Alcohol, Alcoholism, and Cancer

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Internists frequently do not think of cancer when contemplating the medical consequences of alcohol abuse. Perhaps this is because so many of these victims of alcohol are cared for by radiation oncologists or otolaryngologists. In prospective studies of alcoholics, cancer is one of the major causes of increased mortality and morbidity. Conversely, in studies of the epidemiology of cancer, alcohol is the second leading specifically identified cause of cancer, exceeded only by tobacco. There is a wealth of experimental and epidemiologic data elucidating the role of alcohol in causing cancer; these data will be reviewed. In addition, the impact of alcohol abuse on the management of the patient with cancer will be discussed.

ROLE OF ALCOHOL IN CARCINOGENESIS

Alcohol might be associated with cancer in a variety of ways. Alcohol might potentiate the carcinogenic action of some other agents and hence function as a co-carcinogen. Alternatively, it might act after the initial carcinogenic process and serve as a promoter of tumor growth. Finally, the consumption of alcoholic beverages might simply correlate with the cause of the cancer, making alcohol an innocent bystander. Each of these possible roles for alcohol has some evidence to support it. The following sections will discuss the in vitro, animal model, and epidemiologic data relevant to elucidating the role of alcohol carcinogenesis. The data have been well reviewed by both Lieber and Obe. Carcinogen

Modern theories of chemical carcinogenesis distinguish the action of a primary carcinogen ("initiator") from the action of a substance which encourages the growth by which a tumor becomes clinically apparent ("promoter"). Tumor initiators are typically electrophilic molecules capable of acting directly on DNA to effect cellular genetic changes leading to neo-

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plasia. These substances are usually active in animal and in vitro tests of mutagenicity, such as the Ames Salmonella mutagenicity test.\textsuperscript{2}\textsuperscript{,} Chemicals, such as ethyl alcohol do not fit the profile of tumor initiators, and it is negative in both the Ames mutagenicity test and the sister chromatid exchange test, another widely used in vitro screening test for carcinogens.\textsuperscript{36,} \textsuperscript{52} Although there is evidence that alcohol is teratogenic in both animal models and human beings, this is convincingly seen at only high levels of exposure and most likely reflects a complex process not obviously related to tumor initiation.\textsuperscript{1,} \textsuperscript{28} Abnormal chromosomes have been found in the peripheral blood leukocytes of chronic alcoholics.\textsuperscript{52} However, the potential causes of this are multiple (including folate deficiency) and these findings cannot be construed as being due to a mutagenic effect of alcohol. Most reviewers agree that there are no convincing data that alcohol is itself a primary carcinogen.\textsuperscript{43,} \textsuperscript{53}

Metabolites of ethyl alcohol have also been evaluated, and there is evidence that acetaldehyde can cause sister chromatid exchanges, although it is negative in the Ames mutagenicity test.\textsuperscript{42}

Another approach has been to look for carcinogens amongst the myriad chemicals present in alcoholic beverages. Such classic carcinogens as polycyclic hydrocarbons and nitrosamines have been documented in beer and hard liquors.\textsuperscript{74} The Ames mutagenicity test is positive for a variety of types of liquor, reflecting potentially carcinogenic activity for some of their constituents.\textsuperscript{38,} \textsuperscript{51}

Co-Carcinogen

Although alcohol is itself ineffective in tumor initiation, there is some evidence that it can act as a co-carcinogen, activating or potentiating the action of other substances capable of tumor initiation. One mechanism by which alcohol might so act is by solubilizing a true carcinogen (from food, tobacco smoke residue, or alcoholic beverages), allowing higher concentrations of the carcinogen to reach the target tissues. Although this mechanism is frequently mentioned, there are few experimental data to support it. Kuratsune and coworkers did show that benz[a]pyrene, a known carcinogen, did penetrate mouse esophageal mucosa better when dissolved in alcohol than when dissolved in olive oil. However, an aqueous solution was not demonstrably inferior to the alcohol solution in terms of penetration of the mucosa.\textsuperscript{30} Although these authors did see a number of esophageal cancers in mice given carcinogen-alcohol solutions, aqueous solutions were not tested.\textsuperscript{30} Hence, the importance of alcohol as solute in these experiments is not clear.

