4.8 Alcoholic drinks

ALCOHOLIC DRINKS, AND THE RISK OF CANCER

In the judgement of the Panel, the factors listed below modify the risk of cancer. Judgements are graded according to the strength of the evidence.

	DECREASES RISK		INCREASES RISK	
	Exposure	**Cancer site**	**Exposure**	**Cancer site**
Convincing			**Alcoholic drinks**	**Mouth, pharynx and larynx** **Oesophagus** **Colorectum (men)[1]** **Breast (pre- and postmenopause)**
Probable			**Alcoholic drinks**	**Liver[2]** **Colorectum (women)[1]**
Limited — suggestive				
Substantial effect on risk unlikely	Alcoholic drinks (adverse effect): kidney[3]			

1 The judgements for men and women are different because there are fewer data for women. Increased risk is only apparent above a threshold of 30 g/day of ethanol for both sexes.
2 Cirrhosis is an essential precursor of liver cancer caused by alcohol. The International Agency for Research on Cancer has graded alcohol as a class 1 carcinogen for liver cancer. Alcohol alone only causes cirrhosis in the presence of other factors.
3 The evidence was sufficient to judge that alcoholic drinks were unlikely to have an *adverse* effect on the risk of kidney cancer; it was inadequate to draw a conclusion regarding a protective effect.

For an explanation of all the terms used in the matrix, please see chapter 3.5.1, the text of this section, and the glossary.

Many plant and some animal foods can be fermented to produce alcoholic drinks; alcohol has been made this way for thousands of years.

The main alcoholic drinks consumed, in ascending order of alcohol (ethanol) content, are beers and ciders; wines; wines 'fortified' with spirits; and spirits (liquors) and liqueurs. The alcohol content of the many different drinks within each of these categories varies.

Alcoholic drinks induce changes in mood; they also produce physical effects such as loss of coordination. In most countries they are the legal 'intoxicant' of choice, used as a social and professional lubricant; however, certain cultures forbid the drinking of alcohol.

With industrialisation and urbanisation, and the ready availability of alcoholic drinks (which may or may not be taxed), consumption tends to rise.

Alcohol relaxes people's social inhibitions, but it is addictive; dependency on alcohol can seriously affect people's personal and professional lives.

It has been known for a long time that prolonged high consumption of alcohol is a cause of cirrhosis of the liver, though not all people are equally susceptible. Knowledge of its other ill-effects is more recent.

Overall, *the Panel judges* that alcoholic drinks are a cause of cancers of a number of sites and that, in general, the evidence is stronger than it was in the mid-1990s. The evidence does not show any 'safe limit' of intake. The effect is from ethanol, irrespective of the type of drink. Ethanol is classified by the International Agency for Cancer Research as a human carcinogen.

***The Panel judges* as follows:**
The evidence that alcoholic drinks are a cause of cancers of the mouth, pharynx, and larynx, oesophagus, colorectum (men), and breast is convincing. They are probably a cause of liver cancer, and of colorectal cancer in women. It is unlikely that alcoholic drinks have a substantial adverse effect on the risk of kidney cancer.

In final summary, the evidence is that alcoholic drinks are a cause of cancers of the mouth, pharynx, and larynx; the oesophagus; the colorectum in men, and the breast; and probably of liver cancer and colorectal cancer in women. It is unlikely that alcoholic drinks have a substantial adverse effect on the risk of kidney cancer.

Chapter 4.8 concerns all alcoholic drinks.

Alcoholic drinks have been popular in most societies ever

since the effects on mood of the fermented products of plant foods and some animal foods were discovered, probably in Palaeolithic or even earlier times.

Ethanol is the active ingredient in alcoholic drinks; the concentration varies, depending on the type of drink. In the past, beers were made from grains, ciders from fruits, mead from honey, and brews from milk; these were followed by wines, generally made from grapes and with higher concentrations of ethanol. The process of distillation was a later invention, which produced more highly concentrated alcoholic drinks made from grains, fruits, sugar, and other substrates.

Alcohol is liable to be addictive. Its specific effects are to induce a mood of euphoria and disinhibition, which may be dangerous. Much domestic and other violence, and many reckless and violent incidents, and crimes such as arson, wounding, homicide, and car crashes, are alcohol-related.

Reports concerned with food, nutrition, and the prevention of disease have often excluded alcohol. This is because alcohol is also a drug, the impact of which is behavioural and social, as well as biological. More recently, alcoholic drinks have been included in such reports because of the evidence that low to moderate consumption protects against coronary heart disease (but not cerebrovascular disease), and also because of the evidence on cancer, given that ethanol is a human carcinogen.

4.8.1 Definitions and sources

Alcohol is the common term for ethanol, one of a family of alcohols, produced in nature when sugar molecules are broken down to release energy by yeasts. This process of fermentation is used to produce alcoholic drinks. Alcohol is a source of dietary energy (see chapter 4.10.1). It also acts as a drug, affecting both mental and physical responses (alcohol intoxication). Alcoholic drinks include beers, wines, and spirits. Other alcoholic drinks that may be locally important include fermented milks, fermented honey-water (mead), and fermented apples (cider).

Most alcoholic drinks are manufactured industrially. Some are made domestically or illegally, as 'moonshine' or 'hooch'.

4.8.1.1 Beers

Beer, ale, and lager are traditionally produced from barley; today other cereal grains are used. Beer contains between 3 and 7 per cent alcohol. The grain starches are converted to sugars and then fermented by yeasts. The term 'beer' in this Report includes ales and lagers.

4.8.1.2 Wines

Wines are usually produced from grapes and contain between around 9 to 15 per cent alcohol; they are crushed to produce juice and must, which is then fermented. The colour of the grapes and the length of fermentation determine the colour and strength of the final product. Grape vines grow best in temperate regions. Wines can also be produced from other fruits and from rice (sake). Here, wine is taken to mean grape wines. Wines may be fortified with spirits (see chapter 4.8.2.2) to produce drinks of alcohol content between about 16 and 20 per cent.

4.8.1.3 Spirits/liquors

Spirits are usually produced from cereal grains and sometimes from other plant foods. They are distilled, to give a drink with a higher concentration of ethanol than either beers or wines — around 35–50 per cent or higher. Some of the most globally familiar spirits are brandy (distilled wine), whisky and gin (distilled from grains), rum (from molasses), aguardente also known as cachaça (from sugar), vodka (sometimes from grain, sometimes potatoes), and tequila and mescal (from agave and cactus plants). Spirits and liqueurs are also made from fruits.

4.8.2 Composition

Alcohol has an energy content of 7 kilocalories per gram, and is metabolised in the liver. On average, blood alcohol levels reach a maximum between 30 and 60 minutes after drinking an alcoholic drink, and the body can metabolise 10–15 g alcohol per hour.

Alcohol alters the way the central nervous system functions. Very high alcohol consumption (where blood alcohol reaches 0.4 per cent) can be fatal, as can long-term, regular, high intakes.

4.8.2.1 Beers

There are many varieties of beer, with different compositions. Their alcohol content ranges from around 3 to 7 per cent by volume; beers generally contain a variety of bioavailable phenolic and polyphenolic compounds, which contribute to the taste and colour, many of which have antioxidant properties. Beer is also a source of magnesium, potassium, riboflavin, folate, and other B vitamins.

4.8.2.2 Wines

The composition of wine depends on the grape varieties used, as well as the growing conditions and the wine-making methods, which may vary between vineyards. The alcohol content ranges from around 9 to 15 per cent by volume. Red wines contain high levels of phenolic and polyphenolic compounds (up to a total of around 800–4000 mg/l), particularly resveratrol, derived from the grape skins. Like those in beer, these phenolic compounds add taste and colour. White wines contain fewer phenolics. Red wine has been shown to have antioxidant activity in laboratory experiments. Wine also contains sugars (mainly glucose and fructose), volatile acids (mainly acetic acid), carboxylic acids, and varying levels of calcium, copper, iron, magnesium, potassium, and vitamins B1, B2, B6, and C. Wines may be flavoured with herbs and fortified with spirits (see chapter 4.8.2.3) to produce drinks of alcohol content between about 16 and 20 per cent.

4.8.2.3 Spirits/liquors

The alcohol content of spirits/liquors and liqueurs is usually between 35 and 50 per cent by volume, but can be even higher. Distilled drinks may have herbs and other ingredients added to give them their distinctive character.

4.8.3 Consumption patterns

Much of the information on average consumption of alcoholic drinks, internationally and nationally, is not informative. Within almost all populations, consumption varies widely, usually as a function of availability, price, culture or religion, and dependency. In general, men consume substantially more alcoholic drinks than women. In countries where considerable amounts of alcoholic drinks are produced domestically and by artisanal methods, overall consumption will (if only for this reason) be underestimated. In many countries, alcohol is a public health problem. This is not so much because of the average level of intake, but because a minority of the population, which in high-income countries includes an increasing number of young people, drink alcohol excessively ('binge' drinking).

