

The Interaction Between Biological and Sociocultural Factors Increases Risk of Cancer in East Asian Alcohol Flushers

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Abstract

One of the most common causes of human cancer is alcohol consumption. There has been evidence that shows drinking increases the risk of cancer in the mouth and throat, larynx, colon, liver, female breast, and especially the esophagus. However, much of the existing data is collected from Western countries. This literature review aims to evaluate the interaction between genetic influences, behaviors, and environments for the development of cancer through the consumption of alcohol in East Asian individuals. The targeted population was selected specifically for their unique facial flushing reaction after consuming alcohol. Alcohol flushing is an allergic response triggered mainly by the inactive aldehyde dehydrogenase-2 (ALDH2) genotype. Study participants range from adults in East Asian countries (China, Japan, and Korea) to college students with East Asian ethnicities in the United States. While previous research has suggested the association between ALDH2 inactive gene flushing response and alcohol-associated cancers, Asian flushers are more at risk due to social, psychological, and cultural influences on drinking behavior.

Keywords: Alcohol Consumption, Sociocultural Context, Inactive Aldehyde Dehydrogenase-2, Asian Flush, Cancer Risk

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Introduction - Biopsychosocial Factors in Alcohol Associated Cancers: A Literature Review

While alcohol could be consumed recreationally and considered a social lubricant when consumed at a moderate level, it is also a well-established risk factor for carcinogenesis (Choi et al., 2017). Many epidemiological studies have pointed out that the mass proportion of cancer cases is alcohol-related. However, few studies have investigated the role of sociocultural factors that may moderate the amount consumed, and thus cancer risk. Furthermore, there has been limited literature about the risk among the East Asian population. Notably, the difference in genetic makeup and sociocultural factors between Asian and Western countries must be considered.

Most East Asian populations inherited the deficient alcohol-metabolizing enzyme ALDH2, resulting in a unique physical reaction called Asian flush in response to alcohol consumption. Individuals with the inactive enzyme have been shown to have an increased risk of alcohol-related cancer, in which drinking is responsible for an extra 58%-69% chance of esophageal cancer (Brooks et al., 2009). Despite having a lower tolerance for alcohol compared with other ethnic groups, binge drinking behavior in Asian flushers is mostly characterized by social purposes (Grant et al., 2004; Ko & Sohn., 2018). Multiple social factors like social settings, social context, and the presence of peers could contribute greatly to mass alcohol consumption. Additionally, Asian cultures' belief in the importance of maintaining social harmony should also be taken into account. This demonstrates how ethnic differences in genetic makeup, reactions to alcohol, and beliefs in Asian descent individuals interact and contribute to their alcohol-related cancer development. A better understanding of this relationship will help primary intervention for alcohol-related cancer (Hendershot et al., 2010).

The purpose of this review is to examine the interconnections between genetic predisposition and sociocultural factors to the development of cancers in persons of Asian ancestry. Filling the gap of understanding the facial flushing reaction and an individual's perception, motivation, and behaviors related to alcohol drinking will aid risk prevention. Many studies were conducted qualitatively with questionnaires and self-reports to gain insight into individuals' alcohol consumption habits. The facial flushing reaction was based on the results of self-reports and genetic screening for the ALDH2 gene. Participants represent East Asian populations and Asian Americans of the same national origins. From the literature, it was found that the strong gene-environment interaction between the ALDH2 inactive genotype and the socio-cultural context of drinking can impact the risk of cancer development in Asian populations.

The Flushing Response

Wolff was the first to identify flushing as an ethnic difference in alcohol reaction between Caucasian and Asian individuals in 1972 (as cited in Johnson & Nagoshi, 1990). Through photometric measures of the skin after administering a small amount of alcohol to participants, adults of Asian ancestry flushed (facial redness) while Caucasians did not. The same result was observed in children who were not previously exposed to alcohol. The study demonstrated that flushing reactions did not mitigate due to constant exposure to alcohol. Wolff's findings asserted the phenomenon of the 'Asian flush' and laid the foundation for future research on the underlying mechanisms of this difference. Approximately 40% of the

East Asian population experience facial flushing after consuming alcohol, which demonstrates the possession of the inactive alcohol metabolizing gene (Lee et al., 2014).

