

## **No Amount of Alcohol Is Safe**

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### **Responsible Drinking? Not Very**

"Responsible drinking" has become a 21st-century mantra for how most people view alcohol consumption. But when it comes to cancer, no amount of alcohol is safe. That is the conclusion of the 2014 World Cancer Report (WCR), issued by the World Health Organization's International Agency for Research on Cancer (IARC).

Declared a carcinogen by the IARC in 1988, alcohol is causally related to several cancers. "We have known for a long time that alcohol causes esophageal cancer, says Jürgen Rehm, PhD, WCR contributor on alcohol consumption, and Senior Scientist at the Centre for Addictions and Mental Health in Toronto, Ontario, Canada, "but the relationship with other tumors, such as breast cancer, has come to our attention only in the past 10-15 years."

### **The Risk Is Dose-Dependent**

The more alcohol that a person drinks, the higher the risk. The alcohol/cancer link has been strengthened by the finding of a dose/response relationship between alcohol consumption and certain cancers. A causal relationship exists between alcohol consumption and cancers of the mouth, pharynx, larynx, esophagus, colon-rectum, liver, and female breast; a significant relationship also exists between alcohol consumption and pancreatic cancer.

Links have also been made between alcohol consumption and leukemia; multiple myeloma; and cancers of the cervix, vulva, vagina, and skin, but fewer studies have looked at these relationships and more research is needed to establish a confirmed association. For bladder, lung, and stomach cancers, the evidence for an alcohol-cancer link is conflicting.

### **How Solid Are These Data?**

"For the cancers that have been identified as being causally linked with alcohol, we are absolutely certain that alcohol causes these cancers," says Dr. Rehm. "About a few cancers, such as pancreatic cancer, we are not yet certain," he says. "We believe that we have good evidence showing that alcohol can cause pancreatic cancer, but we would not go so far as we would for esophageal cancer or breast cancer. And for renal cancer, the IARC has said that there are indications that there may be an effect, but we don't have the same level of evidence that we have for cancers that are clearly detrimentally linked to alcohol."

But surely, light drinking doesn't cause or contribute to cancer? Apparently, it does. In a meta-analysis of 222 studies comprising 92,000 light drinkers and 60,000 nondrinkers with cancer, light drinking was associated with risk for oropharyngeal cancer, esophageal squamous cell carcinoma, and female breast cancer. From this meta-analysis, it was estimated that in 2004 worldwide, 5000 deaths from oropharyngeal cancer, 24,000 from esophageal squamous cell carcinoma, and 5000 from breast cancer were attributable to light drinking. Light drinking was not associated with cancer of the colon-rectum, liver, or larynx.

However, a caveat is in order here. When alcohol use is self-reported, respondents might underestimate, or underreport, their actual alcohol intake. This can result in finding associations between cancer and light to moderate drinking, when in reality, alcohol intake is much higher.

### **The Nuts and Bolts of Increased Risk**

The biological mechanisms that mediate alcohol-related cancer are not fully understood. Alcoholic beverages can contain at least 15 carcinogenic compounds, including acetaldehyde, acrylamide,

aflatoxins, arsenic, benzene, cadmium, ethanol, ethyl carbamate, formaldehyde, and lead. Ethanol is the most important carcinogen in alcoholic beverages, and the rate of ethanol metabolism is genetically determined.

The first and most toxic product of alcohol metabolism is acetaldehyde. Ingested ethanol is oxidized by the enzymes alcohol dehydrogenase, cytochrome P4502E1, and catalase to form acetaldehyde. Acetaldehyde also occurs naturally in alcoholic beverages. This metabolite is carcinogenic and genotoxic when in contact with the mucosa of the upper aerodigestive tract (pharynx, oral cavity, esophagus, larynx), where high concentrations of acetaldehyde induce mucosal hyperproliferation. Even low doses of alcohol in direct contact with these areas can increase the risk for cancer.

