2.3 Alcohol consumption

2 ETIOLOGY

Jürgen Rehm
Kevin Shield

Naomi E. Allen (reviewer)
Min Dai (reviewer)
Elisabete Weiderpass (reviewer)

Summary

- The relationship between alcohol consumption and cancer risk has been known since the beginning of the 20th century. Epidemiological and biological research on the association has established that alcohol consumption causes cancers of the mouth, pharynx, larynx, oesophagus, liver, colorectum, and female breast.
- Typically, for cancer types caused by alcohol consumption, a dose–response association has been established.
- For 2010, alcohol-attributable cancers were estimated to be responsible for 337 400 deaths worldwide, predominantly among men, with liver cancer accounting for the largest proportion of deaths among the different tumour types.
- Alcoholic beverages are complex mixtures, but ethanol, mediating a genotoxic effect upon metabolism to acetaldehyde, is recognized as the agent predominantly accounting for carcinogenesis.
- The burden of alcohol-attributable cancer can be reduced through alcohol policy measures such as reduction of availability, increases in price, and marketing bans.

The association between alcohol consumption and risk of cancer was known as early as the beginning of the 20th century, when Lamy observed that approximately 8 out of 10 patients with either cancer of the oesophagus or cancer of the cardiac region of the stomach were alcohol misusers [1]. This observation was followed by an ecological study indicating that people who were more likely to consume alcohol (such as people involved in the production and distribution of alcoholic beverages) had a higher risk of head and neck cancers compared with people who abstained from drinking for religious reasons, and that such abstainers had a markedly lower risk of these forms of cancers compared with the population as a whole [2]. After these early observations, several thousand more analytical studies followed to explore the biology and epidemiology of the relationship between alcohol consumption and risk of cancer. As a result, alcoholic beverages were declared “carcinogenic to humans” (Group 1) by the IARC Monographs Programme, first in 1988 [2] and then again in 2007 and in 2010 [3–5]. Tumour types caused by drinking alcoholic beverages include cancers of the oral cavity, pharynx, larynx, oesophagus, liver, colorectum, and female breast. For renal cell carcinoma and non-Hodgkin lymphoma, there is “evidence suggesting lack of carcinogenicity” for alcohol consumption [4,5].

Most cultures throughout the world have traditionally consumed some form of alcoholic beverages, and local specialty alcoholic beverages still account for the majority. Only a small number have evolved into commodities that are produced commercially on a large scale, such as beer from barley, wine from grapes, and certain distilled beverages. Further known beverages are other fruit wines, cider, and a broad range of very diverse spirits, including shochu, sake, lotus- or agave-based spirits, and various types of country-made liquor in India. In many developing countries, various types of home-made or locally produced alcoholic beverages, such as sorghum beer, palm wine, or sugar-cane spirits, continue to be the main available beverage types. Alcopops – flavoured, often sweet, alcoholic beverages – have received special attention mainly in a European context.

A large variety of substances that are not intended for human

Table 2.3.1. Cancers where alcohol consumption may be a component cause

Disease	ICD-10 code	Effect[a]	Epidemiological evidence[a]
Malignant neoplasms			
Cancers of the upper aerodigestive tract			
Cancer of the oral cavity and pharynx	C00–C13	Detrimental	Causally related
Cancer of the larynx	C32	Detrimental	Causally related
Cancer of the oesophagus	C15	Detrimental	Causally related
Cancer of the colorectum	C18–C21	Detrimental	Causally related
Cancer of the liver and hepatobiliary tract	C22	Detrimental	Causally related
Cancer of the stomach	C16	Detrimental	Insufficient causal evidence
Cancer of the pancreas	C25	Detrimental	Causality may need to be re-evaluated
Cancer of the lung	C33–C34	Detrimental	Insufficient causal evidence
Cancer of the female breast	C50	Detrimental	Causally related
Cancer of the prostate	C61	Detrimental	Insufficient causal evidence
Cancer of the kidney and cancer of the urinary bladder	C64–C66, C68 (except C68.9)	Beneficial[b]/no association[a] (renal cell carcinoma only)	Insufficient causal evidence
Cancers of the lymphatic and haematopoietic system			
Hodgkin lymphoma	C81	Beneficial[c]/no association[a]	Insufficient causal evidence
Non-Hodgkin lymphoma	C82–C85, C96	Beneficial[d]/no association[a]	Insufficient causal evidence

