

Alcohol and cancer

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A causal association has been established between alcohol consumption and cancers of the oral cavity, pharynx, larynx, oesophagus, liver, colon, rectum, and, in women, breast; an association is suspected for cancers of the pancreas and lung. Evidence suggests that the effect of alcohol is modulated by polymorphisms in genes encoding enzymes for ethanol metabolism (eg, alcohol dehydrogenases, aldehyde dehydrogenases, and cytochrome P450 2E1), folate metabolism, and DNA repair. The mechanisms by which alcohol consumption exerts its carcinogenic effect have not been defined fully, although plausible events include: a genotoxic effect of acetaldehyde, the main metabolite of ethanol; increased oestrogen concentration, which is important for breast carcinogenesis; a role as solvent for tobacco carcinogens; production of reactive oxygen species and nitrogen species; and changes in folate metabolism. Alcohol consumption is increasing in many countries and is an important cause of cancer worldwide.

Introduction

A causal link has been established between alcohol consumption and cancers of the oral cavity, pharynx, oesophagus, liver, colon, rectum, and, in women, breast (figure).¹ For other cancers, a causal association is suspected. The importance of alcohol as a human carcinogen is often underestimated: consumption is rising in many countries as a result of both increasing numbers of alcohol drinkers and intake of alcohol, especially for women and in regions of rapid economic growth such as east Asia.² Alcohol is probably the main factor responsible for increased risk of head and neck cancer recorded in various countries, particularly in central and eastern Europe.³ Evidence suggests that genetic susceptibility plays an important part in alcohol-related cancer, and knowledge of possible mechanisms of the carcinogenic action of alcohol has increased in recent years.

Here, we review the carcinogenic effects of alcohol consumption in human beings. Alcohol modifies the risk of several diseases other than cancer, but a detailed review of these effects is beyond the scope of this review. Briefly, the major non-neoplastic diseases caused by alcohol are: alcoholic polyneuropathy; alcoholic cardiomyopathy; alcoholic gastritis; depression and other mental disorders;^{4,5} hypertension;⁶ haemorrhagic stroke;⁷ liver cirrhosis and fibrosis;⁸ and acute and chronic pancreatitis.⁹ Moreover, alcohol consumption is a major cause of several types of injuries,⁵ and the drinking of alcohol during pregnancy is associated with various adverse effects including fetal alcohol syndrome, spontaneous abortion, low birthweight, premature birth, and intrauterine growth retardation.¹⁰

However, evidence suggests that moderate consumption (up to two drinks per day) of alcohol reduces the risk of ischaemic heart disease,¹¹ ischaemic stroke,⁷ and coledithiasis.⁵ A global assessment of the burden of alcohol consumption on human health is complicated by several factors, including: background frequency of major diseases such as ischaemic heart disease and liver cirrhosis; age distribution of a population, since incidence of many alcohol-related injuries decreases with age whereas that of cancer and ischaemic heart disease increases with age; and pattern

of consumption, since the protective effect on ischaemic heart disease is not present at high intake.

The most comprehensive estimate of the number of deaths caused and prevented by alcohol has been done as part of WHO's global burden of disease project.⁵ According to this assessment, alcohol caused 185 000 deaths of men in developed countries in 2000, whereas it prevented 71 000 deaths in men for the same year. For women in developed countries, 277 000 deaths were prevented compared with the 142 000 caused by alcohol. However, in developing countries, a lower burden of cardiovascular disease and a greater incidence of injuries compared with developed countries led to 1 524 000 deaths in men and 301 000 in women in 2000.

Lancet Oncol 2006; 7: 149–56

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Figure: A causal association has been established between alcohol consumption and cancer

	Cases	Controls	Relative risk (95% CI)	p for trend	Ref
Oral, pharynx					
Men					
None	13	78	1.00 (Reference)	<0.001	13
<1 OWE	20	90	1.33 (0.57–3.13)		
1.0–2.9 OWE	19	48	2.37 (1.00–5.64)		
3.0–6.9 OWE	13	27	2.89 (1.10–7.60)		
≥7 OWE*	8	11	4.36 (1.39–13.68)		
Women					
None	55	192	1.00 (Reference)	1.0	13
<1 OWE*	34	127	0.93 (0.53–1.64)		
1.0–2.9 OWE*	7	28	0.87 (0.29–2.59)		
3.0–6.9 OWE*	1	8	0.44 (0.03–7.09)		
≥7 OWE*	3	4	2.62 (0.51–13.34)		
Non-drinkers	4	202	1.00 (Reference)	0.03	14
<35 years of drinking	16	382	2.9 (0.9–9.2)		
≥35 years of drinking	22	278	3.6 (1.2–11.2)		
Missing data	0	2			
Oesophagus					
Never drinkers	91	423	1.00 (Reference)	0.002	15
1–24 mL ethanol/day	14	65	1.43 (0.72–2.84)		
25–49 mL ethanol/day	12	43	1.61 (0.75–3.48)		
50–149 mL ethanol/day	14	69	1.77 (0.85–3.67)		
≥150 mL ethanol/day	9	18	5.70 (2.11–15.44)		
Missing data	4	12			
Larynx					
<8 drinks/day	31	142	1.00 (Reference)	NA	16
≥8 drinks/day	9	18	2.46 (0.98–6.20)		

OWE=ounces of whiskey equivalent: combined intake of beer, wine, and liquor.

Table 1: Relative risk of cancer of upper aerodigestive tract with alcohol consumption, never-smokers

Therefore, the global burden of alcohol amounts to 1 804 000 deaths a year, or 3.2 % of all deaths a year.