Several different causative pathways are implicated in alcohol-related cancer. For example, alcohol is a folate antagonist, and an alteration in folate metabolism and folate malabsorption are believed to interact with ethanol to impair DNA methylation. In breast cancer, alcohol can increase estrogen levels and the activity of insulin-like growth factor receptors, which can stimulate mammary cell proliferation. In digestive tract cancers, an individual's genotype could play a role. Other mechanisms that have been proposed include the production of reactive oxygen and nitrogen species, and a role for alcohol as a solvent of tobacco carcinogens.

### **The Hard Truth About Hard Liquor**

The relative risk for alcohol-associated cancer depends on where ingested alcohol contacts body tissue, according to Dr. Rehm. Alcohol first contacts the oral cavity, followed by the esophagus, and for these sites the relative risk for alcohol-related cancer is highest. Next are the colon, rectum, and liver, and the relative risks for those cancers are lower than for the anatomical sites first in contact with ingested alcohol.

The type of alcohol -- wine, beer, spirits -- doesn't usually matter, except in the case of cancer of the esophagus. The esophagus is covered with very fine cilia that are easily destroyed by high concentrations of ethanol, such as found in hard liquor.

### **A Drink and a Smoke: Dangerous Combination**

Smoking has long been established as a risk factor for cancer. But smoking and drinking -- considered by many to be a pleasurable combination -- is a particularly dangerous mix. A synergistic effect has been found for tobacco smoking and alcohol consumption with respect to the risk for cancers of the oral cavity, pharynx, larynx, and esophagus; the highest risks are seen in those who are both heavy drinkers and heavy smokers. The esophageal mucosa of patients who both drink and smoke have shown a dose-dependent increase in esophageal mucosal cell proliferation. Avoidance of cigarettes and alcohol could prevent up to 80% of oral cancer cases and 90% of laryngeal cancer cases.

### **Isn't Modest Drinking Cardioprotective?**

Alcohol is a double-edged sword. Two decades ago, studies that explored the "French paradox" began to appear in the medical literature and were also picked up as news by the mainstream media. Light to moderate alcohol consumption appeared to have a cardioprotective effect. According to observational studies, the French, who had the highest alcohol intake (particularly of wine), also had the lowest incidence of cardiovascular disease.

John Q. Public, who may have viewed these results as a "get out of jail free" card, may also have ignored the "small print" that cautioned against alcohol consumption as a measure to prevent cardiovascular disease. The evidence showing lower risks for diabetes mellitus, stroke, heart failure, and total mortality stand in stark contrast to the harms associated with excessive alcohol consumption.

Another problem with the notion of alcohol's protective effect on cardiovascular disease is that this effect depends on a consistent light to moderate drinking pattern, without episodic heavy or "binge" drinking. The ideal pattern seems to be daily low- to moderate-dose alcohol intake (preferably red

wine) before or during the evening meal, which is associated with the strongest reduction in adverse cardiovascular outcomes. However, more is not better; in fact, more is dramatically worse. Heavy alcohol use causes hypertension, atrial fibrillation, ischemic and hemorrhagic stroke, and nonischemic dilated cardiomyopathy.

The evidence for the harmful effects of alcohol is stronger than the evidence for its beneficial effects. Moreover, the risk-to-benefit ratio of drinking appears to be higher in younger individuals, who also have higher rates of excessive or binge drinking and more frequently suffer the adverse consequences of acute intoxication (accidents, violence, and social problems). In fact, among males aged 15-59 years, alcohol abuse is the leading risk factor for premature death.

And yet, other than celebrity drunk-driving stories, we rarely see headlines about the harm caused by alcohol. Dr. Rehm comments, "I do not know why a beneficial link would be more important than a detrimental link, if the beneficial link overall is about one tenth of the detrimental link. We have counted how many studies are reported in the press, and there are many more reports on the beneficial link than on the detrimental link between alcohol and health."

