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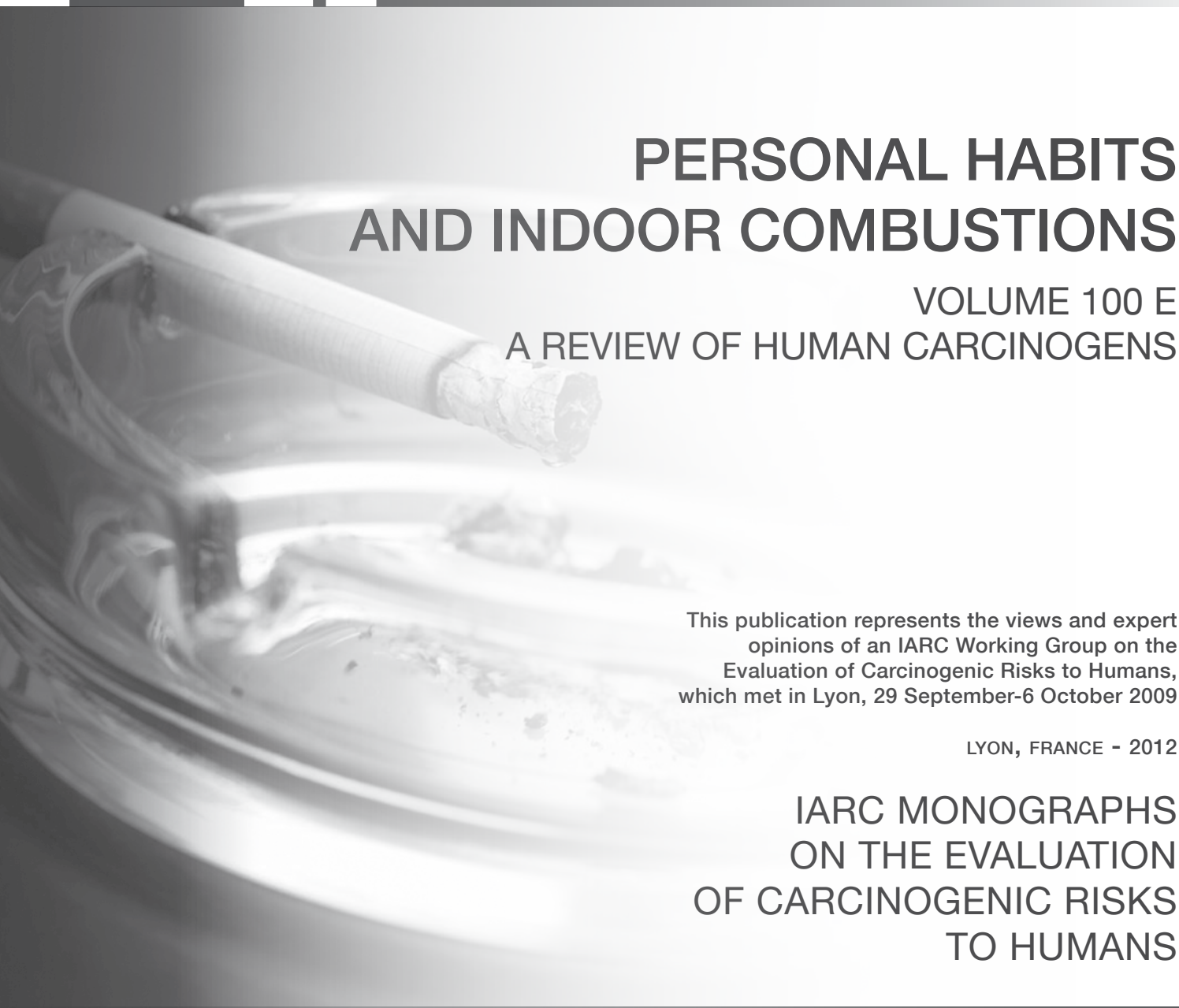

PERSONAL HABITS AND INDOOR COMBUSTIONS

VOLUME 100 E
A REVIEW OF HUMAN CARCINOGENS

This publication represents the views and expert opinions of an IARC Working Group on the Evaluation of Carcinogenic Risks to Humans, which met in Lyon, 29 September-6 October 2009

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IARC MONOGRAPHS ON THE EVALUATION OF CARCINOGENIC RISKS TO HUMANS

International Agency for Research on Cancer
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CONSUMPTION OF ALCOHOLIC BEVERAGES

Consumption of alcoholic beverages was considered by previous IARC Working Groups in 1987 and 2007 (IARC, 1988, 2010). Since that time, new data have become available, these have been incorporated into the *Monograph*, and taken into consideration in the present evaluation.

1. Exposure Data

1.1 Types and ethanol content of alcoholic beverages

1.1.1 Types of alcoholic beverages

The predominant types of commercially produced alcoholic beverages are beer, wine and spirits. Basic ingredients for beer are malted barley, water, hops and yeast. Wheat may be used. Nearly all wine is produced from grapes, although wine can be also made from other fruits and berries. Spirits are frequently produced from cereals (e.g. corn, wheat), beet or molasses, grapes or other fruits, cane sugar or potatoes. Main beverage types (i.e. beer, wine and spirits) may be consumed in combination with each other to fortify the strength of an alcoholic beverage (e.g. fortified wine, in which spirits are added to wine) (WHO, 2004).

In addition to commercialized products, in many developing countries different types of home- or locally produced alcoholic beverages such as sorghum beer, palm wine or sugarcane spirits are consumed (WHO, 2004). Home- or locally produced alcoholic beverages are produced through fermentation of seed, grains, fruit, vegetables or parts of palm trees, by a fairly simple production process.

1.1.2 Ethanol content of alcoholic beverages

Percentage by volume (% vol) is used to indicate the ethanol content of beverages, which is also called the French or Gay-Lussac system. Alcohol content differs according to the main beverage type and may also vary by country. Commonly, 4–5% vol are contained in beer, about 12% vol in wine and about 40% vol in distilled spirits. However, lower or higher ethanol content in alcoholic beverages is also possible. The ethanol content in beer can range from 2.3% vol to over 10% vol (lower alcohol content in home- or locally produced alcoholic beverages such as sorghum beer), in wine from 8 to 15% vol, and in spirits from 20% vol (aperitifs) to well over 40% vol (e.g. 80% vol in some kinds of absinthe). There is a trend in recent years towards higher (13.5–14.5%) alcohol volume in consumed wines, associated with technology advances and increasing proportion in overall consumption of wines produced outside the traditional wine-growing regions of Europe (IARC, 2010).

To calculate the amount of ethanol contained in a specific drink, the amount (e.g. ml) of

alcoholic beverage consumed for each type of beverage (e.g. a 330-mL bottle of beer) is multiplied by the precentage of alcohol by volume, i.e. the proportion of the total volume of the beverage that is alcohol (e.g. (330 mL) × (0.04) = 13.2 mL of ethanol in a bottle of beer). Conversion factors may be used to convert the volume of alcoholic beverage into grams of ethanol, or volumes of alcohol may be recorded in 'ounces'. Conversion factors for these different measures (WHO, 2000) are as follows:

- 1 mL ethanol = 0.79 g
- 1 UK oz = 2.84 cL = 28.4 mL = 22.3 g
- 1 US fluid oz = 2.96 cL = 29.6 mL = 23.2 g

1.2 Chemical composition

The main components of most alcoholic beverages are ethanol and water. Some physical and chemical characteristics of anhydrous ethanol are as follows (O'Neil, 2001):

Chem. Abstr. Services Reg. No.: 64–17.5
Formula: C_2H_5OH
Relative molecular mass: 46.07
Synonyms and trade name: Ethanol, ethyl alcohol, ethyl hydroxide, ethyl hydrate, absolute alcohol, anhydrous alcohol, dehydrated alcohol
Description: Clear, colourless, very mobile, flammable liquid, pleasant odour, burning taste
Melting-point: –114.1 °C
Boiling-point: 78.5 °C
Density: d_4^{20} 0.789
Refractive index: n_D^{20} 1.361

In addition to ethanol and water, wine, beer and spirits contain volatile and non-volatile compounds. Volatile compounds include aliphatic carbonyl compounds, alcohols, monocarboxylic acids and their esters, nitrogen- and sulfur-containing compounds, hydrocarbons, terpenic compounds, and heterocyclic and aromatic compounds. Non-volatile extracts of alcoholic beverages comprise unfermented sugars, di- and tribasic carboxylic acids, colouring substances, tannic and polyphenolic substances and inorganic salts (IARC, 2010).

Occasionally, toxic additives, that are not permitted for use in commercial production have been identified in alcoholic beverages. These include methanol, diethylene glycol (used as sweetener) and chloroacetic acid or its bromine analogue, sodium azide and salicylic acid, which are used as fungicides or bactericides (Ough, 1987).

Contaminants may also be present in alcoholic beverages. Contaminants are defined as substances that are not intentionally added but are present in alcoholic beverages due to production, manufacture, processing, preparation, treatment, packing, packaging, transport or holding, or as a result of environmental contamination. Contaminants and toxins found in alcoholic beverages are nitrosamines, mycotoxins, ethyl carbamate, pesticides, thermal processing contaminants, benzene, and inorganic contaminants such as lead, cadmium, arsenic, copper, chromium, inorganic anions, and organometals (IARC, 2010).

In view of the potential carcinogenicity of acetaldehyde and its known toxic properties, recent studies attempted to estimate exposure to acetaldehyde from alcoholic beverages outside ethanol metabolism at known levels of alcohol exposure. The average exposure to acetaldehyde as a result of consumption of alcoholic beverages, including "unrecorded alcohol," was estimated at 0.112 mg/kg body weight/day (Lachenmeier *et al.*, 2009a). Levels of acetaldehyde in alcoholic beverages vary from less than 1 g/hl of pure alcohol up to 600 g/hl, and high concentrations of acetaldehyde were documented in alcoholic beverages commonly consumed in many parts of the world, including distilled beverages from Brazil, the People's Republic of China, Guatemala, Mexico, and the Russian Federation, as well as calvados and fortified wines and fruit and marc spirits from Europe (Lachenmeier &

Sohnius, 2008; Linderborg *et al.*, 2008; Kanteres *et al.*, 2009; Lachenmeier *et al.*, 2009b).

1.3 Trends in consumption of alcoholic beverages

Volume, pattern and quality of consumed alcohol are included in the description of differential exposure to alcohol.

In a development of the WHO Global Alcohol Database, WHO has developed the Global Information System on Alcohol and Health (WHO, 2008). In 2008–09, WHO conducted the Global Survey on Alcohol and Health, collecting data on alcohol consumption, alcohol-related harm and policy responses from its Member States.

Total adult per capita consumption in litres of pure alcohol is defined as the total amount of alcohol consumed per person, taking into account recorded consumption (i.e. alcoholic beverages consumed that are recorded in official statistics of production, trade or sales) and unrecorded consumption (i.e. alcoholic beverages consumed that are not recorded in official statistics and that can come from a variety of sources such as home- or informally produced alcohol, illegal production and sale, smuggling and cross-border shopping), and subtracting consumption by tourists, if possible. Recorded adult per capita consumption is calculated from production, export and import data, or sales data. Unrecorded consumption is computed from representative surveys, specific empirical investigations or expert opinion. The percentage of lifetime and past-year abstainers provide important information about drinking in a population and complement the indicator on total adult (15+ years) per capita consumption.

Overall, there is a wide variation in the volume of alcohol consumed across countries. As presented in Table 1.1 and Table 1.2 (available at http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-06-Table1.2.pdf), the countries with the highest overall consumption of alcohol per capita among the adult (15+ years) population can be found in the the WHO Regional Office for European Region (12.2 L of pure alcohol per capita), and more specifically in eastern Europe. The next highest alcohol consumption is in the WHO Region of the Americas (8.7 L of pure alcohol per capita). Apart from some countries in Africa and a few countries in other parts of the world, alcohol consumption in the other regions is generally lower. The WHO Eastern Mediterranean Region ranks lowest with 0.7 litres of alcohol consumed per adult. Total adult (15+ years) per capita consumption in litres of pure alcohol by region and country is an indicator of the alcohol consumption level of the adult population, irrespective of the number of abstainers (i.e. people who do not drink alcohol) in the country.

Globally, men consume more alcohol than women. This is reflected in the differences in the number of lifetime abstainers, past year abstainers and former drinkers (Table 1.2 on-line). Lifetime abstainers are defined as the proportion of people (15+ years) in a given population who have not consumed any alcohol during their lifetime, assessed at a given point in time. Past year abstainers are people aged 15+ years who did not consume any alcohol during the past year. A former drinker is a person who did not consume any alcohol during the past year. Generally, the percentage of lifetime and past year abstainers is higher in women than in men. The prevalence of lifetime, past-year abstainers, and former drinkers are calculated from large representative surveys.

Table 1.2 (on-line) provides information about the trend (i.e. robust estimate of five-year change) in per capita consumption (2001–05) of recorded alcohol, that is, indicates if consumption remained stable, increased, decreased, or if no conclusion could be drawn. To estimate five-year change in recorded adult (15+ years) per

Table 1.1 Estimate for total adult (15+ years) per capita consumption, by WHO region, average 2003–05

WHO Region	Adult (15+) per capita consumption*, total (recorded and unrecorded), average 2003–05
African Region (AFRO)	6.2
Region of the Americas (AMRO)	8.7
Eastern Mediterranean Region (EMRO)	0.7
European Region (EURO)	12.2
South-East Asian Region (SEARO)	2.2
Western Pacific Region (WPRO)	6.3

* in litres of pure alcohol
Source: WHO (2008)
AFRO: Algeria, Angola, Benin, Botswana, Burkina Faso, Burundi, Cameroon, Cape Verde, Central African Republic, Chad, Comoros, Congo, Côte d'Ivoire, Democratic Republic of the Congo, Equatorial Guinea, Eritrea, Ethiopia, Gabon, Gambia, Ghana, Guinea, Guinea-Bissau, Kenya, Lesotho, Liberia, Madagascar, Malawi, Mali, Mauritania, Mauritius, Mozambique, Namibia, Niger, Nigeria, Rwanda, Sao Tome and Principe, Senegal, Seychelles, Sierra Leone, South Africa, Swaziland, Togo, Uganda, United Republic of Tanzania, Zambia, Zimbabwe
AMRO: Antigua and Barbuda, Argentina, Bahamas, Barbados, Belize, Bolivia, Brazil, Canada, Chile, Colombia, Costa Rica, Cuba, Dominica, Dominican Republic, Ecuador, El Salvador, Grenada, Guatemala, Guyana, Haiti, Honduras, Jamaica, Mexico, Nicaragua, Panama, Paraguay, Peru, Saint Kitts and Nevis, Saint Lucia, Saint Vincent and the Grenadines, Suriname, Trinidad and Tobago, United States of America, Uruguay, Venezuela (Bolivarian Republic of)
EMRO: Afghanistan, Bahrain, Djibouti, Egypt, Islamic Republic of Iran, Iraq, Jordan, Kuwait, Lebanon, Libyan Arab Jamahiriya, Morocco, Oman, Pakistan, Qatar, Saudi Arabia, Somalia, Sudan, Syrian Arab Republic, Tunisia, United Arab Emirates, Yemen
EURO: Albania, Andorra, Armenia, Austria, Azerbaijan, Belarus, Belgium, Bosnia and Herzegovina, Bulgaria, Croatia, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Georgia, Germany, Greece, Hungary, Iceland, Ireland, Israel, Italy, Kazakhstan, Kyrgyzstan, Latvia, Lithuania, Luxembourg, Malta, Monaco, Montenegro, Netherlands, Norway, Poland, Portugal, Republic of the Republic of Moldova, Romania, Russian Federation, San Marino, Serbia, Slovakia, Slovenia, Spain, Sweden, Switzerland, Tajikistan, The former Yugoslav Republic of Macedonia, Turkey, Turkmenistan, Ukraine, United Kingdom, Uzbekistan
SEARO: Bangladesh, Bhutan, Democratic People's Republic of Korea, India, Indonesia, Maldives, Myanmar, Nepal, Sri Lanka, Thailand, Timor-Leste
WPRO: Australia, Brunei Darussalam, Cambodia, China, Cook Islands, Fiji, Japan, Kiribati, Lao People's Democratic Republic, Malaysia, Marshall Islands, Federated States of Micronesia, Mongolia, Nauru, New Zealand, Niue, Palau, Papua New Guinea, Philippines, Republic of Korea, Samoa, Singapore, Solomon Islands, Tonga, Tuvalu, Vanuatu, Viet Nam

capita consumption, three-year moving averages were calculated for per capita consumption of recorded alcohol for each year in the five-year period from 2001 to 2005.

Recent data on trends in consumption of alcoholic beverages indicate that the European Region and the Region of the Americas maintain a steady high consumption of alcoholic beverages, with 20% of all countries showing an increase in consumption. Alcohol consumption remains low in the Eastern Mediterranean Region. In the African Region, out of 50 countries, 20% show a decrease and 20% an increase in consumption. There is a recent and continuing increase in alcohol consumption in several low and middle-income countries in the South-East Asia and Western Pacific Regions, which probably reflects economic development and increases in consumers' purchasing power as well as increases in the marketing of branded alcoholic beverages (WHO, 2007).

2. Cancer in Humans

2.1 Description of cohort studies

2.1.1 Studies in the general population

Cohort studies are classified by the country in which the study was conducted (Table 2.1 available at http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-06-Table2.1.pdf). The majority of

cohort studies have been conducted in the USA, western Europe and Japan. Since the previous *IARC Monograph* (IARC, 2010), data on the association between alcohol consumption and risk of cancer have been published from several cohorts, including updates of cohorts described previously (Bongaerts *et al.*, 2006, 2008; Li *et al.*, 2006, 2009b; Weinstein *et al.*, 2006; Ericson *et al.*, 2007; Ferrari *et al.*, 2007; Ishihara *et al.*, 2007; Ozasa, 2007; Sutcliffe *et al.*, 2007; Thygesen *et al.*, 2007, 2008a, b; Fan *et al.*, 2008; Ide *et al.*, 2008; Kabat *et al.*, 2008; Nielsen & Grønbaek, 2008; Rohrmann *et al.*, 2008, 2009; Shimazu *et al.*, 2008; Friberg & Wolk, 2009; Ishiguro *et al.*, 2009; Heinen *et al.*, 2009; Klatsky *et al.*, 2009; Rod *et al.*, 2009; Thun *et al.*, 2009; Weikert *et al.*, 2009) and reports from recently established cohorts and some older cohorts from which data on alcohol consumption and risk of cancer were not available (Nakaya *et al.*, 2005; Velicer *et al.*, 2006; Akhter *et al.*, 2007; Chlebowski *et al.*, 2007; Freedman *et al.*, 2007a, b; Friborg *et al.*, 2007; Gwack *et al.*, 2007; Khurana *et al.*, 2007; Lim *et al.*, 2007; Mørch *et al.*, 2007; Sung *et al.*, 2007; Tsong *et al.*, 2007; Visvanathan *et al.*, 2007; Zhang *et al.*, 2007a; Ansems *et al.*, 2008; Brinton *et al.*, 2008, 2009; Chao *et al.*, 2008; Lim & Park, 2008; Muwonge *et al.*, 2008; Ohishi *et al.*, 2008; Toriola *et al.*, 2008, 2009; Allen *et al.*, 2009; Duffy *et al.*, 2009; Engeset *et al.*, 2009; Gibson *et al.*, 2009; Gong *et al.*, 2009; Jiao *et al.*, 2009; Johansen *et al.*, 2009; Lew *et al.*, 2009; Setiawan *et al.*, 2009; Chao *et al.*, 2010).

2.1.2 Studies in special populations

This group of studies is characterized by the assumption that the study subjects have a pattern of consumption of alcoholic beverages that is different from that of the general population, e.g. alcoholics, brewery workers, members of a temperance organization (Table 2.2 available at http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-06-Table2.2.pdf). Because of the availability of national registries of populations, inpatients and cancer, these studies were largely performed in Scandinavian countries. The estimation of risk in these individuals is not based upon a comparison of exposed and unexposed subjects within the cohort, but with the expected rates of cancer in the general population. Thygesen *et al.* (2009) is the only report from cohorts of special populations that has been published since IARC (2010).

2.2 Cancers of the upper aerodigestive tract

2.2.1 Cancer of the oral cavity and pharynx

It was concluded in the previous *IARC Monograph* (IARC, 2010) that consumption of alcoholic beverages is causally related to cancer of the oral cavity and pharynx, and that the risk increases in a dose-dependent manner.

(a) Overview of cohort and case–control studies

The association of consumption of alcoholic beverages and risk of cancer of the oral cavity and/or pharynx has been assessed in six cohort studies (Freedman *et al.*, 2007a; Friborg *et al.*, 2007; Ide *et al.*, 2008; Muwonge *et al.*, 2008; Allen *et al.*, 2009; Weikert *et al.*, 2009; Table 2.3 available at http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-06-Table2.3.pdf). Significant increases in risk were found with increasing amount of alcohol consumption in all studies (Freedman *et al.*, 2007a; Friborg *et al.*, 2007; Ide *et al.*, 2008; Allen *et al.*, 2009; Weikert *et al.*, 2009), increasing frequency of consumption (Friborg *et al.*, 2007; Muwonge *et al.*, 2008), and duration of consumption (Muwonge *et al.*, 2008). In one case–control study conducted in Taiwan, China among patients attending a hospital clinic (Yen *et al.*, 2008) no association was found among non-smokers and a positive association among drinkers and smokers (Table 2.4 available at http://monographs.iarc.fr/ENG/Monographs/

vol100E/100E-06-Table2.4.pdf). [No information on the quantity of alcohol or tobacco consumption was available.] In a case–control study in Uruguay (De Stefani *et al.*, 2009) a significant positive association with a predominantly alcohol-based dietary pattern and cancer of the oral cavity and pharynx was found (data not shown). [No specific assessment of alcohol intake was presented and the contribution of other foods to this dietary pattern was not known.]

Undifferentiated nasopharyngeal carcinoma (NPC), which is common in parts of Southern Asia, North Africa and the Arctic, is associated with Epstein-Barr virus and preserved foods (see the *Monograph* on Chinese-style Salted Fish in this volume). Friborg *et al.* (2007) confirmed earlier results suggesting limited or no association between alcohol and undifferentiated NPC (Yu *et al.*, 2002). However, in a Western population where differentiated forms of NPC are more common, a significantly increased risk of NPC has been associated with heavy drinking (> 21 drinks per week) (Vaughan *et al.*, 1996), indicating a difference in ethiology between differentiated and undifferentiated types of NPC (Table 2.4 on-line).

Thygesen *et al.* (2009) reported a significantly higher rate of cancer of the oral cavity and pharynx among Danish alcohol abusers compared with national rates. [This cohort study provided no information on individual exposures or results adjusted for potential confounders.] See Table 2.5 available at http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-06-Table2.5.pdf.

(b) Intensity and duration

Previous studies consistently showed that consumption of alcoholic beverages is associated with an increased risk of cancer of the oral cavity and/or pharynx, although the nature of the dose–response relationship is not fully understood (IARC, 2010). In most studies an approximate threefold increased risk was found at relatively high levels of intake (i.e. > 60 g/day). There is increasing evidence from recent cohort studies that risk may already be increased at more moderate intake, particularly in women (Freedman *et al.*, 2007a; Allen *et al.*, 2009; Weikert *et al.*, 2009).

A pooled analysis of the International Head and Neck Cancer Epidemiology Consortium, which specifically examined the association of alcohol consumption and duration, found that among drinkers of 10 drinks per day or less, the association with total drink-years increased with increasing drinks/day, indicating that more drinks/day for a shorter duration was more deleterious than fewer drinks/day for a longer duration (Lubin *et al.*, 2009).

(c) Effect of cessation

A meta-analysis of 13 case–control studies of cancer of the oral cavity and pharynx combined found that compared with current drinkers, risk did not decrease until 10 years or more after cessation of drinking (odds ratio (OR), 0.67; 95%CI: 0.63–0.73) (Rehm *et al.*, 2007) (Table 2.6 available at http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-06-Table2.6.pdf). Consistent with many earlier studies, risks were found to be elevated among recent former drinkers, most likely due to ill health directly related to the cancer or its precursors.

(d) Types of alcoholic beverage

Some studies have assessed whether the association of consumption of alcoholic beverages on risk varies by beverage type, and have found broadly similar associations in wine, beer and spirit drinkers (Freedman *et al.*, 2007a; Allen *et al.*, 2009).

(e) Population characteristics

The association of consumption of alcoholic beverages with risk of cancer of the oral cavity and pharynx is increased in both men and women (Freedman *et al.*, 2007a; Weikert *et al.*, 2009).

Studies have been hampered with low numbers of women at the highest levels of exposure.

(f) Histological subtype

Very few studies have examined the association of consumption of alcoholic beverages by histological subtype for cancers of the oral cavity and pharynx. From a large-scale cohort study, Weikert *et al.* (2009) reported that both baseline and lifetime alcohol intake were associated with an increased risk of squamous cell carcinoma of the oral cavity and the pharynx, with an increased risk of 10% (95%CI: 8–13%) per 10 g per day increase in lifetime alcohol intake.

(g) Association among non-smokers

There is evidence from a pooled analysis of 15 case–control studies that increasing consumption of alcoholic beverages increases risk of cancer of the oral cavity and oropharynx/hypopharynx cancer among never smokers, with risk estimates of 1.23 (95%CI: 0.59–2.57) and 5.50 (95%CI: 2.26–13.36), for 5 or more drinks/day versus never drinkers, for the two cancer sites, respectively (Hashibe *et al.*, 2007; Table 2.6 on-line). One study in Taiwan, China found no association with alcohol consumption among non-smoking ever-drinkers for cancer of the oral cavity (Yen *et al.*, 2008). [No information was provided on the quantity of alcohol consumed.]

(h) Joint effect of alcoholic beverages and tobacco smoking

It is well established that there is a joint effect of tobacco smoking and consumption of alcoholic beverages on the risk of cancer of the oral cavity and pharynx, with very high risks observed in individuals who are both heavy drinkers and heavy smokers, corresponding to a greater than a multiplicative interaction (IARC, 2010). The joint effect of alcohol consumption and tobacco smoking on the risk of cancers of the oral cavity and pharynx is described in Section 2.20 of the *Monograph* on Tobacco Smoking in this volume.

2.2.2 Cancer of the larynx

It was concluded in the previous *IARC Monograph* (IARC, 2010) that consumption of alcoholic beverages is causally related to cancer of the larynx, and that the risk increases in a dose-dependent manner.

(a) Overview of cohort and case–control studies

Since IARC (2010), the association of consumption of alcoholic beverages and risk of cancer of the larynx has been assessed in three general-population cohort studies (Freedman *et al.*, 2007a; Allen *et al.*, 2009, Weikert *et al.*, 2009; Table 2.7 available at http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-06-Table2.7.pdf) and one case–control study (Garavello *et al.*, 2006; Table 2.8 available at http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-06-Table2.8.pdf), all of which found significant increases in risk associated with alcohol consumption. In one further case–control study in Uruguay (De Stefani *et al.*, 2009) a significant positive association with a predominantly alcohol-based dietary pattern and cancer of the larynx was found (data not shown). [No specific assessment of alcohol intake was presented and the contribution of other foods to this dietary pattern was not known.]

Thygesen *et al.* (2009) reported a significantly higher rate of cancer of the larynx among Danish alcohol abusers compared with national rates (Table 2.5 on-line). This study provided no information on individual exposures or results adjusted for potential confounders

(b) Intensity and duration

Previous studies consistently showed that increasing alcohol consumption is associated with an increased risk of cancer of the larynx (IARC, 2010). Bagnardi *et al.* (2001) reported risk

estimates of 1.38 (95%CI: 1.32–1.45) for intake of 25 g alcohol per day, 1.94 (95%CI: 1.78–2.11) for 50 g per day, and 3.95 (95%CI: 3.43–4.57) for 100 g per day from a meta-analysis of 20 case–control studies, including over 3500 cases. An increased risk for cancer of the larynx was found for women drinking above one drink/day in a large cohort of United Kingdom women [equivalent to an increased risk of 1.44 (95%CI: 1.10–1.88) per 10 g alcohol per day] (Allen *et al.*, 2009). This is consistent with the 1.38 (95%CI: 1.10–1.73) estimate per 10 g per day reported among women in the European Prospective Investigation into Cancer and Nutrition (Weikert *et al.*, 2009). Compatible with this, Freedman *et al.* (2007a) reported a risk estimate of 2.15 (95%CI: 0.82–5.65) among women associated with 3 or more drinks/day from the NIH-AARP Diet and Health Study. Among men, the dose–response relationship is slightly weaker (Freedman *et al.*, 2007a; Weikert *et al.*, 2009), although it is difficult to determine whether these differences are due to chance because of the relatively low number of cases in women. In a large case–control study in Italy there was clear evidence of a dose–response relationship for men and women combined (Garavello *et al.*, 2006).

A pooled analysis of the International Head and Neck Cancer Epidemiology Consortium, which specifically examined the association of quantity and duration of alcohol consumption, found that among drinkers of 10 drinks per day or less, the association with total drink-years increased with increasing drinks/day, indicating that more drinks/day for a shorter duration was more deleterious than fewer drinks/day for a longer duration (Lubin *et al.*, 2009).

(c) Effect of cessation

Few studies have assessed whether the risk for cancer of the larynx declines since stopping drinking. Altieri *et al.* (2002) reported a risk estimate of 0.53 (95%CI: 0.15–1.94) for stopping drinking for 20 years or more ago compared with current drinkers; the risk for never-drinkers was 0.56 (95%CI: 0.31–0.99).

(d) Types of alcoholic beverage

Evidence suggests that the most frequently consumed beverage in a population tends to be associated with the highest risk of cancer of the larynx. Data published recently largely supports this view (Garavello *et al.*, 2006). The NIH-AARP Diet and Health Study found a stronger association for spirits than for beer or wine consumption among men (Freedman *et al.*, 2007a). [The Working Group noted the small number of cases.]

(e) Risk among non-smokers

There is evidence from a pooled analysis of 11 case–control studies, based on 121 cases of laryngeal cancer, that increasing alcohol consumption increases the risk for cancer of the larynx among never smokers, with a risk estimate of 2.98 (95%CI: 1.72–5.17) for 5 or more drinks/day versus never drinkers (Hashibe *et al.*, 2007; Table 2.6 on-line).

(f) Joint effect of alcoholic beverages and tobacco smoking

Evidence suggests that there exists a joint effect of tobacco smoking and consumption of alcoholic beverages on the risk of cancer of the larynx, with very high risks observed in individuals who are both heavy drinkers and heavy smokers. More recent studies that have examined the joint effect of alcohol consumption and tobacco smoking on the risk of cancer of the larynx are described in Section 2.20 of the *Monograph* on Tobacco Smoking in this volume.

2.2.3 Cancer of the oesophagus

It was concluded in the previous *IARC Monograph* (IARC, 2010) that consumption of alcoholic beverages is causally associated with cancer of the oesophagus. The increased risk is

largely restricted to squamous cell carcinoma, with little or no association for adenocarcinoma of the oesophagus.

(a) Overview of cohort and case–control studies

Since IARC (2010), the association of consumption of alcoholic beverages and risk of cancer of the oesophagus has been assessed in six cohort studies (Freedman *et al.*, 2007b; Ozasa *et al.*, 2007; Fan *et al.*, 2008; Allen *et al.*, 2009; Ishiguro *et al.*, 2009; Weikert *et al.*, 2009; Table 2.9 available at http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-06-Table2.9 pdf) and four case–control studies (Lee *et al.*, 2005; Vioque *et al.*, 2008; Benedetti *et al.*, 2009; Pandeya *et al.*, 2009; Table 2.10 available at http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-06-Table2.10.pdf), all of which found significant increases in risk with alcohol consumption. A case–control study in Uruguay (De Stefani *et al.*, 2009) found a significant positive association with a predominantly alcohol-based dietary pattern and cancer of the oesophagus (data not shown). [No specific assessment of alcohol intake was presented and the contribution of other foods to this dietary pattern was not known.]

Thygesen *et al.* (2009) reported a significantly higher rate of cancer of the oesophagus among Danish alcohol abusers compared with national rates (Table 2.5 on-line). [This study provided no information on individual exposures or results adjusted for potential confounders.]

(b) Intensity and duration

Data reviewed previously (IARC, 2010) consistently showed that increasing consumption of alcoholic beverages is associated with an increased risk of cancer of the oesophagus. Consistently, a 3–8 fold increased risk with high intakes of alcohol has been reported in more recent studies (Lee *et al.*, 2005; Freedman *et al.*, 2007b; Ozasa *et al.*, 2007; Fan *et al.*, 2008; Vioque *et al.*, 2008; Ishiguro *et al.*, 2009; Pandeya *et al.*, 2009). Smaller increases in risk at lower amounts of alcohol intake have been found by analysis of large cohorts in Europe, with a significant increased risk of approximately 20% per 10 g alcohol per day (Allen *et al.*, 2009; Weikert *et al.*, 2009).

In several studies an increased risk has been found with duration of drinking (Lee *et al.*, 2005; Ozasa *et al.*, 2007; Fan *et al.*, 2008, Vioque *et al.*, 2008), frequency of drinking (Ozasa *et al.*, 2007), a lower age at starting drinking (Ozasa *et al.*, 2007; Fan *et al.*, 2008), or cumulative intake (Benedetti *et al.*, 2009). Risk is similar when alcohol consumption is based on measures of either baseline or lifetime alcohol consumption (Fan *et al.*, 2008; Weikert *et al.*, 2009).

(c) Effect of cessation

In several studies the risk for cancer of the oesophagus was reduced with increasing time since cessation of drinking. In a meta-analysis of 5 case–control studies Rehm *et al.* (2007) reported that compared with current drinkers, risk was not reduced until 5 years or more after cessation of drinking (OR, 0.85; 95%CI: 0.78–0.92) and approached that of nondrinkers after 15 years or more since quitting drinking (Table 2.6 on-line). Similar results were obtained from a cohort study (Ozasa *et al.*, 2007). Risks are elevated among more former drinkers, who most likely cease drinking due to ill health directly related to the cancer or its precursors (Rehm *et al.*, 2007; Vioque *et al.*, 2008; Ozasa *et al.*, 2007).

(d) Types of alcoholic beverage

Most previous studies found no material difference in the association of consumption of alcoholic beverages on risk of cancer of the oesophagus according to specific beverage types, with the most commonly consumed beverage tending to be associated with the highest risk. This is supported by data from more recent studies (Lee *et al.*, 2005; Freedman *et al.*, 2007b; Fan *et al.*, 2008; Vioque *et al.*, 2008; Allen *et al.*, 2009; Pandeya *et al.*, 2009).

(e) Population characteristics

All recent studies have found significant positive associations in both men (Fan *et al.*, 2008; Benedetti *et al.*, 2009; Ishiguro *et al.*, 2009) and women (Allen *et al.*, 2009), and in studies that have stratified by sex (Pandeya *et al.*, 2009).

(f) Risk associated with facial flushing response

One cohort study in Japan examined the association of consumption of alcoholic beverages with cancer of the oesophagus according to whether the cohort members experienced a facial flushing response. Although the risk associated with a high alcohol intake among men with a flushing response was higher than among those with no flushing response, the differences were not significant. Details of the association of alcohol consumption according to genetic variants in alcohol-metabolizing genes related to the flushing response are presented in Section 2.19.

(g) Histological subtypes

In the previous *IARC Monograph* it was concluded that consumption of alcoholic beverages is causally related to squamous cell carcinoma of the oesophagus (OSCC), with no or little association with adenocarcinoma of the oesophagus (IARC, 2010). Data published since a strong association with OSCC or non-adenocarcinoma (Lee *et al.*, 2005; Freedman *et al.*, 2007b; Fan *et al.*, 2008; Vioque *et al.*, 2008; Allen *et al.*, 2009; Benedetti *et al.*, 2009; Ishiguro *et al.*, 2009; Pandeya *et al.*, 2009; Weikert *et al.*, 2009), and no association with alcohol consumption and adenocarcinoma of the oesophagus (Freedman *et al.*, 2007b; Allen *et al.*, 2009; Benedetti *et al.*, 2009; Pandeya *et al.*, 2009).

(h) Association among non-smokers

Data on the association of consumption of alcoholic beverages with risk of cancer of the oesophagus among non-smokers are limited. Pandeya *et al.* (2009) reported higher risks with increasing alcohol consumption among current smokers compared to never smokers from a case–control study in Australia. [The low numbers of highly exposed cases among never smokers makes it difficult to draw any conclusions.]

(i) Joint effect of alcoholic beverages and tobacco smoking

Evidence suggests a joint effect of tobacco smoking and consumption of alcoholic beverages on the risk for cancer of the oesophagus, with very high risks observed in individuals who were both heavy drinkers and heavy smokers. Recent studies that have examined the joint effect of alcohol consumption and tobacco smoking on the risk of cancer of the oesophagus are described in Section 2.20 of the *Monograph* on Tobacco Smoking in this volume.

2.2.4. Cancers of the upper aerodigestive tract combined

(a) Overview of cohort and case–control studies

In the previous *IARC Monograph* (IARC, 2010) the association between consumption of alcoholic beverages and risk of cancer of the upper aerodigestive tract combined was not evaluated. Since then, three cohort studies (Thygesen *et al.*, 2007; Allen *et al.*, 2009; Weikert *et al.*, 2009; Table 2.11 available at http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-06-Table2.11.pdf) and one case–control study (Zaridze *et al.*, 2009; Table 2.12 available at http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-06-Table2.12.pdf) have examined the association of alcoholic beverage consumption and cancers of the upper aerodigestive tract (i.e. oral cavity, pharynx, larynx and oesophagus combined), and one reported on cancers of the oral cavity, pharynx and larynx combined (Freedman *et al.*, 2007a). All studies reported significant increases in risk with alcoholic beverage consumption, observed in both men and women (Freedman

et al., 2007a; Thygesen *et al.*, 2007; Allen *et al.*, 2009; Weikert *et al.*, 2009; Zaridze *et al.*, 2009).

(b) Intensity and duration

In one cohort study an increased risk for cancer of the upper aerodigestive tract combined was observed only among those who had a relatively high alcohol intake (i.e. 42 drinks/week or more) (Thygesen *et al.*, 2007). Other studies have reported increases in risk at more moderate levels of consumption, particularly among women (Freedman *et al.*, 2007a; Allen *et al.*, 2009; Weikert *et al.*, 2009).

(c) Types of alcoholic beverage

The association of consumption of alcoholic beverages on risk of cancer of the upper aerodigestive tract combined does not vary by beverage type, as found in a meta-analysis of 15 case–control studies (Purdue *et al.*, 2009; Table 2.6 on-line) and cohort studies (Allen *et al.*, 2009; Weikert *et al.*, 2009).

(d) Association among non-smokers

Few studies have had sufficient statistical power to assess reliably the association of consumption of alcoholic beverages by smoking status with cancers of the upper aerodigestive tract combined. Most previous studies (as outlined in IARC, 2010), as well as recent data from the European Prospective Investigation into Cancer and Nutrition have found similar increased risks with increasing alcohol intake among both non-smokers and smokers (Weikert *et al.*, 2009). In a large cohort study among women in the United Kingdom with a low to moderate alcohol intake, alcohol consumption was not associated with an increased risk of cancers of the upper aerodigestive tract in never smokers or former smokers, but was strongly associated with an increased risk among current smokers (Allen *et al.*, 2009).

2.3 Cancer of the colorectum

In the previous *IARC Monograph* (IARC, 2010) it was concluded that consumption of alcoholic beverages is causally related to cancer of the colorectum. This conclusion was largely based on a pooled analysis of eight cohort studies of alcohol intake and cancer of the colorectum conducted in Europe and North America, which found a relative risk (RR) of about 1.4 for cancer of the colorectum with regular consumption of high intakes of alcohol (≥ 45 g/d), compared to non-drinkers, in men and women combined, and which was not related to beverage type (Cho *et al.*, 2004).

2.3.1 Cohort studies and meta-analyses of cohort studies

Since IARC (2010), 12 cohort studies have evaluated the association between consumption of alcoholic beverages and risk of cancer of the colorectum and/or cancer of the colon and rectum separately (Table 2.13 available at http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-06-Table2.13.pdf). Of the nine cohort studies that examined the association of consumption of alcoholic beverages and risk of cancer of the colorectum, seven confirmed a significant positive association (Akhter *et al.*, 2007; Ferrari *et al.*, 2007; Ishihara *et al.*, 2007; Tsong *et al.*, 2007; Bongaerts *et al.*, 2008; Thygesen *et al.*, 2008b; Toriola *et al.*, 2008). In only two cohort studies was no overall association reported, although both of these likely included very few cases with a high alcohol intake (Kabat *et al.*, 2008; Lim & Park, 2008). In one further study (Engeset *et al.*, 2009) no association with a predominantly alcohol-based dietary pattern and cancer of the colorectum was found. [No quantitative assessment of alcohol intake per se was provided and the contribution of other foods to this dietary pattern was not known.] Of the seven studies that evaluated cancer of the colon and rectum

separately (Akhter *et al.*, 2007; Ferrari *et al.*, 2007; Ozasa, 2007; Tsong *et al.*, 2007; Thygesen *et al.*, 2008b; Bongaerts *et al.*, 2008; Allen *et al.*, 2009), three reported a significant increased risk with alcohol intake for both sites (Akhter *et al.*, 2007; Ferrari *et al.*, 2007; Tsong *et al.*, 2007). This is consistent with findings from one meta-analysis and one pooled analysis (Table 2.14 available at http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-06-Table2.14.pdf). In a meta-analysis of 21 cohort studies a significant increased risk for cancer of the colorectum, and for colon and rectal cancer separately, for heavy drinkers compared to light or non-drinkers was found (Huxley *et al.*, 2009). There was also a significant positive association of consumption of alcoholic beverages for men and women with both cancer of the colon and of the rectum in a pooled analysis of five cohort studies in Japan (Mizoue *et al.*, 2008). Thygesen *et al.* (2008b) reported an increased risk for colon cancer and not for rectal cancer; in two other studies a significant increased risk for rectal cancer and a weaker, non-significant positive association for colon cancer was found (Ozasa, 2007; Bongaerts *et al.*, 2008). [Such inconsistency may be due to the small numbers of heavy drinkers in each subsite.] In the largest study to date, with over 4000 cases of colon and over 2000 cases of rectal cancer, no association of alcohol intake was found with colon cancer and a small, but statistically significant, increased risk for rectal cancer (Allen *et al.*, 2009). [The Working Group noted that the reason for the lack of association with colon cancer in this study of United Kingdom women is not clear, but may, in part, relate to the narrower range of alcohol intake (which was mostly low to moderate), resulting in limited power to detect an association at higher levels of alcohol intake]. Most of the studies in which the association of alcohol intake has been examined by more detailed subsite definitions within the colon are more consistent in showing a positive association with alcohol intake for cancer of the distal colon, but a weak or null association for cancer of the proximal colon (Akhter *et al.*, 2007; Ferrari *et al.*, 2007; Bongaerts *et al.*, 2008; Thygesen *et al.*, 2008b).

2.3.2 Cohort studies in special populations

Since IARC (2010), in one cohort study in the Netherlands a significantly higher rate of rectal cancer among male alcohol abusers compared with national rates, but no association with colon cancer was found (Table 2.15 available at http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-06-Table2.15.pdf). Among women, rates of both colon and rectal cancer were similar among alcohol abusers and the national population, although there were relatively low numbers for each cancer site (Thygesen *et al.*, 2009). [This study provided no information on individual exposures or results adjusted for potential confounders.]

2.3.3 Case–control studies

Since IARC (2010), reports on the association of consumption of alcoholic beverages and cancer of the colorectum have come from 10 case–control studies. There was a significant positive association in five, three of which found an increased risk of cancer of the colorectum at relatively high levels of consumption (Gao *et al.*, 2008; Lightfoot *et al.*, 2008; Benedetti *et al.*, 2009) and for two studies in the Far East an increased risk among drinkers was reported (Sriamporn *et al.*, 2007; Wei *et al.*, 2009). [Information on quantity of intake was not available for these studies.] (Table 2.16 available at http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-06-Table2.16.pdf). No association for consumption of alcoholic beverages and cancer of the colorectum was reported for five case–control studies (Wang *et al.*, 2006a; Murtaugh *et al.*, 2007; Pereira Serafim *et al.*, 2008; Ganesh *et al.*, 2009; Wu *et al.*, 2009). [These studies were conducted in populations with a low

intake of alcoholic beverages (Wang *et al.*, 2006a; Murtaugh *et al.*, 2007; Ganesh *et al.*, 2009) and/or had a small sample size and limited exposure information (Pereira Serafim *et al.*, 2008; Ganesh *et al.*, 2009; Wu *et al.*, 2009).]

2.3.4 Dose–response relationship

One pooled analysis of eight cohort studies (Cho *et al.*, 2004) and several independent studies found an increased risk for cancer of the colorectum for an alcohol intake of 20 g/day or more (Gao *et al.*, 2008), 30 g/day or more (Ferrari *et al.*, 2007; Bongaerts *et al.*, 2008) or 45 g/day or more (Akhter *et al.*, 2007). A pooled analysis of five cohort studies conducted in Japan also found an increased risk for cancer of the colorectum above 23 g/day, evident for both cancer of the colon and of the rectum for both men and women (Mizoue *et al.*, 2008). Other studies found an increased risk for cancer of the colorectum or rectum only with lower amounts of alcohol (i.e. of the order of 1 drink/d or 10 g/d) (Tsong *et al.*, 2007; Thygesen *et al.*, 2008b; Allen *et al.*, 2009).

2.3.5 Types of alcoholic beverage

(a) Other metrics of exposure

Few studies have examined the association between cancer of the colorectum and other metrics of exposure (average alcohol intake, over a lifetime or specifically during early adulthood, age at starting, duration). The limited evidence suggests that there is no strong association with duration of drinking in years or age at started drinking (Ferrari *et al.*, 2007; Ozasa, 2007; Wu *et al.*, 2009). In most earlier studies and some recent studies the risk associated with a baseline measure of intake is similar to a measure of average lifetime intake (Ferrari *et al.*, 2007; Thygesen *et al.*, 2008b), Benedetti *et al.* (2009) reported an increased risk with increasing cumulative intake. There is also very limited information on whether the frequency of drinking is an important determinant of risk. In three studies no association with frequency of alcohol intake (drinks/day) was found (Ozasa, 2007; Lim & Park, 2008; Benedetti *et al.*, 2009), while in others the frequency of intake was associated with an increased risk among those with a high intake of alcohol (> 15 g/d), but not among those with lower intake of alcohol (Mizoue *et al.*, 2008; Thygesen *et al.*, 2008b).

The association of consumption of alcoholic beverages and cancer of the colorectum does not appear to differ by beverage type (Ferrari *et al.*, 2007; Tsong *et al.*, 2007; Bongaerts *et al.*, 2008; Thygesen *et al.*, 2008b).

2.3.6 Population characteristics

The association of consumption of alcoholic beverages and cancer of the colorectum appears to be similar for men and women (Ferrari *et al.*, 2007; Bongaerts *et al.*, 2008). There is a causal association between cigarette smoking and risk for cancer of the colorectum (see the *Monograph* on Tobacco Smoking in this volume). Most studies of consumption of alcoholic beverages have adjusted for smoking status. In studies that statified the analysis by smoking status most found an increased risk among both never and current smokers, with the risk estimates slightly higher in current or ever smokers compared to never smokers (Akhter *et al.*, 2007; Ferrari *et al.*, 2007; Tsong *et al.*, 2007).

Ferrari *et al.* (2007) did not find a statistically significant interaction term between alcohol drinking and smoking with regard to cancers of the colorectum. Tsong *et al.* (2007) reported that the interaction effect between alcohol and smoking was not statistically significant on risk of cancer of the colorectum overall and rectal cancer alone (both $P > 0.19$), while the interaction effect on colon cancer risk was of marginal statistical significance ($P = 0.051$).

Few studies have examined whether the association of alcohol with cancer of the colorectum

varies by folate status; the European Prospective Investigation into Cancer and Nutrition found some evidence that the risk for colorectal cancer associated with alcohol intake was stronger in individuals with a low folate intake, but the interaction term was of marginal statistical significance (Ferrari *et al.*, 2007), and two other studies found no evidence that the association of alcohol intake with risk differed according to intake of folate, or intake of related nutrients such as vitamin B6, vitamin B12 or methionine (Ishihara *et al.*, 2007; Kabat *et al.*, 2008).

2.4 Cancer of the liver and hepatobiliary tract

In the previous *IARC Monograph* (IARC, 2010) it was concluded that consumption of alcoholic beverages is causally related to risk of cancer of the liver. This conclusion was based on a considerable number of cohort and case–control studies.

Chronic infection with hepatitis viruses B and C are the major causes of cancer of the liver. The increased risk associated with consumption of alcoholic beverages has been found consistently among individuals infected with hepatitis viruses as well as among uninfected individuals. Quantification of the effect of consumption of alcoholic beverages on the risk of cancer of the liver cannot be determined reliably since cirrhosis and other liver disorders that often predate cancer of the liver tend to lead to a decrease in or the cessation of consumption of alcoholic beverages many years before the occurrence of cancer of the liver.

The previous *IARC Monograph* did not separately evaluate the effect of consumption of alcoholic beverages on the risk of cholangiocarcinoma.

2.4.1 Hepatocellular carcinoma

Three cohort studies (Gwack *et al.*, 2007; Ohishi *et al.*, 2008; Allen *et al.*, 2009; Table 2.17 available at http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-06-Table2.17.pdf) and three case–control studies (Hassan *et al.*, 2008; Benedetti *et al.*, 2009; Zaridze *et al.*, 2009; Table 2.18 available at http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-06-Table2.18.pdf) on the general population and one cohort study on alcoholics (Thygesen *et al.*, 2009; Table 2.19 available at http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-06-Table2.19.pdf) have been identified since IARC (2010). No new meta-analysis or studies on the joint effect of alcohol beverage and virus infection were found.

In the three cohort studies, Gwack *et al.* (2007) in Republic of Korea, Ohishi *et al.* (2008) in Japan, and Allen *et al.* (2009) in the United Kingdom, an association between consumption of alcoholic beverages and cancer of the liver was found. Hassan *et al.* (2008) reported from a study in USA an increased risk for cancer of the liver in women with increasing alcohol consumption. Among men, the risk for cancer of the liver was only increased among those with an ethanol intake of ≥ 60 ml per day. Zaridze *et al.* (2009) found an increased risk of cancer of the liver with consumption of alcoholic beverages (usually vodka) among both men and women in the Russian Federation as did Benedetti *et al.* (2009) from Canada. Thygesen *et al.* (2009) reported a higher risk of cancer of the liver among both alcoholic men and women compared to the general population. [There were only 8 cases among women.]

2.4.2 Cholangiocarcinoma

Ten studies on the association between consumption of alcoholic beverages and cholangiocarcinoma (CCA) in the general population were identified (Parkin *et al.*, 1991; Shin *et al.*,

1996, Donato *et al.*, 2001; Kuper *et al.*, 2001; Yamamoto *et al.*, 2004; Honjo *et al.*, 2005; Shaib *et al.*, 2007; Hsing *et al.*, 2008; Lee *et al.*, 2008a; Zhou *et al.*, 2008), all of which were case–control studies (Table 2.20 available at http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-06-Table2.20.pdf). An increased risk for cholangiocarcinoma among heavy drinkers (≥ 80 g/day) was reported in two studies from the Republic of Korea (Shin *et al.*, 1996 for CCA; Lee *et al.*, 2008a for intrahepatic CCA) and one study from the USA (Shaib *et al.*, 2007 for both intrahepatic and extrahepatic CCA), among current drinkers in a study from China (Hsing *et al.*, 2008 for extrahepatic CCA), and among regular drinkers in Thailand (Honjo *et al.*, 2005 for CCA). In another study in Thailand a non-significant increased risk among regular drinkers was found (Parkin *et al.*, 1991 for CCA). There was no association in three studies on intrahepatic CCA from Italy (Donato *et al.*, 2001), Japan (Yamamoto *et al.*, 2004), and China (Zhou *et al.*, 2008) (Table 2.20 on-line). Kuper *et al.* (2001) did not find any association between consumption of alcoholic beverages and cholangiocarcinoma in a low-risk Caucasian population in Greece [data not shown due to only six cases].

Cholangiocarcinoma is a recognized complication of primary sclerosing cholangitis. A study among patients with primary sclerosing cholangitis (26 cases of CCA following primary sclerosing cholangitis, 87 controls with primary sclerosing cholangitis) reported alcohol drinking as one of the risk factor for developing CCA (Chalasani *et al.*, 2000).

2.5 Cancer of the stomach

In the previous *IARC Monograph* (IARC, 2010), results on the risk for cancer of the stomach associated with the consumption of alcoholic beverages were considered inconsistent. Since then, four cohort studies (Freedman *et al.*, 2007; Larsson *et al.*, 2007; Sung *et al.*, 2007; Allen *et al.*, 2009) and three case–control studies (Lucenteforte *et al.*, 2008; Benedetti *et al.*, 2009; Zaridze *et al.*, 2009) in the general population, and one cohort study in alcoholics (Thygesen *et al.*, 2009) have been published.

2.5.1 Cohort studies in the general population

Among cohort studies, no general association between alcohol intake and cancer of the stomach was found in three studies (Freedman *et al.*, 2007; Larsson *et al.*, 2007; Allen *et al.*, 2009), while Sung *et al.* (2007) reported a slight increase in risk (Table 2.21 available at http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-06-Table2.21.pdf).

2.5.2 Cohort studies in special populations (alcohol abusers)

Thygesen *et al.* (2009) reported a higher risk of cancer of the stomach in alcoholics than in the general population (Table 2.22 available at http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-06-Table2.22.pdf). The increase was statistically significant in men (68 cases) but not in women (7 cases). [This study provided no information on individual exposures or results adjusted for potential confounders.]

2.5.3 Case–control studies

None of the case–control studies (Lucenteforte *et al.*, 2008; Benedetti *et al.*, 2009; Zaridze *et al.*, 2009; Table 2.23 available at http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-06-Table2.23.pdf) found an overall association between alcohol intake and risk for cancer of the stomach. Benedetti *et al.* (2009) reported a statistically significant increase in the risk of cancer of the stomach among those who consumed 1–6 drinks per week, but not among those who drank 7 or more per week.

2.5.4 Types of alcoholic beverage

Analyses by different types of alcoholic beverages are presented in Table 2.24 (available at http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-06-Table2.24.pdf). Larsson *et al.* (2007) found an increased risk for cancer of the stomach with intake of medium or strong beer, while no effects were found with light beer, wine or hard liquor. Freedman *et al.* (2007) reported an increased risk for cancer of gastric cardia among those with high intake of hard liquor while no such association was found in the case of non-cardia gastric adenocarcinoma. Benedetti *et al.* (2009) reported a statistically significant increase in risk for cancer of the stomach among those who consumed 1–6 drinks per week of any of beer, wine or hard liquor, but not with those who drank 7 or more per week.

2.5.5 Confounding

In the previous Monograph, significantly increased risks were reported in some studies, including those from Japan, China, Poland and the Russian Federation. In no study was it possible to stratify or adjust fully for lifetime infection with *Helicobacter pylori*. It was concluded that since most of the population in areas where an association between consumption of alcoholic beverages and stomach cancer emerged had probably been infected by the bacterium, potential confounding by *H. pylori* infection was not a major concern. Of concern, however, was the likelihood that dietary deficiencies exist in those populations and that the consumption of alcoholic beverages might be accompanied by other unfavourable lifestyle factors, such as low socioeconomic class and low intake of fresh fruit, vegetables and various micronutrients (IARC, 2010).

New studies did not provide any additional information of potential confounders.

2.6 Cancer of the pancreas

In the previous *IARC Monograph* (IARC, 2010), it was concluded that there was not strong evidence for an association between the consumption of alcoholic beverages and risk of cancer of the pancreas.

2.6.1 Meta- and pooled analyses

A pooled analysis of 14 cohort studies (Genkinger *et al.*, 2009) and a meta-analysis of 21 case–control studies and 11 cohort studies (one of which was the pooled analysis) (Tramacere *et al.*, 2009) reported a small, statistically significant, increased risk for cancer of the pancreas associated with high intakes of alcoholic beverages (Table 2.25 available at http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-06-Table2.25.pdf). In the pooled analysis, with over 2000 incident cases of cancer of the pancreas, a relative risk of 1.22 (95%CI: 1.03–1.45) for those drinking ≥ 30 g/day versus none was found, with no significant difference by beverage type (Genkinger *et al.*, 2009). Tramacere *et al.* (2009) reported a relative risk of 1.22 (95%CI: 1.12–1.34) for those drinking ≥ 3 drinks/day [approx. 30 g/day] versus none or occasional drinkers.

2.6.2 Cohort studies in the general population

In addition to the cohort studies included in the pooled analysis by Genkinger *et al.* (2009), the association of alcoholic beverage consumption and risk for cancer of the pancreas has been independently examined in six cohort studies (Table 2.26 available at http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-06-Table2.26.pdf). A nested case–control study within the Veterans Health Administration Cohort [the control population consisted of all participants without cancer of the pancreas enrolled in the study] found a significant negative association between alcohol use and cancer of the pancreas.

[Only data on current alcohol use were collected by the clinical provider, and duration and intensity of alcohol use were not recorded. It is possible that patients might have stopped drinking due to ill health, thereby causing a spuriously high risk among the non-drinkers (Khurana *et al.*, 2007).] In another study, high alcohol consumption, defined according to a scoring system that was based on a self-administered questionnaire designed to detect alcoholism and on serum levels of γ-glutamyl transferase [a biomarker of excessive drinking], was associated with an increased risk for cancer of the pancreas (Johansen *et al.*, 2009). [Data on the amount of alcohol consumption were not available.] In the Million Women Study in the United Kingdom, with approximately 1300 incident cases, there was no association between alcohol intake and risk for cancer of the pancreas among this population of low to moderate drinkers (only 5% drank ≥ 15 drinks/week) (Allen *et al.*, 2009). In the European Prospective Investigation of nutrition and Cancer there was also no association with alcohol intake (Rohrmann *et al.*, 2009), although there was some suggestion of an increased risk among those with a high average lifetime intake of spirits (RR for ≥ 10 g/day versus 0.1–4.9 g/day: 1.40; 95%CI: 0.93–2.10). This finding is based on small numbers and should be interpreted with caution, in the NIH-AARP study (based on over 1000 incident cases) there was also a positive association between high alcohol intake and risk for cancer of the pancreas (RR for ≥ 3 versus > 0 – < 1 drinks/day: 1.45; 95%CI: 1.17–1.80), which was stronger among those with a high intake of spirits (RR for ≥ 3 drinks/day versus > 0 – < 1 drinks/day: 1.62, 95%CI: 1.24–2.10); there was no association for increasing intake of beer or wine, although few participants were heavy wine or beer drinkers (Jiao *et al.*, 2009). In the Netherlands Cohort Study the increased risk was limited to heavy drinkers (RR for ≥ 30 g/day versus none: 1.57; 95%CI: 1.03–2.39), and was similar in a subgroup of individuals who reported a stable alcohol intake for the previous five years (RR for ≥ 30 g/day versus none: 1.82, 95%CI: 1.05–3.15), but there was no association with a specific beverage type (Heinen *et al.*, 2009). The increased risk was observed only during the first 7 years of follow-up and not with longer follow-ups.

