Head and Neck Cancer

Chapter 3

Alcohol and Head and Neck Cancer: do the Two Mix?

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Abstract

Head and neck cancer (HNC) represents the seventh most common cancer globally. Being that alcohol is one of the major carcinogens of HNC, it has been confirmed that it is heavily involved in the tumorigenesis and development of HNC. Acetaldehyde, a metabolite of alcohol, has been proven to cause carcinogenic effects resulting in a higher risk of HNC development. Furthermore, alcohol has been proven to disrupt DNA methylation via the activation of oncogenes and the silencing of tumor suppressor genes, increase reactive oxygen species (ROS) through enhanced CYP2E1 expression levels and electron leakage from the mitochondrial respiratory chain, and suppress the immune system by altering the actions of cell populations in the innate and adaptive immune response. In addition to the effects of only alcohol, alcohol has been evidenced to combine with other carcinogens such as tobacco, betel nut,

and the human papillomavirus (HPV) to increase the risk of HNC to an even greater degree. Despite knowing alcohol plays a role in alcohol-induced HNC, more research is still needed to determine the specific role alcohol plays in HNC treatment and the mechanisms of alcohol-induced HNC.

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Keyword: Alcohol, Head and neck cancer, Environmental factors, Molecular mechanism, Carcinogen

Abbreviations: 4-HNE: 4-hydroxynonenal; 4-NQO: 4-nitroquinoline-1-oxide; ADH: Alcohol dehydrogenase; ALDH: Aldehyde dehydrogenase; CYP2E1: Cytochrome P450 2E1; DNMTs: DNA methyl transferases; HNC: Head and neck cancer; HPV: Human papillomavirus; hr-HPV: High-risk HPV; NADH: Nicotinamide adenine dinucleotide; N2-EtdG: N2-ethyl-2'-deoxyguanosine; N2-EtidG: N2-ethylidene-deoxyguanosine; SAMe: s-adenosyl-l-methionine; ROS: Reactive oxygen species; RR: Relative risk; SNP: Single nucleotide polymorphism.

1. Introduction

Globally, head and neck cancer (HNC) is ranked seventh among the most common cancers, totaling a staggering 890,000 new cases and 450,000 deaths in 2018 [1]. Over 90% of HNC originates from squamous cells, which cover on the surface of the nasopharynx, oropharynx, and laryngopharynx. There are several high-risk factors of HNC, including alcohol, smoking, betel nut, and human papillomavirus (HPV).

Alcohol is listed as a Group 1 carcinogen by the International Agency for Research on Cancer of the World Health Organization [2]. For HNC located in oropharynx and laryngopharynx, alcohol consumption plays a vital role in tumorigenesis, corresponding to 26.4% of all lip and oral cavity cancers, 30.5% of all other pharyngeal cancers (excluding nasopharyngeal cancers), 21.6% of all laryngeal cancers, and 16.9% of all esophageal cancers [3]. HNC in older patients with heavy use of tobacco and alcohol is slowly declining globally, in part because of decreased usage of tobacco [4,5]. Conversely, the consumption of alcohol is steadily increasing for the most of world. The annual average alcohol consumption of pure ethanol per person is 8.3 liters worldwide and 8.7 liters in the United States [6]. Recently, it has been brought to light that increased alcohol consumption, as a single and co risk factor, has been strongly associated with HNC new cases.

2. Alcohol is the Vital Risk Factor of HNC

Alcohol induces HNC by multiple mechanisms, such as dissolving carcinogens from smoking, dissolving lipids components of the epithelium thus increasing the permeability of oral mucosa, suppressing the innate and acquired immunity, and increasing susceptibility to infections. Moreover, alcohol metabolites have genotoxic and mutagenic effects that interfere with DNA synthesis and repair.

2.1.The direct effect of alcohol on tumorigenesis in HNC

2.1.1. Epidemiology of HNC

For decades, most prospective and case-control studies have confirmed the risks alcohol consumption plays in HNC. Compared with non-drinkers, people who consume 50 grams of ethanol per day display a 2-3-fold increase in the relative risk (RR) for HNC located in the oral cavity, pharynx, larynx, and esophagus [7]. The incidence of HNC also has a dose-dependent relationship with alcohol consumption. The RR of HNC from a light to a heavy drink is 1.13 to 5.13 for oral cavity and pharynx cancer and 1.26 to 4.95 for esophageal squamous cell carcinoma [8].

