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Induction of skin carcinogenicity by alcohol and ultraviolet light

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Summary

In western societies, casual consumption of alcohol during such outdoor activities as barbecuing and sunbathing is common. The current literature shows that alcohol drinkers have increased episodes of sunburn and a higher prevalence of skin cancer. Moreover, recent evidence suggests that the combination of subcarcinogenic (minimal) ultraviolet (UV) exposure with other behavioural, environmental and xenobiotic factors has resulted in increased incidents of skin-related health problems that also result in skin-cancer formation. We hypothesize that the combination of alcohol consumption with UV radiation can potentiate the skin carcinogenic effects through the intermediate biproducts or metabolites of alcohol, which serve as the photosensitizers, consequently enhancing the cellular damage. We have proposed a mechanism that explains the combined alcohol–UV radiation carcinogenicity and its potential involvement in enhancing skin damage in the multistep skin carcinogenesis process. Previous literature has explored this mutual effect but no studies have definitively ascribed the reasons for increased skin cancer prevalence among alcohol drinkers. Nevertheless, the preceding epidemiological data and clinical studies recognize this matter, making the further testing of this hypothesis necessary.

Introduction

The prevalence of skin cancer in western society is increasing exponentially. More than 1 million new cases of nonmelanoma skin cancers (NMSC) are diagnosed each year in the USA, accounting for almost 50% of all cancer cases.[1] The incidence is increasing by > 10% a year, leading to a 30% lifetime risk in the USA population of developing a basal cell carcinoma (BCC).[2] The lifetime risk of squamous cell carcinoma (SCC) is estimated to be 9–14% among men and 4–9% among women.[3]

Skin carcinogenesis is a multistep process comprising of initiation, promotion and progression, in which environmental carcinogens and lifestyle-related factors play a major role.[4] Although many aetiologies have been suggested, solar ultraviolet (UV) radiation is thought to be the major cause of skin cancer in human populations.[2,3] There is convincing evidence that excessive exposure to UV radiation is the principal cause of DNA damage, at least for NMSC, and is a complete carcinogen with both initiating and promoting activities.[5] However, recent evidence suggest that subcarcinogenic (minimal) UV exposure in combination with other behavioural, environmental and xenobiotic factors results in increasing episodes of skin-related health problems that also result in the formation of skin cancers.[5–9] This compelling evidence suggests that the combination of environmental and lifestyle-related factors can increase the carcinogenic effects of these agents to a level greater than their individual states alone at subcarcinogenic doses.

In western societies, casual consumption of alcohol during such outdoor activities as barbecuing and sunbathing is common. Excessive alcohol consumption, seen in teenagers and adults, is often seen on public beaches in the USA and Europe, as well as many other parts of the world. We hypothesized that alcohol consumption in combination with sunlight can potentiate the carcinogenic effects, which is supported by recent literature. In an article by Warthan *et al.*,[10] it was

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shown that alcohol use increases sunburn severity, thus repeated simultaneous exposure to UV radiation may lead to a greater incidence of precancerous and malignant skin lesions. In another study by Mukamal,[11] a survey was used to examine the relationship between alcohol consumption and prevalence of sunburn. The results of the survey indicated a positive association between the extent of drinking and number of sunburns, accrediting about 18% of all sunburn cases to alcohol use.[11]

Alcohol consumption and carcinogenicity

Alcohol is among the most widely misused addictive drug in the US and other western societies. A marked increase in alcohol consumption has been noted, particularly in teenagers, during the past decade in 14 European countries.[12] It is estimated that 7% of the adult population in the USA have an alcohol problem.[13] According to recent statistics provided by the US Centers for Disease Control and Prevention, 48% of adults ≥ 18 years of age were current regular drinkers and 12% were current infrequent drinkers.[14] The overall alcohol consumption per capita in the USA increased during the period 1935–2005 (Fig. 1).[15] Excessive alcohol consumption has been associated with increased incidence of a variety of sociobehavioural disturbances and illnesses, including cancers.[16] Many published studies support the notion that heavy alcohol consumption is a significant risk for certain cancers (including liver, oesophagus, oropharyngeal, colorectal and breast cancers).