2.6.3 Cohort studies in special populations

In one cohort study conducted in the Netherlands there was a significantly higher rate of cancer of the pancreas among male alcohol abusers compared with the national average. Among women, rates of cancer of the pancreas were similar among alcohol abusers and the national population (Thygesen *et al.*, 2009; Table 2.27 available at http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-06-Table2.27.pdf). [The Working Group noted the low number of cases. This study provided no information on individual exposures or results adjusted for potential confounders.]

2.6.4 Case–control studies

In the previous *IARC Monograph* (IARC, 2010) reports of 29 case–control studies with quantitative data on the association of alcoholic beverage intake and the risk for cancer of the pancreas were considered. Most of these found no association, although some suggested that heavy alcoholic beverage drinking (e.g. ≥ 15 drinks/week) may be associated with an increased risk, while others found significant reductions in risk with increasing alcoholic beverage intake. Since then, four further case–control studies have been published (Table 2.28 available at http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-06-Table2.28.pdf). In a case–control study in the USA, with over 800 cases, a significant positive association with heavy consumption of alcoholic beverages and risk for cancer of the pancreas was found (≥ 60 versus < 60 mL ethanol/day: RR, 1.6;

95%CI: 1.1–2.5) (Hassan *et al.*, 2007). A positive association with high lifetime consumption of alcohol, and which was strongest for intake of spirits, was found in a small study in Canada (with 83 cases) (Benedetti *et al.*, 2009). In another study in Canada, with over 400 cases, no association with alcohol intake was found (Anderson *et al.*, 2009). [In this study the range of alcohol intake was narrow and the response rate among the cases was low (24% of all identified cases; 45% of contacted living cases), which may have led to some response bias.] In a study conducted in the Russian Federation with 366 pancreatic cancer deaths no significant association between a very high intake of vodka and death from cancer of the pancreas was found; however, the numbers were small (52 men and 4 women in the highest intake group) and exposure information was obtained from proxies of the decedents [which may have led to some misclassification of exposure] (Zaridze *et al.*, 2009). [Other studies with a high proportion of proxy respondents may also be prone to recall bias (Benedetti *et al.*, 2009). On the other hand, given the lethality of the disease, studies that only included self-respondents (Hassan *et al.*, 2007) may be prone to selection bias if alcohol consumption is associated with tumour aggressiveness.]

2.6.5 Patient characteristics

Some studies have shown higher risks in men than in women (Heinen *et al.*, 2009; Jiao *et al.*, 2009; Zaridze *et al.*, 2009) [there were too few women in the highest category of alcohol intake to drawn meaningful comparisons.] Most studies, including the meta- and pooled analyses, have found no significant difference in risk estimates between men and women (Genkinger *et al.*, 2009; Rohrmann *et al.*, 2009; Tramacere *et al.*, 2009). No evidence of a significant interaction between alcohol intake and pancreatic risk was found by either smoking status (Anderson *et al.* 2009; Genkinger *et al.*, 2009; Heinen *et al.*, 2009; Jiao *et al.*, 2009; Johansen *et al.*, 2009; Rohrmann *et al.*, 2009), folate intake (Genkinger *et al.*, 2009; Heinen *et al.*, 2009; Jiao *et al.*, 2009) or body mass index (Johansen *et al.*, 2009; Rohrmann *et al.*, 2009), although Genkinger *et al.* (2009) found that the association of alcohol consumption with risk was stronger among normal-weight individuals compared with overweight and obese individuals.

2.6.6 Potential confounders

Since individuals who consume high amounts of alcohol are also often smokers, it is possible that the positive association observed with alcohol intake may, in part, be due to residual confounding by smoking. In the pooled analysis no association with increasing alcohol consumption among non-smokers was found but a small increased risk among past and current smokers (Genkinger *et al.*, 2009). Although these differences were not statistically significant, it suggests that residual confounding by smoking cannot be ruled out. Evidence from other smaller studies is inconsistent, perhaps due to the low numbers of heavily exposed cases among non-smokers (Anderson *et al.*, 2009; Heinen *et al.*, 2009; Johansen *et al.*, 2009; Jiao *et al.*, 2009; Rohrmann *et al.*, 2009). [The Working Group noted that among smokers, it is difficult to disentangle the effects of alcohol from that of smoking due to differences in the amount of cigarettes consumed.]

2.7 Cancer of the lung

A possible link between consumption of alcoholic beverages and risk for cancer of the lung has long been speculated; in the previous *IARC Monograph* (IARC, 2010) it was concluded that the available data were inadequate to determine a causal association between the consumption of alcoholic beverages and lung cancer.

Two case–control studies (Kubík *et al.*, 2004; Benedetti *et al.*, 2009), eight cohort studies (Takezaki *et al.*, 2003; Nakaya *et al.*, 2005; Chao *et al.*, 2008; Shimazu *et al.*, 2008; Allen *et al.*, 2009; Thun *et al.*, 2009; Thygesen *et al.*, 2009; Toriola *et al.*, 2009), two meta-analyses (Chao, 2007; Fan & Cai, 2009) and one systematic review (Wakai *et al.*, 2007) were not considered in the previous *IARC Monograph* (IARC, 2010). More detailed analyses with regard to cancer of the lung for one of the case–control studies (Benedetti *et al.*, 2009) were available in an earlier publication (Benedetti *et al.*, 2006); therefore, the earlier publication is considered for this evaluation. This section reviews all available data.

A high correlation has been identified between tobacco smoking and alcohol drinking in many populations. As such, careful adjustment for smoking is one of the most important requirements for a valid interpretation for the association between alcohol drinking and cancer of the lung.

2.7.1 Overview of studies

(a) Cohort studies in the general population

Among 29 cohort studies of the general population that provided tobacco smoking-adjusted risk estimates for total alcoholic beverage use, of which one was a pooled analysis of seven cohort studies (Freudenheim *et al.*, 2005), a significant elevated risk for cancer of the lung associated with alcoholic beverage consumption was reported in 16 (Klatsky *et al.*, 1981; Pollack *et al.*, 1984; Stemmermann *et al.*, 1990; Chow *et al.*, 1992; Potter *et al.*, 1992; Doll *et al.*, 1994; Murata *et al.*, 1996; Prescott *et al.*, 1999; Lu *et al.*, 2000; Korte *et al.*, 2002 [which includes two separate studies: the Cancer Prevention Study (CPS) I and II]; Balder *et al.*, 2005; Nakaya *et al.*, 2005; Nishino *et al.*, 2006; Chao *et al.*, 2008; Toriola *et al.*, 2009) (the new studies are summarized in Table 2.29 available at http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-06-Table2.29.pdf). In some of these studies an increased risk at high levels of consumption was found (Klatsky *et al.*, 1981; Pollack *et al.*, 1984; Potter *et al.*, 1992; Doll *et al.*, 1994; Murata *et al.*, 1996; Prescott *et al.*, 1999; Lu *et al.*, 2000; Korte *et al.*, 2002 [CPS I and II]; Balder *et al.*, 2005; Nakaya *et al.*, 2005; Chao *et al.*, 2008), while no association at the highest consumption category but with moderate consumption was found in other studies (Stemmermann *et al.*, 1990; Chao *et al.*, 2008, [only for drinking < 1 drink beer per week versus non-drinkers]), among former drinkers (Nakaya *et al.*, 2005; Nishino *et al.*, 2006), or among binge drinkers (Toriola *et al.*, 2009). No significant association was observed in the other cohort studies with results adjusted for smoking, including the pooled analysis of seven cohorts (Kvåle *et al.*, 1983; Kono *et al.*, 1986; Bandera *et al.*, 1997; Yong *et al.*, 1997; Woodson *et al.*, 1999; Breslow *et al.*, 2000; Djoussé *et al.*, 2002; Takezaki *et al.*, 2003; Freudenheim *et al.*, 2005; Rohrmann *et al.*, 2006; Shimazu *et al.*, 2008; Allen *et al.*, 2009; Thun *et al.*, 2009). In some of these studies, levels of alcohol intake among the participants were moderate (Kono *et al.*, 1986; Breslow *et al.*, 2000; Freudenheim *et al.*, 2005; Allen *et al.*, 2009).

(b) Cohort studies in special populations

The risk for cancer of the lung among alcoholics or patients with alcohol use disorders was examined in seven cohort studies (Schmidt & Popham, 1981; Adami *et al.*, 1992; Tønnesen *et al.*, 1994; Sigvardsson *et al.*, 1996; Sørensen *et al.*, 1998; Boffetta *et al.*, 2001; Thygesen *et al.*, 2009) are summarized in Table 2.30 available at http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-06-Table2.30.pdf. All reported elevated risk of cancer of the lung. However, due to the lack of control for tobacco smoking in all of the studies, the observed association may be largely explained by the confounding effect of tobacco smoking.

(c) Case–control studies

In all, 22 case–control studies reported tobacco smoking-adjusted odds ratios for total consumption of alcoholic beverages and the risk for cancer of the lung (the new studies are summarized in Table 2.31 available at http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-06-Table2.31.pdf). In seven population-based studies (Koo, 1988; Bandera *et al.*, 1992; Mayne *et al.*, 1994; Carpenter *et al.*, 1998; Hu *et al.*, 2002; Freudenheim *et al.*, 2003; Benedetti *et al.*, 2006) and 11 hospital-based studies (Williams & Horm, 1977; Herity *et al.*, 1982; Kabat & Wynder, 1984; Mettlin, 1989; Pierce *et al.*, 1989; Rachtan & Sokolowski, 1997; Zang & Wynder, 2001; De Stefani *et al.*, 2002; Pacella-Norman *et al.*, 2002; Ruano-Ravina *et al.*, 2004; Kubík *et al.*, 2004) no significant association between any level of alcoholic beverage consumption and the risk for cancer of the lung was found, while in four hospital-based studies (De Stefani *et al.*, 1993; Dosemeci *et al.*, 1997; Rachtan, 2002; Gajalakshmi *et al.*, 2003) an association was found.

(d) Meta- and pooled analyses

Korte *et al.* (2002) found an increased risk for lung cancer with an ethanol intake of at least 2000 g per month (≥ 5 drinks/day): the relative risk from cohort studies was 1.53 (95%CI: 1.04–2.25) and the odds ratio from case–control studies was 1.86 (95%CI: 1.39–2.49) [the estimated risks for intake of 2000 g/month or more were based on only one study for both cohort and case–control studies]; lower intakes were not associated with increased risk (Table 2.32 available at http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-06-Table2.32.pdf). [The exposure studied most extensively was the frequency of drinking. Other parameters of alcoholic beverage exposure, such as duration and age at initiation of drinking and the relevant exposure period were not considered.] In another meta-analysis Fan & Cai (2009) provided estimates for total alcohol drinking, and did not find a significant association with risk of lung cancer. In a pooled analysis of 7 cohort studies, Freudenheim *et al.* (2005) found a slightly greater risk of cancer of the lung with the consumption of ≥ 30 g alcohol per day than with no alcohol consumption (RR, 1.21; 95%CI: 0.91–1.61 in men, RR, 1.16; 95%CI: 0.94–1.43 in women).

2.7.2 Types of alcoholic beverage

Findings from studies examining risk estimates for the consumption of different types of alcoholic beverages (i.e. beer, wine, and hard liquor) have been inconsistent (Pollack *et al.*, 1984; Mettlin, 1989; Bandera *et al.*, 1992; Chow *et al.*, 1992; De Stefani *et al.*, 1993; Carpenter *et al.*, 1998; Prescott *et al.*, 1999; Woodson *et al.*, 1999; De Stefani *et al.*, 2002; Hu *et al.*, 2002; Rachtan 2002; Kubík *et al.*, 2004; Ruano-Ravina *et al.*, 2004; Freudenheim *et al.*, 2005; Benedetti *et al.*, 2006) (the new studies are summarized in Table 2.31 on-line). Risk estimates for different types of alcoholic beverages were also reported in two meta-analyses (Chao, 2007; Fan & Cai, 2009) using results adjusted for smoking (Table 2.32 on-line). Both found a slightly increased risk associated with beer drinking; there was also a slight association between drinking of liquor (Chao, 2007) and spirits (Fan & Cai, 2009) and risk for cancer of the lung. However, when one of the meta-analyses included only the studies with more comprehensive adjustments for smoking (Chao, 2007), there was no significant association.

2.7.3 Smoking status

Several cohort studies have examined the effect of alcoholic beverage consumption among both never smokers and smokers, and the interaction between these two risk factors (Korte *et al.*, 2002; Freudenheim *et al.*, 2005; Nishino *et al.*, 2006; Rohrmann *et al.*, 2006; Chao *et al.*, 2008;

Shimazu *et al.*, 2008; Thun *et al.*, 2009; Toriola *et al.*, 2009; Table 2.33 available at http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-06-Table2.33.pdf, and Table 2.34 available at http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-06-Table2.34.pdf). Korte *et al.* (2002) found an increased risk for cancer of the lung associated with drinking ≥ 500 g of alcohol per month among both never smoker men and women in CPS I but not in CPS II. In a pooled study of seven cohorts, Freudenheim *et al.* (2005) found an elevated pooled relative risk for alcoholic beverage consumption among never-smoking men but not among never-smoking women. A dose–response was also observed among men with a sixfold increase in risk among never smokers who consumed ≥ 15 g/day (pooled multivariate RR, 6.38; 95%CI: 2.74–14.90; *P for trend* < 0.001).

In contrast, Nishino *et al.* (2006), Rohrmann *et al.* (2006), Shimazu *et al.* (2008), Thun *et al.* (2009), and Toriola *et al.* (2009) reported no association among never smokers. [These analyses may have the limitation that most of the cases of cancer of the lung were smokers.] In a detailed analysis examining the effect of consumption of alcoholic beverages by smoking behaviour, Woodson *et al.* (1999) found no differences in the relative risks across smoking categories (< 20, 20–29, ≥ 30 cigarettes/day) [results were on smokers only]. However, Shimazu *et al.* (2008) found an increased risk for cancer of the lung among current smokers who drank 300–449 g ethanol per week (hazard ratio (HR, 1.66; 95%CI: 1.04–2.65) as well as those who drank ≥ 450 g/wk (HR, 1.69; 95%CI: 1.05–2.72; *P* for trend = 0.02) compared to current smokers who drank occasionally. Toriola *et al.* (2009) also found a significant positive association among smokers that was independent of the number of cigarettes smoked or the duration of smoking. However, the analysis was limited to binge drinkers.

Three case–control studies based on populations of never smokers (Kabat & Wynder, 1984; Koo, 1988; Hu *et al.*, 2002) found no significant risks for consumption of alcoholic beverages [There is a lack of power to examine the risk associated with heavy drinking, as it is uncommon to find heavy drinkers among never smokers.] In contrast, Rachtan (2002) observed a significantly elevated risk associated with alcoholic beverage intake among women who never smoked and a strong positive dose–response. Other studies on total alcohol intake with results stratified by smoking status have found positive associations between alcohol drinking and risk for cancer of the lung among smokers and no association among non-smokers (Dosemeci *et al.*, 1997; Zang & Wynder, 2001) or found associations among heavy smokers and no association among non-smokers and low/moderate-smokers combined (Herity *et al.*, 1982; Bandera *et al.*, 1992; Benedetti *et al.*, 2006 [men only]).

There is also some evidence that consumption of alcoholic beverages results in an inverse association with risk of cancer of the lung. Two studies reported an inverse association between wine consumption and lung cancer, one case–control study among non-smokers (Kubík *et al.*, 2004) [results not adjusted for consumption of other alcoholic beverages], and one cohort study (Chao *et al.*, 2008) among smokers.

2.7.4 Histological subtypes

Two cohort studies (Rohrmann *et al.*, 2006; Shimazu *et al.*, 2008), one pooled analysis (Freudenheim *et al.*, 2005) and eight case–control studies (Koo, 1988; Dosemeci *et al.*, 1997; Carpenter *et al.*, 1998; Zang & Wynder, 2001; De Stefani *et al.*, 2002; Djoussé *et al.*, 2002; Rachtan, 2002; Benedetti *et al.*, 2006) presented smoking-adjusted risk estimates for consumption of alcoholic beverages by histological type of cancer of the lung (the new studies are summarized in Table 2.35 available at http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-06-Table2.35.pdf). There appears to be no consistent pattern of

effect estimates by histological type. [Estimates for subtype of cancer of the lung were mostly based on small numbers of cases, which leads to difficulties in interpreting results due to wide confidence intervals and the possibility of chance findings.] Few studies have reported results by histological type among never smokers (Koo, 1988).

2.7.5 Population characteristics

Several studies conducted analyses stratified by sex using the same exposure categories (Williams & Horm, 1977; Bandera *et al.*, 1997; Prescott *et al.*, 1999; Korte *et al.*, 2002; Pacella-Norman *et al.*, 2002; Freudenheim *et al.*, 2005; Benedetti *et al.*, 2006; Rohrmann *et al.*, 2006). No significant findings that differed by sex have been reported.

2.8 Cancer of the breast

2.8.1 Cancer of the female breast

The previous *IARC Monograph* (IARC, 2010) concluded that occurrence of cancer of the female breast was causally associated with the consumption of alcoholic beverages. This conclusion was based on data from more than 100 epidemiological studies, together with a pooled analysis of 53 studies on more than 58000 women with breast cancer, which found a linear increase in risk for breast cancer with increasing levels of alcoholic beverage consumption (increase per 10 g/d of 7.1%, 95%CI: 5.5–8.7%) (Hamajima *et al.*, 2002).

(a) Cohort studies in the general population

Since IARC (2010), thirteen cohort studies have examined the association of consumption of alcoholic beverages and risk of cancer of the breast (Table 2.36 available at http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-06-Table2.36.pdf), eight of which showed a significant positive association (Ericson *et al.*, 2007; Mørch *et al.*, 2007; Zhang *et al.*, 2007a; Thygesen *et al.*, 2008a; Allen *et al.*, 2009; Duffy *et al.*, 2009; Lew *et al.*, 2009; Li *et al.*, 2009b), and four no significant association (Trentham-Dietz *et al.*, 2007; Visvanathan *et al.*, 2007; Kabat *et al.*, 2008; Gibson *et al.*, 2009), [In two of these latter studies the number of drinkers was small and there was no quantitative assessment of alcohol intake.] One further study found no association with a predominantly alcohol-based dietary pattern and risk of cancer of the breast (Engeset *et al.*, 2009) [No specific assessment of alcohol intake was presented and the contribution of other foods to this dietary pattern was not known.] The Million Women Study in the United Kingdom, with over 28 000 incident cancers, is the largest single study to estimate reliably the risk for cancer of the breast at low to moderate levels of alcohol consumption. A linear increase in risk of cancer of the breast with increasing alcohol intake (increase per 10 g/day [equivalent to about one drink regularly consumed per day] of 12%, 95%CI: 9–14%) was found (Allen *et al.*, 2009). This estimate is slightly higher than the 7.1% increase in risk reported in the pooled analysis by Hamajima *et al.* (2002). [Allen *et al.* (2009) were able to take measurement error into account by repeating the alcohol consumption measure approximately three years after recruitment].

(b) Cohort studies in special populations

Since IARC (2010), Thygesen *et al.* (2009) reported a significantly higher rate of cancer of the breast among female alcoholics compared with national rates from a cohort study among Danish alcohol abusers (Table 2.37 available at http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-06-Table2.37.pdf) [This study provided no information on individual exposures or adjusted for potential confounders.]

(c) Case–control studies

The association of consumption of alcoholic beverages and risk for incident cancer of the female breast has been examined in 11 case–control studies (Table 2.38 available at http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-06-Table2.38.pdf). A significant positive association has been reported from six studies (Beji & Reis, 2007; Kruk, 2007; Berstad *et al.*, 2008; Kocić *et al.*, 2008; Knight *et al.*, 2009; Newcomb *et al.*, 2009) and a significant inverse association in one (Zaridze *et al.*, 2009). [This latter study was conducted in the Russian Federation where alcohol consumption is very high relative to other populations and exposure information was obtained from proxies of the decedents (case and control status was based on death certification information). Reasons for the inverse association with very high intake are not clear and information on potential confounders was unavailable.] Null associations were found in four studies (Terry *et al.*, 2007; Bessaoud & Daurès, 2008; Dolle *et al.*, 2009; Brown *et al.*, 2010), although they either had a very low alcohol intake (Bessaoud & Daurès, 2008; Dolle *et al.*, 2009; Brown *et al.*, 2010) or did not adjust for potential confounding factors (Terry *et al.*, 2007).

(d) Other metrics of exposure

Very few investigators have examined whether the frequency of drinking, age at started drinking or the cumulative lifetime intake influences risk; in one cohort study in Denmark some evidence was found that binge drinking at the weekend may additionally increase risk (Mørch *et al.*, 2007). Another cohort study in Denmark found that risk was attenuated when using updated alcohol information (i.e. most recent intake measured after recruitment), with the suggestion that there may be a long latent period between consumption of alcoholic beverages and development of cancer of the breast (Thygesen *et al.*, 2008a). In contrast, Berstad *et al.* (2008) reported a positive association for recent intake (i.e. in the last five years), but no association with lifetime intake or intake at a young age from a case–control study in the USA.

(e) Types of alcoholic beverage

There is consistent evidence from both cohort and case–control studies that the risk for cancer of the female breast does not vary significantly by beverage type (Zhang *et al.*, 2007a; Berstad *et al.*, 2008; Bessaoud & Daurès, 2008; Allen *et al.*, 2009; Lew *et al.*, 2009; Li *et al.*, 2009b; Newcomb *et al.*, 2009). Among wine drinkers, the risk does not vary by intake of red wine, white wine or a mixture of both (Allen *et al.*, 2009; Newcomb *et al.*, 2009).

(f) Other factors affecting risk

There is consistent evidence that the association does not vary by folate intake (Zhang *et al.*, 2007a; Duffy *et al.*, 2009; Lew *et al.*, 2009) or by menopausal status (Mørch *et al.*, 2007; Terry *et al.*, 2007; Visvanathan *et al.*, 2007; Zhang *et al.*, 2007a; Kabat *et al.*, 2008), although in two case–control studies there was a slightly stronger association of consumption of alcoholic beverages and risk for cancer of the breast in postmenopausal than in premenopausal women (Kruk, 2007; Newcomb *et al.*, 2009).

It remains unclear whether the association of consumption of alcoholic beverages with risk of cancer of the breast varies by use of hormone-replacement therapy. In the Copenhagen City Heart Study, and to a lesser extent, the Women's Health Study, a positive association between alcohol intake and risk for cancer of the breast among current users, and no association among non-users of hormone-replacement therapy was found (Zhang *et al.*, 2007a; Nielsen & Grønbaek, 2008), whereas others have found no such differences (Bessaoud & Daurès, 2008; Allen *et al.*, 2009; Lew *et al.*, 2009).

Most of the data for an association of consumption of alcoholic beverages on risk for

cancer of the breast comes from Caucasian populations; there is very limited data among Asian populations (Gibson *et al.*, 2009; Brown *et al.*, 2010), perhaps due to the generally low prevalence of alcohol consumption. Most studies that included different ethnic groups estimated risk after adjusting for ethnicity; in two studies that stratified by ethnic group there was no difference in the risk associated with consumption of alcoholic beverages (Berstad *et al.*, 2008; Li *et al.*, 2009b).

There is accumulating evidence that cigarette smoking may increase risk for cancer of the breast (see Monograph on Tobacco Smoking in this Volume), and because drinking and smoking are highly correlated, most studies that have evaluated the association of consumption of alcoholic beverages on risk for cancer of the breast have adjusted for smoking, to a greater or lesser extent. Hamajima *et al.* (2002) found that the association of consumption of alcoholic beverages with risk for cancer of the breast was similar in never, ever and current smokers. No subsequent studies have had sufficient statistical power to evaluate this in more detail, although the evidence to date suggests that the association of consumption of alcoholic beverages on risk of cancer of the breast is unlikely to be confounded by smoking. Another potentially important confounder is body size; in those studies that have examined potential effect modification by body mass index no significant differences have been found (Zhang *et al.*, 2007a; Berstad *et al.*, 2008; Lew *et al.*, 2009).

(g) Contralateral cancer of the breast

The association of consumption of alcoholic beverages with risk for contralateral cancer of the breast was not evaluated in IARC (2010). To date, four cohort (Table 2.39 available at http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-06-Table2.39.pdf) and one case–control study (Table 2.40 available at http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-06-Table2.40.pdf) have examined whether consumption of alcoholic beverages increases the risk of a subsequent contralateral cancer of the breast. In one cohort study alcohol consumption at the time of the first diagnosis and during the period between the first and second diagnosis was positively associated with the risk of contralateral cancer of the breast (Li *et al.*, 2009a), although no association was found in other cohort studies (Bernstein *et al.*, 1992; Li *et al.*, 2003b; Trentham-Dietz *et al.*, 2007). In the case–control study women with a contralateral breast cancer were more likely to have drunk regularly and to have drunk for a prolonged period of time compared with women who only had one diagnosis of cancer of the breast, although regular drinking during the period between the first and second diagnosis was not significantly associated with risk (Knight *et al.*, 2009).

(h) Tumour receptor status

The association of consumption of alcoholic beverages and risk for cancer of the breast by estrogen (ER) and progesterone (PR) receptor status has been examined in six cohort studies (Table 2.41 available at http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-06-Table2.41.pdf). Similar associations for ER+ and ER- tumours were reported by Chlebowski *et al.* (2007), Visvanathan *et al.* (2007), Lew *et al.* (2009) and Setiawan *et al.* (2009). Lew *et al.* (2009) found a slightly stronger association with alcohol intake and ER+/PR+ tumours than for ER+/PR- or ER-/PR- tumours. Li *et al.* (2009b) and Zhang *et al.* (2007a) in contrast reported positive associations for ER+ and PR+ tumours (together with the subgroup of ER+/PR+) and no association with ER- or PR- tumours. Tumour receptor status has also been evaluated in five case–control studies (Table 2.42 available at http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-06-Table2.42.pdf). In the largest, with approximately 1000 cases with information on receptor status, an increased risk for all

ER+ tumours, and no significant association for ER- tumours, irrespective of PR status, was found; the relative risk per 10 g alcohol/day for ER+/PR+ tumours was 1.14 (95%CI:1.07–1.20), that for ER+/PR- tumours was 1.07 (95%CI: 0.95–1.21) (Deandrea *et al.*, 2008). The association was slightly stronger among pre/perimenopausal women and among women with a high folate intake, although the numbers in these subgroups were small (Deandrea *et al.*, 2008). In a meta-analysis of 16 case–control studies and 3 cohort studies (Table 2.43 available at http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-06-Table2.43.pdf) an increased risk per 10 g/day increase in alcohol intake for all ER+ tumours was found (12% increased risk), and for the subtypes of ER+/PR+ tumours (11%) and ER+/PR- tumours (15%), and a smaller positive association for all ER- (7%), but no association with ER-/PR- or ER-/PR+ tumours (Suzuki *et al.*, 2008).

There are limited data on the association of consumption of alcoholic beverages with tumours that are characterized as triple-negative or basal-like (defined as ER-/PR-/HER2-), largely because of the recency of available data on HER2 status (human epidermal growth factor receptor). From a case–control study among premenopausal women Dolle *et al.* (2009) reported no association between consumption of alcoholic beverages with triple-negative or non triple-negative tumours, and in another case–control study no significant association with triple-negative or luminal B tumours (ER+ and/or PR+/HER2+) was found, but a stronger positive association for luminal A tumours (ER+ and/or PR+/HER2-) and HER2+ overexpressing tumours (defined as ER-/PR-/HER2+) (Trivers *et al.*, 2009). [The small numbers in some of these subgroups limits interpretation]. No significant differences in drinking status between women with luminal A tumours (the most common tumour type) and women diagnosed with triple-negative or HER2+ overexpressing tumours were reported by Kwan *et al.* (2009) and Millikan *et al.* (2008) from case-only analyses; one found that women with luminal B tumours were less likely to be drinkers (Kwan *et al.*, 2009), while there was no difference in the other study (Millikan *et al.*, 2008). [The null associations seen for the rarer subtypes of ER+/PR- and ER-/PR+ tumours may reflect limited power of the studies.]

(i) *Histological subtype*

To date, the NIH-AARP (Lew *et al.*, 2009) is the only cohort study to have examined the association of consumption of alcoholic beverages by histological subtype among postmenopausal women; similar positive associations were reported for ductal, lobular and ductal-lobular subtypes (Table 2.44 available at http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-06-Table2.44.pdf). This is consistent with findings from one case–control study (Nasca *et al.*, 1994; Table 2.45 available at http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-06-Table2.45.pdf), while a slightly stronger positive association for alcohol intake with the risk for lobular tumours compared with ductal tumours, particularly among postmenopausal women, was found in two others (Li *et al.*, 2003a, 2006). [The low numbers of cases in some subgroups resulted in limited power to detect a significant difference, and these may be chance findings. In addition, it should be noted that the histological data from all of these studies was derived from hospital records and were not subject to central pathology review, leading to potential misclassification due to observer variability.]

2.8.2 Cancer of the male breast

It was concluded in the previous *IARC Monograph* (IARC, 2010) that the evidence for an association of consumption of alcoholic beverages and risk of cancer of the male breast was inconsistent.

(a) Cohort studies

Since IARC (2010), the association between consumption of alcoholic beverages and the risk for cancer of the male breast has been assessed in two cohort studies (Table 2.46 available at http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-06-Table2.46.pdf). In the NIH-AARP Study no evidence was found that alcohol intake was associated with the risk for cancer of the male breast (Brinton *et al.*, 2008). In a large cohort of US Army Veterans no association with alcoholism as recorded from hospital records and risk for cancer of the male breast was found (Brinton *et al.*, 2009).

(b) Studies in special populations

Thygesen *et al.* (2009) reported similar rates of cancer of the breast among male Danish alcoholics compared with national rates (Table 2.47 available at http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-06-Table2.47.pdf) [This was based on a very small number of cases and provided no information on individual exposures.]

2.9 Cancer of the uterine cervix

It was concluded in IARC (2010) that the evidence for an association between consumption of alcoholic beverages and risk for cancer of the uterine cervix was sparse. Although some studies of special populations showed positive associations, bias and confounding could not be excluded.

2.9.1 Cohort studies

The association between consumption of alcoholic beverages and risk for cancer of the uterine cervix has been examined in 8 cohort studies, seven of which were carried out in women who were treated for alcohol abuse or alcoholism (Prior, 1988; Adami *et al.*, 1992; Tønnesen *et al.*, 1994; Sigvardsson *et al.*, 1996; Weiderpass *et al.*, 2001; Thygesen *et al.*, 2009) or worked as waitresses (Kjaerheim & Andersen, 1994), and one in the general population (Allen *et al.*, 2009) (the new studies are summarized in Table 2.48 available at http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-06-Table2.48.pdf).

The majority of studies were conducted in Scandinavia (Adami *et al.*, 1992; Kjaerheim & Andersen, 1994; Tønnesen *et al.*, 1994; Sigvardsson *et al.*, 1996; Weiderpass *et al.*, 2001; Thygesen *et al.*, 2009), where the use of the unique identification numbers makes it possible to work on large, registry based data. Two cohort studies were conducted in the United Kingdom (Prior, 1988; Allen *et al.*, 2009). In all seven studies conducted in special populations elevated risk estimates for invasive cancer of the uterine cervix among alcoholic women were found compared to the general population. [None of the studies adjusted for known risk factors for cancer of the uterine cervix, namely human papilloma virus (HPV) infection, number of sexual partners and tobacco smoking, or attendance at cervical cancer screening programmes. It is possible that women with alcohol abuse have other behavioural patterns that may affect risk for cancer of the uterine cervix, such as non-compliance to screening, tobacco smoking and having a higher prevalence of HPV than the general population in their respective countries.]

In the Million Women Study (Allen *et al.*, 2009) non-drinking women had an elevated risk for cancer of the uterine cervix compared to drinkers. Among drinkers, there was no association between the amount of alcohol consumed and risk for cancer of the uterine cervix. The analyses were adjusted for socioeconomic status, smoking, body mass index, physical activity, oral contraceptives and hormone replacement therapy use, but not for particular risk factors of cancer of the uterine cervix, including HPV infection and factors related to a sexual behaviour such as the

number of lifetime sexual partners or age at first intercourse.

2.9.2 Case–control studies

The association between consumption of alcoholic beverages and cancer of the uterine cervix was evaluated in 12 case–control studies, seven of which were hospital-based (two from Italy, two from Thailand, one from Uganda, one from United Kingdom, one from the USA), three were register or cohort based (from the USA and Zimbabwe), and two were based on both hospital and population controls (one from Lesotho and one large multicentric study from Latin America). No or no significant increased risk for cancer of the uterine cervix among alcoholic drinkers was found in eight studies (Williams & Horm, 1977; Harris *et al.*, 1980; Marshall *et al.*, 1983; Cusimano *et al.*, 1989; Licciardone *et al.*, 1989; Thomas *et al.*, 2001a, b; Chiaffarino *et al.*, 2002). In the three studies from Africa (Martin & Hill, 1984; Parkin *et al.*, 1994; Newton *et al.*, 2007), women who drank alcohol had a significant or borderline significant elevated risk for cancer of the uterine cervix. [Adjustment for confounding in these studies was incomplete.] In the study from Latin America, in which adjustment for possible confounders was adequate, there was an elevated risk for cancer of the uterine cervix among occasional drinkers (confidence intervals not given) but no association with heavy drinking (Herrero *et al.*, 1989).

2.9.3 Evidence of a dose–response

The cohort studies on alcoholics did not provide convincing evidence of a dose–response between risk for cancer of the uterine cervix and duration of exposure, which was roughly estimated as years since cohort enrolment (first hospitalization/clinical treatment for alcoholism).

A case–control study from Latin America (Herrero *et al.*, 1989), which adjusted for important risk factors such as tobacco smoking and number of sexual partners, showed an inverse dose–response association. In four other case–control studies in which there was an indication of a higher risk for cancer of the uterine cervix with higher alcohol consumption, the observed association was weak in two (Harris *et al.*, 1980; Marshall *et al.*, 1983) and significant in two other studies (Martin & Hill, 1984; Parkin *et al.*, 1994), but adjustment for possible confounders was incomplete. In one study, a positive trend was observed among consumers in the category "wine and other alcoholic beverages" (Chiaffarino *et al.*, 2002).

2.9.4 Types of alcoholic beverage

The effect of specific types of alcoholic beverages (beer, wine and spirits) on risk for cancer of the uterine cervix was not investigated in the cohort studies.

In almost all case–control studies that evaluated specific types of alcoholic beverage (Marshall *et al.*, 1983; Martin & Hill, 1984; Chiaffarino *et al.*, 2002) no consistent differences in risk for cancer of the uterine cervix between drinkers and non-drinkers of a certain alcohol type were found. Williams & Horm (1977) found a non-significant higher risk for cancer of the uterine cervix among wine drinkers, while Marshall *et al.* (1983) found beer drinkers were at higher risk.

2.10 Cancer of the endometrium

In the previous *IARC Monograph* (IARC, 2010) it was concluded that the evidence for an association between consumption of alcoholic beverages and risk for cancer of the endometrium was inconsistent.

2.10.1 Cohort studies in the general population

The association between consumption of alcoholic beverages and cancer of the endometrium in the general population has been evaluated in eight cohort studies (Gapstur *et al.*, 1993; Terry *et al.*, 1999; Folsom *et al.*, 2003; Loerbroks *et al.*, 2007; Kabat *et al.*, 2008; Setiawan *et al.*, 2008; Allen *et al.*, 2009; Friberg & Wolk, 2009) (the new studies or updates are summarized in Table 2.49 available at http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-06-Table2.49.pdf). These studies were conducted in North America (Gapstur *et al.*, 1993; Folsom *et al.*, 2003; Kabat *et al.*, 2008; Setiawan *et al.*, 2008) and in Europe, one in the Netherlands (Loerbroks *et al.*, 2007), one in the United Kingdom (Allen *et al.*, 2009) and two in Sweden (Terry *et al.*, 1999; Friberg & Wolk, 2009). Risk estimates adjusted for multiple possible confounders (body size and reproductive factors) were presented in seven reports (Gapstur *et al.* 1993; Terry *et al.*, 1999; Loerbroks *et al.*, 2007; Kabat *et al.*, 2008; Setiawan *et al.*, 2008; Allen *et al.*, 2009; Friberg & Wolk, 2009) while only five of these (Jain *et al.*, 2000a [an earlier report from the same study as Kabat *et al.* (2008) in which results were not adjusted for smoking]; Loerbroks *et al.*, 2007; Setiawan *et al.*, 2008; Allen *et al.*, 2009; Friberg & Wolk, 2009) adjusted the analysis of consumption of alcoholic beverages for smoking. Smoking showed non-significant negative association in almost all studies except for Friberg & Wolk (2009), where the risk estimates for cancer of the endometrium were decreased among never smokers, especially in women drinking more than 10 g of alcohol daily.

There was no clear evidence of association between consumption of alcoholic beverages and the risk for cancer of the endometrium in any of these studies. In four (Terry *et al.*, 1999; Loerbroks *et al.*, 2007; Kabat *et al.*, 2008; Setiawan *et al.*, 2008) some elevated risk for cancer of the endometrium among drinking women was found. Only Setiawan *et al.* (2008) reported a statistically significant association, which was among women who consumed more than 2 drinks per day. In one study (Folsom *et al.*, 2003), an inverse association was found. No association was found in the other studies (Gapstur *et al.*, 1993; Allen *et al.*, 2009; Friberg & Wolk, 2009).

2.10.2 Cohort studies in special populations

Three earlier cohort studies examined the association between alcoholic beverage intake and the risk for cancer of the endometrium in special populations, namely women hospitalized or being treated for alcohol dependence (Tønnesen *et al.*, 1994; Sigvardsson *et al.*, 1996; Weiderpass *et al.*, 2001, which was an update of Adami *et al.*, 1992). Thygesen *et al.* (2009) conducted the most recent study (Table 2.50 available at http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-06-Table2.50.pdf).

Weiderpass *et al.* (2001) found an inverse association between alcoholic beverage consumption and cancer of the endometrium. [The analytical models did not include important covariates that may have confounded the association, such as cigarette smoking and body size.] In the other studies, there was no evidence of an association.

2.10.3 Case–control studies

Case–control studies that have investigated the relationship between alcoholic beverage consumption and the risk for cancer of the endometrium were carried out in North America, Japan and western Europe.Eight of these were hospital-based (La Vecchia *et al.*, 1986; Cusimano *et al.*, 1989; Austin *et al.*, 1993; Levi *et al.*, 1993; Parazzini *et al.*, 1995a; Kalandidi *et al.*, 1996; Petridou *et al.*, 2002; Hosono *et al.*, 2008), two were based on cases and controls from a cancer survey or registry database (Williams & Horm, 1977; Kato *et al.*, 1989) and eight were

population-based (Webster *et al.*, 1989; Shu *et al.*, 1991; Swanson *et al.*, 1993; Goodman *et al.*, 1997; Newcomb *et al.*, 1997; Jain *et al.*, 2000b; McCann *et al.*, 2000; Weiderpass & Baron, 2001). The most recent study (Hosono *et al.*, 2008) is summarized in Table 2.51 (available at http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-06-Table2.51.pdf)

Eleven studies (Cusimano *et al.*, 1989; Kato *et al.*, 1989; Webster *et al.*, 1989; Austin *et al.*, 1993; Swanson *et al.*, 1993; Parazzini *et al.*, 1995a; Kalandidi *et al.*, 1996; Newcomb *et al.*, 1997; Weiderpass & Baron, 2001; Petridou *et al.*, 2002; Hosono *et al.*, 2008) were designed to examine the association between consumption of alcoholic beverages, other lifestyle factors such as cigarette smoking, use of hormone replacement therapy and other risk factors in the etiology of cancer of the endometrium. Six studies (LaVecchia *et al.*, 1986; Shu *et al.*, 1991; Levi *et al.*, 1993; Goodman *et al.*, 1997; Jain *et al.*, 2000b; McCann *et al.*, 2000) were designed to evaluate nutritional factors. Potentially confounding factors were considered in all the studies except for one (Cusimano *et al.*, 1989), although adjustment may have been incomplete in three studies (Williams & Horm, 1977, [age, race and smoking]; Shu *et al.*, 1991, [pregnancies and weight]; Levi *et al.*, 1993, [only adjusted for age and centre]).

The results of case–control studies were not consistent. In 10 studies little or no association between consumption of alcoholic beverages and the risk for cancer of the endometrium was found (Kato *et al.*, 1989; Webster *et al.*, 1989; Austin *et al.*, 1993; Swanson *et al.*, 1993; Kalandidi *et al.*, 1996; Goodman *et al.*, 1997; Newcomb *et al.*, 1997; McCann *et al.*, 2000; Weiderpass & Baron, 2001; Petridou *et al.*, 2002). An inverse association was found in three (Williams & Horm, 1977; Jain *et al.*, 2000b; Hosono *et al.*, 2008), which was significant in two (Jain *et al.* 2000b; Hosono *et al.* 2008) among moderate drinking women. An increased risk for cancer of the endometrium with high consumption of alcoholic beverages was found by LaVecchia *et al.* (1986), Cusimano *et al.* (1989), Shu *et al.* (1991), Levi *et al.* (1993) and Parazzini *et al.* (1995a); in two the association was non-significant (Cusimano *et al.*, 1989; Shu *et al.*, 1991), in one it was significant (Parazzini *et al.*, 1995a) and one (Levi *et al.*, 1993) found a positive association relative to wine and liquor, but not to beer.

2.10.4 Evidence of a dose–response

There was no evidence of a trend of increasing risk for cancer of the endometrium with increasing consumption of alcoholic beverages in the cohort studies, nor a suggestion of a dose–response among long-term drinkers only (Friberg & Wolk, 2009).

In most case–control studies there was no dose–response relationship between consumption of alcoholic beverages and the risk for cancer of the endometrium. A negative dose–response association with significant trend was observed by Jain *et al.* (2000b) and Hosono *et al.* (2008), while one study showed a clear positive dose–response trend (Parazzini *et al.*, 1995a). In another study, there was an indication of a negative dose–response in the association but no formal test for trend was presented (Webster *et al.*, 1989).

2.10.5 Types of alcoholic beverage

The effect of specific types of alcoholic beverages (beer, wine, sprits) on the risk for cancer of the endometrium was investigated in three cohort studies, with no clear evidence of heterogeneity between different types of beverages (Gapstur *et al.*, 1993; Loerbroks *et al.*, 2007; Setiawan *et al.*, 2008).

Consumption of different alcoholic beverages in relation to risk for cancer of the endometrium was evaluated in seven case–control studies (Williams & Horm, 1977; Austin *et al.*, 1993; Levi *et al.*, 1993; Swanson *et al.*, 1993; Parazzini

et al., 1995a; Goodman *et al.*, 1997; Weiderpass & Baron, 2001). Levi *et al.* (1993) and Parazzini *et al.* (1995a) found increased risk for cancer of the endometrium with increasing consumption of wine and hard liquor, but not beer. Overall, there were no consistent patterns of association between any specific type of alcoholic beverage and risk for cancer of the endometrium.

2.10.6 Interactions

Only Setiawan *et al.* (2008) reported detailed results of interaction between other risk factors and consumption of alcoholic beverages for cancer of the endometrium. There was no clear effect modification by body mass index, postmenopausal hormone use, parity, oral contraceptive use or smoking status, though the power to detect such interactions was limited. The Million Women Study Collaborators (2005) investigated alcohol only as an interacting factor with hormone replacement therapy and found no evidence for an effect modification. Results from stratified analyses did not show any effect modification by age, smoking, body mass index, folic acid intake, or postmenopausal hormone use (Friberg & Wolk, 2009).

2.11 Cancer of the ovary

In the previous *IARC Monograph* (IARC, 2010), it was concluded that the evidence for an association between consumption of alcoholic beverages and risk for cancer of the ovary in both cohort and case–control studies was sparse and inconsistent. Since IARC (2010), one cohort study in alcoholics (Thygesen *et al.*, 2009) and one case–control study (Kolahdooz *et al.*, 2009) have evaluated the association between consumption of alcoholic beverages and risk of cancer of the ovary.

2.11.1 Cohort studies

A total of five cohort studies have examined the association between consumption of alcoholic beverages and the risk for cancer of the ovary in special populations, women hospitalized or being treated for alcohol dependence, four early (Adami *et al.*, 1992; Tønnesen *et al.*, 1994, Sigvardsson *et al.*, 1996; Lagiou *et al.*, 2001) and one more recent (Thygesen *et al.*, 2009; Table 2.52 available at http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-06-Table2.52.pdf); the association in the general population has been examined in seven cohort studies (Kushi *et al.*, 1999; Kelemen *et al.*, 2004; Schouten *et al.*, 2004; Chang *et al.*, 2007; Kabat *et al.*, 2008; Tworoger *et al.*, 2008; Allen *et al.*, 2009). The studies were conducted in North America (USA and Canada) and Europe (the Netherlands, the United Kingdom and Scandinavia). The reports on studies in special populations presented results adjusted for age and calendar period only, whereas in the population based cohort studies results were adjusted for a large variety of factors.

There was no evidence of an overall association between consumption of alcoholic beverages and the risk for cancer of the ovary in these studies.

2.11.2 Case–control studies

Twenty-four case–control studies investigated the relationship between alcoholic beverage consumption and the risk for cancer of the ovary in North America, Japan, Australia, India, western Europe and Scandinavia, including one recent (Kolahdooz *et al.*, 2009; Table 2.53 available at http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-06-Table2.53.pdf). Eleven were hospital-based (West, 1966; Williams & Horm, 1977; Byers *et al.*, 1983; Tzonou *et al.*, 1984; Mori *et al.*, 1988; Hartge *et al.*, 1989; LaVecchia *et al.*, 1992; Nandakumar *et al.*, 1995; Tavani *et al.*, 2001a; Yen *et al.*, 2003; Pelucchi *et al.*, 2005),

one was based on cases and controls who were included in a cancer registry database (Kato *et al.*, 1989), 11 were population-based (Gwinn *et al.*, 1986; Polychronopoulou *et al.*, 1993; Godard *et al.*, 1998; Kuper *et al.*, 2000; Goodman & Tung, 2003; McCann *et al.*, 2003; Modugno *et al.*, 2003; Riman *et al.*, 2004; Webb *et al.*, 2004; Peterson *et al.*, 2006; Kolahdooz *et al.*, 2009) and one used controls chosen both among general population and hospital patients (Whittemore *et al.*, 1988). The recent study (Kolahdooz *et al.*, 2009) examined dietary patterns, including a predominantly snack and alcohol-based dietary pattern, and cancer of the ovary. [No specific assessment of alcohol intake was presented.] Confounding factors were considered in all studies, although adjustment was more extensive in more newly published studies than in studies published during the 1980s.

Overall, the results of case–control studies do not suggest any association between consumption of alcoholic beverages and risk for cancer of the ovary, although a few studies indicated either positive or negative associations.

2.11.3 Types of alcoholic beverage

In four population-based cohort studies the association with different types of alcoholic beverages was investigated (Kelemen *et al.*, 2004; Schouten *et al.*, 2004; Chang *et al.*, 2007; Tworoger *et al.*, 2008). Intake of wine during the year before baseline was associated with an increased risk for cancer of the ovary in one study (Chang *et al.*, 2007), but was not confirmed in the others (Kelemen *et al.*, 2004; Schouten *et al.*, 2004; Tworoger *et al.*, 2008).

Seven case–control studies evaluated different alcoholic beverages in relation to risk for cancer of the ovary (Gwinn *et al.*, 1986; LaVecchia *et al.*, 1992; Tavani *et al.*, 2001a; Goodman & Tung, 2003; Modugno *et al.*, 2003; Webb *et al.*, 2004; Peterson *et al.*, 2006). Overall, there were no consistent patterns of association between any specific type of alcoholic beverage (beer, wine and spirits) and risk for cancer of the ovary.

2.11.4 Interactions

Kelemen *et al.* (2004), Schouten *et al.* (2004) and Chang *et al.* (2007) evaluated their data for possible interaction between alcoholic beverage intake and other variables. Kelemen *et al.* (2004) found a statistically significant interaction between folate intake and alcohol consumption with regard to risk for cancer of the ovary. A similar association was observed by Chang *et al.* (2007) for women drinking more than one glass of wine daily. No other consistent interactions were reported. Among the case–control studies, there was no consistent evidence of interaction between alcoholic beverage consumption and different variables known or suspected to be associated with risk of cancer of the ovary, such as reproductive history, education, body size or diet.

2.12 Cancer of the prostate

In the previous *IARC Monograph* (IARC, 2010) it was concluded that the evidence for the association between consumption of alcoholic beverages and risk of cancer of the prostate is inconsistent. Increased risk for cancer of the prostate at elevated levels of consumption of alcoholic beverages was suggested from a few cohort studies, but there was no consistent dose–response relationship and in many cohort studies there was no association. The majority of case–control studies also showed no association between consumption of alcoholic beverages and cancer of the prostate.

2.12.1 Cohort studies in the general population

For studies of cancer of the prostate that were conducted more recently, there should be concern if no attempt is made to distinguish between cases that are detected by screening, with a possibility that many might not have presented clinically during the lifetime of the individual in the absence of screening, and those that present clinically and are more likely to be progressive. Among the 23 cohort studies six studies (Platz *et al.*, 2004; Baglietto *et al.*, 2006; Sutcliffe *et al.*, 2007; Rohrmann *et al.*, 2008; Gong *et al.*, 2009; Chao *et al.*, 2010; Table 2.54 available at http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-06-Table2.54.pdf) have considered the stage or grade of the disease. None found any association between alcoholic beverage consumption and risk of advanced cases of cancer of the prostate. However in one study (Gong *et al.*, 2009) a strong association of increased risk of high-grade cancer of the prostate with heavy alcohol consumption in the whole study population was found (RR 2.01; 95%CI: 1.33–3.05), as well as among heavy beer drinkers (RR, 2.89; 95%CI: 1.76–3.76) compared to non-drinkers. In a few of the other cohort studies that did not make a distinction of cancer stage or grade there was an increased risk for cancer of the prostate at elevated levels of alcoholic beverage consumption (Hirayama, 1992; Schuurman *et al.*, 1999; Putnam *et al.*, 2000; Sesso *et al.*, 2001), but there was no consistent dose–response relationship. Many other cohort studies showed no association. The risk associated with different types of alcoholic beverages was inconsistent, with increased risks for both beer (Gong *et al.*, 2009) and white wine consumption (Velicer *et al.*, 2006), as well as null associations (Sutcliffe *et al.*, 2007; Chao *et al.*, 2010) for all alcoholic beverages. Most studies collected data on consumption of alcoholic beverages only at baseline. Two studies examined lifetime alcohol use up to baseline (Rohrmann *et al.*, 2008) and another alcohol use at ages 18 and 45 (Velicer *et al.*, 2006) and did not find associations.

2.12.2 Cohort studies in special populations

Two of the nine studies of special populations showed an association between alcoholic beverage consumption and cancer of the prostate. Tønnesen *et al.* (1994) and more recently Thygesen *et al.* (2009) (Table 2.55 available at http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-06-Table2.55.pdf) studying Danish alcohol abusers observed greater numbers of cancers of the prostate compared with the number expected from the general population. None of the studies provided information on individual exposures or adjusted for potential confounders.

2.12.3 Case–control studies

Studies published since IARC (2010) are summarized in Table 2.56 available at http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-06-Table2.56.pdf. Six of the 38 case–control studies considered aggressiveness of disease. In the study of Walker *et al.* (1992), 90% of the cases were advanced at presentation, and in the study by Li *et al.* (2008b), almost 50% of the cases were advanced and about 40% of moderately differentiated tumour presentation. The majority of the studies showed no association between consumption of alcoholic beverages and cancer of the prostate. Six studies found a positive association (De Stefani *et al.*, 1995; Hayes *et al.*, 1996; Sharpe & Siemiatycki, 2001; Chang *et al.*, 2005; Gallus *et al.*, 2007; Benedetti *et al.*, 2009). De Stefani *et al.*, (1995) found a borderline elevation of risk for high levels of consumption of beer, but the risk at high levels of total alcohol consumption was not significantly elevated. Hayes *et al.* (1996) found significant elevations in risk for 'heavy' and 'very heavy' consumers of alcoholic beverages, with higher risks among

those with poorly or undifferentiated tumours, or with regional or distant metastases. Sharpe & Siemiatycki (2001) reported an elevation in risk for those with long duration of drinking, with the greatest elevation in risk for those who started drinking at age < 15 years. An elevated risk with increasing drink/year [with close to significant trend] was reported by Benedetti *et al.* (2009) among beer drinkers, as well as a borderline increased risk among moderate red wine drinkers. Gallus *et al.* (2007) reported an increased risk among men with poorly differentiated tumours (Gleason score ≥ 7). This association was not significant for all cancers of the prostate combined (regardless of the stage/differentiation status). Chang *et al.* (2005) found an association between consumption of alcoholic beverages (in g/week) and risk of cancer of the prostate with a borderline trend; there was no association with advanced cancer, whereas localized cancer showed significant association but without a dose–response relationship. De Stefani *et al.* (2009) analysed dietary patterns consisting of alcoholic beverages and processed meat and found no significant association with cancer of the prostate.

2.12.4 Meta-analyses

A meta-analysis that included six cohort and 27 case–control studies that were reported before July 1998 resulted in a relative risk estimate of 1.05 (95%CI: 0.98–1.11) for ever consumption of alcoholic beverages and of 1.05 (95%CI: 0.91–1.20) for each additional drink of alcohol per day (Dennis, 2000). The latter estimate was based on 15 studies reporting amount of alcohol consumed. Based on these 15 studies, the estimated relative risk for 4 drinks/day was 1.21 (95%CI: 1.05–1.39) (Table 2.57 available at http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-06-Table2.57.pdf). Middleton-Fillmore *et al.* (2009) conducted a meta-analysis in which 14 cohorts and 21 case–control studies were included, reporting a weak but statistically significant association of incidence of cancer of the prostate with alcohol consumption levels in population case–control studies (RR, 1.24; 95%CI: 1.14–1.34), but meta-analyses of 7 hospital-based case–control studies and 14 cohort studies found no associations between consumption of alcoholic beverages and cancer of the prostate.

2.13 Cancer of the kidney

In the previous *IARC Monograph* (IARC, 2010) it was concluded that both cohort and case–control studies provide consistent evidence of no increase in risk for cancer of the kidney with consumption of alcoholic beverages (IARC, 2010). In several studies, increasing intake of alcoholic beverages was associated with a significantly lower risk for cancer of the kidney. These inverse trends were observed in both men and women and with multiple types of alcoholic beverage.

Since IARC (2010), one cohort (Table 2.58 available at http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-06-Table2.58.pdf) and three case–control studies (Table 2.59 available at http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-06-Table2.59.pdf) have been identified.

Allen *et al.* (2009) reported a decrease in risk for cancer of the kidney associated with moderate alcohol intake in women. The relative risk associated with ≥ 15 drinks per week was 0.66 (95%CI: 0.48–0.92); the reduction in risk per 10 g alcohol/day was 12% (95%CI: 1% to 22%).

Greving *et al.* (2007) (855 cases) reported an inverse association between alcohol intake measured as gram of ethanol per month and cancer of the kidney. Pelucchi *et al.* (2008) (1534 cases), in an update of a previous study (Pelucchi *et al.* (2002) together with a new study from the same area, found an inverse association between total alcohol intake or intake of wine measured as drinks per day and cancer of the kidney;

however, they did not find any effect of duration (years) of drinking or age of starting. Benedetti *et al.* (2009) (156 cases) found no effect of alcohol intake on the risk of cancer of the kidney.

2.14 Cancer of the urinary bladder

In the previous *IARC Monograph* (IARC, 2010) it was concluded that the evidence for an association between consumption of alcoholic beverages and risk for cancer of the urinary bladder was inconsistent.

One cohort (Allen *et al.*, 2009) and three case–control studies (Cao *et al.*, 2005; Jiang *et al.*, 2007; Zaridze *et al.*, 2009) on the general population and one cohort study on alcoholics (Thygesen *et al.*, 2009) have been identified since IARC (2010).

Allen *et al.* (2009) found no association between consumption of alcoholic beverages and cancer of the urinary bladder in women (Table 2.60 available at http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-06-Table2.60.pdf). Likewise, Thygesen *et al.* (2009) reported no effect of alcohol on cancer of the urinary bladder among alcoholics (Table 2.61 available at http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-06-Table2.61.pdf).

Two of the case–control studies (Cao *et al.*, 2005; Zaridze *et al.*, 2009) found no consistent association between consumption of alcoholic beverages and risk for cancer of the urinary bladder (Table 2.62 available at http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-06-Table2.62.pdf). However, Jiang *et al.* (2007) in a large case–control study (1671 cases) found a statistically significant reduced risk both in relation to frequency of alcohol intake, duration (in years), and age of initiation. The reduction in risk was particularly large among those who urinated frequently. [The reduced risk for cancer of the urinary bladder among those who urinated frequently may to some extent be due to a high liquid intake and dilution of potential carcinogens.]

2.15 Cancers of the lymphatic and haematopoietic system

Lymphomas and haematopoietic malignancies comprise a heterogeneous group of malignancies and their respective etiologies are not fully understood. In the previous *IARC Monograph* (IARC, 2010) it was concluded that there was *evidence suggesting lack of carcinogenicity* in humans for alcoholic beverages and non-Hodgkin lymphoma (NHL). The results of cohort studies and evidence from some very large case–control studies showed an inverse association or no association between the consumption of alcoholic beverages and the risk for NHL. In general, there was no evidence of substantial differences in the effect of specific beverage types or for specific histological subtypes of NHL. The evidence for an association between consumption of alcoholic beverages and risk for Hodgkin disease was sparse, and no consistent pattern of association was observed for leukaemia and multiple myeloma (IARC, 2010).