2.1.2. Effect of alcohol feeding on animal models

Alcohol has been confirmed as a direct carcinogen in multiple animal models with mice and rats [9]. Induction of HNC by alcohol is strongly related to exposure time in animal models. In lifetime exposure models with 10% alcohol in drinking water, rats developed malignant tumors on the oral cavity, lips, and tongue [7,10]. More commonly, alcohol has been wildly coupled with smoking derived carcinogens to induce HNC in animal models, such as 4-nitroquinoline-1-oxide (4-NQO) [11].

2.2. Alcohol combines with other carcinogens to increase HNC risk

2.2.1. The synergistic effect of alcohol and tobacco in HNC

Smoking, a major risk factor of HNC cancer, generates various kinds of carcinogens, such as nitrosamines, benzopy¬renes and aromatic amines, and tar [12]. The co-consumption of alcohol and tobacco synergistically induces HNC, accounting for approximately 75% of oral cancers [13]. RR for oesophageal carcinoma is 44 with co-consumption, which is significantly higher than alcohol (RR=18, 80g/day) or cigarette (RR=5, 20 cigarettes/day) consumption independently.

2.2.2. The synergistic effect of alcohol with betel nut

Betel nut, the fruit of Areca catechu, is widely used as a socially endorsed masticatory product. Nearly 700 million individuals are consuming betel nut in different forms across the globe, most of whom are located in South-East Asia and the Indian subcontinent [14]. Betel nut, which is listed as a group 1 carcinogen, induces oral cancer mainly through the damage of the oral mucus and the carcinogenic effect of arecoline. Co-consumption of alcohol, betel nut, and cigarettes is common. In a previous study, betel nut chewing played a vital role in the development of esophageal squamous cell carcinoma and augmented the carcinogenetic effects of smoking tobacco and drinking alcohol [15]. Another experiment displayed that individuals

from China with all three habits had a higher risk of HNC (odds ratio OR = 20.60, 95% CI 11.75, 36.12) than individuals who had one or two of the three habits of interest. However, because of limited statistical power, the log-likelihood tests did not detect any interactions between two or three of the habits of interest [16]. Consequently, the amplified effect of alcohol in HNC induced by betel nut chewing still requires more analysis in larger populations from different regions.

2.2.3. The synergistic effect of alcohol and HPV

The human papillomavirus (HPV) family has more than 100 genotypes which specifically infect the basal cells of the epithelial mucosa [17]. Based on its ability to undergo cellular transformation, HPV is classified into low-risk and high-risk types. Low-risk HPV is associated with benign lesions such as warts, while high-risk HPV (hr-HPV) causes malignant lesions. HPV6, 11, 16, and 18 are classified as hr-HPV and infect mucosal epithelial cells of the anogenital tract, uterine cervix, the oral cavity, and oropharynx [17]. Alcohol is a potent modulator of immune function, which leads to immune deficiency and increased susceptibility to various infectious diseases. Multiple studies show that alcohol consumption increases the prevalence of genital HPV infection in different populations [18]. Oral HPV is primarily transmitted to the mouth by oral sex. HPV was confirmed as a risk factor especially for oropharyngeal and oral cancer about four decades ago. The number of young patients with HPV positive HNC has significantly increased in recent years. However, evidence about the causal association between HPV, alcohol, and HNC is still limited. Recently, one study evaluated the effect of hr-HPV infection, alcohol, and tobacco on the high incidence of HNC in the North-East region of India [19]. A significant association was observed between hr-HPV infection and habitual alcohol consumption ($p = 0.02$). The study demonstrated that chewing tobacco and alcohol consumption may act as risk factors for hr-HPV infection in HNC. The results suggested that alcohol, tobacco, and hr-HPV infection act synergistically or complement each other in the process of HNC development and progression [19].

