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Review Article

The Carcinogenicity of Alcoholic Beverages: A Review

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ABSTRACT

There is convincing evidence that alcohol consumption increases the risk of oral cavity, pharynx, esophagus, gastric, breast, prostate, colorectal, and liver cancers. Lifestyle behaviors, including drinking patterns and smoking status can synergistically increase the adverse outcomes of alcohol intake. This review aims at summarizing published data considering alcohol consumption as a risk factor for major cancers and possible mechanisms in its pathogenesis. A literature search was carried out in PubMed, Science direct, Google scholar, Medline, and Web of Science (ISI) databases. The search was limited to studies published in English. 59 eligible articles were identified. The available data provided adequate scientific evidence which pointed toward a positive association between alcohol intake and development of oral, pharynx, esophagus, gastric, breast, prostate, colorectal, and liver cancer. This review provided sufficient evidence that alcohol, even at low intakes, significantly increases the risk of cancer in those sites where there is direct contact with alcohol such as the oral cavity, pharynx, and esophagus. Clinicians should always evaluate the patient-specific risk, considering the additive/synergistic behaviors, including drinking pattern and smoking status together.

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Introduction

Cancer is a chronic disease that has become an important public health problem, worldwide (1). Based on the GLOBOCAN 2008 estimates, about 12.7 million cancer cases and 7.6 million cancer deaths are estimated to have occurred in 2008. Of these, 56% of the cases and 64% of the deaths occurred in economically developing countries (2). By the year 2030, 20.3 million incident cases and 13.2 million deaths from cancer are expected (1). Besides non-modifiable risk factors such as age and genetics, most of the risk factors for developing cancer are considered modifiable, highlighting a sedentary lifestyle, unhealthy diet, smoking, and alcoholism. When an individual is exposed to more than one of these factors, the risk of developing cancer and adverse outcomes increases. Thus, primary prevention measures are required, focusing mainly on modifiable risk factors (3), especially the use of tobacco and alcohol.

Alcohol is one of the few psychoactive drugs that are encouraged and accepted by some societies. Its consumption is increasing worldwide, especially in developing countries. According to Cancer Research UK (2012), there is evidence that compared to individuals who do not consume alcohol and do not use

tobacco; those who drink and smoke have 50 times more chance of developing some forms of cancer. Globally, 6.2% and 1.1% of all male and female deaths are attributable to alcohol, and deaths that are related to the consumption of alcoholic beverages amount to 1,804,000 per year or 3.2% of all deaths in the world (4, 5). In addition, when consumed excessively, alcohol may also be responsible for the development of heart disease, hypertension, stroke, pancreatitis, and gastric ulcer (5). According to the World Health Organization (WHO), the number of deaths and limitations caused by alcohol exceeds those caused by tobacco use. The World Cancer Research Foundation and the American Institute for Cancer Research (2007) reported that there is convincing evidence linking the consumption of alcoholic beverages to cancers of the oral cavity, pharynx, esophagus, gastric, breast ,prostate, colorectum and mainly liver (4, 6, 7). Based on the potent association of alcohol with cancers, an International Agency for Research on Cancer working group recently considered alcoholic beverages as "carcinogenic to humans"(8).

Materials and Methods

A literature search was carried out in PubMed, Science direct, Google scholar, Medline, and Web of Science (ISI) databases using keywords such as meta-analysis, smoking, risk factors, oral cancer, pharynx cancer, esophagus cancer, gastric cancer, breast cancer, prostate cancer, colorectal cancer, and liver cancer in combination with alcoholic beverages, wine, and alcohol. The search was limited to studies published in English. For the sake of completeness, we also reviewed references from all relevant studies, reviews and meta-analyses published on the relationship between alcohol and the risk of developing cancer to identify additional studies.