Worldwide, alcoholic drinks supply an average of 2.3 per cent of total dietary energy. This ranges from around 10 per cent in some northern European countries, to (as recorded) practically zero in Islamic countries. Average consumption is nearly four times higher in high-income compared with low-income countries, and tends to be highest in Europe, North America, and Oceania. Consumption varies within countries: many people do not consume alcoholic drinks, some drink occasionally and others consume 15–25 per cent or more of their dietary energy as alcohol.

Alcoholic drinks are illegal in Islamic countries. In countries where these drinks are legal, there are often restrictions on price and availability to adults, and in particular to young people.

Many countries recommend restriction of alcohol intake for health reasons. In the USA, men are advised not to exceed two drinks per day and women one drink per day. In the UK, the government advises men not to exceed 3–4 units per day and women 2–3 units per day. One US 'drink' is equivalent to about 15 g ethanol, almost two UK units; a unit is 10 ml or 8 g of pure ethanol.

Box 4.8.1 Types of alcoholic drink

The Panel judges that alcoholic drinks are or may be a cause of various cancers, irrespective of the type of alcoholic drink. The causal factor is evidently alcohol (ethanol) itself. There is no significant evidence that alcohol protects against any cancer. The extent to which alcoholic drinks are a cause of various cancers depends on the amount of alcohol drunk.

Epidemiological studies commonly identify the type of alcoholic drink consumed. Some of the evidence reviewed in chapter 4.8.5 does appear to show that some types of drink seem to have different effects. For example, for cancers of the mouth, pharynx, and larynx, the evidence is stronger for consumption of beer and spirits than for wine. Here is the possibility of residual confounding: wine drinkers in many countries tend to have healthier ways of life than beer or spirit drinkers.

Apparent discrepancies in the strength of evidence may also be due partly to variation in the amounts of different types of alcoholic drinks consumed. In general, the evidence suggests similar effects for different types of alcoholic drink.

4.8.3.1 Beers

Beers are the most widely consumed alcoholic drinks worldwide. They provide an average of 1 per cent of dietary energy, with a peak of more than 6 per cent in parts of northern Europe. People living in Europe, North America, and Oceania tend to drink the most beer.

4.8.3.2 Wines

Wines provide an average of 0.2 per cent of dietary energy worldwide. They are drunk mainly in Europe, Australasia, and the Americas, with highest levels of consumption in western and southern Europe.

4.8.3.3 Spirits/liquors

There are few data on average consumption of spirits/liquors.

4.8.4 Interpretation of the evidence

4.8.4.1 General

For general considerations that may affect interpretation of the evidence, see chapters 3.3 and 3.5, and boxes 3.1, 3.2, 3.6 and 3.7.

'Relative risk' (RR) is used in this Report to denote ratio measures of effect, including 'risk ratios', 'rate ratios', 'hazard ratios', and 'odds ratios'.

4.8.4.2 Specific

Confounding. At high levels of consumption, the effects of alcohol are heavily confounded by other behaviours, such as smoking tobacco.

Reporting bias. Self-reporting of consumption of alcoholic drinks is liable to underestimate consumption, sometimes grossly, because alcohol is known to be unhealthy and undesirable, and is sometimes drunk secretly. Heavy drinkers usually underestimate their consumption, as do drinkers of illegal or unregulated alcoholic drinks.

Measurement. In recent years, the strength and serving size of some alcoholic drinks have increased. For example, in the UK, wine is commonly served in 250 ml glasses as opposed to the standard 125 or 175 ml glass. In addition, alcohol content of drinks varies widely. Studies that measure consumption in terms of number of drinks may be referring to very different amounts of alcohol (also see box 4.8.1).

4.8.5 Evidence and judgements

The full systematic literature review (SLR) is contained on the CD included with this Report.

4.8.5.1 Alcoholic drinks

There are two different measures of exposure: the number of alcoholic drinks per time period and/or ethanol intake in grams or millilitres per time period. The former measure is likely to be less precise because the size and strength of each drink are unknown.

Figure 4.8.1 Alcoholic drinks and mouth, pharynx, and larynx cancer; cohort and case-control studies

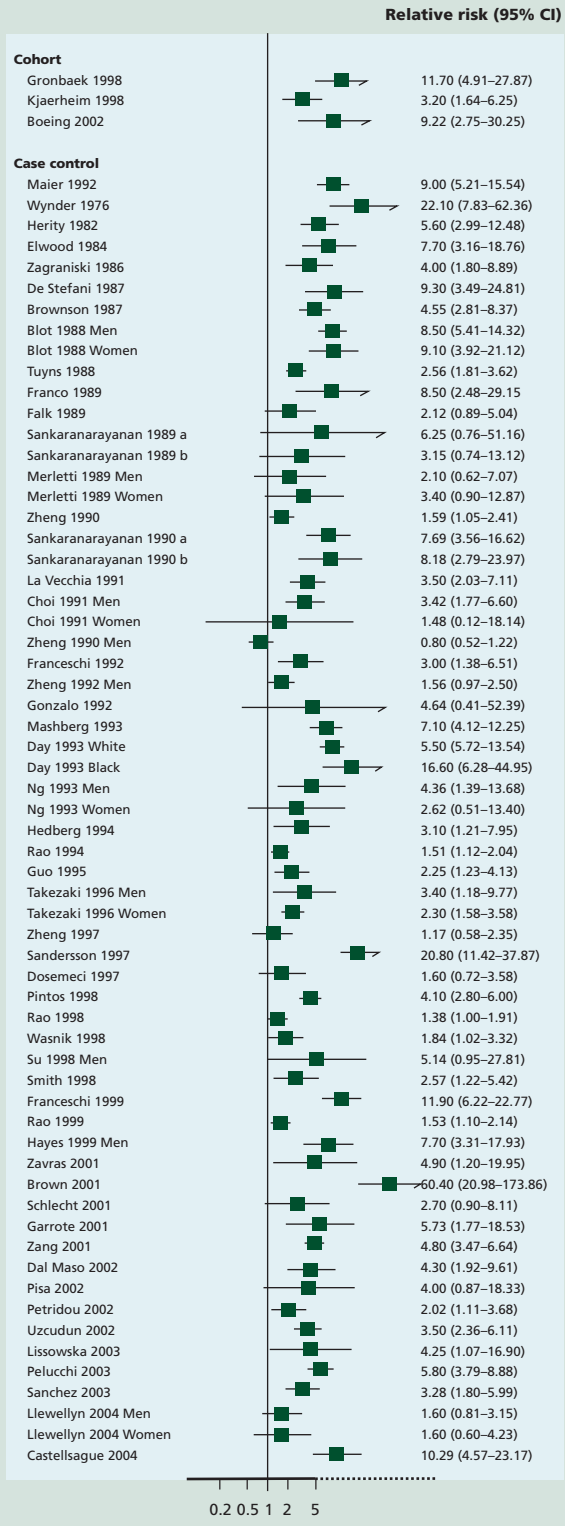
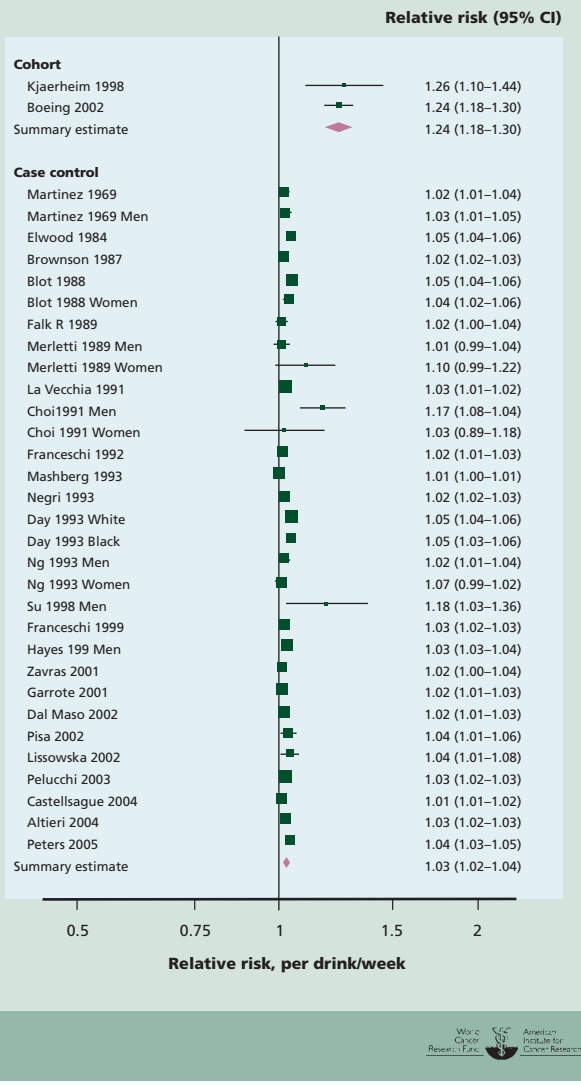


Figure 4.8.2 Alcoholic drinks and mouth, pharynx, and larynx cancer; cohort and case-control studies



Mouth, pharynx, and larynx

Five cohort studies,[1-6] 89 case-control studies,[7-93] and 4 ecological studies[94-97] investigated alcoholic drinks and mouth, pharynx, and larynx cancers.