2.2.4. Alcohol association with oral microbes

Acetaldehyde is the major carcinogenic metabolite of ethanol and previous studies have shown that oral microorganisms are capable of producing acetaldehyde from ethanol [20,21]. Salivary acetaldehyde levels can reach 10-100 times higher than blood acetaldehyde levels. Levels of salivary acetaldehyde can be reduced substantially by rinsing the mouth with antibacterial chlorhexidine, indicating that oral bacteria are the major contributors to the local production of acetaldehyde [22]. The overgrowth of oral microorganisms often results from poor oral hygiene which is a risk factor for HNC that is independent of smoking and alcohol. In addition to the microbial production of acetaldehyde in the oral cavity, acetaldehyde in the oral cavity may also be derived from human ethanol metabolism in the parotid gland [23,24].

3. Molecular Mechanisms behind Alcohol-associated HNC

3.1. Carcinogenic effect of acetaldehyde

The metabolism of alcohol (ethanol) occurs when acetaldehyde is first generated by alcohol dehydrogenase (ADH) from ethanol and is then converted to acetate by aldehyde dehydrogenase (ALDH). Acetaldehyde is considered to be the major metabolite of alcohol which contributes to its carcinogenic effect in HNC [25]. Single nucleotide polymorphism (SNP) of ADH and ALDH, which regulates the generation and degradation acetaldehyde, has been linked to the incidence of HNC. Class I is the main form out of the five classes of ADH in humans, which consists of α, β, and γ subunits that are encoded by the genes ADH1A, ADH1B, and ADH1C. SNPs exist in ADH1B and ADH1C [26]. ALDH2 is the major family member of ALDH. Alcohol consumption, oral hygiene (as a proxy measure for the growth of oral microorganisms), and alcohol-metabolizing genes (ADH1B and ALDH2) are the risk factors of HNC [27]. Compared with the parent, the ADH1C variant in which its valine is substituted for isoleucine, increases the metabolism of ethanol by 2.5-fold, according to high acetaldehyde levels in the saliva. SNP G-A (amino acid, lysine-glutamine) of the ALDH2 gene dramatically decreases the activity of enzymes, which accounts for 40-50% of Asians. Salivary acetaldehyde (except when derived from the blood) is also generated in the parotid gland, which has a relevant association with ALDH2-deficiency [28]. Microbial production of acetaldehyde may play a key role in increasing the risk of HNC for alcohol drinkers who carry the slow ADH1B genotypes, with the highest HNC risk occurring in alcohol drinkers with worst oral hygiene [23]. Oral cavity and esophagus cells have more damages induced as a result of containing up to 100-fold more acetaldehyde than other head and neck regions. Acetaldehyde interferes with DNA synthesis and induces DNA damage by induction of DNA adducts. N2-ethylidene-deoxyguanosine (N2-EtidG) is the most abundant acetaldehyde adduct from the reaction with deoxyguanosine [29]. It is quickly converted to a stable adduct N2-ethyl-2'-deoxyguanosine (N2-EtdG) by a reducing agent such as glutathione or ascorbic acid [30]. α-methyl-γ-OH-propano-deoxyguanosine is another DNA adduct with more a mutagenic effect than the N2-EtidG [7].

3.2. The effect of alcohol on DNA methylation and ROS generation

DNA methylation is one of the epigenetic mechanisms hijacked by cancer cells through hypermethylation of tumor suppressor genes and hypomethylation of oncogenes. Alcohol disrupts DNA methylation causing carcinogenesis through the activation of oncogenes and the silencing of tumor suppressor genes. Disruption of methyl transfer by alcohol and metabolites is one possible mechanism in HNC carcinogenesis. Alcohol decreases the methyl transfer reaction through the inhibition of S-adenosyl-l-methionine (SAMe) synthesis, which is the universal methyl group donor and enzyme activator [31,32]. Moreover, acetaldehyde inhibits