Epidemiology of alcohol-related cancer

From the articles identified by our search, we focused on those that reported risk estimates for alcohol consumption, particularly ones that assessed: dose-response relations; differences by type of alcoholic beverage; and interactions with other risk factors for a particular cancer. When meta-analyses were available for a particular cancer, we reported the most recently published summary estimate.

Squamous-cell carcinoma of oral cavity, pharynx, larynx, and oesophagus

A causal relation between raised alcohol consumption and squamous-cell carcinoma of the oral cavity, pharynx, larynx, and oesophagus has been noted since the mid 1950s.¹² Epidemiological studies¹² of these tumours have shown a neoplastic effect of heavy alcohol intake and a linear correlation with both duration and amount of consumption. A synergism between alcohol intake and tobacco smoking was reported in the 1970s, and has since become a paradigm of interaction of two environmental factors in human carcinogenesis. A carcinogenic effect of alcohol independently from that of smoking (ie, an increased risk in non-smokers) was first reported in 1961,¹² and has been replicated since.^{13–16} These subsequent studies have shown a fairly consistent dose-

response relation between alcohol consumption and risk of cancer in the upper aerodigestive tract for non-smokers. Table 1^{13–16} shows selected studies that assessed dose-response trends for oral, pharyngeal, laryngeal, and oesophageal cancer for never-smokers. Analyses by type of alcoholic drink have not given consistent results, and in general the beverage associated with greatest risk was the one consumed most commonly in every study, which thus might have been the result of inadequate power to assess uncommon drinks, under-reporting, or misclassification of consumption.¹⁷ Investigators¹² have assessed differences in the carcinogenicity of alcohol drinks on subsites of the head and neck, and evidence suggests a high risk for anatomical sites in closest contact on ingestion of alcohol such as the mobile part of the tongue and the hypopharynx.

Adenocarcinoma of the oesophagus

Studies on the association of alcohol and adenocarcinoma of the oesophagus have been inconsistent. Some studies reported an increase in risk of 1.5–4.0 times of adenocarcinoma of the oesophagus and gastric cardia with alcohol consumption, as reviewed by Wu and colleagues.¹⁸ Many studies that have reported risk estimates for adenocarcinoma of the oesophagus have tended to be small, whereas larger studies^{19–21} have reported no association with ever consumption of alcohol and no dose-response relations. Moreover, these larger studies tended to report a protective effect overall or for specific types of drink, although inverse dose-response relations were not reported. These studies also had large series of gastric cardia adenocarcinoma, but did not report increased risks due to alcohol consumption. In summary, findings do not lend support to an association between risk of adenocarcinoma of the oesophagus and alcohol consumption.

Stomach cancer

No consistent evidence suggests that alcohol intake affects the risk of stomach cancer. A review²² of 52 epidemiological studies found significant positive associations in two of 12 cohort studies and eight of 40 case-control studies. The two positive cohort studies were based on a small number of deaths and did not record dose-response relations. Of the eight positive case-control studies, four reported risk estimates of 1.5–1.7 times with non-drinkers as the reference group.

Since the review,²² several further studies from Europe, Asia and USA have mostly reported no association between alcohol consumption and risk of stomach cancer. Studies that noted an overall increased risk did not report dose-response relations. A few studies reported increased risk of stomach cancer for specific alcoholic drinks, including vodka in Russia,¹⁹ wine in Italy,²⁰ and hard liquor and beer in Uruguay;²¹ however, an association between stomach cancer and alcohol consumption has not been defined clearly.

Colorectal cancer

Several studies lend support, although inconsistently, to an association between increased intake of alcohol and risk of colorectal adenoma and adenocarcinoma. A review²² of 27 epidemiological studies showed that cohort studies reported risk estimates of 1.0–1.7 for colon cancer and the same for rectal cancer. The researchers concluded that such findings were consistent with either no increase in risk of colorectal cancer as a result of alcohol consumption, or a very moderate increase in risk. Meta-analysis²³ of cohort and case-control studies combined have reported moderately increased risks of colorectal cancer, with a dose-response relation for rising alcohol consumption. A pooled analysis²⁴ of eight cohort studies recorded a dose-response relation between risk of colorectal cancer and amount of alcohol consumption. These analyses^{23,24} did not detect any differences in risk for type of alcoholic drink or in risk of colon cancer versus that for rectal cancer.

Dietary factors such as low folate intake are thought to increase the risk of colorectal cancer by 2–5 times,²⁵ and alcohol adversely affects folate metabolism.²⁶ Alcohol consumption and low folate intake might interact synergistically, or alcohol could act through folate metabolism to increase risk of colorectal cancer. Because the risk estimates suggest a moderate association between alcohol and risk of colorectal cancer, residual confounding by such dietary factors is of concern.

The risk estimates from the pooled analysis²⁴ of cohort studies were adjusted for multivitamin use and folate intake from food, and a clear dose-response relation was recorded for alcohol intake and risk of colorectal cancer. In stratified analysis,²⁴ risk of colorectal cancer due to alcohol was slightly, but not significantly, higher for individuals who did not use multivitamins, who were in the lowest tertile for folate intake, who were in the lowest two tertiles for methionine intake, and who were current or past smokers. Interactions with alcohol consumption were not suggested for multivitamin use, folate intake, methionine intake, or smoking status on risk of colorectal cancer.²⁴ That residual confounding accounts entirely for the recorded increases in risk of colorectal cancer with alcohol consumption is doubtful. Thus, we conclude that although effects might be moderate, there seems to be a causal relation between alcohol consumption and risk of colorectal cancer.

Liver cancer

Heavy alcohol intake increases the risk of hepatocellular carcinoma. Dose-response relations for the amount of alcohol consumed and risk of hepatocellular carcinoma have been shown by a meta-analysis,²⁷ which reported a 1.8-times increase in risk for the heaviest drinkers (ie, 100 g a day). This study²⁷ also showed that alcohol consumption was a strong risk factor for liver cirrhosis, with a 27-times increase in risk on drinking 100 g a day.