ICD-10, *International Classification of Diseases, 10th Revision.*
[a] For more information, see [4].
[b] For more information, see [4,9–11].
[c] For more information, see [4,6].
[d] For more information, see [4,7,8].

consumption are nevertheless being consumed as alcohol (surrogate alcohol such as hairspray, aftershaves, lighter fluid, medicines, or alcohol-containing mouthwash). They often contain very high concentrations of ethanol and may also contain higher alcohols and toxic concentrations of methanol and other chemicals [5].

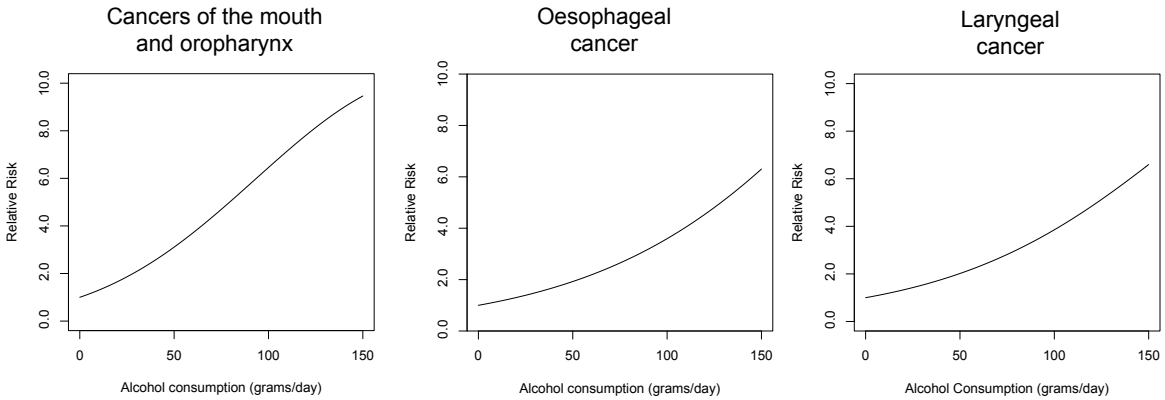
Epidemiological evidence

Since the association between alcohol and various forms of cancer is relatively modest at lower levels of consumption, there have been multiple individual observational studies, where the majority of participants consume low to moderate amounts of alcohol, that have found a significant positive association, an absence of a significant association, or a significant negative association between alcohol consumption and the risk of mortality and morbidity from certain cancers. To determine whether an association exists between alcohol consumption and various forms of cancer, the results of numerous case–control and cohort studies have been combined using meta-analytical techniques. These meta-analyses establish that a significant positive dose–response association exists between alcohol consumption and cancers of the mouth, pharynx, oesophagus, colorectum, liver, larynx, pancreas, female breast, and prostate, while a significant negative association or no association have been observed for each of Hodgkin lymphoma [4,6], non-Hodgkin lymphoma [4,7,8], and renal cell carcinoma [4,9–11]. When epidemiological criteria were examined for causality [12], the association between alcohol consumption and cancers of the mouth, pharynx, oesophagus, colorectum, liver, larynx, and female breast was found to be causal [4,5,13]. Table 2.3.1 provides a list of cancers that have been found to be associated with alcohol consumption through at least one meta-analysis and shows the level of evidence supporting these associations.

