CME LIVE OPEN ACCESS

International Journal of Nursing & Care

Short Communication

Mechanisms of the Carcinogenic Effects of Alcohol

Fliuryk S., Dremza I., Bon E.I., Shpakovskaya I., Belevich E., Hrabitskaya V., Karonchyk D., Abdul. L. Sh, Sham. F. Sh., Muhammed. Sh. J. A. L

Grodno State Medical University, Gorkogo St, Grodno, Republic of Belarus.

Corresponding Author: Elizaveta I Bon, Candidate of biological science, Assistant professor of pathophysiology, Belarus

Received: 2025 May 26 **Accepted:** 2025 June 03 **Published:** 2025 June 18

Abstract

According to the Global Burden of Disease project (based on a group of mortality-related indicators), the World Health Organization states that alcohol is a major cause of high mortality in the world, contributing to 1.8 million deaths per year. In 2018, according to WHO data, about 4.2 million people in the European region were diagnosed with cancer (excluding non-melanoma skin cancer), with 4.3% of cases linked to alcohol consumption. So around 180,000 cancer cases (70,000 among women and more than 110,000 among men) were associated with alcohol consumption, resulting in nearly 92,000 cancer-related deaths.

Keywords: Carcinogenic Effects, Alcohol, Metabolism.

According to the Global Burden of Disease project (based on a group of mortality-related indicators), the World Health Organization states that alcohol is a major cause of high mortality in the world, contributing to 1.8 million deaths per year [17] [1].

In 2018, according to WHO data, about 4.2 million people in the European region were diagnosed with cancer (excluding non-melanoma skin cancer), with 4.3% of cases linked to alcohol consumption. So around 180,000 cancer cases (70,000 among women and more than 110,000 among men) were associated with alcohol consumption, resulting in nearly 92,000 cancer-related deaths.

Analysis of literature sources shows that alcohol abuse increases the risk of salivary gland cancer among men by 2.5 times [19] [2]. Epidemiological studies indicate a dose-dependent relationship between alcohol consumption and colon and rectal cancer [6] [3]. According to some studies, up to 25% of breast cancer cases are attributed to alcohol exposure [13] [4].

The combined alcohol abuse and smoking significantly increases the risk of cancer. People who smoke and abuse alcohol have a 35 times higher risk of developing oral and esophageal cancer than those who don't drink or smoke [15] [5].

There are different mechanisms of the carcinogenic effect of alcohol. Alcohol leads to a defect in the mucous membrane, which increases the risk of gastrointestinal cancer [9-14] [6-17].

According to global studies, alcohol abuse is associated with a twofold increase in the risk of hepatocellular carcinoma (HCC) [18]. Chronic alcohol consumption leads to the development of liver cirrhosis, which subsequently progresses to HCC, a common malignant neoplasm [19].

Alcohol consumption in Republic of Belarus is a topical issue and according to the statistics we can see that in 2021 it affected 12,734 people, but in 2020 there were 13,016 people (Belstat statistics). An analysis of statistical data on the production and consumption of alcohol in Belarus shows the presence of a negative trend of significant growth in these indicators and an unfavorable current alcohol situation [19]. During to the last 12 years, the production of alcohol in the country has increased.

Alcohol is absorbed in the stomach and intestines, while 90% of it is transported through the portal vein to the liver and the remaining portion is excreted through respiration and urine [19].

There are two pathways of the metabolism of ethanol in the liver: oxidative and non-oxidative. [20].

The main pathway of ethanol metabolism is oxidative. It consists of two steps. First, ethanol is oxidized to acetaldehyde with the help of alcohol dehydrogenase (ADH). The second step in the oxidative way is the conversion of acetaldehyde into acetate with the help of aldehyde dehydrogenase (ALDH). Acetate is metabolized into carbon dioxide, fatty acids, and water in peripheral tissues, not the liver [21].

The role of catalase in ethanol metabolism hasn't been definitively studied yet. Inside the cell, catalase is localized in peroxisomes, which are responsible to oxidate a lot of biologically active substances. In chronic alcohol intoxication, the role of the catalase-mediated oxidation way increases due to several factors. One of them is that the main alcohol dehydrogenase pathway of ethanol oxidation is insufficient, since it requires the presence of oxidized NAD+, the concentration of which decreases with repeated or massive alcohol intoxication. When studying an experimental model of alcoholism, it was found that the number of peroxisomes in liver cells and their peroxide-generating activity increases. The existence of an autonomous system of complete oxidation of alcohol to acetate in peroxisomes has also been established [1-12].

Excess acetaldehyde alters the functions and structures of mitochondria in liver cells, reduces the activity of enzymes in the Krebs cycle and the pentose phosphate shunt, which are important for the body. This creates a devastating "vicious cycle" for the body — acetaldehyde, accumulating during alcohol abuse, affects its processing systems, which leads to an even greater accumulation of acetaldehyde and, accordingly, to even greater damage to its processing systems [22]. Under the influence of highly toxic acetaldehyde, hepatocytes are destroyed, and dystrophic processes develop in the liver. It also has a carcinogenic effect and is capable of causing mutations and gross chromosomal aberrations. In the liver, acetaldehyde binds to nucleotide sequences in oncogenes and tumor suppressor genes to form stable products. This mechanism represents one of the ways in which acetaldehyde contributes to tumor development [23].