Drinking Patterns

The drinking pattern includes the type of beverage, as well as how much, when and how often an alcoholic beverage is consumed (9). Three main drinking states can be identified, apart from alcoholism disorders, named abstention, low to moderate intake and heavy episodic drinking (binge pattern). According to the WHO, the abstention group includes both "lifetime abstainers", who have never consumed alcohol, and "former drinkers", who previously consumed alcohol, but who did not in the last 12 months (6). The heavy binge drinking group includes mainly young subjects with an intake of at least 60 or more grams of pure ethanol (>5 drinks) at least once in the past seven days, generally during the weekend. In the middle, a regular and low to moderate consumption includes light alcohol intake, and usually includes one drink/day(4, 10), while moderate consumption to one to two drinks/day. The drinking pattern intensely affects health consequences, at both short-term (acute) and long-term (chronic) levels (4).The importance of drinking patterns is highlighted for oral cancer (6). The maximum oral cancer incidence and mortality are recorded in populations distributed in Eastern European countries such as Hungary, Slovakia, and Romania, where the consumption of spirits is higher than other nations (11). Unsweetened, distilled, alcoholic drinks that have an alcohol content of at least 20% alcohol by volume are called spirits (12). Likewise, in North-Eastern regions of Italy, where the daily intake of spirits, in addition to wine, is a usual habit due to cultural traditions, the highest percentage of oral cancer morbidity and mortality can be observed (13).These findings are also consistent with a recent study on the Korean population, associating frequency of heavy binge drinking and mortality from oro-pharynx cancer (14). Most of the data come from studies that focused on the effect of moderate/high alcohol intakes, while little is known about light alcohol drinking (≤12.5 g ethanol; ≤1 drink/day). From a public health point of view, it is important to know that light drinking increases the risk of oral cavity , pharynx, esophagus, and female breast cancers (4). However, further research on the association between individual alcohol abuse and general unhealthy behaviors are pivotal. Many reports suggest that unhealthy lifestyles have a tendency to occur together, especially that heavy binge alcohol drinking is associated with smoking, as well as to lower compliance to screening health programs (14).

Mechanisms and Pathogenesis "Alcohol as a Carcinogen"

The stomach absorbs 20% of alcohol; the rest is absorbed by the duodenum and small Intestine. Alcohol dehydrogenase (ADH) enzyme which

is located in the cytoplasm of hepatocytes, metabolizes most of the consumed alcohol. ADH-dependent alcohol metabolism results in oxidation of alcohol to acetaldehyde (15). Acetaldehyde is further oxidized to acetate by the mitochondrial form of aldehyde dehydrogenase. The resulting acetate is then incorporated to form acetyl coenzyme A and oxidized in the Krebs cycle (16). The cytochrome P450 2E1 of the microsomal ethanol oxidizing system in the hepatocytes also plays an important role in hepatic carcinogenesis. In moderate state of alcohol intake, the microsomal ethanol oxidizing system CYP2E1 pathway accounts for a small fraction of alcohol metabolism, ADH representing the more common pathway for alcohol oxidization (17-19). Chronic alcohol abuse leads to noticeable induction of CYP2E1, leading to increased hepatic acetaldehyde production (20, 21). Acetaldehyde has been shown to have mutagenic and carcinogenic effects in several in vitro and in vivo experiments, including prokaryotic and eukaryotic cell cultures and animal models. Acetaldehyde has been found to cause point mutations in human lymphocytes, as well as forms DNA adducts (i.e. covalent bonds with DNA, leading to carcinogenesis), and induces sister chromatid exchanges and gross chromosomal aberrations (22-24). Moreover, it has also been found that acetaldehyde interfere with DNA repair mechanisms, inhibiting the O6-methylguanine transferase enzyme responsible for the repair of damage caused by alkalizing agents, and to induce mutations in the TP53 tumor suppressor gene,which is a common genetic alteration involved in human cancers, especially esophageal cancer (25). Furthermore, the mutagenic properties of acetaldehyde have also been associated with breast cancer (26). Recent experimental evidence has shown that the mutagenic adducts formed by acetaldehyde can occur in cellular concentrations of 100 μM and above (23). The lowest concentration of acetaldehyde that has induced sister chromatid exchange in Chinese hamster ovary cells in an in vitro study was 3.9 mg/l (88 μM) (27).Throughout alcohol consumption, an important mechanism is the local formation of acetaldehyde in the digestive system by microbes representing normal oral or gut flora. Ethanol oxidation also occurs in nearby tissues in limited amounts. As ethanol is circulated evenly to the whole aqueous phase of the human body, it is metabolized continuously to acetaldehyde as long as it remains in the blood and saliva. This leads to accumulation of acetaldehyde in the saliva and intestinal contents during and after the consumption of alcohol. Therefore, an important factor is the limited ability of oral microbes and mucous membranes to detoxify acetaldehyde. Via swallowing, salivary acetaldehyde is transported from the mouth to the mucous membranes of the pharynx, oesophagus, and stomach (28, 29).