2.15.1 Cohort studies in the general population

In seven cohort studies, associations of consumption of alcoholic beverages and the risk for lymphatic and/or haematopoietic cancers were examined (Boffetta *et al.*, 1989; Kato *et al.*, 1992; Chiu *et al.*, 1999; Lim *et al.*, 2006; Lim *et al.*, 2007; Allen *et al.*, 2009; Klatsky *et al.*, 2009). Studies published since the previous Monograph (IARC, 2010) are summarized in Table 2.63 (available at http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-06-Table2.63.pdf)

For NHL specifically, Chiu *et al.* (1999) found a non-significant inverse association with consumption of alcoholic beverages among postmenopausal women in the USA. This relationship

persisted after adjustment for several potential confounding factors including age, total energy intake, residence (farm, no farm), education, marital status, history of transfusion and diabetes, and intake of red meat and fruit. [The Working Group noted that the level of alcohol intake was very low in this study.] Lim *et al.* (2006) found weak evidence of an inverse association among Finnish male smokers in a multivariate analysis. The three cohort studies published recently and conducted among retired persons in the USA (Lim *et al.*, 2007), among middle-aged women in the United Kingdom (Allen *et al.*, 2009), and in a multiethnic USA population (Klatsky *et al.*, 2009) have shown significantly decreased risk of NHL among people with moderate alcohol intake A borderline significant inverse association was also shown for consumers of 7 or more drinks per week who were diagnosed with B-cell lymphoma, chronic lymphocytic lymphoma or small lymphocytic lymphoma, as well as an inverse (although non-significant) association of Hodgkin lymphoma risk with consumption of alcoholic beverages (Lim *et al.*, 2007).

In a study among American men of Japanese ancestry that also considered several potential lifestyle, medical and dietary confounding factors, consumption of ≥ 30 ml alcohol per day compared with non-drinkers was associated with a threefold higher risk for lymphoma and leukaemia combined (Kato *et al.*, 1992). In the multiethnic cohort in the USA (Klatsky *et al.*, 2009) risk for myelocytic leukaemia among regular drinkers compared with never-drinkers plus those reporting < 1 drink/month, and risk for lymphocytic leukaemia among people drinking more than 2 drinks per week versus drinkers who drank < 1 drink/week showed inverse associations (p for trend 0.01 and 0.03, respectively). Allen *et al.* (2009) did not find any association between alcohol intake and risk of all leukaemias combined.

In the four cohort studies that assessed consumption of alcoholic beverages and the risk for multiple myeloma, no association was found in three (Lim *et al.*, 2006; Allen *et al.*, 2009; Klatsky *et al.*, 2009) and in one a lower risk among ever regular drinkers compared with never regular drinkers was found (Boffetta *et al.*, 1989).

2.15.2 Cohort studies in special populations

Five studies among heavy alcoholic beverage users or brewery workers have investigated the risk for lymphatic and/or haematopoietic cancers (Hakulinen *et al.*, 1974; Jensen, 1979; Robinette *et al.*, 1979; Schmidt & Popham, 1981; Carstensen *et al.*, 1990).

Three studies examined lymphatic and haematopoietic cancers combined (Jensen, 1979; Robinette *et al.*, 1979; Carstensen *et al.*, 1990), Jensen (1979) found no significant differences between the observed number of cases among Danish brewery workers compared with the expected number of cases computed from age-, sex-, and area-specific rates. Carstensen *et al.* (1990) found slightly increased risk for these cancers among Swedish brewery workers compared to the expected cases calculated using age, follow-up time, and area-standardized rates of the Swedish male population. Robinette *et al.* (1979) found a non-significant decreased risk among chronic alcoholic male USA veterans compared with expected numbers computed from age- and time-specific rates for the US male population.

In two studies, the observed number of cases of lymphoma among alcoholics was lower than that expected based on rates for the local population (Hakulinen *et al.*, 1974; Schmidt & Popham, 1981).

In studies among alcoholics, the observed number of cases of leukaemia did not differ significantly from those expected in one study (Hakulinen *et al.*, 1974), and was non-significantly lower in two other studies (Robinette *et al.*, 1979; Schmidt & Popham, 1981). In studies among brewery workers, Jensen (1979) found

no significant difference between the observed and expected number of leukaemia deaths, while Carstensen *et al.* (1990) found a 1.6-fold higher risk of mortality among brewery workers compared with those expected from the local population.

2.15.3 Case–control studies

(a) Lymphomas

Associations between consumption of alcoholic beverages and the risk for lymphoma were evaluated in 22 case–control studies (Williams & Horm, 1977; Cartwright *et al.*, 1988; Brown *et al.*, 1992; Nelson *et al.*, 1997; Tavani *et al.*, 1997; De Stefani *et al.*, 1998; Matsuo *et al.*, 2001a; Tavani *et al.*, 2001b; Briggs *et al.*, 2002; Chiu *et al.*, 2002; Morton *et al.*, 2003; Chang *et al.*, 2004; Willett *et al.*, 2004; Besson *et al.*, 2006a, b; Nieters *et al.*, 2006; Deandrea *et al.*, 2007; Casey *et al.*, 2007; Gorini *et al.*, 2007b; Willett *et al.*, 2007; Monnereau *et al.*, 2008; Benedetti *et al.*, 2009). Studies published since the previous Monograph (IARC, 2010) are summarized in Table 2.64 available at http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-06-Table2.64.pdf).

Most case–control studies of consumption of alcoholic beverages and lymphoma focused specifically on NHL and/or its histological subtypes. Chang *et al.* (2004) found no overall association of NHL risk with moderate consumption of alcoholic beverages, although there was a suggestive possible increased risk of NHL among men. In that study, all cases and controls were free of human immunodeficiency viral infection and several potential confounding factors including age, tobacco smoking and occupational exposure to pesticides were considered. Briggs *et al.* (2002) also found no difference in the risk for NHL between drinkers and non-drinkers after adjustment for age, ethnicity and smoking status. Casey *et al.* (2007) found no significant associations of different characteristics of consumption of alcoholic beverages considering drinkers versus non drinkers, current and former drinking, age at drinking debut, drinking duration or daily intake for all lymphoid neoplasms and B-cell lymphomas. An inverse association for ever alcohol drinking and NHL was observed in a large multicentric study (Monnereau *et al.*, 2008) with 399 NHL cases (OR, 0.7; 95%CI: 0.5–1.0).

Most individual studies of NHL have limited power to conduct detailed analyses of consumption of alcoholic beverages and risk for this disease, particularly for specific beverage types and histological subtypes. Therefore, data from nine case–control studies conducted in Italy, Sweden, the United Kingdom and the USA were pooled to include 6492 cases of NHL and 8683 controls (Morton *et al.*, 2005). The analysis showed a significantly lower risk for NHL for ever drinkers when compared to non-drinkers; however, there was no consistent dose–response relationship between risk and frequency of consumption of alcoholic beverages, duration of alcoholic beverage consumption or age at starting drinking. The risk for NHL for current drinkers was lower than that for former drinkers. There was no difference in association by alcoholic beverage type or for the combination of beverages types consumed. For specific subtypes of NHL, no significantly elevated risks were found. The lowest risk associated with ever drinking versus non-drinker was that for Burkitt lymphoma (OR, 0.51; 95%CI: 0.33–0.77). Low risks for diffuse B-cell, follicular and T-cell lymphomas associated with ever drinking were also noted. The findings were unchanged when the analyses were restricted to studies that had a high response rate.

A multicentre case–control study of NHL and consumption of alcoholic beverages included data from five European countries and comprised 1742 cases and 2465 controls (Besson *et al.*, 2006a). Overall, there were no associations observed for ever drinking, age at starting drinking, duration of drinking or monthly consumption with risk for all NHL or with any

histological subtype; similarly, no associations with risk of NHL were found with any specific type of alcoholic beverage. However, a lower risk associated with regular alcoholic beverage intake was observed for men (OR, 0.76; 95%CI: 0.62–0.93; 691 exposed cases) and for non-Mediterranean countries (OR, 0.73; 95%CI: 0.61–0.86).

Among the nine studies that examined Hodgkin lymphoma specifically (Williams & Horm, 1977; Tavani *et al.*, 1997; Besson *et al.*, 2006b; Nieters *et al.*, 2006; Deandrea *et al.*, 2007; Gorini *et al.*, 2007b; Willett *et al.*, 2007; Monnereau *et al.*, 2008; Benedetti *et al.*, 2009), a consistent inverse association was found almost in all. In the large multicentre European study, the odds ratio for Hodgkin lymphoma associated with ever regular drinking compared with never regular drinking was 0.61 (95%CI: 0.43–0.87; 81 exposed cases); this association was consistent for younger and older adults (Besson *et al.*, 2006b). Other multicentre studies have also shown an inverse association of Hodgkin lymphoma risk and frequent alcohol consumption of the order of 0.50 (Gorini *et al.*, 2007b; Monnereau *et al.*, 2008). Willett *et al.* (2007) found that the risk of Hodgkin lymphoma was higher among non-drinkers and persons with low alcohol consumption.

Inverse associations were also observed between specific alcoholic beverage types, namely wine and aperitif, and Hodgkin lymphoma (Gorini *et al.*, 2007b; Monnereau *et al.*, 2008).

(b) Leukaemia

The association of consumption of alcoholic beverages with risk for adult leukaemia was examined in eight case–control studies (Williams & Horm, 1977; Brown *et al.*, 1992; Wakabayashi *et al.*, 1994; Chang *et al.*, 2004; Pogoda *et al.*, 2004; Rauscher *et al.*, 2004; Gorini *et al.*, 2007a; Monnereau *et al.*, 2008). Studies published since the previous Monograph are summarized in Table 2.65 (available at http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-06-Table2.65.pdf). No consistent patterns of associations between total consumption of alcoholic beverages and risk for all leukaemias combined were observed. In two studies a non-significant two- to threefold higher risk for acute lymphocytic leukaemia associated with heavy drinking (Wakabayashi *et al.*, 1994) or with any drinking (Brown *et al.*, 1992) was found, while in another no association of drinking with risk for this type of leukaemia was found (Gorini *et al.*, 2007a). Similarly, there was no consistent evidence of associations with acute non-lymphocytic leukaemia, chronic lymphocytic leukaemia or chronic myeloid leukaemia in these studies. Chang *et al.* (2004) found a positive significant association between high wine intake and risk for chronic lymphocytic leukaemia.

(c) Multiple myeloma

Associations between consumption of alcoholic beverages and the risk for multiple myeloma were examined in nine case–control studies, five in the USA, one in Canada, two in Italy and one in France (Williams & Horm, 1977; Gallagher *et al.*, 1983; Linet *et al.*, 1987; Brown *et al.*, 1992; Brown *et al.*, 1997; Deandrea *et al.*, 2007; Gorini *et al.*, 2007b; Hosgood *et al.*, 2007; Monnereau *et al.*, 2008). Studies published since the previous Monograph are summarized in Table 2.66 (available at http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-06-Table2.66.pdf). In the largest studies, there was a statistically significant lower risk for multiple myeloma among drinkers compared with non-drinkers in white men (Hosgood *et al.*, 2007) and to a lesser extent in black men and white women (Brown *et al.*, 1997) and among both men and women (Gorini *et al.*, 2007b), but the latter associations were non-significant. Brown *et al.* (1997) found a non-significant 2.8-fold higher risk for multiple myeloma for white women who consumed ≥ 22 drinks per week. Non-significantly increased risk of multiple myeloma for consumption of alcoholic beverages was found by Deandrea *et al.* (2007)

and Monnereau *et al.* (2008) after adjustment for age, centre, sex and tobacco. No consistent association patterns were observed among the other case–control studies. Most studies collected data on alcoholic beverage consumption from proxy respondents, and some included prevalent cases. In addition, not all studies controlled for the potential confounding effects of tobacco smoking, and only two controlled for other factors such as farming, family history of cancer and occupational exposure to high-risk chemicals (Brown *et al.*, 1992; Monnereau *et al.*, 2008).

2.16 Other cancers

In the previous *IARC Monograph* (IARC, 2010) it was noted that the evidence for an association of consumption of alcoholic beverages with risk of other female cancers (vulva and vagina) and cancers of the testis, brain, thyroid, and skin melanoma was generally sparse and/or inconsistent.

2.16.1 Cancers of the vulva and vagina

In two cohort studies the association between consumption of alcoholic beverages and risk for other female cancers was examined. These were carried out in women being treated for alcohol abuse or alcoholism in Sweden (Sigvardsson *et al.*, 1996; Weiderpass *et al.*, 2001). In one study an elevated risk for vaginal cancer but not for vulva cancer was found (Weiderpass *et al.*, 2001). Sigvardsson *et al.* (1996) reported high relative risks for both vulva and vaginal cancers combined. In these studies relative risk estimates could not be adjusted for factors that may have confounded the association between alcoholic beverage consumption and vulva and vaginal cancers, such as HPV infections, number of sexual partners and tobacco smoking. It is possible that women who abuse alcohol have other behavioural patterns that may affect risks for these cancers.

Four case–control studies investigated the association between consumption of alcoholic beverages and risk for vulva cancer, conducted in Italy (Parazzini *et al.*, 1995b) and in the USA (Williams & Horm, 1977; Mabuchi *et al.*, 1985; Sturgeon *et al.*, 1991); one study from Denmark (Madsen *et al.*, 2008) investigated both cancer of the vulva and vagina. Studies published since the previous Monograph (IARC, 2010) are summarized in Table 2.67 available at http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-06-Table2.67.pdf). Three were hospital-based studies (Williams & Horm, 1977; Mabuchi *et al.*, 1985; Parazzini *et al.*, 1995b), one was population-based (Sturgeon *et al.*, 1991), while Madsen *et al.* (2008) used two sets of controls, population- and hospital-based. Confounding factors were considered in four studies (Williams & Horm, 1977; Sturgeon *et al.*, 1991; Parazzini *et al.*, 1995b; Madsen *et al.*, 2008), but only two of these provided risk estimates adjusted for both smoking and sexual behaviour (Sturgeon *et al.*, 1991; Madsen *et al.*, 2008). Williams & Horm (1977), Mabuchi *et al.* (1985), Sturgeon *et al.* (1991) and Parazzini *et al.* (1995b) reported no association between alcoholic beverage consumption and risk for vulva cancer. Madsen *et al.* (2008) found a higher risk among drinkers compared to non-drinkers, for both vaginal and vulva cancers.

There was no evidence of dose–response for consumption of alcoholic beverages and vulva cancer, in any of these studies, either in terms of frequency of alcohol consumption (Parazzini *et al.*, 1995b), in terms of years of alcohol consumption (Madsen *et al.*, 2008), or when providing two defined levels of alcohol consumption (Williams & Horm, 1977). Williams & Horm (1977), Mabuchi *et al.* (1985) and Sturgeon *et al.* (1991) investigated risk of vulva cancer in relation to consumption of different alcoholic beverages. No significant associations were found with any type of alcoholic beverage.

2.16.2 Other sites

No new studies have been identified for cancer of testis, one on brain cancer and thyroid cancer, and three on skin cancer (malignant melanoma, basal cell carcinoma and squamous cell carcinoma).

In a large cohort study of women in the United Kingdom (Allen *et al.*, 2009) no association of consumption of alcoholic beverages was found with brain cancer (Table 2.68 available at http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-06-Table2.68.pdf), but a significant inverse association with thyroid cancer (Table 2.69 available at http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-06-Table2.69.pdf).

No association between consumption of alcoholic beverages and malignant melanomas was found by Allen *et al.* (2009) (Table 2.70 available at http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-06-Table2.70.pdf) or by Benedetti *et al.* (2009) in a case–control study (Table 2.71 available at http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-06-Table2.71.pdf). In a cohort study in Australia Ansems *et al.* (2008) found no significant association between overall basal cell carcinoma or squamous cell carcinoma risk and total alcohol intake or intake of beer, white wine, red wine or sherry and port (Table 2.70 on-line). Among those with a prior skin cancer history, there was a significant increase in risk of squamous cell carcinoma for above-median consumption of sherry and port compared with abstainers (multivariable adjusted RR, 2.46; 95%CI: 1.06–5.72).

2.17 Parental exposure and childhood cancers

Associations of paternal consumption of alcoholic beverages before pregnancy and/or maternal consumption of alcoholic beverages during pregnancy with risk for haematopoietic cancers in children were examined in nine case–control studies in Australia, Canada, France, the Netherlands, the United Kingdom and the USA (McKinney *et al.*, 1987; Severson *et al.*, 1993; van Duijn *et al.*, 1994; Shu *et al.*, 1996; Infante-Rivard *et al.*, 2002; Menegaux *et al.*, 2005; Menegaux *et al.*, 2007; MacArthur *et al.*, 2008; Rudant *et al.*, 2008). Studies published since the previous Monograph are summarized in Table 2.72 (available at http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-06-Table2.72.pdf).

No association between maternal alcoholic beverage intake 1 month or 1 year before pregnancy with risk of any childhood leukaemia or lymphoma was reported by Severson *et al.* (1993), Shu *et al.* (1993) and van Duijn *et al.* (1994), whereas a borderline significant association for acute leukaemia and ALL was observed by MacArthur *et al.* (2008) and Infante-Rivard *et al.* (2002) found a positive association for ALL.

For maternal alcoholic beverage consumption during pregnancy, no association was found with leukaemia or lymphoma (McKinney *et al.*,1987) or with ALL (Rudant *et al.*, 2008), while Infante-Rivard *et al.* (2002) found a reduced risk for ALL when comparing any intake with no intake. Statistically significant two- to 2.4-fold increased risk for acute non-lymphocytic leukaemia were associated with any maternal alcoholic beverage consumption during pregnancy in two studies (van Duijn *et al.*, 1994; Menegaux *et al.*, 2005). Similarly, statistically significant positive associations between maternal alcoholic beverage consumption and risk for ALL (Shu *et al.*, 1993; Menegaux *et al.*, 2005, 2007; MacArthur *et al.*, 2008) and acute myeloid leukaemia (Severson *et al.*, 1993; Shu *et al.*, 1993) were observed. The strongest associations observed in the studies of alcoholic beverages and acute myeloid leukaemia were for children diagnosed at 10 years of age or younger (Severson *et al.*, 1993; Shu *et al.*, 1993). Overall, there was no consistent evidence of dose–response relationships for maternal or

paternal alcoholic beverage intake or for intake of any specific type of alcohol beverage and risk for any childhood haematopoietic cancer. Most studies adjusted for potential confounding factors including maternal age, maternal smoking, and child's sex. Importantly, whether any of the observed associations between maternal or paternal consumption of alcoholic beverages and risk for childhood haematopoietic cancers are attributed to recall bias is unclear.

2.18 Polymorphisms and genetic susceptibility

Studies that identify associations between genetic polymorphisms and inter-individual differences in susceptibility to the agent(s) being evaluated may contribute to the identification of carcinogenic hazards to humans. If the polymorphism has been demonstrated experimentally to modify the functional activity of the gene product in a manner that is consistent with increased susceptibility, these data may be useful in making causal inferences. Similarly, studies that measure cell functions, enzymes or metabolites that are thought to be the basis of susceptibility may provide evidence that reinforces biological plausibility. If the known phenotype of a genetic polymorphism can explain the carcinogenic mechanism of the agent being evaluated, data on this phenotype may be useful in making causal inferences.

However, when data on genetic susceptibility originate from multiple comparisons in subgroup analyses, false-positive results and inconsistencies across studies can be generated. Furthermore, many of the identified susceptibility genes have no or unknown functional characterization; only for a few genes (e.g. ALDH2) are functional studies available; and generally induction of enzymes is not considered. Such data therefore require careful evaluation.

A challenge in the interpretation of the associations between the polymorphisms affecting alcohol and/or acetaldehyde metabolism and cancer is that the genes coding for more active alcohol oxidizing enzyme and/or less active acetaldehyde oxidizing enzyme, may both promote and inhibit the development of cancer. Carriers of genes enhancing alcohol oxidation and/or inhibiting acetaldehyde oxidation on average consume less alcohol (Matsuo *et al.*, 2006b, 2007; Zintzaras *et al.*, 2006) and thus may be protected from harmful chronic effects (e.g. cancer) induced by alcohol unless they drink heavily. Thus, in studying the mechanisms of the associations between these polymorphisms and cancer, it is essential to control for differences in alcohol drinking.

2.18.1 Alcohol dehydrogenase-1B (ADH1B)

ADH1B (previously called *ADH2*) is polymorphic, and its superactive *ADH1B*2* allele is highly prevalent among East Asians (54–96%; Goedde *et al.*, 1992), but relatively rare among Caucasians (1–23%). Individuals with the *ADH1B*1/*1* genotype code less active ADH, which is a risk factor for excessive alcohol consumption in both East Asians and Caucasians (Zintzaras *et al.*, 2006; Matsuo *et al.*, 2007).

(a) Cancer of the oesophagus

Individuals with the *ADH1B*1/*1* genotype were at increased risk for oesophageal cancer in 15 case–control studies among several populations (Hori *et al.*, 1997; Yokoyama *et al.*, 1998; Chao *et al.*, 2000; Matsuo *et al.* 2001b; Yokoyama *et al.*, 2001, 2002; Boonyaphiphat *et al.*, 2002; Yang *et al.*, 2005; Yang *et al.*, 2007; Guo *et al.*, 2008; Hashibe *et al.*, 2008; Lee *et al.*, 2008b; Cui *et al.*, 2009; Ding *et al.*, 2009) and in a cohort study in cancer-free Japanese alcoholics (Yokoyama *et al.*, 2006b) (Tables 2.73, 2.74). The difference was not significant in two Japanese studies (Tanabe *et al.* 1999; Yokoyama *et al.*, 2006a) and one study in South

Africa (Li *et al.*, 2008a). [Many studies did not control for the amount of alcohol consumption, which makes it difficult to make firm conclusions about the etiology of the *ADH1B*1/*1* associated cancers.]

(b) Upper aerodigestive tract cancers combined

In four Japanese studies (Yokoyama *et al.*, 2001, 2006b; Asakage *et al.*, 2007; Hiraki *et al.*, 2007), one European study (Hashibe *et al.*, 2006) and one Indian study (Solomon *et al.*, 2008) an *ADH1B*1/*1*-associated increased risk for upper aerodigestive tract cancers was found in alcohol drinkers. No significant association was found in another European study (Risch *et al.*, 2003; Tables 2.74, 2.75).

A recent large multicentre study from Europe and Latin America of *ADH* genes and UADT cancer that focused on seven separate *ADH* variants known to change an amino acid (missense substitution) included a total of 3800 cases and 5200 controls (Hashibe *et al.*, 2008). One variant in *ADH1B* (rs1229984) that codes for fast ethanol metabolism was associated with a strong decreased risk for UADT cancer, after adjusting for amount of alcohol consumed (OR for dominant model, 0.56; 95%CI: 0.47–0.66; $P = 4 \times 10^{-11}$). The odds ratio was 0.45 (95%CI: 0.35–0.57) for oral/pharyngeal cancers combined and 0.71 (95%CI: 0.57–0.88) for laryngeal cancer.

(c) Cancers of the stomach, colorectum and pancreas

One Polish study showed no significant effects of the *ADH1B* polymorphism on risk for cancer of the stomach (Zhang *et al.*, 2007b; Table 2.76 available at http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-06-Table2.76.pdf). For cancer of the colorectum, two Japanese case–control studies of alcohol drinkers found an increased risk in *ADH1B*1/*1* subjects compared with *ADH1B*2* carriers without stratification of *ALDH2* genotypes (Matsuo *et al.*, 2006a; Yin *et al.*, 2007). However, stratification by *ALDH2* genotypes rendered the association opposite within the *ALDH2*1/*1* subjects in one of the studies (Matsuo *et al.*, 2006a), while no such effect was seen in the other study (Yin *et al.*, 2007). In a Chinese study the *ADHB1*2/*2* genotype tended to increased the risk for cancer of the colorectum regardless of the *ALDH2* genotype (Gao *et al.*, 2008). Also, a study in Spain reported a non-significant decrease in risk for cancer of the colorectum for the *ADH1B*2/*2* versus *ADH1B*1/*1* (Landi *et al.*, 2005).

The *ADH1B*2* allele has been associated with an increase in risk for cancer of the pancreas and consumption of alcoholic beverages among Japanese (Kanda *et al.*, 2009).

(d) Hepatocellular cancer

In two studies in Japan and in a study in China it was concluded that the *ADH1B* polymorphism had no significant impact on the risk for hepatocellular carcinoma (Takeshita *et al.*, 2000b; Sakamoto *et al.*, 2006; Ding *et al.*, 2008; Table 2.76 on-line).

(e) Cancer of the breast

In a study in Germany (Lilla *et al.*, 2005), a decreased risk for cancer of the breast with consumption of alcoholic beverages ≥ 12 g ethanol/day compared with no intake was observed in women with the *ADH1B*2* allele, whereas no such association was found in women with the *ADH1B*1/*1* genotype. In four other studies from Japan, United Kingdom and the USA, no significant differences in the risk by *ADH1B* polymorphism were observed (Cox *et al.*, 2007; Terry *et al.*, 2007b; Visvanathan *et al.*, 2007; Kawase *et al.*, 2009; Table 2.76 on-line).

2.18.2 ADH1C

ADH1C (previously called *ADH3*) is a major gene polymorphism among Caucasians. The homodimer encoded by the *ADH1C*1* allele catalyses the production of acetaldehyde

Table 2.73 Case-control studies and meta-analyses of *ALDH2, ADH1B* and *ADH1C* genotype-associated risk for cancer of the oesophagus

Reference, study location, period	Cancer site and/or type	Genes involved	No of cases/deaths	Relative risk (95% CI)[1]	Comments
Hori *et al.* (1997), Tokyo, Japan, study period NR	Squamous cell carcinoma	***ALDH2***			No adjustment was reported
		**1/*1*	20	1.0	
		**1/*2*	70	4.4 (2.5–7.7)	
		**2/*2*	3	0.9 (0.2–3.6)	
		ADH1B			
		**2/*2*	40	1.0	
		**1/*2*	33	1.7 (0.9–3.0)	
		**1/*1*	21	6.2 (2.6–14.7)	
Yokoyama *et al.* (1998), Kanagawa, Japan, 1987–97	Oesophagus NOS	***ALDH2***			Male alcoholics; because the differences in odds ratio between the incident cases and the prevalent cases were slight, the cases were combined. Adjusted for age, alcohol drinking and cigarette smoking. Possible partial overlap with Yokoyama *et al.* (2001)
		**1/*1*	41	1.00	
		**1/*2*	46	12.50 (7.23–21.61)	
Tanabe *et al.* (1999), Hokkaido, Japan, 1994–97	Squamous cell carcinoma	***ALDH2***		NS	Alcohol consumption and smoking did not differ between the cases and controls.
		**1/*1*	8		
		**1/*2*	11		
		**2/*2*	0		
Chao *et al.* (2000), Taipei, Taiwan, China, 1997–99	Oesophagus	***ALDH2***		Allele **2* was associated with risk ($P < 0.001$) Allele **1* was associated with risk ($P < 0.025$) No significant difference in prevalence of alleles in alcoholics with different diseases and between alcoholic and non-alcoholic oesophageal cancer cases	Alcoholics and non-alcoholic oesophageal cancer cases and alcoholic and non-alcoholic controls. No adjustment
		**1/*1*	22		
		**1/*2*	37		
		**2/*2*	0		
		ADH1B			
		**1/*1*	17		
		**1/*2*	26		
		**2/*2*	16		
		ADH1C			
		**1/*1*	38		
		**1/*2*	21		
		**2/*2*	0		

Table 2.73 (continued)

Reference, study location, period	Cancer site and/or type	Genes involved	No of cases/deaths	Relative risk (95% CI)[1]	Comments
Matsuo *et al.* (2001b), Aichi, Japan, 1999–2000 (cases were first diagnosed as having esophageal cancer between 1984–2000 and visited the study centre in 1999–2000)	Oesophagus NOS	***ALDH2***			Adjusted for age, sex, drinking, smoking. Heavy drinkers defined as those drinking 75 mL ethanol/d, ≥ 5 d/wk. "Other participants" refers to those who were not heavy drinker
		All participants			
		**1/*1*	35	1.00	
		**1/*2*	66	3.72 (1.88–7.36)	
		**2/*2*	1	0.80 (0.09–6.88)	
		Heavy drinkers			
		**1/*1*	22	1.00	
		**1/*2*	46	16.4 (4.41–61.2)	
		**2/*2*	0	–	
		Other participants			
		**1/*1*	13	1.00	
		**1/*2*	20	1.68 (0.78–3.62)	
		**2/*2*	1	0.42 (0.28–1.25)	
Yokoyama *et al.* (2001), Kanagawa, Japan, 1993–2000	Squamous cell carcinoma	***ALDH2***			Male alcoholics. Adjusted for age, drinking, smoking, *ALDH2* and *ADH1B* genotypes. Possible partial overlap with Yokoyama *et al.* (1998)
		**1/*1*	50	1.00	
		**1/*2*	62	13.50 (8.06–22.60)	
		ADH1B			
		**1/*2 + *2/*2*	56	1.00	
		**1/*1*	56	2.64 (1.62–4.31)	

Table 2.73 (continued)

Reference, study location, period	Cancer site and/or type	Genes involved	No of cases/deaths	Relative risk (95% CI)[1]	Comments
Boonyaphiphat *et al.* (2002), Songkhla, Thailand, 1997–2000	Squamous cell carcinoma	**By alcohol intake**			Unlike Japanese and Chinese studies, frequency of inactive *ALDH2* is low in the Thais: 20% in cases, 18% in controls. Adjusted for age, sex, smoking, betel chewing (drinking, *ALDH2* and *ADH1B* genotypes for overall)
		ALDH2			
		Non-drinker			
		**1/*1*	40	1.00	
		**1/*2*	12	1.56 (0.65–3.70)	
		≤ 60 g/d			
		**1/*1*	42	2.16 (1.11–4.21)	
		**1/*2*	8	2.52 (0.85–7.46)	
		> 60 g/d			
		**1/*1*	79	5.28 (2.70–10.32)	
		**1/*2*	20	10.83 (3.37–34.69) Interaction $P = 0.031$	
		ADH1B			
		Non-drinker			
		**1/*2*	35	1.00	
		**1/*1*	18	0.89 (0.41–1.93)	
		≤ 60 g/d			
		**1/*2*	28	2.00 (0.97–4.11)	
		**1/*1*	22	2.34 (1.06–5.11)	
		> 60 g/d			
		**1/*2*	38	3.35 (1.50–7.02)	
		**1/*1*	61	11.46 (5.16–25.45) Interaction $P = 0.064$	
Itoga *et al.* (2002), Chiba, Japan [study period NR]	Oesophagus NOS	Habitual drinkers			No adjustment was reported
		ALDH2*1	47	1.0	
		ALDH2*2	18	4.9 ($P < 0.0001$)	
Watanabe *et al.* (2002), Kagawa, Japan, 1998–2001	Squamous cell carcinoma	***ALDH2***		See comments	Prevalence of **2* allele was significantly higher in cases than in controls.
		**1/*1*	10		
		**1/*2*	18		
		**2/*2*	1		

Table 2.73 (continued)

Reference, study location, period	Cancer site and/or type	Genes involved	No of cases/deaths	Relative risk (95% CI)[1]	Comments
Yokoyama *et al.* (2002), Tokyo, Chiba, Kanagawa, Osaka, Japan, 2000–01	Squamous cell carcinoma	**By alcohol intake**			Only male participants. Multivariate odds ratio of *ALDH2*2/*2* in comparison with *ALDH2*1/*1* was 7.83 (1.33–46.08). However, most men with **2/*2* genotype drank rarely or never and the risk was evaluated based on a small sample size (2 cases/43 controls). For *ADH1C* genotype the relative risk was associated with less active *ADH1C*1/*1* versus active **1/*2* or **2/*2*. When the linkage disequilibrium between *ADH1B* and *ADH1C* was taken into consideration, the *ADH1C* genotype did not significantly affect the risk for cancer. Adjusted for age, strong alcoholic beverage, green-yellow vegetables and fruit (and alcohol drinking, *ALDH2*, *ADH1B* and *ADH1C* genotypes for overall association). Cases included in Yokoyama *et al.* (2001) were excluded from this study.
		ALDH2			
		**1/*1*			
		< 22 g/wk	0	0.0 (not calculable)	
		22–197 g/wk	3	1.00	
		198–395 g/wk	23	5.58 (1.54–20.25)	
		≥ 396 g/wk	33	10.38 (2.85–37.84)	
		Former drinker	4	8.81 (1.53–50.76)	
		**1/*2*			
		< 22 g/wk	3	0.75 (0.14–4.11)	
		22–197 g/wk	21	5.82 (1.59–21.38)	
		198–395 g/wk	63	55.84 (15.40–202.51)	
		≥ 396 g/wk	73	88.88 (23.97–329.57)	
		Former drinker	9	50.50 (9.18–277.95)	
		**2/*2*			
		< 22 g/wk	2	1.44 (0.22–9.54)	
		ADH1B			
		**1/*2 or *2/*2*			
		< 22 g/wk	4	0.21 (0.06–0.68)	
		22–197 g/wk	20	1.00	
		198–395 g/wk	68	4.09 (2.25–7.42)	
		≥ 396 g/wk	80	7.01 (3.77–13.04)	
		Former drinker	11	5.73 (2.03–16.20)	
		**1/*1*			

Table 2.73 (continued)

Reference, study location, period	Cancer site and/or type	Genes involved	No of cases/deaths	Relative risk (95% CI)[1]	Comments
Yokoyama *et al.* (2002) Contd.		< 22 g/wk	1	4.25 (0.41–43.82)	
		22–197 g/wk	4	3.97 (1.01–15.63)	
		198–395 g/wk	18	33.30 (11.14–99.50)	
		≥ 396 g/wk	26	38.64 (13.27–112.55)	
		Former drinker	2	19.63 (1.65–233.20)	
		ADH1C			
		**1/*1*			
		< 22 g/wk	5	0.23 (0.08–0.68)	
		22–197 g/wk	22	1.00	
		198–395 g/wk	69	3.66 (2.04–6.55)	
		≥ 396 g/wk	88	6.64 (3.66–12.05)	
		Former drinker	12	8.44 (2.94–24.25)	
		**1/*2 or *2/*2*			
		< 22 g/wk	0	Not calculable	
		22–197 g/wk	2	0.81 (0.17–3.99)	
		198–395 g/wk	17	13.32 (5.28–33.63)	
		≥ 396 g/wk	18	23.83 (7.67–74.06)	
		Former drinker	1	1.01 (0.09–11.93)	
Yang *et al.* (2005), Aichi, Japan, 2001–04	Oesophagus NOS	**Overall analyses**			Results from overall analyses were adjusted for age, sex, smoking and alcohol drinking. Results by alcohol intake were adjusted for smoking. *P* for interaction between alcohol intake and genotypes for *ALDH2* was 0.03 for ≤ 250 g/wk and < 0.01 for > 250 g/wk alcohol intake. *P* for interaction for *ADH1B* was 0.24 for ≤ 250 g/wk and 0.32 for > 250 g/wk alcohol intake
		ALDH2			
		**1/*1*		1.00	
		**1/*2*		6.43 (4.02–10.3)	
		**2/*2*		1.92 (0.23–15.7)	
		ADH1B			
		**2/*2*		1.00	
		**1/*2*		1.57 (1.04–2.36)	
		**1/*1*		0.62 (0.22–1.72)	
		By alcohol intake			
		ALDH2			
		**1/*1*			

Table 2.73 (continued)

Reference, study location, period	Cancer site and/or type	Genes involved	No of cases/deaths	Relative risk (95% CI)[1]	Comments
Yang *et al.* (2005), Contd.		Non drinker		1.00	
		≤ 250 g/wk		1.88 (0.42–8.37)	
		> 250 g/wk		4.62 (0.93–23.1)	
		**1/*2*			
		Non-drinker		1.00	
		≤ 250 g/wk		9.64 (3.23–28.8)	
		> 250 g/wk		95.4 (28.7–317)	
		ADH1B			
		**2/*2*			
		Non-drinker	38	1.00	
		< 1200 g/yr	126	5.03 (1.67–15.1)	
		≥ 1200 g/yr	1	25.8 (8.01–83.3)	
		**1/*2* or **1/*1*			
		Non-drinker	74	1.00	
		< 1200 g/yr	85	8.50 (1.90–38.0)	
		≥ 1200 g/yr	6	33.9 (7.34–157)	
Cai *et al.* (2006), Taixing, Jiangsu Province, China, 2000	Squamous cell carcinoma	***ALDH2***			Adjusted for age, sex, education level, body mass index, and history of smoking and alcohol drinking. An elevation of the risk for ESCC was pronounced most among carriers of *ALDH2* *2/*2 and *XRCC1* 399Gln/Gln or Gln/Arg who consumed a low level of dietary selenium (adjusted OR, 4.16; 95% CI: 1.14–15.12).
		**1/*1*	119	1.00	
		**1/*2*	61	0.76 (0.50–1.16)	
		**2/*2*	25	1.72 (0.85–3.48)	

Table 2.73 (continued)

Reference, study location, period	Cancer site and/or type	Genes involved	No of cases/deaths	Relative risk (95% CI)[1]	Comments
Yokoyama *et al.* (2006a), Tokyo, Chiba, Kanagawa, Osaka, Japan, 2000–04	Squamous cell carcinoma	**By alcohol intake**			Only female participants. Adjusted for age, smoking, green-yellow vegetables and fruit, hot food and beverages
		ALDH2*1/*1			
		< 22 g/wk	12	1	
		22–197 g/wk	5	0.80 (0.24–2.60)	
		198–395 g/wk	4	1.99 (0.52–7.68)	
		≥ 396 g/wk	4	3.16 (0.65–15.48)	
		ALDH2*1/*2			
		< 22 g/wk	8	0.5 (0.2–1.3)	
		22–197 g/wk	5	2.0 (0.5–7.1)	
		198–395 g/wk	2	4.7 (0.7–31)	
		≥ 396 g/wk	3	59 (4.7–750)	
		ADH1B		NS	
Hashibe *et al.* (2006), Romania, Poland, the Russian Federation, Slovakia, Czech Republic, 2000–02	Squamous cell carcinoma	***ADH1B*** *R48H*			*ALDH2* +82A > G, +348C > T and –261C > T showed linkage disequilibrium and were associated with risk for oesophageal squamous-cell carcinoma. Adjusted for age, sex, country, yr of alcohol drinking, pack-yr of tobacco smoking.
		**1/*1*	163	1.00	
		**1/*2 + *2/*2*	4	0.19 (0.07–0.53)	
		ADH1C *I350V*			
		Ile/Ile (slow)	42	1.00	
		Ile/Val	92	1.61 (1.07–2.43)	
		Val/Val (fast; **1/*1*)	30	1.74 (1.02–2.98)	
		ADH1C *R272Q*			
		Arg/Arg (slow)	42	1.00	
		Arg/Gln	88	1.62 (1.07–2.44)	
		Gln/Gln (fast; **1/*1*)	30	2.03 (1.18–3.47)	
		ALDH2 *+82A > G*			

Table 2.73 (continued)

Reference, study location, period	Cancer site and/or type	Genes involved	No of cases/deaths	Relative risk (95% CI)[1]	Comments
Hashibe *et al.* (2006), Contd.		A/A	82	1.00	
		A/G	69	2.11 (1.46–3.05)	
		G/G	15	4.14 (2.03–8.46)	
		ALDH2 *+348C > T*			
		T/T	83	1.00	
		T/C	71	2.29 (1.59–3.30)	
		C/C	12	3.71 (1.73–7.97)	
		ALDH2 *–261C > T*			
		T/T	85	1.00	
		T/C	71	2.32 (1.61–3.35)	
		C/C	12	3.85 (1.78–8.36)	
Homann *et al.* (2006), Germany, 1999–2003	Oesophagus NOS	*ADH1C*1/*1* in heavy drinkers		2.93 (1.84–4.67)	Study participants were heavy alcohol drinkers: 123 oesophageal cancer cases and 525 controls with benign tumours. Adjusted for age, sex and smoking. [The reference group was not reported: *ADH1C*2/*2* or *ADH1C*2/*2* + *ADH1C*1/*1*.]
Yang *et al.* (2007), Yanting, Sichuan Province, China, 2003–04	Oesophagus (96% squamous cell carcinoma)	***ADH1B*** **2/*2*			Adjusted for age, sex, smoking, rapid food eating, quality of drinking-water, consumption of picked vegetables and fresh fruits, vegetables and eggs. Non-drinkers also included ex-drinkers.
		Non-drinker	37	1.0	
		Current drinker	41	1.88 (0.86–4.15)	
		**1/*2 or *1/*1*			
		Non-drinker	43	1.21 (0.63–2.33)	
		Current drinker	70	3.94 (1.76–8.81)	
		ALDH2 **1/*1*			
		Non-drinker	33	1.0	
		Current drinker	57	3.15 (1.39–7.13)	
		**1/*2 or *2/*2*			
		Non-drinker	47	2.03 (1.03–3.99)	
		Current drinker	54	4.82 (2.06–11.27)	

Table 2.73 (continued)

Reference, study location, period	Cancer site and/or type	Genes involved	No of cases/deaths	Relative risk (95% CI)[1]	Comments
Terry *et al.* (2007a), Connecticut, New Jersey and Washington, USA, 1993–95	Squamous cell carcinoma	***ADH1C***			Adjusted for age, gender and geographic site
		**2/*2*	4	1.0	
		**1/*2*	10	1.0 (0.3–3.3)	
		**1/*1*	9	1.7 (0.5–5.9)	
	Oesophageal and gastric cardia adenocarcinoma	***ADH1C***			
		**2/*2*	17	1.0	
		**1/*2*	52	1.2 (0.6–2.5)	
		**1/*1*	45	2.0 (1.0–4.2)	
Guo *et al.* (2008), Lanzhou, Gansu Province, China, 2004–07	Squamous cell carcinoma	***ALDH2***			Variables for which the results were adjusted were NR
		**1/*1*	37	1.00	
		**1/*2*	43	2.89 (1.11–5.64)	
		**2/*2*	0	–	
		ADH1B			
		**1/*1*	17	1.00	
		**2/*1*	25	3.67 (1.26–8.73)	
		**2/*2*	38	1.46 (0.71–2.59)	
		By alcohol intake			
		ALDH2			
		**1/*1*			
		0–200 g/wk	7	1.00	
		> 200 g/wk	30	2.29 (0.91–5.57)	
		**1/*2*			
		0–200 g/wk	7	0.56 (0.20–1.59)	
		> 200 g/wk	36	8.58 (3.28–22.68)	
		**2/*2*			
		0–200 g/wk	0	–	
		ADH1B			
		**1/*2* or **2/*2*			
		0–200 g/wk	13	1.00	
		> 200 g/wk	50	4.75 (2.53–9.38)	
		**1/*1*			
		0–200 g/wk	1	1.00 (0.18–9.22)	
		> 200 g/wk	16	27.12 (8.52–70.19)	

Table 2.73 (continued)

Reference, study location, period	Cancer site and/or type	Genes involved	No of cases/deaths	Relative risk (95% CI)[1]	Comments
Lee *et al.* (2008b), Taipei and Kaohsiung, Taiwan, China, 2000–05	Squamous cell carcinoma	**By alcohol intake**			Adjusted for age, sex, study hospital, ethnicity, smoking, education, smoking, betel quid chewing, and consumption of fruits and vegetables. Another publication from this study (Lee *et al.*, 2009), reported that heterozygous ALDH2 increased the oesophageal cancer risk more prominently in younger population.
		ALDH2			
		**1/*1*			
		Non-drinker	17	1.0	
		0.1–30 g/d	45	2.2 (1.1–4.5)	
		> 30 g/d	49	7.2 (3.3–15.9)	
		**1/*2*			
		Non-drinker	38	1.1 (0.6–2.3)	
		0.1–30 g/d	114	14.5 (7.1–29.6)	
		> 30 g/d	129	102.6 (38.3–274.8)	
		**2/*2*			
		Non-drinker	8	1.2 (0.4–3.4)	
		0.1–30 g/d	3	17.3 (1.4–213.7)	
		> 30 g/d	3	– (0 control subject)	
		ADH1B			
		**2/*2*			
		Non-drinker	29	1.0	
		0.1–30 g/d	58	3.5 (1.9–6.5)	
		> 30 g/d	53	11.1 (5.0–24.4)	
		**1/*2*			
		Non-drinker	26	0.8 (0.4–1.6)	
		0.1–30 g/d	59	4.2 (2.2–7.9)	
		> 30 g/d	64	14.2 (6.6–30.6)	
		**1/*1*			
		Non-drinker	8	1.2 (0.4–3.6)	
		0.1–30 g/d	45	10.6 (4.7–23.7)	
		> 30 g/d	64	71.9 (22.6–228.5)	

Table 2.73 (continued)

Reference, study location, period	Cancer site and/or type	Genes involved	No of cases/deaths	Relative risk (95% CI)[1]	Comments
Ding *et al.* (2008), Taixing, Jiangsu Province, China, 2005–06	Oesophagus NOS	**By alcohol intake**			Adjusted for income
		ADH1B			
		Non-drinker			
		**2/*2*	50	1.00	
		**1/*2*	42	1.31 (0.70–2.46)	
		**1/*1*	4	2.10 (0.35–12.54)	
		**1/*2 or *1/*1*	46	1.37 (0.74–2.54)	
		Drinker			
		**2/*2*	56	1.00	
		**1/*2*	54	1.18 (0.64–2.16)	
		**1/*1*	15	2.90 (0.85–9.90)	
		**1/*2 or *1/*1*	69	1.36 (0.76–2.43)	
		ALDH2			
		Non-drinker			
		**1/*1*	26	1.00	
		**1/*2*	43	1.29 (0.65–2.55)	
		**2/*2*	27	4.67 (1.63–13.38)	
		**1/*2 or *2/*2*	70	1.78 (0.94–3.37)	
		Drinker			
		**1/*1*	64	1.00	
		**1/*2*	46	2.47 (1.27–4.82)	
		**2/*2*	15	8.63 (2.07–35.95)	
		**1/*2 or *2/*2*	61	3.08 (1.65–5.78)	
Li *et al.* (2008a), Cape Town, South Africa, 1997–2003	Squamous cell carcinoma	***ADH1B***			Results for participants from black racial groups (282 cases and 348 controls). All results for those with mixed ancestry (192 cases and 188 controls) were non-significant. Non-adjusted results.
		**1* allele	265	1.00	
		**2* allele	4	NS	
		**3* allele	13	NS	
		ADH1C			
		**1* allele	153	1.00	
		**2* allele	129	1.80 (P = 0.0004)	
		ALDH2			
		**1* allele	155	1.00	
		**2* allele	27	2.35 (P = 0.008)	

Table 2.73 (continued)

Reference, study location, period	Cancer site and/or type	Genes involved	No of cases/deaths	Relative risk (95% CI)[1]	Comments
Hashibe *et al.* (2008), Multicenter study (see Comments), 2000–05	Oesophagus	***ADH1B***			427 cases of oesophageal cancer. Pooled analysis of studies conducted in the Russian Federation (Moscow), Poland (Lodz), Romania (Bucharest), Czech Republic (Prague, Olomouc), Slovakia (Banska´ Bystrica), France (Paris), Greece (Athens), Italy (Aviano, Padova, Torino), Norway (Oslo), United Kingdom (Edinburgh, Manchester, Newcastle), Spain (Barcelona), Croatia (Zagreb), Cuba, Argentina (Buenos Aires) and Brazil (Goianna, Pelotas, Rio de Janeiro, Sao Paulo) Adjusted for age, sex, centre, cumulative alcohol consumption and smoking
		**1/*1*		1	
		**1/*2* or **2/*2*		0.34 (0.20–0.56)	
		ADH1C G > A was in linkage disequilibrium with *ADH1B*			
Cui *et al.* (2009), Japan (see Comments)	Squamous cell carcinoma	***ALDH2***			Case samples (n = 1070) were from BioBank Japan, a collaborative network of 66 hospitals in Japan. Control samples in the first stage (n = 938) were obtained from volunteers in Osaka, Japan. The control groups for the second stage and replication analysis consisted of 1898 individuals who were registered in BioBank Japan as subjects with diseases other than cancers. Adjusted for age, gender, alcohol and smoking. Heterozygous ALDH2 increased the oesophageal cancer risk more prominently in younger population.
		**1/*1*	314	1.00	
		**1/*2*	735	3.48 (2.99–4.06)	
		**2/*2*	17	0.47 (0.28–0.78)	
		ADH1B			
		**2/*2*	510	1.00	
		**1/*2*	363	1.17 (1.01–1.37)	
		**1/*1*	194	4.10 (3.24–5.18)	
		By alcohol intake			
		ALDH2			
		**2/*1* vs *1*1* + **2/*2*			
		0–96.5 g/wk		3.35 (2.66–4.22)	
		> 96.5 g/wk		6.20 (4.76–8.09)	
		ADH1B			
		**1/*1* vs **1/*2* + **2/*2*			
		0–96.5 g/wk		3.18 (2.28–4.43)	
		> 96.5 g/wk		4.74 (3.21–6.99)	

Table 2.73 (continued)

Reference, study location, period	Cancer site and/or type	Genes involved	No of cases/deaths	Relative risk (95% CI)[1]	Comments
Meta-analysis					
Lewis & Smith (2005)	Oesophagus NOS	*ALDH2*1/*1* *ALDH2*1/*2* *ALDH2*2/*2*		1.0 3.19 (1.86–5.47) 0.39 (0.16–0.80)	Meta-analysis of the studies: Hori *et al.* (1997), Matsuo *et al.* (2001b), Boonyaphiphat *et al.* (2002), Itoga *et al.* (2002), Yokoyama *et al.* (2002) [Reduced risk with *2/*2 likely due to markedly lower levels of alcohol consumption in *2/*2 versus *1/*1 homozygotes.]

*ALDH2 *1* is more active, *ADH1B *1* is less active, and *ADH1C *1* is more active alleles than the other allele in the respective genes.
ALDH, aldehyde dehydrogenase; *ADH*, alcohol dehydrogenase; CI, confidence intervall d, day or days; NOS, not otherwise specified; NR, not reported; NS, not significant; vs, versus; wk, week or weeks

Table 2.74 Cohort study of *ALDH2* and *ADH1B* genotype-associated risk for cancer of the oesophagus and upper aerodigestive tract

Reference, location	Cohort description	Exposure assessment	Cancer and site	Exposure categories	No. of subjects/ squamous-cell carcinoma	Hazard ratio (95% CI)	Adjustment factors	Comments
Yokoyama *et al.* (2006b), Kanagawa, Japan	808 Japanese alcoholic men confirmed cancer-free by endoscopic screening during 1993–2005; endoscopic follow-up from 1 to 148 mo (median, 31 mo)	*ALDH2*, *ADH1B* genotyping at baseline examination in 556 patients	Upper aerodigestive tract squamous-cell carcinoma	***ALDH2***			Age	
				**1/*1*	484/27	1		
				**1/*2*	72/26	11.6 (5.7–23.3)		
				ADH1B				
				**1/*2 + *2/*2*	381/28	1		
				**1/*1*	175/25	2.0 (1.02–4.0)		
			Oesophageal squamous-cell carcinoma	***ALDH2***				
				**1/*1*	484/14	1		
				**1/*2*	72/19	13.0 (5.2–32.1)		
				ADH1B				
				**1/*2 + *2/*2*	381/18	1		
				**1/*1*	175/15	1.6 (0.7–3.9)		
			Oropharyngolaryngeal squamous-cell carcinoma	***ALDH2***				
				**1/*1*	484/17	1		
				**1/*2*	72/13	11.7 (4.7–29.5)		
				ADH1B				
				**1/*2 + *2/*2*	381/16	1		
				**1/*1*	175/14	2.0 (0.8–5.0)		

ADH, alcohol dehydrogenase; *ALDH*, aldehyde dehydrogenase; CI, confidence interval; mo, month or months

from ethanol at a rate 2.5 times faster than the homodimer encoded by the *ADH1C*2* allele (Bosron & Li, 1986).

(a) Cancer of the oesophagus

Associations between *ADH1C* genotype and oesophageal cancer have been investigated in five studies in populations mainly composed of Caucasians. A higher *ADH1C*1/*1*-associated risk was found in four (Visapää *et al.*, 2004; Hashibe *et al.*, 2006; Homann *et al.*, 2006; Terry *et al.*, 2007a; Table 2.73), in one of which all UADT cancers were combined (Visapää *et al.*, 2004; Table 2.75). However, no association was observed when the linkage disequilibrium between *ADH1B*2* and *ADH1C*1* was taken into consideration in one study (Hashibe *et al.*, 2006). Both *ADH1B*2* and *ADH1C*1* were in linkage disequilibrium in an analysis by Hashibe *et al.* (2008).

In contrast to the overall direction in Caucasian populations, in two Japanese studies it was reported that the *ADH1C*2* allele increases the risk for oesophageal cancer (Yokoyama *et al.*, 2002; Muto *et al.*, 2005). Again, when the linkage disequilibrium between *ADH1B* and *ADH1C* was taken into consideration, no relationship was found between *ADH1C* genotype and UADT cancer risk (Yokoyama *et al.*, 2002). No significant associations were observed in a Chinese study (Chao *et al.*, 2000). An association between *ADH1C*2* allele and risk of oesophageal cancer was reported in an African population (Li *et al.*, 2008a).

(b) Other upper aerodigestive tract cancers

In six studies of Caucasians (Coutelle *et al.*, 1997; Harty *et al.*, 1997; Homann *et al.*, 2006; Hashibe *et al.*, 2006, 2008; Arndt *et al.*, 2008) increased risk of other upper aerodigestive tract cancer cancers associated with the *ADH1C*1/*1* genotype was reported (Table 2.75). In two other studies of Caucasians (Schwartz *et al.*, 2001; Peters *et al.*, 2005), two studies from Japan and India (Asakage *et al.*, 2007; Solomon *et al.*, 2008) and one Brazilian study of a mixed population (Nishimoto *et al.*, 2004) opposite results were reported, with the *ADH1C*2/*2* genotype increasing the risk. When the linkage disequilibrium between *ADH1B* and *ADH1C* was taken into consideration (Asakage *et al.*, 2007), no relationship was found between *ADH1C* genotype and cancer risk. No significant associations were observed in six other studies of Caucasians (Bouchardy *et al.*, 2000; Olshan *et al.*, 2001; Sturgis *et al.*, 2001; Zavras *et al.*, 2002; Risch *et al.*, 2003; Wang *et al.*, 2005), or in a study of Japan (Muto *et al.*, 2005).

(c) Cancers of the stomach and colorectum

In one study in the USA increased risk of gastric adenocarcinomas associated with the *ADH1C*1/*1* genotype was reported (Terry *et al.*, 2007a) but in a Polish study no significant effects of the *ADH1C* polymorphism on stomach cancer risk was found (Zhang *et al.*, 2007b) (Table 2.76 on-line).

Regarding the risk for cancer of the colorectum, in two European studies an increased risk in *ADH1C*1/*1* carriers compared with *ADH1C*2* subjects was found (Tiemersma *et al.*, 2003; Homann *et al.*, 2009). However, an increased risk with *ADH1C*2/*2* genotype was reported in another study (Giovannucci *et al.*, 2003). A trend with the *ADH1C*2/*2* genotype increasing the risk for cancer of the colorectum was also observed in another study of Caucasians [which was perhaps explained by higher alcohol consumption by those with **2/*2* genotype] (Jung *et al.*, 2008). In two other studies of primarily Caucasians (van der Logt *et al.*, 2006; Curtin *et al.*, 2007) and a study on Japanese subjects (Yin *et al.*, 2007) no significant associations between *ADH1C* polymorphism and cancer of the colorectum were found.