The most probable mechanism of alcohol-related liver carcinogenicity is through development of liver cirrhosis, although other events such as changes in hepatic metabolism of carcinogens might have a role. Alcohol-associated liver cirrhosis is probably the most important risk factor for hepatocellular carcinoma in populations with low prevalence of infection with hepatitis B virus and hepatitis C virus such as the USA and northern Europe. Risk of liver cancer is thought to be affected by synergistic interactions between tobacco and alcohol and between hepatitis B virus or hepatitis C virus and alcohol.¹²

Pancreatic cancer

Although most studies that have assessed the association between alcohol and pancreatic cancer have been negative, a few studies have recorded an increased risk. A meta-analysis²⁸ of 17 studies found no association between alcohol intake and pancreatic-cancer risk. The positive studies reported an increased risk for heavy alcohol drinkers: in one study,²⁹ for example, risk of pancreatic cancer was increased 3-times for individuals who drank four or more drinks a day. Since tobacco smoking is a strong risk factor for pancreatic cancer, residual confounding cannot be ruled out in these studies. The available evidence for an association between pancreatic cancer and alcohol consumption is not convincing. However, if such an association exists, a probable mechanism is through development of chronic pancreatitis as a result of drinking alcohol.

Breast cancer

Several studies have noted an association between alcohol consumption and risk of breast cancer. In a meta-analysis³⁰ of 38 epidemiological studies, rounded pooled risk estimates were 1.1 (95% CI 1.1–1.2) for one alcoholic drink a day, 1.2 (1.1–1.3) for two drinks a day, and 1.4 (1.2–1.6) for three or more drinks a day, compared with non-drinkers. A pooled analysis³¹ of six cohort studies reported similarly modest increases in risk, with a dose-response relation after adjustment for major risk factors of breast cancer, such as reproductive factors or a family history of cancer. A comprehensive assessment³² of 53 epidemiological studies (58 515 patients with breast cancer) reported an increased risk of 7.1% (5.5–8.7) for every additional 10 g a day increase in alcohol intake. Furthermore, the effect of alcohol on breast-cancer risk was the same in women who smoked as for those who had never smoked. Differences in risk by type of alcohol drink have not been noted.³³ The association between alcohol consumption and risk of breast cancer has been reported for both premenopausal and postmenopausal women, and whether the period of life in which drinking occurs modifies the carcinogenic effect of alcohol is unknown.³³ Although the magnitude of excess risk of breast cancer due to alcohol is not very large, the high incidence of this cancer results in more

women with breast cancer attributable to alcohol than for any other type of cancer.³⁴

Lung cancer

An association between alcohol consumption and lung cancer has been postulated, but current evidence is insufficient, according to a review of eight case-control studies and nine cohort studies.³⁵ A meta-analysis³⁶ of alcohol consumption and risk of lung cancer did not find strong evidence, although an increased risk with heavy consumption could not be excluded. The same conclusion was derived from a pooled analysis³⁷ of data from seven prospective studies, from which the strongest effect of alcohol was noted for men who did not smoke, suggesting that residual confounding by tobacco smoking can be ruled out as an explanation for the increased risk of lung cancer for heavy drinkers.

Other cancers

Alcohol does not seem to increase the risk of endometrial,³⁸ bladder,³⁹ or prostate cancer.⁴⁰ A possible protective effect of alcohol on risk of ovarian and kidney cancer needs further investigation.^{41,42} A pooled analysis⁴³ of nine case-control studies of non-Hodgkin lymphoma reported a reduced risk for alcohol drinkers—an effect that might differ by lymphoma type, which would partly explain inconsistencies between previously reported results for alcohol and lymphoma.

Genetic susceptibility to alcohol-related cancer

Evidence suggests that the risk of cancer for alcohol drinkers is modulated by genetic factors. Research has focused on variants in genes for alcohol metabolism, folate metabolism, and DNA repair.

Genes for alcohol metabolism

Alcohol dehydrogenases (ADH) are enzymes that oxidate ethanol to acetaldehyde.⁴⁴ Subsequent oxidation of acetaldehyde to acetate is catalysed by enzymes called aldehyde dehydrogenases (ALDH). Efficiency in the conversion of ethanol to acetaldehyde, and subsequent oxidation to acetate, is mainly determined by the ADH and ALDH gene families; potential differences between individuals exist in acetaldehyde exposure as a result of common, functional genetic variants.

The functionally important polymorphic sites for *ADH1B* (previously called *ADH2*) are thought to be Arg48His (accession number rs1229984) in exon 3 and Arg370Cys (accession number rs2066702) in exon 9.⁴⁴ Histidine at aminoacid position 48 constitutes the *2 allele, and cysteine at position 370 constitutes the *3 allele; the *1 allele is the wildtype haplotype, which corresponds to arginine at positions 48 and 370. The functionally important polymorphic sites for *ADH1C* (previously called *ADH3*) are thought to be Ile350Val (accession number rs698) and Arg272Gln (accession number rs1693482); valine at codon 350 and glutamine

at codon 272 constitute the *ADH1C**1 allele.⁴⁴ This allele and the *ADH1B**2 allele encode enzymes that result in fast metabolism of ethanol. *ADH1C**1 increases ethanol oxidation by about 2.5 times compared with *ADH1C**2 (ie, isoleucine at aminoacid position 350), and *ADH1B**2 and *ADH1B**3 increase ethanol oxidation by 40 times and 90 times, respectively, compared with *ADH1B**1.⁴⁵ *ADH1B* and *ADH1C* are only 16 kb apart on chromosome 4, and linkage disequilibrium between *ADH1C**1 and *ADH1B**2 has been shown in several populations.⁴⁶

ADH1B has not been associated with alcohol-related cancer in European populations,^{47,48} and studies of breast cancer⁴⁷ and laryngeal cancer⁴⁸ reported no effect of polymorphisms in this gene and risk of alcohol-related cancer. Studies⁴⁹ of Asian populations, although of small sample size, have consistently associated the *ADH1B**1 allele with an increased risk of oesophageal cancer.