Depending upon the quality of oral hygiene, alcohol consumption has been found to result in salivary acetaldehyde concentrations of 50–200 μM (30). Moreover, combination with smoking has resulted in salivary acetaldehyde concentration of over 250 μM (31). Epidemiological studies have found that increases in salivary acetaldehyde concentrations are associated with linear or even multiplicatively increased risk for upper digestive tract cancer (32). The combined evidence from in vitro experiments and human drinking and smoking studies points to mutagenic acetaldehyde concentrations in ranges as low as 50–150 μM (33). It is noteworthy that some groups of alcoholic beverages may lead to short term salivary acetaldehyde concentrations of more than 150 μM. This is demonstrated by the first experimental evidence recently provided by Yokoyama and colleagues, which confirmed considerable differences in salivary acetaldehyde immediately after the consumption of different alcoholic beverages. In the following period, between 30-180 minutes after drinking, the salivary acetaldehyde concentrations were then unrelated to beverage type (28). CYP2E1 dependent alcohol metabolism results in increased hepatic oxidative stress and production of reactive oxygen species (ROS), especially hydroxyethyl radicals. ROS are directly associated with the formation of DNA and protein adducts. They can also react with lipid molecules in the cell membrane, resulting in production of biologically reactive aldehyde molecules, such as 4-hydroxynonenal and malondialdehyde (MDA) compounds similar to acetaldehyde.

Chronic alcohol consumption leads to increased conversion of several procarcinogens, including nitrosamines and azo compounds to carcinogen derivatives through CYP2E1-dependent metabolism (34). In addition, chronic alcohol

consumption alters the balance of bacterial flora within the gastrointestinal tract and increases gut penetrability to lipopolysaccharides. The increased intrahepatic lipopolysaccharide levels lead to the activation of the liver's Kupffer cells (KCs), which in turn release proinflammatory cytokines, such as TNFα, prostaglandins, and interleukins. The role of KCs in interceding the harmful effects of alcohol on the liver has been demonstrated through the use of antibiotics to reduce total gastrointestinal bacteria and by the depletion of KCs (using gadolinium chloride). These approaches considerably prevent ethanol-related hepatic injury (35-37).

Alcohol Consumption and the Risk of Cancer in Organs of the Digestive System

A meta-analysis assessed the association between alcohol consumption and esophageal cancer. After checking the effect of tobacco, increased risk with dose response for squamous cells carcinoma of the esophagus from the consumption of 3 doses/day was found (38). Evaluating the risk of squamous cell cancer of the esophagus due to the light consumption of alcoholic beverages (up to 1dose/day), without adjusting for tobacco, according to the gender and geographical area, an increased risk among men and the Asian population was observed (4). Looking at alcohol consumption and the risk of gastric cancer, a meta-analysis examined the association between moderate and excessive intake, anatomical location and dose response from 59 studies. In the crude analysis there was an increased risk of cancer among individuals who consumed alcohol in any amount, with this risk becoming higher among those with excess consumption (>50g/day) and non-Asians who consumed ≥4 doses/day. When adjusted for smoking, consumption of alcoholic beverages was statistically associated with the risk of gastric cancer (39). One meta-analysis pointed to the increased risk of colorectal cancer among alcohol users, with dose response effect for drinking ≥2 servings/day for both men and women (40).

Another publication recognized a statistically significant association between alcohol consumption and the risk of colon and rectum cancer and when analyzing the dose-response, it was observed that, for an increase of 100g of alcohol consumption per week among men, there was an 18% increase in the risk of colon cancer and a 19% increase in the risk of rectal cancer, but this result was not observed among women (41). The association between alcohol consumption and cancer of the pancreas was studied by a meta-analysis defined as heavy alcohol intake of 3 or more doses per day has a strong correlation with increased risk of 23% after controlling for the tobacco effect (42).

Alcohol Consumption and the Risk of Respiratory Organs Cancer

A meta-analysis examining individuals who had never used tobacco found an association and dose response relation between alcohol consumption and the risk of lung cancer (43). A meta-analysis that adjusted for the effects of smoking, gender and age, reported a 50% higher risk of laryngeal cancer among those who consumed 1-4 doses/day and 2.46 times higher among those with a consumption of more than 4 doses/day (44). In a meta-analysis investigating the relationship between alcohol consumption and the risk of cancer of the oral cavity and pharynx it was observed that, without adjustment for smoking, alcohol intake, at any amount, enhances the risk of developing cancer of the oral cavity and pharynx: 20% higher for a consumption of 10g/day to up to 13 times higher for a consumption of 125g/day (45). In an unadjusted analysis for tobacco, a meta-analysis found an increased risk of cancer of the oral cavity and pharynx in individuals who consume up to 1dose/day in men (4). Oral cancer has been, thus, causally associated with ethanol intake, mostly when consumed above the suggested upper limits of two drinks (30 g of ethanol) a day in men, and one drink (15 g of ethanol) a day in women (46, 47).