Another mechanism whereby alcohol could serve as a co-carcinogen is through effects on carcinogen activation or catabolism. It is well established that chronic ingestion of alcohol leads to increased levels of microsomal enzymes, both in liver and other tissues.\textsuperscript{57} It has been known for some time that microsomal preparations can activate certain carcinogens and that inducers of the cytochrome P-450 microsomal enzyme system potentiate this activation.\textsuperscript{58} It is also well known that this enzyme system is induced by ingestion of alcohol. It should therefore be no surprise that a variety of animal models have shown that alcohol increases hepatic microsomal activation of such mutagens as nitrosopyrrolidine and dimethylnitro-

\textsuperscript{samine}.\textsuperscript{18,} \textsuperscript{40} Animal models also show similar enhancement of carcinogen activation in tissues other than liver.\textsuperscript{37}

A slightly different co-carcinogenic mechanism for alcohol is that proposed for its interaction with vinyl chloride. Alcohol is thought to compete with vinyl chloride, blocking hepatic uptake and catabolism and hence increasing effective exposure to the carcinogen.\textsuperscript{41} An untested mechanism for co-carcinogenesis by alcohol would be through enhancement of the direct effects of a carcinogen, possibly through the known effects of alcohol on cell redox potential and NADH:NAD ratio. Such interactions have been reported for alcohol with regard to the cytotoxicity of both radiation and bleomycin.\textsuperscript{30,} \textsuperscript{40}

Promoter

By modern dogma, tumor promoters are not capable of initiating malignant change but may be necessary for development of the neoplasm after the action of the tumor initiator.\textsuperscript{47,} \textsuperscript{56} Tumor promoters are generally not electrophilic molecules with mutagenic activity. They do tend to be chronic irritants or otherwise cause tissue hyperplasia. Tumor promotion typically requires repeated or continuous exposure to the promoting agent over time, and, unlike tumor initiators, there may be a threshold of dose or time of exposure below which the promoting agent is entirely safe.\textsuperscript{56}

Although tumor promoting activity can be demonstrated in certain animal models, there is no in vitro test for this activity analogous to the Ames mutagenicity test. Another problem in identifying pure tumor-promoting agents is that many tumor initiators are also promoters (complete carcinogens) and that repeated exposure to promoting agents will increase the incidence of spontaneously initiated tumors. Thus, promoting activity is experimentally indistinguishable from activity as a complete carcinogen or co-carcinogen. Nevertheless, alcohol has been identified as a tumor promoter and there is considerable evidence to support this designation.\textsuperscript{50}

In animal models, alcoholic beverages have shown some tumor-promoting activity when applied topically.\textsuperscript{12,} \textsuperscript{31} Further evidence to support a promoting role for alcohol comes from epidemiologic studies. The association of cancers with alcoholic cirrhosis of the liver, and hence very prolonged use of alcohol, is consistent with action as a tumor promoter.\textsuperscript{29} Moreover, these cancers tend to occur either at sites of direct contact with ingested alcohol (mouth, pharynx, esophagus) or known sites of alcohol toxicity (liver), consistent with the chronic irritation caused by many promoting agents. Specifically, the work of Anderson suggests that atypia occurs throughout the oral mucosa, but that oral cancers develop in cavities where oral secretions (or ingested alcohol) would tend to pool.\textsuperscript{5} The strong association of hepatocellular carcinoma with alcohol and alcoholic cirrhosis also suggests a promoting role for alcohol, although other factors, such as chronic hepatitis B virus infection, may be operative.\textsuperscript{29,} \textsuperscript{37,} \textsuperscript{72}