Total alcoholic drinks

All five cohort studies showed increased risk for the highest intake group when compared to the lowest (figure 4.8.1),[1-6] which was statistically significant in four.[1 2 4 6] Meta-analysis was possible on two studies, giving a summary effect estimate of 1.24 (95% confidence interval (CI) 1.18–1.30) per drink/week, with no heterogeneity (figures 4.8.2 and 4.8.3).[1 2] All cohort studies adjusted for smoking.

Almost all of the case-control studies showed increased risk for the highest intake group when compared to the lowest (figure 4.8.1),[7-19 21-32 34-70 72-93] which was statistically significant in more than half (as can be seen from the high to low

Figure 4.8.3 Alcoholic drinks and mouth, pharynx, and larynx cancer; cohort studies: dose response

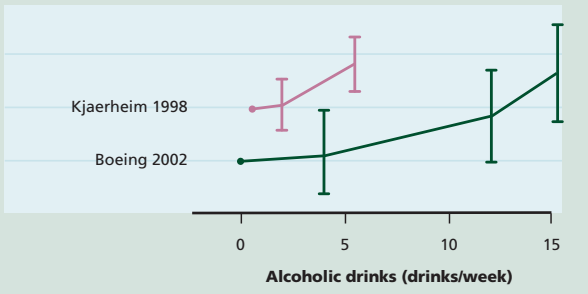
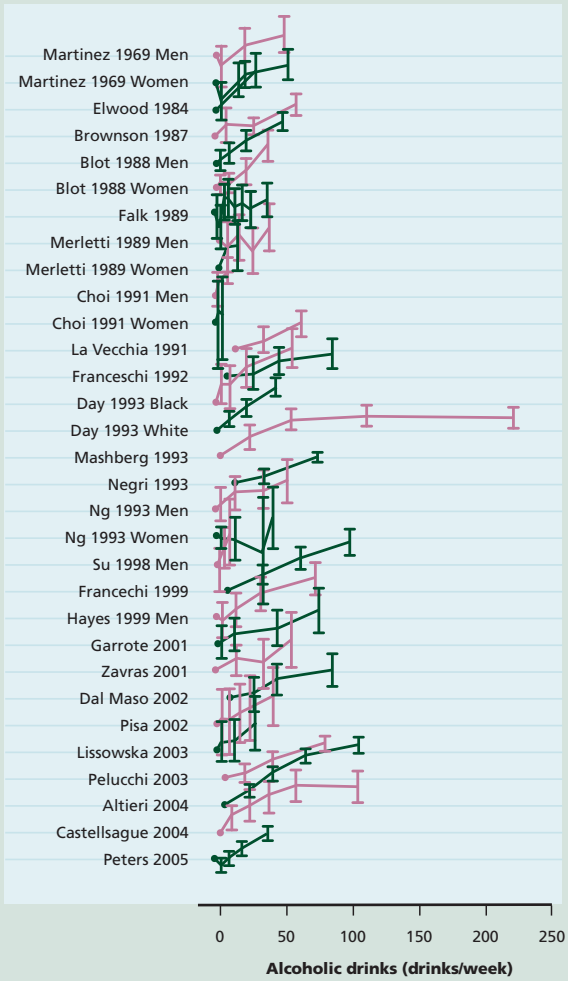


Figure 4.8.4 Alcoholic drinks and mouth, pharynx, and larynx cancer; case-control studies: dose response



comparison plot).[8-19 21 23-25 28-32 34-36 40-48 52 54-57 59-67 70 72-75 77-86 89-91 93] No studies reported statistically significant contradictory results. Meta-analysis was possible on 25 studies, giving a summary effect estimate of 1.03 (95% CI 1.02–1.04) per drink/week, with high heterogeneity (figures 4.8.2 and 4.8.4).[17 21 26 27 32 34 35 40-42 52 57 60 62 65 67 69 75 78-80 83-85 89] Heterogeneity related to the size, and not the direction, of effect, and is largely explained by varying design and quality of studies.

A continuous curvilinear dose-response relationship was apparent from cohort and case-control data with no obvious threshold (figures 4.8.3 and 4.8.4).

There was some evidence of publication bias as a result of small studies that did not report a significant association being unpublished. However, such small studies may suffer from issues of quality.

Ecological studies tended to show increased risk with increased consumption.[94-97]

Beers

Two cohort studies,[1 6] 27 case-control studies,[25 26 32 33 36 42 47 58 62 64 65 68 79 83-85 98-105] and 4 ecological studies[94-96 106] reported separately on beer drinking.

Both cohort studies showed statistically significant increased risk with increased intake; both studies adjusted for smoking.[1 6] Almost all case-control studies also showed increased risk,[25 26 32 33 36 42 47 58 62 64 65 68 83-85 98-104] which was statistically significant in many.[36 42 47 62 68 83-85 98-102] Meta-analysis was possible on six case-control studies, giving a summary effect estimate of 1.06 (95% CI 1.03–1.08), with high heterogeneity. Most studies adjusted for smoking. The ecological studies did not show any consistent or statistically significant effect.[94-96 106]

Wines

Twenty-six case-control studies[25 26 32 33 42 58 62 64 65 68 79 83-85 98 99 101 102 104 105 107-109] and four ecological studies[94-96 110] reported separately on wine drinking.

Most of the case-control studies showed increased risk with increased intake,[25 32 33 58 62 64 68 79 84 85 101 102 105 107-109] which was statistically significant in less than half.[32 33 58 62 68 79 85 108 109] Five studies showed decreased risk,[26 65 83 98 99] which was statistically significant in one.[98 99] Meta-analysis was possible on 11 case-control studies, giving a summary effect estimate of 1.02 (95% CI 1.01–1.03), with high heterogeneity.[32 33 62 68 79 83-85 102 105 109] All studies adjusted for smoking. All four ecological studies showed statistically significant increased risk.[94-96 110]

Spirits

One cohort study,[1] 35 case-control studies,[19 25 26 28 31-33 36 38 42 47 49 50 58 62 64 65 68 79 83-85 98 100-102 104 105 108 109 111-113] and 5 ecological studies[94-96 106 114] reported separately on spirits.

The single cohort study showed a non-significant increased risk with increased intake.[1] Almost all case-control studies

showed increased risk, which was statistically significant in many. Meta-analysis was possible on nine case-control studies, giving a summary effect estimate of 1.03 (95% CI 1.04–1.05), with high heterogeneity. Most studies adjusted for smoking. One ecological study reported a significant increased risk; the others tended to show non-significant increased risk in men and non-significant decreased risk in women.

The general mechanisms through which alcohol could plausibly cause cancer are outlined below. In addition, alcohol acts as a synergistic carcinogen with tobacco. Tobacco may induce specific mutations in DNA that are less efficiently repaired in the presence of alcohol. Alcohol may also function as a solvent, enhancing penetration of other carcinogenic molecules into mucosal cells.

There is ample and consistent evidence, both from case-control and cohort studies, with a dose-response relationship. There is robust evidence for mechanisms operating in humans. The evidence that alcoholic drinks are a cause of mouth, pharynx, and larynx cancers is convincing. Alcohol and tobacco together increase the risk of these cancers more than either acting independently. No threshold was identified.

The Panel is aware that since the conclusion of the SLR, one cohort[115] and four case-control studies[116-119] have been published. This new information does not change the Panel judgement (see box 3.8).

Oesophagus

Eight cohort studies,[1 3 120-125] 56 case-control studies,[33 61 67 80 126-182] and 10 ecological studies[2 94 95 114 183-189] investigated alcoholic drinks and oesophageal cancers.

Total alcoholic drinks

Eight cohort studies,[1 3 120-125] 56 case-control studies,[33 61 67 80 126-137 139-182] and 10 ecological studies[2 94 95 114 183-189] reported on total alcoholic drinks.

Six cohort studies showed increased risk for the highest intake group when compared to the lowest (figure 4.8.5),[1 3 120-122 124] which was statistically significant in four,[1 120 122 124] and in men, but not in women in a fifth study.[121] Two studies showed non-significant decreased risk.[123 125] Effect estimates for all studies are shown in the high to low forest plot (figure 4.8.5). Four studies did not adjust for smoking.[122-125]

Most case-control studies showed increased risk for the highest intake group when compared to the lowest (figure 4.8.5),[33 61 67 80 126 128-137 139 141-148 150-166 169 170 172 174 175 177-182] which was statistically significant in 25.[33 61 67 80 128 129 132 133 135 137 139 141 145 147 148 150 152 153 155-166 170 172 174 175 178-180 182] A few studies showed decreased risk, but none was statistically significant.[140 149 167 168 171 173 176] Meta-analysis was possible on 20 case-control studies, giving a summary effect estimate of 1.04 (95% CI 1.03–1.05) per drink/week, with high heterogeneity (figures 4.8.6 and 4.8.7).[33 61 67 131 133 137 144 149 150 156 157 160 161 170 178-182] Heterogeneity is related predominantly to size, rather than direction, of effect and may

Figure 4.8.5 **Alcoholic drinks and oesophageal cancer; cohort and case-control studies**

