteine. *S*-Adenosylmethionine is a major methyl donor for methylation reactions, whereby it donates a methyl group to many compounds, such as proteins, DNA, RNA, and phospholipids. A decreased SAMe:*S*-adenosylhomocysteine ratio can inhibit activities of many methyltransferases, leading to global hypomethylation of DNA, which is an early feature of neoplastic transformation of epithelial cells. Thus, alcohol-induced inhibition of methionine synthase activity may promote neoplastic growth through decreasing SAMe levels.

Dr. Dennis R. Petersen discussed the connection among alcohol intake, iron-associated oxidative stress, and cancer. Chronic alcohol intake is associated with increased accumulation of iron in the liver cells, including hepatocytes and Kupffer cells. Hepatic iron overload also develops in many individuals who consume alcohol on

a chronic basis. Both alcohol and iron are known prooxidants. The metabolism of alcohol through CYP2E1 can lead to generation of superoxide and hydrogen peroxide. On the other hand, hydrogen peroxide can react with ferrous iron (Fe^{2+}), through the Fenton reaction, and generate hydroxyl radicals, which are highly reactive. Hydroxyl radicals can react with lipid molecules, initiating chain reactions that lead to lipid peroxidation and generation of products, such as acrolein, crotonaldehyde, malondialdehyde, and 4-hydroxynonenal (4-HNE). The 4-HNE is known to cause mutations of *p53* gene, which may initiate the development of HCC. Thus, it is possible that sustained oxidative stress associated with chronic alcohol consumption and hepatic iron overload could play an important role in the initiation and promotion of carcinogenesis. Indeed, a synergistic effect of alcohol intake and iron accumulation on HCC has been reported in patients with hemochromatosis. An excess of iron accumulated in hepatic macrophage (Kupffer cells) in response to chronic alcohol intake can activate, by means of oxidative stress, nuclear factor-kappa B, which can increase the transcription of the proinflammatory cytokine tumor necrosis factor-alpha. Thus, in alcoholics, alcohol and iron together may initiate chronic inflammation, which is a known risk factor for cancer.

Dr. Xiang-Dong Wang discussed the role of alcohol in impairing vitamin A metabolism and its possible connection with cancer. Vitamin A (retinol) is oxidized by retinol dehydrogenase to retinal, which is further oxidized to retinoic acid by retinal dehydrogenase. In addition, ADH and ALDH participate in the metabolism of retinol to retinal and retinoic acid. Retinoic acid is the most active form of vitamin A, as well as a ligand for both retinoic acid receptors (RARs) and retinoid X receptors (RXRs). Retinoic acid is known to control cell proliferation, growth, and differentiation as well as apoptosis. Perturbation (impaired homeostasis) of these activities may render cells susceptible to carcinogenesis. Alcoholics generally have reduced levels of vitamin A (retinol and retinyl esters), which is likely to reduce the levels of retinoic acid. Chronic ethanol ingestion may impair retinoid metabolism in three ways: (1) by inhibiting retinol metabolism to retinoic acid through competing for ADH and ALDH, (2) by accelerating catabolism of vitamin A by inducing CYP2E1, and (3) by increasing mobilization of vitamin A from the liver to other tissues. Alcohol-induced impairment of retinoic acid homeostasis may interfere with vitamin A action and signaling. For example, alcohol may interfere with retinoic acid signaling, including by down-regulating retinoid target gene expression and inhibiting RARs binding activity to retinoic acid responsive element (RARE). In addition, alcohol may interfere with retinoic acid cross talk with MAPK signaling pathway, which is involved in cellular proliferation, apoptosis, oxidative stress, and carcinogenesis. Thus, chronic alcohol ingestion may promote cancer by perturbing homeostasis of retinoic acid metabolism and by impairing its action and signaling.

Dr. Chi-Hin Cho discussed the role of nicotine in the induction and promotion of gastric cancer. Nicotine is a major active component of tobacco smoke, which is a major risk factor for gastric cancer. Long-term administration of nicotine initiated an early development of gastric tumors in rats. In athymic nude mice, with gastric cells orthotopically implanted into the gastric wall, nicotine administration in drinking water for 3 months resulted in the development of large tumors. This was associated with increased cell proliferation and angiogenesis, activation of ERK phosphorylation, and increased expression of cyclooxygenase-2 (COX-2) and vascular endothelial growth factor (VEGF) in the tumors. A selective COX-2 inhibitor (SC-236) attenuated the nicotine-induced tumor growth and angiogenesis by reducing expression of COX-2 and ERK phosphorylation. In vitro, exposure of gastric cancer cells to nicotine promoted cancer cell proliferation, activated ERK phosphorylation, increased COX-2 expression, and increased prostaglandin E_2 and VEGF release. Pretreatment with specific mitogen-activated protein kinase kinase (MEK) inhibitors (U0126 or PD98059) attenuated COX-2 expression and subsequent prostaglandin E_2 release by nicotine. Furthermore, the stimulatory action of nicotine on cancer cell growth and angiogenic factor VEGF production was suppressed by inhibitors of MEK (U0126) and COX-2 (SC-236). These findings reveal a direct promoting action of nicotine on the growth of gastric tumor and angiogenesis through sequential activation of the ERK/COX-2/VEGF signaling pathway.