Studies⁴⁴ in populations of European origin have focused on *ADH1C*, and in particular there is little evidence of a strong effect of this gene on risk of head and neck cancer. A pooled analysis⁴⁴ of seven published case-control studies (1325 cases and 1760 controls) found no increased risk of head and neck cancer for the *ADH1C* Ile350Val polymorphism (ie, *1 allele), although an interaction of this genotype and alcohol consumption was noted. Subsequent published studies of *ADH1C* have mostly reported null results for head and neck cancer. For other cancers, two studies of colorectal cancer lend support to modification of risk with alcohol consumption by the *ADH1C**1 allele. Studies of breast cancer have found no such modification of risk by ADH genes.

ALDH2 contains an inactive Glu487Lys (also known as Glu504Lys; accession number rs671) small-nucleotide polymorphism: lysine at aminoacid position known as the *2 allele. Homozygote *2 carriers (ie, Lys/Lys) are unable to oxidise acetaldehyde, and heterozygote carriers (ie, Lys/Glu) do so inefficiently.⁵⁰ Because the ALDH2 isoenzyme is a tetramer, only one of every 16 ALDH2 enzymes is functional in heterozygous individuals.⁵¹ Thus, individuals homozygous or heterozygous for *ALDH2**2 have a build-up of acetaldehyde, resulting in a toxic reaction that includes hot flushes, increased heart rate, and nausea. *ALDH2**2 is frequently found in Asian populations, whereas nearly all Europeans are homozygous for the *ALDH2**1 allele (ie, Gln/Gln).⁴⁴ Studies in Japan⁴⁹ have consistently reported an increased risk of oral, pharyngeal, laryngeal, and oesophageal cancer linked to the *ALDH2**2 allele. Although the study of genetic variation in genes that metabolise alcohol and risk of cancer is a promising area of research, whether the recorded associations are true and whether they will have clinical or public-health relevance is unclear at present.

Cytochrome P-450 2E1 (CYP2E1) is induced by ethanol, and oxidises ethanol into acetaldehyde and activates tobacco procarcinogens including nitrosamines.¹⁷ Sever-

Potential target organs	
Strong evidence	
DNA damage by acetaldehyde	Head and neck, oesophagus, and liver
Increased oestrogen concentration	Breast
Moderate evidence	
Solvent for other carcinogens	Head and neck, and oesophagus
Production of reactive-oxygen species and nitrogen species	Liver and others
Changes in folate metabolism	Colon and rectum, breast, and others
Weak evidence	
DNA damage by ethanol	Head and neck, oesophagus, and liver
Nutritional deficiencies (eg, in vitamin A)	Head and neck, and others
Reduced immune surveillance	Liver and others
Carcinogenicity of constituents other than ethanol	Head and neck, oesophagus, liver, and others
Classifications are subjective on the basis of strength of evidence.	

Table 2: Possible mechanisms of carcinogenicity of alcoholic drinks

al polymorphisms have been identified: *RsaI* (accession number rs2031920), *DraI* (accession number rs6413432), and *TaqI* (accession number rs2070676). For *RsaI*, the *c2* allele is thought to have lower enzyme activity than does the *c1* allele; the functional relevance of *DraI* and *TaqI* polymorphisms are unclear. A meta-analysis⁵² of five studies on the CYP2E1 *RsaI* polymorphism and risk of oesophageal cancer, and a meta-analysis⁵³ of all three CYP2E1 polymorphisms and risk of hepatocellular cancer, recorded no associations. Several investigators have focused on CYP2E1 polymorphisms and risk of cancers of the head and neck, breast, and colorectum, but conclusions on such associations cannot be made.

Genes for folate metabolism

Methylenetetrahydrofolate reductase (*MTHFR*) converts 5,10-methylenetetrahydrofolate to 5-methylenetetrahydrofolate, which is important for DNA synthesis and methylation. Research on sequence variants in *MTHFR* has focused mainly on the 677C>T (accession number rs1801133) variant, which reduces enzyme activity. A review⁵⁴ of ten studies of this variant and risk of colon cancer reported that the results lend support to a moderately protective effect for the TT genotype.

An interaction has been noted between the *MTHFR* 677C>T polymorphism and folate or alcohol consumption and risk of colorectal cancer.⁵⁴ In particular, the TT genotype seems to be protective only in individuals who were non-drinkers or light drinkers. *MTHFR* 677C>T has also been studied for other cancers including breast, head and neck, oesophageal, and pancreatic, but findings to date are inconclusive.

DNA-repair genes

Sequence variants in genes such as *XPC*, *ERCC2*, and *ERCC1* of the nucleotide-excision pathway, and *XRCC1* and *OGG1* on the base-excision pathway have been

studied as susceptibility factors for various cancers. Research has focused on sequence variants that change the activity of DNA-repair enzymes (eg, *OGG1* Ser326Cys; accession number rs1052134) or variants located in evolutionarily conserved regions (eg, *XRCC1* Arg194Trp (accession number rs1799782) and Arg399Gln; accession number rs25487).

Studies of head and neck cancer have assessed interactions between sequence variants in DNA-repair genes and alcohol consumption, and differences in risks due to these variants by alcohol-drinking status. Strong interactions have not been reported; however, small, usually insignificant differences in risk were noted between current drinkers and non-drinkers for sequence variants in *XRCC1*, *OGG1*, *XPC*, and *ERCC2*.⁵⁵ Risks associated with *XRCC1* polymorphisms seem to differ by alcohol-drinking status for other cancers such as those of the oesophagus and colorectum. However, these studies had small sample sizes and thus might have had insufficient power to detect a gene–environment interaction.