Alcohol Consumption and the Risk of Breast and Prostate Cancer

In a meta-analysis, in studies with high quality, excess risk related to alcohol drinking was 22%. When the dose response effect was measured, an increased risk of 10% for each 10 g of ethanol/day was found and the risk stayed irrespective of the type of beverage consumed (beer, wine, or spirits) (48). Another study, after adjustment for smoking, showed a dose response effect with a 7% increase in the risk of developing breast cancer for each 10g/day of alcohol consumed ($P<0.001$) (49). A meta-analysis that adjusted

for age, family history, parity, menopause, use of oral contraceptives and hormone replacement therapy, reported an increase of 3% in the risk of breast cancer after drinking alcohol beverages (50). Not adjusting for the risk of tobacco consumption, an article reported a risk increase of 5% for breast cancer for the consumption of 1 dose/day of alcohol (4). Prostate cancer was the subject of one meta-analysis, which observed a 16% increase in the risk of developing prostate cancer per daily dose of alcohol consumption. When analyzing by type of study, case-control studies remained statistically significant, with an increased risk of prostate cancer by 24% per daily dose. It should be mentioned that these results were not adjusted for tobacco consumption (51).

Alcohol Consumption and the Risk of Hepatocellular Carcinoma

Epidemiological evidence supports that alcohol is an independent and powerful risk factor for hepatocellular carcinoma (HCC) (34). There is evidence on health-promoting effects of wine which are based on the high content of a variety of beneficial bioactive compounds, such as phytochemicals (52). On the other hand, Phytochemicals in wine seem not to have any influence on cancer risk, possibly because they are present at low levels and poorly absorbed, reaching human levels much below the effective concentrations evaluated in preclinical studies. Currently, there is no clear causal correlation between phytochemicals in wine and health outcomes (53). In addition, the heavy wine intake (at least more than three drinks/day) has been intensely associated with a dose dependent risk of liver diseases, such as fatty liver, cirrhosis and hepatic carcinoma, so there is no safety limit for the effects of alcohol on liver (6, 34). Alcohol enhances the formation of reactive oxygen species (ROS), which are highly reactive, oxygen-containing molecules that can damage cellular molecules, such as fats, proteins, or DNA. Alcohol metabolism in the liver leads to ROS production, induction of activity of cytochrome P450s, and reduction of antioxidants. ROS production and oxidative stress in hepatocytes play an important role in the development of alcoholic liver disease and HCC (54). Evidences report that chronic alcohol intake of more than 80 g/d for longer than 10 years increases the risk for HCC by 5-fold (55). In a meta-analysis of alcohol drinking and cancer risk, increased trends in risk were reported for cancers of the liver (relative risk [RR]: 1.86). Higher risks were found even for the lowest dose of alcohol (25 g/d) equal to approximately 2 drinks per day (56). A meta-analysis of 4 studies carried out to evaluate the decline of liver cancer risk with time for former drinkers, found that the risk of liver cancer decreases after cessation by 6% to 7% a year, but an estimated time period of 23 years is needed after drinking cessation, for the risk of liver cancer to be equal to that of nondrinkers (57). Alcohol acts synergistically with pre-existing life style behaviors, such as smoking, to further increase the risk of HCC (34). The interaction of alcohol and smoking in causation of HCC has been difficult to study due to high dominance of their coexistence in the majority of patients. Some studies, however, have found interactive effects. It is assumed that carcinogenic compounds in cigarette smoke have an increased effect in the presence of heavy alcohol use, because they exert their carcinogenicity in the context of liver injury. Cellular proliferation from injury and repair may predispose the liver to developing cancer. In addition, as the liver plays an important role in metabolizing carcinogens absorbed from tobacco use, CYP2E1 induction by alcohol may alter and increase the carcinogenic potential of agents in tobacco (34, 58, 59).

Conclusion

This review summarized the current scientific evidence about the real risks posed by the consumption of alcohol in cancer development. The total amount of drinking by the individual is more important than the type of beverage consumed. The risk increases in individuals who consume alcohol and tobacco simultaneously. However, even though alcohol and tobacco are factors that act synergistically, ensuring the increased risk, alcohol is considered an independent risk factor for many types of cancer. It is necessary to perform further studies to monitor the effect of tobacco as a probable confounding variable in the observed association, because most individuals who smoke also consume alcoholic beverages. There is a definite relationship between alcohol consumption and cancers of the mouth, pharynx, esophagus, liver, gastric, colorectal, prostate, and breast. This

review provided sufficient evidence that alcohol, even at low intakes, significantly increases the risk of cancer in those sites where there is direct contact with alcohol such as the oral cavity, pharynx, and esophagus. The drinking patterns and type of population under examination can affect cancer risk. Clinicians should always evaluate the patient-specific risk, considering the additive/synergistic behaviors, including drinking pattern and smoking status together.

Conflict of Interest

None declared.

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