The mechanisms by which alcohol ingestion promotes carcinogenesis are not well understood. Several mechanisms have been proposed, such as induction of microsomal cytochrome P450 enzymes that activate procarcinogens; generation of acetaldehyde and reactive free radicals and intermediates; formation of DNA strand breaks; impairment of the liver's ability to metabolize dietary nitrosamines; and impairment of the immune system and nutritional status.[17] Although alcohol itself is not a known carcinogen, it has been suggested that the carcinogenic effects of alcohol consumption is primarily due to its conversion to acetaldehyde (AcH) soon after its ingestion. AcH is a major metabolite of ethanol and is a known classified carcinogen.[18]

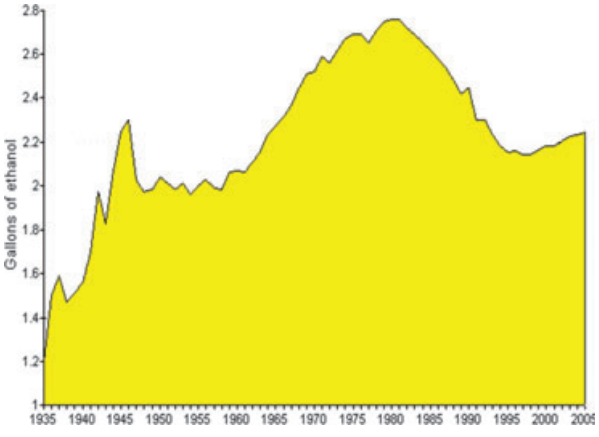

Figure 1 Total per capita ethanol consumption, USA, 1935–2005.

Alcohol consumption and cancer of the skin

Accumulative epidemiological data suggests that alcohol consumption is a risk factor for increased incidence of cancer of the skin, mouth and epithelial surfaces of the head and neck.[14] Skin cancers such as BCC, SCC and melanoma have been found to have a higher incidence in alcohol drinkers than in nondrinkers.[5,10,17,19–22] UV radiation alone can act on skin as a complete carcinogen, at least for NMSC, with both initiating and promoting activities.[5] However, epidemiological studies strongly suggest that alcohol drinkers are more susceptible than nondrinkers to the acute and chronic damaging effects of the sun on skin. Acute exposure to UV radiation can cause a marked sunburn reaction that leads to severe erythema, oedema, pigmentation and blistering, with histological evidence of increased inflammation and hyperplasia of the skin,[5] while chronic exposure may result in premature skin ageing and cancer.[5] A survey by Warthan *et al.* revealed that people who consumed alcohol during time spent at the beach had more severe sunburns and required more frequent analgesic use for postsunburn recovery than nondrinkers.[11] Furthermore, in a large population-based survey conducted by Mukamal[11] on > 300 000 adults, alcohol consumption was positively associated with an increased number of sunburns. This evidence is further supported by several epidemiological studies. BCCs comprise nearly 80% of all skin cancers, with a prevalence of more than 1 million new cases per year in the USA.[1] Several large population cohort studies,[19–21] including a carefully undertaken study by Freedman *et al.*,[21] investigated the association between alcohol intake and BCC adjusting for various health, sun exposure and sun-sensitivity factors; their results indicated significant increase in incidence of BCC with alcohol intake ($P < 0.0001$), which was increased in those with a history of moderate to high sun exposure plus alcohol intake. Those who reported no alcohol consumption, those who drank < 1–2, 3–6, 7–14 and > 14 drinks/week had multivariate risks of 1.1 (95% CI 0.9–1.3), 1.3 (1.1–1.5), 1.4 (1.2–1.7) and 1.0