Facial redness is only one of many reactions to alcohol intoxication; Erikson (2006) summarized the available acetaldehyde research and some other notable effects were found to be increased skin temperature, subjective hotness, increased heart and respiration rates, reduced blood pressure, dry mouth or throat, nausea and headache, and even euphoria. Alcohol dehydrogenase (ADH) and acetaldehyde dehydrogenase 2 (ALDH2) are the two key enzymes responsible for the metabolism of alcohol in the liver. However, ALDH2 is often assessed in the association between genetic polymorphism and flushing, due to its role in converting the toxic intermediate acetaldehyde found in alcohol to nontoxic acetate Matsumura et al. (2019). The study mimicked human ALDH2 deficiency in mice through molecular and clinical phenotype modifications. Both the genetic correction and the control group underwent acute alcohol treatment. Results of the study showed an increased level of blood acetaldehyde levels, indicating the incompetence of alcohol metabolism in the liver of ALDH2 deficient mice. These findings support the genetic basis of differences in alcohol reaction, which is consistent with Wolff's original study (1972).

Additionally, the mice who were genetically treated for ALDH2 deficiency performed better in behavioral tests in comparison to the untreated ALDH2 control group (Matsumura et al., 2019). The result indicated that alcohol-induced maladaptive behavior could be associated with ALDH2 deficiency. While translating results from mice to humans has proved challenging, the result suggested a review of alcohol-related behavior in humans with the ALDH2 flushing gene is necessary to further understand the role that the Asian flush symptom plays in an individual's decision to consume alcohol.

Alcohol Drinking Behavior in East Asian Individuals

Given the prevalence of Matsumura and colleagues' (2019) findings of the association between maladaptive behaviors and genetic variations of the ALDH2 gene, a review of studies involving drinking behavior in individuals with ALDH2 deficiency. These include the cultural and social context in which the behavior of alcohol consumption took place (K. Kim et al., 2019; Ko & Sohn, 2018; Nie et al., 2018; O'Shea et al., 2017; Parrish et al., 1990).

Sociocultural Context of Alcohol Consumption

The consumption of alcoholic drinks has been widely accepted as social behavior. Alcohol could be consumed either ceremoniously, religiously, or dismissively. The contexts of consumption might be universal, but underlying factors like motivations and attitudes towards drinking, or manner of consumption vary between countries (Ko & Sohn, 2018). Especially in East Asian countries where social harmony (members of a community maintain its peace collectively) is prioritized over individual needs, alcohol consumption is characterized more by adherence to group norms. As cited by Lincoln (2016), Craig (2002) found that the behavior of collective alcohol consumption in Vietnam was often accompanied by a chant. Not only does the chant inflict peer pressure on members of the party, but the sharing of alcohol between members after hearing the chants has also become customary. Within the same review, the author used MacAndrew and Edgerton's (1969) findings to suggest that alcohol temporarily relieved hierarchies between members. This result suggests that an extended function of alcohol within social-professional contexts exists. Employees could conform to the drinking behavior of their supervisors to benefit their professional

development. Ko and Sohn (2018) recognized the lack of literature regarding drinking culture and drinking as social behavior outside of Western countries. They studied data collected from 1,185 subjects in Korea with a drinking frequency of at least once a month. Drinking behavior was measured by examining the amount and frequency of drinking across different situations. Results from the study demonstrated that drinking in Korea is most prominent in social situations as shown by the large proportion of social drinking compared to drinking alone. For example, going out with friends made up 44.2% of drinking occasions, while drinking with meals at home was only 27.5% ($P < .001$). Results were even consistent across different age groups, with only a notable increase in social professional contexts in individuals older than 50. The results confirmed the importance of the presence of others in compliance with alcohol consumption. Based on the findings of the study, the primary source of drinking in Korea was to promote interpersonal connections or develop professional relationships (Ko & Sohn., 2018).

As the belief in social harmony is consistent across East Asian countries, this is not limited to Koreans. A cross-sectional study conducted in China utilized self-reported ratings to assess the relationship between harmful drinking behavior and social capital (Nie et al., 2018). Since there is no universal measurement for social capital, researchers (2018) used participants' self-ratings of social cohesion, membership in social organizations, and frequency of participation to operationally define social contexts ($N = 13,610$). Participants across 3 different cities in China reported a higher prevalence of drinking behavior with their membership in social organizations, which was also noted by Ko and Sohn (2018). In their study, drinking was found most prominent in social settings. Nie and colleagues (2018) also demonstrated the gender difference in social contexts in which harmful drinking behavior occurred. They found that men engaged in harmful drinking behaviors more often with a frequency of social participation, while harmful drinking behaviors ascended with high social cohesion among women. This suggests that different social contexts could elicit different drinking behaviors.

