
ALCOHOL ALERT

National Institute on Alcohol Abuse and Alcoholism No. 21 PH 345 July 1993

Alcohol and Cancer

Cancer kills an estimated 526,000 Americans yearly, second only to heart disease (1). Cancers of the lung, large bowel, and breast are the most common in the United States. Considerable evidence suggests a connection between heavy alcohol consumption and increased risk for cancer, with an estimated 2 to 4 percent of all cancer cases thought to be caused either directly or indirectly by alcohol (2).

A strong association exists between alcohol use and cancers of the esophagus, pharynx, and mouth, whereas a more controversial association links alcohol with liver, breast, and colorectal cancers. Together, these cancers kill more than 125,000 people annually in the United States (1). The following sections discuss alcohol's role in these cancers.

What Is Cancer?

Cancer is a group of diseases characterized by cells that grow out of control; in many cases, they form masses of cells, or tumors, that infiltrate, crowd out, and destroy normal tissue. Although the body strictly regulates normal cells to grow within the confines of tissues, cancer cells reproduce independently, uninhibited by tissue boundaries. Cancer develops in three stages: initiation, promotion, and progression. Cancer-causing agents, known as carcinogens, can contribute to the first two stages.

Cancer initiation occurs when a cell's DNA (the substance that genes are made of) is irreversibly changed so that, once triggered to divide, the cell will reproduce indefinitely. The "change" involves mutations to the cell's genes that can occur spontaneously or can be induced by a carcinogen. In some cancers, it has been shown that the mutations occur in oncogenes, genes that normally promote cell division, or in suppressor genes, genes that normally suppress cell division. Thus, it is believed that cancer-causing mutations result in overpromotion or undersuppression of cell reproduction. During cancer promotion, the initiated cell is stimulated to divide. The stimulus can be natural, as when tissue damage requires proliferation of new cells, or it can be caused by a carcinogen. During cancer progression, tumors produced by the replicating mass of cells metastasize, or spread, from the initial or primary tumor to other parts of the

body, forming secondary cancers.

Alcohol's Link to Cancer

Two types of research link alcohol and cancer. Epidemiologic research has shown a dose-dependent association between alcohol consumption and certain types of cancer; as alcohol consumption increases, so does risk of developing certain cancers. More tenuous results have come from research into the mechanism by which alcohol could contribute to cancer development.

Epidemiologic Research

The strongest link between alcohol and cancer involves cancers of the upper digestive tract, including the esophagus, the mouth, the pharynx, and the larynx (3). Less consistent data link alcohol consumption and cancers of the liver, breast, and colon (3).

Upper digestive tract. Chronic heavy drinkers have a higher incidence of esophageal cancer than does the general population. The risk appears to increase as alcohol consumption increases (4-6). An estimated 75 percent of esophageal cancers in the United States are attributable to chronic, excessive alcohol consumption (7).

Nearly 50 percent of cancers of the mouth, pharynx, and larynx are associated with heavy drinking (7). People who drink large quantities of alcohol over time have an increased risk of these cancers as compared with abstainers (8,9). If they drink and smoke, the increase in risk is even more dramatic (5,6).

Liver. Prolonged, heavy drinking has been associated in many cases with primary liver cancer. However, it is liver cirrhosis, whether caused by alcohol or another factor, that is thought to induce the cancer (10,11). In areas of Africa and Asia, liver cancer afflicts 50 or more people per 100,000 per year, usually associated with cirrhosis caused by hepatitis viruses. In the United States, liver cancer is relatively uncommon, afflicting approximately 2 people per 100,000, but excessive alcohol consumption is linked to as many as 36 percent of these cases by some investigators (2,12).

The association between alcohol use and liver cancer is difficult to interpret, because liver cirrhosis and hepatitis B and C virus infections often confound data (13). Studies of the interactions between alcohol, hepatitis viruses, and cirrhosis will help clarify these associations with liver cancer (see below).

Breast. Chronic alcohol consumption has been associated with a small (averaging 10 percent) increase in a woman's risk of breast cancer (14-17). According to these studies, the risk appears to increase as the quantity and duration of alcohol consumption increases. Other studies, however, have found no evidence of such a link (18-20).

The inconsistency and weakness of epidemiologic findings suggest that a third confounding factor, such as nutrition, may be responsible for the link between alcohol and breast cancer (15). However, studies that adjusted for dietary factors such as fat intake

found that the association between alcohol and breast cancer remained (14,21,22).

Recent studies suggest that alcohol may play an indirect role in the development of breast cancer. These studies indicate that alcohol increases estrogen levels in premenopausal women, which, in turn, may promote breast cancer (23).

Colon. Epidemiologic studies have found a small but consistent dose-dependent association between alcohol consumption and colorectal cancer (15,24), even when controlling for fiber and other dietary factors (15,25,26). Despite the large number of studies, however, causality cannot be determined from the available data.

Other cancers. A few studies have linked chronic heavy drinking with cancers of the stomach, pancreas, and lungs (3). However, the association is consistently weak and the majority of studies have found no association (3).