Mechanisms of alcohol carcinogenicity

The mechanisms by which alcoholic drinks exert their carcinogenic effect are not understood fully and probably differ by target organ, as do other carcinogens that act at many sites. Table 2 lists known or suspected mechanisms of carcinogenicity of alcoholic drinks, together with our subjective assessment of the strength of the available evidence.

Pure ethanol does not act as a carcinogen in animal studies,^{1,2} and thus alcoholic drinks might act as a solvent for penetration of carcinogens through the mucosa of upper aerodigestive organs.⁵⁶ Although this mechanism would explain the synergistic effect of tobacco smoking and alcohol drinking, it could not account for the increased risk noted for never-smokers.

The primary metabolite of ethanol—acetaldehyde—is a plausible candidate for the carcinogenic effect of alcoholic drinks, although evidence for acetaldehyde as a direct cause of cancer in human beings is weak.⁵⁷ Acetaldehyde forms adducts with DNA in human cells in vitro,⁵⁸ and in rats who had lifetime exposure to ethanol.⁵⁹ In animal studies,⁵⁷ acetaldehyde inhalation causes tumours of the respiratory tract, particularly adenocarcinomas and squamous-cell carcinomas of the nasal mucosa in rats and laryngeal carcinomas in hamsters. Furthermore, acetaldehyde damages hepatocytes, leading to increased proliferation.⁶⁰ In a study⁶¹ of 24 heavy alcohol users and 12 controls, the mean number of acetaldehyde–DNA adducts in lymphocytes was 7-times higher in the alcohol users than in controls. Autoantibodies against acetaldehyde-modified proteins have been detected in blood and bone marrow of heavy alcohol users,⁶² and autoantibody concentrations are higher in patients with alcohol-induced liver disease than in either non-drinking

controls or in heavy drinkers without liver disease.⁶³ Overall, these studies suggest that DNA damage occurs in human beings after heavy alcohol consumption, and that such damage can be caused by acetaldehyde. Increasing evidence of a role for polymorphisms in enzymes for oxidation of ethanol and acetaldehyde in the modulation of alcohol-related cancer risk lends further support to a mechanistic role for acetaldehyde.

Production of reactive oxygen species and nitrogen species is a possible mechanism of alcohol-related carcinogenesis.⁶⁴ Oxidative stress leads to lipid peroxidation, the products of which are reactive electrophilic compounds that react with DNA to form exocyclic DNA adducts⁶⁵ and reactive aldehydes. This mechanism is particularly relevant for liver carcinogenesis and might explain the synergistic effect of alcohol and viral infection. In the liver, oxidative stress is induced by alcohol through induction of CYP2E1, stimulation of parenchymal cells in response to cytokines, and activation of Kupffer cells.⁶⁶

Heavy alcohol use might lead to nutritional deficiencies by reduced intake of foods rich in micronutrients,⁶⁷ by impaired intestinal absorption, and by changes in metabolic pathways. The most relevant effect seems to be on folate metabolism, which changes DNA methylation and thus the control of genes with a potential role in carcinogenesis.⁶⁸ Alcohol might affect intake, absorption, and metabolism of vitamin B12 and vitamin B6, resulting in further changes in DNA-methylation pathways. Deficiency in vitamin A has also been proposed as an alcohol-mediated carcinogenic mechanism. Heavy alcohol users have a low concentration of serum vitamin A and β -carotene,⁶⁹ and metabolism of vitamin A is changed by chronic alcohol intake.⁷⁰ Alcohol drinking can reduce immune surveillance, thus favouring cancer development and metastatic potential.⁷¹ Data for alcohol-exposed mice that shows reduced resistance to metastasis lends support to this idea.⁷²

Components of alcoholic drinks other than ethanol, including impurities and contaminants, might increase cancer risk. Polycyclic aromatic hydrocarbons have been found in hard liquors (eg, whiskey), and N-nitrosoamines have been identified in beers;¹² however, information on the ingredients of alcoholic beverages, especially hard liquors, is limited. If the components of alcoholic beverages were important contributors to carcinogenicity, risk may vary by type of drink. However, the relation between type of alcoholic drink and cancer of the head and neck is inconsistent, and no adequate data exist for other target organs.

The mechanisms discussed above apply mainly to head and neck, liver, and colorectal carcinogenesis. For breast cancer, alcohol carcinogenicity is thought to be due to increased oestrogen concentration.³³ Evidence is strongest for postmenopausal women who use hormone-replacement therapy, but data suggest an effect in other groups of women too. Other possible

mechanisms for breast cancer include increased susceptibility to endogenous and exogenous carcinogens, enhanced potential for invasiveness,³³ and an effect mediated by folate metabolism. Epidemiological data for increased risk of breast cancer for women who drink alcohol are consistent with animal studies that have shown increased incidence of spontaneous and chemically induced breast tumours in rats and mice.⁷³

Conclusion

Alcohol consumption is one of the most important known causes of human cancer after tobacco smoking, chronic infections, and possibly obesity. With the exception of aflatoxin, for no dietary factor is there such strong and consistent evidence for carcinogenicity. In central and eastern Europe, the burden of alcohol-associated cancer, and of other alcohol-associated disease, is substantial. Alcohol consumption is increasing rapidly in many parts of the world, such as east Asia.² For breast cancer and colorectal cancer, a causal association with alcohol consumption has been established only in the past 10–15 years, and the implications of these associations for public health have not been elucidated fully. In many countries, people of low income or education consume more alcohol than do those of high income and education, which contributes to social inequalities in cancer burden.⁷⁴

Despite its importance in human carcinogenesis, research on alcohol and cancer remains limited in terms of clinical, epidemiological, and experimental settings. Priorities for research on alcohol-related carcinogenicity include: better epidemiological studies of the effect of drinking patterns (in particular binge drinking, the frequency of which is increasing in many countries)⁷⁵ and of specific alcoholic drinks; investigations of the risk of cancer in suspected target organs, including the pancreas and kidney; and elucidation of the role of genetic variants in modifying the risk of alcohol-associated cancer, which would elucidate possible mechanisms of action.