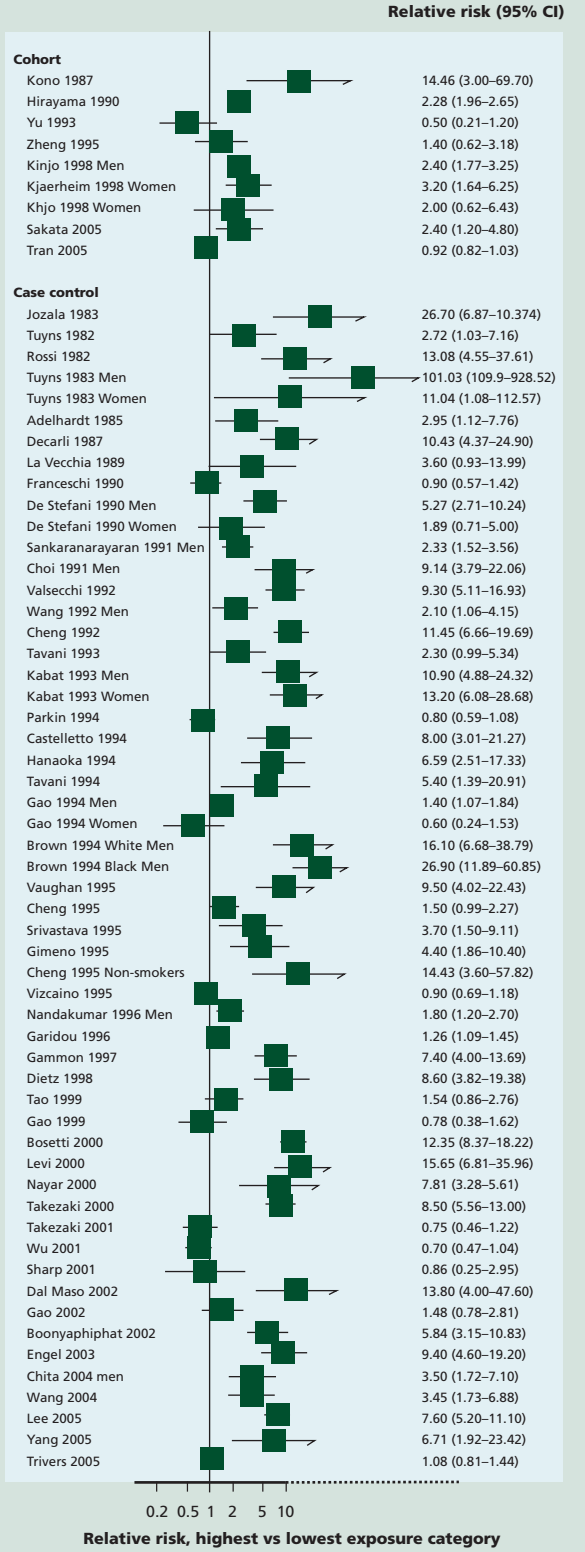


Figure 4.8.6 **Alcoholic drinks and oesophageal cancer; cohort and case-control studies**

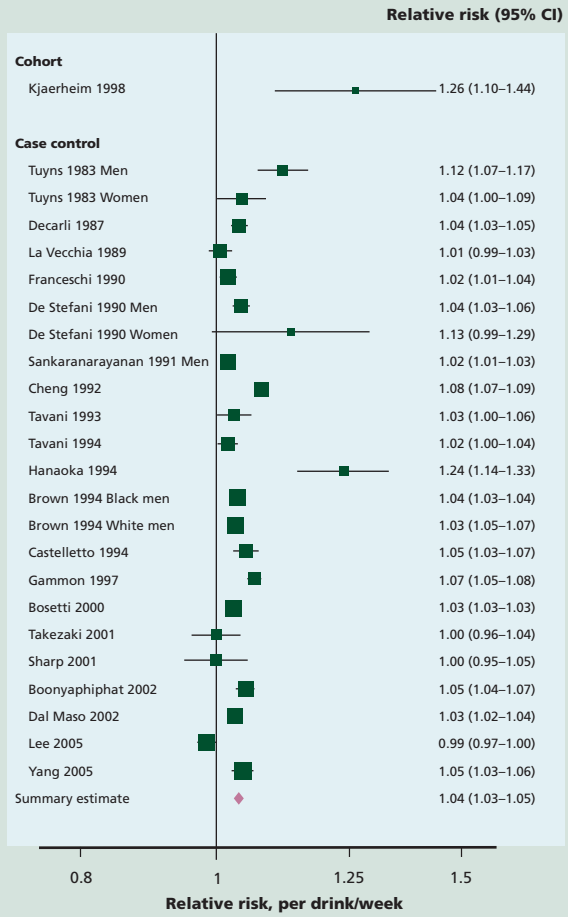
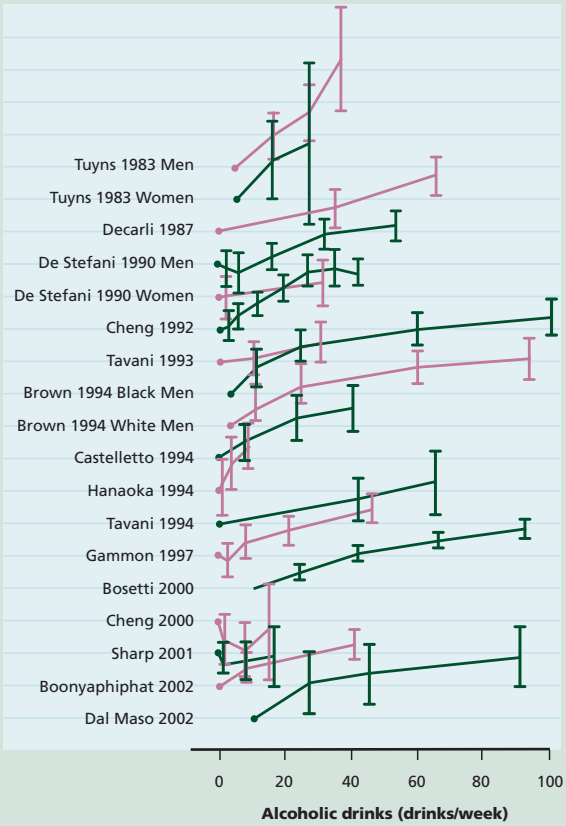


Figure 4.8.7 **Alcoholic drinks and oesophageal cancer; case-control studies: dose response**



be partially explained by the variation in measurement of alcohol intake, variation in the outcome measured (oesophageal or upper aerodigestive tract), or by inadequate adjustment for smoking in some studies. There is a trend for smaller effect estimates from more recent publications, which could be due to improved methods of adjustment for confounders. Not all studies adjusted for smoking.

There is some evidence of publication bias; with smaller studies tending to report larger effects.

The ecological studies were not consistent.[2 94 95 114 183-189] Two reported statistically significant results, both in the direction of increased risk.[94 186]

Beers

One cohort study,[4] 15 case-control studies,[103 129 143 144 159 170 173 176 190-197] and seven ecological studies[94 95 106 184 187 198 199] reported separately on beer drinking.

The single cohort study showed statistically significant increased risk with increased intake after adjustment for smoking.[4] All case-control studies with the exception of two[173 176] also showed increased risk, which was statistically significant in seven.[103 129 144 159 170 191 193 195-197] Meta-analysis was possible on five case-control studies, giving a summary effect estimate of 1.05 (95% CI 1.03–1.07), with high heterogeneity.[144 159 170 193 197] About half of the studies did not adjust for smoking. The ecological studies were inconsistent and one reported a statistically significant result, which was in the direction of increased risk.[94]

Wines

Ten case-control studies,[143 144 159 161 170 173 190 194 195] one cross-sectional study,[200] and five ecological studies[94 95 106 184 198] reported separately on wine drinking.

All but one of the case-control studies showed increased risk with increased intake,[144] which was statistically significant in seven.[159 161 170 190 195] About half of the studies adjusted for smoking. The single cross-sectional study showed non-significant increased risk.[200] Most ecological

studies were in the direction of increased risk.[94 106 184 198]

Spirits

One cohort study,[4] 15 case-control studies,[139 143-145 159 170 173 181 190 191 194-196 201 202] one cross-sectional study,[200] and five ecological studies[94 95 106 184 198] reported separately on spirits.

The single cohort study showed statistically significant increased risk with increased intake after adjustment for smoking.[4] All of the case-control studies also showed increased risk, which was statistically significant in eight.[139 144 145 191 194 195 201 202] Most studies adjusted for smoking. The single cross-sectional study showed non-significant increased risk.[200] The ecological studies were inconsistent and two reported statistically significant results; both were in the direction of increased risk.[94 106]

The general mechanisms through which alcohol could plausibly cause cancer are outlined below. In addition, alcohol acts as a synergistic carcinogen with tobacco. Tobacco may induce specific mutations in DNA that are less efficiently repaired in the presence of alcohol. Alcohol may also function as a solvent, enhancing penetration of other carcinogenic molecules into mucosal cells.

There is ample and consistent evidence, both from cohort and case-control studies, with a dose-response relationship. There is robust evidence for mechanisms operating in humans. The evidence that alcoholic drinks are a cause of oesophageal cancer is convincing. No threshold was identified.