Innocent Bystander

Despite the above experimental and clinical data, it is still possible that alcohol and cancer are not causally related, but are only associated via some third variable, which is the cause of the excess cancer. The most
obvious such association would be between alcohol and cigarette smoking. This will be dealt with in detail in later sections, but suffice it to say that cigarette smoking does not explain all of the excess cancers. Another obvious association is that between alcohol and diet. It is clear that a significant proportion of alcoholic patients have major nutritional deficiencies of folate, thiamine, pyridoxine, nicotinic acid, vitamin C, calcium, magnesium, phosphorus, and zinc, as well as protein-energy malnutrition. In an animal model, zinc deficiency clearly promotes the development of tumors. In epidemiologic studies, deficiency of vitamin A and C has been associated with cancer of the larynx and oral cavity. Also, vitamin and mineral deficiencies have been associated with esophageal cancer. These nutritional deficiencies almost certainly interact with alcohol, but it seems unlikely that they explain the majority of alcohol-related cancers.


dating variables must be recognized and the independent contribution of each be ascertained through appropriate stratification or multivariate analysis in order to draw meaningful conclusions.

Despite the above problems, many epidemiologic studies demonstrate a relationship between alcohol and cancer and meet accepted criteria for the evaluation of such associations.

GENERAL RESULTS

Magnitude of the Problem

Prospective studies of heavy drinkers and alcoholics show an overall increase of about 70 per cent in death from cancer. However, the majority of these excess deaths are related to the use of tobacco, and can be ascribed to the strong association of heavy drinking with heavy smoking. About 30 per cent of the excess cancer mortality was due to cancer in sites associated with alcohol, so that a generous estimate would be a 10 to 20 per cent increase in cancer mortality in heavy drinkers attributable to alcohol itself. In fact, Schmidt found no significant increase in cancer mortality attributable to alcohol when he used a group of veterans with similar smoking histories as controls. However, the use of this control group could be questioned (different geographic and socioeconomic group, unknown drinking history). In a series that used contemporaneous controls matched for smoking history, Klatky did find a 40 per cent excess cancer mortality in a group of heavy drinkers.

Approaching this question another way, one can calculate the proportion of given types of cancer attributable to alcohol, knowing the risk ratio for alcohol and the prevalence of alcohol abuse. These estimates give the same results: about 3 per cent of cancer deaths can be attributed to alcohol, with about 11,000 deaths per year from this cause.

Dose Response

Almost all the epidemiologic studies show an increased risk of cancer with increasing exposure to alcohol. For the most part, data are stratified, and it is difficult to ascertain the shape of the dose-response curve. The data of Tuyns for esophageal cancer are an exception and show a convincing logarithmic rise in the risk of cancer with increasing alcohol exposure. The data from a variety of studies on alcohol and cancer of the upper aerodigestive tract seem to be compatible with this dose-response relationship. The conclusion to be drawn is that the major portion of the risk of cancer from alcohol is with very heavy drinkers and that there may be a threshold of alcohol consumption which is relatively risk-free. This sort of relationship also suggests the role of alcohol as a tumor promoter, as discussed above. The situation is to be contrasted with that for tobacco: the risk is linearly proportional to exposure; there is no safe level of exposure, and the agent is known to be a complete carcinogen.

Type of Alcoholic Beverage

It is only reasonable to suppose that different types of alcoholic beverages would give different risks for cancer. However, there are scant data
to support this hypothesis. Many studies of cancer of the upper aerodigestive tract show a strong correlation with drinking hard liquors (whiskey, rum, apple brandy) but it is difficult to separate this observation from the dose-response effect, since most heavy drinkers drink hard liquor.\textsuperscript{3,36} The data of Marshberg are exceptional in that beer or wine is associated with a higher risk of oral cancer than whiskey; this divergent result may be due to the extremely heavy drinking habits of the control population, possibly a more appropriate test for studies of effect of type of beverage.\textsuperscript{35} Most writers conclude that type of beverage is of little importance compared with amount of alcohol.\textsuperscript{10,36} Of special interest here are the epidemiologic and in vitro studies of apple brandy, which has been shown to contain carcinogens and has been implicated in the high incidence of esophageal cancer in the Normandy region of France.\textsuperscript{36,69} Another possible special case is the recent report of a relationship between gastric cancer and red wine; other types of alcoholic beverages had a distinctly lower risk ratio than red wine.\textsuperscript{25}

Tobacco-Alcohol Interactions

The relationship between alcohol and tobacco in carcinogenesis of the upper aerodigestive tract has been of great interest. On a theoretical basis, a strongly synergistic interaction would support the concept of alcohol serving as a co-carcinogen by dissolving tobacco carcinogens and increasing mucosal concentrations of these substances. Practically, it would have public health implications, in that if there were strong synergy between the two risk factors, stopping either one would markedly decrease incidence. However, if the factors are independent, then stopping exposure to both alcohol and tobacco would be necessary to minimize incidence.

