

The alcohol flushing syndrome: A risk factor for cancer

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Globally, alcohol consumption is responsible for an estimated 3 million deaths annually and contributes to over 740,000 new cancer cases each year.¹ Acetaldehyde, a byproduct of alcohol metabolism, has been designated as first-class carcinogens by the International Agency for Research on Cancer.² In East Asian countries such as China, Japan and Korea, approximately 36% of the population cannot effectively metabolise alcohol due to an inherited deficiency in the enzyme aldehyde dehydrogenase 2 (ALDH2).³ This deficiency leads to the accumulation of acetaldehyde in the blood, causing alcohol flushing syndrome (AFS), characterised by facial flushing, palpitations and nausea.⁴ AFS is a predictor of inactive ALDH2 and is associated with a higher risk of cancer development.

To date, numerous studies have confirmed the relationship between AFS and esophageal squamous cell carcinoma (ESCC).⁵ However, evidence remains inconclusive for many other cancers such as those of the pancreas, stomach and lung. Additionally, the impact of different drinking patterns, including frequency and quantity, on cancer risk has not been thoroughly investigated. Previous studies have been limited by the types of cancers studied, single-centre designs and relatively small sample size.⁶ Therefore, a comprehensive analysis of the impact of AFS on cancer risk is urgently needed, particularly in East Asia where hereditary factors, drinking patterns and cancer types differ significantly from those in the West.

In an article published in this issue of the *Annals*, Sim et al. respond to this need through a systematic review and meta-analysis, which investigated the risk of cancers associated with AFS and examined the presence of a dose-response relationship.⁷ The analysis included 18 studies from East Asian countries, encompassing 387,521 participants across various types of cancers. The results showed that AFS was associated with an increased risk of all cancers, with the most significant relationships observed in ESCC, gastric adenocarcinoma and

male flushers. These findings align with global research on alcohol consumption, which has revealed that 4.1% of all new cases over a 10-year period are attributable to alcohol consumption. Males accounted for more than 500,000 (76.7%) of total alcohol-attributable cancer cases, with esophageal and liver cancers contributing the most cases.⁸

Subgroup analysis based on alcohol consumption levels showed that flushers who drank more than 200 g of pure ethanol/week had a higher risk of cancer compared to those who drank less than 200 g of pure ethanol/week. Furthermore, the increase in cancer risk for flushers was more pronounced at higher levels of regular alcohol consumption compared to non-flushers who drank the same amount. These results provide evidence of a dose-response relationship between alcohol intake and cancer risk, suggesting that certain drinking patterns exacerbate the risk. Additionally, the findings confirm the biological mechanism whereby the East Asian-specific ALDH2 loss-of-function mutation leads to acetaldehyde accumulation, causing AFS and increasing cancer risk. This meta-analysis, based on large population-level data, supports the association between AFS and increased cancer risk, as well as a dose-response relationship.

The impact of AFS on cancer risk is particularly concerning in East Asian populations. Individuals often overcome the discomfort of flushing to continue drinking, developing some level of alcohol tolerance. One reason for this behaviour is the lack of knowledge about the causes of flushing and its potential outcomes. Without formal alcohol education in schools, changing long-standing attitudes towards drinking through social media promotion is essential. Providing accurate information about the cause of AFS and its associated risks could raise awareness and offer practical genetic feedback to drinkers.⁹ Social pressures and relationship maintenance also contribute to continued drinking among flushers.

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Heavy drinking occasions, particularly those involving celebrations, etiquette requirements and drinking goals, often override concerns for flushers. Developing motivational strategies to create social expectations for bystanders to assist friends who flush by reducing or stopping their drinking is crucial. An increasing number of young people, including college students, suffer from AFS and seek ways to hide the visible effects.¹⁰ University professionals must increase students' awareness of the link between AFS and cancer risks. It is also important to remind students that taking allergy medications before drinking is problematic, as it raises blood alcohol levels without altering acetaldehyde metabolism. Internet-based interventions and reminders from friends are recommended to reduce or stop drinking.

In summary, AFS is associated with a higher cancer risk in East Asian male populations, particularly in ESCC and gastric adenocarcinoma. Certain drinking patterns, such as daily drinking and consuming more than 200 g of pure ethanol/week, further exacerbate the cancer risks in flushers. Based on the findings, a simple facial flushing questionnaire is suggested to quickly identify individuals at high risk of cancer. Moreover, education about the cause of AFS and its potential hazards from alcohol consumption is urgently needed to protect against chronic alcoholism and cancer risks. Public health support targeting flushers at high risk of cancer must be focused and integrated to reduce or stop their drinking.

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