Guest Editorial

Alleles of alcohol and acetaldehyde metabolism genes modulate susceptibility to oesophageal cancer from alcohol consumption

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Alcohol abuse has multiple adverse effects on health, but few people are aware that an increased risk of cancer is one of the consequences of heavy alcohol use. In 1988, however, the International Agency for Research on Cancer (IARC) considered the available evidence for the relationship between alcohol drinking and cancer risk. It concluded that alcoholic beverage consumption is causally related to an increased risk of cancer of the liver and of the upper aerodigestive tract (UADT), which includes the oral cavity, pharynx, larynx and oesophagus. Although the finding that alcoholic beverages are carcinogenic to humans was significant, this did not necessarily mean that alcohol was itself the carcinogenic factor. Left open was the possibility that other chemicals in alcoholic beverages might be responsible for the carcinogenicity. Recently, this picture has changed, with significant implications for public health and the way that physicians should evaluate their patients' alcohol consumption, with a newly identified role for common genetic variants that alter the metabolism of alcohol and thereby alter risk.

In February 2007, the IARC convened a new working group to consider new evidence that had come to light since 1988. The 2007 working group, which included one of us (PJ.B.), drew several conclusions which substantially altered the way we think about the relationship between alcohol consumption and cancer, from both epidemiological and mechanistic standpoints.[1] First, on the basis of the evidence available, both from epidemiological and from animal studies, the 2007 working group concluded that ethanol itself is carcinogenic to humans. Secondly, the group added two additional alcohol-related cancers: colorectal cancer and cancer of the female breast. Regarding mechanism, the group concluded that there is substantial evidence to indicate a role for acetaldehyde, the first metabolite of ethanol, in the pathogenesis of oesophageal cancer resulting from alcohol consumption. This last conclusion was based largely on studies by Yokoyama and colleagues of oesophageal cancer risk in Asian individuals, who are *ALDH2* deficient owing to the *ALDH2* G487K allele.[2] A summary of the 2007 IARC working group conclusions has been published.[3]

In addition to the deficient *ALDH2* variant that is common in Asians, there is now also evidence that genetic variation in other alcohol and acetaldehyde metabolism genes increases susceptibility to cancer after alcohol consumption. Much of this evidence comes from large studies carried out by intramural investigators at the IARC on cancer risk in several

central European countries. Central Europe has some of the highest rates of squamous cell oesophageal cancer in the world, owing in large part to high rates of smoking and alcohol abuse.[4] A 2006 study[4] provided evidence that in these populations, which do not carry the inactive *ALDH2* allele common in Asians, other polymorphisms in the alcohol dehydrogenase (*ADH*) and aldehyde dehydrogenase 2 (*ALDH2*) genes are associated with UADT cancers, and these interact substantially with alcohol consumption to elevate cancer risk. Specifically, the high-activity *ADH1B* R48H allele (also known as *ADH1B***1*) was protective against UADT cancer, whereas three *ALDH2* variants were associated with an increased risk of alcohol-related UADT cancers. It should be noted, however, that, unlike the *ADH1B* R48H and the Asian *ALDH2* G487K alleles, both of which encode enzymes with alter activity, the functional significance of these other *ALDH2* variants, if any, remains to be determined.

Earlier in 2008, the same group both confirmed and substantially extended the results presented in its 2006 publication. In this new study,[5] the authors investigated six *ADH* genetic variants in relation to alcohol-related UADT cancer in a combined analysis of three different study populations: one from a central European sample, one from western Europe and one from Latin America. In total, they examined 3,876 cancer cases and over 5,278 controls.

These authors replicated their earlier finding that the *ADH1B* 48H allele is protective against alcohol-related UADT cancer. This finding was replicated not only in the central European sample, but also in the two other study populations. The overall odds ratio (OR) for the *ADH1B* R48H allele was 0.56, with a 95 per cent confidence interval (CI) of 0.47–0.66. An interesting additional finding from this work is that a polymorphism in *ADH7* (rs1573496; G92A) is protective against UADT cancers from alcohol consumption. As with *ADH1B*, the protective effect of the *ADH7* variant was consistently observed across all three study populations. For this allele, the overall OR was 0.68 (95 per cent CI 0.60–0.78). The two protective *ADH* alleles had an additive effect, in that the OR for both alleles was 0.45 (95 per cent CI 0.34–0.60).