A tool that has been proposed in recent years to overcome some limitations of the human evidence is the establishment of consortia of studies of molecular and genetic epidemiology. One example is the INHANCE (international head and neck cancer epidemiology) consortium of epidemiological studies of head and neck cancer (<http://inhance.iarc.fr>), which aims to address research questions that are difficult to answer in individual studies. The pooling of data greatly enhances the power to investigate patterns of alcohol consumption for never-smokers and of gene–environment interactions.

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 example, the most recent version of the European code

Search strategy and selection criteria

We searched Medline using the keywords “alcohol drinking”, “neoplasms”, and “risk factor” from 1966 to 2005. There were no language restrictions.

against cancer¹ recommends keeping daily consumption within two drinks (ie, 20–30 g alcohol) for men and one drink for women. Total avoidance of alcohol, although optimum for cancer control, cannot be recommended in terms of a broad perspective of public health, in particular in countries with high incidence of cardiovascular disease.

Conflict of interest

We declare no conflicts of interest.

References

- Boyle P, Autier P, Bartelink H, et al. European code against cancer and scientific justification: third version (2003). *Ann Oncol* 2003; **14**: 973–1005.
- World Health Organization. Global status report on alcohol. Geneva: World Health Organization, 1999.
- Bray I, Brennan P, Boffetta P. Projections of alcohol- and tobacco-related cancer mortality in Central Europe. *Int J Cancer* 2000; **87**: 122–28.
- Merikangas KR, Mehta RL, Molnar BE, et al. Comorbidity of substance use disorders with mood and anxiety disorders: results of the International Consortium in Psychiatric Epidemiology. *Addict Behav* 1998; **23**: 893–907.
- Rehm J, Room R, Monteiro M, et al. Alcohol use. In: Ezzati M, Murray C, Lopez AD, Rodgers A (eds). Comparative quantification of health risks: global and regional burden of disease attributable to selected major risk factors. Geneva: World Health Organization, 2004: 959–1108.
- Keil U, Liese A, Filipiak B, et al. Alcohol, blood pressure and hypertension. *Novartis Found Symp* 1998; **216**: 125–44.
- Reynolds K, Lewis B, Nolen JDL, et al. Alcohol consumption and risk of stroke: a meta-analysis. *JAMA* 2003; **289**: 579–88.
- Corrao G, Bagnardi V, Zambon A, Torchio P. Meta-analysis of alcohol intake in relation to risk of liver cirrhosis. *Alcohol Alcoholism* 1998; **33**: 381–92.
- Thakker KD. An overview of health risks and benefits of alcohol consumption. *Alcoholism Clin Exper Res* 1998; **22**: S285–98.
- Connor PD, Streissguth AP. Effects of prenatal exposure to alcohol across the life span. *Alcohol Health Res World* 1996; **20**: 170–74.
- Corrao G, Rubbiati L, Bagnardi V, et al. Alcohol and coronary heart disease: a meta-analysis. *Addiction* 2000; **95**: 1505–23.
- International Agency for Research on Cancer. Alcohol drinking. IARC monographs on the evaluation of carcinogenic risks to humans, vol 44. Lyon: IARC, 1988.
- Ng SK, Kabat GC, Wynder EL. Oral cavity cancer in non-users of tobacco. *J Natl Cancer Inst* 1993; **85**: 743–45.
- Fioretti F, Bosetti C, Tavani A, et al. Risk factors for oral and pharyngeal cancer in never smokers. *Oral Oncol* 1999; **35**: 375–78.
- Castellsague X, Munoz N, De Stefani E, et al. Independent and joint effects of tobacco smoking and alcohol drinking on the risk of oesophageal cancer in men and women. *Int J Cancer* 1999; **82**: 657–64.
- Bosetti C, Gallus S, Franceschi S, et al. Cancer of the larynx in non-smoking alcohol drinkers and in non-drinking tobacco smokers. *Br J Cancer* 2002; **87**: 516–18.
- Brennan P, Boffetta P. Mechanistic considerations in the molecular epidemiology of head and neck cancer. In: Buffler P, Rice J, Baan R, et al (eds). Mechanisms of carcinogenesis: contributions of molecular epidemiology. International Agency for Research on Cancer scientific publication number 157. Lyon: IARC, 2004: 393–414.