"The public's acknowledgment of the risk associated with an exposure depends on the strength of that relationship. Because 80%-90% of cancer deaths are caused by tobacco, the risk is common knowledge. If your neighbor dies, the first thing people ask is whether he was a smoker. The relationship of alcohol with other cancers, however, might be in the range of 5%-40%. So if your neighbor dies of breast cancer, people wouldn't ask whether she was a drinker."

### **Warning: Drinking Is Hazardous to Your Health**

Alcohol is no ordinary consumer commodity; it requires extensive public policy in the form of regulation, taxation, and human services to cope with the damage that it causes. As one might expect, the interests of public health and the alcohol industry are sharply divided on alcohol policy. Contributors to the WCR consider certain forms of alcohol policy in the best interest of the public.

"The prevalence of harmful use of alcohol," says Dr. Puska, "is closely related to the level of alcohol consumption in the general population." Accordingly, he believes that interventions should not be confined to high-risk alcohol users, but should address general alcohol consumption and be population-based.

Dr. Rehm suggests that in a modern society with consumer rights, a warning label mentioning cancer risk associated with alcohol consumption should be considered for all alcohol products. Some countries already have warning labels, but they typically mention only avoidance of alcohol during pregnancy. Warning labels should convey the risks associated with alcohol consumption in a language that is informative to the consumer.

Controlling the affordability of alcohol through pricing and taxation can reduce the volume of alcohol consumed, and thereby alcohol-related health and social harms, including cancer and mortality. Increasing the price of alcohol affects all drinkers, from young people to heavy or problem drinkers. Dr. Puska explains:

The most cost-effective way to reduce alcohol problems in any country is reduction of total alcohol consumption. The more that alcohol is consumed in any country, the more alcohol-related problems there are. The experts and the World Health Organization are quite clear that price and availability are the most effective policy instruments to influence alcohol consumption. Price is usually regulated by taxation. Availability relates to such issues as to whom, where, and when alcohol is sold. In addition, drunk-driving policies and mini-interventions in health services have some effect. Health information campaigns alone are not effective, but they are valuable as background for alcohol control measures (Table).

In summary, any level of alcohol consumption increases the risk of developing an alcohol-related cancer, and that the risk rises in accordance with the level of consumption. That is a discouraging message. However, the flip side is that any reduction in alcohol consumption will lower the cancer

risk. Although no absolutely safe level of alcohol intake can be promoted, a return to the days of prohibition is not necessary to derive the health benefits of reduced cancer risk. However, what is essential is to increase public awareness about alcohol-related cancer risk and seek sensible ways to reduce that risk.

As Dr. Puska points out, "The risks associated with alcohol are not limited to cancer. Alcohol is related to multiple health problems. Patients should be informed about these, and should be concerned about the overall risk to their health. The clear relationship between alcohol and cancer is news for most people. However, that is only one component of the overall health message that should be delivered about alcohol."

#### Table. 10 Strategies to Reduce the Personal and Public Costs of Alcohol

##### Personal health behaviors:

- Monitor your alcohol intake ("know your number"). This is similar to knowing your blood pressure, cholesterol level, or calorie intake.
- Limit consumption to 20 g daily for men and 15 g daily for women (1.5 drinks for men and 1 drink for women, by US standards).
- Less is more: Lower alcohol consumption leads to greater health and longevity.
- Take a day off. Not drinking for 1-2 days each week can help the liver recover from the effects of alcohol and reduce the risk for liver complications.

##### Government intervention:

- Apply a minimum pricing policy to alcohol to reduce consumption of cheap alcohol, especially by young people.
- Label the amount of alcohol in grams (like food labeling) to allow consumers to track the exact amount of alcohol they are consuming.
- Limit the times and places alcohol can be purchased to reduce impulse buying, and avoid contact with alcohol in shops and supermarkets.
- Provide treatment to benefit individuals and society; offer to all people with an alcohol dependence problem.
- Invest in research to develop new approaches to addiction.
- Develop alternatives to alcohol -- investigate new drugs that mimic the milder effects of alcohol; simulate relaxation without the negative side effects of alcohol.