(0.7–1.6), respectively.[20,21] From these studies it was concluded that those who consumed > 30 g of alcohol were 40% more likely than abstainers to have a BCC.[20,21] Chronic patients with alcoholism have an increased incidence of infiltrative BCC, which is an aggressive subtype.[23] In general, the clinical course of a disease in patients with alcoholism has been noted to be more aggressive than in people who do not have alcoholism.[13] Alcohol consumption has also been shown in multiple epidemiological studies to enhance the risk of SCC of the mouth and head and neck region.[24] Melanoma, the most malignant of all skin cancer types, accounts for 75% of deaths from skin cancer.[1] Its association with alcohol consumption was mostly limited to case–control studies in the past decade.[17,25] However, in a large population cohort study, melanoma risk increased with increasing alcohol use (risk ratio 2.1 and 95% CI 0.9–4.8 for > 14 drinks/week compared with no alcohol).[22] In conclusion, the aforementioned clinical epidemiological studies strongly support the notion that alcohol consumption is a risk factor for NMSC and melanoma. However, the precise mechanism by which alcohol induces cancers including skin cancer is unknown. Various epidemiologists advocate that this should be further investigated to understand the underlying mechanism.[10,20,22] Our current hypothesis provides a possible mechanism relating alcohol intake to sun exposure, as well as their mutual carcinogenic effect.

Possible mechanism(s) of carcinogenesis induced by alcohol and ultraviolet light

We hypothesize that alcohol (ethanol) intake in the presence of UV radiation can substantially enhance cellular damage and subsequently lead to formation of skin cancers. Ethanol is converted to AcH and metabolized into the body organs soon after its ingestion. This highly reactive chemical serves as a photosensitizer, generating reactive oxygen species (ROS) and related intermediates (ROI) upon exposure to UV radiation. ROS generated by AcH-UV further induces oxidative DNA damage, enhances the binding of AcH to DNA (genetic effect), and activates signal-transduction cascades and prostaglandin synthesis (epigenetic effect). Thus, the combination of alcohol and UV exposure potentiates both initiating and promoting activities, thereby leading to synergistic carcinogenicity.

The underlying cellular mechanisms for the damaging effects of alcohol consumption are poorly defined and the extent of their effects on different cell systems are not clear.[26] Acute and chronic alcohol consumption appears to result in different patterns of tissue injury. ROS, neutrophils, cytokines and chemokines are some of the factors known to contribute to alcohol injury.[26] Ethanol is distributed rapidly into body fluids and can be sampled from multiple body fluids, including blood, sweat, saliva, urine and expired air (breath alcohol). Almost all the alcohol that enters the body is metabolized, primarily to AcH and acetate by the enzymes alcohol dehydrogenase (ADH) and aldehyde dehydrogenase (ALDH), respectively.[27] ADH and AcH, present in body tissues, including skin, contribute to the overall metabolism of ethanol.

AcH is a highly reactive chemical and can complex with tissue proteins and other biological compounds to form AcH adducts.[28] Production of free radicals as a result of AcH oxidation by enzymes and cellular fractions result in the production of AcH adducts in various tissues including skin, the presence of which has been identified by *in vitro*[29,30] and *in vivo* experiments with oral administration of ethanol.[27,31,32] These adducts persist for hours to days in the body after the elimination of ethanol and can be quantified experimentally, but the acetate concentrations are known to be related to recent alcohol consumption only.[29 33]

Throughout the years, evidence has accumulated suggesting an important role of AcH and/or its metabolism in the different actions of alcohol. For example, increased levels of human AcH cause a number of typical skin effects, such as vasodilation associated with increased skin temperature, a subjective feeling of heat and facial flushing.[28] AcH metabolism can give rise to the formation of ROS, and evidence exists that oxidative stress is enhanced in tissues exposed to alcohol.[26,34] However, local accumulation of ROS and related free-radical species reflects a balance between their formation and conversion, a balance that appears to be carefully regulated by signalling systems that are part of the cellular stress response systems. Ethanol treatment may affect this balance, not only by enhanced formation of ROS or depletion of oxidative stress defences but also by interfering with the control of cellular stress signalling. Such common underlying mechanisms of action of ethanol may result in differential effects in individual tissues, depending on the functional context and on other tissue-specific stress conditions including external physical stimuli, such as UV radiation exposure, as in our hypothesis.[26]

Testing the hypothesis

Overwhelming evidence indicates that ROS and related intermediates play an important role in the initiation and promotion of carcinogenesis.[5] Although other