Dr. Zuo-Feng Zhang presented an epidemiologic review of marijuana and cancer risk. In one cohort study, use of marijuana was associated with increased risk for prostate and cervical cancers, but not for lung, colorectal, or UADT cancers. In another cohort study, use of marijuana was associated with a moderate increase in risk for adult-onset glioma. In a case–control study, marijuana use was associated with increased risk for head and neck squamous cell carcinoma. In another case–control study, however, no link was detected between squamous cell carcinoma of oral cavity and marijuana use. Data were presented for two lung cancer studies conducted in North Africa. In the Tunisian study, marijuana use increased the risk of lung cancer by eightfold, but the results could have been a mixed effect of marijuana and tobacco because both agents are used together in that region. In the Moroccan study, the results were confounded because of mixed use of tobacco and marijuana. In two studies on non-Hodgkin's lymphoma, the results were null to inverse association with lifetime use of marijuana. It was concluded that adequate studies are not available to evaluate the impact of marijuana on cancer risk.

3. Overall summary

Chronic alcohol consumption is associated with an increased risk for cancers of various organs. The risk for

development of cancer varies from low to moderate to high, depending on the type of organ affected as well as the amount of alcohol consumed. The risk of cancer is relatively high for oral cavity, pharynx, larynx, and esophagus, and moderate for breast, liver, ovary, colon, rectum, and stomach. For other organs, the risk is low or nonsignificant. For many cancers, the risk is significant even with moderate alcohol consumption (25 g per day or two drinks).

Acetaldehyde may be a major causal agent responsible for alcohol-associated cancers of the UADT and large intestine. It can be formed in the digestive tract from the metabolism of ethanol by ADH of mucosa and salivary glands. An excess of acetaldehyde can accumulate in the gastrointestinal tract owing to its weak ALDH activity as well as to increased acetaldehyde production by microbes (aerobic bacteria and yeast) in the oral cavity and large intestine after alcohol consumption. Individuals heterozygous for inactive *ALDH2* encoded by *ALDH2*1/2*2* allele or homozygous for hyperactive *ADH* encoded by *ADH1C*1* allele are at increased risk for cancers of the UADT and large intestine because of the accumulation of acetaldehyde after alcohol consumption. Acetaldehyde may promote carcinogenesis by causing point mutations, inducing sister-chromatid exchanges, impairing DNA repair, inducing metaplasia of epithelium, and forming adducts with DNA. Chronic ethanol intake is known to induce CYP2E1 in various organs, including liver, pancreas, and gastrointestinal tract. The CYP2E1 may contribute to carcinogenesis by metabolizing ethanol to acetaldehyde, by converting various procarcinogens to carcinogens, and by releasing ROS, which have been implicated in the genesis of cancer. In the liver, in addition to acetaldehyde and CYP2E1, an alcohol-induced up-regulation of Gi proteins and ERK–MAPK signaling may contribute to the progression of HCC. In the pancreas, in addition to alcohol-induced oxidative stress, alcohol-associated chronic inflammation (pancreatitis) is a risk factor for pancreatic cancer. In the breast tissue, alcohol metabolism can lead to the production of acetaldehyde and ROS. In addition, inactivation of *BRCA1* and increased estrogen responsiveness may contribute to alcohol-associated breast cancer. *S*-Adenosylmethionine deficiency, induced by chronic consumption of ethanol, may predispose liver and other organs to malignant transformation by inducing global hypomethylation of DNA, which is an early feature of neoplastic transformation of epithelial cells. Folate deficiency may promote neoplastic growth by causing SAMe deficiency. Alcohol-induced accumulation of iron in the liver and other organs may promote neoplastic growth through generation of ROS (hydroxyl radicals) and by initiating inflammatory process. Chronic alcohol ingestion may promote cancer by perturbing homeostasis of retinoic acid metabolism and by impairing its action and signaling. Nicotine seems to promote the growth of gastric tumor and angiogenesis through sequential activation of ERK/COX-2/VEGF signaling pathway. The role of marijuana use in carcinogenesis is not clear.

4. Conclusions

Chronic ethanol consumption may promote carcinogenesis by (1) production of acetaldehyde; (2) induction of CYP2E1 and associated oxidative stress and conversion of procarcinogens to carcinogens; (3) depletion of SAMe and, consequently, induction of global DNA hypomethylation; (4) induction of increased production of Gi proteins and ERK–MAPK signaling; (5) accumulation of iron and associated oxidative stress; (6) inactivation of *BRCA1* and increased estrogen responsiveness (primarily in breast); and (7) impairment of retinoic acid metabolism. Nicotine may promote carcinogenesis through activation of ERK/COX-2/VEGF signaling pathway.

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Disclaimer

The opinions expressed herein are those of authors and do not necessarily reflect the official position of NIAAA, NIDA, NIDDK, or any other part of the National Institutes of Health.

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