The role of culture as a determinant of drinking behavior was investigated by the correlation between consumption level and the embarrassment affect related to the flushing reaction among Japanese ($N = 846$) and Japanese-Americans ($N = 737$) (Parrish et al., 1990). Drinkers with identified flushing status were interviewed regarding their estimated alcohol intake in the past 2 weeks, their flushing tendency, and their frequency of subjective drunkenness. Each participant was then asked whether they felt embarrassed about flushing. While flushers reported consuming less alcohol, the difference between the frequency of drunkenness between those who were embarrassed by flushing and those that did not flush was insignificant. Furthermore, Japanese participants reported that they were less embarrassed by their flushing reactions than their Japanese-American counterparts (Parrish et al., 1990). Cultural differences in the emotional appraisal of alcohol-induced flushing between Japanese and Japanese Americans highlight the social nature of drinking in East Asia. Taken together, these observations demonstrate that drinking behavior in East Asian individuals is strongly influenced by both cultural customs and social engagement. While turning red signals individuals to stop drinking, the protective role of flushing may be canceled out by the pro-drinking social cultures of East Asian populations.

Drinking Behavior in Flushers

The sub-population of overseas East Asian individuals, especially at Western universities, is of special concern due to the social nature of their environment (Brooks et al., 2009). O'Shea

and colleagues (2017) were the first to investigate the relationship between drinking behavior in East Asian college students who possess the inactive ALDH2 gene and the drinking behavior of peers around them ($N = 318$). Researchers looked at students' reports of the amount of alcohol consumed and the number of intoxicated friends within a social setting. Overall, the amount of alcohol consumed by East Asian college students was positively correlated with peer drunkenness. While non-flushing students consumed more alcohol overall, flushing students conformed to peer drunkenness (drunken behavior by peers) more. The result showed alcohol consumption at the highest level when peer drunkenness was also at the highest. This is important because it demonstrates how peer drunkenness establishes a temporary social norm that influences the perceived permissiveness of alcohol consumption in flushers. The risk effects of exposure to peer pressure were also reported in K. Kim and colleagues' (2019) mixed-method study of drinking behavior among flushers college students in Singapore. Findings from these studies also demonstrated the impact of membership in a highly social group, such as college or university, on the tendency to consume alcohol, as also found by Nie and colleagues (2018).

While the survey did not report a heightened amount of alcohol consumed by flushers compared to non-flushers, flushers reported feeling unspoken pressures in drinking sessions (K. Kim et al., 2019). During the group discussion, flushers demonstrated the need for intoxication to conform to non-flusher peers. They refrained from discussing alcohol-associated health risks with flushers within the drinking environment to maintain social harmony. Still, they reported supportive intentions to their flusher friends outside of pro-alcohol social settings (K. Kim et al., 2019). This is important because it demonstrated the bidirectional ambivalence of peer pressure within an alcohol session. First, flushers overestimate expectations from their peers and drink more than what their peers expect of them. Their peers then feel pressured to not disrupt the subjective norm for drinking created by flushers'. This suggests that the permissive drinking norms within a social context are cultivated by both flushers and non-flusher peers, leading to pressure-driven drinking among flushers.

Lack of Knowledge of Asian Flush-Related Risk

The poor knowledge about the flushing reaction, the moderate drinking guideline, and the long-term consequences of drinking put East Asian college students who flush at greater risk (K. Kim et al., 2019). Both flushers and non-flushers participants generally reported poor management of their drinking behavior due to a lack of understanding of what constituted a standard alcoholic drink. Thus, participants reported subjective measures of drinking to quantify excessive consumption rather than keeping counts. For example, drunkenness was reported to be measured with physiological reactions and mental or emotional states. Also apparent was the lack of knowledge about Asian flush, with more than half of the participants reported not knowing about both the explanation and the symptoms. Furthermore, K. Kim and colleagues found that only 42% of flushers reported knowing about alcohol-related long-term health effects. The results highlighted the need for education about alcohol-related risks and moderate drinking guidelines for Asian flushers. Psychoeducation can also illuminate the roles of beliefs, behavior, and motivations to advocate for better impulse control within social drinking circumstances.

Risk of Alcohol-Related Cancer Among Flushers

Given the prevalence of alcohol-related cancer risk and mortality, individuals with the inactive alcohol metabolizing gene may be at an elevated risk.