This problem has been studied by a number of investigators with somewhat dissimilar results. The data of Rothman on both laryngeal and oropharyngeal cancer indicate a "moderate" synergy. For laryngeal cancer there is about 50 per cent more risk of cancer seen with combined exposure than would be expected by the summed individual risk.\textsuperscript{10,66} The conclusion to be drawn is that both tobacco and alcohol are significant individual risks and that synergy is also present. Exposure to both would have to be eliminated to minimize risk. For oropharyngeal cancer, Rothman estimates that 43 per cent of disease can be attributed to alcohol, 33 per cent to smoking.\textsuperscript{65}

**SPECIFIC SITES**

**Head and Neck**

The association of squamous cell carcinoma of the head and neck region with excessive drinking of alcoholic beverages has been recognized since the nineteenth century.\textsuperscript{42} This association was given statistical support by a case-control study by Wynder in 1956, in which he demonstrated a relative risk of 10 (ten times increased risk) of laryngeal cancer in people who drank over 7 ounces per day of whiskey.\textsuperscript{79} Subsequent case-control studies have consistently shown similar results with squamous cell carcinomas of the oral cavity (including tongue), pharynx, and larynx.\textsuperscript{7,20,24,45,46,80} The only common site of cancer in this region which is not associated with alcohol is the nasopharynx, and this is likely due to the strong association of nasopharyngeal carcinoma with Epstein-Barr virus infection.\textsuperscript{32}

The relative risk associated with alcohol is dose dependent, as discussed above, and ranges from about 1.1 to 7 for low tobacco use groups and about 5 to 20 for high tobacco use groups. Although a case has been made for a stronger relative risk for sites that come in direct contact with alcohol,\textsuperscript{44} comparison of many studies does not demonstrate a significantly lower relative risk for the larynx, which does not come into direct contact with ingested alcohol. This would argue against a role of alcohol as a carcinogen solute or chronic mucosal irritant, at least for the larynx. The effect of alcohol in these cancers is clearly not due to a confounding effect of tobacco, and in most analyses, alcohol is at least as important as tobacco.\textsuperscript{66} Other etiologic factors which have been proposed include: poor dentition, hot beverages, deficiency of vitamins A and C, asbestos, and dental radiographs.\textsuperscript{7,20,21,24,44,46} These factors do not seem to be as important as alcohol and tobacco.

**Esophagus**

The incidence of esophageal cancer varies more throughout the world than any other neoplasm, with markedly high rates in certain areas of China, Iran, and the Soviet Union.\textsuperscript{66} In American and European studies, alcohol has long been recognized as an important etiologic factor.\textsuperscript{66,78} Although there are some studies in which esophageal cancer has closely paralleled the head and neck cancers, there do appear to be some significant epidemiologic differences. First, the role of alcohol in comparison to tobacco is stronger for esophageal cancer.\textsuperscript{73} In one study of black residents of Washington, D.C., tobacco could not even be identified with certainty as a risk factor.\textsuperscript{60} The relative risk for esophageal cancer rises logarithmically with increasing use of alcohol; for high levels of alcohol consumption, the risk factor is about 20 times, even when corrected for tobacco use.\textsuperscript{70} Overall, for Western countries, about 80 per cent of esophageal cancers can be attributed to alcohol and tobacco abuse.\textsuperscript{70,78}

There are a variety of other known causes of esophageal cancer: iron deficiency (Plummer-Vinson syndrome), ingestion of lye, and diet. The latter has been demonstrated in both Western case-control studies and in international population statistics studies.\textsuperscript{60,71} These studies indicate an association between esophageal cancer and corn- or wheat-based diets and deficiencies of riboflavin, nicotinic acid, magnesium, and zinc. It is of interest that the markedly high incidence of esophageal cancer in China is apparently not related to alcohol.\textsuperscript{84}