A small fraction of ethanol is metabolized by non-oxidative pathway [21]. A small amount of alcohol is nonoxidatively conjugated to various endogenous metabolites by different enzymes. For example, enzymatic esterification of alcohol with fatty acids leads to the formation of ethyl esters of fatty acids, and phospholipase D catalyzes transphosphatidylation of phosphatidylcholine with ethanol to form phosphatidylethanol. In addition, alcohol conjugated to glucuronic acid and sulfate generates ethyl glucuronide and ethyl sulfate [23].

Liver is the main organ responsible for metabolizing ethanol, so it suffers the most. Acetaldehyde, acetate, fatty acid ethanol esters, ethanol-protein adducts, have been regarded as hepatotoxins that directly and indirectly exert their toxic effect on the liver [Rocco A,]. Excessive alcohol consumption activates the non-oxidative pathway, increases the expression and activity of cytochrome P450 and promotes the production of acetaldehyde through the formation of reactive oxygen species [23].

In experimental colorectal carcinogenesis the inhibition of acetaldehyde dehydrogenase with elevated acetaldehyde levels results in an acceleration of cancer development [4]. Genetic studies in humans provide additional evidence that acetaldehyde is, to a certain extent, a carcinogen [17].

People with a slow conversion rate of acetaldehyde to acetate due to polymorphisms and/or mutations in genes encoding enzymes responsible for acetaldehyde formation and detoxification have an increased risk of developing hepatocellular carcinoma (HCC) [8].

Aberrant epigenetic mutations, including altered DNA methylation, characterize a wide range of diseases, including tumors [21]. The epigenome of tumor cells is more unstable and changes more frequently in DNA methylation and histone modification [Rodriguez], including the following: hypomethylation of specific promoters, leading to aberrant activation of oncogenes and causing loss of imprinting in other DNA regions.

According to the last researches alcohol can induce epigenetic changes, particularly aberrant DNA methylation, which may also be significant factors contributing to alcohol-induced carcinogenesis. For example, excessive alcohol use is associated with increased risk of liver cancer, which is characterized by global DNA hypomethylation as well as hypermethylation of certain genes [6].

Promoter hypermethylation of DNA repair gene and cell division control gene become abnormally "silent", which leads to epigenetic disorders in tumors [8].

Ethanol can also contribute to carcinogenesis through the induction of oxidative stress which is recognised as a key determinant of disease initiation [9]. The generation of reactive oxygen species (ROS) results from increased secretion of inflammatory cytokines caused by chronic inflammation [5]. ROS-induced DNA damage, genomic vulnerability of hepatocytes and T-lymphocyte suppression contribute to HCC development [5].

Oxidative stress can be caused by the activation of certain pathways that produce reactive oxygen species (ROS), such as superoxide anion and hydrogen peroxide. One pathway by which ethanol achieves this is through increased CYP2E1 activity which produces high quantities of ROS whilst oxidising ethanol to acetaldehyde [10]. It was shown that alcohol abuse increases the expression of CYP2E1 in the esophagus [10]. Other sources of ROS during ethanol metabolism include the mitochondrial respiratory chain and some cytosolic enzymes [3]. As ROS are highly reactive, their presence can lead to lipid peroxidation producing aldehydes which can bind to DNA forming etheno-DNA adducts [11]. These ethe-DNA adducts, namely 1, N6-ethenodeoxyadenosine and 3, N4-ethenodeoxycytidine, are highly mutagenic as they lead to mutations in several genes involved in key cell cycle regulation and tumour suppression [14].

Reactive oxygen species (ROS) van damage cellular metabolism [15]. ROS can act as messengers in intracellular signaling pathways for activation of various transcription factors such as nuclear factor-κB (NF-κB) [16]. ROS can promote cell proliferation and metastasis by interfering with mitogen-activated protein kinase signaling pathways and

activating vascular endothelial growth factor (VEGF) and monocyte chemoattractant protein-1 (MCP-1), which can stimulate angiogenesis [13].

Moreover, studies performed on mice fed an alcohol diet have shown exacerbation of inflammation, epithelial-mesenchymal transition (EMT) and fibrosis, and consequent progression to HCC [2]. Pure ethanol does not directly cause inflammation and liver damage, however, toxic by-products of alcohol catabolism such as accumulation of acetaldehyde and free radicals can influence oxidative stress, apoptotic cell death, necrosis and necroptosis [18].