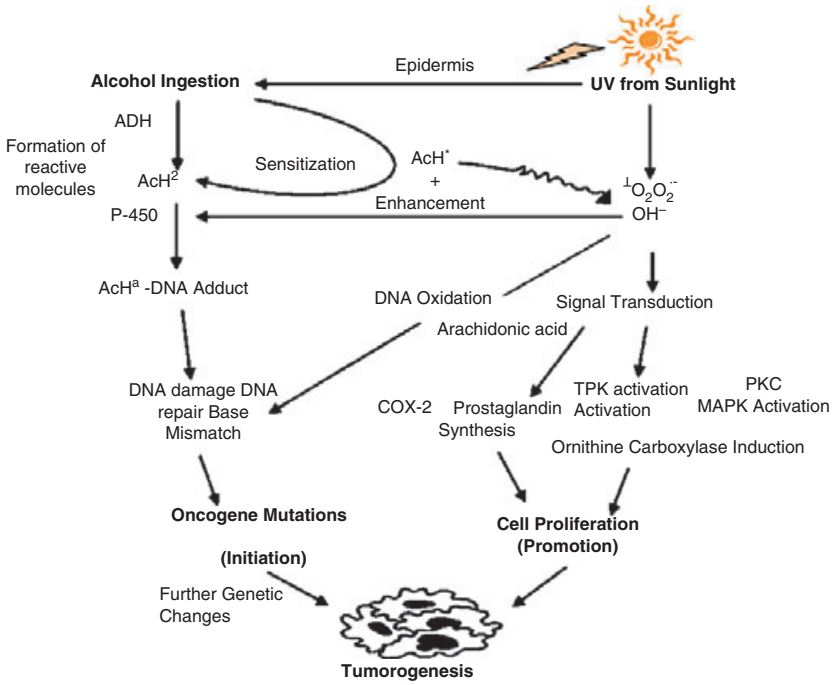

Figure 2 Alcohol photocarcinogenesis model. AcH[a]: metabolic acetaldehyde (AcH), a highly reactive byproduct of ethanol converted by the alcohol dehydrogenase enzyme (ADH); AcH*: a photodynamically triple state of AcH.

mechanisms may exist, we propose a 'ROS-centred' hypothesis that alcohol metabolites serve as a photosensitizer to generate massive numbers of ROS upon UV irradiation (Fig. 2). From this central hypothesis, the primary and secondary hypotheses have been derived. The primary hypothesis: ROS cause oxidative DNA damage and enhance the AcH–DNA binding (genetic effect), thus resulting in genetic mutation and leading to the initiation of carcinogenesis. The secondary hypothesis: ROS potentiate the activation of signal-transduction cascades (epigenetic effect), thereby stimulating cell proliferation and leading to tumour promotion. Accordingly, the combination of alcohol and UV radiation synergistically potentiate carcinogenicity. The uniqueness of this hypothesis is that the interaction between alcohol and UV radiation results in 'a third genetic damage' (oxidative DNA damage) and sensitization of signal-transduction cascades. There is supporting evidence that UV irradiation in combination with chemicals leads to generation of singlet oxygen and superoxide anions[28] and that the photosensitizing chemicals enhance the production of H_2O_2 and the formation of 8-hydroxydeoxyguanosine in UV-irradiated human cells, similar to results found in mouse skin.[4] This damage subsequently leads to cancer formation.[5] Therefore, the proposed hypothesis has a good rationale, is substantiated by clinical and epidemiological information and can be tested experimentally.

Learning points

- The prevalence of skin cancer in western society is increasing exponentially.
- Carcinogenesis is a multistep process comprising initiation, promotion and progression.
- UV radiation in combination with behavioural, environmental and xenobiotic factors can increase susceptibility to skin cancer.
- Alcohol consumption has seen a marked increase in recent years and has been associated with increased incidence of cancers.
- Alcohol consumption increases the incidence of skin cancer in mice, the prevalence of sunburns in humans, and the incidences of BCC, SCC and melanoma.
- Although alcohol itself is not a known carcinogen, its metabolite, AcH, is a highly reactive chemical that can persist after ethanol is eliminated.
- Ethanol is distributed rapidly into body tissues and almost all the alcohol that enters the body is metabolized.
- It is hypothesized that the intermediate byproducts of alcohol, which serve as photosensitizers, can enhance cellular damage in combination with UV radiation, increasing the risk for carcinogenesis.

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