Table 2.75 Studies of *ALDH2, ADH1B* and *ADH1C* genotype-associated risk for cancers of the head and neck

Reference, study location, period	Cancer and site	Genes involved	Relative risk (95% CI)[1]	Comments
Coutelle *et al.* (1997), Bordeaux, France, study period NR	Oropharynx, larynx	***ADH1C***		Study participants were classified as alcoholics and consumed > 100 g ethanol per d for > 10 yr; 21 with oropharyngeal cancer, 18 with laryngeal cancer, and 37 controls with no cancer. ORs adjusted for age. Risk for laryngeal cancer in alcoholics who were $GST\mu^-$ and *ADH3*1/*1* was 12.9 (95% 1.8–92) compared with those who were $GST\mu^-$ and *ADH3*1/*2* or **2/*2*
	Both cancer sites	**1/*2, *2/*2*	1.0	
		**1/*1*	3.6 (0.7–10.0)	
	Oropharynx	**1/*2, *2/*2*	1	
		**1/*1*	2.6 (0.7–10.0)	
	Larynx	**1/*2, *2/*2*	1	
		**1/*1*	6.1 (1.3–28.6)	
Harty *et al.* (1997), Puerto Rico, 1992–95	Oral cavity and pharynx		**Alcohol intake**	Patients (n = 137) with histologically confirmed oral cancer, and 146 controls ORs adjusted for sex, age, cigarette use, other tobacco use, fruit and vegetable intake
		ADH1C	Non-drinkers	
		**1/*1*	1.0	
		**1/*2*	0.9 (0.2–3.7)	
		**2/*2*	–	
			0–14 drinks/wk	
		**1/*1*	1.2 (0.3–5.2)	
		**1/*2*	0.9 (0.2–4.2)	
		**2/*2*	1.0 (0.1–12.2)	
			15–56 drinks/wk	
		**1/*1*	3.5 (0.8–15.8)	
		**1/*2*	4.1 (0.9–18.7)	
		**2/*2*	6.3 (1.1–36.8)	
			≥ 57 drinks/wk	
		**1/*1*	40.1 (5.4–296.0)	
		**1/*2*	7.0 (1.4–35.0)	
		**2/*2*	4.4 (0.6–33.3)	
Yokoyama *et al.* (1998), Japan, 1987–97	Oropharynx-larynx		11.1 (5.1–24.4)	Adjusted for age, drinking, smoking. Because the differences in odds ratio between the incident cases and the prevalent cases were small, the cases were combined.
Katoh *et al.* (1999), Japan, 1992–98	Oral squamous-cell carcinoma	Overall		Alcoholic beverage drinking not significantly associated with the risk for oral cancer. Adjusted for age, sex, smoking.
		ALDH2	1.2 (0.7–2.1)	

Table 2.75 (continued)

Reference, study location, period	Cancer and site	Genes involved	Relative risk (95% CI)[1]	Comments
Bouchardy *et al.* (2000), France, 1988–92	UADT squamous-cell carcinoma	***ADH1C***		Hospital-based case–control study. Patients with oral cavity or pharyngeal cancer (n = 121), laryngeal cancer (n = 129), and 172 controls. Patients had histologically confirmed primary SCC. All were regular smokers. Adjusted for age, sex, alcohol drinking and smoking.
	All oral cavity and pharynx	**2/*2*	1.0	
		**1/*2*	1.1 (0.6–2.2)	
		**1/*1*	0.7 (0.4–1.4)	
	Oral cavity	**2/*2*	1.0	
		**1/*2*	0.9 (0.4–2.0)	
		**1/*1*	0.8 (0.4–1.8)	
	Pharynx	**2/*2*	1.0	
		**1/*2*	1.7 (0.7–4.3)	
		**1/*1*	0.8 (0.3–2.1)	
	Larynx	**2/*2*	1.0	
		**1/*2*	0.7 (0.4–1.4)	
		**1/*1*	1.0 (0.5–1.8)	
Nomura *et al.* (2000)	Oral squamous cell carcinoma	***ALDH2***		Hospital-based case–control study. Habitual drinking increased the risk for oral cancer (odd ratio [95%CI], 3.9 [2.4–6.3])
		Habitual drinkers	2.9 (1.1–7.8)	
Olshan *et al.* (2001), North Carolina, USA, 1994–96	UADT squamous cell carcinoma	***ADH1C***	**Alcohol intake**	Patients (n = 182), and 202 controls. Patients had pathologically confirmed SCC of oral cavity, pharynx, larynx. Adjusted for tobacco use, age, sex and race
			Non-drinkers	
		**1/*1 + *1/*2*	1.1 (0.3–4.8)	
		**2/*2*	1.0	
			1–19 drinks/wk	
		**1/*1 + *1/*2*	1.4 (0.3–5.8)	
		**2/*2*	1.5 (0.3–8.6)	
			20–59 drinks/wk	
		**1/*1 *1/*2*	2.8 (0.6–12.5)	
		**2/*2*	2.4 (0.2–29.2)	
			≥ 60 drinks/wk	
		**1/*1 + *1/*2*	5.2 (0.9–27.7)	
		**2/*2*	– (no controls)	

Table 2.75 (continued)

Reference, study location, period	Cancer and site	Genes involved	Relative risk (95% CI)[1]	Comments
Schwartz *et al.* (2001), Washington, USA, 1985–89	Oral squamous cell carcinoma	***ADH1C***	**Alcohol intake**	Population-based case–control study. Oral SCC cases (n = 333) and 541 controls Distribution of *ADH1C* among cases and controls: *ADH1C *1/*1*: 32.7% vs 36.5% *ADH1C *1/*2*: 49.0% vs 43.1% *ADH1C *2/*2*: 18.3% vs 20.3% ORs adjusted for age, race and cigarette smoking
			< 1 drinks/wk	
		**1/*1*	2.1 (0.8–5.9)	
		**1/*2*	1.7 (0.6–4.7)	
		**2/*2*	1.0	
			1–14 drinks/wk	
		**1/*1*	2.0 (0.8–5.3)	
		**1/*2*	2.1 (0.8–5.3)	
		**2/*2*	1.4 (0.5–4.1)	
			15–28 drinks/wk	
		**1/*1*	3.4 (1.1–10.8)	
		**1/*2*	3.9 (1.3–11.8)	
		**2/*2*	3.4 (1.0–11.5)	
			≥ 29 drinks/wk	
		**1/*1*	6.1 (1.9–19.5)	
		**1/*2*	8.7 (2.9–26.1)	
		**2/*2*	10.0 (2.5–40.2)	
			Overall	
		**1/*1*	1.3 (0.8–2.0)	
		**1/*2*	1.3 (0.9–2.0)	
		**2/*2*	1.0	

Table 2.75 (continued)

Reference, study location, period	Cancer and site	Genes involved	Relative risk (95% CI)[1]	Comments
Sturgis *et al.* (2001), Houston, TX, USA, 1995–2000	Oral cavity, pharynx	***ADH1C***		Cases (n = 229), histologically confirmed SCC of the oral cavity and pharynx, matched by age, sex and smoking status with 575 controls. ORs controlled for age, sex, and smoking status.
			Never drinkers	
		**1/*1*	1.0	
		**1/*2*	1.5 (0.7–3.1)	
		**2/*2*	1.2 (0.5–3.0)	
			Former drinkers	
		**1/*1*	2.9 (1.3–6.3)	
		**1/*2*	2.1 (1.0–4.4)	
		**2/*2*	3.4 (1.3–8.6)	
			Current drinkers	
		**1/*1*	2.6 (1.2–5.5)	
		**1/*2*	2.4 (1.2–4.9)	
		**2/*2*	3.6 (1.6–8.1)	
			Total	
		**1/*1*	1.0	
		**1/*2*	1.0 (0.7–1.4)	
		**2/*2*	1.2 (0.8–1.9)	

Table 2.75 (continued)

Reference, study location, period	Cancer and site	Genes involved	Relative risk (95% CI)[1]	Comments
Yokoyama *et al.* (2001), Kanagawa, Japan, 1993–2000	Oropharyngo-laryngeal squamous-cell carcinoma	***ALDH2***		Adjusted for age, drinking, smoking, *ALDH2* and *ADH1B* genotypes
		**1/*1*	1.00	
		**1/*2*	18.52 (7.72–44.44)	
		ADH1B		
		**1/*2 +*2/*2*	1.00	
		**1/*1*	6.68 (2.81–15.90)	
	Oral cavity/ oropharyngeal squamous-cell carcinoma	***ALDH2***		
		**1/*1*	1.00	
		**1/*2*	20.83 (6.62–65.49)	
		ADH1B		
		**1/*2 +*2/*2*	1.00	
		**1/*1*	5.48 (1.77–16.96)	
	Epilaryngeal/ hypolaryngeal squamous-cell carcinoma	***ALDH2***		
		**1/*1*	1.00	
		**1/*2*	20.83 (6.62–65.49)	
		ADH1B		
		**1/*2 +*2/*2*	1.00	
		**1/*1*	5.48 (1.77–16.96)	
Yokoyama et al. (2002a), Tokyo, Chiba, Japan, 1998–99	Multiple primary cancer with oesophageal squamous-cell carcinoma	***ALDH2*** **2/*2* or **1/*2* vs **1/*1*	5.3 (1.1–51.1)	107 patients. Multiple cancers included both multiorgan cancer and multiple intra-oesophageal squamous-cell carcinoma. Adjusted for age, sex, drinking, smoking.
	Multiorgan primary cancer with head and neck squamous-cell carcinoma	***ALDH2*** **2/*2* or **1/*2* vs **1/*1*	7.4 (1.3–80.1)	
	Oesophageal SCC	***ALDH2***		Desophageal cancer, *n* = 48; oropharyngolaryngeal cancer, *n* = 29; combination, *n* = 30 ORs for multiple cancer, adjusted for age, drinking, smoking
		**1/*1*	1.0	
		**1/*2*	5.26 (1.08–51.1)	
	Oropharyngolaryngeal SCC (alone or in combination)	**2/*2*	7.36 (1.29–80.7)	

Table 2.75 (continued)

Reference, study location, period	Cancer and site	Genes involved	Relative risk (95% CI)[1]	Comments
Zavras *et al.* (2002), Athens, Greece, 1995–98	Oral cavity	***ADH1C***	**Alcohol intake**	93 cases and 99 controls. Adjusted for sex, smoking and referring hospital.
			Non-drinker	
		**1/*1*	1.0	
		**1/*2*	0.7 (0.3–2.0)	
		**2/*2*	0.4 (0.1–1.8)	
			1–28 drinks/wk	
		**1/*1*	1.7 (0.6–4.6)	
		**1/*2*	1.0 (0.3–3.0)	
		**2/*2*	3.4 (0.7–17.0)	
			> 28–42 drinks/wk	
		**1/*1*	1.9 (0.3–11.6)	
		**1/*2*	2.2 (0.4–12.3)	
		**2/*2*	– (no subjects)	
			> 42 drinks/wk	
		**1/*1*	3.0 (0.6–15.8)	
		**1/*2*	11.2 (1.1–112.1)	
		**2/*2*	– (no subjects)	

Table 2.75 (continued)

Reference, study location, period	Cancer and site	Genes involved	Relative risk (95% CI)[1]	Comments
Risch *et al.* (2003), Heidelberg, Germany, 1998–2000	Larynx	***ADH1C***	Low intake	Cases (n = 257) of histologically confirmed SCC of the larynx and 251 age- and sex-matched controls. Adjusted for tobacco use. Alcohol intake (gram/d): low, 0–16.95; medium, > 16.95–50.16; high, > 50.16.
		**1/*2 +*2/*2*	1.00	
		**1/*1*	1.14 (0.5–2.6)	
			Medium intake	
		**1/*2 +*2/*2*	0.85 (0.4–2.0)	
		**1/*1*	1.21 (0.6–2.5)	
			High intake	
		**1/*2 +*2/*2*	1.46 (0.7–3.1)	
		**1/*1*	1.14 (0.6–2.3)	
		ADH1B	Low intake	
		**1/*1*	1.00	
		**1/*2*	0.63 (0.2–2.8)	
			Medium intake	
		**1/*1*	0.94 (0.5–1.7)	
		**1/*2*	1.85 (0.2–14.3)	
			High intake	
		**1/*1*	1.16 (0.7–2.0)	
		**1/*2*	0.89 (0.3–2.5)	
Nishimoto *et al.* (2004), Sao Paulo, Brazil, 1995–2001	UADT (oral cavity, oropharynx, hypopharynx and larynx) cancers	***ADH1C***	Lifetime alcohol intake	Adjusted for age, sex and cancer in first-degree relative
			< 100 kg	
		**1/*1 + *1/*2*	1.0	
		**2/*2*	3.8 (1.5–9.7)	
			≤ 100 kg	
		**1/*1 + *1/*2*	1.0	
		**2/*2*	0.5 (0.2–1.2)	
Muto *et al.* (2005), Kashiwa, Japan, Japan, 1999–2001	Squamous-cell carcinoma, oesophagus and head and neck (multiple cancers only)	***ALDH2***		Male and female patients, development of multiple carcinomas, adjusted for age and sex
		**1* allele	1.0	
		**2* allele	5.45 (2.37 – 12.56)	
		ADH1C		
		**1* allele	1.0	
		**2* allele	2.08 (0.86–4.99)	

Table 2.75 (continued)

Reference, study location, period	Cancer and site	Genes involved	Relative risk (95% CI)[1]	Comments
Wang *et al.* (2005), Iowa, USA, 1994–97 and 2000–02	UADT (oral cavity, oropharynx, hypopharynx and larynx) squamous cell carcinoma	***ADH1C*1/*2***		Adjusted for age and tobacco pack-yr. "Total" were additionally adjusted for alcohol drinking. Reference group for each drinking level, *2/*2
		Never drinker	0.95 (0.4–2.0)	
		1–21 drinks/wk	0.5 (0.2–1.1)	
		≥ 22 drinks/wk	0.9 (0.4–2.1)	
		Total	0.8 (0.5–1.2)	
		ADH1C*1/*1		
		Never drinker	0.8 (0.4–1.8)	
		1–21 drinks/wk	0.6 (0.3–1.2)	
		≥ 22 drinks/wk	0.8 (0.3–1.9)	
		Total	0.7 (0.4–1.1)	
Peters *et al.* (2005), USA, 1999–2003	UADT (oral cavity, oropharynx, hypopharynx and larynx) squamous cell carcinoma	***ADH1C*1/*1 + *1/*2***		Adjusted for age, gender, race and smoking. Cutpoint for heavy alcohol is > 30 drinks per wk. Test for heavy drinking x ADH interaction, $P = 0.05$. *ADH1B* and *ADH1C* showed linkage disequilibrium.
		Non drinker	1.0	
		Light drinker	0.9 (0.6–1.3)	
		Heavy drinker	2.3 (1.4–3.8)	
		ADH1C*2/*2		
		Non drinker	0.8 (0.4–1.8)	
		Light drinker	0.9 (0.6–1.6)	
		Heavy drinker	7.1 (2.3–22.0)	
Hashimoto *et al.* (2006), Yamaguchi, Japan, 2002–04	UADT (oral cavity, oropharynx, hypopharynx and larynx) cancer	Case versus controls *ALDH2*	Not significantly different	More cases < 66 yr were drinkers than cases ≥ 66 yr.
		Case drinkers *ALDH2*	Significantly increased ($P < 0.009$) in cases < 66 yr compared with cases ≥ 66 yr	
Homann *et al.* (2006), Germany, 1999–2003	All tumours	***ADH1C*1/*1*** in heavy drinkers		818 patients with alcohol-associated esophageal ($n = 123$), head and neck ($n = 84$) and hepatocellular cancer ($n = 86$) as well as in patients with alcoholic pancreatitis ($n = 117$), alcoholic liver cirrhosis ($n = 217$), combined liver cirrhosis and pancreatitis ($n = 17$) and in alcoholics without gastrointestinal organ damage ($n = 174$). [The reference group was not reported: *ADH1C*2/*2* or *ADH1C*2/*2* + *ADH1C*1/*1*.]
		Malignant versus benign tumour	2.77 (1.89–4.07)	
		Malignant vs benign tumour	2.2 (1.11–4.36)	

Table 2.75 (continued)

Reference, study location, period	Cancer and site	Genes involved	Relative risk (95% CI)[1]	Comments
Hashibe *et al.* (2006), Czech Republic, Poland Romania, the Russian Federation, Slovakia, 2000–02	UADT (oral cavity, oropharynx, hypopharynx and larynx) squamous cell carcinoma	***ADH1B*** *R48H *1/*2 + *2/*2*		Reference groups were as following: *ADH1B R48H,* *1/*1; *ADH1C I350V*, Ile/Ile; *ADH1C* R272Q, Arg/Arg; *ALDH2* +82A > G, A/A; *ALDH2* +348C > T, T/T; *ALDH2* –261C > T, T/T. Frequency of alcohol use was as following: Never/light drinkers, ≤ 2 times/wk; Medium/heavy ≥ 3 times/wk. Adjusted for age, sex, country, and pack-yr of tobacco smoking. Overall results were additionally adjusted for yr of alcohol drinking. Results for oral, pharyngeal, laryngeal and oesophageal cancers were also presented in the article. When results were analysed by subsite, strong main effects for *ALDH2* variants were observed for squamous cell carcinoma of the oesophagus; among other subsites, only the association between *ALDH2 +82A > G* (A/G versus A/A) and pharyngeal cancer remained statistically significant.
		Overall	0.47 (0.32–0.70)	
		Never/light alcohol use	0.57 (0.36–0.91)	
		Medium/heavy use	0.36 (0.17–0.77)	
		P for interaction	0.33	
		ADH1C *I350V*		
		Val/Val (*1/*1)		
		Overall	1.38 (1.01–1.88)	
		Never/light alcohol use	1.48 (1.02–2.15)	
		Medium/heavy use	1.48 (0.80–2.73)	
		P for interaction	0.52	
		ADH1C *R272Q*		
		Gln/Gln (*1/*1)		
		Overall	1.49 (1.08–2.05)	
		Never/light alcohol use	1.69 (1.15–2.46)	
		Medium/heavy use	1.42 (0.76–2.66)	
		P for interaction	0.30	
		ALDH2 *+82A > G*		
		G/G		
		Overall	1.63 (0.94–2.82)	
		Never/light alcohol use	1.70 (0.88–3.29)	
		Medium/heavy use	4.38 (1.32–14.5)	
		P for interaction	0.02	
		ALDH2 *+348C > T*		
		C/C		
		Overall	1.63 (0.92–2.89)	
		Never/light alcohol use	1.28 (0.65–2.55)	
		Medium/heavy use	5.79 (1.49–22.5)	
		P for interaction	0.009	

Table 2.75 (continued)

Reference, study location, period	Cancer and site	Genes involved	Relative risk (95% CI)[1]	Comments
Hashibe *et al.* (2006) Contd.		***ALDH2*** *–261C > T*		
		C/C		
		Overall	1.66 (0.93–2.95)	
		Never/light alcohol use	1.29 (0.65–2.58)	
		Medium/heavy use	5.79 (1.49–22.5)	
		P for interaction	0.007	
Asakage *et al.* (2007), Tokyo, Chiba, Kanagawa, Osaka, Japan 2000–03	Oral and hypo- and oropharynx		**Alcohol intake**	Patients with oropaharyngeal or oral/oropharynx cancer (*n* = 53) and with hypopharyngeal cancer (*n* = 43) and 642 cancer-free men. Moderate-to-heavy drinkers: 22 g/drink, ≥ 9 drinks/wk. Adjusted for age, strong alcoholic beverage use, smoking, green-yellow vegetable use, and subcategory of alcohol drinking. When the linkage disequilibrium between *ADH1B* and *ADH1C* was taken into consideration, no relationship was found between *ADH1C* genotype and cancer risk
		ALDH2	Never or light	
		**1/1*	1	
		**1/2*	0.56 (0.20–1.59)	
			Moderate-heavy	
		**1/1*	2.29 (0.94–5.57)	
		**1/2*	8.26 (3.30–20.68)	
		ADH1B	Never or light	
		**1/*2 + *2/*2*	1	
		**1/*1*	1.00 (0.10–10.22)	
			Moderate-heavy	
		**1/*2 + *2/*2*	4.75 (2.44–9.23)	
		**1/*1*	26.40 (9.57–72.84)	
		ADH1C	Never or light	
		**1/*1*	1	
		**1/*2 + *2/*2*	2.34 (0.58–9.48)	
			Moderate-heavy	
		**1/*1*	5.64 (2.82–11.31)	
		**1/*2 + *2/*2*	17.93 (6.43–50.00)	

Table 2.75 (continued)

Reference, study location, period	Cancer and site	Genes involved	Relative risk (95% CI)[1]	Comments
Hiraki *et al.* (2007), Aichi, Japan, 2001–04	Squamous cell carcinoma of the lip and oral cavity, pharynx, larynx	***ADH1B** His/His*		Adjusted for age, sex and smoking. No cases of heavy drinkers in *ALDH2 Lys/Lys* carriers. *P* trend for heavy drinkers for ADH1B, 0.002 *P* trend for heavy drinkers for ALDH2, 0.003
		Never drinker	1.0	
		Moderate drinker	1.08 (0.66–1.77)	
		Heavy drinker	1.98 (1.20–3.30)	
		P for trend	0.005	
		***ADH1B** His/Arg*		
		Never drinker	1.22 (0.63–2.35)	
		Moderate drinker	1.06 (0.58–1.94)	
		Heavy drinker	1.66 (1.51–4.71)	
		P for trend drinker	0.056	
		***ADH2** Arg/Arg*		
		Never drinker	0.50 (0.06–4.11)	
		Moderate drinker	2.46 (0.89–6.73)	
		Heavy drinker	9.52 (3.89–23.3)	
		P for trend	0.008	
		***ALDH2** Glu/Glu*		
		Never drinker	1.0	
		Moderate drinker	0.66 (0.32–1.36)	
		Heavy drinker	1.41 (0.69–2.89)	
		P for trend	0.058	
		***ALDH2** Glu/Lys*		
		Never drinker	0.75 (0.37–1.53)	
		Moderate drinker	1.05 (0.50–2.20)	
		Heavy drinker	3.13 (1.46–6.72)	
		P for trend	< 0.001	
		***ALDH2** Lys/Lys*		
		Never drinker	0.56 (0.22–1.43)	
		Moderate drinker	3.14 (0.45–21.6)	
		Heavy drinker	n/a	
		P for trend	0.44	

Table 2.75 (continued)

Reference, study location, period	Cancer and site	Genes involved	Relative risk (95% CI)[1]	Comments
Visapää *et al.* (2004), Mannheim and Heidelberg, Germany, study period NR	UADT	***ADH1C***		Hospital-based case–control study. Cases (n = 107) of UADT cancer (99 smokers) and 103 control patients (95 smokers) with liver cirrhosis (n = 39), alcoholic pancreatitis (n = 38) or without organ injury (n = 26), whose alcohol intake was similar to that of the UADT patients. Adjusted for alcohol use, smoking, age, sex
		**2/*2*	1.00	
		**1/*1*	1.69 (1.12–2.56)	
Hashibe *et al.* (2008), Multicenter study (see Comments), 2000–05		***ADH1B***		Pooled analysis of studies conducted in the Russian Federation (Moscow), Poland (Lodz), Romania (Bucharest), Czech Republic (Prague, Olomouc), Slovakia (Banska´ Bystrica), France (Paris), Greece (Athens), Italy (Aviano, Padova, Torino), Norway (Oslo), United Kingdom (Edinburgh, Manchester, Newcastle), Spain (Barcelona), Croatia (Zagreb), Cuba, Argentina (Buenos Aires) and Brazil (Goianna, Pelotas, Rio de Janeiro, Sao Paulo). Mostly Caucasian populations, men and women, adjusted for age, gender, centre, alcohol and tobacco use. The OR (95% CI) for codominant model was 0.59 (0.50–0.69) for all four cancer sites combined.
	Oral/pharynx	**1/*1*	1.00	
		**1/*2+*2/*2*	0.45 (0.35–0.57)	
	Larynx	**1/*1*	1.00	
		**1/*2+*2/*2*	0.71 (0.57–0.88)	
	Oral, pharynx, larynx, and oesophagus	**1/*1*	1.00	
		**1/*2+*2/*2*	0.56 (0.47–0.66)	
		ADH7		
	Oral/pharynx	**1/*1*	1.00	
		**1/*2+*2/*2*	0.70 (0.59–0.84)	
	Larynx	**1/*1*	1.00	
		**1/*2+*2/*2*	0.78 (0.59–0.93)	
	Oral, pharynx, larynx, and oesophagus	**1/*1*	1.00	
		**1/*2+*2/*2*	0.68 (0.60–0.78)	
Solomon *et al.* (2008), Tamil Nadu, India, study period NR	Squamous-cell carcinoma, oral cavity	***ADH1B***	Heavy drinkers	
		**2/*1 + *2/*2*	1.00	
		**1/*1*	1.62 (1.08–2.14)	
		ADH1C		
		**1/*1 +*1/*2*	1	
		**2/*2*	2.65 (1.78–3.53)	
Arndt *et al.* (2008), Poznan, Poland, 2006–08	Laryngeal cancer	***ADH1C***		No adjustment was reported
		**2/*2*	1.00	
		**1/*2*	1.40 (0.68–2.85)	
		**1/*1*	1.53 (0.67–3.46)	

Table 2.75 (continued)

Reference, study location, period	Cancer and site	Genes involved	Relative risk (95% CI)[1]	Comments
Yokoyama *et al.* (2008), Japan	Development to multiple carcinomas in oropharyngolarynx	***ALDH2***		Prospective part of study
		**1/*1*	1.0	
		**1/*2*	4.3 (1.4–12.9)	
		ADH1B2		
		**1/*2 + *2/*2*	1.0	
		**1/*1*	0.8 (0.3–2.0)	
Meta-analysis				
Boccia *et al.* (2009)	Head and neck cancer	*ALDH2*1/*1*	1.0	Meta-analysis of six Japanese studies. [Reduced risk with *2/*2 likely due to markedly lower levels of alcohol consumption in *2/*2 versus *1/*1 homozygotes.]
		*ALDH2*1/*2*	1.83 (1.21–2.77)	
		*ALDH2*2/*2*	0.53 (0.28–1.00)	

*ALDH2 *1* is more active, *ADH1B *1* is less active, and *ADH1C *1* is more active alleles than the other allele in the respective genes.
ALDH, aldehyde dehydrogenase; *ADH*, alcohol dehydrogenase; CI, confidence interval; mo, month or months; NR, not reported; SCC, squamous cell carcinoma; vs, versus; wk, week or weeks

(d) Hepatocellular cancer

Two European studies investigated associations between *ADH1C* genotype and hepatocellular carcinoma. Covolo *et al.* (2005) reported negative results and Homann *et al.* (2006) found a positive association between *ADH1C*1/*1* and the risk for alcohol-associated hepatocellular carcinoma (Table 2.76 on-line).

(e) Cancer of the lung

No significant effect of the *ADH1C* polymorphism on the risk for cancer of the lung was found in one Japanese study (Minegishi *et al.*, 2007) and one study in the USA (Freudenheim *et al.*, 2003) (Table 2.76 on-line).

(f) Cancer of the female breast

Six studies conducted in Germany and the USA investigated the relationship between *ADH1C* genotype and the risk for cancer of the female breast. Three of them showed an increased risk in *ADH1C*1/*1* versus *ADH1C*1/*2* and *ADH1C*2/*2* carriers (Freudenheim *et al.*, 1999; Coutelle *et al.*, 2004; Terry *et al.*, 2006; Table 2.76 on-line). In two studies the association was more pronounced among premenopausal women (Freudenheim *et al.*, 1999; Terry *et al.*, 2006). No significant associations between *ADH1C* polymorphism and the risk for cancer of the female breast were observed in the three other studies (Hines *et al.*, 2000; Terry *et al.*, 2007b; Visvanathan *et al.*, 2007) as well as in one large pooled study (Breast Cancer Association Consortium, 2006).

(g) Cancer of the urinary bladder

An increased risk for cancer of the urinary bladder cancer in moderate drinkers of the *ADH1C*1/*1* genotype was reported from a Dutch study (van Dijk *et al.*, 2001) (Table 2.76 on-line).

2.18.3 Other ADHs

In a pooled study a rare allele of *ADH7* was found to be significantly protective against UADT cancer (Hashibe *et al.*, 2008). The role of this allele in the functional activity of the enzyme is not yet known.

2.18.4 CYP2E1

CYP2E1 is induced by chronic alcoholic beverage consumption and in addition to ethanol oxidation it plays a role in the metabolic activation of many carcinogens, including *N*-nitrosamines, benzene and aniline. The *CYP2E1* gene contains several single nucleotide polymorphisms, including C1053T (*CYP2E1*5*; also referred to as *Rsa*I polymorphism), G1293A (*CYP2E1*5*; also referred to as *Pst*I polymorphism), T7632TA (*CYP2E1*6*; also referred to as *Dra*I polymorphism) and G71T (*CYP2E1*7*).

(a) Cancer of the oesophagus

A *CYP2E1*5B* (earlier denoted **c2*; **1A* is the wild-type allele, earlier denoted **c1*) allele-associated risk of oesophageal cancer has been reported from one study of East-Asians (Tsutsumi *et al.*, 1993). Opposite results, with the **5B* allele decreasing the risk for oesophageal cancer, have been observed in four studies of East-Asians (Tan *et al.*, 2000; Lu *et al.*, 2005; Guo *et al.*, 2008; Qin *et al.*, 2008). The absence of significant results were reported from seven studies of East-Asians (Morita *et al.*, 1997; Hori *et al.*, 1997; Tanabe *et al.*, 1999; Chao *et al.*, 2000; Gao *et al.*, 2002; Yang *et al.*, 2005; Wang *et al.*, 2006b), and studies of Europeans (Lucas *et al.*, 1996), South Africans (Li *et al.*, 2005) and Brazilians (Rossini *et al.*, 2007) (Table 2.77 available at http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-06-Table2.77.pdf).

(b) Other upper aerodigestive tract cancers combined

In seven studies from East-Asia, India, Brazil and Europe an increased risk for other upper aerodigestive tract cancer cancers in carriers of the *CYP2E1*5B* allele was found (Hildesheim *et al.*, 1997; Hung *et al.*, 1997; Bouchardy *et al.*, 2000; Gattás *et al.*, 2006; Sugimura *et al.*, 2006; Olivieri *et al.*, 2009; Ruwali *et al.*, 2009). In contrast, an inverse association between the **5B* allele and oral cancer has been reported in the USA (Liu *et al.*, 2001). No significant associations were reported from eight European studies (Jahnke *et al.*, 1996; Lucas *et al.*, 1996; González *et al.*, 1998; Matthias *et al.*, 1998; Zavras *et al.*, 2002; Boccia *et al.*, 2008), three Japanese studies (Katoh *et al.*, 1999; Morita *et al.*, 1999; Tanabe *et al.*, 1999), and two studies from USA (Buch *et al.*, 2008) and India (Soya *et al.*, 2008).

(c) Cancers of the stomach and colorectum

In three studies, two of Chinese (Cai *et al.*, 2001; Wu *et al.*, 2002) and one of Caucasians (Boccia *et al.*, 2007), increased risk for cancer of the stomach by polymorphic alleles of *CYP2E1* was found. Opposite results with the **5B* allele decreasing risk of cancer of the stomach were reported from one study from Brazil (Nishimoto *et al.*, 2000). Lack of significant associations between the **5B* allele and risk of cancer of the stomach has been reported from four studies of East-Asian populations (Kato *et al.*, 1995, 1997; Gao *et al.*, 2002; Nan *et al.*, 2005).

With regard to cancer of the colorectum, in two studies, one of Hungarians (Kiss *et al.*, 2000) and one study of Chinese (Gao *et al.*, 2007), an increased risk for cancer of the colorectum was demonstrated in carriers of the *CYP2E1*5B* allele. From one study in Hawaii, USA (Le Marchand *et al.*, 2002), and one study in Japan (Morita *et al.*, 2009) an increased risk of cancer of the colorectum with 5′ 96-bp insertion variant in *CYP2E1* was reported. In three other studies, one from China (Fan *et al.*, 2007) and two from Europe (Landi *et al.*, 2005; van der Logt *et al.*, 2006), significant associations between *CYP2E1* polymorphism and cancer of the colorectum were not reported. In one study in Japan a decreased risk for rectal cancer in carriers of the **5B* allele was found (Morita *et al.*, 2009).

(d) Hepatocellular cancer

A **5B* allele-associated increased risk for hepatocellular carcinoma was reported from three studies of Japanese and European populations (Ladero *et al.*, 1996; Koide *et al.*, 2000; Munaka *et al.*, 2003). No significant association was observed in four other East Asian populations (Lee *et al.*, 1997; Wong *et al.*, 2000; Yu *et al.*, 2002; Kato *et al.*, 2003). A decreased risk with **5B* allele was reported from a Taiwan, China study (Yu *et al.*, 1995).

(e) Cancer of the lung

An increased risk for cancer of the lung associated with the *CYP2E1*5B* allele was found in one Japanese study (Oyama *et al.*, 1997) and one study of mainly Caucasians (el-Zein *et al.*, 1997c). A similar association was reported in another Japanese study (Minegishi *et al.*, 2007), but the genotype distribution was not in Hardy–Weinberg equilibrium in the control population [so the finding of an association with cancer of the lung is most likely a false-positive result]. Opposite results with the **5B* allele decreasing risk for cancer of the lung have been obtained in studies from Sweden, USA and Republic of Korea (Persson, *et al.*, 1993; Wu *et al.*, 1997; Le Marchand *et al.*, 1998; Eom *et al.*, 2009). In eight studies, two of East Asians (Watanabe *et al.*, 1995; Persson *et al.*, 1999), four of mixed South and North American populations (Kato *et al.*, 1994; Hamada *et al.*, 1995; London *et al.*, 1996; Quiñones *et al.*, 2001), and one of Finns (Hirvonen *et al.*, 1993), no significant associations were observed.

(f) Cancer of the breast

In one Korean study a non-significant increased risk for cancer of the breast associated with the **5B/*5B* genotype was found (Choi *et al.*, 2003), while in a study from Taiwan, China, an inverse association between the **5B/*5B* genotype and breast cancer risk was found (Wu *et al.*, 2006).

(g) Other cancers

For cancer of the urinary bladder no significant associations to the **5B* allele were observed in an Egyptian (Anwar *et al.*, 1996) and a German population (Brockmöller *et al.*, 1996). Also for cancer of the kidney (renal cell) and urothelial cancer no significant associations were found in one study from Germany (Farker *et al.*, 1998a). Three studies on East-Asian populations demonstrated a decreased risk for cancer of the prostate associated with the **5B* allele (Murata *et al.*, 2001; Yang *et al.*, 2006a; Yang *et al.*, 2009). No association between polymorphism in *CYP2E1* and risk of cancer of the pancreas was observed in an East-Asian population (Lee *et al.* 2007).

2.18.5 ALDH2

The variant allele *2 that encodes an inactive subunit of *ALDH2* is prevalent among East Asians (28–45%; Goedde *et al.*, 1992), but is rare in most other populations. Individuals with inactive *ALDH2* generally abstain from heavy alcohol drinking due to subsequent acetaldehydaemia and alcoholic flushing responses. Most homozygotes for inactive *ALDH2*2/*2* are non-drinkers or occasional drinkers, but substantial percentages of East Asians who are habitual drinkers, including alcoholics, are heterozygous *ALDH2*1/*2*.

(a) Cancer of the oesophagus

The *ALDH2*2* allele has been found to be a risk factor for oesophageal cancer in 19 East-Asian studies (Hori *et al.*, 1997; Yokoyama *et al.*, 1998, 2001, 2002, 2006a, b; Tanabe *et al.*, 1999; Chao *et al.*, 2000; Matsuo *et al.*, 2001b; Boonyaphiphat *et al.*, 2002; Itoga *et al.*, 2002; Watanabe *et al.*, 2002; Yokoyama *et al.*, 2002; Yang *et al.*, 2005, 2007; Cai *et al.*, 2006; Guo *et al.*, 2008; Lee *et al.*, 2008b; Cui *et al.*, 2009; Ding *et al.*, 2009; Tables 2.73, 2.74). The magnitude of the *ALDH2*-associated risk depends on the extent of the association between oesophageal cancer and alcohol consumption. The risk was observed in light-to-moderate drinkers as well as heavy drinkers, but was higher among heavier drinkers including alcoholics than the other drinkers. The findings were also supported by a meta-analysis (Lewis & Smith, 2005). In two large case–control studies in Taiwan, China (Lee *et al.*, 2009) and Japan (Cui *et al.*, 2009) heterozygous *ALDH2* increased the oesophageal cancer risk more prominently in younger populations. Heterozygous *ALDH2* has been consistently reported to be a strong risk factor for multiple cancers in Japanese patients with oesophageal cancer (Yokoyama *et al.*, 2001, 2002; Muto *et al.*, 2005).

Case–control studies in high-risk rural regions in Mainland China showed modest-positive associations (Cai *et al.*, 2006; Yang *et al.*, 2007; Ding *et al.*, 2009; Guo *et al.*, 2008) between heterozygous *ALDH2* and oesophageal cancer risk. In these studies, the risks were more distinct where the impact of alcohol consumption on oesophageal cancer was more distinct and when only male populations were evaluated. Tian *et al.* (1998) reported no significant association between *ALDH2* polymorphism and oesophageal cancer, but this study included only cases of oesophageal squamous carcinoma and the *ALDH2* gene frequencies were compared just to other published data. In addition to the data on East-Asian populations, the association between oesophageal cancer and the *ALDH2*2* allele has been found in a study in South Africa (Li *et al.*, 2008a). In addition, the +82A > G, +348C > T and −261C > T variants of *ALDH2* (without known functional actions) have been related to

oesophageal cancer in a large pooled European study (Hashibe *et al.*, 2006).

(b) Other upper aerodigestive tract cancer

In 10 Japanese studies, the *ALDH2*2* allele has been shown to be a risk factor for upper aerodigestive tract cancer (Yokoyama *et al.*, 1998, 2001, 2002, 2006b, 2008; Nomura *et al.*, 2000; Muto *et al.*, 2005; Hashimoto *et al.*, 2006; Asakage *et al.*, 2007; Hiraki *et al.*, 2007; Table 2.75). In one Japanese study significant associations between the **2* allele and oral cancer were not found (Katoh *et al.*, 1999); in this study a significant association between risk of oral cancer and consumption of alcoholic beverages was not found either. A meta-analysis of these Japanese studies showed that heterozygous *ALDH2* increased upper aerodigestive tract cancer risks more strongly in heavy drinkers including alcoholics than the other drinkers (Boccia *et al.*, 2009). In one Japanese study a higher frequency of heterozygous *ALDH2* in younger drinkers with upper aerodigestive tract cancer was found (Hashimoto *et al.*, 2006). Heterozygous *ALDH2* has been reported to be a strong risk factor for multiple cancers in Japanese patients with upper aerodigestive tract cancers (Yokoyama *et al.*, 2001, 2002, 2008; Muto *et al.*, 2005). The other *ALDH2* variants (reported by Hashibe *et al.*, 2006) did not significantly affect the risk of oral and other upper aerodigestive tract cancers (excluding oesophageal cancer).

(c) Cancers of the stomach, colorectum and pancreas

In two Japanese studies an increased risk for cancer of the stomach by the *ALDH2*2* allele has been reported (Yokoyama *et al.*, 1998, 2007b; Table 2.76 on-line). Such an association was reported from another Japanese study (Yokoyama *et al.*, 2001) when all gastric cancer cases, including gastric cancer alone or combined with upper aerodigestive tract cancers were considered. However, when only cases of cancer of the stomach alone were included in the analyses, there was no association with *ALDH2*. In a study of Polish consumers of alcoholic beverages an increased risk for cancer of the stomach by the *ALDH2 +82A > G* alleles was found (Zhang *et al.*, 2007b). No significant associations with the **2* allele were reported from a study from Republic of Korea (Nan *et al.*, 2005).

Increased risks of colon and/or rectal cancer have been associated with the **2* allele in three East-Asian studies (Yokoyama *et al.*, 1998; Murata *et al.*, 1999; Matsuo *et al.*, 2002). The **2* allele has also been associated with lower risk in one Chinese (Gao *et al.*, 2008) and a Japanese (Yin *et al.*, 2007) study. No significant differences were seen in four Japanese studies (Takeshita *et al.*, 2000a; Hirose *et al.*, 2005; Otani *et al.*, 2005; Matsuo *et al.*, 2006a).

In one of two Japanese studies Kanda *et al.* (2009) reported increased risk for the *ALDH2*2* allele for cancer of the pancreas; no significant associations were found by Miyasaka *et al.* (2005).

(d) Hepatocellular cancer

In four of 11 Japanese and Chinese studies an increased risk for hepatocellular carcinoma in carriers of the *ALDH2*2* allele has been found (Kato *et al.*, 2003; Munaka *et al.*, 2003; Sakamoto *et al.*, 2006; Ding *et al.*, 2008) (Table 2.76 on-line). Four Japanese (Shibata *et al.*, 1998; Yokoyama *et al.*, 1998; Koide *et al.*, 2000; Takeshita *et al.*, 2000b) and one Chinese (Yu *et al.*, 2002) study reported no significant associations between *ALDH2* polymorphism and hepatocellular cancer.

(e) Cancer of the lung

An increased risk for lung cancer associated with *ALDH2*2* alleles has been observed in three studies, two from Japan (Yokoyama *et al.*, 1998; Minegishi *et al.*, 2007) and one from Republic of Korea (Eom *et al.*, 2009) (Table 2.76 on-line).

(f) Cancer of the female breast

No significant association between *ALDH2* polymorphism and risk of cancer of the breast has been observed in a Korean (Choi *et al.*, 2003) and a Spanish population (Ribas *et al.*, 2008) (Table 2.76 on-line).

2.19 Synthesis

2.19.1 Oral cavity and pharynx

Data published since the previous *IARC monograph* (IARC, 2010) support the conclusion that consumption of alcoholic beverages is causally related to cancer of the oral cavity and pharynx. Increasing alcohol consumption increases risk in a dose-dependent manner, does not vary materially by beverage type or sex and the association is not due to chance, bias or confounding.

2.19.2 Larynx

Data published since the previous *IARC Monograph* (IARC, 2010) supports the conclusion that consumption of alcoholic beverages is causally related to cancer of the larynx. Increasing alcohol consumption increases risk in a dose-dependent manner, does not vary materially by beverage type or sex, and chance, bias and confounding can be ruled out.

2.19.3 Oesophagus

Data published since the previous *IARC Monograph* (IARC, 2010) supports the conclusion that consumption of alcoholic beverages is causally related to squamous cell carcinoma of the oesophagus. Increasing alcohol consumption increases risk in a dose-dependent manner, does not vary materially by beverage type or sex, and chance, bias and confounding can be ruled out. There is now a substantial body of evidence that alcoholic beverage consumption is not associated with adenocarcinoma of the oesophagus.

2.19.4 Upper aerodigestive tract combined

There is evidence that consumption of alcoholic beverages is causally related to cancer of the upper aerodigestive tract, as it is for cancer of the oral cavity and pharynx, larynx and oesophagus separately. Increasing alcohol consumption increases risk in a dose-dependent manner, does not vary materially by beverage type or sex and chance, bias and confounding can be ruled out.

2.19.5 Colon and rectum

Data published since the previous *IARC Monograph* (IARC, 2010) supports the conclusion that consumption of alcoholic beverages is causally related to cancer of the colorectum. Most of the evidence suggests that consumption of alcoholic beverages is positively associated with both cancer of the colon and cancer of the rectum, and is similar in men and women, although the data are not entirely consistent. Similarly, there is some evidence that risk may only be increased at relatively high levels of intake (i.e. > 30 g/d). There is consistent evidence that risk does not differ by beverage type; whether the risk associated with consumption of alcoholic beverages differs by smoking status or intake of dietary folate is inconsistent.

2.19.6 Liver

Data published since the previous IARC *Monograph* (IARC, 2010) support the previous conclusion that the consumption of alcoholic beverages is causally related to hepatocellular carcinoma. It is not possible to draw any conclusion concerning consumption of alcoholic beverages and risk of cholangiocarcinoma.

2.19.7 Stomach

Results on the association between consumption of alcoholic beverages and cancer of the stomach are difficult to interpret due to the lack

of information on important confounders, such as possible dietary deficiencies.

2.19.8 Pancreas

There is accumulating evidence that high alcohol intake (i.e. ≥ 30 g/d) is associated with a small increased risk for cancer of the pancreas. However, the possibility that residual confounding by smoking may partly explain this association cannot be excluded. Whether the risk associated with heavy alcohol consumption differs by beverage type, smoking status or body mass index is unclear.

2.19.9 Lung

Available data are inadequate to determine a causal association between the consumption of alcoholic beverages and cancer of the lung. Although adjustment for tobacco smoking was attempted in many studies, residual confounding cannot be excluded for those analyses that found a positive association with consumption of alcoholic beverages. For those studies that attempted to evaluate risk for cancer of the lung from the consumption of alcoholic beverages in non-smokers, small numbers of cases, or few subjects with high consumption of alcoholic beverages, precluded detection of an association.

2.19.10 Breast

Occurrence of cancer of the female breast is causally associated with the consumption of alcoholic beverages. Cancer risk increases proportionately according to the amount of alcohol consumed, with an increase in risk of up to 12% for each additional drink consumed regularly each day (equivalent to about 10 g/d). The risk does not appear to vary significantly by beverage type or smoking status. It remains unclear whether the association of alcohol beverage consumption with risk for cancer of the female breast varies by use of hormone-replacement therapy or by tumour receptor status.

The evidence that alcoholic beverage consumption is associated with cancer of the male breast remains inconsistent.

2.19.11 Uterine cervix

The weak associations noted in some studies for consumption of alcoholic beverages and risk of cancer of the uterine cervix are sufficient to draw any conclusion on causality. Few studies were able to adjust for the known risk factors for the disease.

2.19.12 Endometrium

The evidence for an association between consumption of alcoholic beverages and risk for cancer of the endometrium is inconsistent. The majority of studies show no association; the few that show an inverse association were not able to adjust for tobacco smoking.

Among both the cohort and case–control studies, there was no consistent evidence of an interaction between consumption of alcoholic beverages and different variables known or suspected to be associated with cancer of the endometrium, such as use of hormone replacement therapy, body size, age, tobacco smoking, parity, education, physical activity, energy intake and other dietary aspects, oral contraceptive use or menopausal status.

2.19.13 Ovary

There is little evidence for an association between consumption of alcoholic beverages and risk for cancer of the ovary. The majority of studies show no association.

2.19.14 Prostate

There is little evidence for an association between consumption of alcoholic beverages and risk of cancer of the prostate. Although in some studies positive associations were found for advanced disease, the majority of studies show no association.

2.19.15 Kidney

There is no causal association between consumption of alcoholic beverages and cancer of the kidney.

2.19.16 Urinary bladder

Overall, the studies on cancer of the urinary bladder suggest no association with consumption of alcoholic beverages.

2.19.17 Haematopoietic malignancies

In cohort studies in the general population, most forms of lymphomas and leukaemias have shown no or inverse associations with consumption of alcoholic beverages; studies that assessed risk for non-Hodgkin lymphoma, the form of lymphomas and leukaemias most studied, generally found an inverse association.

There were consistent inverse associations in case–control studies investigating ever alcohol consumption and risk for Hodgkin lymphoma, with no significant differences between alcoholic beverage types. A large pooled study observed a lower risk of several histological subtypes, such as Burkitt, B-cell, follicular and T-cell lymphomas among ever drinkers.

No clear patterns of association between consumption of alcoholic beverages and risk of all leukaemias combined were shown in case–control studies. Two studies indicated increased risk of acute lymphocytic leukaemia with any or heavy alcohol drinking, and also increased risk of chronic lymphocytic leukaemia among wine drinkers, but there was no consistent pattern of association for different types of leukaemias. In most studies on multiple myeloma no consistent results were observed.

2.19.18 Other cancers

It is not possible to draw any conclusions regarding the association between intake of alcoholic beverages and risk for cancers of the brain and thyroid, melanoma and non-melanoma skin cancers.

2.19.19 Parental exposure and childhood cancers

Results for the association between maternal consumption of alcohol before or during pregnancy and risk of acute lymphocytic leukaemia, acute lymphocytic leukaemia and acute leukaemia in the offspring are inconsistent.

2.19.20 Polymorphisms and genetic susceptibility

(a) ADH1B

The available genetic epidemiological data suggest a positive association between *ADH1B*1/*1* polymorphism and cancer of the oesophagus, and cancers of the upper aerodigestive tract combined. The relationship between *ADH1B* genotype and cancer in other organs is inconclusive because of the small number of studies.

(b) ADH1C

The relationship between *ADH1C* genotype and cancer at any site is inconclusive, primarily because of the small number of studies.

(c) ALDH2

The available genetic epidemiological data provides ample evidence for a strong contribution of heterozygous *ALDH2* genotype to the

development of alcohol-related cancer in the oesophagus and in the upper aerodigestive tract. While it is often difficult to differentiate clearly between exact locations of tumours in the oropharyngolaryngeal area based on the available published data, there is also strong evidence for a contribution of heterozygous *ALDH2* genotype to the development of alcohol-related cancer in the oropharyngolarynx as a whole, and especially in the hypopharynx. However, the epidemiological studies provide suggestive but inconclusive data for some association of heterozygous *ALDH2* genotype and alcohol-related cancers in the individual oropharyngolaryngeal subsites of the oral cavity, oropharynx and larynx.

The evidence for cancers of the stomach, colorectum, pancreas, liver, breast, bladder and prostate is inconclusive.

3. Cancer in Experimental Animals

Consumption of alcoholic beverages was evaluated in 2007 (IARC, 2010). The studies described below were considered; no new studies have been published since.

An issue in evaluating bioassays of ethanol is the nutritive value of this substance, which results in a hyperalimentation of alcohol-fed animals. For rigorous evaluation of the carcinogenicity of alcohol by ingestion in experimental animals, controls must be pair fed to equalize caloric intake.

3.1 Oral administration of ethanol in the drinking-water

Study design and results of studies of oral administration of ethanol in drinking-water are presented in Table 3.1.

3.1.1 Rat

Eight groups of 50 male and 50 female Sprague-Dawley rats received either 1% or 3% ethanol or an equicaloric amount of glucose in a semisynthetic liquid diet for 120 weeks (Holmberg & Ekström, 1995). Males were given 70 mL/day and females 60 mL/day of liquid diet. No tumours developed in male rats. There was a significant ($P < 0.05$) increase in pituitary tumours [not further specified] among 3% ethyl alcohol-treated females (80%) than among high-dose glucose-treated animals (58%). There was also an increase ($P < 0.05$) in mammary gland fibromas, fibroadenomas and adenomas combined, in the 1% ethyl alcohol-treated females compared with the low-dose glucose animals [no incidence provided].

Male Sprague-Dawley rats administered 5% ethanol in the drinking-water for 130 weeks developed hepatocellular carcinomas (8/79 versus 1/80 control rats). Additionally, the authors reported an increase in the incidence of hyperplastic liver nodules in the ethanol group. Pancreatic adenomas, adrenal gland adenomas, and pituitary adenomas occurred in the ethanol group in 18% (14/79), 18% (14/79), and 33% (26/79) of the animals, respectively. No tumours of the pancreas or adrenal gland were found in control rats. Pituitary adenomas were found in 8/80 control rats (Radike *et al.*, 1981).

In other experiments, the chronic administration of 5% or 10% ethanol had no effect on liver carcinogenesis of Wistar or F344 rats (Shibayama *et al.*, 1993; Yamagiwa *et al.*, 1994; Wanibuchi *et al.*, 2006).

Sprague-Dawley rats and their offspring received either 10% ethanol or no ethanol in the drinking-water *ad libitum* starting at 39 weeks of age, 7 days before mating or from embryo life (offspring) until death. The intake of fluid was lower in the treated group but no difference in body weight was noted. An increased incidence of total malignant tumours was noted in female

Table 3.1 Carcinogenicity studies on ethyl alcohol administered in the drinking-water to experimental animals

Species, strain (sex) Duration Reference	Dosing regimen, Animals/group at start	Incidence of tumours		Significance	Comments
Rat, Sprague-Dawley (M) 130 wk Radike *et al.* (1981)	5% 7 d/wk 79 animals 80 animals (controls)	Liver	Carcinoma Control (1/80) 5% Ethanol (8/79)	[$P < 0.05$]	
		Pituitary gland	Adenoma Control (8/80) 5% Ethanol (26/79)	[$P < 0.001$]	
		Adrenal gland	Adenoma Control (0/80) 5% Ethanol (14/79)	[$P < 0.0001$]	
		Pancreas	Adenoma Control (0/80) 5% Ethanol (14/79)	[$P < 0.0001$]	
		Testes	Seminoma Control (0/80) 5% Ethanol (3/79)	[NS]	
Rat, Sprague-Dawley (M) 140 wk Soffritti *et al.* (2002a)	10% 7 d/wk 110 animals 110 animals (controls)	Forestomach	Benign Control (1/110) 10% Ethanol (8/110)	[$P < 0.01$]	Animals were breeder
			Benign and malignant Control (1/110) 10% Ethanol (10/110)	[$P < 0.01$]	
		Head and other sites	Osteosarcoma Control (1/110) 10% Ethanol (12/110)	[$P = 0.0042$]	
		Oral cavity, lips and tongue	Carcinoma Control (3/110) 10% Ethanol (15/110)	$P < 0.01$	
		Testes	Interstitial cell adenoma Control (9/110) 10% Ethanol (23/110)	[$P = 0.013$]	
Rat, Sprague-Dawley (F) 140 wk Soffritti *et al.* (2002a)	10% 7 d/wk 110 animals 110 animals (controls)	Lymphomas and leukaemias	Control (17/110) 10% Ethanol (46/110)	[$P < 0.0001$]	
		Oral cavity, lips and tongue	Carcinoma Control (2/110) 10% Ethanol (12/110)	$P < 0.05$	

Table 3.1 (continued)

Species, strain (sex) Duration Reference	Dosing regimen, Animals/group at start	Incidence of tumours		Significance	Comments
Rat, Sprague-Dawley (M) 179 wk Soffritti *et al.* (2002a)	10% 7 d/wk 30 animals 49 animals (controls)	Oral cavity, lips and tongue	Carcinoma Control (2/49) 10% Ethanol (10/30)	$P < 0.01$	Animals were offspring
Rat, Sprague-Dawley (F) 179 wk Soffritti *et al.* (2002a)	10% 7 d/wk 39 animals/group 55 animals (controls)	Oral cavity, lips and tongue	Carcinoma Control (3/55) 10% Ethanol (16/39)	$P < 0.01$	Animals were offspring
Mouse B6C3F1 (M) 104 wk Beland *et al.* (2005)	0 (control), 2.5%, 5% 7 d/wk 48 animals/group	Liver	Adenoma or Carcinoma Control (12/46) 2.5% Ethanol (16/47) 5% Ethanol (25/48)	$P < 0.05$ dose-related trend, $P = 0.056$ (5% ethanol)	
			Adenoma Control (7/46) 2.5% Ethanol (12/47) 5% Ethanol (19/48)	$P < 0.05$ dose-related trend, $P < 0.05$ (5% Ethanol)	
Mouse, ICR (F) 106 wk Watabiki *et al.* (2000)	10–15% 7 d/wk 20 animals/group	Mammary gland	Adenocarcinoma Control (0/20) 10–15% Ethanol (9/20)	[$P = 0.012$]	
Mouse, C57/BL6APCmin (M) 10 wk Roy *et al.* (2002)	15% alternating with 20% every other d 12 animals/group	Intestine	Adenoma Tumor multiplicity Control (26.8) 15–20% Ethanol (36.9)	$P < 0.05$	

d, day or days; F, female; M, male; NS, not significant; wk, week or weeks

breeders and male offspring. This was due to a significant increase in the incidence of head and neck carcinomas (oral cavity, lips, tongue) in male and female breeders and male and female offspring; benign and combined benign and malignant tumours of the forestomach in male breeders; and combined lymphomas and leukemias in female breeders. Increases in the incidence of interstitial-cell adenomas of the testis and osteosarcomas of the head and other sites were also observed in male breeders (Soffritti *et al.*, 2002a). [The Working Group noted that some statements reporting increased incidence were not supported by statistical analyses performed by the Working Group].

3.1.2 Mouse

$B6C3F_1$ male and female mice received 2.5% or 5% of ethanol in drinking-water for 104 weeks. No significant difference in tumour incidence at any site was observed in females. There was a significant dose-related trend for the incidence of hepatocellular adenomas, and hepatocellular adenomas and carcinomas combined in male mice. The administration of 5% ethanol resulted in an increase in the incidence of hepatocellular adenomas ($P < 0.05$) and a marginal increase ($P = 0.056$) in the incidence of hepatocellular adenomas and carcinomas combined in male mice (NTP, 2004; Beland *et al.*, 2005).

ICR female mice received 10% ethanol in the drinking-water for 2 months and then 15% ethanol in the drinking-water for 23 months. Mammary gland tumours (papillary or medullary adenocarcinomas) were found in 9/20 mice given ethanol in drinking-water compared with 0/20 control mice [$P = 0.012$] (Watabiki *et al.*, 2000).

C57BL/6^{APCmin} male mice received ethanol in drinking-water at doses between 15 and 20% daily for 10 weeks. This treatment increased intestinal adenoma multiplicity (Roy *et al.*, 2002).

3.2 Oral administration of acetaldehyde in drinking-water

See Table 3.2.

Acetaldehyde was evaluated in 1984 (IARC, 1985), 1998 (IARC, 1999), and 2007 (IARC, 2010).

3.2.1 Rat

Sprague-Dawley male and female rats received acetaldehyde in the drinking-water at doses of 50, 250, 500, 1500 and 2500 mg/L for 161 weeks. With the exception of male rats treated with 1500 mg/L, the administration of acetaldehyde to male Sprague-Dawley rats resulted in a marginal dose-dependent increase in incidence of pancreatic islet cell adenomas. The incidence of pancreatic islet cell adenoma was significantly higher (18%; 9/50) in male rats exposed to the high dose of acetaldehyde (2500 mg/L) compared to 4% (2/50) in the control group. Acetaldehyde caused an increased incidence of head osteosarcomas in the 50 and 2500 mg/L groups. Additionally, ingestion of acetaldehyde resulted in a higher incidence of lymphomas and leukemias in male rats exposed to acetaldehyde at doses of 50 mg/L and 1500 mg/L. Acetaldehyde also caused an increase in lymphomas and leukemias in female rats, 16% in rats exposed to 250 mg/mL compared to 4% in control animals. A higher incidence of mammary gland adenocarcinomas and uterine adenocarcinomas was found in the groups of females exposed to 500 mg/L and 250 mg/L, respectively (Soffritti *et al.*, 2002b). [The Working Group noted that a variety of tumours were increased. However, no obvious dose–response relationship was observed.]

3.3 Co-carcinogenicity studies on alcohol administered in drinking-water

A comprehensive analysis of the studies on the co-carcinogenicity of ethanol was presented in the previous *IARC Monograph* (IARC, 2010). Simultaneous administration of alcohol with known carcinogens enhanced tumour development. A selection of positive studies is summarized below.

3.3.1 Rat

Chronic administration of ethanol potentiates the development of tumours in experimental animals induced by chemical agents.

Two groups of 80 Sprague-Dawley rats received either vinyl chloride or vinyl chloride and 5% ethanol in the drinking-water for 130 weeks. Increases in the incidence of liver carcinomas and liver angiosarcomas were observed in the vinyl chloride and ethanol group compared to the vinyl chloride treated control rats. In rats exposed to vinyl chloride and ethanol 15% developed pancreatic adenomas, whereas no tumours were found in control rats (Radike *et al.*, 1981).

Fischer 344/DuCrj rats were fed 200 ppm 2-amino-3,8-dimethylimidazo[4,5]quinoxaline (MeIQx). After 8 weeks, rats were subdivided to receive either drinking-water or 0.1, 0.3, 1, 3, or 10% ethanol in the drinking-water. In rats administered MeIQx in the diet, the incidence of hepatocellular adenoma, carcinoma and adenoma plus carcinoma was increased by ethanol consumption in a dose-dependent manner ($P < 0.001$) (Kushida *et al.*, 2005).

Chronic ethanol administration in drinking-water to male F344 rats for 55 weeks after treatment with the chemical carcinogens *N*′-nitrosonornicotine (NNN) or 4-(methylnitrosoamino)-1-(3-pyridyl)-1-butanone (NNK) increased the incidence of tumours of the oesophagus, oral cavity and lungs. NNK also induced liver tumours, which were significantly increased by ethanol ingestion (Nachiappan *et al.*, 1994). Similarly, administration of 5% ethanol to male Wistar rats enhanced the oesophageal tumourigenesis induced by *N*-nitrosomethylbenzylamine (Tsutsumi *et al.*, 2006). The enhancing effect of ethanol on *N*-nitrosodiethylamine (NDEA)-induced oesophageal carcinogenesis was also observed in male Fischer 344 rats. Two groups of Fischer 344 rats received either 50 ppm NDEA dissolved in 10% ethanol or 50 ppm NDEA solution in water, respectively, for 8 weeks. Rats were maintained on tap water and basal diet for 96 weeks. The incidence of oesophageal papillomas or carcinomas in rats that received NDEA dissolved in 10% ethanol was higher than in rats that received NDEA alone ($P < 0.01$) (Aze *et al.*, 1993).

Chronic intake of 10% ethanol for 56 weeks enhanced hepatocarcinogenesis induced by oral administration of combined ethinylestradiol and norethindrone acetate in male and especially female Wistar rats (Yamagiwa *et al.*, 1994). Long-term ethanol treatment had a similar effect in male rats on liver preneoplastic lesions induced by aflatoxin B_1 (Tanaka *et al.*, 1989), *N*-nitrosomorpholine (Tatsuta *et al.*, 1997), MeIQx (Wanibuchi *et al.*, 2006), and NDEA and 2-acetylaminofluorene (Pires *et al.*, 2008).