The Panel is aware that since the conclusion of the SLR, one cohort[203] and four case-control studies[204-207] have been published. This new information does not change the Panel judgement (see box 3.8).

Colorectum

Twenty-four cohort studies investigated alcoholic drinks and colorectal cancer.[124 208-235] Thirteen cohort studies[214 216 219 227 230 232 236-251] and 41 case-control studies investigated ethanol intake and colorectal cancer.

Total alcoholic drinks

Eighteen cohort studies showed increased risk for the highest intake group when compared to the lowest,[124 209 210 212-217 220-223 225-228 233-235] which was statistically significant in four.[209 210 216 227] One study showed non-significant increased risk in men and non-significant decreased risk in women.[211 219] Two studies reported no effect on risk[218 231] and three studies reported decreased risk; none was statistically significant.[208 224 229 230 232] Meta-analysis was possible on six cohort studies, giving a summary effect estimate of 1.01 (95% CI 0.95–1.08) per drink/day, with no heterogeneity (figure 4.8.8).

Alcohol (as ethanol)

Eleven of the cohort studies showed increased risk for the highest intake group when compared to the lowest (figure 4.8.9),[214 216 219 227 230 232 237 239-251] which was statistically significant in six.[219 227 230 240 244 245 251] One study reported no effect on risk for men and non-significant decreased risk for women,[238] and one study reported no statistically significant association.[236] Meta-analysis was possible on nine cohort studies, of which one reported on colorectal cancer and eight reported on colon cancer, giving a summary effect estimate of 1.09 (95% CI 1.03–1.14) per 10 g/day, with moderate heterogeneity(figures 4.8.10 and 4.8.11).

In a separate meta-analysis of nine studies for rectal cancer, the summary effect estimate was 1.06 (95% CI 1.01–1.12) per 10 g/day, with low heterogeneity (figure 4.8.12). It is apparent from the meta-analysis that the reported effect for men was larger and more often statistically significant than for women. Stratified meta-analyses for colorectal cancer gave summary effect estimates of 1.09 (95% CI 1.02–1.15) for seven studies for men, and 1.00 (95% CI 0.89–1.40) for three studies for women. There was no statistically significant difference with cancer site. There was, however, apparent sexual dimorphism, with a larger effect in men than in women, which explains the bulk of the observed heterogeneity.

Figure 4.8.8 Alcoholic drinks and colorectal cancer; cohort studies

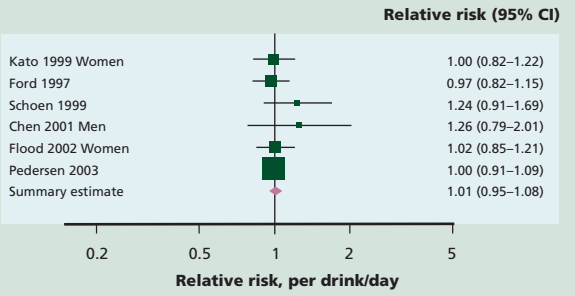


Figure 4.8.9 Ethanol and colorectal cancer; cohort studies

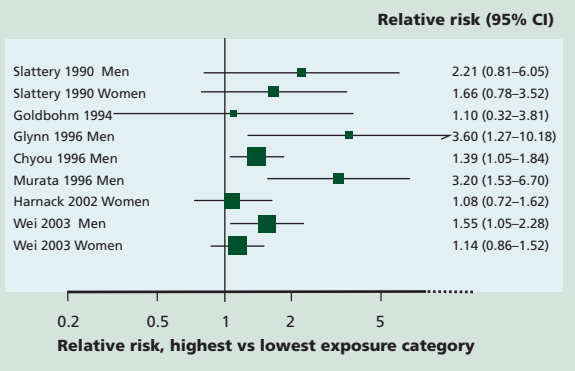


Figure 4.8.10 Ethanol and colon cancer; cohort studies

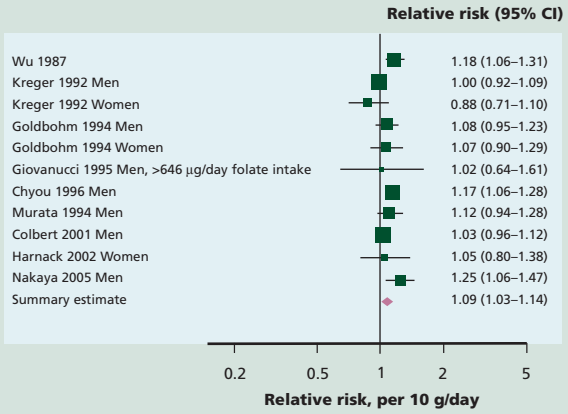


Figure 4.8.12 Ethanol and colorectal cancer; cohort studies

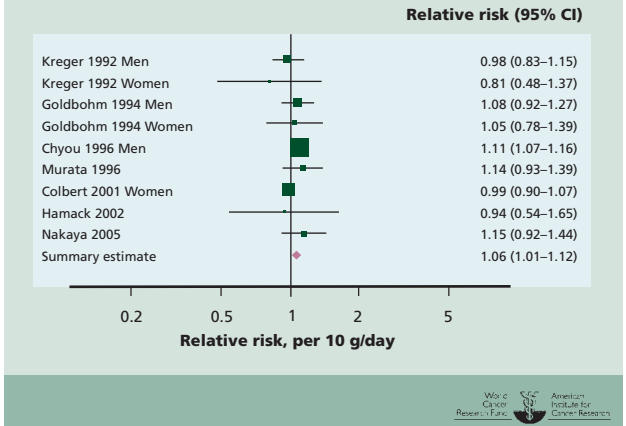
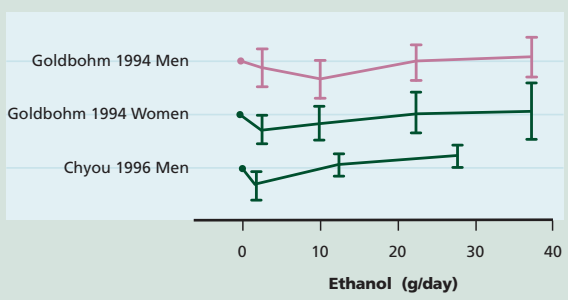


Figure 4.8.11 Ethanol and colon cancer incidence; cohort studies: dose response



When data were analysed separately for drink type (beers, wines, or spirits), they became insufficient to draw any firm conclusions.

Pooled analysis from 8 cohort studies (over 475 000 participants, followed up for 6 to 16 years, more than 4600 colorectal cancer cases) showed a significant increased risk for the highest intake group when compared to the lowest, with an effect estimate of 1.41 (95% CI 1.16–1.72) for those who consumed 45 g/day or greater.[252] No increased risk was observed below intakes of 30 g/day. No significant heterogeneity was observed by sex or cancer site.

In addition, a published meta-analysis of 27 studies reported a statistically significant increased risk, with a summary effect estimate of 1.10 (95% CI 1.05–1.14) per two drinks/day.

Because of the abundant prospective data from cohort studies, case-control studies were not summarized.

The general mechanisms through which alcohol could plausibly cause cancer are outlined below. In addition, the association between alcohol intake and colorectal cancer risk is modified by acetaldehyde dehydrogenase and alcohol dehydrogenase genetic status.[253 254] Alcohol may induce folate deficiency in the colon and rectum, possibly by reducing absorption of folate or by inhibition of critical enzymes. Also, alcohol may disrupt one-carbon metabolism (see Chapter 2). Intestinal bacteria, because of their high alcohol dehydrogenase activity, can oxidise ethanol in colorectal tissue to produce levels of acetaldehyde up to 1000-fold higher than that in blood.

The more elevated risk related to alcohol intake among men compared with women may be because of the generally lower consumption of alcohol among women. That is, it is possible that men exhibit a greater range in the amount of alcohol drunk, which makes effects easier to detect. Also, preferred beverages may differ between the sexes, or there may be hormone-related differences in alcohol metabolism or susceptibility to alcohol.

There is ample and generally consistent evidence from cohort studies. A dose-response is apparent. There is evidence for plausible mechanisms. The evidence that consumption of more than 30 g/day of ethanol from alcoholic drinks is a cause of colorectal cancer in men is convincing, and probably also in women.

The Panel is aware that since the conclusion of the SLR, four cohort[255-258] and four case-control studies[259-262] have been published. This new information does not change the Panel judgement (see box 3.8).

Breast

Eleven cohort studies,[183 263-271] 31 case-control studies[272-310] and 2 ecological studies[311 312] investigated total alcoholic drinks and breast cancer at all ages. Four cohort studies[313-316] and 19 case-control studies[289 302 317-333] investigated alcoholic drinks. Twenty-five cohort studies,[315 334-364] 29 case-

control studies,[280 282 317 318 332 333 365-391] and 4 ecological studies[392-395] investigated ethanol intake.