Alcohol Consumption Increases Risk of Cancer

While the development of cancer is a result of both genetic makeup and maladaptive behaviors, Lichtenstein and colleagues (2000) found that behavioral factors (72%) are more dominant than genetic factors (28%) (as cited in H. Kim et al., 2019). Among those behavioral factors, the consumption of alcohol is of particular interest. H. Kim et al., (2019) conducted a case-control study including 440 cases of newly diagnosed gastric cancer to examine the associated risk and alcohol consumption in Korea. Gastric cancer patients were asked about their drinking status, frequency, and amount. Results showed no statistically significant connection between alcohol consumption status or frequency to gastric cancer risk, the same was observed in alcohol consumption frequency. However, higher alcohol amounts were significantly correlated with a higher risk for gastric cancer. When stratified by sex, the positive association between alcohol consumption of $\geq 40\text{g/day}$ for men was not found to be significant by H. Kim and colleagues. Meanwhile, women who consumed half the amount (20g/day) still have significantly increased risk.

Although large consumption of alcohol is often found to be associated with an increased risk for gastric cancer (H. Kim et al., 2019), few studies have considered light and moderate amounts, which are the more prevalent levels of alcohol consumed within social contexts (Choi et al., 2017). Results from Choi and colleagues were inconsistent with H. Kim's findings due to a much larger sample size ($N = 23,323,730$) with various types of cancers (esophageal, gastric, colorectal). Researchers conducted a nationwide survey all over Korea using questionnaires regarding the amount and frequency of alcohol consumed. Individuals who consumed more than 30g/day were defined as heavy drinkers and less than 30g/day were classified as mild to moderate. After a median 5.4 years follow-up, even individuals who reported consuming less than 10g/day were found to have one of the three types of cancer. Moreover, the risk continuously increased until the daily amount was 20g . However, only the risk of esophageal cancer was found to be dose-dependent by H. Kim's team (2019). Choi and colleagues' findings contradict H. Kim et al. showing a stronger effect of alcohol consumption, suggesting that consumption of alcohol in any amount elevates the risk of developing various cancers, especially esophageal.

Additionally, given the higher risk of alcohol-related cancer risk in women due to a lower alcohol metabolic rate (H. Kim et al., 2019), individuals with an inherently lower amount of aldehyde dehydrogenase due to the inactive alcohol metabolic gene may be at even more at risk.

While Asian flushers were not found to consume more alcohol (K. Kim et al., 2019), East Asian individuals who flush because of the inactive ALDH2 gene are of particular interest in the study of genetic and environmental interaction in the development of cancer because even light drinking is found to be associated with increased cancer risk (Choi et al., 2017).

Elevated Cancer Risk in ALDH2 Inactive Flushers

Studies consistently demonstrated the association between the presence of inactive ALDH2 and alcohol-related cancer risk (Matsuo et al., 2013; T. Yokoyama et al., 1999; 2013). To test the effect of the inactive ALDH2 genotype on alcohol-related cancer susceptibility, researchers took DNA samples from 668 Japanese alcoholic men (91 with esophageal cancer) (T. Yokoyama et al., 1999). They also investigated the relationship between flushing and cancer by asking 82 alcoholic cancer patients about current or former flushing responses after alcohol consumption. Cancer risk was found to be significantly higher for alcoholics, however, alcoholics with the inactive ALDH2 gene ($OR = 12.76$) were found to be six times more likely to develop cancer than those without ($OR = 2.03$). Furthermore, alcoholic esophageal cancer patients were more likely to have the inactive allele compared to alcoholics without ($OR = 0.560$ vs. $OR = 0.099$, respectively). Knowing that any amount of drinking is associated with an elevated risk of cancer (Choi et al., 2017), the study's findings suggest that cancer susceptibility among heavy drinkers can vary based on their ALDH2 genotypes. This is important because it highlights how impaired alcohol metabolism caused by the inactive ALDH2 gene could exacerbate the consequences of heavy drinking.

Based on the finding that drinking is strongly associated with, but not limited to, esophageal cancer (Choi et al., 2017), Matsuo et al., (2013) studied the relationship between polymorphed ALDH2 and alcohol drinking in the risk of stomach cancer. Researchers compared 697 cancer cases and 1372 non-cancer control subjects in Japan between 2001 and 2005. Similar to the study of T. Yokoyama and colleagues in 1999, the inactive ALDH2 genotype was examined using a DNA test, and information on alcohol consumption was gathered using a self-administered questionnaire. The results were unsurprising, heavy drinkers showed a higher risk of stomach cancer ($OR = 1.72$) compared to non-drinkers. Moreover, cancer risk was found to be significantly higher for heavy drinkers with the inactive gene ($OR = 3.93$) than for those with the regular ALDH2 ($OR = 1.28$) relative to non-drinkers ($P = 0.0054$). Since the researchers did not find any significant connection between cancer and individuals with the regular ALDH2 gene, the result further confirmed the genetic-environmental interaction in the risk of carcinogenesis. Additionally, the statistical significance ($P = 0.007$) in the interaction between the presence of inactive ALDH2 and atrophic gastritis suggests the role of ALDH2 as a risk factor in the precancerous stage of stomach cancer. This is important because it suggests that screening for ALDH2 could be a preventive measure against cancer, especially within East Asian populations where the inactive gene is most prominent.