**Liver**

The incidence of hepatocellular carcinoma also has a marked international variability; identified risk factors have been reviewed by Popper.\textsuperscript{57} In Europe and America, alcohol abuse has long been recognized as an important risk factor. Autopsy series in Europe have shown a remarkably high incidence of 30 per cent for hepatocellular carcinoma in patients with
alcoholic cirrhosis. These extraordinary rates cannot be confirmed by American data. In a prospective study of Canadian alcoholics, Schmidt found 68 deaths with cirrhosis and no liver cancer, despite a 55 per cent autopsy rate. In a retrospective Veterans Administration study, Keller found a greater than 30-fold increase in the relative frequency of liver cancer, but these cases still represented less than 10 per cent of cases carrying the diagnoses of cirrhosis and cancer. Prospective studies in Europe have also indicated a rather mild increased risk of liver cancer with use of alcohol (relative risk 1.5). It should be noted that hepatocellular carcinoma can be seen in alcoholics without cirrhosis. Thus, alcohol definitely has a role in hepatocellular carcinoma, but its relative importance appears to be much less than was once thought.

The epidemiology of hepatocellular carcinoma has been revolutionized by the demonstration of a close association with hepatitis-B virus. The relevance of this finding to alcohol-associated liver cancer has been demonstrated by Bréchot, who found that among 20 patients with alcoholic cirrhosis and hepatocellular carcinoma, all had signs of previous hepatitis-B virus infection. This study used a sensitive test for hepatitis B virus DNA in the liver cells; the test was positive in only about 40 per cent of patients with alcoholic liver disease without liver cancer. This startling finding is corroborated by evidence that chronic hepatitis B virus infection sensitizes patients to the hepatotoxic effects of alcohol and appears to accelerate the development of hepatocellular carcinoma in patients with chronic hepatitis B virus infections.

Rectum

Population statistics show an association between consumption of beer and rectal cancer inODE state to state comparisons in the United States. Looking at international time trends in beer consumption and colorectal cancer, MeMichael and Potter have made a similar association. Since it is known that chronic alcohol ingestion can be associated with diarrhea, steatorrhea, and increased bile salt secretion, there is some reason to give credence to this association. Data from the Third National Cancer Survey also support an association between alcohol and colorectal cancer. However, these studies are all subject to error from confounding variables, of which there are many for beer consumption.

Two prospective studies have addressed this particular issue and come to different conclusions. A study of Danish brewery employees showed no increased risk of colorectal cancer, whereas a study of Irish brewery workers showed a modest 1.8 times increased risk of rectal cancer in that population of heavy beer drinkers. At present, this issue must be regarded as unsettled. However, if there is an effect of beer or alcohol consumption on rectal cancer incidence, it seems that it will be relatively minor compared to other dietary variables such as fat or fiber.

Stomach

Data from the Third National Cancer Survey show a weak association between alcohol and gastric carcinoma. This association might be shap-
tion and breakdown of incisions and grafts with surgery, mucositis and necrosis with radiation, and pancytopenia and mucositis with chemotherapy—is increased in alcoholic patients. The alcoholic's predisposition for these complications is generally attributed to the malnutrition that usually accompanies the condition. Malnutrition has been clearly identified as a risk factor for complications of cancer therapy. Although there is some in vitro evidence that alcohol can act as a specific radiation or chemotherapy sensitizer, there are no animal or clinical data to suggest such a specific interaction.

Some types of toxicity are peculiar to the alcoholic. Postoperative delirium tremens has been well recognized in the surgical literature, and should be considered in planning surgery for any patient with head and neck or esophageal cancer. Such patients should be admitted to the hospital several days in advance of surgery and treated with diazepam or other sedatives. Such patients may also benefit from preoperative nutritional support and antibiotics.