Reference

1. Rehm, J., Taylor, B., Mohapatra, S., Irving, H., Baliunas, D., Patra, J., & Roerecke, M. (2010). Alcohol as a risk factor for liver cirrhosis: a systematic review and meta-analysis. *Drug and alcohol review, 29*(4), 437-445.
2. Yan, G., Wang, X., Sun, C., Zheng, X., Wei, H., Tian, Z., & Sun, R. (2017). Chronic alcohol consumption promotes diethylnitrosamine-induced hepatocarcinogenesis via immune disturbances. *Scientific reports, 7*(1), 2567.
3. Albano, E. (2006). Alcohol, oxidative stress and free radical damage. *Proceedings of the nutrition society, 65*(3), 278-290.
4. Mohamed, A. E., Kew, M. C., & Groeneveld, H. T. (1992). Alcohol consumption as a risk factor for hepatocellular carcinoma in urban southern African blacks. *International journal of cancer, 51*(4), 537-541.
5. Bartosch, B., Thimme, R., Blum, H. E., & Zoulim, F. (2009). Hepatitis C virus-induced hepatocarcinogenesis. *Journal of hepatology, 51*(4), 810-820.
6. Ogunwobi, O. O., Harricharran, T., Huaman, J., Galuza, A., Odumuwagun, O., Tan, Y., ... & Nguyen, M. T. (2019). Mechanisms of hepatocellular carcinoma progression. *World journal of gastroenterology, 25*(19), 2279.
7. Varela-Rey, M., Woodhoo, A., Martinez-Chantar, M. L., Mato, J. M., & Lu, S. C. (2013). Alcohol, DNA methylation, and cancer. *Alcohol research: current reviews, 35*(1), 25.
8. Seitz, H. K., & Homann, N. (2006, April). The role of acetaldehyde in alcohol-associated cancer of the gastrointestinal tract. In *Acetaldehyde-Related Pathology: Bridging the Trans-Disciplinary Divide: Novartis Foundation Symposium 285* (Vol. 285, pp. 110-124). Chichester, UK: John Wiley & Sons, Ltd.
9. Barve, S., Chen, S. Y., Kirpich, I., Watson, W. H., & McClain, C. (2017). Development, prevention, and treatment of alcohol-induced organ injury: the role of nutrition. *Alcohol research: current reviews, 38*(2), 289.
10. Millonig, G., Wang, Y., Homann, N., Bernhardt, F., Qin, H., Mueller, S., ... & Seitz, H. K. (2011). Ethanol-mediated carcinogenesis in the human esophagus implicates CYP2E1 induction and the generation of carcinogenic DNA-lesions. *International journal of cancer, 128*(3), 533-540.
11. Haorah, J., Ramirez, S. H., Floreani, N., Gorantla, S., Morsey, B., & Persidsky, Y. (2008). Mechanism of alcohol-induced oxidative stress and neuronal injury. *Free Radical Biology and Medicine, 45*(11), 1542-1550.
12. Linhart, K., Bartsch, H., & Seitz, H. K. (2014). The role of reactive oxygen species (ROS) and cytochrome P-450 2E1 in the generation of carcinogenic etheno-DNA adducts. *Redox biology, 3,* 56-62.
13. Ratna, A., & Mandrekar, P. (2017). Alcohol and cancer: mechanisms and therapies. *Biomolecules, 7*(3), 61.
14. Seitz, H. K., & Stickel, F. (2007). Molecular mechanisms of alcohol-mediated carcinogenesis. *Nature Reviews Cancer, 7*(8), 599-612.
15. Wu, W. S. (2006). The signaling mechanism of ROS in tumor progression. *Cancer and Metastasis Reviews, 25*, 695-705.
16. Morgan, M. J., & Liu, Z. G. (2011). Crosstalk of reactive oxygen species and NF-κB signaling. *Cell research, 21*(1), 103-115.
17. Longnecker, M. P. (1994). Alcoholic beverage consumption in relation to risk of breast cancer: meta-analysis and review. *Cancer Causes & Control, 5*, 73-82.
18. Ramadori, P., Cubero, F. J., Liedtke, C., Trautwein, C., & Nevzorova, Y. A. (2017). Alcohol and hepatocellular carcinoma: adding fuel to the flame. *Cancers, 9*(10), 130.
19. Cederbaum, A. I. (2012). Alcohol metabolism. *Clinics in liver disease, 16*(4), 667-685.
20. Lieber C.S. Metabolism of alcohol. Clin. Liver Dis. 2005; V.9, P. 1–35.
21. Leung, T. M., & Nieto, N. (2013). CYP2E1 and oxidant stress in alcoholic and non-alcoholic fatty liver disease. *Journal of hepatology, 58*(2), 395-398.
22. Ramadori. P, Cubero FJ, Liedtke C, TrautweinC, Nevzorova YA. Alcohol and Hepatocellular Carcinoma: Adding Fuel to the Flame. Cancers (Basel) 2017; P. 9.
23. Zakhari, S. (2006). Overview: how is alcohol metabolized by the body?. *Alcohol research & health, 29*(4), 245.
24. Heier, C., Xie, H., & Zimmermann, R. (2016). Nonoxidative ethanol metabolism in humans—from biomarkers to bioactive lipids. *Iubmb Life, 68*(12), 916-923.
25. Portela, A., & Esteller, M. (2010). Epigenetic modifications and human disease. *Nature biotechnology, 28*(10), 1057-1068.
26. Holford, N. H. (1987). Clinical pharmacokinetics of ethanol. *Clinical pharmacokinetics, 13*, 273-292.