The administration of ethanol (15% in the drinking-water) during the initiation and promotion stages of mammary gland carcinogenesis, induced by *N*-methylnitrosourea in female Sprague-Dawley rats, increased the number of mammary adenocarcinomas compared to control rats. Likewise, ethanol intake during the promotion stage resulted in a greater number of mammary adenocarcinomas (Singletary *et al.*, 1995). The administration of ethyl alcohol to pregnant female Sprague-Dawley rats during gestation significantly increased mammary gland tumours induced by 7,12-dimethylbenz[*a*]anthracene (DMBA) in offspring, as evidenced

Table 3.2 Carcinogenicity studies on acetaldehyde administered with drinking-water to rats

Species, strain (sex) Duration Reference	Dosing regimen, Animals/group at start	Incidence of tumours		Significance	Comments
Rat, Sprague-Dawley (M) 161 wk Soffritti *et al.* (2002b)	50 mg/L 7 d/wk 50 animals/group	Head	Osteosarcoma Control (0/50) Acetaldehyde (5/50)	$P < 0.05$	
	2500 mg/L 7 d/wk 50 animals/group	Head	Osteosarcoma Control (0/50) Acetaldehyde (7/50)	$P < 0.05$	
	50 mg/L 7 d/wk 50 animals/group	Lymphomas and leukemias	Control (6/50) Acetaldehyde (14/50)	[$P = 0.039$]	
	1500 mg/L 7 d/wk 50 animals/group	Lymphomas and leukemias	Control (6/50) Acetaldehyde (15/50)	[$P = 0.024$]	
	2500 mg/L 7 d/wk 50 animals/group	Pancreas	Islet cell adenoma Control (2/50) Acetaldehyde (9/50)	[$P = 0.026$]	
Rat, Sprague-Dawley (F) 161 wk Soffritti *et al.* (2002b)	250 mg/L 7 d/wk 50 animals/group	Lymphomas and leukemias	Control (2/50) Acetaldehyde (8/50)	[$P = 0.046$]	
	500 mg/L 7 d/wk 50 animals/group	Mammary gland	Adenocarcinoma Control (3/50) Acetaldehyde (10/50)	[$P = 0.036$]	
	250 mg/L 7 d/wk 50 animals/group	Uterus	Adenocarcinoma Control (0/50) Acetaldehyde (5/50)	[$P = 0.028$]	

d, day or days; F, female; M, male; wk, week or weeks

by a greater tumour multiplicity (Hilakivi-Clarke *et al.*, 2004).

3.3.2 Mouse

Treatment of CF-1 male mice with 6% ethanol in the drinking-water increased development of invasive pancreatic adenocarcinoma induced by DMBA (Wendt *et al.*, 2007).

As part of the study to investigate the effect of ethanol on the carcinogenicity of NDEA, strain A male mice were administered NDEA in the drinking-water with or without 10% ethanol for 4 weeks and were maintained thereafter for 32 weeks on tap-water and basal diet. Ethanol strongly potentiated the tumorigenic effect of NDEA in the forestomach and the lung (Anderson *et al.*, 1993).

The effect of ethanol on the carcinogenicity of nitrosamines was comprehensively summarized in the previous *IARC Monographs* (IARC, 1988, 2010).

3.4 Synthesis

Administration of ethanol in the drinking-water increased the incidence of cancers of the head and neck and the liver, benign tumours of the adrenal glands, pituitary gland, testes, and pancreas, osteosarcomas of the head and other sites, forestomach tumours, and combined lymphomas and leukemias in rats and liver tumours and mammary gland adenocarcinomas in mice.

Administration of acetaldehyde in the drinking-water increased the incidence of pancreatic adenomas, combined lymphomas and leukaemias, uterine and mammary gland adenocarcinomas, and head osteosarcomas in rats.

Co-administration of ethanol in the drinking-water with several known carcinogens enhanced tumour development in rats and mice.

4. Other Relevant Data

The current knowledge on mechanistic and other data relevant to the carcinogenicity of alcoholic beverages was reported in the recent *IARC Monograph* (IARC, 2010). A synthesis of these data is presented below.

4.1 Absorption, distribution, metabolism and excretion

The biomedical effects of alcoholic beverages either originate from the properties of the ethanol major component, or from its metabolism. The metabolism of ethanol is depicted in Fig. 4.1. Ethanol is metabolized to acetaldehyde by three major pathways: the alcohol dehydrogenase (ADH) pathway, the microsomal ethanol oxidizing cytochrome P450 (CYP) pathway, and the catalase-H_2O_2 system. Acetaldehyde, to which many deleterious effects of ethanol can be attributed, is oxidized to acetate primarily by acetaldehyde dehydrogenases (ALDHs) (Vasiliou *et al.*, 2004). The four pharmacokinetic parameters, absorption, distribution, metabolism and excretion, that define the level of ethanol and/or its metabolites in different tissues, are relevant for consideration.

4.1.1 Ethanol

(a) Absorption and distribution

The absorption of orally ingested alcohol starts in the upper digestive mucosa and the stomach, but the bulk is absorbed by simple diffusion in the small intestine into the bloodstream. Hereafter, alcohol is distributed into the body water. The absorption, immediately followed by the distribution phase, largely determines the ascending part and the peak of the blood-alcohol curve. Food in conjunction with alcohol drinking lowers the rate of absorption and diminishes the peak alcohol concentration, while fasting and dehydration create opposite effects. The distribution process produces slightly lower ethanol levels in venous blood (Jones *et al.*, 2004) and urine (Jones 2006) compared with arterial blood levels during the absorption phase. More fat and less body water per unit body-mass create higher blood alcohol levels, which explains why women on average reach a 10–15% higher blood-alcohol concentration compared with the same amount of alcohol per body-mass ingested by men (Goist & Sutker, 1985).

(b) Metabolism and excretion

It is generally believed that more than 90% of the ingested alcohol is oxidized in the liver. The remaining extrahepatic alcohol oxidation and other modes of elimination take place in the gastrointestinal mucosa and bacteria, via oral bacteria, the kidneys and other peripheral tissues, by excretion of body fluids (urine and sweat) and via exhalation. First-pass metabolism, i.e. when the ethanol is oxidized at its first passage through the oral cavity, gut and liver, reduces the amount of ethanol that reaches target organs. The relative contribution of first-pass metabolism to alcohol oxidation is debatable (Lim *et al.*, 1993; Levitt & Levitt, 2000). However, the smaller the alcohol amount and the slower the alcohol absorption, the greater the relative contribution of first-pass

oxidation in overall alcohol elimination (Levitt & Levitt, 1998).

(i) Endogenous alcohol formation

In addition to ingestion via consumption of alcoholic beverages, small amounts of ethanol are also produced endogenously in normal intermediary metabolism (Ostrovsky, 1986) and by microbial formation, especially in the gastrointestinal tract (Krebs & Perkins, 1970). The resulting concentrations in human venous blood are estimated to vary between 0–50 μM (Jones *et al.*, 1983; Watanabe-Suzuki *et al.*, 1999). Based on case reports (Kaji *et al.*, 1984; Spinucci *et al.*, 2006) and on data from experimental animals (Krebs & Perkins, 1970), it has been shown that considerably higher concentrations exist in the gastrointestinal tract. The relevance of endogenous metabolism is further discussed in Section 4.3.1.

(ii) Alcohol dehydrogenase pathway

The oxidation of ethanol is largely catalysed by cytosolic ADHs, primarily by the low-K_m variants in the liver. Because of the low K_m (0.05–4.2 mM) ADH quickly becomes saturated and the reaction follows zero-order kinetics with a constant rate for ethanol oxidation. In addition to the enzyme activity, the ADH-mediated ethanol oxidation rate is strictly regulated by the mitochondrial reoxidation of the reduced co-enzyme nicotinamide adenine dinucleotide (NADH) to the oxidized form, nicotinamide adenine nucleotide (NAD^+) (Zakhari, 2006). This explains why, in spite of huge variations in ADH activity, relatively small effects on the overall alcohol oxidation rate have been observed. The impact of the hepatic redox state is even more apparent under fasting conditions, which are well known to slow down the rate of alcohol oxidation (Rogers *et al.*, 1987), most likely due to limitations in the mitochondrial reoxidation of NADH (Lisander *et al.*, 2006). The less alcohol is ingested the larger the contribution of ADH activity in the regulation of the rate of alcohol oxidation (see Fig. 4.1).

Human ADHs

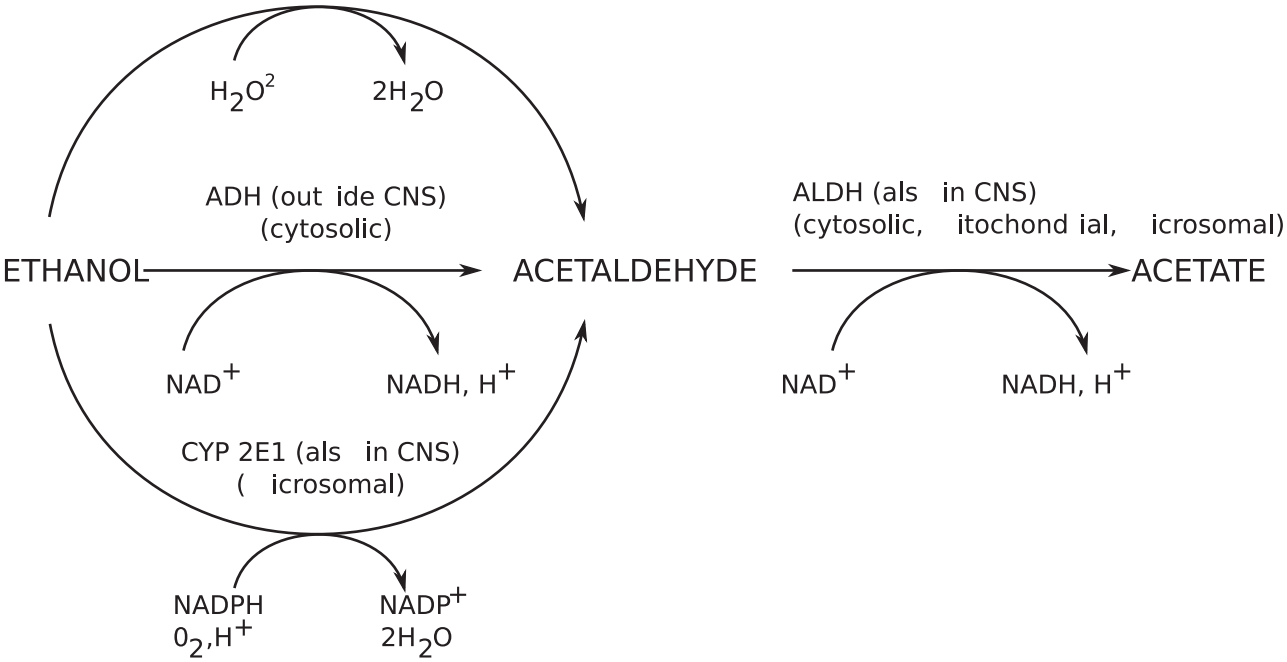
Three different nomenclature systems have been proposed for the human ADH genes (Table 4.1). The official nomenclature approved by the Human Genome Organization (HUGO) (www.gene.ucl.ac.uk/nomenclature) will be used here throughout.

Seven human ADHs have been isolated that are divided into five classes on the basis on similarities in their amino acid sequences and kinetic properties (Table 4.1). They are dimeric enzymes consisting of two 40kDa subunits named α, β, γ, π, χ and either σ or μ. Class I comprises three enzymes: ADH1A, which contains at least one α subunit (αα, αβ, or αγ), ADH1B (ββ or βγ), and ADH1C (γγ).Class II contains ADH4 (ππ). Class III contains ADH5 (χχ). Class IV contains ADH7 (μμ or σσ). Class V contains ADH6 for which there is no subunit designation (Parkinson & Ogilvie, 2008).

The low-K_m class I ADHs (α, β and γ subunits, formerly called ADH-1, -2, and -3) account for most of the ethanol-oxidizing capacity in the liver and gastrointestinal mucosa (Lee *et al.*, 2006). Class I *ADH* is also expressed in several other tissues, such as the upper and lower digestive tracts (Yin *et al.*, 1993; Seitz *et al.*, 1996; Yin *et al.*, 1997; Jelski *et al.*, 2002), pancreas (Chiang *et al.*, 2009), lungs (Engeland & Maret, 1993), breast (Triano *et al.*, 2003), blood vessels (Jelski *et al.*, 2009) and salivary glands (Visapää *et al.*, 2004). In brain no functionally significant class I ADH has been detected (Estonius *et al.*, 1996).

Allelic variants have been identified in the *ADH1B* and *ADH1C* genes that encode for the β1, β2, β3, γ1, and γ2 subunits, which can combine as homodimers or can form heterodimers with each other and with the α subunit. ADH1B enzymes that differ in the type of β subunit are known as allelozymes, as are ADH1C enzymes that differ in the type of γ subunit. Allelozymes

Fig. 4.1 Ethanol and acetaldehyde metabolism



ADH, alcool dehydrogenase; ALDH, aldehyde dehydrogenase; CYP, cytochrome P450; CNS, central nervous system; NADPH, nicotinamide-adenine dinucleotide phosphate.
Adapted from Vasiliou *et al.* (2004).

present different kinetic properties (Table 4.1) and so differ in their capacity to oxidize ethanol. The allelozymes that are homodimers or heterodimers of β2 subunit (encoded by the *ADH1B*2* allele) are especially active ethanol oxidizing enzymes. The ADH1B*2 allelic variant is found in 90% of the Pacific Rim Asian population and is responsible for the unusually rapid conversion of ethanol to acetaldehyde in this population. ADH1B*2 is also more common in people of Jewish origin compared to people of other Caucasian descent (where it is found in 0 to < 20%) (Neumark *et al.* 1998). The ADH1B*1 allele is most common in Caucasians (up to 95%) and ADH1B*3 is found mostly in African and African Americans (~24%). These population differences in ADH1B alloenzyme expression potentially contribute to ethnic differences in alcohol consumption and toxicity. Unlike the ADH1B allelozymes, the ADH1C variants do not differ much in their ethanol oxidizing activities (Parkinson & Ogilvie, 2008).

The class II π-ADH (subunit encoded by *ADH4*) also contributes to hepatic ethanol oxidation, especially at higher concentrations (Edenberg 2007; Birley *et al.*, 2009; Kimura *et al.*, 2009). *ADH4* expression has been found in most epithelial tissues.

Little is known about the functional role of class III, IV and V ADHs (encoded by the genes *ADH5*, *7* and *6*, respectively) in the oxidation of alcohol.

Microbial ADHs

There is a large population of microorganisms present in the gastrointestinal tract that may contribute to ethanol oxidation. Another local site for microbial alcohol oxidation is the oral cavity. Microorganisms express numerous forms of ADH, the role of which may become

Table 4.1 Major allele variants and biochemical properties of human alcohol dehydrogenases (ADHs)

Official nomenclature[a]	Former nomenclature[b]	Additional nonstandard nomenclature[c]	Sequence[d]	Allele	Amino Acid differences between alleles	Protein subunit	Class[e]	K_m (mM) [f]	V_{max} (min^{-1}) [g]
ADH1A	*ADH1*		NM_000667	*ADH1A*		α	I	4.0	30
ADH1B	*ADH2*		NM_000668	*ADH1B*1*	Arg48, Arg370	β1	I	0.05	4
				*ADH1B*2*	His48, Arg370	β2	I	0.9	350
				*ADH1B*3*	Arg48, Cys370	β3	I	40	300
ADH1C	*ADH3*		NM_000669	*ADH1C*1*	Arg272, Ile350	γ1	I	1.0	90
				*ADH1C*2*	Gln212, Val350	γ2	I	0.6	40
				*ADH1C*352Thr*	[h]Thr352	NR	I	NR	NR
ADH4	*ADH4*	*ADH2*	NM_000670	*ADH4*1*		π	II	30	40
				*ADH4*2*		π	II	NR	NR
ADH5	*ADH5*	*ADH3*	NM_000671			χ	III	> 1000	100
ADH6	*ADH6*	*ADH5*	NM_000672				V	NR	NR
ADH7	*ADH7*	*ADH4*	NM_000673			σ or μ	IV	30	1800

[a] Nomenclature approved by the Human Genome Organization (HUGO) Gene Nomenclature Committee (www.gene.ucl.ac.uk/nomenclature/), as used by the National Center for Biotechnology Information (NCBI)

[b] Former nomenclature

[c] Non-standard nomenclature proposed by Duester *et al.* (1999)

[d] Reference sequence number as listed in the NCBI RefSeq database (www.ncbi.nlm.nih.gov/RefSeq/)

[e] ADH proteins have been divided into five classes based on sequence and structural similarities

[f] V_{max} indicates how many molecules of ethanol the enzyme will convert to acetaldehyde in 1 minute at saturating ethanol concentrations.

[g] K_m indicates the concentration of ethanol at which the enzyme works at 50 percent capacity.

[h] *ADHIC+352Thr* has been found in Native Americans as an additional variation on chromosomes with the Val350 characteristics of ADH1C*2 (Osier *et al.*, 2002); the protein has not been isolated for study. The kinetic constants are noted for the homodiners of the ADH subunits listed (heterodimers behave as if the active sites were independent).

NR, not reported

Adapted from Edenberg (2007)

even more significant wherever microbial overgrowth occurs (Salaspuro, 2003).

(iii) Cytochrome P450 oxidation pathway

See Fig. 4.1.

Cytochrome P450 2E1 (CYP2E1) is constitutively expressed in the endoplasmic reticulum of the liver and many other tissues including the brain, in contrast to the expression of ADHs. Its K_m for ethanol is about 10 mM; thus CYP2E1 may assume a greater role in the first-order oxidation reaction at high blood-alcohol levels. Other cytochrome enzymes, CYP1A2 and CYP3A4, also contribute to the oxidation of ethanol, albeit to a lesser extent (Lieber, 2004). CYP2E1 has the unique property of being induced as a result of chronic alcohol intake, which explains part of the increased alcohol elimination rate after chronic alcohol ingestion (Lieber, 2004). The CYP2E1-mediated ethanol oxidation is associated with nicotinamide-adenine dinucleotide phosphate (NADPH)-CYP reductase in the endoplasmic reticulum, and reduces molecular oxygen to water as ethanol is oxidized to acetaldehyde. CYP2E1 is unusually 'leaky' and generates reactive oxygen species including hydroxyl radical, superoxide anion, hydrogen peroxide and hydroxyethyl radical. Thus, CYP2E1 is a major source of alcohol-related oxidative stress (Caro & Cederbaum, 2004).

Genetic variants of *CYP2E1*

Several allele variants of *CYP2E1* have been described in humans (see Table 4.2).

The allele variant commonly denoted as c2, *CYP2E1*5B* according to the new recommended nomenclature, has been found more frequently in East Asian individuals (~40%) compared with Caucasians (~8%) (Garte *et al.*, 2001). Early studies showed an increased *CYP2E1* expression and activity in ethanol oxidation associated with the **5B* allele (Hayashi *et al.*, 1991; Tsutsumi *et al.*, 1994; Watanabe *et al.*, 1994), but this finding has not been confirmed in other studies (Carrière *et al.*, 1996; Kim *et al.*, 1996; Powell *et al.*, 1998; Kato *et al.*, 2003), and contrasting results have been reported (Huang *et al.*, 2003). So it is unclear to what extent the functional activities regarding ethanol oxidation differ from those of the corresponding wild types. Other variants of *CYP2E1* polymorphisms, such as *CYP2E1*6*, have also been shown to be more common in East Asians (ca. 52%) compared with Caucasian individuals (ca. 15%) (Garte *et al.*, 2001).

(iv) Ethanol oxidation by catalase (Fig. 4.1)

Catalase is constitutively expressed in the peroxisomal part of the endoplasmic reticulum in virtually all tissues. It is an important antioxidant enzyme that detoxifies H_2O_2 into oxygen and water and thus limits the deleterious effects of reactive oxygen species. The functional role of catalase in the oxidation of ethanol in humans is not known. Although catalase-mediated ethanol oxidation is very limited compared with ADH-mediated reactions, it may play a significant role in specific organs and tissues that lack the functional ADH. Based on experimental animal research, catalase seems to contribute to alcohol oxidation in the brain (Cohen *et al.*, 1980; Zimatkin *et al.*, 2006). As with CYP2E1, catalase also has a high K_m and, thus, the impact on alcohol oxidation would be higher at high alcohol levels. No functional polymorphism regarding alcohol oxidation or its effects has been reported.

(v) Non-oxidative ethanol metabolism

Ethanol can be non-oxidatively metabolized to form fatty-acid ethyl esters (FAEEs), which are toxic for cells (Laposata & Lange, 1986; Laposata *et al.*, 2002). These esters are formed during the hydrolysis of fatty-acid esters (e.g. triglycerides) in the presence of ethanol. Such esterification activity has been detected in humans mainly with the two high-K_m enzymes fatty-acid ethyl ester synthases (FAEEs) (Wright *et al.*, 1987) and acyl-coenzyme A:ethanol O-acyltransferase (AEAT) (Diczfalusy *et al.*, 2001). Highest activities have

Table 4.2 Major allelic variants and biochemical properties of humans cytochrome P450 2E1 (CYP2E1)

Recommended nomenclature[a]	Alternative nomenclature[a]	Protein	Nucleotide changes, Gene	RFLP	Effect	Enzyme activity	
						In_vivo	*In_vitro*
*CYP2E1*1A*	*CYP2E1*1*	CYP2E1.1	None			Normal	Normal
*CYP2E1*1B*	*CYP2E1*2*	CYP2E1.1	9896C > G	*Taq*I-			
*CYP2E1*1C*		CYP2E1.1	6 repeats in the 5′ flanking region				
*CYP2E1*1D*		CYP2E1.1	8 repeats in the 5′ flanking region	*Dra*I and *Xba*I		Incr. activity after alcohol exposure and in obese subjects	
*CYP2E1*2*		CYP2E1.2	1132G > A		R76H		Reduced
*CYP2E1*3*		CYP2E1.3	10023G > A		V389I		Normal
*CYP2E1*4*		CYP2E1.4	4768G > A		V179I		Normal
*CYP2E1*5A*		CYP2E1.1	–1293G > C; –1053C > T (c1 > c2); 7632T > A	*Pst*I+ *Rsa*I- *Dra*I-			
*CYP2E1*5B*	*CYP2E1*3*	CYP2E1.1	–1293G > C; –1053C > T (c1 > c2)	*Pst*I+ *Rsa*I-			
*CYP2E1*6*	*CYP2E1*4*	CYP2E1.1	7632T > A	*Dra*I-			
*CYP2E1*7A*		CYP2E1.1	–333T > A				
*CYP2E1*7B*		CYP2E1.1	–71G > T; –333T > A				
*CYP2E1*7C*		CYP2E1.1	–333T > A; –352A > G				
not included	*CYP2E1*5*						
not included	*CYP2E1*6*						

[a] Two different nomenclature systems were developed for the CYP2E1 alleles simultaneously. The authors of both nomenclature systems have agreed in July 2000 that the nomenclature system given in the first column should be the recommended one, see Ingelman-Sundberg *et al.* (2001); the other nomenclature that was proposed by Garte & Crosti (1999) is given in the second column.

RFLP, restriction fragment length polymorphism

Adapted from http://www.cypalleles.ki.se/cyp2e1.htm

been located in the liver and pancreas, and in the liver and duodenum, for FAEEs and AEAT, respectively (Diczfalusy *et al.*, 2001). Lower activities of both enzymes were found in heart, lung, adipose, gall bladder and gastric tissues. Although FAEE may be important in the etiology of alcohol-mediated cellular toxicity, especially in the case of long-term accumulation during chronic alcohol intake, the relative contribution to overall alcohol elimination is rather small. In addition to FAEEs, alcohol also forms other conjugates, such as ethyl glucuronide, often used as a marker for recent alcohol drinking (Wurst *et al.*, 2003).

4.1.2 Acetaldehyde

Acetaldehyde is the first metabolite in the oxidation of ethanol (Fig. 4.1). Interindividual variations of the acetaldehyde-mediated effects will depend on the genetic polymorphisms and other factors affecting the metabolism and levels of acetaldehyde, and the effects on the target organs.

(a) Origin of acetaldehyde

(i) Endogenous formation

Several degradation reactions are known to form endogenous acetaldehyde in the human body (Krebs & Perkins, 1970). Without external alcohol ingestion, acetaldehyde concentrations are below the level of detection, except in the gastrointestinal tract (Väkeväinen *et al.*, 2000). However, under conditions of inhibited acetaldehyde-oxidation capacity, endogenous acetaldehyde levels may be detected in the blood (Eriksson, 1985). The relevance of the endogenous acetaldehyde is further discussed in Section 4.3.1.

(ii) Acetaldehyde in alcoholic beverages

A small part of the total acetaldehyde to which the body is exposed comes directly from ingested alcoholic beverages. All alcoholic beverages contain acetaldehyde in variable amounts: average levels in different types vary between 60 to > 7000 µM (Lachenmeier & Sohnius, 2008). The magnitude and the significance of exposure to acetaldehyde from alcoholic beverages are further discussed in Section 4.3.1.

(iii) Acetaldehyde formation by oxidation of exogenous ethanol

The major part of the total acetaldehyde to which the body is exposed during alcohol ingestion originates from ethanol oxidation catalysed by the ADH, CYP2E1 and catalase enzymes. The liver and the gut are the primary sites of acetaldehyde formation to such an extent that the rate of alcohol oxidation exceeds the rate of acetaldehyde breakdown, which consequently leads to diffusion of the surplus acetaldehyde into the bloodstream. Under normal conditions, i.e. without reduced capacity for acetaldehyde oxidation or considerably increased acetaldehyde formation, the acetaldehyde produced at other sites is usually directly oxidized within the tissue. The exception is the aerodigestive tract, where acetaldehyde is produced at least partly by microbial alcohol oxidation. Consequently, acetaldehyde can be detected both in breath and saliva during alcohol intoxication (Eriksson, 2007).

(b) Metabolism

The bulk of the acetaldehyde formed in the liver is directly oxidized by NAD^+-dependent aldehyde dehydrogenases (ALDHs) to acetate. The efficacy of normal hepatic oxidation of the alcohol-derived acetaldehyde is estimated to be close to 99% (Eriksson & Fukunaga, 1993). In addition, a minor part of the acetaldehyde is probably oxidized by aldehyde oxidase and CYP2E1. In addition, acetaldehyde reacts with a variety of chemical compounds in the body.

(i) Aldehyde dehydrogenase pathway

Acetaldehyde is metabolized by ALDHs (Fig. 4.1), which are widely expressed in the mitochrondria (low-K_m enzyme) and cytosol (high-K_m enzyme) of most tissues (Crabb, 1995). Oxidation of acetaldehyde is regulated by the rate of acetaldehyde formation, ALDH activity and the cytosolic and mitochondrial redox states. Ethanol consumption is not known to induce *ALDH* expression. Chronic alcohol abuse, especially associated with liver disease, has been reported to reduce the ALDH activity (Nuutinen *et al.*, 1983).

The major allelic variants of human ALDHs, their respective K_m and their ethnical distribution are summarized in Table 4.3. The high-K_m ALDH1A1 accounts for most of the acetaldehyde-oxidizing capacity in the cytosolic compartment of the liver and other tissues. This enzyme is also abundant in the erythrocytes. Several variant alleles of *ALDH1A1* with potential functional relevance have recently been reported in the promoter (Spence *et al.*, 2003), intron and untranslated regions (Lind *et al.*, 2008) (Table 4.1).

The low-K_m (about 5 μM for acetaldehyde) ALDH2 is located in the mitochondria and is believed to be responsible for the bulk of the oxidation of the ethanol-derived acetaldehyde. This enzyme is not significantly expressed in the erythrocytes. Of all the polymorphisms in genes encoding enzymes that metabolize alcohol and acetaldehyde, the *ALDH2*2* allele has the greatest functional impact on the human phenotype. This allele is common in East-Asian populations, about 5–10% homozygotes and 30–40% heterozygotes (Brennan *et al.*, 2004). In these individuals the acetaldehyde levels are elevated, which creates several toxic effects and also euphoric reinforcing reactions (Eriksson, 2001). The relevance of the elevated acetaldehyde for the development of cancers is discussed in section 4.3.1. In addition to the **2* allele, promoter-region variants have been reported (Harada *et al.*, 1999). The functional significance of these other variants remains to be established. The relevance of other ALDHs, including ALDH1B1 and other classes of ALDH, also remains to be elucidated.

(ii) Other pathways in the metabolism and reactions of acetaldehyde

In addition to the ALDH-catalysed reactions, acetaldehyde may also be oxidized to a minor extent by CYP2E1 (Terelius *et al.*, 1991) and by different oxidases (Deitrich *et al.*, 2007).

Due to its chemical reactivity, most, if not all, of the ethanol-derived acetaldehyde that is not further oxidized binds to a variety of constituents. These interactions vary between easily reversible and firm covalent bonds. Different kinds of Schiff's base, which are formed by acetaldehyde and the free amino groups of amino acids, peptides and proteins, are the most common products (Eriksson & Fukunaga, 1993, Niemelä, 2007). Some of these unstable products become stable under reducing conditions, such as during alcohol intoxication. Although only a small fraction of all acetaldehyde formed during ethanol oxidation produces these adducts, they are important in some of the chronic toxic actions of alcohol. The role of the acetaldehyde adducts in the carcinogenic effects of alcohol is further discussed in Sections 4.2.2, 4.3.1 and 4.4.2.

(c) Levels of acetaldehyde in tissues

From the liver, where most of the ethanol-derived acetaldehyde is formed and oxidized, the remaining acetaldehyde, free and/or loosely bound, escapes into the *vena hepatica*, reaching concentrations of approximately 70 μM under normal conditions (Eriksson & Fukunaga, 1993). Thereafter, the concentration of acetaldehyde in the blood will be diluted by the *vena cava* blood and further reduced by the circulation in the heart and the lungs before reaching peripheral tissues. Human data show that acetaldehyde levels in pulmonary arterial blood are in the

Table 4.3 Major allelic variants, biochemical properties, and ethnical distribution of human acetaldehyde dehydrogenases (ALDHs)

Gene Locus	Allele	Km μM[a]	Ethnic/national distribution[b]	References
ALDH1A1		50	All	Vasiliou *et al.* (2000)
ALDH2	*ALDH2*1*	< 5	All	
	*ALDH2*2*		Asia	Crabb *et al.* (1989)
	*ALDH2*3*		Taiwan, People's Republic of China	Novoradovsky *et al.* (1995)
ALDH1B1 (ALDH5)	*ALDH1B1*1*	NR		
	*ALDH1B1*2*	NR		Sherman *et al.* (1993)
ALDH9A1	*ALDH9A1*1*	30	All	Kurys *et al.* (1989)
	*ALDH9A1*2*			Lin (1996)

[a] Kinetic constant of the enzyme when acetaldehyde is the substrate
[b] The column labelled ethnic/national distribution indicates which populations have high allele frequencies for these variants. The alleles are not limited to those populations.
NR, not reported
Compiled by the Working Group

range of 0–4.4 μM, 30 and 60 minutes after ethanol consumption (DeMaster *et al.*, 1983) during normal alcohol oxidation. Acetaldehyde in peripheral arterial or venous blood is below the limit of detection (< 1 μM) during normal alcohol intoxication in Caucasian male populations (Eriksson & Fukunaga, 1993). However, in Caucasian women, acetaldehyde levels of 1–8 μM have been detected during the use of oral contraceptives and during the high-estradiol phase of the normal cycle (Eriksson *et al.*, 1996).

Except for the blood and the liver, in which acetaldehyde concentration should be approximately the same as in the *vena hepatica*, little is known about acetaldehyde levels in other tissues during normal alcohol oxidation in humans. Acetaldehyde levels should rise in tissues where the ethanol oxidation rate exceeds the capacity of acetaldehyde oxidation. Breath acetaldehyde concentrations of 10–20 and 20–40 nM at blood alcohol levels of about 10 and 20 mM, respectively, imply corresponding tissue acetaldehyde levels of 2–8 μM in the respiratory tract (Jones, 1995; Eriksson, 2007). Part of this acetaldehyde is derived by microbial ethanol oxidation (Pikkarainen *et al.*, 1980). Also, acetaldehyde levels in the saliva, which almost exclusively are derived from microbiological alcohol oxidation, correlate positively with the blood alcohol concentration (Väkeväinen *et al.*, 2001; Eriksson, 2007). Levels varying between 15 to 25 μM and 20 to 40 μM at corresponding blood ethanol concentrations of 10 to 20 mM, respectively, have been reported (Homann *et al.*, 1997; Eriksson, 2007). The role of the acetaldehyde concentrations in the upper aerodigestive tract in the carcinogenic effects of alcohol is discussed in Section 4.3.1.

Under certain conditions, such as chronic alcohol consumption especially in combination with increased alcohol oxidation rate and/or liver disease and genetically determined deficiency in the ALDHs, acetaldehyde levels are considerably elevated. Peripheral venous blood acetaldehyde concentrations of 14 μM have been detected during alcohol intoxication (after a dose of 0.8 g per kg) in alcoholics (Nuutinen *et al.*, 1984). In Asian subjects carrying the ALDH*2 allele, blood acetaldehyde levels above 200 μM have been reported (Eriksson & Fukunaga, 1993). In addition to ALDH2 polymorphism, the *ADH1B*2* and *ADH1C*1* variant alleles, which encode more active ADHs, in turn may elevate ethanol-derived acetaldehyde levels. This possibility was suggested by Visapää *et al.* (2004) who

reported increased acetaldehyde concentrations in saliva of individuals with the *ADH1C*1/*1* genotype. The relevance of the *ALDH* and *ADH* genotypes for the etiology of cancer is further discussed in Section 4.3.1.

4.2 Genotoxicity

4.2.1 Humans

Studies of genotoxic effects of alcoholic beverages have been reviewed (Obe & Anderson, 1987; IARC, 1988, 2010).

(a) Genotoxic effects in alcoholics

Maffei *et al.* (2000, 2002) and Castelli *et al.* (1999) found that alcoholics had significantly more chromosomal aberrations and cells with micronuclei than either non-drinking controls or abstinent alcoholics. The three groups were matched for age, sex and smoking (Maffei *et al.*, 2002). When centromeric fluorescence in situ hybridization (FISH) was combined with the analysis of micronuclei, the alcoholics showed an increase in the number of lymphocytes with centromere-positive micronuclei, indicating an elevated formation of micronuclei harbouring whole chromosomes, ie, an aneugenic effect (Maffei *et al.*, 2000). In a combined analysis of three biomonitoring studies, Iarmarcovai *et al.* (2007) observed a small but significant increase in micronucleus frequency in alcoholic beverage users compared with controls (OR, 1.24; 95%CI: 1.01–1.53).

While the majority of published studies showed no increase in chromosomal alterations in alcoholics following abstinence from ethanol compared to non-drinkers, some studies reported positive results (De Torok, 1972; Matsushima, 1987). Gattás & Saldanha (1997) compared the frequency of structural or numerical chromosomal aberrations in lymphocytes of alcoholics who had been abstinent for 1 month to 32 years, with those in subjects not consuming alcoholic beverages. They noted a significant increase in the frequency of cells with structural chromosomal aberrations in the abstinent alcoholics. Burim *et al.* (2004) observed that the frequencies of chromosomal aberrations in lymphocytes of 29 chronic alcoholics and 11 alcoholics in abstinence were higher than those in 10 control individuals. The level of chromosomal aberrations was not statistically significantly different when smoking and non-smoking alcoholics were compared, which indicated a lack of interaction.

There is some indication that ethanol may lead to chromosomal aneuploidy in human sperm. Robbins *et al.* (1997) used FISH of the sex chromosomes and chromosome 18 to investigate the potential contribution of common lifestyle exposures to aneuploidy load in sperm from 45 healthy male volunteers. Consumption of alcoholic beverages was significantly associated with increased frequencies of aneuploidy XX18, XY18–18 apparent diploidy, or XX18–18 duplication phenotype, after controlling for caffeine, smoking and donor age.

Härkönen *et al.* (1999) reported a significant negative association between alcohol intake and sperm aneuploid for chromosomes 1 and 7 (1-1-7 and 1-7-7 constitutions and diploid sperm) among 30 agricultural workers before pesticide exposures, while no statistically significant findings were related to alcohol intake after the exposure. [These inconclusive findings may reflect moderate alcohol consumption (average 6 drinks/week).]

In a case–control study Kagan-Krieger *et al.* (2002) found no association between self-reported paternal or maternal alcohol consumption and Turner syndrome in offspring.

Pool-Zobel *et al.* (2004) used the comet assay to study DNA damage and repair in human rectal cells obtained from biopsies and found that male alcoholic beverage abusers had significantly less DNA strand-breaks than male controls. This may be the result of an enhancing effect on endogenous defence, e.g. through upregulation of DNA

repair in response to damage. [Alternatively, a reduced amount of DNA in the comet tails could reflect DNA–protein crosslinks resulting from exposure to endogenous acetaldehyde.]

van Zeeland *et al.* (1999) and Lodovici *et al.* (2000) did not detect any increase in 8-hydroxydeoxyguanosine (8-OHdG) levels [measure of oxidative DNA damage] in leukocyte DNA in relation to alcoholic beverage consumption. In a multicentre study in Europe, Bianchini *et al.* (2001) observed an inverse relationship between alcoholic beverage consumption and levels of 8-OHdG in leukocyte DNA. However, an increased level of 8-OHdG in leukocyte DNA was observed in ALDH2-deficient subjects who consumed alcoholic beverages (Nakajima *et al.*, 1996).

Frank *et al.* (2004) reported a significant increase in 1,N^6-ethenodeoxyadenosine DNA adducts in seven subjects diagnosed with alcoholic fatty liver and three diagnosed with alcoholic fibrosis. Patients with alcoholic fibrosis had a much higher level of these adducts than patients with alcoholic fatty liver. [No diagnostic criteria were provided for patients identified as 'alcoholic'.]

Wang *et al.* (2009) observed that protein-bound 4-hydroxynonenal [a major lipid peroxidation product] and both 1,N^6-ethenodeoxyadenosine and 3,N^4-ethenodeoxycytidine DNA adducts strongly correlated with CYP2E1 expression in fine-needle liver biopsy samples obtained from 14 German patients with alcoholic liver disease (r = 0.97, P < 0.01). [The results support the assumption that, particularly in non-Asian populations, ethanol-mediated induction of hepatic CYP2E1, leading to highly miscoding DNA lesions derived from lipid peroxidation, may play a central role in hepatocarcinogenesis in patients with alcoholic liver disease.]

A statistically significantly higher frequency of sister chromatid exchange in lymphocytes was observed in Japanese subjects deficient in *ALDH2* (at least one **2* allele) compared to those who were proficient in *ALDH2* (**l/*l* genotype) and drank alcohol almost daily; such an effect was not seen in subjects who drank less or did not drink at all (Morimoto & Takeshita, 1996).

(b) *Effects of polymorphisms for metabolic enzymes*

A significant difference in micronucleus frequency between the *ALDH2*2* allele carriers and the individuals carrying the *ALDH2*1/*1* genotype was found at all levels of alcohol consumption; the highest micronucleus levels were seen in the *ALDH2*2* allele carriers consuming more than 100 g of alcohol per week and more than 3 times a week (Ishikawa *et al.*, 2003).

In non-smoking regular or occasional Japanese drinkers, the frequency of micronuclei was shown to be higher in *ALDH2*2/*2* homozygotes versus *ALDH2*2/*1* heterozygotes and in *ADH1B*1/*1* homozygotes versus *ADH1B*1/*2* heterozygotes. The highest micronucleus levels were seen in regular drinkers carrying both the *ALDH2*2* and *ADH1B*1* alleles. Nonetheless, due to the low number of subjects, a statistically significant increase of micronuclei was only seen for regular drinkers who carry the more common combination, i.e. *ALDH2*2* and *ADH1B*2* alleles (Ishikawa *et al.*, 2007).

Regular drinkers with the *CYP2E1*1/*1* genotype showed a significantly higher micronucleus frequency than drinkers carrying the *CYP2E1*3* allele; and drinkers with combined *ALDH2*2* and *CYP2E1*1/*1* genotypes showed the highest micronucleus frequency (Ishikawa *et al.*, 2006).

4.2.2 Experimental systems

(a) *Ethanol*

The genotoxic potential of ethanol has been extensively evaluated in lower organisms, plants, mammalian systems and in human cells, as reviewed previously (IARC, 1988, 2010; Phillips & Jenkinson, 2001).

Ethanol gave negative results in bacterial mutagenicity tests, even in the presence of exogenous metabolic activation systems. These findings are consistent with the negative findings obtained with acetaldehyde, the primary *in vivo* metabolite of ethanol, in bacterial genotoxicity assays (IARC, 2010).

Positive results were reported for the induction of DNA strand breaks and chromosome malsegregation by ethanol in fungi and sister chromatid exchange in plants without exogenous metabolic activation. [These findings were obtained at very high concentrations (16000–39100 μg/ml) exceeding those usually recommended as the highest allowable concentrations in genotoxicity testing.]

In mammalian cells *in vitro*, ethanol was not usually able to produce gene mutations or chromosomal aberrations, but one study in mouse preimplantation embryos *in vitro* showed an induction of sister chromatid exchanges and chromosomal aberrations. In these experiments, sister chromatid exchange disappeared in the presence of 4-methylpyrazole, an inhibitor of alcohol dehydrogenase. This suggests that preimplantation embryos are able to convert ethanol to acetaldehyde.

A single study reported ethanol-induced DNA strand breaks in various types of human cells (Blasiak *et al.*, 2000). The majority of studies showed no induction of chromosome damage by ethanol in human lymphocytes and lymphoblastoid cells *in vitro*. [The Working Group noted that in most of the *in vitro* genotoxicity studies, external metabolic activation systems were not used, which reduces the value of the negative findings.]

Ethanol induced micronuclei in human lymphoblastoid cells without external metabolic activation (Kayani & Parry, 2010). This effect appeared to be independent of acetaldehyde, since the micronuclei mostly contained whole chromosomes, while those induced by acetaldehyde harboured chromosomal fragments. Thus, ethanol produced micronuclei *in vitro* by an aneugenic mechanism while acetaldehyde was clastogenic.

In animals *in vivo*, ethanol induced DNA adducts, DNA strand breaks, and sister chromatid exchanges and dominant lethal mutations. No effect of ethanol was seen in the micronucleus or chromosome aberration assays *in vivo*. In rats, exposure to ethanol increased mitochondrial DNA (mt DNA) oxidation and decreased the amount of mt DNA (Cahill *et al.*, 1997, 2005). Several studies showed that the administration of ethanol to rats and mice leads to changes in the activity and amount of DNA-repair proteins in the liver (Navasumrit *et al.*, 2001a; Bradford *et al.*, 2005).

The ethanol-induced DNA single-strand breaks in liver parenchymal cells of rat closely matched the timing of CYP2E1 induction and was inhibited by dietary antioxidants (Navasumrit *et al.*, 2000). Ethanol also increased the level of the lipid peroxidation-derived DNA adduct, ethenodeoxycytidine in rats (Navasumrit *et al.*, 2001b) and N^2-ethyl-2′-desoxyguanosine (N^2EtdG) adducts, not detectable in controls, were seen in liver DNA of ethanol-treated mice (Fang & Vaca, 1995). Rats and mice fed ethanol showed increased levels of oxidative DNA damage (abasic sites and 8-hydroxydeoxyguanosine) in the liver (Bradford *et al.* 2005); this effect was observed in transgenic mice that expressed human CYP2E1, but not in CYP2E1-knockout mice or in the presence of a CYP2E1 inhibitor. Increased levels of 1,N^6-ethenodeoxyadenosine and 3,N^4-ethenodeoxycytidine DNA adducts (measured by immunohistochemistry) were observed in the liver of ethanol-fed lean (Fa/Fa) and obese (fa/fa) Zucker rats (Wang *et al.*, 2009). The number of hepatocyte nuclei that stained positively for these etheno-DNA adducts correlated significantly with CYP2E1 expression.

(b) Acetaldehyde

Numerous *in vitro* studies have consistently shown that acetaldehyde causes DNA–protein crosslinks, DNA strand breaks, DNA adducts, sister chromatid exchanges, chromosomal aberrations, and micronuclei in eukaryotic cells *in vitro* (Speit *et al.*, 2008; Kayani & Parry, 2010; IARC, 2010). In comparison with other assays, the comet assay requires relatively high concentrations of acetaldehyde to show a positive result, probably reflecting the formation of crosslinks (Speit *et al.*, 2008).

Acetaldehyde induced also DNA protein crosslinks, sister chromatid exchanges, and chromosomal aberrations in rodents *in vivo* (IARC, 2010).

4.2.3 Genotoxicity of acetaldehyde

(a) DNA adduct formation

The structure of acetaldehyde-derived DNA adducts is depicted in Fig. 4.2.

(i) N^2-Ethyl-2′-deoxyguanosine (N^2EtdG)

The most abundant DNA adduct that results from the reaction of acetaldehyde is N^2-ethylidenedeoxyguanosine (N^2EtidG). This adduct is too unstable to be purified and isolated, but can be converted into the stable adduct N^2EtdG, by treatment with a reducing agent (sodium cyanoborohydride). The reduction step can also be carried out by a mixture of GSH and ascorbic acid, which may occur *in vivo* (Fang & Vaca, 1995; Wang *et al.*, 2006c).

Fang & Vaca (1997) examined the levels of the N^2EtdG adduct in a group of Swedish alcohol abusers compared to controls. They found that chronic alcoholics had higher levels of the N^2EtdG adduct in both lymphocytes and granulocytes compared with controls. The levels of adduct found in both cell types were on the order of one lesion/10^7 nucleotides. [The Working Group noted that the alcoholic subjects were also heavy smokers, whereas the control subjects were not. However, the authors reported that N^2EtdG levels were undetectable in the DNA sample from the one moderate smoker in the control group, and also stated that no adducts were detectable in samples obtained from five additional heavy smokers (> 20 cigarettes/week)].

Inclusion of a reducing agent (cyanoborohydride) in the DNA isolation and digestion solutions allowed N^2EtidG to be converted quantitatively to N^2EtdG. Wang *et al.* (2006c) concluded that N^2EtidG is in fact an endogenous DNA adduct that is present in every animal and human liver DNA at levels in the range of 0.1 lesion/10^6 normal nucleotides.

Balbo *et al.* (2008) measured the level of N^2-EtdG in blood leukocyte DNA of two groups of subjects, one consisting of alcohol drinkers and abstainers and the other of heavy drinkers. A significant trend between N^2-EtdG level and daily alcohol dose was found. In the first group, the mean level of N^2-EtdG was significantly higher in drinkers (5270 ± 8770 fmol/μmol dG) than in non-drinkers (2690 ± 3040 fmol/μmol dG; $P = 0.04$) after adjusting for potential confounders. Taking into account the dose, the adduct level was higher in younger than older drinkers.

Matsuda *et al.* (1999) reported that detectable levels of N^2EtdG were found in the urine of healthy Japanese individuals who had abstained from ethanol for at least 1 week. These authors proposed that the lesion resulted from endogenously formed acetaldehyde.

(ii) Other acetaldehyde-derived DNA adducts

In addition to the major adduct N^2EtidG, three acetaldehyde-derived DNA adducts have been identified. These are: N^2-(2,6-dimethyl-1,3-dioxan-4-yl) deoxyguanosine (N^2-Dio-dG); an interstrand crosslink, and two diastereisomers (R and S) of α-methyl-γ-hydroxy-1,N^2-propanodeoxyguanosine (α-Me-γ-OH-PdG) (Wang *et al.*, 2000).

Matsuda *et al.* (2006) analysed the levels of acetaldehyde-derived DNA adducts in DNA samples from peripheral white blood cells of Japanese alcoholic beverage abusers with two different *ALDH2* genotypes: **1/*1* versus **1/*2*. The groups were matched by age, smoking and alcoholic beverage consumption. These authors developed very sensitive and specific liquid chromatograph–mass spectrometry assays for the DNA adducts: N^2EtdG, α-Me-γ-OH-PdG (both R and S isomers) and N^2-Dio-dG. The N^2-Dio-dG adduct was not detected in any of the samples studied. Levels of the other three adducts were significantly higher in **1/*2* carriers than in **1/*1* genotypes.

The formation of the methyl-hydroxypropano-dG adducts can be facilitated by including basic amino acids, histones (which are rich in basic amino acids), or polyamines in the reaction mixture. In the presence of physiologically relevant polyamine concentrations, detectable amounts of these adducts were formed from concentrations as low as 100 μM acetaldehyde (Theruvathu *et al.*, 2005). Such concentrations are within the range of acetaldehyde concentrations formed in the saliva of human volunteers who drank alcoholic beverage in a laboratory setting (Homann *et al.*, 1997). Finally, acetaldehyde can react with malondialdehyde, and the resulting conjugate can form DNA adducts *in vitro* (Pluskota-Karwatka *et al.*, 2006).

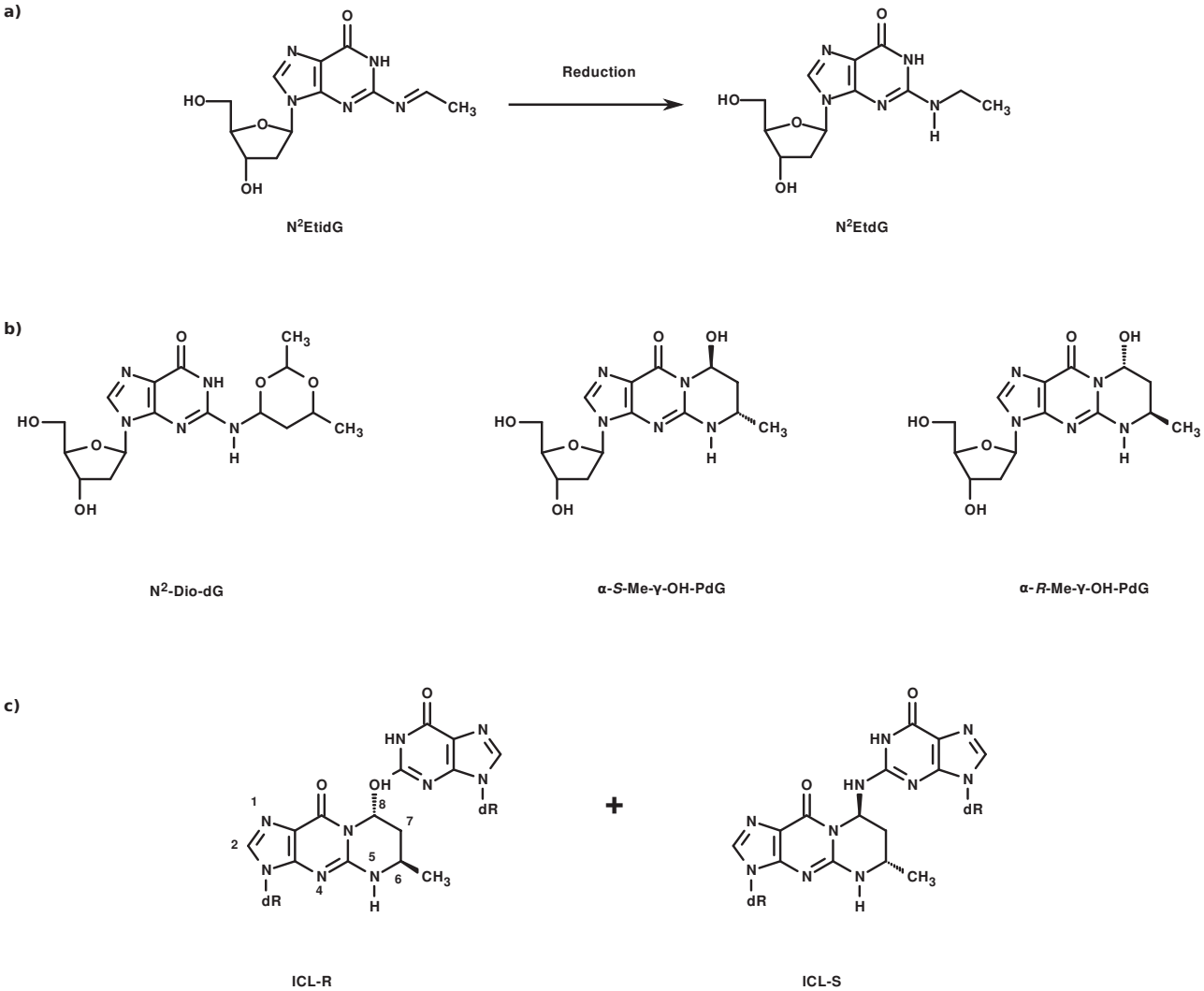
(b) *Mutagenicity of acetaldehyde-derived DNA adducts*

The mutagenic potential of DNA adducts can be tested with single-stranded DNA vectors that contain a single adduct located within a reporter gene. These constructs can then be transfected into cells, allowed to replicate and the resulting replication products analysed for mutations in various ways, depending on the specific nature of the reporter gene. Using such an approach, the N^2EtdG adduct was only minimally mutagenic to the *supF* gene in the reporter plasmid pLSX (mean mutant fraction, 0.9 ± 0.2% for the adduct-containing construct versus 0.4 ± 0.2% for the lesion-free control) when replicated in *E. coli* ($P = 0.09$). When deoxyuridines were placed on the complementary strand at 5′ and 3′ positions flanking the adduct, the mutant fractions increased to 1.4 ± 0.5% for the lesion versus 0.6 ± 4% for the control ($P = 0.04$) (Upton *et al.*, 2006). The mutation spectrum generated by the N^2EtdG adduct included mainly G to T transversions and single base deletions three bases downstream from the adduct. [This study was carried out with N^2EtdG, whereas, *in vivo*, most probably N^2EtidG is formed predominantly.]

Two separate studies have shown that methylhydroxypropano-dG adducts result in mutant fractions of 5–11% when inserted into a shuttle vector and replicated in either monkey kidney cells (Fernandes *et al.*, 2005) or human xeroderma pigmentosum A (XPA) cells (Stein *et al.*, 2006). In both cases, the predominant mutagenic event observed was a G to T transversion, but G to A and G to C mutations were also found. In comparison, the ethenodeoxyadenosine adduct resulted in mutant fractions as a high as 70% in COS7 monkey kidney cells (Pandya & Moriya, 1996), but the mutant fraction was only 7–14% in human cells (Levine *et al.*, 2000). [Methodological differences, differences in the host cells used or in the local sequence in the shuttle vectors may be responsible for the results.]

An important feature of the methylhydroxypropano-dG adducts, which is not shared by N^2EtidG or N^2EtdG, is that these adducts can undergo ring-opening when located in double-stranded DNA (Mao *et al.*, 1999). The ring-opened forms of the methylhydroxypropano-dG adducts can react with proteins to generate DNA–protein crosslinks (Kurtz & Lloyd, 2003). With a deoxyguanosine residue in the opposite strand of the helix, a DNA-intrastrand crosslink can be formed (Wang *et al.*, 2000). Intrastrand crosslinks generated in this manner are also mutagenic (mutant fraction 3–6%) in mammalian cells, generating

Fig. 4.2 Structure of acetaldehyde-derived DNA adducts



a) The immediate reaction of acetaldehyde with DNA is the unstable Schiff base adduct, N^2-ethylidene-2-deoxyguanosine (N^2EtidG). This adduct is reduced into the more stable N^2-ethyl-2-deoxyguanosine (N^2EtdG), the most abundant acetaldehyde-derived DNA adduct.
b) Three additional acetaldehyde-derived DNA adducts: N^2-(2,6-dimethyl-1,3-dioxan-4yl) deoxyguanosine (N^2-Dio-dG) and the two diastereisomers (R and S) of α-methyl-8-hydroxy-1,N^2-propanodeoxyguanosine (α-Me-γ-OH-PdG).
c) Structure of R and S interstrand crosslinks (ICL-R) and ICL-R).
Adapted from Wang *et al.* (2006c) and Matsuda *et al.* (2006).

primarily G to T transversions, as well as deletion and insertion mutations (Liu *et al.*, 2006). Matsuda *et al.* (1998) exposed plasmid DNA that contains a *supF* mutation reporter gene to acetaldehyde concentrations up to 1M, and allowed the plasmid to replicate in human XPA cells, which are deficient in nucleotide excision repair. In contrast to the results for the methylhydroxypropano-dG adducts, these authors observed specific tandem GG to TT mutations. The DNA lesions responsible for these mutations are most probably not propano-dG adducts, but the intrastrand crosslinks.

4.3 Synthesis: Mechanistic considerations

Although alcoholic beverages may contain several potentially carcinogenic compounds, this synthesis focuses on the role of ethanol and acetaldehyde in the carcinogenesis associated with alcoholic beverages.

4.3.1 Ethanol-related mechanisms of carcinogenesis

The role of ethanol metabolism in tumour initiation is implied by the associations observed between different forms of cancer and polymorphisms in genes involved in the oxidation of ethanol. Whether, or to what degree, these associations are explained by redox changes, formation of radicals, effects on intermediary metabolism and/or effects on other pro-carcinogens cannot be established from current findings.

(a) Oxidative stress

Ethanol-induced CYP2E1 produces various reactive oxygen species, which lead to the formation of lipid peroxidation products such as 4-hydroxy-nonenal and the condition of oxidative stress. Chronic tissue inflammation and increased iron content exacerbate these actions. The increased reactive oxygen species and oxidative stress, which damage the DNA and affect its repair, has been associated with ethanol-induced carcinogenesis in many organs, such as the breast, liver and pancreas.

(b) Cirrhosis

Ethanol causes hepatocellular injury that can lead to enhanced fibrogenesis and finally cirrhosis. Liver cirrhosis is strongly associated with an increased risk for developing hepatocellular carcinoma. Ethanol-related hepatocellular carcinoma without pre-existing cirrhosis is rare, which indicates that the pathogenic events that lead to cirrhosis precede those that cause cancer, or that the structural alterations in the liver during cirrhosis, together with other factors, favour the transformation of hepatocytes.

(c) Interaction between alcohol and tobacco smoking

This aspect is discussed in Section 4 of the *Monograph* on Tobacco Smoking in this Volume.

(d) Ethanol and sex hormones

Estrogens and androgens are well known activators of cellular proliferation, which is associated with an increased risk for carcinogenesis. Alcoholic beverage consumption in women causes an increase in the levels of estrogen and androgen, which has been suggested to contribute to the development of breast cancer. ADH-mediated alcohol oxidation, which increases the hepatic redox state, which in turn inhibits catabolism of sex steroids, has been suggested as the mechanism for the alcohol-mediated elevation in steroid levels.

(e) Folate metabolism and DNA methylation

Folate deficiency is associated with different forms of cancer, of which cancer of the colon is the most common. Ethanol per se, and an underlying unhealthy lifestyle associated with high alcoholic beverage consumption, cause

folate deficiency. Several studies have shown interactions between alcohol use and polymorphisms of genes involved in folate metabolism in determining the risk for colon cancer and other cancers. The degree to which the relation between alcohol drinking, folate deficiency and cancer may be explained by the metabolism of ethanol is not known.

Other postulated modes of action of ethanol relevant to its carcinogenicity, such as tumour promotion, induction of the formation of polyunsaturated fatty acids, overproduction of mitogen-activated protein kinases, and effects on vitamin A (retinol) or insulin-like growth factors have not been rigorously established by published studies.