One can anticipate that the dose-limiting pancytopenia will be more severe in an alcoholic patient undergoing chemotherapy because of general nutritional status as well as specific folate deficiency, alcohol suppression of the bone marrow, and any degree of portal hypertension and hydropsplenism the patient may have (see article by Larkin, this issue). Alcoholism will also predispose to the complications of pancytopenia: infections (especially pneumonia—see article by Adams and Jordan) and bleeding (especially gastrointestinal—see article by Burbige et al.). For these reasons, it is probably wise to start such patients at somewhat reduced doses of chemotherapy, subsequently escalating to full doses as tolerated. The drug procarbazine can cause a disulfiram-like reaction with alcohol, and the drug should be given with caution to the alcohol abusing patient.

There will frequently be situations in which a patient's history of alcohol abuse will alter decisions on primary management of cancer; it is therefore imperative that an accurate alcohol and social history be obtained before treatment is planned. For example, an alcoholic with cancer of the true vocal cords, with a poor social support system, would be a poor candidate for speech rehabilitation; this might lead to a decision to use radiotherapy instead of surgery for an intermediate lesion. Radiotherapists have recommended surgery over radiation for some alcoholic patients because of their severe radiation reactions. For other patients, hospitalization may be necessary for a course of radiation therapy in order to give nutritional support and ensure completion of treatment. Initial chemotherapy, which is an increasingly popular but still experimental treatment for patients with advanced head and neck cancer, is probably contraindicated in the alcoholic patient; excess toxicity can be expected, and poor compliance may leave the patient without any definitive therapy.

Alcoholism will also complicate follow-up and palliative care. Continued drinking and poor nutrition exacerbate the serious problem of cancer cachexia. Personal experience indicates that alcoholic patients have more problems with analgesic abuse, and the physician may need to take a much more strict stance regarding dispensing narcotic analgesics than is usually advocated in hospice-style palliative care. In terminal care, alcoholic pa-

tients may be less able to deal with the reality of impending death than other patients—possibly because of guilt or anger over their lifestyle. Their resulting unrealistic expectations may put a severe strain on the doctor-patient relationship.

Terminal care of the alcoholic can also be complicated by the absence of responsible family. Frequently, the spouse is also alcoholic; the family caring for the patient may actually have been estranged from the patient for some time; or the patient may be entirely alone. It is the responsibility of the primary physician to be aware of these situations and to be prepared to arrange institutional care when appropriate.

An obvious issue in caring for the alcoholic with cancer is the question of intervention in drinking habits. This will hinge to a major extent on prognosis and the site of cancer. The patient with a potentially curable head and neck cancer deserves a maximal effort directed toward cessation of both drinking and smoking, especially in view of the extraordinarily high incidence of second primary head and neck or lung cancers in these patients. On the other hand the patient with a T-4 head and neck cancer or esophageal carcinoma should probably not have major interventions to alter lifestyle. It is unknown how many of these patients will spontaneously alter their habits when faced with a terminal illness.

**SUMMARY**

Excessive consumption of alcoholic beverages clearly results in an increased risk of certain types of cancer. The basis for this association is not known with certainty and may differ for different types of cancer. Alcohol itself is not a true carcinogen. It is probable that alcohol acts at least in part as a tumor promoter—a chronic irritant or stimulus that encourages the growth of cancers from precancerous cells.

The major risk of cancer seems to be associated with very high levels of alcohol consumption; low levels may be relatively safe. For most cancer sites, the type of alcoholic beverage consumed appears to be less important than the amount of alcohol consumed. Alcohol appears to act synergistically with tobacco in the etiology of cancers of the upper aerodigestive tract.

Squamous cell carcinomas of the head and neck region and of the esophagus are the most important alcohol-associated malignant processes. Alcohol is also clearly associated with development of hepatocellular carcinoma, although its role here may well be secondary to that of hepatitis B virus. Evidence to link alcohol to carcinoma of the gastric cardia is accruing. The role of alcohol in the etiology of rectal cancer and pancreatic cancer has been suspected but not convincingly demonstrated.

A patient with cancer and a history of alcohol abuse poses certain special problems. Decreased tolerance for cancer therapy may dictate changes in primary or palliative treatment. Nutritional and social complications of cancer are liable to be exacerbated in such a patient. It is important to have an accurate drinking history in all cancer patients in order to anticipate these complications.
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