- Wu AH, Wan P, Bernstein L. A multiethnic population-based study of smoking, alcohol and body size and risk of adenocarcinomas of the stomach and esophagus. *Cancer Causes Control* 2001; **12**: 721–32.
- Zaridze D, Borisova E, Maximovitch D, Chkhikvadze V. Alcohol consumption, smoking and risk of gastric cancer: case-control study from Moscow, Russia. *Cancer Causes Control* 2000; **11**: 363–71.
- D’Avanzo B, La Vecchia C, Franceschi S. Alcohol consumption and the risk of gastric cancer. *Nutr Cancer* 1994; **22**: 57–64.
- De Stefani E, Boffetta P, Carzoglio J, et al. Tobacco smoking and alcohol drinking as risk factors for stomach cancer: a case-control study in Uruguay. *Cancer Causes Control* 1998; **9**: 321–29.
- Franceschi S, La Vecchia C. Alcohol and the risk of cancers of the stomach and colon-rectum. *Dig Dis* 1994; **12**: 276–89.
- Corrao G, Bagnardi V, Zambon A, Arico S. Exploring the dose-response relationship between alcohol consumption and the risk of several alcohol-related conditions: a meta-analysis. *Addiction* 1999; **94**: 551–73.
- Cho E, Smith-Warner SA, Ritz J, et al. Alcohol intake and colorectal cancer: a pooled analysis of 8 cohort studies. *Ann Intern Med* 2004; **140**: 603–13.
- Giovannucci E. Epidemiologic studies of folate and colorectal neoplasia: a review. *J Nutr* 2002; **132** (suppl 8): 2350S–55S.
- Giovannucci E. Alcohol, one-carbon metabolism, and colorectal cancer: recent insights from molecular studies. *J Nutr* 2004; **134**: 2475S–81S.
- 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**: 613–9.
- Bagnardi V, Blangiardo M, La Vecchia C, Corrao G. A meta-analysis of alcohol drinking and cancer risk. *Br J Cancer* 2001; **85**: 1700–05.
- Zheng W, McLaughlin JK, Gridley G, et al. A cohort study of smoking, alcohol consumption, and dietary factors for pancreatic cancer (United States). *Cancer Causes Control* 1993; **4**: 477–82.
- Longnecker MP. Alcoholic beverage consumption in relation to risk of breast cancer: meta-analysis and review. *Cancer Causes Control* 1994; **5**: 73–82.
- Smith-Warner SA, Spiegelman D, Yaun SS, et al. Alcohol and breast cancer in women: a pooled analysis of cohort studies. *JAMA* 1998; **279**: 535–40.
- Hamajima N, Hirose K, Tajima K, et al. Alcohol, tobacco and breast cancer—collaborative reanalysis of individual data from 53 epidemiological studies, including 58 515 women with breast cancer and 95 067 women without the disease. *Br J Cancer* 2002; **87**: 1234–45.
- Singletary KW, Gapstur SM. Alcohol and breast cancer: review of epidemiologic and experimental evidence and potential mechanisms. *JAMA* 2001; **286**: 2143–51.
- Alcohol—attributable deaths and years of potential life lost—United States, 2001. *MMWR Morb Mortal Wkly Rep* 2004; **53**: 866–70.
- Bandera EV, Freudenheim JL, Vena JE. Alcohol consumption and lung cancer: a review of the epidemiologic evidence. *Cancer Epidemiol Biomarkers Prev* 2001; **10**: 813–21.
- Korte JE, Brennan P, Henley SJ, Boffetta P. Dose-specific meta-analysis and sensitivity analysis of the relation between alcohol consumption and lung cancer risk. *Am J Epidemiol* 2002; **155**: 496–506.
- Freudenheim JL, Ritz J, Smith-Warner SA, et al. Alcohol consumption and risk of lung cancer: a pooled analysis of cohort studies. *Am J Clin Nutr* 2005; **82**: 657–67.
- Bandera EV, Kushi LH, Olson SH, et al. Alcohol consumption and endometrial cancer: some unresolved issues. *Nutr Cancer* 2003; **45**: 24–29.
- Kogevinas M, Trichopoulos D. Urinary bladder cancer. In: Adami HO, Hunter D, Trichopoulos D (eds). Textbook of cancer epidemiology. New York: Oxford University Press, 2002: 446–66.
- Dennis LK. Meta-analysis for combining relative risks of alcohol consumption and prostate cancer. *Prostate* 2000; **42**: 56–66.
- Gertig D, Hunter D. Ovarian cancer. In: Adami HO, Hunter D, Trichopoulos D (eds). Textbook of cancer epidemiology. New York: Oxford University Press, 2002: 378–99.