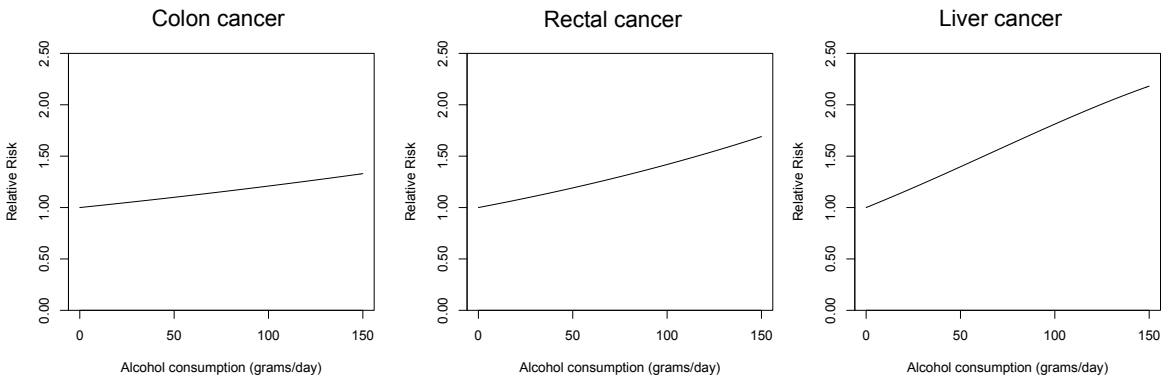
The relationship between average daily alcohol consumption and the risk of mortality from cancers of the upper digestive tract (except cancers of the mouth and oral cavity) and from cancer of the female breast is exponential. The relationship between alcohol consumption and the risk of mortality from cancers of the lower digestive tract and from cancers of the mouth and oral cavity is linear. For cancers of the upper digestive tract, lower digestive tract, mouth, oral cavity, and female breast, former drinkers (people who have not consumed alcohol within the past year but who have consumed it before in their lifetime) were found to have a higher risk of cancer compared with lifetime abstainers. It should be noted that there is evidence that the risk of head and neck cancers decreases with time since cessation of drinking [14]; however, more data are needed to explore the effect of drinking

Box 2.3.1. The relationship between average daily alcohol consumption and relative risk of cancer.

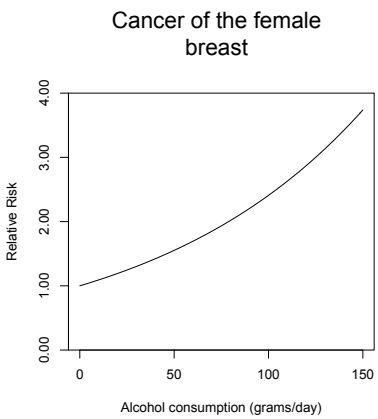
Neoplasms of the upper digestive tract



Neoplasms of the lower digestive tract



Other neoplasms



cessation on risk over time for other alcohol-related cancer sites. Box 2.3.1 provides plots of the relative risk functions for all cancers that are currently determined to be causally associated with alcohol consumption [13]. The relative risk functions presented in Box 2.3.1 are not separated by cancer mortality and incidence. However, the relative risk functions for alcohol-related cancers may be different for mortality and incidence (as a difference between relative risks of mortality and incidence has been observed for other alcohol-related diseases, such as liver cirrhosis [15]). Thus, more research is needed to systematically determine whether there is a difference between the relative risks of incidence and mortality for alcohol-related cancers.

Evidence suggests a synergistic effect of tobacco smoking and consumption of alcoholic beverages on the risk of cancer of the oral cavity, pharynx, larynx, and oesophagus, with very high risks observed in individuals who are both heavy drinkers and heavy smokers [4].

Observational research has suggested that there is a significant positive dose–response association between alcohol consumption and risk of prostate cancer, with multiple meta-analyses confirming this relationship. Biological pathways indicating how alcohol consumption may increase the risk of prostate cancer are currently unknown (see below), and thus additional research is needed to clarify a possible causal association.

Conflicting epidemiological evidence exists for the association between alcohol consumption and cancers of the bladder, lung, and stomach. A nonsignificant positive association has been observed between alcohol consumption and

cancers of the endometrium and ovary [13].

One pooled analysis and one meta-analysis found that in cohort and case–control studies, heavy alcohol consumption – drinking more than 30 g of pure alcohol per day – has been consistently related to an increase in the risk of pancreatic cancer (cited in [4]); however, as mentioned in [4], confounding of smoking could not be excluded as a possible explanation of these results.

