GENERAL REMARKS

This ninety-sixth volume of the *IARC Monographs* contains evaluations of the carcinogenic hazard to humans of alcohol consumption and ethyl carbamate (sometimes called urethane), a frequent contaminant of yeast-fermented foods and beverages. Alcohol drinking was reviewed in Volume 44 (IARC, 1988), and ethyl carbamate in Volume 7 (IARC, 1974) of the *IARC Monographs*. A large number of epidemiological and experimental studies have been published since then, and these are reviewed in this Volume. A summary of the findings was published in *The Lancet Oncology* (Baan *et al*., 2007).

Although moderate alcohol consumption has some health benefits, in particular with respect to cardiovascular problems (WHO, 2004), the consumption of alcohol has been identified as one of the top-10 risks contributing to the worldwide burden of disease (Ezzati *et al.*, 2004). In 2002, more than 1900 million people (≥15 years of age) around the world were estimated to be regular consumers of alcoholic beverages, with an average daily consumption of 13 g of ethanol (about one drink). In general, men drink alcohol more often and in larger quantities than women do. On the basis of production data, *per-capita* consumption is highest in Eastern Europe and the Russian Federation. In Africa, South America, and Asia, alcohol consumption is comparatively lower, but in those regions a large proportion of alcohol is produced locally and remains unrecorded. Over the past four decades, alcohol consumption has remained stable in most regions of the world except in the Western Pacific region — predominantly China — where it has increased about five times during that period. In addition to ethanol and water, alcoholic beverages can contain many different substances derived from fermentation — e.g., ethyl carbamate —, from contamination, and from the use of additives or flavours.

The Working Group reviewed the epidemiological evidence on the possible association between alcoholic beverage consumption and cancer at 27 anatomical sites, and re-affirmed the previous conclusion (IARC, 1988) that cancers of the upper digestive tract (*oral cavity*, *pharynx*, *larynx*, *oesophagus*) and the *liver* are causally related to the consumption of alcoholic beverages. In addition, the Working Group considered that there is *sufficient evidence* to conclude that cancer of the *colorectum* and the female *breast* also belong in this list.

Regular consumption of alcoholic beverages is associated with an increased risk for cancers at different sites along the upper digestive tract (see above): daily intake of around 50 g of ethanol increases the risk for these cancers two- to three-fold, compared with the risk in non-drinkers. For these cancer types the effects of drinking and smoking seem to be multiplicative, which demonstrates the harmful effect of the combination of these two habits.

Consumption of alcoholic beverages was confirmed as an independent risk factor for primary liver cancer. Cirrhosis and other liver diseases often occur before the cancer becomes manifest and patients with these disorders generally reduce their alcohol intake.

Therefore, the effect of alcohol consumption on the risk for liver cancer is difficult to quantify.

The Working Group reviewed more than 100 epidemiological studies that assessed the association between alcoholic beverage consumption and female breast cancer. A pooled analysis of studies on more than 58 000 women with breast cancer showed that daily consumption of about 50 g of alcohol is associated with a relative risk of approximately 1.5 (95% confidence interval 1.3–1.6), compared with that in non-drinkers. Due to the very large size of this study population, a statistically significant relative risk could even be established for regular consumption of about 18 g of alcohol, about 1–2 drinks daily.

Pooled results from eight cohort studies on the association between alcoholic beverage consumption and colorectal cancer, and data from a number of meta-analyses provided evidence of an increased relative risk of about 1.4 for colorectal cancer resulting from regular consumption of about 50 g of alcohol per day, compared with that in non-drinkers. This association seems to be similar for colon cancer and for rectal cancer.

For non-Hodgkin lymphoma and cancer of the kidney the results of the available studies led the Working Group to conclude that there is evidence of the absence of an increased risk with increasing alcohol consumption. For kidney cancer this inverse trend was seen in both men and women.

The epidemiological studies on the risk for stomach cancer and those on lung cancer in association with alcoholic beverage consumption showed inconsistent results, in both cases due to confounding factors. In the case of *lung* cancer, tobacco smoking is an obvious confounder, and although some studies presented data on the risk for lung cancer in non-smokers the results were inconsistent. Likewise, the epidemiological studies on the risk for *stomach* cancer showed variable results, probably because alcohol drinking may have been accompanied by dietary deficiencies and other unfavourable lifestyle factors that impact on stomach-cancer incidence.

For other cancers, the evidence of an association between alcoholic beverage consumption and cancer risk was generally sparse or inconsistent.

With regard to cancer in experimental animals, the Working Group reviewed a large number of bio-assays, including those that had become available since the previous evaluation (IARC 1988). For ethanol, the evidence of carcinogenicity in experimental animals is now considered *sufficient*, where it had been judged *inadequate* before. For acetaldehyde, the primary metabolite of ethanol, the *sufficient evidence* of carcinogenicity in experimental animals, already indicated in Volume 36 (IARC, 1985), was re-affirmed.

The metabolism of ethanol, the key component in alcoholic beverages, is surprisingly simple and proceeds in two dehydrogenation steps. In humans, the major enzymes involved are the alcohol dehydrogenases (ADH), which oxidize ethanol to acetaldehyde, and the aldehyde dehydrogenases (ALDH), which detoxify acetaldehyde to acetate. In contrast, the genetic variations within the two groups of dehydrogenases are very complex, showing wide differences in enzyme kinetics and substrate specificities.

A striking example of a genetic polymorphism that strongly influences the response to alcoholic beverage consumption is the variant allele *ALDH2*2*, which encodes an

inactive subunit of the enzyme ALDH2. This allele is dominant and highly prevalent in certain eastern-Asian populations (28–45%), but rare in other ethnic groups. Most homozygous carriers of this allele (*ALDH2*2/*2*) are abstainers or infrequent drinkers, because – when they consume alcohol – the enzyme deficiency would cause a strong facial flushing response, physical discomfort, and severe toxic reactions. In heterozygous carriers (*ALDH2*1/*2*, with about 10% residual ALDH2 activity) these acute adverse effects are less severe, but compared with those with fully active enzyme (*ALDH2*1/*1* genotype), these persons have higher levels of acetaldehyde in their blood and saliva after alcohol drinking, and higher levels of acetaldehyde-related DNA adducts in their lymphocytes. In addition, when they consume alcohol these individuals are at highly elevated risk for several alcohol-related aerodigestive cancers.

In recent years, a number of epidemiological studies have focused on the functional effect of this and other genetic polymorphisms in ADH and ALDH iso-enzymes in different human populations, and analyzed the ensuing risks for cancers associated with consumption of alcoholic beverages. Because of their obvious relevance for the mechanistic considerations regarding the role of ethanol and its metabolite acetaldehyde in carcinogenesis, these genetic epidemiological studies are reviewed and discussed in the subsection 'Genetic susceptibility' of Section 4 in this Volume.

On the basis of the epidemiological evidence, which showed little indication that the carcinogenic effects of alcoholic beverage consumption depend on the type of alcoholic beverage, and given the *sufficient evidence* that ethanol causes cancer in experimental animals, the Working Group evaluated "Ethanol in alcoholic beverages" as *carcinogenic to humans*. In addition, the Working Group acknowledged the important role of acetaldehyde in the development of alcohol-related cancer, especially of the oesophagus, but refrained from making a formal evaluation.

References

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