Total alcoholic drinks

Six cohort studies showed increased risk for the highest intake group of total alcoholic drinks when compared to the lowest,[263 264 267-271] which was statistically significant in three.[267 269 270] Three studies showed non-significant decreased risk[265 266]; one study showed no effect on risk.[183] Meta-analysis was possible on three cohort studies, giving a summary effect estimate of 1.07 (95% CI 0.89–1.29) per five times/week, with no heterogeneity (figures 4.8.13 and 4.8.14).[263 271]

Two cohort studies reported separately on premenopausal breast cancer.[264 268] Both showed increased risk for the highest intake group when compared to the lowest, which was statistically significant in one.[268] Three cohort studies reported separately on postmenopausal breast cancer.[264 268 269] Two showed increased risk for the highest intake group when compared to the lowest,[264 269] which was statistically significant in one.[269] The other study showed non-significant decreased risk.[268]

Four additional cohort studies investigated alcoholic drinks.[313-316] All four showed non-significant increased risk for breast cancer at unspecified ages. One study also reported statistically significant increased risk for postmenopausal breast cancer and non-significant decreased risk for premenopausal breast cancer.[315]

Most of the 22 case-control studies that reported on all-age breast cancer and total alcoholic drinks showed increased risk for the highest intake group when compared to the lowest,[273 274 280 282-285 287 288 290 295 297 301-303 305-309 318] which was statistically significant in seven.[273 284 285 306 318] A few studies showed decreased risk, none was statistically significant.[276 291 295 298 302 304] Meta-analysis was possible on 10 case-control studies reporting on breast cancer at all ages, giving a summary estimate of 1.05 (95% CI 1.03–1.07) for an increment of five times/week, with high heterogeneity (figures 4.8.13 and 4.8.14).[274 276 284 286 287 296 306 307] No heterogeneity was apparent with menopausal status. Twelve case-control studies reported separately on premenopausal breast cancer.[272 275 277-279 281 282 292-294 297 299 300 306 310 318] Ten showed increased risk,[272 275 277 279 281 292-294 299 300 306 318] which was statistically significant in two.[272 281 294 299 300 306] One study showed no effect on risk[297] and the other study showed non-significant decreased risk.[278 282 310] Six studies reported separately on postmenopausal breast cancer.[277 278 281 282 289 297 306 310] Five of these showed increased risk,[278 281 282 289 306 310] which was statistically significant in one.[306] The other study reported non-significant decreased risk.[297]

In addition, 19 case-control studies investigated alcoholic drinks.[289 302 318-323 325-331 333] Most showed increased risk for the highest intake group when compared to the lowest, which was statistically significant in six.[302 318 321 323 327 329] Two studies showed non-significant decreased risk[317 324]; one study showed no effect on risk.[332] Four studies reported separate results for premenopausal breast cancer.[318 320 322 333] Of these, two studies showed non-significant increased risk,[318 333] one showed statistically significant increased risk in

Figure 4.8.13 **Alcoholic drinks and breast cancer; cohort and case-control studies**

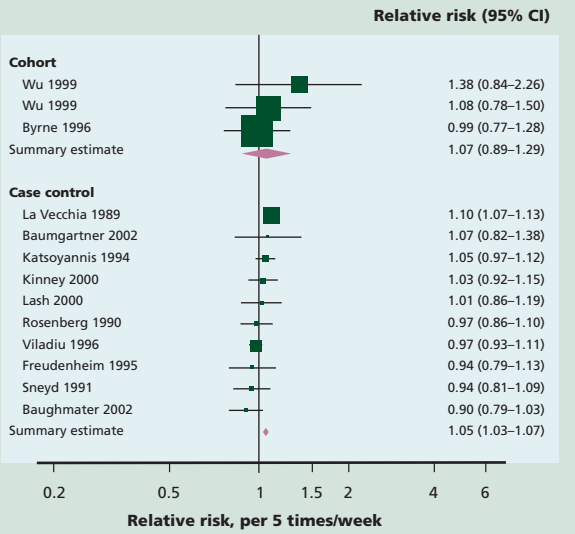
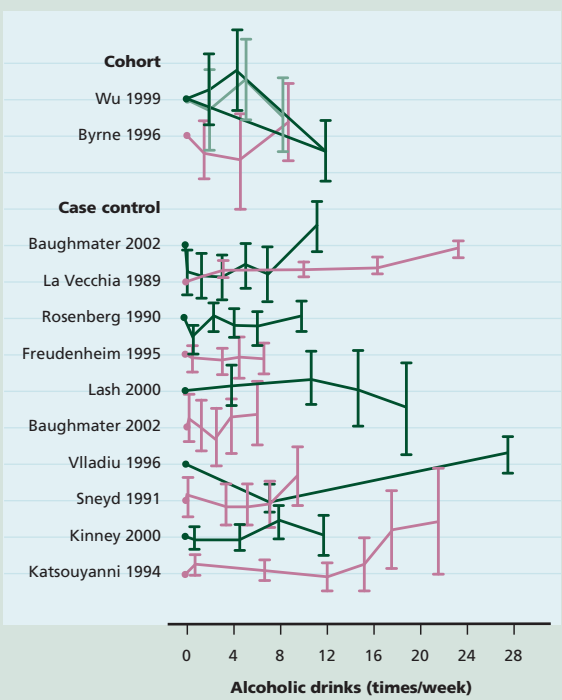


Figure 4.8.14 **Alcoholic drinks and breast cancer; cohort and case-control studies: dose response**



parous women,[322] and one showed non-significant decreased risk.[320] Seven studies reported separately on postmenopausal breast cancer.[289 318 320-322 326 333] All seven studies showed increased risk for the highest intake group when compared to the lowest, which was statistically significant in three,[318 321 333] and in oestrogen-sensitive cancers in a fourth study.[326]

Both ecological studies showed statistically significant, positive associations.[311 312]

When data were analysed separately for drink type (beers, wines, or spirits), they became insufficient to draw any firm conclusions.

Alcohol (as ethanol)

Twelve cohort studies investigated ethanol intake and all-age breast cancer.[315 336 338-341 343-350 352-354 361-364] Eight cohort studies showed increased risk for the highest intake group when compared to the lowest,[315 336 338-341 343 344 346-348 350 352-354 361 362] which was statistically significant in six.[338 341 344 350 352 354 361] Four studies showed decreased risk,[345 349 363 364] which was statistically significant in one.[364] Meta-analysis was possible on nine cohort studies, giving a summary effect estimate of 1.10 (95% CI 1.06–1.14) per 10 g/day, with high heterogeneity (figure 4.8.15). Heterogeneity could be partly explained by differential adjustment for age and reproductive history.

Seven cohort studies reported separately on premenopausal breast cancer.[315 340 343 347 348 352-354 361] Six studies showed increased risk,[340 343 347 348 352-354 361] which was statistically significant in three.[340 348 352] One study showed a non-significant decreased risk.[315] Meta-analysis was possible on five studies, giving a summary estimate of 1.09 (95% CI 1.01–1.17) per 10 g/day, with moderate heterogeneity.[315 340 343 347 352] Eighteen cohort studies reported separately on postmenopausal breast cancer.[315 334 335 337 339 340 342 347 348 351-361] Fifteen studies showed increased risk,[315 335 337 339 342 347 348 351 353-361] which was statistically significant in seven.[315 335 337 339 342 347 357-359] Three studies showed non-significant decreased risk.[334 340 352] Meta-analysis was possible on 11 studies, giving a summary effect estimate of 1.08 (95% CI 1.05–1.10) per 10g/day, with moderate heterogeneity.[315 334 335 339 340 347 352 355 358-360]

Pooled analysis from 6 cohort studies (over 320 000 participants, followed up for up to 11 years, more than 4300 breast cancer cases) showed a significant increased risk with increasing intake, with an effect estimate of 1.09 (95% CI 1.04–1.03) per 10 g/day.[396] No significant heterogeneity was observed by menopausal status.

A separate pooled analysis of 53 case-control studies (more than 58 000 cases and more than 95 000 controls) showed a significant increased risk with increasing intake, with an effect estimate of 7.1 per cent increased risk (95% CI 5.5–8.7%; $p < 0.00001$) per 10 g/day.[397] No significant heterogeneity was observed by menopausal status.

Eighteen case-control studies investigated ethanol intake and all-age breast cancer.[280 282 317 318 332 365-371 374 378 379 381 383 384 386 387 390 391] Twelve case-control studies showed increased risk for the highest intake group when compared to the lowest,[280 318 332 365 367-369 374 379 381 383 384 386 387 391] which was statistically significant in five.[280 318 368 369 374 381 384] Five studies showed decreased risk,[317 366 370 371 378 390] which was statistically significant in one[378]; and one study showed no effect on risk.[282] Meta-analysis was possible on seven case-control studies, giving a summary effect estimate of 1.06 (95% CI 1.04–1.09) per 10 g/day, with moderate heterogeneity (figure 4.8.16).

