Editorial

Genetic polymorphisms may explain association between alcohol consumption and bladder cancer risk in East Asian men

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Bladder cancer (BC) is the second most common malignancy of the urinary tract, with an estimated 430,000 new diagnoses and 165,000 BC deaths per year worldwide (1). Unfortunately, only a few preventable risk factors for BC exist. Tobacco smoking represents the main risk factor for BC and BC incidence and mortality patterns and trends reflect corresponding smoking histories in each country (1). For example, the high BC incidence rates observed among US and Spanish men are likely to be the consequence of a very high smoking prevalence in the 1970s–1980s. Although Alcohol is a known risk factor for several malignancies, studies report conflicting results regarding BC incidence and alcohol consumption (2). Despite conflicting clinical data, the association between alcohol and BC has a biological rationale: alcohol is metabolized into several metabolites including acetaldehyde (ACE) which is carcinogenic.

In the article that accompanies this editorial Masaoka *et al.* (3) conducted a population-based cohort study using the Japan Public Health Center-based Prospective Study (JPHC study) (4) to investigate the association between facial flushing and BC risk stratified by alcohol consumption. Although previous epidemiological studies have examined the association between alcohol and BC risk in the USA and Europe and demonstrated no significant association (5) only two such studies have been conducted in Asia, both in Japan (5) where men have the highest incidence of BC in East Asia, and one of these showed a statistically significant increased risk of BC among alcohol drinkers (6). These findings indicate an association between alcohol consumption and BC risk in East Asian populations, contrary to Western populations, and might also account for the higher incidence of other alcohol-related cancers such as oesophageal cancer in these countries (7). Alcohol is metabolized to ACE which causes facial flushing and can also cause DNA damage and is carcinogenic (8). ACE is broken down by aldehyde dehydrogenase 2 (ALDH2). Genes encoding ALDH2 display polymorphism with varying and often reduced enzymatic activity and are known to differ in East Asian populations compared to the West. For example, approximately half of Japanese have the inactive ALDH2 Lys allele which shows significantly reduced enzymatic activity (9,10) and is associated with the flushing response (11,12). The authors therefore hypothesized that information on the flushing response can be used as a surrogate marker of ACE accumulation as a result of its reduced metabolism and reflect its carcinogenic effect on the bladder. Since ACE is excreted through the urinary tract (13) exposure of the urothelium to ACE may provide the explanation for an increased risk of BC associated with ACE accumulation in urine (14).

In this study the proportion of flushers in men decreased with increasing alcohol consumption and overall was not associated with increased BC risk. However, subgroup

analysis showed that moderate drinkers with a flushing response had an increased risk of BC compared with non/occasional and heavy drinkers. In contrast, no statistically significant association between alcohol drinking and BC risk was observed in men without the flushing response. To remove confounding by cigarette smoking the authors performed subgroup analysis on never smokers and showed that they had a similar association between alcohol consumption, flushing response and BC risk.

On the basis that ACE exposure plays an important role in the development of BC and facial flushing, if those with a flushing response all had the inactive ALDH2 Lys alleles one may expect that their risk of BC would increase with increasing alcohol consumption. However, the results show that among flushers the highest risk of BC is in moderate drinkers and not heavy drinkers. The authors suggest that these surprising findings may be explained by a poor correlation between self-reported facial flushing (which is very subjective) and ALDH2 genotype and indeed report several studies have shown that about 50% of flushers carry the *ALDH2 Glu/Glu* gene (15,16) whilst 86% of moderate drinkers with the flushing response carry the *ALDH2 Lys* gene and would be consistent with the suggestion that most moderate drinkers with a flushing response have ALDH2 Lys alleles, but that heavy drinkers with a flushing response include a considerable number of ALDH2 Glu/Glu carriers. This explanation appears to be supported by the author's own previous case-control study which showed that those with the ALDH2 Lys alleles who account for a large proportion of moderate drinkers had a higher risk of BC with increasing alcohol consumption, whereas those with ALDH2 Glu/Glu had no increase in risk even if they drank heavily (11) and this may attenuate the BC risk associated with heavy drinking.

Whilst these findings are interesting and point to genetic polymorphism as the underlying basis for epidemiological variations in different populations the study has several limitations. All subjects in the Tokyo area and some subjects in Osaka were excluded and since these are major centres of population in Japan, this may have had a bearing on the findings and their interpretation. In addition, the JPHC study relied on self-administered questionnaires with questions on lifestyle, alcohol consumption, flushing response after drinking alcohol and smoking habit and therefore under-reporting or over-reporting of the flushing response (which is very subjective and may be subject to recall bias) may have occurred. Finally, alcohol consumption and facial flushing was assessed differently between the two cohorts and the authors converted reported alcohol consumption to grams of pure ethanol per week both of which may inadvertently led to inaccuracies in the analysis. The authors recommend a prospective study to assess the role of *ALDH2* gene polymorphisms in ACE metabolism in an East Asian population to verify their hypothesis.

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None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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