Meta-analyses have found no association or a significant negative association between alcohol consumption and the risk of renal cell carcinoma, Hodgkin lymphoma, and non-Hodgkin lymphoma [5,6]. These apparently protective observed effects should be interpreted with caution since the biological mechanisms are not understood and confounding and/or misclassification of abstainers may be responsible for the observations that have been made.

Associations have been reported between alcohol consumption and cancer of the cervix, endometrium, ovary, vulva and vagina, testis, brain, thyroid, and skin (malignant melanoma, basal cell carcinoma, and squamous cell carcinoma) as well as leukaemia and multiple myeloma [5]; however, few studies have examined these associations. Epidemiological research is required to support previous study results, and biological studies are needed to determine the mechanisms by which alcohol intake affects the risk of developing these cancers.

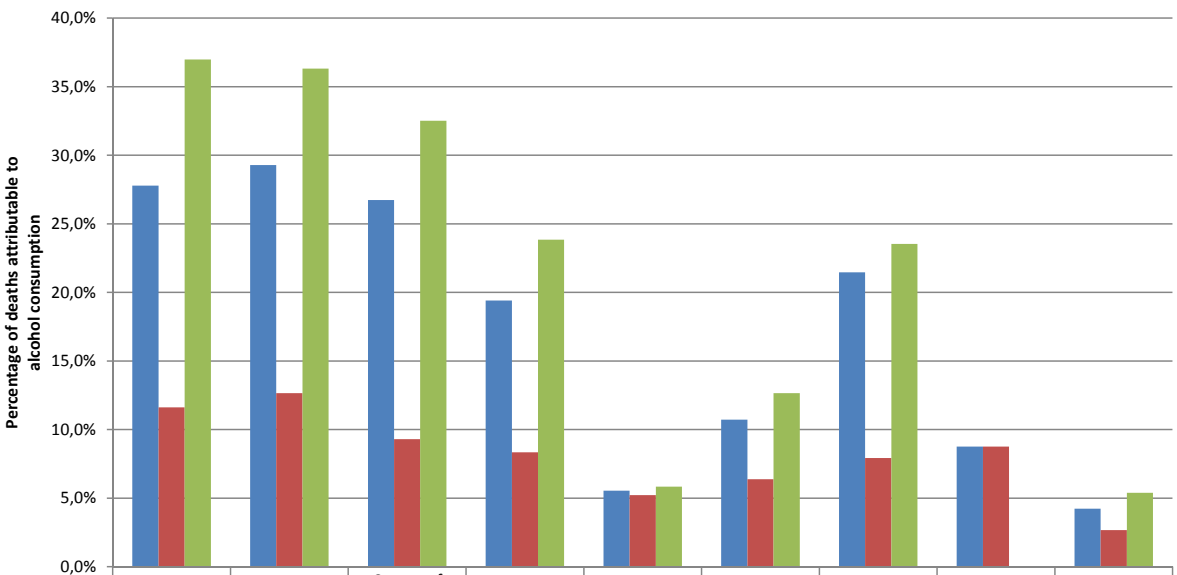
Global rates of alcohol-attributable cancers

The number of deaths and number of disability-adjusted life years (DALYs) lost (a measure that combines years of life lost due to premature mortality and years of healthy life lost due to disability) from cancers that are currently determined to be causally associated with alcohol consumption and from other disease conditions and injuries, in each case for 2010, can be calculated using mortality and morbidity data (see the WHO Global Information System on Alcohol and Health for global alcohol exposure estimates since 1960), with reference to the alcohol-attributable fraction methodology of the 2010 Global Burden of Disease study (see [16]).

In 2010, 337 400 deaths (91 500 of women and 245 900 of men) and 8 670 000 DALYs lost (2 252 000 for women and 6 418 000 for men) were caused by malignant neoplasms attributable to alcohol consumption. This burden represents 0.6% of all deaths (0.4% of all deaths of women and 0.8% of all deaths of men) and 0.3% of all DALYs lost (0.2% of all DALYs lost for women and 0.5% of all DALYs lost for men) in 2010. It should be noted that alcohol-attributable cancer data for 2010 reflect the level of drinking in the early 1990s, due to the long time it takes for cancer to develop [17].