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- 42 Lindblad P, Adami HO. Kidney cancer. In: Adami HO, Hunter D, Trichopoulos D (eds). Textbook of cancer epidemiology. New York: Oxford University Press, 2002: 467–85.
- 43 Morton LM, Zheng T, Holford TR, et al. Alcohol consumption and risk of non-Hodgkin lymphoma: a pooled analysis. *Lancet Oncol* 2005; **6**: 469–76.
- 44 Brennan P, Lewis S, Hashibe M, et al. Pooled analysis of alcohol dehydrogenase genotypes and head and neck cancer: a HuGE review. *Am J Epidemiol* 2004; **159**: 1–16.
- 45 Bosron WF, Crabb DW, Li TK. Relationship between kinetics of liver alcohol dehydrogenase and alcohol metabolism. *Pharmacol Biochem Behav* 1983; **18** (suppl 1): 223–27.
- 46 Osier M, Pakstis AJ, Kidd JR, et al. Linkage disequilibrium at the *ADH2* and *ADH3* loci and risk of alcoholism. *Am J Hum Genet* 1999; **64**: 1147–57.
- 47 Lilla C, Koehler T, Kropp S, et al. Alcohol dehydrogenase 1B (*ADH1B*) genotype, alcohol consumption and breast cancer risk by age 50 years in a German case-control study. *Br J Cancer* 2005; **92**: 2039–41.
- 48 Risch A, Ramroth H, Raedts V, et al. Laryngeal cancer risk in caucasians is associated with alcohol and tobacco consumption but not modified by genetic polymorphisms in class I alcohol dehydrogenases *ADH1B* and *ADH1C*, and glutathione-S-transferases *GSTM1* and *GSTT1*. *Pharmacogenetics* 2003; **13**: 225–30.
- 49 Yokoyama A, Omori T. Genetic polymorphisms of alcohol and aldehyde dehydrogenases and risk for esophageal and head and neck cancers. *Jpn J Clin Oncol* 2003; **33**: 111–21.
- 50 Novoradovsky A, Tsai SJ, Goldfarb L, et al. Mitochondrial aldehyde dehydrogenase polymorphism in Asian and American Indian populations: detection of new *ALDH2* alleles. *Alcohol Clin Exp Res* 1995; **19**: 1105–10.
- 51 Osier MV, Pakstis AJ, Soodyall H, et al. A global perspective on genetic variation at the ADH genes reveals unusual patterns of linkage disequilibrium and diversity. *Am J Hum Genet* 2002; **71**: 84–99.
- 52 Yang CX, Matsuo K, Wang ZM, Tajima K. Phase I/II enzyme gene polymorphisms and esophageal cancer risk: a meta-analysis of the literature. *World J Gastroenterol* 2005; **11**: 2531–38.
- 53 Wong NA, Rae F, Simpson KJ, et al. Genetic polymorphisms of cytochrome p4502E1 and susceptibility to alcoholic liver disease and hepatocellular carcinoma in a white population: a study and literature review, including meta-analysis. *Mol Pathol* 2000; **53**: 88–93.
- 54 Sharp L, Little J. Polymorphisms in genes involved in folate metabolism and colorectal neoplasia: a HuGE review. *Am J Epidemiol* 2004; **159**: 423–43.
- 55 Hung RJ, Van der Hel O, Tavtigian SV, et al. Perspectives on the molecular epidemiology of aerodigestive tract cancers. *Mutat Res* published online July 12, 2005. DOI: 10.1016/j.mrfmmm.2005.06.007.
- 56 Wight AJ, Ogdan GR. Possible mechanisms by which alcohol may influence the development of oral cancer—a review. *Oral Oncol* 1998; **34**: 441–47.
- 57 International Agency for Research on Cancer. Acetaldehyde. IARC monographs on the evaluation of carcinogenic risks to humans. Re-evaluation of some organic chemicals, hydrazine and hydrogen peroxide (part two). Volume 71. Lyon: IARC, 1999: 319–35.
- 58 Vaca CE, Nilsson JA, Fang JL, Grafstrom RC. Formation of DNA adducts in human buccal epithelial cells exposed to acetaldehyde and methylglyoxal in vitro. *Chem Biol Interact* 1998; **108**: 197–208.
- 59 Rintala J, Jaatinen P, Parkkila S, et al. Evidence of acetaldehyde–protein adduct formation in rat brain after lifelong consumption of ethanol. *Alcohol Alcohol* 2000; **35**: 458–63.
- 60 Clemens DL, Forman A, Jerrells TR, et al. Relationship between acetaldehyde levels and cell survival in ethanol-metabolizing hepatoma cells. *Hepatology* 2002; **35**: 1196–204.
- 61 Fang JL, Vaca CE. Detection of DNA adducts of acetaldehyde in peripheral white blood cells of alcohol abusers. *Carcinogenesis* 1997; **18**: 627–32.
- 62 Latvala J, Parkkila S, Melkko J, Niemela O. Acetaldehyde adducts in blood and bone marrow of patients with ethanol-induced erythrocyte abnormalities. *Mol Med* 2001; **7**: 401–05.
- 63 Viitala K, Makkonen K, Israel Y, et al. Autoimmune responses against oxidant stress and acetaldehyde-derived epitopes in human alcohol consumers. *Alcohol Clin Exp Res* 2000; **24**: 1103–09.
- 64 Molina PE, Hoek JB, Nelson S, et al. Mechanisms of alcohol-induced tissue injury. *Alcohol Clin Exp Res* 2003; **27**: 563–75.
- 65 el Ghissassi F, Barbin A, Nair J, et al. Formation of 1,N6-ethenoadenine and 3,N4-ethenocytosine by lipid peroxidation products and nucleic acid bases. *Chem Res Toxicol* 1995; **8**: 278–83.
- 66 Hoek JB, Pastorino JG. Ethanol, oxidative stress, and cytokine-induced liver cell injury. *Alcohol* 2002; **27**: 63–68.
- 67 Lieber CS. Relationships between nutrition, alcohol use, and liver disease. *Alcohol Res Health* 2003; **27**: 220–31.
- 68 Voigt MD. Alcohol in hepatocellular cancer. *Clin Liver Dis* 2005; **9**: 151–69.
- 69 Leo MA, Lieber CS. Alcohol, vitamin A, and beta-carotene: adverse interactions, including hepatotoxicity and carcinogenicity. *Am J Clin Nutr* 1999; **69**: 1071–85.
- 70 Wang XD. Retinoids and alcohol-related carcinogenesis. *J Nutr* 2003; **133**: 287S–90S.
- 71 Cook RT. Alcohol abuse, alcoholism, and damage to the immune system—a review. *Alcohol Clin Exp Res* 1998; **22**: 1927–42.
- 72 Wu WJ, Pruett SB. Suppression of splenic natural killer cell activity in a mouse model for binge drinking. I. Direct effects of ethanol and its major metabolites are not primarily responsible for decreased natural killer cell activity. *J Pharmacol Exp Ther* 1996; **278**: 1325–30.
- 73 Singletary KW, Gapstur SM. Alcohol and breast cancer: review of epidemiologic and experimental evidence and potential mechanisms. *JAMA* 2001; **286**: 2143–51.
- 74 Møller H, Tønnesen H. Alcohol drinking, social class and cancer. In: Kogevinas M, Pearce N, Susser M, Boffetta P (eds). Social inequalities and cancer. International Agency for Research on Cancer scientific publication number 138. Lyon: IARC, 1997: 251–63.
- 75 Kuntsche E, Rehm J, Gmel G. Characteristics of binge drinkers in Europe. *Social Science and Medicine* 2004; **59**: 113–27.