Acknowledging the interaction between inactive ALDH2 gene and heavy drinking in the risk of esophageal cancer in East Asian populations, T. Yokoyama and colleagues (2013) invented the health-risk appraisal (HRA) model that takes into account the alcohol flushing response, drinking behavior, smoking, and diet to identify esophageal cancer risk in Japanese men who drink. A higher score indicated heavier and more frequent consumption of alcoholic beverages, thus, the higher the subject's cancer risk. The HRA questionnaire then was administered to 2221 Japanese men aged 50 and older, before getting screened for upper gastrointestinal cancer. Researchers found a higher cancer detection rate among those with HRA scores higher than 11 (4.27%) than the rate of 0.67% in the group who scored lower. The findings proposed the adaptation of HRA in alcohol-related cancer risk public education campaigns to encourage individuals who engage in maladaptive drinking behavior to undergo endoscopic screening. A future HRA model incorporating ALDH2 genetic screening may be better at identifying cancer risk than just flushing tendency. With that, the ALDH2

incorporated HRA questionnaire would have better implications for screening in larger East Asian populations.

Conclusion

The studies reviewed demonstrate a genetic-environment interaction for alcohol-related cancer risk in East Asian populations. Through a biopsychosocial approach, those of East Asian descent are at particular risk because of their inherited lower alcohol metabolic rate and the normalization of alcohol consumption in social contexts. The most common reasons for alcohol consumption are social group involvement, maintaining social harmony, peer pressure, and promoting interpersonal connections.

Genetic feedback and flushing questionnaire have been identified as feasible preventive methods not only for cancer but also for changing heavy drinking behaviors. This suggests that individuals who engage in heavy social drinking are more motivated to reduce their drinking, knowing the long-term effects of alcohol on their physiological response. Furthermore, individuals are also at a higher risk due to a lack of knowledge about the Asian flush response and the ALDH2 inactive gene (Hendershot et al., 2010).

The studies reviewed do have some limitations. Except for Hendershot et al., (2010), these studies did not consider participants' prior knowledge of the interaction between alcohol and cancer, or of cancer and inactive ALDH2 gene. Notably, only two of the 10 studies included women. The lack of gender validity has overlooked the possible effect of alcohol on the naturally low level of ALDH2 in women. Also, specific populations were represented more often than others. Of all studies discussed, subjects were limited to individuals of Korean, Japanese, or Chinese descent. However, despite the limited diversity in the represented populations, the overlaps in the presence of flushing, deficient ALDH2, social drinking behaviors, and increased cancer risk suggest common genetic-environmental interaction among East Asian individuals. Methodological issues and limitations needed to be discussed. A central limitation of research on the social nature of drinking was the inconsistencies across studies on the conceptual definitions of social drinking. For example, social drinking was defined as drinking to promote both social and professional relationships by Ko & Sohn (2018), while O'Shea and colleagues (2017) suggested it to be conforming to peer drunkenness. If studies vary in the definition of social drinking, the degree to which it affects the development of cancer may also vary. Furthermore, how participants' drinking behavior is assessed was mainly self-reports. That is, subjects' biases when reporting their drinking behaviors should be taken into account when viewing the correlation between social drinking and cancer risk. Moreover, other variables like diet, sleep schedule, exercise, stress, and substance use were excluded from many of the studies. Maladaptive behaviors within the context of these variables could be proposed in the same vein in the development of cancer.

As mentioned above, further inquiry is needed to examine the possible role of health-related behaviors in the risk of cancer among East Asian individuals. Direct observational and diary methods could provide a more accurate insight into an individual's drinking compared to self-report. Future research should consider the use of genetic feedback to detect the presence of the inactive gene as preventative measures for alcohol-related health risks. In combination with psychological approaches, knowing the risks from genetic detection could benefit the rehabilitation process for alcohol use disorder. Taking into account the social role of alcohol, widespread efforts should be made to promote moderate consumption within social contexts rather than just abstinence.

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