the activity of DNA methyl transferases (DNMTs) which induces oncogene hypomethylation. In rats, acetaldehyde inhibits global hepatic DNA methylation except in tumor suppressor gene TP53. Hypomethylation of oncogenes induces cell transformation without strict surveillance of p53. Reactive oxygen species (ROS) are believed to be one vital cause of cancer and can be generated by the cytochrome P450 2E1 (CYP2E1)-dependent microsomal mono-oxygenase system or mitochondrial respiratory chain. Ethanol magnifies ROS generation through enhanced CYP2E1 expression levels and electron leakage from the mitochondrial respiratory chain, which is associated with the stimulation of reduced nicotinamide adenine dinucleotide (NADH) shuttling into mitochondria. 4-hydroxynonenal (4-HNE) is a lipid peroxidation product consequently generated as a result of the ROS produced by CYP2E1. 4-HNE reacts with DNA bases to form the exocyclic DNA adducts such as 1, N6-ethenodeoxyadenosine, and 3, N4-ethenodeoxycytidine [7,32]. These adducts are highly mutagenic and lead to a mutation at codon 249 of TP53 which renders cells more resistant to apoptosis and causes uncontrolled proliferation [33]. Mutations in TP53 at codon 249 are common in hepatocellular carcinoma, but rare in squamous-cell carcinoma of the head and neck [34,35].

3.3. The effect of alcohol on immunosuppression

The immune system defends humans from an array of conditions, ranging from pathogenic assault to malignant transformation. Alcohol suppresses the immune system via altering the actions of cell populations in the innate and adaptive immune response [36]. Increased HPV infection in the oral cavity may be directly induced by the immunosuppressive effects of alcohol. Acute alcohol consumption inhibits inflammatory responses in the innate immune system whereas chronic alcohol consumption accelerates inflammatory responses to promote pro inflammatory immune responses. Chronic alcohol exposure also disrupts the normal function of cellular and humoral immunity in the adaptive immune response. All these effects enhance HPV infections and ROS generation through sterile inflammation in the oral cavity. Moreover, alcohol suppresses the immune system to modulate the composition of pathogenic and commensal organisms in the microbiome of the oral cavity [36]. Microbiomes with elevated ADH expression, which generate high amounts of acetaldehyde, have been found in a greater abundance in alcoholic HNC patients [37]. Cancer recurrence may be promoted by immunosuppression of alcohol due to decreased immune surveillance in HNC. One retrospective review study exhibits evidence for increased risk of cancer recurrence in HNC patients who continue to drink [38,39].

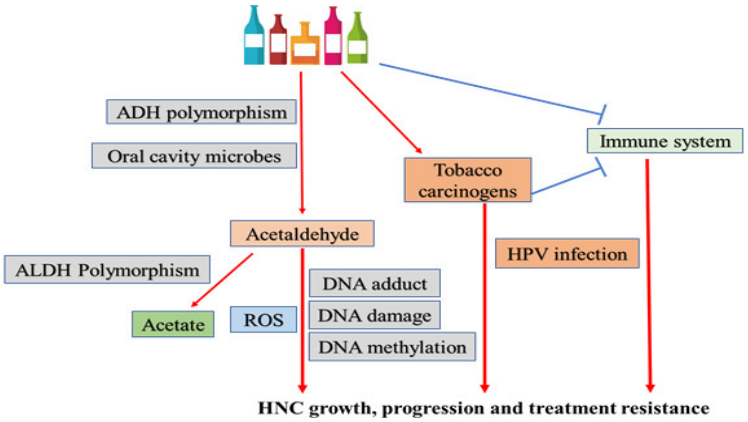

Figure 1: The potential mechanisms of alcohol on the tumorigenesis in HNC

4. Conclusions

As one of the major carcinogens of HNC, alcohol is heavily involved in tumorigenesis and the development of HNC. Recently, mounting studies show HNC with alcohol consumption presents a more aggressive phenotype and a poor response to therapy. Limited alcohol consumption is important not only for the prevention of HNC but also for treatments of HNC such as chemotherapy, radiotherapy, and immunotherapy, especially for cases regarding oral cancer and esophageal cancer. The insufficient knowledge about the specific role alcohol plays in HNC treatment results in missed opportunities to improve the overall quality of treatment of HNC patients, highlighting the need for rigorous scientific studies to further uncover the mechanisms by which alcohol disrupts HNC therapies. By the same token, researches urgently need to pinpoint the mechanisms of alcohol in HPV induced HNC, as there has been a dramatic increase in patients showcasing HPV positive HNC.

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6. Competing interests

The authors declare no competing financial interests.

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