When case-control data were analysed separately by menopausal status, the meta-analysis for premenopausal breast cancer was consistent with that for all ages (1.08 (95% CI 1.04–1.13) per 10 g/day; nine studies),[317 318 369 373 376 377 380 383 389] but the meta-analysis for postmenopausal breast cancer was not (1.00 (95% CI 0.98–1.01) per 10 g/day; 10 studies).[318 369 372 373 375 380 382 383 385 388]

All four ecological studies showed statistically significant positive associations.[392-395]

The general mechanisms through which alcohol could plausibly cause cancer are outlined below. In addition, most experimental studies in animals have shown that alcohol intake is associated with increased breast cancer risk. Alcohol interferes with oestrogen pathways in multiple ways,

Figure 4.8.15 Ethanol and breast cancer; cohort studies

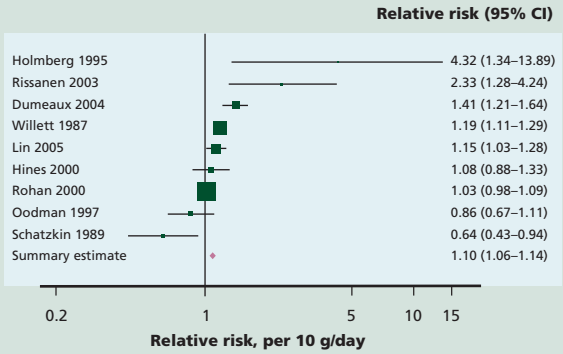
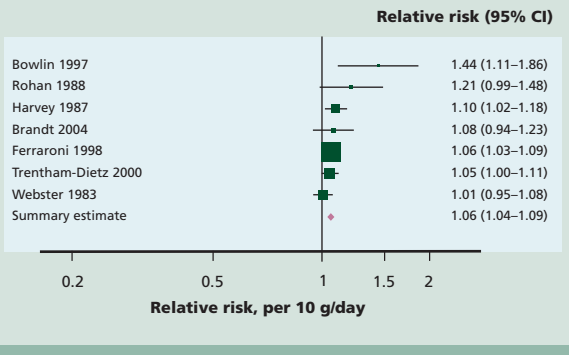


Figure 4.8.16 Ethanol and breast cancer; case-control studies



influencing hormone levels and oestrogen receptors.[398]

There is an interaction between folate and alcohol affecting breast cancer risk: increased folate status partially mitigates the risk from increased alcohol consumption.[399]

There is ample, generally consistent evidence from case-control and cohort studies. A dose-response relationship is apparent. There is robust evidence for mechanisms operating in humans. The evidence that alcoholic drinks are a cause of premenopausal and postmenopausal breast cancer is convincing. No threshold was identified.

The Panel is aware that since the conclusion of the SLR, one case-control study[400] has been published. This new information does not change the Panel judgement (see box 3.8).

Liver

Fifteen cohort studies[120 208 220 227 401-422] and 33 case-control studies[158 423-460] investigated alcoholic drinks and liver cancer. Fourteen cohort studies[6 120 227 244 403 404 409 410 412 416 422 461-468] and 21 case-control studies[158 427 431 434 436 440 446 452 456 459 469-485] investigated ethanol intake.

Total alcoholic drinks

Data are available from 15 cohort studies.[120 208 220 227 401-422] Eleven cohort studies showed increased risk for the highest intake group when compared to the lowest,[120 220 227 401-404 407-410 413 414 416 417 420 422] which was statistically significant in two.[120 401] Two studies showed non-significant decreased risk.[405 406 412 418 419] Two studies stated that there was no significant difference but did not provide further data.[411 415 421] Heterogeneity is partially explained by differences in whether and how studies have adjusted for hepatitis virus status. The effect estimates of eight studies are given in the high to low comparison forest plot (figure 4.8.17).

Data are available from 33 case-control studies.[158 423-460] Twenty-eight case-control studies showed increased risk for the highest intake group when compared to the lowest,[158 423-432 434-448 451-456 460] which was statistically significant in 12 (one of these studies reported a non-significant decreased risk in women, but a statistically significant increased risk in men[440]).[158 423 427 429-432 434 439 440 442 444 446 447 454-456] Two studies showed non-significant decreased risk.[449] Three studies stated that there was no significant effect on risk.[433 450 457-459] Meta-analysis was possible on five studies, giving a summary effect estimate of 1.18 (95% CI 1.11–1.26) per drink/week, with high heterogeneity (figure 4.8.18).[158 425 434 449 460]

A dose-response relationship is apparent from case-control but not cohort data.

Alcohol (as ethanol)

Ten cohort studies showed increased risk for the highest intake group when compared to the lowest,[6 120 244 403 404 409 410 416 422 461 465-468] which was statistically significant in five (one of these studies reported a non-significant increased risk in women, but a statistically significant increased risk in men[461]).[6 120 244 416 461 465 468] Three studies in men with cirrhosis showed non-significant decreased risk.[227 412 462 463] One study stated that there was no significant effect on risk.[464] Meta-analysis was possible on six cohort studies, giving a summary effect estimate of 1.10 (95% CI 1.02–1.17) per 10 g/day or 10 ml/day, with no heterogeneity (figure 4.8.19).

Twenty case-control studies showed increased risk for the highest intake group when compared to the lowest,[158 427 431 434 436 440 446 452 456 469 470 472-475 477-479 481-485] which was statistically significant in 12.[158 427 431 434 440 446 456 474 475 477-479 481 483-485] One study showed non-significant decreased risk.[476] Meta-analysis was possible on 14 case-control studies, giving a summary effect estimate of 1.17 (95% CI 1.09–1.25) per 10 g/day or 10 ml/day, with high heterogeneity (figure

Figure 4.8.17 **Alcoholic drinks and liver cancer: cohort and case-control studies**