4.3.2 The role of acetaldehyde in alcohol-induced carcinogenesis

Over the past decade, epidemiological evidence of enhanced cancer risks among heterozygous carriers of the inactive ALDH enzyme has become much stronger, in particular for oesophageal cancer: practically all studies conducted in East-Asian populations who consumed alcoholic beverages show significantly increased odds ratios for carriers of the inactive ALDH allele. In addition, several studies have demonstrated associations between the polymorphism of ADH1B and upper aerodigestive tract cancers, which have been explained either by more active ADH producing more acetaldehyde or by less active ADH causing prolonged exposure to lower levels of ethanol-derived acetaldehyde. These data imply that acetaldehyde is the key compound in the development of cancers of the oesophagus and other upper aerodigestive tract cancers associated with alcoholic beverage consumption. The considerations that support this suggestion are:

1. there is an established causal relationship between alcoholic beverage consumption and cancers of the oesophagus, oral cavity, pharynx and larynx;
2. it is generally accepted that ethanol in alcoholic beverages is the principal ingredient that renders these beverages carcinogenic;
3. in the body, ethanol is converted by ADH and CYP2E1 to acetaldehyde, which is oxidized by ALDH to acetate;
4. the formation of acetaldehyde starts in the mouth, mediated mostly by oral bacteria, and continues along the digestive tract;
5. the main production of acetaldehyde occurs in the liver and in the gut. However, the highest levels of acetaldehyde after consumption of alcoholic beverages are found in the saliva of the oral cavity, which is in the vicinity of the target organ sites known to be susceptible to ethanol-induced cancer.
6. the upper digestive tract is also the site that is in first contact with the acetaldehyde content of the alcoholic beverages, which in turn are known to increase the salivary acetaldehyde levels;
7. acetaldehyde is a cytotoxic, genotoxic, mutagenic and clastogenic compound. It is carcinogenic in experimental animals;
8. after alcoholic beverage consumption, carriers of an inactive allele of the ALDH2 enzyme show accumulating levels of acetaldehyde in the peripheral blood, a direct consequence of their enzyme deficiency, and show increased levels of N^2EtdG and methylhydroxypropano-dG adducts in lymphocyte DNA. The latter adducts have been shown to be formed from acetaldehyde; during DNA replication, these methylhydroxypropano-dG adducts cause mutations;
9. consumers of alcoholic beverages have a higher frequency of chromosomal aberrations, sister chromatid exchange and micronucleus formation in the peripheral lymphocytes than non-consumers. These effects may be attributable to acetaldehyde, which is a clastogen;
10. several of the observations made in ALDH2-deficient individuals have been confirmed in ALDH2-knockout mice.

5. Evaluation

There is *sufficient evidence* in humans for the carcinogenicity of alcohol consumption. Alcohol consumption causes cancers of the oral cavity, pharynx, larynx, oesophagus, colorectum, liver (hepatocellular carcinoma) and female breast. Also, an association has been observed between alcohol consumption and cancer of the pancreas.

For cancer of the kidney and non-Hodgkin lymphoma, there is *evidence suggesting lack of carcinogenicity*.

There is *sufficient evidence* in humans for the carcinogenicity of acetaldehyde associated with the consumption of alcoholic beverages. Acetaldehyde associated with the consumption of alcoholic beverages causes cancers of the oesophagus and of upper aerodigestive tract combined.

There is *sufficient evidence* in experimental animals for the carcinogenicity of ethanol.

There is *sufficient evidence* in experimental animals for the carcinogenicity of acetaldehyde.

Alcohol consumption is *carcinogenic to humans (Group 1)*.

Ethanol in alcoholic beverages is *carcinogenic to humans (Group 1)*.

Acetaldehyde associated with the consumption of alcoholic beverages is *carcinogenic to humans (Group 1)*.

In reaching the second and third evaluations, the Working Group took the following into consideration:

- The epidemiological evidence of the carcinogenicity of alcoholic beverage consumption shows little indication that the carcinogenic effects depend on the type of alcoholic beverage, with ethanol being the common ingredient.
- Upon ingestion of alcoholic beverages, ethanol is converted into acetaldehyde, which is then oxidized to acetate.
- Ethanol and acetaldehyde are both carcinogenic in experimental animals.
- There is sufficient epidemiological evidence showing that humans who are deficient in the oxidation of acetaldehyde to acetate have a substantially increased risk for development of alcohol-related cancers, in particular of the oesophagus and the upper aerodigestive tract.

References

Adami HO, McLaughlin JK, Hsing AW *et al.* (1992). Alcoholism and cancer risk: a population-based cohort study. *Cancer Causes Control*, 3: 419–425. doi:10.1007/BF00051354 PMID:1525322

Akhter M, Kuriyama S, Nakaya N *et al.* (2007). Alcohol consumption is associated with an increased risk of distal colon and rectal cancer in Japanese men: the Miyagi Cohort Study. *Eur J Cancer*, 43: 383–390. doi:10.1016/j.ejca.2006.09.020 PMID:17150353

Allen NE, Beral V, Casabonne D *et al.*Million Women Study Collaborators (2009). Moderate alcohol intake and cancer incidence in women. *J Natl Cancer Inst*, 101: 296–305. doi:10.1093/jnci/djn514 PMID:19244173

Altieri A, Bosetti C, Talamini R *et al.* (2002). Cessation of smoking and drinking and the risk of laryngeal cancer. *Br J Cancer*, 87: 1227–1229. doi:10.1038/sj.bjc.6600638 PMID:12439710

Anderson LM, Carter JP, Driver CL *et al.* (1993). Enhancement of tumorigenesis by N-nitrosodiethylamine, N-nitrosopyrrolidine and N6-(methylnitroso)-adenosine by ethanol. *Cancer Lett*, 68: 61–66. doi:10.1016/0304-3835(93)90220-4 PMID:8422650

Anderson LN, Cotterchio M, Gallinger S (2009). Lifestyle, dietary, and medical history factors associated with pancreatic cancer risk in Ontario, Canada. *Cancer Causes Control*, 20: 825–834. doi:10.1007/s10552-009-9303-5 PMID:19194662

Ansems TM, van der Pols JC, Hughes MC *et al.* (2008). Alcohol intake and risk of skin cancer: a prospective study. *Eur J Clin Nutr*, 62: 162–170. doi:10.1038/sj.ejcn.1602717 PMID:17392700

Anwar WA, Abdel-Rahman SZ, El-Zein RA *et al.* (1996). Genetic polymorphism of GSTM1, CYP2E1 and CYP2D6 in Egyptian bladder cancer patients. *Carcinogenesis*, 17: 1923–1929. doi:10.1093/carcin/17.9.1923 PMID:8824515

Arndt M, Rydzanicz M, Pabiszczak M *et al.* (2008). [Distribution of alcohol dehydrogenase (ADH1C)

genotypes in subjects with tobacco smoke-associated laryngeal cancer] *Przegl Lek*, 65: 466–469. PMID:19189524

Asakage T, Yokoyama A, Haneda T *et al.* (2007). Genetic polymorphisms of alcohol and aldehyde dehydrogenases, and drinking, smoking and diet in Japanese men with oral and pharyngeal squamous cell carcinoma. *Carcinogenesis*, 28: 865–874. doi:10.1093/carcin/bgl206 PMID:17071628

Austin H, Drews C, Partridge EE (1993). A case-control study of endometrial cancer in relation to cigarette smoking, serum estrogen levels, and alcohol use. *Am J Obstet Gynecol*, 169: 1086–1091. PMID:8238164

Aze Y, Toyoda K, Furukawa F *et al.* (1993). Enhancing effect of ethanol on esophageal tumor development in rats by initiation of diethylnitrosamine. *Carcinogenesis*, 14: 37–40. doi:10.1093/carcin/14.1.37 PMID:8425269

Baglietto L, Severi G, English DR *et al.* (2006). Alcohol consumption and prostate cancer risk: results from the Melbourne collaborative cohort study. *Int J Cancer*, 119: 1501–1504. doi:10.1002/ijc.21983 PMID:16615108

Bagnardi V, Blangiardo M, La Vecchia C, Corrao G (2001). A meta-analysis of alcohol drinking and cancer risk. *Br J Cancer*, 85: 1700–1705. doi:10.1054/bjoc.2001.2140 PMID:11742491

Balbo S, Hashibe M, Gundy S *et al.* (2008). N2-ethyldeoxyguanosine as a potential biomarker for assessing effects of alcohol consumption on DNA. *Cancer Epidemiol Biomarkers Prev*, 17: 3026–3032. doi:10.1158/1055-9965.EPI-08-0117 PMID:18990745

Balder HF, Goldbohm RA, van den Brandt PA (2005). Dietary patterns associated with male lung cancer risk in the Netherlands Cohort Study. *Cancer Epidemiol Biomarkers Prev*, 14: 483–490. doi:10.1158/1055-9965.EPI-04-0353 PMID:15734976

Bandera EV, Freudenheim JL, Graham S *et al.* (1992). Alcohol consumption and lung cancer in white males. *Cancer Causes Control*, 3: 361–369. doi:10.1007/BF00146890 PMID:1617124

Bandera EV, Freudenheim JL, Marshall JR *et al.* (1997). Diet and alcohol consumption and lung cancer risk in the New York State Cohort (United States) *Cancer Causes Control*, 8: 828–840. doi:10.1023/A:1018456127018 PMID:9427425

Beji NK & Reis N (2007). Risk factors for breast cancer in Turkish women: a hospital-based case-control study. *Eur J Cancer Care (Engl)*, 16: 178–184. doi:10.1111/j.1365-2354.2006.00711.x PMID:17371428

Beland FA, Benson RW, Mellick PW *et al.* (2005). Effect of ethanol on the tumorigenicity of urethane (ethyl carbamate) in B6C3F1 mice. *Food Chem Toxicol*, 43: 1–19. doi:10.1016/j.fct.2004.07.018 PMID:15582191

Benedetti A, Parent ME, Siemiatycki J (2006). Consumption of alcoholic beverages and risk of lung cancer: results from two case-control studies in Montreal, Canada. *Cancer Causes Control*, 17: 469–480. doi:10.1007/s10552-005-0496-y PMID:16596299

Benedetti A, Parent ME, Siemiatycki J (2009). Lifetime consumption of alcoholic beverages and risk of 13 types of cancer in men: results from a case-control study in Montreal. *Cancer Detect Prev*, 32: 352–362. doi:10.1016/j.canep.2009.03.001 PMID:19588541

Bernstein JL, Thompson WD, Risch N, Holford TR (1992). Risk factors predicting the incidence of second primary breast cancer among women diagnosed with a first primary breast cancer. *Am J Epidemiol*, 136: 925–936. PMID:1456269

Berstad P, Ma H, Bernstein L, Ursin G (2008). Alcohol intake and breast cancer risk among young women. *Breast Cancer Res Treat*, 108: 113–120. doi:10.1007/s10549-007-9578-8 PMID:17468952

Bessaoud F & Daurès JP (2008). Patterns of alcohol (especially wine) consumption and breast cancer risk: a case-control study among a population in Southern France. *Ann Epidemiol*, 18: 467–475. doi:10.1016/j.annepidem.2008.02.001 PMID:18440826

Besson H, Brennan P, Becker N *et al.* (2006a). Tobacco smoking, alcohol drinking and Hodgkin's lymphoma: a European multi-centre case-control study (EPILYMPH). *Br J Cancer*, 95: 378–384. doi:10.1038/sj.bjc.6603229 PMID:16819547

Besson H, Brennan P, Becker N *et al.* (2006b). Tobacco smoking, alcohol drinking and non-Hodgkin's lymphoma: A European multicenter case-control study (Epilymph). *Int J Cancer*, 119: 901–908. doi:10.1002/ijc.21913 PMID:16557575

Bianchini F, Jaeckel A, Vineis P *et al.* (2001). Inverse correlation between alcohol consumption and lymphocyte levels of 8-hydroxydeoxyguanosine in humans. *Carcinogenesis*, 22: 885–890. doi:10.1093/carcin/22.6.885 PMID:11375894

Birley AJ, James MR, Dickson PA *et al.* (2009). ADH single nucleotide polymorphism associations with alcohol metabolism in vivo. *Hum Mol Genet*, 18: 1533–1542. doi:10.1093/hmg/ddp060 PMID:19193628

Blasiak J, Trzeciak A, Malecka-Panas E *et al.* (2000). In vitro genotoxicity of ethanol and acetaldehyde in human lymphocytes and the gastrointestinal tract mucosa cells. *Toxicol In Vitro*, 14: 287–295. doi:10.1016/S0887-2333(00)00022-9 PMID:10906435

Boccia S, Sayed-Tabatabaei FA, Persiani R *et al.* (2007). Polymorphisms in metabolic genes, their combination and interaction with tobacco smoke and alcohol consumption and risk of gastric cancer: a case-control study in an Italian population. *BMC Cancer*, 7: 206 doi:10.1186/1471-2407-7-206 PMID:17996038

Boccia S, Cadoni G, Sayed-Tabatabaei FA *et al.* (2008). CYP1A1, CYP2E1, GSTM1, GSTT1, EPHX1 exons 3 and 4, and NAT2 polymorphisms, smoking, consumption of alcohol and fruit and vegetables and risk of head

and neck cancer. *J Cancer Res Clin Oncol*, 134: 93–100. doi:10.1007/s00432-007-0254-5 PMID:17611777

Boccia S, Hashibe M, Gallì P *et al.* (2009). Aldehyde dehydrogenase 2 and head and neck cancer: a meta-analysis implementing a Mendelian randomization approach. *Cancer Epidemiol Biomarkers Prev*, 18: 248–254. doi:10.1158/1055-9965.EPI-08-0462 PMID:19124505

Boffetta P, Stellman SD, Garfinkel L (1989). A case-control study of multiple myeloma nested in the American Cancer Society prospective study. *Int J Cancer*, 43: 554–559. doi:10.1002/ijc.2910430404 PMID:2703267

Boffetta P, Ye W, Adami H-O *et al.* (2001). Risk of cancers of the lung, head and neck in patients hospitalized for alcoholism in Sweden. *Br J Cancer*, 85: 678–682. doi:10.1054/bjoc.2001.1986 PMID:11531251

Bongaerts BW, de Goeij AF, van den Brandt PA, Weijenberg MP (2006). Alcohol and the risk of colon and rectal cancer with mutations in the K-ras gene. *Alcohol*, 38: 147–154. doi:10.1016/j.alcohol.2006.06.003 PMID:16905440

Bongaerts BW, van den Brandt PA, Goldbohm RA *et al.* (2008). Alcohol consumption, type of alcoholic beverage and risk of colorectal cancer at specific subsites. *Int J Cancer*, 123: 2411–2417. doi:10.1002/ijc.23774 PMID:18752250

Boonyaphiphat P, Thongsuksai P, Sriplung H, Puttawibul P (2002). Lifestyle habits and genetic susceptibility and the risk of esophageal cancer in the Thai population. *Cancer Lett*, 186: 193–199. doi:10.1016/S0304-3835(02)00354-3 PMID:12213289

Bosron WF & Li TK (1986). Genetic polymorphism of human liver alcohol and aldehyde dehydrogenases, and their relationship to alcohol metabolism and alcoholism. *Hepatology*, 6: 502–510. doi:10.1002/hep.1840060330 PMID:3519419

Bouchardy C, Hirvonen A, Coutelle C *et al.* (2000). Role of alcohol dehydrogenase 3 and cytochrome P-4502E1 genotypes in susceptibility to cancers of the upper aerodigestive tract. *Int J Cancer*, 87: 734–740. doi:10.1002/1097-0215(20000901)87:5<734::AID-IJC17>3.0.CO;2-E PMID:10925369

Bradford BU, Kono H, Isayama F *et al.* (2005). Cytochrome P450 CYP2E1, but not nicotinamide adenine dinucleotide phosphate oxidase, is required for ethanol-induced oxidative DNA damage in rodent liver. *Hepatology*, 41: 336–344. doi:10.1002/hep.20532 PMID:15660387

Breast Cancer Association Consortium (2006). Commonly studied single-nucleotide polymorphisms and breast cancer: results from the Breast Cancer Association Consortium. *J Natl Cancer Inst*, 98: 1382–1396. doi:10.1093/jnci/djj374 PMID:17018785

Brennan P, Lewis S, Hashibe M *et al.* (2004). Pooled analysis of alcohol dehydrogenase genotypes and head and neck cancer: a HuGE review. *Am J Epidemiol*, 159: 1–16. doi:10.1093/aje/kwh003 PMID:14693654

Breslow RA, Graubard BI, Sinha R, Subar AF (2000). Diet and lung cancer mortality: a 1987 National Health Interview Survey cohort study. *Cancer Causes Control*, 11: 419–431. doi:10.1023/A:1008996208313 PMID:10877335

Briggs NC, Levine RS, Bobo LD *et al.* (2002). Wine drinking and risk of non-Hodgkin's lymphoma among men in the United States: a population-based case-control study. *Am J Epidemiol*, 156: 454–462. doi:10.1093/aje/kwf058 PMID:12196315

Brinton LA, Carreon JD, Gierach GL *et al.* (2009). Etiologic factors for male breast cancer in the U.S. Veterans Affairs medical care system database. *Breast Cancer Res Treat*, In press PMID:19330525

Brinton LA, Richesson DA, Gierach GL *et al.* (2008). Prospective evaluation of risk factors for male breast cancer. *J Natl Cancer Inst*, 100: 1477–1481. doi:10.1093/jnci/djn329 PMID:18840816

Brockmöller J, Cascorbi I, Kerb R, Roots I (1996). Combined analysis of inherited polymorphisms in arylamine N-acetyltransferase 2, glutathione S-transferases M1 and T1, microsomal epoxide hydrolase, and cytochrome P450 enzymes as modulators of bladder cancer risk. *Cancer Res*, 56: 3915–3925. PMID:8752158

Brown LM, Gibson R, Burmeister LF *et al.* (1992). Alcohol consumption and risk of leukemia, non-Hodgkin's lymphoma, and multiple myeloma. *Leuk Res*, 16: 979–984. doi:10.1016/0145-2126(92)90077-K PMID:1405712

Brown LM, Gridley G, Wu AH *et al.* (2010). Low level alcohol intake, cigarette smoking and risk of breast cancer in Asian-American women *Breast Cancer Res Treat*, 120: 203–210. doi:10.1007/s10549-009-0464-4 PMID:19597702

Brown LM, Pottern LM, Silverman DT *et al.* (1997). Multiple myeloma among Blacks and Whites in the United States: role of cigarettes and alcoholic beverages. *Cancer Causes Control*, 8: 610–614. doi:10.1023/A:1018498414298 PMID:9242477

Buch SC, Nazar-Stewart V, Weissfeld JL, Romkes M (2008). Case-control study of oral and oropharyngeal cancer in whites and genetic variation in eight metabolic enzymes. *Head Neck*, 30: 1139–1147. doi:10.1002/hed.20867 PMID:18642288

Burim RV, Canalle R, Takahashi CS *et al.* (2004). Clastogenic effect of ethanol in chronic and abstinent alcoholics. *Mutat Res*, 560: 187–198. PMID:15157656

Byers T, Marshall J, Graham S *et al.* (1983). A case-control study of dietary and nondietary factors in ovarian cancer. *J Natl Cancer Inst*, 71: 681–686. PMID:6578362

Cahill A, Hershman S, Davies A, Sykora P (2005). Ethanol feeding enhances age-related deterioration of the rat hepatic mitochondrion. *Am J Physiol Gastrointest Liver Physiol*, 289: G1115–G1123. doi:10.1152/ajpgi.00193.2005 PMID:16020655

Cahill A, Wang X, Hoek JB (1997). Increased oxidative damage to mitochondrial DNA following chronic ethanol consumption. *Biochem Biophys Res Commun*, 235: 286–290. doi:10.1006/bbrc.1997.6774 PMID:9199183

Cai L, You NC, Lu H *et al.* (2006). Dietary selenium intake, aldehyde dehydrogenase-2 and X-ray repair cross-complementing 1 genetic polymorphisms, and the risk of esophageal squamous cell carcinoma. *Cancer*, 106: 2345–2354. doi:10.1002/cncr.21881 PMID:16639733

Cai L, Yu SZ, Zhan ZF (2001). Cytochrome P450 2E1 genetic polymorphism and gastric cancer in Changle, Fujian Province. *World J Gastroenterol*, 7: 792–795. PMID:11854903

Cao W, Cai L, Rao JY *et al.* (2005). Tobacco smoking, GSTP1 polymorphism, and bladder carcinoma. *Cancer*, 104: 2400–2408. doi:10.1002/cncr.21446 PMID:16240451

Caro AA & Cederbaum AI (2004). Oxidative stress, toxicology, and pharmacology of CYP2E1. *Annu Rev Pharmacol Toxicol*, 44: 27–42. doi:10.1146/annurev.pharmtox.44.101802.121704 PMID:14744237

Carpenter CL, Morgenstern H, London SJ (1998). Alcoholic beverage consumption and lung cancer risk among residents of Los Angeles County. *J Nutr*, 128: 694–700. PMID:9521630

Carrière V, Berthou F, Baird S *et al.* (1996). Human cytochrome P4502E1 (CYP2E1): from genotype to phenotype. *Pharmacogenetics*, 6: 203–211. doi:10.1097/00008571-199606000-00002 PMID:8807659

Carstensen JM, Bygren LO, Hatschek T (1990). Cancer incidence among Swedish brewery workers. *Int J Cancer*, 45: 393–396. doi:10.1002/ijc.2910450302 PMID:2407667

Cartwright RA, McKinney PA, O'Brien C *et al.* (1988). Non-Hodgkin's lymphoma: case control epidemiological study in Yorkshire. *Leuk Res*, 12: 81–88. doi:10.1016/S0145-2126(98)80012-X PMID:3357350

Casey R, Piazzon-Fevre K, Raverdy N *et al.* (2007). Case-control study of lymphoid neoplasm in three French areas: description, alcohol and tobacco consumption. *Eur J Cancer Prev*, 16: 142–150. doi:10.1097/01.cej.0000220629.00729.65 PMID:17297390

Castelli E, Hrelia P, Maffei F *et al.* (1999). Indicators of genetic damage in alcoholics: reversibility after alcohol abstinence. *Hepatogastroenterology*, 46: 1664–1668. PMID:10430317

Chalasani N, Baluyut A, Ismail A *et al.* (2000). Cholangiocarcinoma in patients with primary sclerosing cholangitis: a multicenter case-control study. Hepatology (Baltimore) *MD*, 31: 7–11.

Chang ET, Canchola AJ, Lee VS *et al.* (2007). Wine and other alcohol consumption and risk of ovarian cancer in the California Teachers Study cohort. *Cancer Causes Control*, 18: 91–103. doi:10.1007/s10552-006-0083-x PMID:17186425

Chang ET, Hedelin M, Adami HO *et al.* (2005). Alcohol drinking and risk of localized versus advanced and sporadic versus familial prostate cancer in Sweden. *Cancer Causes Control*, 16: 275–284. doi:10.1007/s10552-004-3364-2 PMID:15947879

Chang ET, Smedby KE, Zhang SM *et al.* (2004). Alcohol intake and risk of non-Hodgkin lymphoma in men and women. *Cancer Causes Control*, 15: 1067–1076. doi:10.1007/s10552-004-2234-2 PMID:15801490

Chao C (2007). Associations between beer, wine, and liquor consumption and lung cancer risk: a meta-analysis. *Cancer Epidemiol Biomarkers Prev*, 16: 2436–2447. doi:10.1158/1055-9965.EPI-07-0386 PMID:18006934

Chao C, Haque R, Van Den Eeden SK *et al.* (2010). Red wine consumption and risk of prostate cancer: the California men's health study. *Int J Cancer*, 126: 171–179. doi:10.1002/ijc.24637 PMID:19521962

Chao C, Slezak JM, Caan BJ, Quinn VP (2008). Alcoholic beverage intake and risk of lung cancer: the California Men's Health Study. *Cancer Epidemiol Biomarkers Prev*, 17: 2692–2699. doi:10.1158/1055-9965.EPI-08-0410 PMID:18843011

Chao YC, Wang LS, Hsieh TY *et al.* (2000). Chinese alcoholic patients with esophageal cancer are genetically different from alcoholics with acute pancreatitis and liver cirrhosis. *Am J Gastroenterol*, 95: 2958–2964. doi:10.1111/j.1572-0241.2000.02328.x PMID:11051375

Chiaffarino F, Gallus S, Negri E *et al.* (2002). Correspondence re: Weiderpass *et al.*, Alcoholism and risk of cancer of cervix uteri, vagina, and vulva. Cancer Epidemiol. Biomark. Prev., 10: 899–901, 2001. *Cancer Epidemiol Biomarkers Prev*, 11: 325–326. PMID:11895888

Chiang CP, Wu CW, Lee SP *et al.* (2009). Expression pattern, ethanol-metabolizing activities, and cellular localization of alcohol and aldehyde dehydrogenases in human pancreas: implications for pathogenesis of alcohol-induced pancreatic injury. *Alcohol Clin Exp Res*, 33: 1059–1068. doi:10.1111/j.1530-0277.2009.00927.x PMID:19382905

Chiu BC, Weisenburger DD, Cantor KP *et al.* (2002). Alcohol consumption, family history of hematolymphoproliferative cancer, and the risk of non-Hodgkin's lymphoma in men. *Ann Epidemiol*, 12: 309–315. doi:10.1016/S1047-2797(01)00259-9 PMID:12062917

Chiu BC-H, Cerhan JR, Gapstur SM *et al.* (1999). Alcohol consumption and non-Hodgkin lymphoma in a cohort of older women. *Br J Cancer*, 80: 1476–1482. doi:10.1038/sj.bjc.6690547 PMID:10424754

Chlebowski RT, Anderson GL, Lane DS *et al.* Women's Health Initiative Investigators (2007). Predicting risk of breast cancer in postmenopausal women by hormone receptor status. *J Natl Cancer Inst*, 99: 1695–1705. doi:10.1093/jnci/djm224 PMID:18000216

Cho E, Smith-Warner SA, Ritz J *et al.* (2004). Alcohol intake and colorectal cancer: a pooled analysis of

8 cohort studies. *Ann Intern Med*, 140: 603–613. PMID:15096331

Choi JY, Abel J, Neuhaus T *et al.* (2003). Role of alcohol and genetic polymorphisms of CYP2E1 and ALDH2 in breast cancer development. *Pharmacogenetics*, 13: 67–72. doi:10.1097/00008571-200302000-00002 PMID:12563175

Chow WH, Schuman LM, McLaughlin JK *et al.* (1992). A cohort study of tobacco use, diet, occupation, and lung cancer mortality. *Cancer Causes Control*, 3: 247–254. doi:10.1007/BF00124258 PMID:1610971

Cohen G, Sinet PM, Heikkila R (1980). Ethanol oxidation by rat brain in vivo. *Alcohol Clin Exp Res*, 4: 366–370. doi:10.1111/j.1530-0277.1980.tb04833.x PMID:7004234

Coutelle C, Höhn B, Benesova M *et al.* (2004). Risk factors in alcohol associated breast cancer: alcohol dehydrogenase polymorphism and estrogens. *Int J Oncol*, 25: 1127–1132. PMID:15375565

Coutelle C, Ward PJ, Fleury B *et al.* (1997). Laryngeal and oropharyngeal cancer, and alcohol dehydrogenase 3 and glutathione S-transferase M1 polymorphisms. *Hum Genet*, 99: 319–325. doi:10.1007/s004390050365 PMID:9050916

Covolo L, Gelatti U, Talamini R *et al.* (2005). Alcohol dehydrogenase 3, glutathione S-transferase M1 and T1 polymorphisms, alcohol consumption and hepatocellular carcinoma (Italy). *Cancer Causes Control*, 16: 831–838. doi:10.1007/s10552-005-2302-2 PMID:16132793

Cox A, Dunning AM, Garcia-Closas M *et al.*Kathleen Cunningham Foundation Consortium for Research into Familial Breast Cancer; Breast Cancer Association Consortium (2007). A common coding variant in CASP8 is associated with breast cancer risk. *Nat Genet*, 39: 352–358. doi:10.1038/ng1981 PMID:17293864

Crabb DW (1995). Ethanol oxidizing enzymes: roles in alcohol metabolism and alcoholic liver disease. *Prog Liver Dis*, 13: 151–172. PMID:9224501

Crabb DW, Edenberg HJ, Bosron WF, Li TK (1989). Genotypes for aldehyde dehydrogenase deficiency and alcohol sensitivity. The inactive ALDH2(2) allele is dominant. *J Clin Invest*, 83: 314–316. doi:10.1172/JCI113875 PMID:2562960

Cui R, Kamatani Y, Takahashi A *et al.* (2009). Functional variants in ADH1B and ALDH2 coupled with alcohol and smoking synergistically enhance esophageal cancer risk. *Gastroenterology*, 137: 1768–1775. doi:10.1053/j.gastro.2009.07.070 PMID:19698717

Curtin K, Slattery ML, Ulrich CM *et al.* (2007). Genetic polymorphisms in one-carbon metabolism: associations with CpG island methylator phenotype (CIMP) in colon cancer and the modifying effects of diet. *Carcinogenesis*, 28: 1672–1679. doi:10.1093/carcin/bgm089 PMID:17449906

Cusimano R, Dardanoni G, Dardanoni L *et al.* (1989). Risk factors of female cancers in Ragusa population (Sicily)–1. Endometrium and cervix uteri cancers. *Eur J Epidemiol*, 5: 363–371. doi:10.1007/BF00144839 PMID:2792311

De Stefani E, Correa P, Deneo-Pellegrini H *et al.* (2002). Alcohol intake and risk of adenocarcinoma of the lung. A case-control study in Uruguay. *Lung Cancer*, 38: 9–14. doi:10.1016/S0169-5002(02)00153-8 PMID:12367787

De Stefani E, Correa P, Fierro L *et al.* (1993). The effect of alcohol on the risk of lung cancer in Uruguay. *Cancer Epidemiol Biomarkers Prev*, 2: 21–26. PMID:8380549

De Stefani E, Deneo-Pellegrini H, Boffetta P *et al.* (2009). Dietary patterns and risk of cancer: a factor analysis in Uruguay. *Int J Cancer*, 124: 1391–1397. doi:10.1002/ijc.24035 PMID:19058195

De Stefani E, Fierro L, Barrios E, Ronco A (1995). Tobacco, alcohol, diet and risk of prostate cancer. *Tumori*, 81: 315–320. PMID:8804446

De Stefani E, Fierro L, Barrios E, Ronco A (1998). Tobacco, alcohol, diet and risk of non-Hodgkin's lymphoma: a case-control study in Uruguay. *Leuk Res*, 22: 445–452. doi:10.1016/S0145-2126(97)00194-X PMID:9652731

De Torok D (1972). Chromosomal irregularities in alcoholics. *Ann N Y Acad Sci*, 197: 1 Nature and Nu90–100. doi:10.1111/j.1749-6632.1972.tb28125.x PMID:4504611

Deandrea S, Bertuccio P, Chatenoud L *et al.* (2007). Reply to 'Alcohol consumption and risk of Hodgkin's lymphoma and multiple myeloma: a multicentre case-control study' by Gorini *et al. Ann Oncol*, 18: 1119–1121. doi:10.1093/annonc/mdm203 PMID:17586754

Deandrea S, Talamini R, Foschi R *et al.* (2008). Alcohol and breast cancer risk defined by estrogen and progesterone receptor status: a case-control study. *Cancer Epidemiol Biomarkers Prev*, 17: 2025–2028. doi:10.1158/1055-9965.EPI-08-0157 PMID:18708394

Deitrich RA, Petersen D, Vasiliou V (2007). Removal of acetaldehyde from the body. *Novartis Found Symp*, 285: 23–40, discussion 40–51, 198–199. doi:10.1002/9780470511848.ch3 PMID:17590985

DeMaster EG, Redfern B, Weir K *et al.* (1983). Elimination of artifactual acetaldehyde in the measurement of human blood acetaldehyde by the use of polyethylene glycol and sodium azide: normal blood acetaldehyde levels in the dog and human after ethanol. *Alcohol Clin Exp Res*, 7: 436–442. doi:10.1111/j.1530-0277.1983.tb05502.x PMID:6362469

Dennis LK (2000). Meta-analysis for combining relative risks of alcohol consumption and prostate cancer. *Prostate*, 42: 56–66. doi:10.1002/(SICI)1097-0045(20000101)42:1<56::AID-PROS7>3.0.CO;2-P PMID:10579799

Diczfalusy MA, Björkhem I, Einarsson C *et al.* (2001). Characterization of enzymes involved in formation of ethyl esters of long-chain fatty acids in humans. *J Lipid Res*, 42: 1025–1032. PMID:11441128

Ding J, Li S, Wu J *et al.* (2008). Alcohol dehydrogenase-2 and aldehyde dehydrogenase-2 genotypes, alcohol drinking and the risk of primary hepatocellular

carcinoma in a Chinese population. *Asian Pac J Cancer Prev*, 9: 31–35. PMID:18439068

Ding JH, Li SP, Cao HX *et al.* (2009). Polymorphisms of alcohol dehydrogenase-2 and aldehyde dehydrogenase-2 and esophageal cancer risk in Southeast Chinese males. *World J Gastroenterol*, 15: 2395–2400. doi:10.3748/wjg.15.2395 PMID:19452585

Djoussé L, Dorgan JF, Zhang Y *et al.* (2002). Alcohol consumption and risk of lung cancer: the Framingham Study. *J Natl Cancer Inst*, 94: 1877–1882. doi:10.1093/jnci/94.24.1877 PMID:12488481

Doll R, Peto R, Hall E *et al.* (1994). Mortality in relation to consumption of alcohol: 13 years' observations on male British doctors. *BMJ*, 309: 911–918. doi:10.1136/bmj.309.6959.911 PMID:7950661

Dolle JM, Daling JR, White E *et al.* (2009). Risk factors for triple-negative breast cancer in women under the age of 45 years. *Cancer Epidemiol Biomarkers Prev*, 18: 1157–1166. doi:10.1158/1055-9965.EPI-08-1005 PMID:19336554

Donato F, Gelatti U, Tagger A *et al.* (2001). Intrahepatic cholangiocarcinoma and hepatitis C and B virus infection, alcohol intake, and hepatolithiasis: a case-control study in Italy. *Cancer Causes Control*, 12: 959–964. doi:10.1023/A:1013747228572 PMID:11808716

Dosemeci M, Gokmen I, Unsal M *et al.* (1997). Tobacco, alcohol use, and risks of laryngeal and lung cancer by subsite and histologic type in Turkey. *Cancer Causes Control*, 8: 729–737. doi:10.1023/A:1018479304728 PMID:9328195

Duester G, Farrés J, Felder MR *et al.* (1999). Recommended nomenclature for the vertebrate alcohol dehydrogenase gene family. *Biochem Pharmacol*, 58: 389–395. doi:10.1016/S0006-2952(99)00065-9 PMID:10424757

Duffy CM, Assaf A, Cyr M *et al.* (2009). Alcohol and folate intake and breast cancer risk in the WHI Observational Study. *Breast Cancer Res Treat*, 116: 551–562. doi:10.1007/s10549-008-0167-2 PMID:18785003

Edenberg HJ (2007). The genetics of alcohol metabolism: role of alcohol dehydrogenase and aldehyde dehydrogenase variants. *Alcohol Res Health*, 30: 5–13. PMID:17718394

el-Zein R, Zwischenberger JB, Wood TG *et al.* (1997c). Combined genetic polymorphism and risk for development of lung cancer. *Mutat Res*, 381: 189–200. doi:10.1016/S0027-5107(97)00166-8 PMID:9434875

Engeland K & Maret W (1993). Extrahepatic, differential expression of four classes of human alcohol dehydrogenase. *Biochem Biophys Res Commun*, 193: 47–53. doi:10.1006/bbrc.1993.1588 PMID:8503936

Engeset D, Dyachenko A, Ciampi A, Lund E (2009). Dietary patterns and risk of cancer of various sites in the Norwegian European Prospective Investigation into Cancer and Nutrition cohort: the Norwegian Women and Cancer study. *Eur J Cancer Prev*, 18: 69–75. doi:10.1097/CEJ.0b013e328305a091 PMID:19077568

Eom SY, Zhang YW, Kim SH *et al.* (2009). Influence of NQO1, ALDH2, and CYP2E1 genetic polymorphisms, smoking, and alcohol drinking on the risk of lung cancer in Koreans. *Cancer Causes Control*, 20: 137–145. doi:10.1007/s10552-008-9225-7 PMID:18798003

Ericson U, Sonestedt E, Gullberg B *et al.* (2007). High folate intake is associated with lower breast cancer incidence in postmenopausal women in the Malmö Diet and Cancer cohort. *Am J Clin Nutr*, 86: 434–443. PMID:17684216

Eriksson CJP (1985). Endogenous acetaldehyde in rats. Effects of exogenous ethanol, pyrazole, cyanamide and disulfiram. *Biochem Pharmacol*, 34: 3979–3982. doi:10.1016/0006-2952(85)90375-2 PMID:4062972

Eriksson CJP (2001). The role of acetaldehyde in the actions of alcohol (update 2000). *Alcohol Clin Exp Res,*, 25: 15S–32S.

Eriksson CJP (2007). Measurement of acetaldehyde: what levels occur naturally and in response to alcohol? *Novartis Found Symp*, 285: 247–255, discussion 256–260. PMID:17590999

Eriksson CJP & Fukunaga T (1993). Human blood acetaldehyde (update 1992). *Alcohol Alcohol Suppl*, 2: Suppl.29–25. PMID:7748353

Eriksson CJP, Fukunaga T, Sarkola T *et al.* (1996). Estrogen-related acetaldehyde elevation in women during alcohol intoxication. *Alcohol Clin Exp Res*, 20: 1192–1195. doi:10.1111/j.1530-0277.1996.tb01110.x PMID:8904969

Estonius M, Svensson S, Höög JO (1996). Alcohol dehydrogenase in human tissues: localisation of transcripts coding for five classes of the enzyme. *FEBS Lett*, 397: 338–342. doi:10.1016/S0014-5793(96)01204-5 PMID:8955375

Fan C, Jin M, Chen K *et al.* (2007). Case-only study of interactions between metabolic enzymes and smoking in colorectal cancer. *BMC Cancer*, 7: 115 doi:10.1186/1471-2407-7-115 PMID:17603900

Fan L & Cai L (2009). [Meta-analysis on the relationship between alcohol consumption and lung cancer risk] *Wei Sheng Yan Jiu*, 38: 85–89. PMID:19267084

Fan Y, Yuan JM, Wang R *et al.* (2008). Alcohol, tobacco, and diet in relation to esophageal cancer: the Shanghai Cohort Study. *Nutr Cancer*, 60: 354–363. doi:10.1080/01635580701883011 PMID:18444169

Fang J-L & Vaca CE (1995). Development of a 32P-postlabelling method for the analysis of adducts arising through the reaction of acetaldehyde with 2′-deoxyguanosine-3′-monophosphate and DNA. *Carcinogenesis*, 16: 2177–2185. doi:10.1093/carcin/16.9.2177 PMID:7554072

Fang J-L & Vaca CE (1997). Detection of DNA adducts of acetaldehyde in peripheral white blood cells of alcohol abusers. *Carcinogenesis*, 18: 627–632. doi:10.1093/carcin/18.4.627 PMID:9111191

Farker K, Lehmann MH, Kästner R *et al.* (1998a). CYP2E1 genotyping in renal cell/urothelial cancer patients in comparison with control populations. *Int J Clin Pharmacol Ther*, 36: 463–468. PMID:9760005

Fernandes PH, Kanuri M, Nechev LV *et al.* (2005). Mammalian cell mutagenesis of the DNA adducts of vinyl chloride and crotonaldehyde. *Environ Mol Mutagen*, 45: 455–459. doi:10.1002/em.20117 PMID:15690339

Ferrari P, Jenab M, Norat T *et al.* (2007). Lifetime and baseline alcohol intake and risk of colon and rectal cancers in the European prospective investigation into cancer and nutrition (EPIC). *Int J Cancer*, 121: 2065–2072. doi:10.1002/ijc.22966 PMID:17640039

Folsom AR, Demissie Z, Harnack LIowa Women's Health Study (2003). Glycemic index, glycemic load, and incidence of endometrial cancer: the Iowa women's health study. *Nutr Cancer*, 46: 119–124. doi:10.1207/S15327914NC4602_03 PMID:14690786

Frank A, Seitz HK, Bartsch H *et al.* (2004). Immunohistochemical detection of 1,N6-ethenodeoxyadenosine in nuclei of human liver affected by diseases predisposing to hepato-carcinogenesis. *Carcinogenesis*, 25: 1027–1031. doi:10.1093/carcin/bgh089 PMID:14742317

Freedman ND, Abnet CC, Leitzmann MF *et al.* (2007). A prospective study of tobacco, alcohol, and the risk of esophageal and gastric cancer subtypes. *Am J Epidemiol*, 165: 1424–1433. doi:10.1093/aje/kwm051 PMID:17420181

Freedman ND, Abnet CC, Leitzmann MF *et al.* (2007a). A prospective study of tobacco, alcohol, and the risk of esophageal and gastric cancer subtypes. *Am J Epidemiol*, 165: 1424–1433. doi:10.1093/aje/kwm051 PMID:17420181

Freedman ND, Schatzkin A, Leitzmann MF *et al.* (2007b). Alcohol and head and neck cancer risk in a prospective study. *Br J Cancer*, 96: 1469–1474. PMID:17387340

Freudenheim JL, Ambrosone CB, Moysich KB *et al.* (1999). Alcohol dehydrogenase 3 genotype modification of the association of alcohol consumption with breast cancer risk. *Cancer Causes Control*, 10: 369–377. doi:10.1023/A:1008950717205 PMID:10530606

Freudenheim JL, Ram M, Nie J *et al.* (2003). Lung cancer in humans is not associated with lifetime total alcohol consumption or with genetic variation in alcohol dehydrogenase 3 (ADH3). *J Nutr*, 133: 3619–3624. PMID:14608084

Freudenheim JL, Ritz J, Smith-Warner SA *et al.* (2005). Alcohol consumption and risk of lung cancer: a pooled analysis of cohort studies. *Am J Clin Nutr*, 82: 657–667. PMID:16155281

Friberg E & Wolk A (2009). Long-term alcohol consumption and risk of endometrial cancer incidence: a prospective cohort study. *Cancer Epidemiol Biomarkers Prev*, 18: 355–358. doi:10.1158/1055-9965.EPI-08-0993 PMID:19124521

Friborg JT, Yuan JM, Wang R *et al.* (2007). A prospective study of tobacco and alcohol use as risk factors for pharyngeal carcinomas in Singapore Chinese. *Cancer*, 109: 1183–1191. doi:10.1002/cncr.22501 PMID:17315158

Gajalakshmi V, Hung RJ, Mathew A *et al.* (2003). Tobacco smoking and chewing, alcohol drinking and lung cancer risk among men in southern India. *Int J Cancer*, 107: 441–447. doi:10.1002/ijc.11377 PMID:14506745

Gallagher RP, Spinelli JJ, Elwood JM, Skippen DH (1983). Allergies and agricultural exposure as risk factors for multiple myeloma. *Br J Cancer*, 48: 853–857. doi:10.1038/bjc.1983.277 PMID:6652026

Gallus S, Foschi R, Talamini R *et al.* (2007). Risk factors for prostate cancer in men aged less than 60 years: a case-control study from Italy. *Urology*, 70: 1121–1126. doi:10.1016/j.urology.2007.07.020 PMID:18158031

Ganesh B, Talole SD, Dikshit R (2009). A case-control study on diet and colorectal cancer from Mumbai, India. *Cancer Epidemiol*, 33: 189–193. doi:10.1016/j.canep.2009.07.009 PMID:19717354

Gao C, Takezaki T, Wu J *et al.* (2002). Interaction between cytochrome P-450 2E1 polymorphisms and environmental factors with risk of esophageal and stomach cancers in Chinese. *Cancer Epidemiol Biomarkers Prev*, 11: 29–34. PMID:11815398

Gao CM, Takezaki T, Wu JZ *et al.* (2007). CYP2E1 Rsa I polymorphism impacts on risk of colorectal cancer association with smoking and alcohol drinking. *World J Gastroenterol*, 13: 5725–5730. PMID:17963298

Gao CM, Takezaki T, Wu JZ *et al.* (2008). Polymorphisms of alcohol dehydrogenase 2 and aldehyde dehydrogenase 2 and colorectal cancer risk in Chinese males. *World J Gastroenterol*, 14: 5078–5083. doi:10.3748/wjg.14.5078 PMID:18763293

Gapstur SM, Potter JD, Sellers TA *et al.* (1993). Alcohol consumption and postmenopausal endometrial cancer: results from the Iowa Women's Health Study. *Cancer Causes Control*, 4: 323–329. doi:10.1007/BF00051334 PMID:8347781

Garavello W, Bosetti C, Gallus S *et al.* (2006). Type of alcoholic beverage and the risk of laryngeal cancer. *Eur J Cancer Prev*, 15: 69–73. doi:10.1097/01.cej.0000186641.19872.04 PMID:16374233

Garte S & Crosti F (1999). A nomenclature system for metabolic gene polymorphisms. *IARC Sci Publ*, 1485–12. PMID:10493244

Garte S, Gaspari L, Alexandrie AK *et al.* (2001). Metabolic gene polymorphism frequencies in control populations. *Cancer Epidemiol Biomarkers Prev*, 10: 1239–1248. PMID:11751440

Gattás GJ & Saldanha PH (1997). Chromosomal aberrations in peripheral lymphocytes of abstinent alcoholics. *Alcohol Clin Exp Res*, 21: 238–243. doi:10.1111/j.1530-0277.1997.tb03755.x PMID:9113258

Gattás GJF, de Carvalho MB, Siraque MS *et al.* (2006). Genetic polymorphisms of CYP1A1, CYP2E1, GSTM1, and GSTT1 associated with head and neck cancer. *Head Neck*, 28: 819–826. doi:10.1002/hed.20410 PMID:16721740

Genkinger JM, Spiegelman D, Anderson KE *et al.* (2009). Alcohol intake and pancreatic cancer risk: a pooled analysis of fourteen cohort studies. *Cancer Epidemiol Biomarkers Prev*, 18: 765–776. doi:10.1158/1055-9965. EPI-08-0880 PMID:19258474

Gibson LJ, Hery C, Mitton N *et al.* (2009). Risk factors for breast cancer among Filipino women in Manila *Int J Cancer*, PMID:19626603

Giovannucci E, Chen J, Smith-Warner SA *et al.* (2003). Methylenetetrahydrofolate reductase, alcohol dehydrogenase, diet, and risk of colorectal adenomas. *Cancer Epidemiol Biomarkers Prev*, 12: 970–979. PMID:14578131

Godard B, Foulkes WD, Provencher D *et al.* (1998). Risk factors for familial and sporadic ovarian cancer among French Canadians: a case-control study. *Am J Obstet Gynecol*, 179: 403–410. doi:10.1016/S0002-9378(98)70372-2 PMID:9731846

Goedde HW, Agarwal DP, Fritze G *et al.* (1992). Distribution of ADH2 and ALDH2 genotypes in different populations. *Hum Genet*, 88: 344–346. doi:10.1007/BF00197271 PMID:1733836

Goist KC Jr & Sutker PB (1985). Acute alcohol intoxication and body composition in women and men. *Pharmacol Biochem Behav*, 22: 811–814. doi:10.1016/0091-3057(85)90532-5 PMID:4011640

Gong Z, Kristal AR, Schenk JM *et al.* (2009). Alcohol consumption, finasteride, and prostate cancer risk: results from the Prostate Cancer Prevention Trial. *Cancer*, 115: 3661–3669. doi:10.1002/cncr.24423 PMID:19598210

González MV, Alvarez V, Pello MF *et al.* (1998). Genetic polymorphism of N-acetyltransferase-2, glutathione S-transferase-M1, and cytochromes P450IIE1 and P450IID6 in the susceptibility to head and neck cancer. *J Clin Pathol*, 51: 294–298. doi:10.1136/jcp.51.4.294 PMID:9659241

Goodman MT, Hankin JH, Wilkens LR *et al.* (1997). Diet, body size, physical activity, and the risk of endometrial cancer. *Cancer Res*, 57: 5077–5085. PMID:9371506

Goodman MT & Tung KH (2003). Alcohol consumption and the risk of borderline and invasive ovarian cancer. *Obstet Gynecol*, 101: 1221–1228. doi:10.1016/S0029-7844(03)00050-4 PMID:12798528

Gorini G, Stagnaro E, Fontana V *et al.* (2007a). Alcohol consumption and risk of leukemia: A multicenter case-control study. *Leuk Res*, 31: 379–386. doi:10.1016/j.leukres.2006.07.002 PMID:16919329

Gorini G, Stagnaro E, Fontana V *et al.* (2007b). Alcohol consumption and risk of Hodgkin's lymphoma and multiple myeloma: a multicentre case-control study. *Ann Oncol*, 18: 143–148. doi:10.1093/annonc/mdl352 PMID:17047000

Greving JP, Lee JE, Wolk A *et al.* (2007). Alcoholic beverages and risk of renal cell cancer. *Br J Cancer*, 97: 429–433. doi:10.1038/sj.bjc.6603890 PMID:17653076

Guo YM, Wang Q, Liu YZ *et al.* (2008). Genetic polymorphisms in cytochrome P4502E1, alcohol and aldehyde dehydrogenases and the risk of esophageal squamous cell carcinoma in Gansu Chinese males. *World J Gastroenterol*, 14: 1444–1449. doi:10.3748/wjg.14.1444 PMID:18322963

Gwack J, Hwang SS, Ko KP *et al.* (2007). [Fasting serum glucose and subsequent liver cancer risk in a Korean prospective cohort] *J Prev Med Pub Health*, 40: 23–28. doi:10.3961/jpmph.2007.40.1.23 PMID:17310595

Gwinn ML, Webster LA, Lee NC *et al.* (1986). Alcohol consumption and ovarian cancer risk. *Am J Epidemiol*, 123: 759–766. PMID:3962959

Hakulinen T, Lehtimäki L, Lehtonen M, Teppo L (1974). Cancer morbidity among two male cohorts with increased alcohol consumption in Finland. *J Natl Cancer Inst*, 52: 1711–1714. PMID:4834405

Hamada GS, Sugimura H, Suzuki I *et al.* (1995). The heme-binding region polymorphism of cytochrome P4501A1 (*Cyp1A1*), rather than the *RsaI* polymorphism of IIE1 (*CypIIE1*), is associated with lung cancer in Rio de Janeiro. *Cancer Epidemiol. Biomarkers Prev.*, 4: 63–67.

Hamajima N, Hirose K, Tajima K *et al.* Collaborative Group on Hormonal Factors in Breast Cancer (2002). Alcohol, tobacco and breast cancer–collaborative reanalysis of individual data from 53 epidemiological studies, including 58,515 women with breast cancer and 95,067 women without the disease. *Br J Cancer*, 87: 1234–1245. doi:10.1038/sj.bjc.6600596 PMID:12439712

Harada S, Okubo T, Nakamura T *et al.* (1999). A novel polymorphism (-357 G/A) of the ALDH2 gene: linkage disequilibrium and an association with alcoholism. *Alcohol Clin Exp Res*, 23: 958–962. doi:10.1111/j.1530-0277.1999.tb04212.x PMID:10397278

Härkönen K, Viitanen T, Larsen SB *et al.* (1999). Aneuploidy in sperm and exposure to fungicides and lifestyle factors. ASCLEPIOS. A European concerted action on occupational hazards to male reproductive capability. *Environ Mol Mutagen*, 34: 39–46. PMID:10462722

Harris RW, Brinton LA, Cowdell RH *et al.* (1980). Characteristics of women with dysplasia or carcinoma in situ of the cervix uteri. *Br J Cancer*, 42: 359–369. doi:10.1038/bjc.1980.246 PMID:7426342

Hartge P, Schiffman MH, Hoover R *et al.* (1989). A case-control study of epithelial ovarian cancer. *Am J Obstet Gynecol*, 161: 10–16. PMID:2750791

Harty LC, Caporaso NE, Hayes RB *et al.* (1997). Alcohol dehydrogenase 3 genotype and risk of oral cavity and pharyngeal cancers. *J Natl Cancer Inst*, 89: 1698–1705. doi:10.1093/jnci/89.22.1698 PMID:9390539

Hashibe M, Boffetta P, Zaridze D *et al.* (2006). Evidence for an important role of alcohol- and aldehyde-metabolizing genes in cancers of the upper aerodigestive tract. *Cancer Epidemiol Biomarkers Prev*, 15: 696–703. doi:10.1158/1055-9965.EPI-05-0710 PMID:16614111

Hashibe M, Brennan P, Benhamou S *et al.* (2007). Alcohol drinking in never users of tobacco, cigarette smoking in never drinkers, and the risk of head and neck cancer: pooled analysis in the International Head and Neck Cancer Epidemiology Consortium. *J Natl Cancer Inst*, 99: 777–789. doi:10.1093/jnci/djk179 PMID:17505073

Hashibe M, McKay JD, Curado MP *et al.* (2008). Multiple ADH genes are associated with upper aerodigestive cancers. *Nat Genet*, 40: 707–709. doi:10.1038/ng.151 PMID:18500343

Hashimoto T, Uchida K, Okayama N *et al.* (2006). ALDH2 1510 G/A (Glu487Lys) polymorphism interaction with age in head and neck squamous cell carcinoma. *Tumour Biol*, 27: 334–338. doi:10.1159/000096126 PMID:17033202

Hassan MM, Bondy ML, Wolff RA *et al.* (2007). Risk factors for pancreatic cancer: case-control study. *Am J Gastroenterol*, 102: 2696–2707. doi:10.1111/j.1572-0241.2007.01510.x PMID:17764494

Hassan MM, Spitz MR, Thomas MB *et al.* (2008). Effect of different types of smoking and synergism with hepatitis C virus on risk of hepatocellular carcinoma in American men and women: case-control study. *Int J Cancer*, 123: 1883–1891. doi:10.1002/ijc.23730 PMID:18688864

Hayashi S, Watanabe J, Kawajiri K (1991). Genetic polymorphisms in the 5 -flanking region change transcrip - tional regulation of the human cytochrome P450IIE1 gene. *J Biochem*, 110: 559–565. PMID:1778977

Hayes RB, Brown LM, Schoenberg JB *et al.* (1996). Alcohol use and prostate cancer risk in US blacks and whites. *Am J Epidemiol*, 143: 692–697. PMID:8651231

Heinen MM, Verhage BA, Ambergen TA *et al.* (2009). Alcohol consumption and risk of pancreatic cancer in the Netherlands cohort study. *Am J Epidemiol*, 169: 1233–1242. doi:10.1093/aje/kwp028 PMID:19318612

Herity B, Moriarty M, Daly L *et al.* (1982). The role of tobacco and alcohol in the aetiology of lung and larynx cancer. *Br J Cancer*, 46: 961–964. doi:10.1038/bjc.1982.308 PMID:7150489

Herrero R, Brinton LA, Reeves WC *et al.* (1989). Invasive cervical cancer and smoking in Latin America. *J Natl Cancer Inst*, 81: 205–211. doi:10.1093/jnci/81.3.205 PMID:2536087

Hilakivi-Clarke L, Cabanes A, de Assis S *et al.* (2004). In utero alcohol exposure increases mammary tumorigenesis in rats. *Br J Cancer*, 90: 2225–2231. PMID:15150620

Hildesheim A, Anderson LM, Chen CJ *et al.* (1997). CYP2E1 genetic polymorphisms and risk of nasopharyngeal carcinoma in Taiwan. *J Natl Cancer Inst*, 89: 1207–1212. doi:10.1093/jnci/89.16.1207 PMID:9274915

Hines LM, Hankinson SE, Smith-Warner SA *et al.* (2000). A prospective study of the effect of alcohol consumption and ADH3 genotype on plasma steroid hormone levels and breast cancer risk. *Cancer Epidemiol Biomarkers Prev*, 9: 1099–1105. PMID:11045794

Hiraki A, Matsuo K, Wakai K *et al.* (2007). Gene-gene and gene-environment interactions between alcohol drinking habit and polymorphisms in alcohol-metabolizing enzyme genes and the risk of head and neck cancer in Japan. *Cancer Sci*, 98: 1087–1091. doi:10.1111/j.1349-7006.2007.00505.x PMID:17489985

Hirayama T (1992). Life-style and cancer: from epidemiological evidence to public behavior change to mortality reduction of target cancers. *J Natl Cancer Inst Monogr*, 12: 65–74. PMID:1616813

Hirose M, Kono S, Tabata S *et al.* (2005). Genetic polymorphisms of methylenetetrahydrofolate reductase and aldehyde dehydrogenase 2, alcohol use and risk of colorectal adenomas: Self-Defense Forces Health Study. *Cancer Sci*, 96: 513–518. doi:10.1111/j.1349-7006.2005.00077.x PMID:16108833

Hirvonen A, Husgafvel-Pursiainen K, Anttila S *et al.* (1993). The human CYP2E1 gene and lung cancer: DraI and RsaI restriction fragment length polymorphisms in a Finnish study population. *Carcinogenesis*, 14: 85–88. doi:10.1093/carcin/14.1.85 PMID:8093864

Holmberg B & Ekström T (1995). The effects of long-term oral administration of ethanol on Sprague-Dawley rats–a condensed report. *Toxicology*, 96: 133–145. doi:10.1016/0300-483X(94)02917-J PMID:7886684

Homann N, Jousimies-Somer H, Jokelainen K *et al.* (1997). High acetaldehyde levels in saliva after ethanol consumption: methodological aspects and pathogenetic implications. *Carcinogenesis*, 18: 1739–1743. doi:10.1093/carcin/18.9.1739 PMID:9328169

Homann N, König IR, Marks M *et al.* (2009). Alcohol and colorectal cancer: the role of alcohol dehydrogenase 1C polymorphism. *Alcohol Clin Exp Res*, 33: 551–556. doi:10.1111/j.1530-0277.2008.00868.x PMID:19120062

Homann N, Stickel F, König IR *et al.* (2006). Alcohol dehydrogenase 1C*1 allele is a genetic marker for alcohol-associated cancer in heavy drinkers. *Int J Cancer*, 118: 1998–2002. doi:10.1002/ijc.21583 PMID:16287084

Honjo S, Srivatanakul P, Sriplung H *et al.* (2005). Genetic and environmental determinants of risk for cholangiocarcinoma via Opisthorchis viverrini in a densely infested area in Nakhon Phanom, northeast Thailand. *Int J Cancer*, 117: 854–860. doi:10.1002/ijc.21146 PMID:15957169

Hori H, Kawano T, Endo M, Yuasa Y (1997). Genetic polymorphisms of tobacco- and alcohol-related metabolizing enzymes and human esophageal squamous cell carcinoma susceptibility. *J Clin Gastroenterol*, 25: 568–575. doi:10.1097/00004836-199712000-00003 PMID:9451664

Hosgood HD 3rd, Baris D, Zahm SH *et al.* (2007). Diet and risk of multiple myeloma in Connecticut women. *Cancer Causes Control*, 18: 1065–1076. doi:10.1007/s10552-007-9047-z PMID:17694422

Hosono S, Matsuo K, Kajiyama H *et al.* (2008). Reduced risk of endometrial cancer from alcohol drinking in Japanese. *Cancer Sci*, 99: 1195–1201. doi:10.1111/j.1349-7006.2008.00801.x PMID:18422741

Hsing AW, Zhang M, Rashid A *et al.* (2008). Hepatitis B and C virus infection and the risk of biliary tract cancer: a population-based study in China. *Int J Cancer*, 122: 1849–1853. doi:10.1002/ijc.23251 PMID:18076042

Hu J, Mao Y, Dryer D, White KCanadian Cancer Registries Epidemiology Research Group (2002). Risk factors for lung cancer among Canadian women who have never smoked. *Cancer Detect Prev*, 26: 129–138. doi:10.1016/S0361-090X(02)00038-7 PMID:12102147

Huang YS, Chern HD, Su WJ *et al.* (2003). Cytochrome P450 2E1 genotype and the susceptibility to antituberculosis drug-induced hepatitis. *Hepatology*, 37: 924–930. doi:10.1053/jhep.2003.50144 PMID:12668988

Hung HC, Chuang J, Chien YC *et al.* (1997). Genetic polymorphisms of CYP2E1, GSTM1, and GSTT1; Environmental factors and risk of oral cancer. *Cancer Epidemiol. Biomarkers Prev.*, 6: 901–905.