Mechanisms of Alcohol-Related Cancers

The epidemiologic data provide little insight into whether or how alcohol increases the risk for various cancers. For some cancers, such as mouth and esophageal, alcohol is thought to play a direct causal role. For others, such as liver and breast cancers, alcohol is thought to play an indirect role by enhancing mechanisms that may cause cancer. Studies looking at these direct and indirect mechanisms may shed light on alcohol's role in developing cancers.

Oncogenes. Preliminary studies show that alcohol may affect cancer development at the genetic level by affecting oncogenes at the initiation and promotion stages of cancer. It has been suggested that acetaldehyde, a product of alcohol metabolism, impairs a cell's natural ability to repair its DNA, resulting in a greater likelihood that mutations causing cancer initiation will occur (27). It has recently been suggested that alcohol exposure may result in overexpression of certain oncogenes in human cells and, thereby, trigger cancer promotion (28).

Alcohol as a cocarcinogen. Although there is no evidence that alcohol itself is a carcinogen, alcohol may act as a cocarcinogen by enhancing the carcinogenic effects of other chemicals. For example, studies indicate that alcohol enhances tobacco's ability to stimulate tumor formation in rats (29). In humans, the risk for mouth, tracheal, and esophageal cancer is 35 times greater for people who both smoke and drink than for people who neither smoke nor drink (30), implying a cocarcinogenic interaction between alcohol and tobacco-related carcinogens (29).

Alcohol's cocarcinogenic effect may be explained by its interaction with certain enzymes. Some enzymes that normally help to detoxify substances that enter the body can also increase the toxicity of some carcinogens. One of these enzymes is called cytochrome P-450 (31,32). Dietary alcohol is able to induce cytochrome P-450 in the liver, lungs, esophagus, and intestines (29,33), where alcohol-associated cancers occur. Subsequently, carcinogens such as those from tobacco and diet can become more potent as they, too, pass through the esophagus, lungs, intestines, and liver and encounter the activated enzyme (29,33).

Nutrition. Chronic alcohol abuse may result in abnormalities in the way the body processes nutrients and may subsequently promote certain types of cancer. Reduced levels of iron, zinc, vitamin E, and some of the B vitamins, common in heavy drinkers, have been experimentally associated with some cancers (29). Also, levels of vitamin A, hypothesized to have anticancer properties (34), are severely depressed in the liver and esophagus of rats during chronic alcohol consumption (35-37).

A recent study indicates that as few as two drinks per day negates any beneficial effects of a "correct" diet on decreasing risk of colon cancer (38). Although the study suggests that a diet high in folic acid, a B vitamin found in fresh fruits and vegetables, decreases the risk for colon cancer, it also warns that alcohol consumption may counter this protective action and increase the risk for colon cancer by reducing folic acid levels.

Mechanisms of liver cancer. The possible role of alcohol in the development of liver cancer is incompletely understood. In Asia and Africa, hepatitis B virus infection is thought to cause most liver cancer; the association is less frequent in the United States. Eighty percent of patients with liver cancer also have cirrhosis (39), and between 27 and 80 percent test positive for hepatitis B or C infection (40). The chronic heavy drinking that causes liver cirrhosis might exacerbate cirrhosis caused independently by the hepatitis B or C viruses. Some studies indicate that alcohol consumption hastens the development of liver cancer in patients with hepatitis C infection (41), whereas others indicate that alcohol has no compounding effect in such patients (42).

Suppression of immune response. Alcoholism has been associated with suppression of the human immune system. Immune suppression makes chronic alcohol abusers more susceptible to various infectious diseases and, theoretically, to cancer (43).

Summary

Although epidemiologic studies have found a clear association between alcohol consumption and development of certain types of cancer, study findings are often inconsistent and may vary by country and by type of cancer. The key to understanding the association lies in research designed to decipher how alcohol may promote cancer. Such studies examine alcohol's metabolic effects at the cellular and genetic levels. Research examining the ways in which alcohol may induce cancers has found some potential mechanisms, the most promising of which implicates oncogenes.

Alcohol and Cancer--A Commentary by NIAAA Director Enoch Gordis, M.D.

As can be seen from this *Alcohol Alert*, the evidence for alcohol's role in promoting some cancers (e.g., cancers of the mouth and throat) is stronger than the evidence linking alcohol use to other cancers, such as breast cancer. Public health policy should reflect the strength of the evidence of alcohol's role in promoting various cancers. Convincing evidence of alcohol's effects on common cancers--even when these effects are minor--has important public health implications. However, it is equally important that the

public not be subjected to undue alarm when evidence for an increased risk for cancer due to alcohol use is weak or inconclusive.

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ACKNOWLEDGMENT: The National Institute on Alcohol Abuse and Alcoholism wishes to acknowledge the valuable contributions of Edward Tabor, M.D., associate director for biological carcinogenesis at the National Cancer Institute, to the development of this *Alcohol Alert*.



U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

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Updated: October 2000