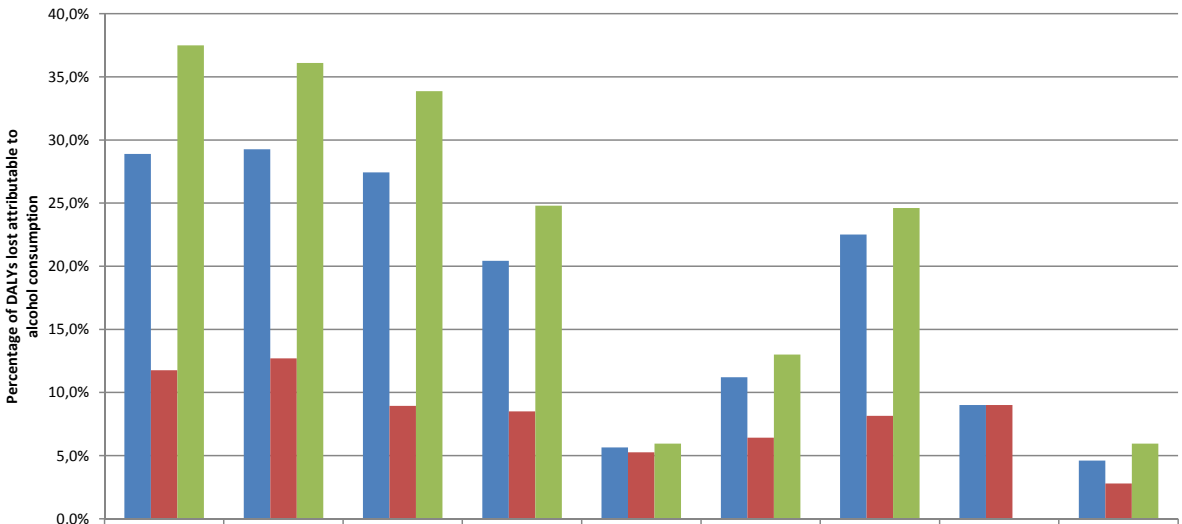
The rates of alcohol-attributable cancer deaths and of alcohol-

Fig. 2.3.1. Percentage of deaths from various forms of cancer attributable to alcohol consumption, in 2010.



	Mouth cancer	Cancer of the nasopharynx	Cancer of other part of pharynx and oropharynx	Oesophageal cancer	Cancers of the colon and rectum	Liver cancer	Laryngeal cancer	Cancer of the female breast	All cancer deaths
Total	27,8%	29,3%	26,7%	19,4%	5,5%	10,7%	21,5%	8,8%	4,2%
Women	11,6%	12,6%	9,3%	8,3%	5,2%	6,4%	7,9%	8,8%	2,7%
Men	37,0%	36,3%	32,5%	23,8%	5,8%	12,7%	23,5%		5,4%

Fig. 2.3.2. Percentage of disability-adjusted life years (DALYs) lost from various forms of cancer attributable to alcohol consumption, in 2010.



	Mouth cancer	Cancer of the nasopharynx	Cancer of other part of pharynx and oropharynx	Oesophageal cancer	Cancers of the colon and rectum	Liver cancer	Laryngeal cancer	Cancer of the female breast	All cancer DALYs lost
Total	28,9%	29,3%	27,4%	20,4%	5,6%	11,2%	22,5%	9,0%	4,6%
Women	11,8%	12,7%	8,9%	8,5%	5,3%	6,4%	8,2%	9,0%	2,8%
Men	37,5%	36,1%	33,9%	24,8%	6,0%	13,0%	24,6%		6,0%

attributable DALYs lost varied globally with reference to regions defined by WHO as Global Burden of Disease regions (see [23]). The number of deaths and the number of DALYs lost per 100 000 people are shown in Tables 2.3.2 and 2.3.3, respectively, by Global Burden of Disease region for 2010. The Eastern Europe region experienced the highest alcohol-attributable cancer burden, with 8.7 cancer deaths per 100 000 people (5.7 per 100 000 women and 12.9 per 100 000 men) and 242.5 DALYs lost per 100 000 people (153.9 per 100 000 women and 357.4 per 100 000 men), while the North Africa/Middle East region experienced the lowest alcohol-attributable cancer burden, with 0.6 cancer deaths per 100 000 people (0.5 per 100 000 women and 0.8 per 100 000 men) and 18.5 DALYs lost per 100 000 people (14.8 per 100 000 women and 22.0 per 100 000 men).