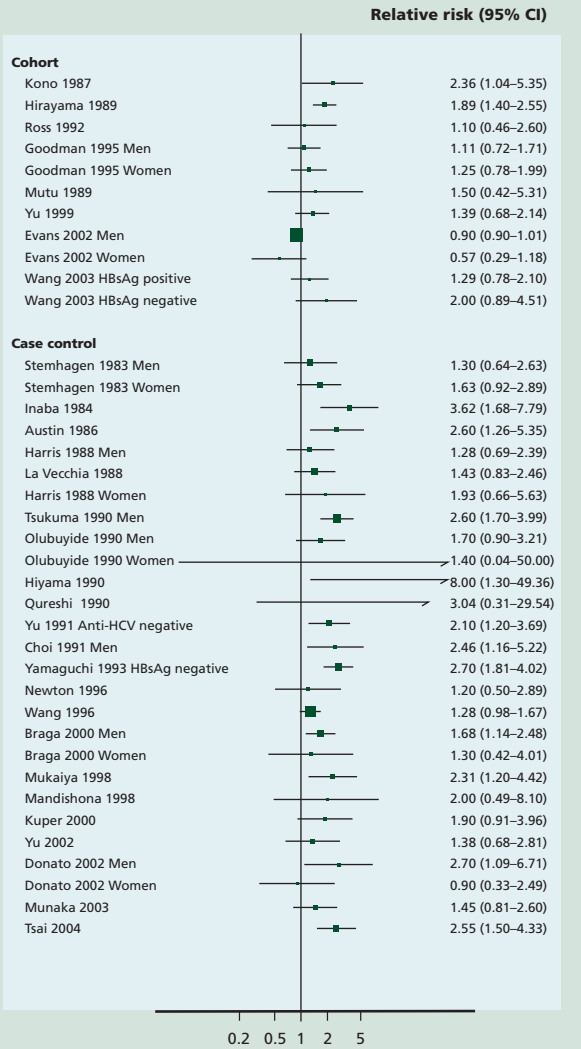


Figure 4.8.18 Alcoholic drinks and liver cancer; case-control studies

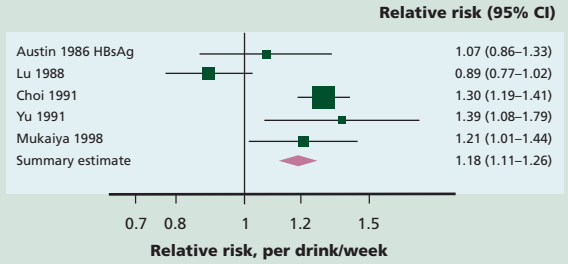


Figure 4.8.19 Ethanol and liver cancer; cohort studies

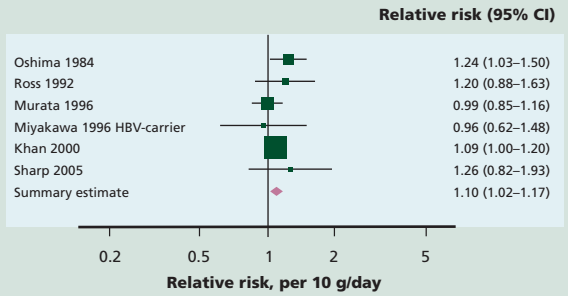


Figure 4.8.20 Ethanol and liver cancer; case-control studies

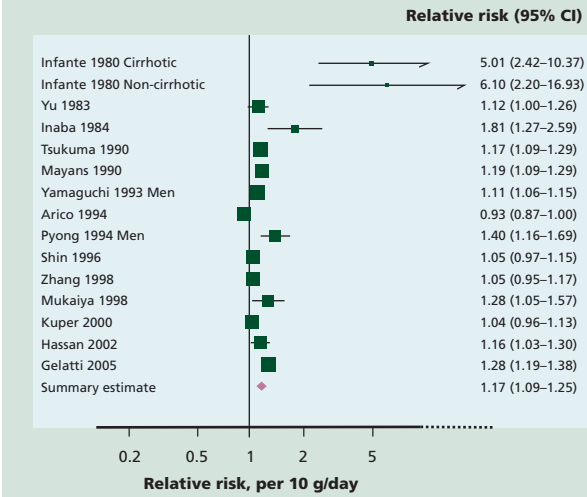
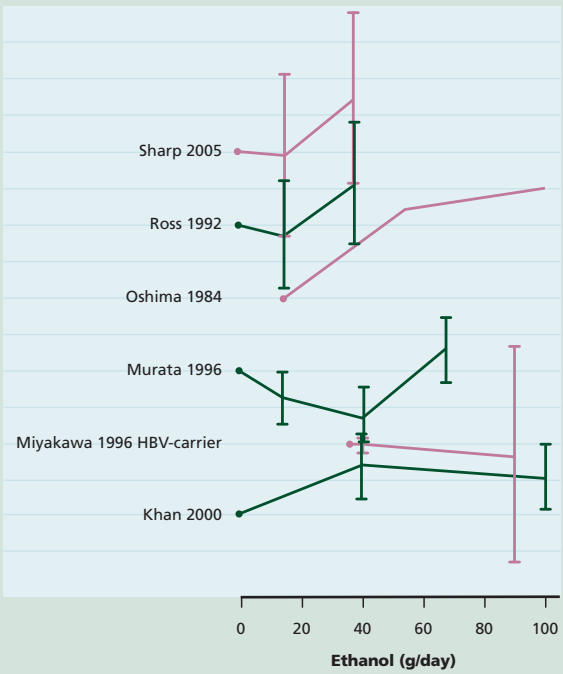


Figure 4.8.21 Ethanol and liver cancer; cohort studies: dose response



4.8.20). Heterogeneity may be due to the inclusion of studies that reported alcoholic behaviour.

A dose-response relationship is apparent from cohort and case-control data (figure 4.8.21).

Beers

Two cohort studies[6 486] and five case-control studies[425 435 444 452 473 479] reported separately on beer drinking.

Both cohort studies showed statistically significant increased risk with increased intake.[6 486] Four case-control studies also showed increased risk,[425 435 444 452 479] which was statistically significant in three.[435 444 452 479] One study reported no effect on risk.[473]

Wines

Three cohort studies[6 410 486] and one case-control study[425] reported separately on wine drinking.

One cohort study showed non-significant increased risk with increased intake.[410] Two studies stated that there was no significant effect on risk.[6 486] The single case-control study showed non-significant increased risk.[425]

Spirits

Two cohort studies[6 486] and five case-control studies[425 444 469 472 479 487] reported separately on spirits.

Both cohort studies showed no significant effect on risk.[6 486] All case-control studies showed increased risk,[425 444 469 472 479 487] which was statistically significant in one[444 479]; and one case-control study showed statistically significant increased risk for consumption of illicit liquor.[487]

Several studies used participants judged to be at high risk of developing liver cancer, that is, people who already had liver cirrhosis. These results are particularly hard to interpret as cirrhosis status affects drinking behaviour. Also the cancer disease path may be different in people with cirrhosis.

Assessment of some studies was hampered by poor exposure assessment, and not all studies adjusted for known confounders such as hepatitis B or C virus.

The general mechanisms through which alcohol could plausibly cause cancer are outlined below. In addition, regular, high levels of alcohol consumption are known to cause liver damage. Tumour promotion has been linked to inflammation in the liver through alcohol-associated fibrosis and hepatitis.[488 489] Alcohol consumption, even at moderate levels, is associated with increases in levels of circulating hepatitis C virus RNA in carriers. Hepatitis C virus infection is highly prevalent among alcoholics with chronic liver disease and appears to accelerate the course of alcoholic liver disease (see chapter 7.8).

There is ample, generally consistent evidence from both cohort and case-control studies. A dose-response relationship is apparent. Alcohol is a cause of cirrhosis that predisposes to liver cancer, but the factors that determine why some people are susceptible to cirrhosis are not known. Alcoholic drinks are a probable cause of liver cancer. No threshold was identified.

The Panel is aware that since the conclusion of the SLR, one case-control study[490] has been published. This new information does not change the Panel judgement (see box 3.8).

Kidney

Three cohort studies[491-493] and 16 case-control studies[308 494-509] investigated alcoholic drinks and kidney cancer. Four cohort studies[6 492 510-513] and five case-control studies[503 504 514-516] investigated ethanol intake.

Total alcoholic drinks

Two cohort studies showed non-significant increased risk for the highest intake group when compared to the lowest.[491 493] One study showed a statistically significant decreased risk.[492] None of the studies was adjusted for smoking; effect estimates were 1.42 (95% CI 0.69–2.9),[493] 1.7 (95% CI 0.8–3.5) for women[491] and 1.2 (95% CI 0.5–2.6) for men,[491] and 0.62 (95% CI 0.41–0.94).[492]

Seven case-control studies showed decreased risk for the highest intake group when compared to the lowest,[308 494 496 499 501-504] of which one was statistically significant[494] and one was statistically significant in women but not in men.[504] Three studies showed no effect on risk[495 497 509]; three studies stated that there was no significant association[505-507]; two studies showed non-significant increased risk[498 500]; one study showed a non-significant decreased risk in men and a non-significant increased risk in women.[508] Meta-analysis was possible on two studies that adjusted for smoking, giving a summary effect estimate of 0.92 (95% CI 0.71–1.20) per serving/day, with moderate heterogeneity (figure 4.8.22).[496 498]

Alcohol (as ethanol)

All four cohort studies showed decreased risk with increased ethanol intake,[6 492 510-513] which was statistically significant in one.[510 512] Meta-analysis was possible on two unadjusted studies, giving a summary effect estimate of 0.48 (95% CI 0.26–0.90) per serving/day, with no heterogeneity.[492 511]

Three case-control studies showed non-significant decreased risk with increased ethanol intake.[504 514 516] One study showed no effect on risk,[515] and one study stated no significant association.[503] Meta-analysis was possible on two unadjusted studies, giving a summary effect estimate of 0.90 (95% CI 0.77–1.05) per serving/day, with no heterogeneity (figure 4.8.23).[514 515]

There is no known mechanism through which alcohol could decrease kidney cancer risk.

It is unlikely that alcohol increases the risk of kidney cancer, though a protective effect cannot be excluded.

Figure 4.8.22 **Ethanol and kidney cancer; case-control studies**

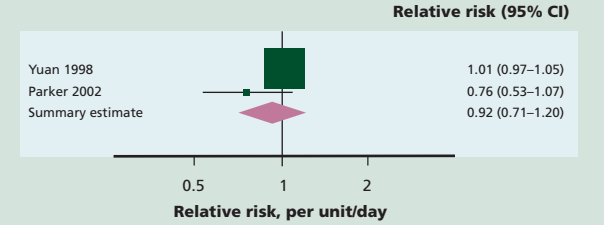
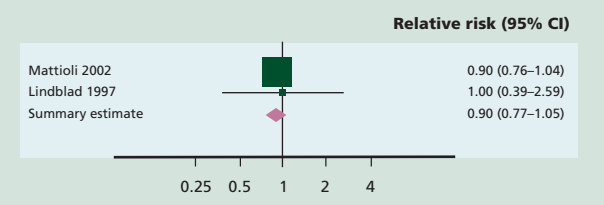


Figure 4.8.23 **Alcoholic drinks and kidney cancer; case-control studies**



The Panel is aware that since the conclusion of the SLR, one cohort study[517] has been published. This new information does not change the Panel judgement (see box 3.8).

General mechanisms

Evidence suggests that reactive metabolites of alcohol, such as acetaldehyde, may be carcinogenic. Additionally, the effects of alcohol may be mediated through the production of prostaglandins, lipid peroxidation, and the generation of free-radical oxygen species. Alcohol also acts as a solvent, enhancing penetration of carcinogens into cells. Alcohol has been demonstrated to alter retinoid status in rodent studies and, as a result, cellular growth, cellular differentiation, and apoptosis are adversely altered. For all these pathways, genetic polymorphisms might also influence risk.[398]

Lastly, heavy consumers of alcohol may have diets deficient in essential nutrients, making tissue susceptible to carcinogenesis.

4.8.6 Comparison with previous report

In general, the evidence that alcohol is a cause of a number of cancers has become stronger since the mid-1990s.

The previous report did not find any distinctions between different types of alcoholic drink. This finding is upheld.

The previous report identified a threshold of modest consumption of alcoholic drinks, below which no effect on cancer risk was observed, with the exception of breast cancer. Current evidence does not identify a generally 'safe' threshold.

Current evidence strengthens the previous judgements on colorectal and breast cancers.

4.8.7 Conclusions

The Panel concludes:

Evidence that alcoholic drinks of any type are a cause of various cancers has, on the whole, strengthened.

The evidence that alcoholic drinks are a cause of cancers of the mouth, pharynx, and larynx, oesophagus, colorectum (men), and breast is convincing. They are probably a cause of colorectal cancer in women, and of liver cancer. It is unlikely that alcoholic drinks have a substantial adverse effect on the risk of kidney cancer.