Huxley RR, Ansary-Moghaddam A, Clifton P *et al.* (2009). The impact of dietary and lifestyle risk factors on risk of colorectal cancer: a quantitative overview of the epidemiological evidence. *Int J Cancer*, 125: 171–180. doi:10.1002/ijc.24343 PMID:19350627

IARC (1985). Allyl compounds, aldehydes, epoxides and peroxides. *IARC Monogr Eval Carcinog Risk Chem Hum*, 36: 1–369.

IARC (1988). Alcohol drinking. *IARC Monogr Eval Carcinog Risks Hum*, 44: 1–378. PMID:3236394

IARC (1999). Re-evaluation of some organic chemicals, hydrazine and hydrogen peroxide. *IARC Monogr Eval Carcinog Risks Hum*, 71: 1–315. PMID:10507919

IARC (2010). Alcohol consumption and ethyl carbamate. *IARC Monogr Eval Carcinog Risks Hum*, 96: 1–1428.

Iarmarcovai G, Bonassi S, Sari-Minodier I *et al.* (2007). Exposure to genotoxic agents, host factors, and lifestyle influence the number of centromeric signals in micronuclei: a pooled re-analysis. *Mutat Res*, 615: 18–27. PMID:17198715

Ide R, Mizoue T, Fujino Y *et al.*JACC Study Group (2008). Cigarette smoking, alcohol drinking, and oral and pharyngeal cancer mortality in Japan. *Oral Dis*, 14: 314–319. doi:10.1111/j.1601-0825.2007.01378.x PMID:18449960

Infante-Rivard C, Krajinovic M, Labuda D, Sinnett D (2002). Childhood acute lymphoblastic leukemia associated with parental alcohol consumption and polymorphisms of carcinogen-metabolizing genes. *Epidemiology*, 13: 277–281. doi:10.1097/00001648-200205000-00007 PMID:11964928

Ingelman-Sundberg M, Oscarson M, Daly AK *et al.* (2001). Human cytochrome P-450 (CYP) genes: a web page for the nomenclature of alleles. *Cancer Epidemiol Biomarkers Prev*, 10: 1307–1308. PMID:11751452

Ishiguro S, Sasazuki S, Inoue M *et al.*JPHC Study Group (2009). Effect of alcohol consumption, cigarette smoking and flushing response on esophageal cancer risk: a population-based cohort study (JPHC study). *Cancer Lett*, 275: 240–246. doi:10.1016/j.canlet.2008.10.020 PMID:19036500

Ishihara J, Otani T, Inoue M *et al.*Japan Public Health Center-based Prospective Study Group (2007). Low intake of vitamin B-6 is associated with increased risk of colorectal cancer in Japanese men. *J Nutr*, 137: 1808–1814. PMID:17585035

Ishikawa H, Ishikawa T, Yamamoto H *et al.* (2007). Genotoxic effects of alcohol in human peripheral lymphocytes modulated by ADH1B and ALDH2 gene polymorphisms. *Mutat Res*, 615: 134–142. doi:10.1016/j.mrfmmm.2006.11.026 PMID:17207821

Ishikawa H, Miyatsu Y, Kurihara K, Yokoyama K (2006). Gene-environmental interactions between alcohol-drinking behavior and ALDH2 and CYP2E1 polymorphisms and their impact on micronuclei frequency in human lymphocytes. *Mutat Res*, 594: 1–9. PMID:16126235

Ishikawa H, Yamamoto H, Tian Y *et al.* (2003). Effects of ALDH2 gene polymorphisms and alcohol-drinking behavior on micronuclei frequency in non-smokers. *Mutat Res*, 541: 71–80. PMID:14568296

Itoga S, Nomura F, Makino Y *et al.* (2002). Tandem repeat polymorphism of the CYP2E1 gene: an association study with esophageal cancer and lung cancer. *Alcohol Clin Exp Res*, 26: Suppl15S–19S. doi:10.1111/j.1530-0277.2002.tb02696.x PMID:12198369

Jahnke V, Matthias C, Fryer A, Strange R (1996). Glutathione S-transferase and cytochrome-P-450 polymorphism as risk factors for squamous cell carcinoma of the larynx. *Am J Surg*, 172: 671–673. doi:10.1016/S0002-9610(96)00298-X PMID:8988674

Jain MG, Howe GR, Rohan TE (2000b). Nutritional factors and endometrial cancer in Ontario, Canada. *Cancer Control*, 7: 288–296. PMID:10832115

Jelski W, Chrostek L, Szmitkowski M, Laszewicz W (2002). Activity of class I, II, III, and IV alcohol dehydrogenase isoenzymes in human gastric mucosa. *Dig Dis Sci*, 47: 1554–1557. doi:10.1023/A:1015871219922 PMID:12141816

Jelski W, Orywal K, Panek B *et al.* (2009). The activity of class I, II, III and IV of alcohol dehydrogenase (ADH) isoenzymes and aldehyde dehydrogenase (ALDH) in the wall of abdominal aortic aneurysms. *Exp Mol Pathol*, 87: 59–62. doi:10.1016/j.yexmp.2009.03.001 PMID:19332052

Jensen OM (1979). Cancer morbidity and causes of death among Danish brewery workers. *Int J Cancer*, 23: 454–463. doi:10.1002/ijc.2910230404 PMID:437924

Jiang X, Castelao JE, Groshen S *et al.* (2007). Alcohol consumption and risk of bladder cancer in Los Angeles County. *Int J Cancer*, 121: 839–845. doi:10.1002/ijc.22743 PMID:17440923

Jiao L, Silverman DT, Schairer C *et al.* (2009). Alcohol use and risk of pancreatic cancer: the NIH-AARP Diet and Health Study. *Am J Epidemiol*, 169: 1043–1051. doi:10.1093/aje/kwp034 PMID:19299403

Johansen D, Borgström A, Lindkvist B, Manjer J (2009). Different markers of alcohol consumption, smoking and body mass index in relation to risk of pancreatic cancer. A prospective cohort study within the Malmö Preventive Project. *Pancreatology*, 9: 677–686. doi:10.1159/000212088 PMID:19684432

Jones AW (1995). Measuring and reporting the concentration of acetaldehyde in human breath. *Alcohol Alcohol*, 30: 271–285. PMID:7545981

Jones AW (2006). Urine as a biological specimen for forensic analysis of alcohol and variability in the urine-to-blood relationship. *Toxicol Rev*, 25: 15–35. doi:10.2165/00139709-200625010-00002 PMID:16856767

Jones AW, Lindberg L, Olsson SG (2004). Magnitude and time-course of arterio-venous differences in blood-alcohol concentration in healthy men. *Clin Pharmacokinet*, 43: 1157–1166. doi:10.2165/00003088-200443150-00006 PMID:15568892

Jones AW, Mårdh G, Anggård E (1983). Determination of endogenous ethanol in blood and breath by gas chromatography-mass spectrometry. *Pharmacol Biochem Behav*, 18: Suppl 1267–272. doi:10.1016/0091-3057(83)90184-3 PMID:6634839

Jung AY, Poole EM, Bigler J *et al.* (2008). DNA methyltransferase and alcohol dehydrogenase: gene-nutrient interactions in relation to risk of colorectal polyps. *Cancer Epidemiol Biomarkers Prev*, 17: 330–338. doi:10.1158/1055-9965.EPI-07-2608 PMID:18268116

Kabat GC, Miller AB, Jain M, Rohan TE (2008). Dietary intake of selected B vitamins in relation to risk of major cancers in women. *Br J Cancer*, 99: 816–821. doi:10.1038/sj.bjc.6604540 PMID:18665162

Kabat GC & Wynder EL (1984). Lung cancer in nonsmokers. *Cancer*, 53: 1214–1221. doi:10.1002/1097-0142(19840301)53:5<1214::AID-CNCR2820530532>3.0.CO;2-8 PMID:6692309

Kagan-Krieger S, Selby P, Vohra S, Koren G (2002). Paternal alcohol exposure and Turner syndrome. *Alcohol Alcohol*, 37: 613–617. PMID:12414557

Kaji H, Asanuma Y, Yahara O *et al.* (1984). Intragastrointestinal alcohol fermentation syndrome: report of two cases and review of the literature. *J Forensic Sci Soc*, 24: 461–471. doi:10.1016/S0015-7368(84)72325-5 PMID:6520589

Kalandidi A, Tzonou A, Lipworth L *et al.* (1996). A case-control study of endometrial cancer in relation to reproductive, somatometric, and life-style variables. *Oncology*, 53: 354–359. doi:10.1159/000227587 PMID:8784467

Kanda J, Matsuo K, Suzuki T *et al.* (2009). Impact of alcohol consumption with polymorphisms in alcohol-metabolizing enzymes on pancreatic cancer risk in Japanese. *Cancer Sci*, 100: 296–302. doi:10.1111/j.1349-7006.2008.01044.x PMID:19068087

Kanteres F, Lachenmeier DW, Rehm J (2009). Alcohol in Mayan Guatemala: consumption, distribution, production and composition of cuxa. *Addiction*, 104: 752–759. doi:10.1111/j.1360-0443.2009.02507.x PMID:19215596

Kato I, Tominaga S, Terao C (1989). Alcohol consumption and cancers of hormone-related organs in females. *Jpn J Clin Oncol*, 19: 202–207. PMID:2810820

Kato S, Onda M, Matsukura N *et al.* (1995). Cytochrome P4502E1 (CYP2E1) genetic polymorphism in a case-control study of gastric cancer and liver disease. *Pharmacogenetics*, 5: Special IssueS141–S144. doi:10.1097/00008571-199512001-00016PMID:7581484

Kato S, Onda M, Matsukura N *et al.* (1997). Helicobacter pylori infection and genetic polymorphisms for cancer-related genes in gastric carcinogenesis. *Biomed Pharmacother*, 51: 145–149. doi:10.1016/S0753-3322(97)85581-3 PMID:9207980

Kato S, Shields PG, Caporaso NE *et al.* (1992). Cytochrome P450IIE1 genetic polymorphisms, racial variation, and lung cancer risk. *Cancer Res*, 52: 6712–6715. PMID:1423319

Kato S, Shields PG, Caporaso NE *et al.* (1994). Analysis of cytochrome P450 2E1 genetic polymorphisms in relation to human lung cancer. *Cancer Epidemiol Biomarkers Prev*, 3: 515–518. PMID:8000304

Kato S, Tajiri T, Matsukura N *et al.* (2003). Genetic polymorphisms of aldehyde dehydrogenase 2, cytochrome p450 2E1 for liver cancer risk in HCV antibody-positive japanese patients and the variations of CYP2E1 mRNA expression levels in the liver due to its polymorphism. *Scand J Gastroenterol*, 38: 886–893. doi:10.1080/00365520310004489 PMID:12940444

Katoh T, Kaneko S, Kohshi K *et al.* (1999). Genetic polymorphisms of tobacco- and alcohol-related metabolizing enzymes and oral cavity cancer. *Int J Cancer*, 83: 606–609. doi:10.1002/(SICI)1097-0215(19991126)83:5<606::AID-IJC6>3.0.CO;2-P PMID:10521794

Kawase T, Matsuo K, Hiraki A *et al.* (2009). Interaction of the effects of alcohol drinking and polymorphisms in alcohol-metabolizing enzymes on the risk of female breast cancer in Japan. *J Epidemiol*, 19: 244–250. doi:10.2188/jea.JE20081035 PMID:19667493

Kayani MA & Parry JM (2010). The in vitro genotoxicity of ethanol and acetaldehyde. *Toxicol In Vitro*, 24: 56–60. doi:10.1016/j.tiv.2009.09.003 PMID:19747536

Kelemen LE, Sellers TA, Vierkant RA *et al.* (2004). Association of folate and alcohol with risk of ovarian cancer in a prospective study of postmenopausal women. *Cancer Causes Control*, 15: 1085–1093. doi:10.1007/s10552-004-1546-6 PMID:15801492

Khurana V, Sheth A, Caldito G, Barkin JS (2007). Statins reduce the risk of pancreatic cancer in humans: a case-control study of half a million veterans. *Pancreas*, 34: 260–265. doi:10.1097/MPA.0b013e318030e963 PMID:17312467

Kim RB, Yamazaki H, Chiba K *et al.* (1996). In vivo and in vitro characterization of CYP2E1 activity in Japanese and Caucasians. *J Pharmacol Exp Ther*, 279: 4–11. PMID:8858968

Kimura Y, Nishimura FT, Abe S *et al.* (2009). Polymorphisms in the promoter region of the human class II alcohol dehydrogenase (ADH4) gene affect both transcriptional activity and ethanol metabolism in Japanese subjects. *J Toxicol Sci*, 34: 89–97. doi:10.2131/jts.34.89 PMID:19182438

Kiss I, Sándor J, Pajkos G *et al.* (2000). Colorectal cancer risk in relation to genetic polymorphism of cytochrome P450 1A1, 2E1, and glutathione-S-transferase M1 enzymes. *Anticancer Res*, 20: 1B519–522. PMID:10769717

Kjaerheim K & Andersen A (1994). Cancer incidence among waitresses in Norway. *Cancer Causes Control*, 5: 31–37. doi:10.1007/BF01830724 PMID:8123777

Klatsky AL, Friedman GD, Siegelaub AB (1981). Alcohol and mortality. A ten-year Kaiser-Permanente experience. *Ann Intern Med*, 95: 139–145. PMID:7258861

Klatsky AL, Li Y, Baer D *et al.* (2009). Alcohol consumption and risk of hematologic malignancies. *Ann Epidemiol*, 19: 746–753. doi:10.1016/j.annepidem.2009.03.005 PMID:19394864

Knight JA, Bernstein L, Largent J *et al.*WECARE Study Collaborative Group (2009). Alcohol intake and cigarette smoking and risk of a contralateral breast cancer: The Women's Environmental Cancer and Radiation Epidemiology Study. *Am J Epidemiol*, 169: 962–968. doi:10.1093/aje/kwn422 PMID:19211621

Kocić B, Petrovic B, Filipovic S (2008). Risk factors for breast cancer: a hospital-based case-control study. *J BUON*, 13: 231–234. PMID:18555470

Koide T, Ohno T, Huang XE *et al.* (2000). HBV/HCV infection, alcohol, tobacco and genetic polymorphisms for hepatocellular carcinoma in Nagoya, Japan. *Asian Pac J Cancer Prev*, 1: 237–243. PMID:12718671

Kolahdooz F, Ibiebele TI, van der Pols JC, Webb PM (2009). Dietary patterns and ovarian cancer risk. *Am J Clin Nutr*, 89: 297–304. doi:10.3945/ajcn.2008.26575 PMID:19056595

Kono S, Ikeda M, Tokudome S *et al.* (1986). Alcohol and mortality: a cohort study of male Japanese physicians. *Int J Epidemiol*, 15: 527–532. doi:10.1093/ije/15.4.527 PMID:3818161

Koo LC (1988). Dietary habits and lung cancer risk among Chinese females in Hong Kong who never smoked. *Nutr Cancer*, 11: 155–172. doi:10.1080/01635588809513983 PMID:2841651

Korte JE, Brennan P, Henley SJ, Boffetta P (2002). Dose-specific meta-analysis and sensitivity analysis of the relation between alcohol consumption and lung cancer risk. *Am J Epidemiol*, 155: 496–506. doi:10.1093/aje/155.6.496 PMID:11882523

Krebs HA & Perkins JR (1970). The physiological role of liver alcohol dehydrogenase. *Biochem J*, 118: 635–644. PMID:5481498

Kruk J (2007). Association of lifestyle and other risk factors with breast cancer according to menopausal status: a case-control study in the Region of Western Pomerania (Poland). *Asian Pac J Cancer Prev*, 8: 513–524. PMID:18260721

Kubík A, Zatloukal P, Tomásek L *et al.* (2004). Lung cancer risk among nonsmoking women in relation to diet and physical activity. *Neoplasma*, 51: 136–143. PMID:15190423

Kuper H, Lagiou P, Mucci LA *et al.* (2001). Risk factors for cholangiocarcinoma in a low risk Caucasian population. *Soz Praventivmed*, 46: 182–185. doi:10.1007/BF01324254 PMID:11565447

Kuper H, Titus-Ernstoff L, Harlow BL, Cramer DW (2000). Population based study of coffee, alcohol and tobacco use and risk of ovarian cancer. *Int J Cancer*, 88: 313–318. doi:10.1002/1097-0215(20001015)88:2<313::AID-IJC26>3.0.CO;2-5 PMID:11004686

Kurtz AJ & Lloyd RS (2003). 1,N2-deoxyguanosine adducts of acrolein, crotonaldehyde, and trans-4-hydroxynonenal cross-link to peptides via Schiff base linkage. *J Biol Chem*, 278: 5970–5976. doi:10.1074/jbc.M212012200 PMID:12502710

Kurys G, Ambroziak W, Pietruszko R (1989). Human aldehyde dehydrogenase. Purification and characterization of a third isozyme with low Km for gamma-aminobutyraldehyde. *J Biol Chem*, 264: 4715–4721. PMID:2925663

Kushi LH, Mink PJ, Folsom AR *et al.* (1999). Prospective study of diet and ovarian cancer. *Am J Epidemiol*, 149: 21–31. PMID:9883790

Kushida M, Wanibuchi H, Morimura K *et al.* (2005). Dose-dependence of promotion of 2-amino-3,8-dimethylimidazo[4,5-f]quinoxaline-induced rat hepatocarcinogenesis by ethanol: evidence for a threshold. *Cancer Sci*, 96: 747–757. doi:10.1111/j.1349-7006.2005.00110.x PMID:16271068

Kvåle G, Bjelke E, Gart JJ (1983). Dietary habits and lung cancer risk. *Int J Cancer*, 31: 397–405. doi:10.1002/ijc.2910310402 PMID:6832851

Kwan ML, Kushi LH, Weltzien E *et al.* (2009). Epidemiology of breast cancer subtypes in two prospective cohort studies of breast cancer survivors. *Breast Cancer Res*, 11: R31 doi:10.1186/bcr2261 PMID:19463150

La Vecchia C, Decarli A, Fasoli M, Gentile A (1986). Nutrition and diet in the etiology of endometrial cancer. *Cancer*, 57: 1248–1253. doi:10.1002/1097-0142(19860315)57:6<1248::AID-CNCR2820570631>3.0.CO;2-V PMID:3002600

La Vecchia C, Negri E, Franceschi S *et al.* (1992). Alcohol and epithelial ovarian cancer. *J Clin Epidemiol*, 45: 1025–1030. doi:10.1016/0895-4356(92)90119-8 PMID:1432017

Lachenmeier DW, Ganss S, Rychlak B *et al.* (2009b). Association between quality of cheap and unrecorded alcohol products and public health consequences in Poland. *Alcohol Clin Exp Res*, 33: Issue 101757–1769. doi:10.1111/j.1530-0277.2009.01013.x PMID:19572980

Lachenmeier DW, Kanteres F, Rehm J (2009a). Carcinogenicity of acetaldehyde in alcoholic beverages: risk assessment outside ethanol metabolism. *Addiction*, 104: 533–550. doi:10.1111/j.1360-0443.2009.02516.x PMID:19335652

Lachenmeier DW & Sohnius EM (2008). The role of acetaldehyde outside ethanol metabolism in the carcinogenicity of alcoholic beverages: evidence from a large chemical survey. *Food Chem Toxicol*, 46: 2903–2911. doi:10.1016/j.fct.2008.05.034 PMID:18577414

Ladero JM, Agúndez JAG, Rodríguez-Lescure A *et al.* (1996). RsaI polymorphism at the cytochrome P4502E1 locus and risk of hepatocellular carcinoma. *Gut*, 39: 330–333. doi:10.1136/gut.39.2.330 PMID:8977352

Lagiou P, Ye W, Wedrén S *et al.* (2001). Incidence of ovarian cancer among alcoholic women: a cohort study in Sweden. *Int J Cancer*, 91: 264–266. doi:10.1002/1097-0215(200002)9999:9999<::AID-IJC1027>3.3.CO;2-B PMID:11146456

Landi S, Gemignani F, Moreno V *et al.*Bellvitge Colorectal Cancer Study Group (2005). A comprehensive analysis of phase I and phase II metabolism gene polymorphisms and risk of colorectal cancer. *Pharmacogenet Genomics*, 15: 535–546. doi:10.1097/01.fpc.0000165904.48994.3d PMID:16006997

Laposata EA & Lange LG (1986). Presence of nonoxidative ethanol metabolism in human organs commonly damaged by ethanol abuse. *Science*, 231: 497–499. doi:10.1126/science.3941913 PMID:3941913

Laposata M, Hasaba A, Best CA *et al.* (2002). Fatty acid ethyl esters: recent observations. *Prostaglandins Leukot Essent Fatty Acids*, 67: 193–196. doi:10.1054/plef.2002.0418 PMID:12324241

Larsson SC, Giovannucci E, Wolk A (2007). Alcoholic beverage consumption and gastric cancer risk: a prospective population-based study in women. *Int J Cancer*, 120: 373–377. doi:10.1002/ijc.22204 PMID:17066442

Le Marchand L, Donlon T, Seifried A, Wikens LR (2002). Read meat intake, *CYP2E1* genetic polymorphisms, and colorectal cancer risk. *Cancer Epidemiol. Biomarkers Prev.*, 11: 1019–1024.

Le Marchand L, Sivaraman L, Pierce L *et al.* (1998). Associations of CYP1A1, GSTM1, and CYP2E1 polymorphisms with lung cancer suggest cell type specificities to tobacco carcinogens. *Cancer Res*, 58: 4858–4863. PMID:9809991

Lee CH, Lee JM, Wu DC *et al.* (2008b). Carcinogenetic impact of ADH1B and ALDH2 genes on squamous cell carcinoma risk of the esophagus with regard to the consumption of alcohol, tobacco and betel quid. *Int J Cancer*, 122: 1347–1356. doi:10.1002/ijc.23264 PMID:18033686

Lee CH, Wu DC, Lee JM *et al.* (2007). Carcinogenetic impact of alcohol intake on squamous cell carcinoma risk of the oesophagus in relation to tobacco smoking. *Eur J Cancer*, 43: 1188–1199. doi:10.1016/j.ejca.2007.01.039 PMID:17383866

Lee CH, Wu DC, Wu IC *et al.* (2009). Genetic modulation of ADH1B and ALDH2 polymorphisms with regard to alcohol and tobacco consumption for younger aged esophageal squamous cell carcinoma diagnosis. *Int J Cancer*, 125: 1134–1142. doi:10.1002/ijc.24357 PMID:19449376

Lee HC, Yoon YB, Kim CY (1997). Association between genetic polymorphisms of the cytochromes P-450 (1A1, 2D6, and 2E1) and the susceptibility to pancreatic cancer. *Korean J Intern Med*, 12: 128–136. PMID:9439147

Lee CH, Lee JM, Wu DC *et al.* (2005). Independent and combined effects of alcohol intake, tobacco smoking and betel quid chewing on the risk of esophageal cancer in Taiwan. *Int J Cancer*, 113: 475–482. doi:10.1002/ijc.20619 PMID:15455377

Lee SL, Chau GY, Yao CT *et al.* (2006). Functional assessment of human alcohol dehydrogenase family in ethanol metabolism: significance of first-pass metabolism. *Alcohol Clin Exp Res*, 30: 1132–1142. doi:10.1111/j.1530-0277.2006.00139.x PMID:16792560

Lee TY, Lee SS, Jung SW *et al.* (2008a). Hepatitis B virus infection and intrahepatic cholangiocarcinoma in Korea: a case-control study. *Am J Gastroenterol*, 103: 1716–1720. doi:10.1111/j.1572-0241.2008.01796.x PMID:18557716

Levi F, Franceschi S, Negri E, La Vecchia C (1993). Dietary factors and the risk of endometrial cancer. *Cancer*, 71: 3575–3581. doi:10.1002/1097-0142(19930601)71:11<3575::AID-CNCR2820711119>3.0.CO;2-0 PMID:8490907

Levine AJ, Siegmund KD, Ervin CM *et al.* (2000). The methylenetetrahydrofolate reductase 677C–>T polymorphism and distal colorectal adenoma risk. *Cancer Epidemiol Biomarkers Prev*, 9: 657–663. PMID:10919734

Levitt MD & Levitt DG (1998). Use of a two-compartment model to assess the pharmacokinetics of human ethanol metabolism. *Alcohol Clin Exp Res*, 22: 1680–1688. PMID:9835281

Levitt MD & Levitt DG (2000). Appropriate use and misuse of blood concentration measurements to quantitate first-pass metabolism. *J Lab Clin Med*, 136: 275–280. doi:10.1067/mlc.2000.109100 PMID:11039847

Lew JQ, Freedman ND, Leitzmann MF *et al.* (2009). Alcohol and risk of breast cancer by histologic type and hormone receptor status in postmenopausal women: the NIH-AARP Diet and Health Study. *Am J Epidemiol*, 170: 308–317. doi:10.1093/aje/kwp120 PMID:19541857

Lewis SJ & Smith GD (2005). Alcohol, ALDH2, and esophageal cancer: a meta-analysis which illustrates the potentials and limitations of a Mendelian randomization approach. *Cancer Epidemiol Biomarkers Prev*, 14: 1967–1971. doi:10.1158/1055-9965.EPI-05-0196 PMID:16103445

Li CI, Daling JR, Malone KE *et al.* (2006). Relationship between established breast cancer risk factors and risk of seven different histologic types of invasive breast cancer. *Cancer Epidemiol Biomarkers Prev*, 15: 946–954. doi:10.1158/1055-9965.EPI-05-0881 PMID:16702375

Li CI, Daling JR, Porter PL *et al.* (2009a). Relationship between potentially modifiable lifestyle factors and risk of second primary contralateral breast cancer among women diagnosed with estrogen receptor-positive invasive breast cancer. *J Clin Oncol*, 27: 5312–5318. doi:10.1200/JCO.2009.23.1597 PMID:19738113

Li CI, Malone KE, Porter PL *et al.* (2003a). The relationship between alcohol use and risk of breast cancer by histology and hormone receptor status among women 65–79 years of age. *Cancer Epidemiol Biomarkers Prev*, 12: 1061–1066. PMID:14578143

Li CI, Malone KE, Porter PL, Daling JR (2003b). Epidemiologic and molecular risk factors for contralateral breast cancer among young women. *Br J Cancer*, 89: 513–518. doi:10.1038/sj.bjc.6601042 PMID:12888823

Li D, Dandara C, Parker MI (2005). Association of cytochrome P450 2E1 genetic polymorphisms with squamous cell carcinoma of the oesophagus. *Clin Chem Lab Med*, 43: 370–375. doi:10.1515/CCLM.2005.067 PMID:15899651

Li DP, Dandara C, Walther G, Parker MI (2008a). Genetic polymorphisms of alcohol metabolising enzymes: their role in susceptibility to oesophageal cancer. *Clin Chem Lab Med*, 46: 323–328. doi:10.1515/CCLM.2008.073 PMID:18254707

Li XM, Li J, Tsuji I *et al.* (2008b). Mass screening-based case-control study of diet and prostate cancer in Changchun, China. *Asian J Androl*, 10: 551–560. doi:10.1111/j.1745-7262.2008.00384.x PMID:18478158

Li Y, Baer D, Friedman GD *et al.* (2009b). Wine, liquor, beer and risk of breast cancer in a large population. *Eur J Cancer*, 45: 843–850. doi:10.1016/j.ejca.2008.11.001 PMID:19095438

Licciardone JC, Wilkins JR 3rd, Brownson RC, Chang JC (1989). Cigarette smoking and alcohol consumption in the aetiology of uterine cervical cancer. *Int J Epidemiol*, 18: 533–537. doi:10.1093/ije/18.3.533 PMID:2807654

Lieber CS (2004). The discovery of the microsomal ethanol oxidizing system and its physiologic and pathologic role. *Drug Metab Rev*, 36: 511–529. doi:10.1081/DMR-200033441 PMID:15554233

Lightfoot TJ, Barrett JH, Bishop T *et al.* (2008). Methylene tetrahydrofolate reductase genotype modifies the chemopreventive effect of folate in colorectal adenoma, but not colorectal cancer. *Cancer Epidemiol Biomarkers Prev*, 17: 2421–2430.

Lilla C, Koehler T, Kropp S *et al.* (2005). Alcohol dehydrogenase 1B (ADH1B) genotype, alcohol consumption and breast cancer risk by age 50 years in a German case-control study. *Br J Cancer*, 92: 2039–2041. doi:10.1038/sj.bjc.6602608 PMID:15886702

Lim HJ & Park BJ (2008). [Cohort study on the association between alcohol consumption and the risk of colorectal cancer in the Korean elderly] *J Prev Med Pub Health*, 41: 23–29. doi:10.3961/jpmph.2008.41.1.23 PMID:18250602

Lim RT Jr, Gentry RT, Ito D *et al.* (1993). First-pass metabolism of ethanol is predominantly gastric. *Alcohol Clin Exp Res*, 17: 1337–1344. doi:10.1111/j.1530-0277.1993.tb05250.x PMID:8116851

Lim U, Morton LM, Subar AF *et al.* (2007). Alcohol, smoking, and body size in relation to incident Hodgkin's and non-Hodgkin's lymphoma risk. *Am J Epidemiol*, 166: 697–708. doi:10.1093/aje/kwm122 PMID:17596266

Lim U, Weinstein S, Albanes D *et al.* (2006). Dietary factors of one-carbon metabolism in relation to non-Hodgkin lymphoma and multiple myeloma in a cohort of male smokers. *Cancer Epidemiol Biomarkers Prev*, 15: 1109–1114. doi:10.1158/1055-9965.EPI-05-0918 PMID:16775167

Lin HJ (1996). Smokers and breast cancer. 'Chemical individuality' and cancer predisposition. *JAMA*, 276: 1511–1512. doi:10.1001/jama.1996.03540180067035 PMID:8903264

Lind PA, Eriksson CJP, Wilhelmsen KC (2008). The role of aldehyde dehydrogenase-1 (ALDH1A1) polymorphisms in harmful alcohol consumption in a Finnish population. *Hum Genomics*, 3: 24–35. PMID:19129088

Linderborg K, Joly JP, Visapää JP, Salaspuro M (2008). Potential mechanism for Calvados-related oesophageal cancer. *Food Chem Toxicol*, 46: 476–479. doi:10.1016/j.fct.2007.08.019 PMID:17892909

Linet MS, Harlow SD, McLaughlin JK (1987). A case-control study of multiple myeloma in whites: chronic antigenic stimulation, occupation, and drug use. *Cancer Res*, 47: 2978–2981. PMID:3567914

Lisander B, Lundvall O, Tomner J, Jones AW (2006). Enhanced rate of ethanol elimination from blood after intravenous administration of amino acids compared with equicaloric glucose. *Alcohol Alcohol*, 41: 39–43. PMID:16087660

Liu S, Park JY, Schantz SP *et al.* (2001). Elucidation of CYP2E1 5′ regulatory RsaI/PstI allelic variants and their role in risk for oral cancer. *Oral Oncol*, 37: 437–445. doi:10.1016/S1368-8375(00)00099-3 PMID:11377232

Liu X, Lao Y, Yang IY *et al.* (2006). Replication-coupled repair of crotonaldehyde/acetaldehyde-induced guanine-guanine interstrand cross-links and their mutagenicity. *Biochemistry*, 45: 12898–12905. doi:10.1021/bi060792v PMID:17042508

Lodovici M, Casalini C, Cariaggi R *et al.* (2000). Levels of 8-hydroxydeoxyguanosine as a marker of DNA damage in human leukocytes. *Free Radic Biol Med*, 28: 13–17. doi:10.1016/S0891-5849(99)00194-X PMID:10656286

Loerbroks A, Schouten LJ, Goldbohm RA, van den Brandt PA (2007). Alcohol consumption, cigarette smoking, and endometrial cancer risk: results from the Netherlands Cohort Study. *Cancer Causes Control*, 18: 551–560. doi:10.1007/s10552-007-0127-x PMID:17437180

London SJ, Daly AK, Cooper J *et al.* (1996). Lung cancer risk in relation to the CYP2E1 Rsa I genetic polymorphism among African-Americans and Caucasians in Los Angeles County. *Pharmacogenetics*, 6: 151–158. doi:10.1097/00008571-199604000-00002 PMID:9156693

Lu Q-J, Yao S-Y, Huang C-Y *et al.* (2000[The cohort study on intake of alcohol and lung cancer risk in the Yunnan Tin Corporation (YTC) miners.]). *China Pub Health*, 16: 707–708.

Lu XM, Zhang YM, Lin RY *et al.* (2005). Relationship between genetic polymorphisms of metabolizing enzymes CYP2E1, GSTM1 and Kazakh's esophageal squamous cell cancer in Xinjiang, China. *World J Gastroenterol*, 11: 3651–3654. PMID:15968714

Lubin JH, Purdue M, Kelsey K *et al.* (2009). Total exposure and exposure rate effects for alcohol and smoking and risk of head and neck cancer: a pooled analysis of case-control studies. *Am J Epidemiol*, 170: 937–947. doi:10.1093/aje/kwp222 PMID:19745021

Lucas D, Ménez C, Floch F *et al.* (1996). Cytochromes P4502E1 and P4501A1 genotypes and susceptibility to cirrhosis or upper aerodigestive tract cancer in alcoholic caucasians. *Alcohol Clin Exp Res*, 20: 1033–1037. doi:10.1111/j.1530-0277.1996.tb01943.x PMID:8892524

Lucenteforte E, Scita V, Bosetti C *et al.* (2008). Food groups and alcoholic beverages and the risk of stomach cancer: a case-control study in Italy. *Nutr Cancer*, 60: 577–584. doi:10.1080/01635580802054512 PMID:18791920

Mabuchi K, Bross DS, Kessler II (1985). Epidemiology of cancer of the vulva. A case-control study. *Cancer*, 55: 1843–1848. doi:10.1002/1097-0142(19850415)55:8<1843::AID-CNCR2820550833>3.0.CO;2-M PMID:3978570

MacArthur AC, McBride ML, Spinelli JJ *et al.* (2008). Risk of childhood leukemia associated with parental smoking and alcohol consumption prior to conception and during pregnancy: the cross-Canada childhood leukemia study. *Cancer Causes Control*, 19: 283–295. doi:10.1007/s10552-007-9091-8 PMID:18283545

Madsen BS, Jensen HL, van den Brule AJ *et al.* (2008). Risk factors for invasive squamous cell carcinoma of the vulva and vagina–population-based case-control study in Denmark. *Int J Cancer*, 122: 2827–2834. doi:10.1002/ijc.23446 PMID:18348142

Maffei F, Fimognari C, Castelli E *et al.* (2000). Increased cytogenetic damage detected by FISH analysis on micronuclei in peripheral lymphocytes from alcoholics. *Mutagenesis*, 15: 517–523. doi:10.1093/mutage/15.6.517 PMID:11077004

Maffei F, Forti GC, Castelli E *et al.* (2002). Biomarkers to assess the genetic damage induced by alcohol abuse in human lymphocytes. *Mutat Res*, 514: 49–58. PMID:11815244

Mao H, Reddy GR, Marnett LJ, Stone MP (1999). Solution structure of an oligodeoxynucleotide containing the malondialdehyde deoxyguanosine adduct N2-(3-oxo-1-propenyl)-dG (ring-opened M1G) positioned in a (CpG)3 frameshift hotspot of the Salmonella typhimurium hisD3052 gene. *Biochemistry*, 38: 13491–13501. doi:10.1021/bi9910124 PMID:10521256

Marshall JR, Graham S, Byers T *et al.* (1983). Diet and smoking in the epidemiology of cancer of the cervix. *J Natl Cancer Inst*, 70: 847–851. PMID:6573528

Martin PM & Hill GB (1984). Cervical cancer in relation to tobacco and alcohol consumption in Lesotho, southern Africa. *Cancer Detect Prev*, 7: 109–115. PMID:6713445

Matsuda T, Kawanishi M, Yagi T *et al.* (1998). Specific tandem GG to TT base substitutions induced by acetaldehyde are due to intra-strand crosslinks between adjacent guanine bases. *Nucleic Acids Res*, 26: 1769–1774. doi:10.1093/nar/26.7.1769 PMID:9512551

Matsuda T, Terashima I, Matsumoto Y *et al.* (1999). Effective utilization of N2-ethyl-2′-deoxyguanosine triphosphate during DNA synthesis catalyzed by mammalian replicative DNA polymerases. *Biochemistry*, 38: 929–935. doi:10.1021/bi982134j PMID:9893988

Matsuda T, Yabushita H, Kanaly RA *et al.* (2006). Increased DNA damage in ALDH2-deficient alcoholics. *Chem Res Toxicol*, 19: 1374–1378. doi:10.1021/tx060113h PMID:17040107

Matsuo K, Hamajima N, Hirai T *et al.* (2002). Aldehyde dehydrogenase 2 (ALDH2) genotype affects rectal cancer susceptibility due to alcohol consumption. *J Epidemiol*, 12: 70–76. doi:10.2188/jea.12.70 PMID:12033531

Matsuo K, Hamajima N, Hirose K *et al.* (2001a). Alcohol, smoking, and dietary status and susceptibility to malignant lymphoma in Japan: results of a hospital-based case-control study at Aichi Cancer Center. *Jpn J Cancer Res*, 92: 1011–1017. doi:10.1111/j.1349-7006.2001.tb01054.x PMID:11676850

Matsuo K, Hamajima N, Shinoda M *et al.* (2001b). Gene-environment interaction between an

aldehyde dehydrogenase-2 (ALDH2) polymorphism and alcohol consumption for the risk of esophageal cancer. *Carcinogenesis*, 22: 913–916. doi:10.1093/carcin/22.6.913 PMID:11375898

Matsuo K, Hiraki A, Hirose K *et al.* (2007). Impact of the alcohol-dehydrogenase (ADH) 1C and ADH1B polymorphisms on drinking behavior in nonalcoholic Japanese. *Hum Mutat*, 28: 506–510. doi:10.1002/humu.20477 PMID:17285601

Matsuo K, Wakai K, Hirose K *et al.* (2006a). A gene-gene interaction between ALDH2 Glu487Lys and ADH2 His47Arg polymorphisms regarding the risk of colorectal cancer in Japan. *Carcinogenesis*, 27: 1018–1023. doi:10.1093/carcin/bgi282 PMID:16332725

Matsuo K, Wakai K, Hirose K *et al.* (2006b). Alcohol dehydrogenase 2 His47Arg polymorphism influences drinking habit independently of aldehyde dehydrogenase 2 Glu487Lys polymorphism: analysis of 2,299 Japanese subjects. *Cancer Epidemiol Biomarkers Prev*, 15: 1009–1013. doi:10.1158/1055-9965.EPI-05-0911 PMID:16702384

Matsushima Y (1987). Chromosomal aberrations in the lymphocytes of alcoholics and former alcoholics. *Neuropsychobiology*, 17: 24–29. doi:10.1159/000118336 PMID:3627389

Matthias C, Bockmühl U, Jahnke V *et al.* (1998). Polymorphism in cytochrome P450 CYP2D6, CYP1A1, CYP2E1 and glutathione S-transferase, GSTM1, GSTM3, GSTT1 and susceptibility to tobacco-related cancers: studies in upper aerodigestive tract cancers. *Pharmacogenetics*, 8: 91–100. doi:10.1097/00008571-199804000-00001 PMID:10022746

Mayne ST, Janerich DT, Greenwald P *et al.* (1994). Dietary beta carotene and lung cancer risk in U.S. nonsmokers. *J Natl Cancer Inst*, 86: 33–38. doi:10.1093/jnci/86.1.33 PMID:8271280

McCann SE, Freudenheim JL, Marshall JR *et al.* (2000). Diet in the epidemiology of endometrial cancer in western New York (United States). *Cancer Causes Control*, 11: 965–974. doi:10.1023/A:1026551309873 PMID:11142531

McCann SE, Freudenheim JL, Marshall JR, Graham S (2003). Risk of human ovarian cancer is related to dietary intake of selected nutrients, phytochemicals and food groups. *J Nutr*, 133: 1937–1942. PMID:12771342

McKinney PA, Cartwright RA, Saiu JM *et al.* (1987). The inter-regional epidemiological study of childhood cancer (IRESCC): a case control study of aetiological factors in leukaemia and lymphoma. *Arch Dis Child*, 62: 279–287. doi:10.1136/adc.62.3.279 PMID:3646026

Menegaux F, Ripert M, Hémon D, Clavel J (2007). Maternal alcohol and coffee drinking, parental smoking and childhood leukaemia: a French population-based case-control study. *Paediatr Perinat Epidemiol*, 21: 293–299. doi:10.1111/j.1365-3016.2007.00824.x PMID:17564585

Menegaux F, Steffen C, Bellec S *et al.* (2005). Maternal coffee and alcohol consumption during pregnancy, parental smoking and risk of childhood acute leukaemia. *Cancer Detect Prev*, 29: 487–493. doi:10.1016/j.cdp.2005.06.008 PMID:16289502

Mettlin C (1989). Milk drinking, other beverage habits, and lung cancer risk. *Int J Cancer*, 43: 608–612. doi:10.1002/ijc.2910430412 PMID:2703270

Middleton Fillmore K, Chikritzhs T, Stockwell T *et al.* (2009). Alcohol use and prostate cancer: a meta-analysis. *Mol Nutr Food Res*, 53: 240–255. doi:10.1002/mnfr.200800122 PMID:19156715

Million Women Study Collaborators (2005). Endometrial cancer and hormone-replacement therapy in the Million Women Study. *Lancet*, 365: 1543–1551.

Millikan RC, Newman B, Tse CK *et al.* (2008). Epidemiology of basal-like breast cancer. *Breast Cancer Res Treat*, 109: 123–139. doi:10.1007/s10549-007-9632-6 PMID:17578664

Minegishi Y, Tsukino H, Muto M *et al.* (2007). Susceptibility to lung cancer and genetic polymorphisms in the alcohol metabolite-related enzymes alcohol dehydrogenase 3, aldehyde dehydrogenase 2, and cytochrome P450 2E1 in the Japanese population. *Cancer*, 110: 353–362. doi:10.1002/cncr.22795 PMID:17559142

Miyasaka K, Kawanami T, Shimokata H *et al.* (2005). Inactive aldehyde dehydrogenase-2 increased the risk of pancreatic cancer among smokers in a Japanese male population. *Pancreas*, 30: 95–98. doi:10.1097/01.mpa.0000147084.70125.41 PMID:15714130

Mizoue T, Inoue M, Wakai K *et al.*Research Group for Development and Evaluation of Cancer Prevention Strategies in Japan (2008). Alcohol drinking and colorectal cancer in Japanese: a pooled analysis of results from five cohort studies. *Am J Epidemiol*, 167: 1397–1406. doi:10.1093/aje/kwn073 PMID:18420544

Modugno F, Ness RB, Allen GO (2003). Alcohol consumption and the risk of mucinous and nonmucinous epithelial ovarian cancer. *Obstet Gynecol*, 102: 1336–1343. doi:10.1016/j.obstetgynecol.2003.08.008 PMID:14662224

Monnereau A, Orsi L, Troussard X *et al.* (2008). Cigarette smoking, alcohol drinking, and risk of lymphoid neoplasms: results of a French case-control study. *Cancer Causes Control*, 19: 1147–1160. doi:10.1007/s10552-008-9182-1 PMID:18781390

Mørch LS, Johansen D, Thygesen LC *et al.* (2007). Alcohol drinking, consumption patterns and breast cancer among Danish nurses: a cohort study. *Eur J Public Health*, 17: 624–629. doi:10.1093/eurpub/ckm036 PMID:17442702

Mori M, Harabuchi I, Miyake H *et al.* (1988). Reproductive, genetic, and dietary risk factors for ovarian cancer. *Am J Epidemiol*, 128: 771–777. PMID:3421242

Morimoto K & Takeshita T (1996). Low Km aldehyde dehydrogenase (ALDH2) polymorphism, alcohol-drinking

behavior, and chromosome alterations in peripheral lymphocytes. *Environ Health Perspect*, 104: Suppl 3563–567. doi:10.2307/3432824 PMID:8781384

Morita M, Le Marchand L, Kono S *et al.* (2009). Genetic polymorphisms of CYP2E1 and risk of colorectal cancer: the Fukuoka Colorectal Cancer Study. *Cancer Epidemiol Biomarkers Prev*, 18: 235–241. doi:10.1158/1055-9965.EPI-08-0698 PMID:19124503

Morita S, Yano M, Shiozaki H *et al.* (1997). CYP1A1, CYP2E1 and GSTM1 polymorphisms are not associated with susceptibility to squamous-cell carcinoma of the esophagus. *Int J Cancer*, 71: 192–195. doi:10.1002/(SICI)1097-0215(19970410)71:2<192::AID-IJC11>3.0.CO;2-K PMID:9139841

Morita S, Yano M, Tsujinaka T *et al.* (1999). Genetic polymorphisms of drug-metabolizing enzymes and susceptibility to head-and-neck squamous-cell carcinoma. *Int J Cancer*, 80: 685–688. doi:10.1002/(SICI)1097-0215(19990301)80:5<685::AID-IJC9>3.0.CO;2-W PMID:10048967

Morton LM, Holford TR, Leaderer B *et al.* (2003). Alcohol use and risk of non-Hodgkin's lymphoma among Connecticut women (United States). *Cancer Causes Control*, 14: 687–694. doi:10.1023/A:1025626208861 PMID:14575367

Morton LM, Zheng T, Holford TR *et al.*InterLymph Consortium (2005). Alcohol consumption and risk of non-Hodgkin lymphoma: a pooled analysis. *Lancet Oncol*, 6: 469–476. doi:10.1016/S1470-2045(05)70214-X PMID:15992695

Munaka M, Kohshi K, Kawamoto T *et al.* (2003). Genetic polymorphisms of tobacco- and alcohol-related metabolizing enzymes and the risk of hepatocellular carcinoma. *J Cancer Res Clin Oncol*, 129: 355–360. doi:10.1007/s00432-003-0439-5 PMID:12759747

Murata M, Tagawa M, Watanabe S *et al.* (1999). Genotype difference of aldehyde dehydrogenase 2 gene in alcohol drinkers influences the incidence of Japanese colorectal cancer patients. *Jpn J Cancer Res*, 90: 711–719. doi:10.1111/j.1349-7006.1999.tb00805.x PMID:10470282

Murata M, Takayama K, Choi BCK, Pak AWP (1996). A nested case-control study on alcohol drinking, tobacco smoking, and cancer. *Cancer Detect Prev*, 20: 557–565. PMID:8939341

Murata M, Watanabe M, Yamanaka M *et al.* (2001). Genetic polymorphisms in cytochrome P450 (CYP) 1A1, CYP1A2, CYP2E1, glutathione S-transferase (GST) M1 and GSTT1 and susceptibility to prostate cancer in the Japanese population. *Cancer Lett*, 165: 171–177. doi:10.1016/S0304-3835(01)00398-6 PMID:11275366

Murtaugh MA, Curtin K, Sweeney C *et al.* (2007). Dietary intake of folate and co-factors in folate metabolism, MTHFR polymorphisms, and reduced rectal cancer. *Cancer Causes Control*, 18: 153–163. doi:10.1007/s10552-006-0099-2 PMID:17245555

Muto M, Takahashi M, Ohtsu A *et al.* (2005). Risk of multiple squamous cell carcinomas both in the esophagus and the head and neck region. *Carcinogenesis*, 26: 1008–1012. doi:10.1093/carcin/bgi035 PMID:15718256

Muwonge R, Ramadas K, Sankila R *et al.* (2008). Role of tobacco smoking, chewing and alcohol drinking in the risk of oral cancer in Trivandrum, India: a nested case-control design using incident cancer cases. *Oral Oncol*, 44: 446–454. doi:10.1016/j.oraloncology.2007.06.002 PMID:17933578

Nachiappan V, Mufti SI, Chakravarti A *et al.* (1994). Lipid peroxidation and ethanol-related tumor promotion in Fischer-344 rats treated with tobacco-specific nitrosamines. *Alcohol Alcohol*, 29: 565–574. PMID:7811340

Nakajima M, Takeuchi T, Takeshita T, Morimoto K (1996). 8-Hydroxydeoxyguanosine in human leukocyte DNA and daily health practice factors: effects of individual alcohol sensitivity. *Environ Health Perspect*, 104: 1336–1338. doi:10.2307/3432971 PMID:9118876

Nakaya N, Tsubono Y, Kuriyama S *et al.* (2005). Alcohol consumption and the risk of cancer in Japanese men: the Miyagi cohort study. *Eur J Cancer Prev*, 14: 169–174. doi:10.1097/00008469-200504000-00013 PMID:15785321

Nan HM, Song YJ, Yun HY *et al.* (2005). Effects of dietary intake and genetic factors on hypermethylation of the hMLH1 gene promoter in gastric cancer. *World J Gastroenterol*, 11: 3834–3841. PMID:15991278

Nandakumar A, Anantha N, Dhar M *et al.* (1995). A case-control investigation on cancer of the ovary in Bangalore, India. *Int J Cancer*, 63: 361–365. doi:10.1002/ijc.2910630310 PMID:7591232

Nasca PC, Liu S, Baptiste MS *et al.* (1994). Alcohol consumption and breast cancer: estrogen receptor status and histology. *Am J Epidemiol*, 140: 980–988. PMID:7985660

Navasumrit P, Margison GP, O'Connor PJ (2001a). Ethanol modulates rat hepatic DNA repair functions. *Alcohol Alcohol*, 36: 369–376. PMID:11524300

Navasumrit P, Ward TH, Dodd NJ, O'Connor PJ (2000). Ethanol-induced free radicals and hepatic DNA strand breaks are prevented in vivo by antioxidants: effects of acute and chronic ethanol exposure. *Carcinogenesis*, 21: 93–99. doi:10.1093/carcin/21.1.93 PMID:10607739

Navasumrit P, Ward TH, O'Connor PJ *et al.* (2001b). Ethanol enhances the formation of endogenously and exogenously derived adducts in rat hepatic DNA. *Mutat Res*, 479: 81–94. PMID:11470483

Nelson RA, Levine AM, Marks G, Bernstein L (1997). Alcohol, tobacco and recreational drug use and the risk of non-Hodgkin's lymphoma. *Br J Cancer*, 76: 1532–1537. doi:10.1038/bjc.1997.590 PMID:9400954

Neumark YD, Friedlander Y, Thomasson HR, Li TK (1998). Association of the ADH2*2 allele with reduced ethanol consumption in Jewish men in Israel: a pilot study. *J Stud Alcohol*, 59: 133–139. PMID:9500299

Newcomb PA, Nichols HB, Beasley JM *et al.* (2009). No difference between red wine or white wine consumption and breast cancer risk. *Cancer Epidemiol Biomarkers Prev*, 18: 1007–1010. doi:10.1158/1055-9965.EPI-08-0801 PMID:19273487

Newcomb PA, Trentham-Dietz A, Storer BE (1997). Alcohol consumption in relation to endometrial cancer risk. *Cancer Epidemiol Biomarkers Prev*, 6: 775–778. PMID:9332758

Newton R, Ziegler J, Casabonne D *et al.*Uganda Kaposi's Sarcoma Study Group (2007). A case-control study of cancer of the uterine cervix in Uganda. *Eur J Cancer Prev*, 16: 555–558. doi:10.1097/01.cej.0000243863.22137.b7 PMID:18090129

Nielsen NR & Grønbaek M (2008). Interactions between intakes of alcohol and postmenopausal hormones on risk of breast cancer. *Int J Cancer*, 122: 1109–1113. doi:10.1002/ijc.23195 PMID:17966122

Niemelä O (2007). Acetaldehyde adduct in circulation. *Novartis Found Symp*, 285: 19–197.

Nieters A, Deeg E, Becker N (2006). Tobacco and alcohol consumption and risk of lymphoma: results of a population-based case-control study in Germany. *Int J Cancer*, 118: 422–430. doi:10.1002/ijc.21306 PMID:16080191

Nishimoto IN, Hanaoka T, Sugimura H *et al.* (2000). Cytochrome P450 2E1 polymorphism in gastric cancer in Brazil: case-control studies of Japanese Brazilians and non-Japanese Brazilians. *Cancer Epidemiol. Biomarkers Prev.*, 9: 675–680.

Nishimoto IN, Pinheiro NA, Rogatto SR *et al.* (2004). Alcohol dehydrogenase 3 genotype as a risk factor for upper aerodigestive tract cancers. *Arch Otolaryngol Head Neck Surg*, 130: 78–82. doi:10.1001/archotol.130.1.78 PMID:14732773

Nishino Y, Wakai K, Kondo T *et al.*JACC Study Group (2006). Alcohol consumption and lung cancer mortality in Japanese men: results from Japan collaborative cohort (JACC) study. *J Epidemiol*, 16: 49–56. doi:10.2188/jea.16.49 PMID:16537984

Nomura T, Noma H, Shibahara T *et al.* (2000). Aldehyde dehydrogenase 2 and glutathione S-transferase M 1 polymorphisms in relation to the risk for oral cancer in Japanese drinkers. *Oral Oncol*, 36: 42–46. doi:10.1016/S1368-8375(99)00048-2 PMID:10889918

Novoradovsky A, Tsai SJ, Goldfarb L *et al.* (1995). Mitochondrial aldehyde dehydrogenase polymorphism in Asian and American Indian populations: detection of new ALDH2 alleles. *Alcohol Clin Exp Res*, 19: 1105–1110. doi:10.1111/j.1530-0277.1995.tb01587.x PMID:8561277

NTP (2004). *Toxicology and Carcinogenesis Studies of Urethane, Ethanol, and Urethane/ethanol (Urethane, CAS No.51-79-6; Ethanol, CAS No. 64-17-5) in B6C3F1 Mice (Drinking Water Studies).* Technical Report Series No. 510, Research Triangle Park, NC.

Nuutinen H, Lindros KO, Salaspuro M (1983). Determinants of blood acetaldehyde level during ethanol oxidation in chronic alcoholics. *Alcohol Clin Exp Res*, 7: 163–168. doi:10.1111/j.1530-0277.1983.tb05432.x PMID:6346918

Nuutinen HU, Salaspuro MP, Valle M, Lindros KO (1984). Blood acetaldehyde concentration gradient between hepatic and antecubital venous blood in ethanol-intoxicated alcoholics and controls. *Eur J Clin Invest*, 14: 306–311. doi:10.1111/j.1365-2362.1984.tb01186.x PMID:6434326

O'Neil MJ, editor (2001). *The Merck Index*, 13th ed. Whitehouse Station, NJ, Merck & Co., Inc., pp. 1818

Obe G & Anderson D (1987). International Commission for Protection against Environmental Mutagens and Carcinogens. ICPEMC Working Paper No. 15/1. Genetic effects of ethanol. *Mutat Res*, 186: 177–200. PMID:3313027

Ohishi W, Fujiwara S, Cologne JB *et al.* (2008). Risk factors for hepatocellular carcinoma in a Japanese population: a nested case-control study. *Cancer Epidemiol Biomarkers Prev*, 17: 846–854. doi:10.1158/1055-9965.EPI-07-2806 PMID:18398026

Olivieri EHR, da Silva SD, Mendonça FF *et al.* (2009). CYP1A2*1C, CYP2E1*5B, and GSTM1 polymorphisms are predictors of risk and poor outcome in head and neck squamous cell carcinoma patients. *Oral Oncol*, 45: e73–e79. doi:10.1016/j.oraloncology.2009.03.004 PMID:19442564

Olshan AF, Weissler MC, Watson MA, Bell DA (2001). Risk of head and neck cancer and the alcohol dehydrogenase 3 genotype. *Carcinogenesis*, 22: 57–61. doi:10.1093/carcin/22.1.57 PMID:11159741

Osier MV, Pakstis AJ, Goldman D *et al.* (2002). A proline-threonine substitution in codon 351 of ADH1C is common in Native Americans. *Alcohol Clin Exp Res*, 26: 1759–1763. doi:10.1111/j.1530-0277.2002.tb02481.x PMID:12500098

Ostrovsky YM (1986). Endogenous ethanol–its metabolic, behavioral and biomedical significance. *Alcohol*, 3: 239–247. doi:10.1016/0741-8329(86)90032-7 PMID:3530279

Otani T, Iwasaki M, Hanaoka T *et al.* (2005). Folate, vitamin B6, vitamin B12, and vitamin B2 intake, genetic polymorphisms of related enzymes, and risk of colorectal cancer in a hospital-based case-control study in Japan. *Nutr Cancer*, 53: 42–50. doi:10.1207/s15327914nc5301_5 PMID:16351505

Ough CS (1987). Chemicals used in making wine. *Chem Eng News*, 65: 19–28. doi:10.1021/cen-v065n001.p019

Oyama T, Kawamoto T, Mizoue T *et al.* (1997). Cytochrome P450 2E1 polymorphism as a risk factor for lung cancer: in relation to p53 gene mutation. *Anticancer Res*, 17: 1B583–587. PMID:9066584

Ozasa KJapan Collaborative Cohort Study for Evaluation of Cancer (2007). Alcohol use and mortality in the Japan Collaborative Cohort Study for Evaluation of

Cancer (JACC). *Asian Pac J Cancer Prev*, 8: Suppl81–88. PMID:18260706

Pacella-Norman R, Urban MI, Sitas F *et al.* (2002). Risk factors for oesophageal, lung, oral and laryngeal cancers in black South Africans. *Br J Cancer*, 86: 1751–1756. doi:10.1038/sj.bjc.6600338 PMID:12087462

Pandeya N, Williams G, Green AC *et al.* Australian Cancer Study (2009). Alcohol consumption and the risks of adenocarcinoma and squamous cell carcinoma of the esophagus. *Gastroenterology*, 136: 1215–1224, e1–e2. doi:10.1053/j.gastro.2008.12.052 PMID:19250648

Pandya GA & Moriya M (1996). 1,N6-ethenodeoxyadenosine, a DNA adduct highly mutagenic in mammalian cells. *Biochemistry*, 35: 11487–11492. doi:10.1021/bi960170h PMID:8784204

Parazzini F, La Vecchia C, D'Avanzo B *et al.* (1995a). Alcohol and endometrial cancer risk: findings from an Italian case-control study. *Nutr Cancer*, 23: 55–62. doi:10.1080/01635589509514361 PMID:7739915

Parazzini F, Moroni S, Negri E *et al.* (1995b). Selected food intake and risk of vulvar cancer. *Cancer*, 76: 2291–2296. doi:10.1002/1097-0142(19951201)76:11<2291::AID-CNCR2820761117>3.0.CO;2-W PMID:8635034

Parkin DM, Srivatanakul P, Khlat M *et al.* (1991). Liver cancer in Thailand. I. A case-control study of cholangiocarcinoma. *Int J Cancer*, 48: 323–328. doi:10.1002/ijc.2910480302 PMID:1645697

Parkin DM, Vizcaino AP, Skinner ME, Ndhlovu A (1994). Cancer patterns and risk factors in the African population of southwestern Zimbabwe, 1963–1977. *Cancer Epidemiol Biomarkers Prev*, 3: 537–547. PMID:7827583

Parkinson A, Ogilvie BW (2008). *Biotransformation of Xenobiotics*. In: *Casarett & Doull's Toxicology: The Basic Science of Poisons*. Klaassen CD, editor. Kansas City: McGraw Hill Medical, pp. 161–304.