In 2010, the largest contributors to the burden of alcohol-attributable cancer deaths were: overall, liver cancer (responsible for 23.9% of all such deaths); for women, breast cancer (responsible for 42.0% of these deaths); and for men, oesophageal cancer (responsible for 27.4% of these deaths). In 2010, the largest contributors to DALYs lost caused by alcohol-attributable cancer were: overall, liver cancer (responsible for 24.7% of all such DALYs lost); for women, breast cancer (responsible for 48.1% of these DALYs lost); and for men, liver cancer (responsible for 28.2% of these DALYs lost).

The percentage of cancer deaths and the percentage of cancer DALYs lost attributable to alcohol consumption are shown in Figs 2.3.1 and 2.3.2, respectively, by cause. In 2010, 4.2% of all deaths caused by cancer were attributable to alcohol consumption (2.7% for women and 5.4% for men) and 4.6% of all DALYs lost caused by cancer were attributable to alcohol consumption (2.8% for women and 6.0% for men). In 2010, alcohol consumption was responsible for the largest percentage of the total deaths and DALYs lost from nasopharyngeal cancer compared with other cancer types; was responsible for 29.3% of all deaths from cancers of the mouth and oropharynx (12.6% for women and 36.3% for men); and was responsible for 29.3% of all DALYs lost from cancers of the mouth and oropharynx (12.7% for women and 36.1% for men).

Contribution of cancer to the total alcohol-attributable burden of disease

Alcohol consumption is related to more than 200 three-digit ICD-10 (*International Classification of Diseases, 10th Revision*) code diseases, conditions, and injuries, such as infectious diseases, malignant neoplasms, diabetes, neuropsychiatric conditions, cardiovascular disease, digestive diseases, conditions arising during the prenatal period, and injuries (for an overview of the conditions related to alcohol consumption, see [16]). In 2010, alcohol consumption was responsible for 2 734 200 deaths (910 800 of

Table 2.3.2. Cancer deaths attributable to alcohol consumption, by sex and by Global Burden of Disease region, for 2010[a]

Global Burden of Disease region[b]	Sex					
	Female		Male		Total	
	Deaths	Deaths per 100 000 people	Deaths	Deaths per 100 000 people	Deaths	Deaths per 100 000 people
Asia Pacific, high-income	4 000	2.4	13 400	8.1	17 400	5.2
Asia, Central	1 200	3.3	2 000	6.2	3 300	4.6
Asia, East	20 300	2.7	99 800	11.8	120 100	7.5
Asia, South	6 300	1.1	27 200	4.2	33 400	2.7
Asia, South-East	4 700	1.9	12 200	4.7	16 900	3.3
Australasia	800	4.1	1 200	5.6	2 000	4.9
Caribbean	400	2.0	1 000	4.4	1 400	3.2
Europe, Central	3 600	3.7	9 900	11.2	13 500	7.2
Europe, Eastern	10 400	5.7	17 300	12.9	27 700	8.7
Europe, Western	18 300	4.8	29 700	8.2	48 000	6.5
Latin America, Andean	400	2.0	300	1.4	700	1.7
Latin America, Central	1 800	1.8	2 800	3.0	4 600	2.4
Latin America, Southern	1 700	4.4	2 200	6.3	3 900	5.3
Latin America, Tropical	2 800	2.8	5 900	6.2	8 600	4.4
North Africa/Middle East	800	0.5	1 300	0.8	2 100	0.6
North America, high-income	8 500	3.4	11 300	4.4	19 800	3.9
Oceania	100	4.6	200	5.6	300	5.1
Sub-Saharan Africa, Central	400	1.8	700	2.9	1 100	2.3
Sub-Saharan Africa, Eastern	2 500	2.8	3 300	3.7	5 900	3.3
Sub-Saharan Africa, Southern	600	2.1	1 600	6.8	2 200	4.3
Sub-Saharan Africa, Western	1 700	2.0	2 700	2.9	4 400	2.4
World	91 500	2.7	245 900	7.1	337 400	4.9