The protective effects of both *ADH* variants appear to be applicable to all UADT sites, but are strongest for oesophageal cancer. Also, the protective effect is due to an interaction with alcohol exposure, because the variants have little or no protective effect in non-drinkers, and the protective effects are more apparent in heavier drinkers. Finally, Hashibe *et al.*[5] stated that neither gene variant seemed to be consistently associated with the amount of alcohol consumed in their studies, and that the effects of these variants are therefore likely to be due to modulating the carcinogenic effect of alcoholic beverages. It should be noted, however, that other studies have shown that *ADH1B* and *ADH7* gene variants can affect alcohol consumption or the risk of alcoholism.[6–8]

These new findings[5] raise some interesting mechanistic issues. Considering *ADH1B* first, the protective effect of the *ADH1B* 48H allele initially seems intuitive, in that a more rapid clearance of ethanol would be associated with reduced cancer risk. This idea, however, is difficult to reconcile with the other evidence from ALDH2-deficient individuals which suggests that it is acetaldehyde, rather than ethanol itself, that is responsible for oesophageal carcinogenesis associated with alcohol drinking. There are at least two possible explanations for this conundrum.

One possibility may be that in populations with fully active ALDH2, where acetaldehyde generated from ethanol oxidation is rapidly converted to acetate, different mechanisms of alcohol-related UADT carcinogenesis are operative. Specifically, the reduced ability to clear ethanol in *ADH1B* R48 homozygotes could result in the induction of CYP2E1, which generates genotoxic oxygen radicals and lipid peroxidation products. Although ethanol induction of CYP2E1 levels are most well documented for the liver, CYP2E1 is present in oesophageal cells, and is also ethanol inducible in this tissue.[9]

A second possibility is that these polymorphisms affect the metabolism of ethanol and acetaldehyde by microorganisms (bacteria and yeast) residing in the human oral cavity. Such organisms, which can metabolise ethanol into acetaldehyde, are being increasingly recognised as important contributors to alcohol-related UADT cancer risk, owing in large part to the pioneering studies of Salaspuro and

colleagues.[10] Yokoyama and colleagues[11] have shown that in a Japanese population, individuals who were homozygous for the less active *ADH1B* R48 allele had significantly higher salivary ethanol and acetaldehyde levels that those with at least one *ADH1B* H48 allele.

Turning to the *ADH7* variant, the product of the *ADH7* gene is ADH4, formerly known as class IV or σ ADH. ADH4 is most highly expressed in the stomach, but is also expressed in cells of the UADT.[12,13] The physiological role for ADH4 is most likely as a retinol dehydrogenase, but this enzyme also has a high capacity for ethanol oxidation.[14] While the K_m of human ADH4 for ethanol (28 mM) is quite high compared with that of ADH1B (4 mM),[15] the concentration of ethanol in many alcoholic beverages is in the molar range. Also, under laboratory conditions, salivary ethanol levels during alcohol drinking are 35–50 mM, depending on the type of beverage.[16] Therefore, it is likely that ADH4 could function as an alcohol dehydrogenase in the human UADT during alcohol drinking. If so, ethanol could act as an inhibitor of retinol metabolism by ADH4, thereby interfering with the retinoid-dependent differentiation of oesophageal cells, which could contribute to alcohol-related carcinogenesis.[17]

It should be noted, however, that the amino acid substitution predicted by the polymorphism shown to be associated with reduced alcohol-related cancer risk, *ADH7* G92A, is a conservative substitution that, based on homology modelling, maps to a region of the protein distal to either the substrate or co-factor binding sites (P.J.B., unpublished observation). As such, the functional relevance of this specific substitution is unclear. It is, of course, possible that this single nucleotide polymorphism is in linkage disequilibrium with a functional polymorphism elsewhere in the *ADH7* gene that remains to be identified.

Summary

An increased risk of certain types of cancer is one of the established health risks of alcohol abuse. There is now evidence in the literature indicating that variation in the alcohol and acetaldehyde metabolism genes *ADH1B*, *ADH7* and *ALDH2* modulate the risk of cancer of the UADT from alcohol drinking. Future studies should focus on the mechanisms by which these polymorphisms interact with alcohol consumption to modulate UADT cancer risk.

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