Pelucchi C, Galeone C, Montella M *et al.* (2008). Alcohol consumption and renal cell cancer risk in two Italian case-control studies. *Ann Oncol*, 19: 1003–1008. doi:10.1093/annonc/mdm590 PMID:18187482

Pelucchi C, La Vecchia C, Negri E *et al.* (2002). Alcohol drinking and renal cell carcinoma in women and men. *Eur J Cancer Prev*, 11: 543–545. doi:10.1097/00008469-200212000-00006 PMID:12457106

Pelucchi C, Mereghetti M, Talamini R *et al.* (2005). Dietary folate, alcohol consumption, and risk of ovarian cancer in an Italian case-control study. *Cancer Epidemiol Biomarkers Prev*, 14: 2056–2058. doi:10.1158/1055-9965.EPI-05-0192 PMID:16103462

Pereira Serafim PV, Cotrim Guerreiro da Silva ID, Manoukias Forones N (2008). Relationship between genetic polymorphism of CYP1A1 at codon 462 (Ile462Val) in colorectal cancer. *Int J Biol Markers*, 23: 18–23. PMID:18409146

Persson I, Johansson I, Bergung H *et al.* (1993). Genetic polymorphism of cytochrome P4502E1 in a Swedish population. Relationship to incidence of lung cancer. *FEBS Lett*, 319: 207–211. doi:10.1016/0014-5793(93)80547-8 PMID:8096192

Persson I, Johansson I, Yue Q-Y *et al.* (1999). Genetic polymorphism of xenobiotic metabolizing enzymes among Chinese lung cancer patients. *Int J Cancer*, 81: 325–329. doi:10.1002/(SICI)1097-0215(19990505)81:3<325::AID-IJC2>3.0.CO;2-S PMID:10209943

Peters ES, McClean MD, Liu M *et al.* (2005). The ADH1C polymorphism modifies the risk of squamous cell carcinoma of the head and neck associated with alcohol and tobacco use. *Cancer Epidemiol Biomarkers Prev*, 14: 476–482. doi:10.1158/1055-9965.EPI-04-0431 PMID:15734975

Peterson NB, Trentham-Dietz A, Newcomb PA *et al.* (2006). Alcohol consumption and ovarian cancer risk in a population-based case-control study. *Int J Cancer*, 119: 2423–2427. doi:10.1002/ijc.22137 PMID:16921486

Petridou E, Koukoulomatis P, Dessypris N *et al.* (2002). Why is endometrial cancer less common in Greece than in other European Union countries? *Eur J Cancer Prev*, 11: 427–432. doi:10.1097/00008469-200210000-00004 PMID:12394239

Phillips BJ & Jenkinson P (2001). Is ethanol genotoxic? A review of the published data. *Mutagenesis*, 16: 91–101. doi:10.1093/mutage/16.2.91 PMID:11230549

Pierce RJ, Kune GA, Kune S *et al.* (1989). Dietary and alcohol intake, smoking pattern, occupational risk, and family history in lung cancer patients: results of a case-control study in males. *Nutr Cancer*, 12: 237–248. doi:10.1080/01635588909514023 PMID:2771801

Pikkarainen P, Baraona E, Seitz H, Lieber CS (1980). Breath acetaldehyde: evidence of acetaldehyde production by oropharynx microflora and by lung microsomes. *Adv Exp Med Biol*, 132: 469–474. PMID:7424726

Pires PW, Furtado KS, Justullin LA Jr *et al.* (2008). Chronic ethanol intake promotes double gluthatione S-transferase/transforming growth factor-alpha-positive hepatocellular lesions in male Wistar rats. *Cancer Sci*, 99: 221–228. doi:10.1111/j.1349-7006.2007.00677.x PMID:18271918

Platz EA, Leitzmann MF, Rimm EB *et al.* (2004). Alcohol intake, drinking patterns, and risk of prostate cancer in a large prospective cohort study. *Am J Epidemiol*, 159: 444–453. doi:10.1093/aje/kwh062 PMID:14977640

Pluskota-Karwatka D, Pawłowicz AJ, Kronberg L (2006). Formation of malonaldehyde-acetaldehyde conjugate adducts in calf thymus DNA. *Chem Res Toxicol*, 19: 921–926. doi:10.1021/tx060027h PMID:16841960

Pogoda JM, Nichols PW, Preston-Martin S (2004). Alcohol consumption and risk of adult-onset acute myeloid leukemia: results from a Los Angeles County case-control study. *Leuk Res*, 28: 927–931. doi:10.1016/j.leukres.2004.01.007 PMID:15234569

Pollack ES, Nomura AM, Heilbrun LK *et al.* (1984). Prospective study of alcohol consumption and

cancer. *N Engl J Med*, 310: 617–621. doi:10.1056/NEJM198403083101003 PMID:6694673

Polychronopoulou A, Tzonou A, Hsieh CC *et al.* (1993). Reproductive variables, tobacco, ethanol, coffee and somatometry as risk factors for ovarian cancer. *Int J Cancer*, 55: 402–407. doi:10.1002/ijc.2910550312 PMID:8375923

Pool-Zobel BL, Dornacher I, Lambertz R *et al.* (2004). Genetic damage and repair in human rectal cells for biomonitoring: sex differences, effects of alcohol exposure, and susceptibilities in comparison to peripheral blood lymphocytes. *Mutat Res*, 551: 127–134. PMID:15225587

Potter JD, Sellers TA, Folsom AR, McGovern PG (1992). Alcohol, beer, and lung cancer in postmenopausal women. The Iowa Women's Health Study. *Ann Epidemiol*, 2: 587–595. doi:10.1016/1047-2797(92)90003-9 PMID:1342310

Powell H, Kitteringham NR, Pirmohamed M *et al.* (1998). Expression of cytochrome P4502E1 in human liver: assessment by mRNA, genotype and phenotype. *Pharmacogenetics*, 8: 411–421. doi:10.1097/00008571-199810000-00006 PMID:9825833

Prescott E, Grønbaek M, Becker U, Sørensen TI (1999). Alcohol intake and the risk of lung cancer: influence of type of alcoholic beverage. *Am J Epidemiol*, 149: 463–470. PMID:10067906

Prior P (1988). Long-term cancer risk in alcoholism. *Alcohol Alcohol*, 23: 163–171. PMID:3390240

Purdue MP, Hashibe M, Berthiller J *et al.* (2009). Type of alcoholic beverage and risk of head and neck cancer–a pooled analysis within the INHANCE Consortium. *Am J Epidemiol*, 169: 132–142. doi:10.1093/aje/kwn306 PMID:19064644

Putnam SD, Cerhan JR, Parker AS *et al.* (2000). Lifestyle and anthropometric risk factors for prostate cancer in a cohort of Iowa men. *Ann Epidemiol*, 10: 361–369. doi:10.1016/S1047-2797(00)00057-0 PMID:10964002

Qin JM, Yang L, Chen B *et al.* (2008). Interaction of methylenetetrahydrofolate reductase C677T, cytochrome P4502E1 polymorphism and environment factors in esophageal cancer in Kazakh population. *World J Gastroenterol*, 14: 6986–6992. doi:10.3748/wjg.14.6986 PMID:19058336

Quiñones L, Lucas D, Godoy J *et al.* (2001). CYP1A1, CYP2E1 and GSTM1 genetic polymorphisms. The effect of single and combined genotypes on lung cancer susceptibility in Chilean people. *Cancer Lett*, 174: 35–44. doi:10.1016/S0304-3835(01)00686-3 PMID:11675150

Rachtan J (2002). Alcoholic beverages consumption and lung cancer cell types among women in Poland. *Lung Cancer*, 35: 119–127. doi:10.1016/S0169-5002(01)00331-2 PMID:11804683

Rachtan J & Sokolowski A (1997). Risk factors for lung cancer among women in Poland. *Lung Cancer*, 18: 137–145. doi:10.1016/S0169-5002(97)00062-7 PMID:9316005

Radike MJ, Stemmer KL, Bingham E (1981). Effect of ethanol on vinyl chloride carcinogenesis. *Environ Health Perspect*, 41: 59–62. doi:10.1289/ehp.814159 PMID:6277614

Rauscher GH, Shore D, Sandler DP (2004). Alcohol intake and incidence of de novo adult acute leukemia. *Leuk Res*, 28: 1263–1265. doi:10.1016/j.leukres.2004.04.004 PMID:15475066

Rehm J, Patra J, Popova S (2007). Alcohol drinking cessation and its effect on esophageal and head and neck cancers: a pooled analysis. *Int J Cancer*, 121: 1132–1137. doi:10.1002/ijc.22798 PMID:17487833

Ribas G, Milne RL, Gonzalez-Neira A, Benítez J (2008). Haplotype patterns in cancer-related genes with long-range linkage disequilibrium: no evidence of association with breast cancer or positive selection. *Eur J Hum Genet*, 16: 252–260. doi:10.1038/sj.ejhg.5201953 PMID:18000525

Riman T, Dickman PW, Nilsson S *et al.* (2004). Some lifestyle factors and the risk of invasive epithelial ovarian cancer in Swedish women. *Eur J Epidemiol*, 19: 1011–1019. doi:10.1007/s10654-004-1633-8 PMID:15648594

Risch A, Ramroth H, Raedts V *et al.* (2003). Laryngeal cancer risk in Caucasians is associated with alcohol and tobacco consumption but not modified by genetic polymorphisms in class I alcohol dehydrogenases ADH1B and ADH1C, and glutathione-S-transferases GSTM1 and GSTT1. *Pharmacogenetics*, 13: 225–230. doi:10.1097/00008571-200304000-00007 PMID:12668919

Robbins WA, Vine MF, Truong KY, Everson RB (1997). Use of fluorescence in situ hybridization (FISH) to assess effects of smoking, caffeine, and alcohol on aneuploidy load in sperm of healthy men. *Environ Mol Mutagen*, 30: 175–183. doi:10.1002/(SICI)1098-2280(1997)30:2<175::AID-EM10>3.0.CO;2-A PMID:9329642

Robinette CD, Hrubec Z, Fraumeni JF Jr (1979). Chronic alcoholism and subsequent mortality in World War II veterans. *Am J Epidemiol*, 109: 687–700. PMID:453188

Rod NH, Hansen AM, Nielsen J *et al.* (2009). Low-risk factor profile, estrogen levels, and breast cancer risk among postmenopausal women. *Int J Cancer*, 124: 1935–1940. doi:10.1002/ijc.24136 PMID:19123466

Rogers J, Smith J, Starmer GA, Whitfield JB (1987). Differing effects of carbohydrate, fat and protein on the rate of ethanol metabolism. *Alcohol Alcohol*, 22: 345–353. PMID:3426763

Rohrmann S, Linseisen J, Boshuizen HC *et al.* (2006). Ethanol intake and risk of lung cancer in the European Prospective Investigation into Cancer and Nutrition (EPIC). *Am J Epidemiol*, 164: 1103–1114. doi:10.1093/aje/kwj326 PMID:16987924

Rohrmann S, Linseisen J, Key TJ *et al.* (2008). Alcohol consumption and the risk for prostate cancer in the European Prospective Investigation into Cancer and Nutrition. *Cancer Epidemiol Biomarkers Prev*, 17: 1282–1287. doi:10.1158/1055-9965.EPI-07-2888 PMID:18483352

Rohrmann S, Linseisen J, Vrieling A *et al.* (2009). Ethanol intake and the risk of pancreatic cancer in the European Prospective Investigation into Cancer and Nutrition (EPIC). *Cancer Causes Control*, 20: 785–794. doi:10.1007/s10552-008-9293-8 PMID:19145468

Rossini A, Rapozo DCM, Soares Lima SC *et al.* (2007). Polymorphisms of GSTP1 and GSTT1, but not of CYP2A6, CYP2E1 or GSTM1, modify the risk for esophageal cancer in a western population. *Carcinogenesis*, 28: 2537–2542. doi:10.1093/carcin/bgm222 PMID:17916905

Roy HK, Gulizia JM, Karolski WJ *et al.* (2002). Ethanol promotes intestinal tumorigenesis in the MIN mouse. Multiple intestinal neoplasia. *Cancer Epidemiol Biomarkers Prev*, 11: 1499–1502. PMID:12433735

Ruano-Ravina A, Figueiras A, Barros-Dios JM (2004). Type of wine and risk of lung cancer: a case-control study in Spain. *Thorax*, 59: 981–985. doi:10.1136/thx.2003.018861 PMID:15516476

Rudant J, Menegaux F, Leverger G *et al.* (2008). Childhood hematopoietic malignancies and parental use of tobacco and alcohol: the ESCALE study (SFCE). *Cancer Causes Control*, 19: 1277–1290. doi:10.1007/s10552-008-9199-5 PMID:18618277

Ruwali M, Khan AJ, Shah PP *et al.* (2009). Cytochrome P450 2E1 and head and neck cancer: interaction with genetic and environmental risk factors. *Environ Mol Mutagen*, 50: 473–482. doi:10.1002/em.20488 PMID:19334053

Sakamoto T, Hara M, Higaki Y *et al.* (2006). Influence of alcohol consumption and gene polymorphisms of ADH2 and ALDH2 on hepatocellular carcinoma in a Japanese population. *Int J Cancer*, 118: 1501–1507. doi:10.1002/ijc.21505 PMID:16187278

Salaspuro MP (2003). Acetaldehyde, microbes, and cancer of the digestive tract. *Crit Rev Clin Lab Sci*, 40: 183–208. doi:10.1080/713609333 PMID:12755455

Schmidt W & Popham RE (1981). The role of drinking and smoking in mortality from cancer and other causes in male alcoholics. *Cancer*, 47: 1031–1041. doi:10.1002/1097-0142(19810301)47:5<1031::AID-CNCR2820470534>3.0.CO;2-C PMID:7226036

Schouten LJ, Zeegers MPA, Goldbohm RA, van den Brandt PA (2004). Alcohol and ovarian cancer risk: results from the Netherlands Cohort Study. *Cancer Causes Control*, 15: 201–209. doi:10.1023/B:CACO.0000019512.71560.2b PMID:15017133

Schuurman AG, Goldbohm RA, van den Brandt PA (1999). A prospective cohort study on consumption of alcoholic beverages in relation to prostate cancer incidence (The Netherlands). *Cancer Causes Control*, 10: 597–605. doi:10.1023/A:1008925103542 PMID:10616828

Schwartz SM, Doody DR, Fitzgibbons ED *et al.* (2001). Oral squamous cell cancer risk in relation to alcohol consumption and alcohol dehydrogenase-3 genotypes. *Cancer Epidemiol Biomarkers Prev*, 10: 1137–1144. PMID:11700261

Seitz HK, Egerer G, Oneta C *et al.* (1996). Alcohol dehydrogenase in the human colon and rectum. *Digestion*, 57: 105–108. doi:10.1159/000201322 PMID:8785998

Sesso HD, Paffenbarger RS Jr, Lee IM (2001). Alcohol consumption and risk of prostate cancer: The Harvard Alumni Health Study. *Int J Epidemiol*, 30: 749–755. doi:10.1093/ije/30.4.749 PMID:11511598

Setiawan VW, Monroe KR, Goodman MT *et al.* (2008). Alcohol consumption and endometrial cancer risk: the multiethnic cohort. *Int J Cancer*, 122: 634–638. doi:10.1002/ijc.23072 PMID:17764072

Setiawan VW, Monroe KR, Wilkens LR *et al.* (2009). Breast cancer risk factors defined by estrogen and progesterone receptor status: the multiethnic cohort study. *Am J Epidemiol*, 169: 1251–1259. doi:10.1093/aje/kwp036 PMID:19318616

Severson RK, Buckley JD, Woods WG *et al.* (1993). Cigarette smoking and alcohol consumption by parents of children with acute myeloid leukemia: an analysis within morphological subgroups–a report from the Childrens Cancer Group. *Cancer Epidemiol Biomarkers Prev*, 2: 433–439. PMID:8220087

Shaib YH, El-Serag HB, Nooka AK *et al.* (2007). Risk factors for intrahepatic and extrahepatic cholangiocarcinoma: a hospital-based case-control study. *Am J Gastroenterol*, 102: 1016–1021. doi:10.1111/j.1572-0241.2007.01104.x PMID:17324130

Sharpe CR & Siemiatycki J (2001). Case-control study of alcohol consumption and prostate cancer risk in Montréal, Canada. *Cancer Causes Control*, 12: 589–598. doi:10.1023/A:1011289108040 PMID:11552706

Sherman D, Davé V, Hsu LC *et al.* (1993). Diverse polymorphism within a short coding region of the human aldehyde dehydrogenase-5 (ALDH5) gene. *Hum Genet*, 92: 477–480. doi:10.1007/BF00216454 PMID:8244338

Shibata A, Fukuda K, Nishiyori A *et al.* (1998). A case-control study on male hepatocellular carcinoma based on hospital and community controls. *J Epidemiol*, 8: 1–5. doi:10.2188/jea.8.1 PMID:9575688

Shibayama Y, Nishijima A, Asaka S, Nakata K (1993). Influence of chronic alcohol consumption on the development of altered hepatocellular foci in rats. *Exp Toxicol Pathol*, 45: 15–19. doi:10.1016/S0940-2993(11)80442-2 PMID:8467195

Shimazu T, Inoue M, Sasazuki S *et al.* Japan Public Health Center-based Prospective Study Group (2008). Alcohol and risk of lung cancer among Japanese men: data from a large-scale population-based cohort study, the

JPHC study. *Cancer Causes Control*, 19: 1095–1102. doi:10.1007/s10552-008-9173-2 PMID:18493860

Shin HR, Lee CU, Park HJ *et al.* (1996). Hepatitis B and C virus, Clonorchis sinensis for the risk of liver cancer: a case-control study in Pusan, Korea. *Int J Epidemiol*, 25: 933–940. doi:10.1093/ije/25.5.933 PMID:8921477

Shu XO, Brinton LA, Zheng W *et al.* (1991). A population-based case-control study of endometrial cancer in Shanghai, China. *Int J Cancer*, 49: 38–43. doi:10.1002/ijc.2910490108 PMID:1874568

Shu CC, Hoffman WE, Thomas C, Albrecht RF (1993). Sympathetic activity enhances glucose-related ischemic injury in the rat.). Sympathetic activity enhances glucose-related ischemic injury in the rat. *Anesthesiology*, 78: 1120–1125. doi:10.1097/00000542-199306000-00015 PMID:8099768

Shu XO, Ross JA, Pendergrass TW *et al.* (1996). Parental alcohol consumption, cigarette smoking, and risk of infant leukemia: a Childrens Cancer Group study. *J Natl Cancer Inst*, 88: 24–31. doi:10.1093/jnci/88.1.24 PMID:8847721

Sigvardsson S, Hardell L, Przybeck TR, Cloninger R (1996). Increased cancer risk among Swedish female alcoholics. *Epidemiology*, 7: 140–143. doi:10.1097/00001648-199603000-00006 PMID:8834552

Singletary K, Nelshoppen J, Wallig M (1995). Enhancement by chronic ethanol intake of N-methyl-N-nitrosourea-induced rat mammary tumorigenesis. *Carcinogenesis*, 16:959–964. doi:10.1093/carcin/16.4.959 PMID:7728981

Soffritti M, Belpoggi F, Cevolani D *et al.* (2002a). Results of long-term experimental studies on the carcinogenicity of methyl alcohol and ethyl alcohol in rats. *Ann N Y Acad Sci*, 982: 46–69. doi:10.1111/j.1749-6632.2002.tb04924.x PMID:12562628

Soffritti M, Belpoggi F, Lambertin L *et al.* (2002b). Results of long-term experimental studies on the carcinogenicity of formaldehyde and acetaldehyde in rats. *Ann N Y Acad Sci*, 982: 87–105. doi:10.1111/j.1749-6632.2002.tb04926.x PMID:12562630

Solomon PR, Selvam GS, Shanmugam G (2008). Polymorphism in ADH and MTHFR genes in oral squamous cell carcinoma of Indians. *Oral Dis*, 14: 633–639. doi:10.1111/j.1601-0825.2007.01437.x PMID:18266839

Sørensen HT, Friis S, Olsen JH *et al.* (1998). Risk of liver and other types of cancer in patients with cirrhosis: a nationwide cohort study in Denmark. *Hepatology*, 28: 921–925. doi:10.1002/hep.510280404 PMID:9755226

Soya SS, Vinod T, Reddy KS *et al.* (2008). CYP2E1 polymorphisms and gene-environment interactions in the risk of upper aerodigestive tract cancers among Indians. *Pharmacogenomics*, 9: 551–560. doi:10.2217/14622416.9.5.551 PMID:18466102

Speit G, Fröhler-Keller M, Schütz P, Neuss S (2008). Low sensitivity of the comet assay to detect acetaldehyde-induced genotoxicity. *Mutat Res*, 657: 93–97. PMID:18755289

Spence JP, Liang T, Eriksson CJP *et al.* (2003). Evaluation of aldehyde dehydrogenase 1 promoter polymorphisms identified in human populations. *Alcohol Clin Exp Res*, 27: 1389–1394. doi:10.1097/01.ALC.0000087086.50089.59 PMID:14506398

Spinucci G, Guidetti M, Lanzoni E, Pironi L (2006). Endogenous ethanol production in a patient with chronic intestinal pseudo-obstruction and small intestinal bacterial overgrowth. *Eur J Gastroenterol Hepatol*, 18: 799–802. doi:10.1097/01.meg.0000223906.55245.61 PMID:16772842

Sriamporn S, Wiangnon S, Suwanrungruang K *et al.* (2007). Risk factors for colorectal cancer in northeast Thailand: lifestyle related. *Asian Pac J Cancer Prev*, 8: 573–577. PMID:18260731

Stein S, Lao Y, Yang IY *et al.* (2006). Genotoxicity of acetaldehyde- and crotonaldehyde-induced 1,N2-propanodeoxyguanosine DNA adducts in human cells. *Mutat Res*, 608: 1–7. PMID:16797223

Stemmermann GN, Nomura AMY, Chyou P-H, Yoshizawa C (1990). Prospective study of alcohol intake and large bowel cancer. *Dig Dis Sci*, 35: 1414–1420. doi:10.1007/BF01536750 PMID:2226103

Sturgeon SR, Ziegler RG, Brinton LA *et al.* (1991). Diet and the risk of vulvar cancer. *Ann Epidemiol*, 1: 427–437. doi:10.1016/1047-2797(91)90012-2 PMID:1669523

Sturgis EM, Dahlstrom KR, Guan Y *et al.* (2001). Alcohol dehydrogenase 3 genotype is not associated with risk of squamous cell carcinoma of the oral cavity and pharynx. *Cancer Epidemiol Biomarkers Prev*, 10: 273–275. PMID:11303599

Sugimura T, Kumimoto H, Tohnai I *et al.* (2006). Gene-environment interaction involved in oral carcinogenesis: molecular epidemiological study for metabolic and DNA repair gene polymorphisms. *J Oral Pathol Med*, 35: 11–18. doi:10.1111/j.1600-0714.2005.00364.x PMID:16393248

Sung NY, Choi KS, Park EC *et al.* (2007). Smoking, alcohol and gastric cancer risk in Korean men: the National Health Insurance Corporation Study. *Br J Cancer*, 97: 700–704. doi:10.1038/sj.bjc.6603893 PMID:17637680

Sutcliffe S, Giovannucci E, Leitzmann MF *et al.* (2007). A prospective cohort study of red wine consumption and risk of prostate cancer. *Int J Cancer*, 120: 1529–1535. doi:10.1002/ijc.22498 PMID:17211860

Suzuki R, Orsini N, Mignone L *et al.* (2008). Alcohol intake and risk of breast cancer defined by estrogen and progesterone receptor status — a meta-analysis of epidemiological studies. *Int J Cancer* 122: 1832–1841. EIN - *Int J Cancer*, 123: 981

Swanson CA, Wilbanks GD, Twiggs LB *et al.* (1993). Moderate alcohol consumption and the risk of endometrial cancer. *Epidemiology*, 4: 530–536. doi:10.1097/00001648-199311000-00009 PMID:8268282

Takeshita T, Morimoto K, Yamaguchi N *et al.* (2000a). Relationships between cigarette smoking, alcohol drinking, the ALDH2 genotype and adenomatous types of colorectal polyps in male self-defense force officials. *J Epidemiol*, 10: 366–371. doi:10.2188/jea.10.366 PMID:11210104

Takeshita T, Yang X, Inoue Y *et al.* (2000b). Relationship between alcohol drinking, ADH2 and ALDH2 genotypes, and risk for hepatocellular carcinoma in Japanese. *Cancer Lett*, 149: 69–76. doi:10.1016/S0304-3835(99)00343-2 PMID:10737710

Takezaki T, Inoue M, Kataoka H *et al.* (2003). Diet and lung cancer risk from a 14-year population-based prospective study in Japan: with special reference to fish consumption. *Nutr Cancer*, 45: 160–167. doi:10.1207/S15327914NC4502_04 PMID:12881009

Tan W, Song N, Wang GQ *et al.* (2000). Impact of genetic polymorphisms in cytochrome P450 2E1 and glutathione S-transferases M1, T1, and P1 on susceptibility to esophageal cancer among high-risk individuals in China. *Cancer Epidemiol Biomarkers Prev*, 9: 551–556. PMID:10868687

Tanabe H, Ohhira M, Ohtsubo T *et al.* (1999). Genetic polymorphism of aldehyde dehydrogenase 2 in patients with upper aerodigestive tract cancer. *Alcohol Clin Exp Res*, 23: Suppl17S–20S. doi:10.1111/j.1530-0277.1999.tb04527.x PMID:10235272

Tanaka T, Nishikawa A, Iwata H *et al.* (1989). Enhancing effect of ethanol on aflatoxin B1-induced hepatocarcinogenesis in male ACI/N rats. *Jpn J Cancer Res*, 80: 526–530. doi:10.1111/j.1349-7006.1989.tb01671.x PMID:2474524

Tatsuta M, Iishi H, Baba M *et al.* (1997). Enhancement by ethyl alcohol of experimental hepatocarcinogenesis induced by N-nitrosomorpholine. *Int J Cancer*, 71: 1045–1048. doi:10.1002/(SICI)1097-0215(19970611)71:6<1045::AID-IJC21>3.0.CO;2-B PMID:9185709

Tavani A, Gallus S, Dal Maso L *et al.* (2001a). Coffee and alcohol intake and risk of ovarian cancer: an Italian case-control study. *Nutr Cancer*, 39: 29–34. doi:10.1207/S15327914nc391_4 PMID:11588899

Tavani A, Gallus S, La Vecchia C, Franceschi S (2001b). Alcohol drinking and risk of non-Hodgkin's lymphoma. *Eur J Clin Nutr*, 55: 824–826. doi:10.1038/sj.ejcn.1601245 PMID:11593342

Tavani A, Pregnolato A, Negri E *et al.* (1997). Diet and risk of lymphoid neoplasms and soft tissue sarcomas. *Nutr Cancer*, 27: 256–260. doi:10.1080/01635589709514535 PMID:9101555

Terelius Y, Norsten-Höög C, Cronholm T, Ingelman-Sundberg M (1991). Acetaldehyde as a substrate for ethanol-inducible cytochrome P450 (CYP2E1). *Biochem Biophys Res Commun*, 179: 689–694. doi:10.1016/0006-291X(91)91427-E PMID:1822117

Terry MB, Gammon MD, Zhang FF *et al.* (2006). ADH3 genotype, alcohol intake and breast cancer risk. *Carcinogenesis*, 27: 840–847. doi:10.1093/carcin/bgi285 PMID:16344274

Terry MB, Gammon MD, Zhang FF *et al.* (2007a). Alcohol dehydrogenase 3 and risk of esophageal and gastric adenocarcinomas. *Cancer Causes Control*, 18: 1039–1046. doi:10.1007/s10552-007-9046-0 PMID:17665311

Terry MB, Knight JA, Zablotska L *et al.* (2007). Alcohol metabolism, alcohol intake, and breast cancer risk: a sister-set analysis using the Breast Cancer Family Registry. *Breast Cancer Res Treat*, 106: 281–288. doi:10.1007/s10549-007-9498-7 PMID:17268812

Terry MB, Knight JA, Zablotska L *et al.* (2007b). Alcohol metabolism, alcohol intake, and breast cancer risk: a sister-set analysis using the Breast Cancer Family Registry. *Breast Cancer Res Treat*, 106: 281–288. doi:10.1007/s10549-007-9498-7 PMID:17268812

Terry P, Baron JA, Weiderpass E *et al.* (1999). Lifestyle and endometrial cancer risk: a cohort study from the Swedish Twin Registry. *Int J Cancer*, 82: 38–42. doi:10.1002/(SICI)1097-0215(19990702)82:1<38::AID-IJC8>3.0.CO;2-Q PMID:10360818

Theruvathu JA, Jaruga P, Nath RG *et al.* (2005). Polyamines stimulate the formation of mutagenic 1,N2-propanodeoxyguanosine adducts from acetaldehyde. *Nucleic Acids Res*, 33: 3513–3520. doi:10.1093/nar/gki661 PMID:15972793

Thomas DB, Qin Q, Kuypers J *et al.* (2001b). Human papillomaviruses and cervical cancer in Bangkok. II. Risk factors for in situ and invasive squamous cell cervical carcinomas. *Am J Epidemiol*, 153: 732–739. doi:10.1093/aje/153.8.732 PMID:11296144

Thomas DB, Ray RM, Koetsawang A *et al.* (2001a). Human papillomaviruses and cervical cancer in Bangkok. I. Risk factors for invasive cervical carcinomas with human papillomavirus types 16 and 18 DNA. *Am J Epidemiol*, 153: 723–731. doi:10.1093/aje/153.8.723 PMID:11296143

Thun MJ, Hannan LM, DeLancey JO (2009). Alcohol consumption not associated with lung cancer mortality in lifelong nonsmokers. *Cancer Epidemiol Biomarkers Prev*, 18: 2269–2272. doi:10.1158/1055-9965.EPI-09-0361 PMID:19661085

Thygesen LC, Keiding N, Johansen C, Grønbaek M (2007). Changes in alcohol intake and risk of upper digestive tract cancer. *Acta Oncol*, 46: 1085–1089. doi:10.1080/02841860701441806 PMID:17851863

Thygesen LC, Mikkelsen P, Andersen TV *et al.* (2009). Cancer incidence among patients with alcohol use disorders–long-term follow-up. *Alcohol Alcohol*, 44: 387–391. PMID:19491282

Thygesen LC, Mørch LS, Keiding N *et al.* (2008a). Use of baseline and updated information on alcohol intake on risk for breast cancer: importance of latency. *Int*

J Epidemiol, 37: 669–677. doi:10.1093/ije/dyn060 PMID:18390878

Thygesen LC, Wu K, Grønbaek M *et al.* (2008b). Alcohol intake and colorectal cancer: a comparison of approaches for including repeated measures of alcohol consumption. *Epidemiology*, 19: 258–264. doi:10.1097/EDE.0b013e31816339e0 PMID:18300715

Tian D, Feng Z, Hanley NM *et al.* (1998). Multifocal accumulation of p53 protein in esophageal carcinoma: evidence for field cancerization. *Int J Cancer*, 78: 568–575. doi:10.1002/(SICI)1097-0215(19981123)78:5<568::AID-IJC7>3.0.CO;2-3 PMID:9808524

Tiemersma EW, Wark PA, Ocké MC *et al.* (2003). Alcohol consumption, alcohol dehydrogenase 3 polymorphism, and colorectal adenomas. *Cancer Epidemiol Biomarkers Prev*, 12: 419–425. PMID:12750236

Tønnesen H, Møller H, Andersen JR *et al.* (1994). Cancer morbidity in alcohol abusers. *Br J Cancer*, 69: 327–332. doi:10.1038/bjc.1994.59 PMID:8297729

Toriola AT, Kurl S, Laukanen JA *et al.* (2008). Alcohol consumption and risk of colorectal cancer: the Findrink study. *Eur J Epidemiol*, 23: 395–401. doi:10.1007/s10654-008-9244-4 PMID:18409007

Toriola AT, Kurl S, Laukkanen JA, Kauhanen J (2009). Does binge drinking increase the risk of lung cancer: results from the Findrink study. *Eur J Public Health*, 19: 389–393. doi:10.1093/eurpub/ckp049 PMID:19369490

Tramacere I, Scotti L, Jenab M *et al.* (2009). Alcohol drinking and pancreatic cancer risk: a meta-analysis of the dose-risk relation. *Int J Cancer*, In press PMID:19816941

Trentham-Dietz A, Newcomb PA, Nichols HB, Hampton JM (2007). Breast cancer risk factors and second primary malignancies among women with breast cancer. *Breast Cancer Res Treat*, 105: 195–207. doi:10.1007/s10549-006-9446-y PMID:17186360

Triano EA, Slusher LB, Atkins TA *et al.* (2003). Class I alcohol dehydrogenase is highly expressed in normal human mammary epithelium but not in invasive breast cancer: implications for breast carcinogenesis. *Cancer Res*, 63: 3092–3100. PMID:12810634

Trivers KF, Lund MJ, Porter PL *et al.* (2009). The epidemiology of triple-negative breast cancer, including race. *Cancer Causes Control*, 20: 1071–1082. doi:10.1007/s10552-009-9331-1 PMID:19343511

Tsong WH, Koh WP, Yuan JM *et al.* (2007). Cigarettes and alcohol in relation to colorectal cancer: the Singapore Chinese Health Study. *Br J Cancer*, 96: 821–827. doi:10.1038/sj.bjc.6603623 PMID:17311023

Tsutsumi M, George J, Ishizawa K *et al.* (2006). Effect of chronic dietary ethanol in the promotion of N-nitrosomethylbenzylamine-induced esophageal carcinogenesis in rats. *J Gastroenterol Hepatol*, 21: 805–813. doi:10.1111/j.1440-1746.2005.04040.x PMID:16704527

Tsutsumi M, Takase S, Takada A (1993). Genetic factors related to the development of carcinoma in digestive organs in alcoholics. *Alcohol Alcohol Suppl*, 1B: 21–26. PMID:8003125

Tsutsumi M, Wang JS, Takase S, Takada A (1994). Hepatic messenger RNA contents of cytochrome P4502E1 in patients with different P4502E1 genotypes. *Alcohol Alcohol Suppl*, 29: Suppl.29–32. PMID:9063815

Tworoger SS, Gertig DM, Gates MA *et al.* (2008). Caffeine, alcohol, smoking, and the risk of incident epithelial ovarian cancer. *Cancer*, 112: 1169–1177. doi:10.1002/cncr.23275 PMID:18213613

Tzonou A, Day NE, Trichopoulos D *et al.* (1984). The epidemiology of ovarian cancer in Greece: a case-control study. *Eur J Cancer Clin Oncol*, 20: 1045–1052. doi:10.1016/0277-5379(84)90107-X PMID:6540687

Upton DC, Wang X, Blans P *et al.* (2006). Mutagenesis by exocyclic alkylamino purine adducts in Escherichia coli. *Mutat Res*, 599: 1–10. doi:10.1016/j.mrfmmm.2005.12.014 PMID:16488449

Väkeväinen S, Tillonen J, Salaspuro M (2001). 4-Methylpyrazole decreases salivary acetaldehyde levels in aldh2-deficient subjects but not in subjects with normal aldh2. *Alcohol Clin Exp Res*, 25: 829–834. doi:10.1111/j.1530-0277.2001.tb02286.x PMID:11410717

Väkeväinen S, Tillonen J, Salaspuro M *et al.* (2000). Hypochlorhydria induced by a proton pump inhibitor leads to intragastric microbial production of acetaldehyde from ethanol. *Aliment Pharmacol Ther*, 14: 1511–1518. doi:10.1046/j.1365-2036.2000.00858.x PMID:11069323

van der Logt EMJ, Bergevoet SM, Roelofs HMJ *et al.* (2006). Role of epoxide hydrolase, NAD(P)H:quinone oxidoreductase, cytochrome P450 2E1 or alcohol dehydrogenase genotypes in susceptibility to colorectal cancer. *Mutat Res*, 593: 39–49. doi:10.1016/j.mrfmmm.2005.06.018 PMID:16039674

van Dijk BAC, van Houwelingen KP, Witjes JA *et al.* (2001). Alcohol dehydrogenase type 3 (ADH3) and the risk of bladder cancer. *Eur Urol*, 40: 509–514. doi:10.1159/000049827 PMID:11752857

van Duijn CM, van Steensel-Moll HA, Coebergh JW, van Zanen GE (1994). Risk factors for childhood acute non-lymphocytic leukemia: an association with maternal alcohol consumption during pregnancy? *Cancer Epidemiol Biomarkers Prev*, 3: 457–460. PMID:8000294

van Zeeland AA, de Groot AJ, Hall J, Donato F (1999). 8-Hydroxydeoxyguanosine in DNA from leukocytes of healthy adults: relationship with cigarette smoking, environmental tobacco smoke, alcohol and coffee consumption. *Mutat Res*, 439: 249–257. PMID:10023075

Vasiliou V, Pappa A, Estey T (2004). Role of human aldehyde dehydrogenases in endobiotic and xenobiotic

metabolism. *Drug Metab Rev*, 36: 279–299. doi:10.1081/DMR-120034001 PMID:15237855

Vasiliou V, Pappa A, Petersen DR (2000). Role of aldehyde dehydrogenases in endogenous and xenobiotic metabolism. *Chem Biol Interact*, 129: 1–19. doi:10.1016/S0009-2797(00)00211-8 PMID:11154732

Vaughan TL, Shapiro JA, Burt RD *et al.* (1996). Nasopharyngeal cancer in a low-risk population: defining risk factors by histological type. *Cancer Epidemiol Biomarkers Prev*, 5: 587–593. PMID:8824359

Velicer CM, Kristal A, White E (2006). Alcohol use and the risk of prostate cancer: results from the VITAL cohort study. *Nutr Cancer*, 56: 50–56. doi:10.1207/s15327914nc5601_7 PMID:17176217

Vioque J, Barber X, Bolumar F *et al.*PANESOES Study Group (2008). Esophageal cancer risk by type of alcohol drinking and smoking: a case-control study in Spain. *BMC Cancer*, 8: 221 doi:10.1186/1471-2407-8-221 PMID:18673563

Visapää JP, Götte K, Benesova M *et al.* (2004). Increased cancer risk in heavy drinkers with the alcohol dehydrogenase 1C*1 allele, possibly due to salivary acetaldehyde. *Gut*, 53: 871–876. doi:10.1136/gut.2003.018994 PMID:15138216

Visvanathan K, Crum RM, Strickland PT *et al.* (2007). Alcohol dehydrogenase genetic polymorphisms, low-to-moderate alcohol consumption, and risk of breast cancer. *Alcohol Clin Exp Res*, 31: 467–476. doi:10.1111/j.1530-0277.2006.00334.x PMID:17295732

Wakabayashi I, Sakamoto K, Masui H *et al.* (1994). A case-control study on risk factors for leukemia in a district of Japan. *Intern Med*, 33: 198–203. doi:10.2169/internalmedicine.33.198 PMID:8069013

Wakai K, Nagata C, Mizoue T *et al.*Research Group for the Development and Evaluation of Cancer Prevention Strategies in Japan (2007). Alcohol drinking and lung cancer risk: an evaluation based on a systematic review of epidemiologic evidence among the Japanese population. *Jpn J Clin Oncol*, 37: 168–174. doi:10.1093/jjco/hyl146 PMID:17332056

Walker AR, Walker BF, Tsotetsi NG *et al.* (1992). Case-control study of prostate cancer in black patients in Soweto, South Africa. *Br J Cancer*, 65: 438–441. doi:10.1038/bjc.1992.89 PMID:1558801

Wang D, Ritchie JM, Smith EM *et al.* (2005). Alcohol dehydrogenase 3 and risk of squamous cell carcinomas of the head and neck. *Cancer Epidemiol Biomarkers Prev*, 14: 626–632. doi:10.1158/1055-9965.EPI-04-0343 PMID:15767341

Wang J, Gajalakshmi V, Jiang J *et al.* (2006a). Associations between 5,10-methylenetetrahydrofolate reductase codon 677 and 1298 genetic polymorphisms and environmental factors with reference to susceptibility to colorectal cancer: a case-control study in an Indian population. *Int J Cancer*, 118: 991–997. doi:10.1002/ijc.21438 PMID:16152599

Wang M, McIntee EJ, Cheng G *et al.* (2000). Identification of DNA adducts of acetaldehyde. *Chem Res Toxicol*, 13: 1149–1157. doi:10.1021/tx000118t PMID:11087437

Wang M, Yu N, Chen L *et al.* (2006c). Identification of an acetaldehyde adduct in human liver DNA and quantitation as N2-ethyldeoxyguanosine. *Chem Res Toxicol*, 19: 319–324. doi:10.1021/tx0502948 PMID:16485909

Wang Y, Millonig G, Nair J *et al.* (2009). Ethanol-induced cytochrome P4502E1 causes carcinogenic etheno-DNA lesions in alcoholic liver disease. *Hepatology*, 50: 453–461. doi:10.1002/hep.22978 PMID:19489076

Wang Z, Tang L, Sun G *et al.* (2006b). Etiological study of esophageal squamous cell carcinoma in an endemic region: a population-based case control study in Huaian, China. *BMC Cancer*, 6: 287 doi:10.1186/1471-2407-6-287 PMID:17173682

Wanibuchi H, Wei M, Karim MR *et al.* (2006). Existence of no hepatocarcinogenic effect levels of 2-amino-3,8-dimethylimidazo[4,5-f]quinoxaline with or without coadministration with ethanol. *Toxicol Pathol*, 34: 232–236. doi:10.1080/01926230600713632 PMID:16698719

Watabiki T, Okii Y, Tokiyasu T *et al.* (2000). Long-term ethanol consumption in ICR mice causes mammary tumor in females and liver fibrosis in males. *Alcohol Clin Exp Res*, 24: Suppl117S–122S. PMID:10803793

Watanabe J, Hayashi S, Kawajiri K (1994). Different regulation and expression of the human CYP2E1 gene due to the RsaI polymorphism in the 5 -flanking region. *J Biochem*, 116: 321–326. PMID:7529759

Watanabe J, Yang JP, Eguchi H *et al.* (1995). An Rsa I polymorphism in the CYP2E1 gene does not affect lung cancer risk in a Japanese population. *Jpn J Cancer Res*, 86: 245–248. doi:10.1111/j.1349-7006.1995.tb03046.x PMID:7744693

Watanabe S, Sasahara K, Kinekawa F *et al.* (2002). Aldehyde dehydrogenase-2 genotypes and HLA haplotypes in Japanese patients with esophageal cancer. *Oncol Rep*, 9: 1063–1068. PMID:12168074

Watanabe-Suzuki K, Seno H, Ishii A *et al.* (1999). Ultrasensitive method for determination of ethanol in whole blood by headspace capillary gas chromatography with cryogenic oven trapping. *J Chromatogr B Biomed Sci Appl*, 727: 89–94. doi:10.1016/S0378-4347(99)00063-8 PMID:10360426

Webb PM, Purdie DM, Bain CJ, Green AC (2004). Alcohol, wine, and risk of epithelial ovarian cancer. *Cancer Epidemiol Biomarkers Prev*, 13: 592–599. PMID:15066924

Webster LA & Weiss NSCancer and Steroid Hormone Study Group (1989). Alcoholic beverage consumption and the risk of endometrial cancer. *Int J Epidemiol*, 18: 786–791. doi:10.1093/ije/18.4.786 PMID:2695474

Wei YS, Lu JC, Wang L *et al.* (2009). Risk factors for sporadic colorectal cancer in southern Chinese. *World J Gastroenterol*, 15: 2526–2530. PMID:19469004

Weiderpass E & Baron JA (2001). Cigarette smoking, alcohol consumption, and endometrial cancer risk: a population-based study in Sweden. *Cancer Causes Control*, 12: 239–247. doi:10.1023/A:1011201911664 PMID:11405329

Weiderpass E, Ye W, Tamimi R *et al.* (2001). Alcoholism and risk for cancer of the cervix uteri, vagina, and vulva. *Cancer Epidemiol Biomarkers Prev*, 10: 899–901. PMID:11489758

Weikert C, Dietrich T, Boeing H *et al.* (2009). Lifetime and baseline alcohol intake and risk of cancer of the upper aero-digestive tract in the European Prospective Investigation into Cancer and Nutrition (EPIC) study. *Int J Cancer*, 125: 406–412. doi:10.1002/ijc.24393 PMID:19378340

Weinstein SJ, Stolzenberg-Solomon R, Pietinen P *et al.* (2006). Dietary factors of one-carbon metabolism and prostate cancer risk. *Am J Clin Nutr*, 84: 929–935. PMID:17023722

Wendt LR, Osvaldt AB, Bersch VP *et al.* (2007). Pancreatic intraepithelial neoplasia and ductal adenocarcinoma induced by DMBA in mice: effects of alcohol and caffeine. *Acta Cir Bras*, 22: 202–209. doi:10.1590/S0102-86502007000300008 PMID:17546293

West RO (1966). Epidemiologic study of malignancies of the ovaries. *Cancer*, 19: 1001–1007. doi:10.1002/1097-0142(196607)19:7<1001::AID-CNCR2820190714>3.0.CO;2-S PMID:5939299

Whittemore AS, Wu ML, Paffenbarger RS Jr *et al.* (1988). Personal and environmental characteristics related to epithelial ovarian cancer. II. Exposures to talcum powder, tobacco, alcohol, and coffee. *Am J Epidemiol*, 128: 1228–1240. PMID:3195564

WHO (2000). *International Guide for Monitoring Alcohol Consumption and Related Harm*. Geneva, World Health Organization,.

WHO (2004). *Global Status Report on Alcohol*. Geneva, World Health Organization.

WHO (2007). Expert Committee on Problems Related to Alcohol Consumption Second Report. WHO.

WHO (2008). *Global Information System on Alcohol and Health*. Available at http://apps.who.int/globalatlas/default.asp

Willett EV, O'Connor S, Smith AG, Roman E (2007). Does smoking or alcohol modify the risk of Epstein-Barr virus-positive or -negative Hodgkin lymphoma? *Epidemiology*, 18: 130–136. doi:10.1097/01.ede.0000248899.47399.78 PMID:17099321

Willett EV, Smith AG, Dovey GJ *et al.* (2004). Tobacco and alcohol consumption and the risk of non-Hodgkin lymphoma. *Cancer Causes Control*, 15: 771–780. doi:10.1023/B:CACO.0000043427.77739.60 PMID:15456990

Williams RR & Horm JW (1977). Association of cancer sites with tobacco and alcohol consumption and socio-economic status of patients: interview study from the Third National Cancer Survey. *J Natl Cancer Inst*, 58: 525–547. PMID:557114

Wong NACS, Rae F, Simpson KJ *et al.* (2000). Genetic polymorphisms of cytochrome p4502E1 and susceptibility to alcohol liver disease and hepatocellular carcinoma in a white population: a study and literature review, including meta-analysis. *J. Clin. Pathol. Mol. Pathol*, 53: 88–93. doi:10.1136/mp.53.2.88

Woodson K, Albanes D, Tangrea JA *et al.* (1999). Association between alcohol and lung cancer in the alpha-tocopherol, beta-carotene cancer prevention study in Finland. *Cancer Causes Control*, 10: 219–226. doi:10.1023/A:1008911624785 PMID:10454067

Wright M, Bieser KJ, Kinnunen PM, Lange LG (1987). Nonoxidative ethanol metabolism in human leukocytes: detection of fatty acid ethyl ester synthase activity. *Biochem Biophys Res Commun*, 142: 979–985. doi:10.1016/0006-291X(87)91510-5 PMID:3827909

Wu IC, Lee CH, Kuo CH *et al.* (2009). Consumption of cigarettes but not betel quid or alcohol increases colorectal cancer risk. *J Formos Med Assoc*, 108: 155–163. doi:10.1016/S0929-6646(09)60046-2 PMID:19251551

Wu MS, Chen CJ, Lin MT *et al.* (2002). Genetic polymorphisms of cytochrome p450 2E1, glutathione S-transferase M1 and T1, and susceptibility to gastric carcinoma in Taiwan. *Int J Colorectal Dis*, 17: 338–343. doi:10.1007/s00384-001-0383-2 PMID:12172927

Wu SH, Tsai SM, Hou MF *et al.* (2006). Interaction of genetic polymorphisms in cytochrome P450 2E1 and glutathione S-transferase M1 to breast cancer in Taiwanese woman without smoking and drinking habits. *Breast Cancer Res Treat*, 100: 93–98. doi:10.1007/s10549-006-9226-8 PMID:16758119

Wu X, Shi H, Jiang H *et al.* (1997). Associations between cytochrome P4502E1 genotype, mutagen sensitivity, cigarette smoking and susceptibility to lung cancer. *Carcinogenesis*, 18: 967–973. doi:10.1093/carcin/18.5.967 PMID:9163682

Wurst FM, Skipper GE, Weinmann W (2003). Ethyl glucuronide–the direct ethanol metabolite on the threshold from science to routine use. *Addiction*, 98: Suppl 251–61. doi:10.1046/j.1359-6357.2003.00588.x PMID:14984242

Yamagiwa K, Mizumoto R, Higashi S *et al.* (1994). Alcohol ingestion enhances hepatocarcinogenesis induced by synthetic estrogen and progestin in the rat. *Cancer Detect Prev*, 18: 103–114. PMID:8025892

Yamamoto S, Kubo S, Hai S *et al.* (2004). Hepatitis C virus infection as a likely etiology of intrahepatic cholangiocarcinoma. *Cancer Sci*, 95: 592–595. doi:10.1111/j.1349-7006.2004.tb02492.x PMID:15245596

Yang CX, Matsuo K, Ito H *et al.* (2005). Esophageal cancer risk by ALDH2 and ADH2 polymorphisms and alcohol consumption: exploration of gene-environment and

gene-gene interactions. *Asian Pac J Cancer Prev*, 6: 256–262. PMID:16235983

Yang J, Gu M, Song NH *et al.* (2009). [Correlation of prostate cancer susceptibility with genetic polymorphism of cytochrome P450 2E1, smoking and drinking: a case-control study in the population of Nanjing area] *Zhonghua Nan Ke Xue*, 15: 7–11. PMID:19288740

Yang J, Qian LX, Wu HF *et al.* (2006a). Genetic polymorphisms in the cytochrome P450 1A1 and 2E1 genes, smoking, drinking and prostate cancer susceptibility: a case-control study in a Han nationality population in Southern China. *Int J Urol*, 13: 773–780. doi:10.1111/j.1442-2042.2006.01401.x PMID:16834659

Yang SJ, Wang HY, Li XQ *et al.* (2007). Genetic polymorphisms of ADH2 and ALDH2 association with esophageal cancer risk in southwest China. *World J Gastroenterol*, 13: 5760–5764. PMID:17963305

Yen ML, Yen BL, Bai CH, Lin RS (2003). Risk factors for ovarian cancer in Taiwan: a case-control study in a low-incidence population. *Gynecol Oncol*, 89: 318–324. doi:10.1016/S0090-8258(03)00088-X PMID:12713998

Yen TT, Lin WD, Wang CP *et al.* (2008). The association of smoking, alcoholic consumption, betel quid chewing and oral cavity cancer: a cohort study. *Eur Arch Otorhinolaryngol*, 265: 1403–1407. doi:10.1007/s00405-008-0659-z PMID:18389268

Yin G, Kono S, Toyomura K *et al.* (2007). Alcohol dehydrogenase and aldehyde dehydrogenase polymorphisms and colorectal cancer: the Fukuoka Colorectal Cancer Study. *Cancer Sci*, 98: 1248–1253. doi:10.1111/j.1349-7006.2007.00519.x PMID:17517051

Yin SJ, Chou FJ, Chao SF *et al.* (1993). Alcohol and aldehyde dehydrogenases in human esophagus: comparison with the stomach enzyme activities. *Alcohol Clin Exp Res*, 17: 376–381. doi:10.1111/j.1530-0277.1993.tb00779.x PMID:8488982

Yin SJ, Liao CS, Wu CW *et al.* (1997). Human stomach alcohol and aldehyde dehydrogenases: comparison of expression pattern and activities in alimentary tract. *Gastroenterology*, 112: 766–775. doi:10.1053/gast.1997.v112.pm9041238 PMID:9041238

Yokoyama A, Kato H, Yokoyama T *et al.* (2002). Genetic polymorphisms of alcohol and aldehyde dehydrogenases and glutathione S-transferase M1 and drinking, smoking, and diet in Japanese men with esophageal squamous cell carcinoma. *Carcinogenesis*, 23: 1851–1859. doi:10.1093/carcin/23.11.1851 PMID:12419833

Yokoyama A, Kato H, Yokoyama T *et al.* (2006a). Esophageal squamous cell carcinoma and aldehyde dehydrogenase-2 genotypes in Japanese females. *Alcohol Clin Exp Res*, 30: 491–500. doi:10.1111/j.1530-0277.2006.00053.x PMID:16499490

Yokoyama A, Muramatsu T, Ohmori T *et al.* (1998). Alcohol-related cancers and aldehyde dehydrogenase-2 in Japanese alcoholics. *Carcinogenesis*, 19: 1383–1387. doi:10.1093/carcin/19.8.1383 PMID:9744533

Yokoyama A, Muramatsu T, Omori T *et al.* (2001). Alcohol and aldehyde dehydrogenase gene polymorphisms and oropharyngolaryngeal, esophageal and stomach cancers in Japanese alcoholics. *Carcinogenesis*, 22: 433–439. doi:10.1093/carcin/22.3.433 PMID:11238183

Yokoyama A, Omori T, Yokoyama T *et al.* (2006b). Risk of squamous cell carcinoma of the upper aerodigestive tract in cancer-free alcoholic Japanese men: an endoscopic follow-up study. *Cancer Epidemiol Biomarkers Prev*, 15: 2209–2215. doi:10.1158/1055-9965.EPI-06-0435 PMID:17119048

Yokoyama A, Omori T, Yokoyama T *et al.* (2008). Risk of metachronous squamous cell carcinoma in the upper aerodigestive tract of Japanese alcoholic men with esophageal squamous cell carcinoma: a long-term endoscopic follow-up study. *Cancer Sci*, 99: 1164–1171. doi:10.1111/j.1349-7006.2008.00807.x PMID:18429959

Yokoyama A, Yokoyama T, Omori T *et al.* (2007b). Helicobacter pylori, chronic atrophic gastritis, inactive aldehyde dehydrogenase-2, macrocytosis and multiple upper aerodigestive tract cancers and the risk for gastric cancer in alcoholic Japanese men. *J Gastroenterol Hepatol*, 22: 210–217. doi:10.1111/j.1440-1746.2006.04377.x PMID:17295873

Yong L-C, Brown CC, Schatzkin A *et al.* (1997). Intake of vitamins E, C, and A and risk of lung cancer. The NHANES I epidemiologic followup study. First National Health and Nutrition Examination Survey. *Am J Epidemiol*, 146: 231–243. PMID:9247007

Yu MW, Gladek-Yarborough A, Chiamprasert S *et al.* (1995). Cytochrome P450 2E1 and glutathione S-transferase M1 polymorphisms and susceptibility to hepatocellular carcinoma. *Gastroenterology*, 109: 1266–1273. doi:10.1016/0016-5085(95)90587-1 PMID:7557094

Yu SZ, Huang XE, Koide T *et al.* (2002). Hepatitis B and C viruses infection, lifestyle and genetic polymorphisms as risk factors for hepatocellular carcinoma in Haimen, China. *Jpn J Cancer Res*, 93: 1287–1292. doi:10.1111/j.1349-7006.2002.tb01236.x PMID:12495467

Zakhari S (2006). Overview: how is alcohol metabolized by the body? *Alcohol Res Health*, 29: 245–254. PMID:17718403

Zang EA & Wynder EL (2001). Reevaluation of the confounding effect of cigarette smoking on the relationship between alcohol use and lung cancer risk, with larynx cancer used as a positive control. *Prev Med*, 32: 359–370. doi:10.1006/pmed.2000.0818 PMID:11304097

Zaridze D, Brennan P, Boreham J *et al.* (2009). Alcohol and cause-specific mortality in Russia: a retrospective case-control study of 48,557 adult deaths. *Lancet*, 373: 2201–2214. doi:10.1016/S0140-6736(09)61034-5 PMID:19560602

Zavras AI, Wu T, Laskaris G *et al.* (2002). Interaction between a single nucleotide polymorphism in the alcohol dehydrogenase 3 gene, alcohol consumption

and oral cancer risk. *Int J Cancer*, 97: 526–530. doi:10.1002/ijc.1642 PMID:11802217

Zhang FF, Hou L, Terry MB *et al.* (2007b). Genetic polymorphisms in alcohol metabolism, alcohol intake and the risk of stomach cancer in Warsaw, Poland. *Int J Cancer*, 121: 2060–2064. doi:10.1002/ijc.22973 PMID:17631643

Zhang SM, Lee IM, Manson JE *et al.* (2007a). Alcohol consumption and breast cancer risk in the Women's Health Study. *Am J Epidemiol*, 165: 667–676. doi:10.1093/aje/kwk054 PMID:17204515

Zhou YM, Yin ZF, Yang JM *et al.* (2008). Risk factors for intrahepatic cholangiocarcinoma: a case-control study in China. *World J Gastroenterol*, 14: 632–635. doi:10.3748/wjg.14.632 PMID:18203300

Zimatkin SM, Pronko SP, Vasiliou V *et al.* (2006). Enzymatic mechanisms of ethanol oxidation in the brain. *Alcohol Clin Exp Res*, 30: 1500–1505. doi:10.1111/j.1530-0277.2006.00181.x PMID:16930212

Zintzaras E, Stefanidis I, Santos M, Vidal F (2006). Do alcohol-metabolizing enzyme gene polymorphisms increase the risk of alcoholism and alcoholic liver disease? *Hepatology*, 43: 352–361. doi:10.1002/hep.21023 PMID:16440362