[a] Numbers have been rounded.
[b] For definitions of regions, see [23].

women and 1 823 400 of men) and 97 118 000 DALYs lost (22 523 000 for women and 74 595 000 for men). Of the total deaths and DALYs lost attributable to alcohol consumption in 2010, alcohol-attributable cancers were responsible for 12.3% of all alcohol-attributable deaths (10.0% for women and 13.5% for men) and 8.9% of all alcohol-attributable DALYs lost (10.0% for women and 8.6% for men).

Possible biological mechanisms

As indicated above, alcohol consumption is carcinogenic and causes a variety of human cancers, and there may be different biological pathways depending on the anatomical site. Alcoholic beverages are multicomponent mixtures containing several carcinogenic compounds, such as ethanol, acetaldehyde, aflatoxins, and ethyl carbamate (see [18]), and all of these compounds may contribute to increase the risk of cancer due to alcohol consumption reported in observational studies. A recent chemical risk analysis concluded that ethanol is the most important carcinogen in alcoholic beverages, with all other carcinogenic compounds contained in alcoholic beverages increasing the risk of cancer below the threshold normally acceptable for food contaminants [18].

The biological mechanisms by which alcohol intake increases the risk of cancer are not fully understood, but the main mechanisms are likely to include a genotoxic effect of acetaldehyde, the induction of cytochrome P450 2E1 and associated oxidative stress, increased estrogen concentration, a role as a solvent for tobacco carcinogens, changes in folate metabolism, and changes in DNA repair [4,5].

For cancers of the digestive tract, especially those of the upper digestive tract, acetaldehyde from alcohol metabolism in the body and from

Table 2.3.3. Cancer disability-adjusted life years (DALYs) lost attributable to alcohol consumption, by sex and by Global Burden of Disease region, for 2010[a]

Global Burden of Disease region[b]	Sex					
	Female		Male		Total	
	DALYs lost	DALYs lost per 100 000 people	DALYs lost	DALYs lost per 100 000 people	DALYs lost	DALYs lost per 100 000 people
Asia Pacific, high-income	81 000	60.8	284 000	196.5	365 000	128.5
Asia, Central	38 000	98.5	58 000	170.9	95 000	132.1
Asia, East	530 000	69.3	2 690 000	318.9	3 221 000	200.0
Asia, South	182 000	28.8	782 000	115.3	964 000	73.9
Asia, South-East	113 000	41.8	342 000	124.7	455 000	82.7
Australasia	17 000	101.3	24 000	129.6	42 000	115.9
Caribbean	12 000	53.6	25 000	113.2	36 000	83.5
Europe, Central	90 000	103.8	253 000	302.9	342 000	199.6
Europe, Eastern	250 000	153.9	461 000	357.4	711 000	242.5
Europe, Western	374 000	121.5	649 000	206.5	1 023 000	163.9
Latin America, Andean	11 000	48.9	9 000	38.0	20 000	43.4
Latin America, Central	47 000	45.9	66 000	67.1	112 000	56.6
Latin America, Southern	38 000	106.8	49 000	144.4	86 000	124.4
Latin America, Tropical	76 000	75.4	167 000	172.7	243 000	122.7
North Africa/Middle East	28 000	14.8	42 000	22.0	70 000	18.5
North America, high-income	205 000	90.0	263 000	112.0	468 000	100.8
Oceania	4 000	124.0	5 000	153.4	9 000	138.7
Sub-Saharan Africa, Central	13 000	47.6	21 000	81.9	34 000	64.4
Sub-Saharan Africa, Eastern	72 000	71.3	98 000	97.9	170 000	84.3
Sub-Saharan Africa, Southern	17 000	56.6	47 000	182.8	63 000	114.9
Sub-Saharan Africa, Western	54 000	53.0	85 000	80.7	139 000	66.9
World	2 252 000	66.0	6 418 000	184.8	8 670 000	125.9

[a] Numbers have been rounded.
[b] For definitions of regions, see [23].

ingestion as a component of alcoholic beverages [19] has been highlighted as a likely and important causal pathway [4,5]. For colorectal cancer, in addition to the genotoxic effect of acetaldehyde, there may be the involvement of folate: alcohol may act through folate metabolism or synergistically with low folate intake (see [5]). The biological mechanisms accounting for how alcohol intake may cause pancreatic cancer are currently unclear; however, potential mechanisms include pancreatitis and the accumulation of fatty acid esters in the pancreas, which may induce inflammatory responses and fibrosis [4].

The biological effects of alcohol intake on the risk of digestive tract cancers are also dependent on the genotype of the consumer; individuals with the *ALDH2* Lys487 allele (and therefore a deficiency of ALDH2) experience a higher risk of oesophageal cancer for the same amount of alcohol consumed. The *ALDH2* Lys487 allele is thought to modify the risk of all cancers that are caused by the metabolites of alcohol [4,5].

In relation to breast cancer, alcohol intake has been shown to increase levels of estrogen and plasma insulin-like growth factor produced by the liver, to enhance mammary gland susceptibility to carcinogenesis (by altering mammary gland structural development and by stimulating cell proliferation), to increase mammary DNA damage, and to facilitate the ability of breast cancer cells to migrate [20].

Implications for prevention

The relationship between alcohol consumption and cancer has been observed as monotonic and without threshold (see above and

[3,4]). Thus, as the amount of alcohol consumed increases, the risk of developing cancer increases. This means that any reduction in alcohol consumption will be beneficial for health through the reduction of cancer risk. There are cost-effective ways to reduce alcohol consumption: most notably, restrictions in availability; increases in price for alcoholic beverages, which could be achieved by increasing taxation or increasing minimum prices; and marketing bans [21]. In addition, the risk of cancer for high-risk heavy alcohol consumers can be reduced by providing more opportunities for brief interventions and treatment for alcohol use disorders [22].

Fig. 2.3.3. Female drinking has risen steadily for the past 20 years, with more women than men drinking heavily on single occasions.

References

1. Lamy L (1910). Clinical and statistical study of 134 cases of cancer of the oesophagus and of the cardia [in French]. *Arch Mal Appar Dig Mal Nutr*, 4:451–475.
2. IARC (1988). Alcohol drinking. *IARC Monogr Eval Carcinog Risks Hum*, 44:1–378. PMID:3236394
3. Baan R, Straif K, Grosse Y *et al.*; WHO IARC Monograph Working Group (2007). Carcinogenicity of alcoholic beverages. *Lancet Oncol*, 8:292–293. http://dx.doi.org/10.1016/S1470-2045(07)70099-2 PMID:17431955
4. IARC (2012). Personal habits and indoor combustions. *IARC Monogr Eval Carcinog Risks Hum*, 100E:1–575. PMID: 23193840
5. IARC (2010). Alcohol consumption and ethyl carbamate. *IARC Monogr Eval Carcinog Risks Hum*, 96:1–1428. PMID:21735939
6. Tramacere I, Pelucchi C, Bonifazi M *et al.* (2012). A meta-analysis on alcohol drinking and the risk of Hodgkin lymphoma. *Eur J Cancer Prev*, 21:268–273. http://dx.doi.org/10.1097/CEJ.0b013e328350b11b PMID:22465910
7. Tramacere I, Pelucchi C, Bonifazi M *et al.* (2012). Alcohol drinking and non-Hodgkin lymphoma risk: a systematic review and a meta-analysis. *Ann Oncol*, 23:2791–2798. PMID:22357444
8. 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. http://dx.doi.org/10.1016/S1470-2045(05)70214-X PMID:15992695
9. Bellocco R, Pasquali E, Rota M *et al.* (2012). Alcohol drinking and risk of renal cell carcinoma: results of a meta-analysis. *Ann Oncol*, 23:2235–2244. http://dx.doi.org/10.1093/annonc/mds022 PMID:22398178
10. Song DY, Song S, Song Y, Lee JE (2012). Alcohol intake and renal cell cancer risk: a meta-analysis. *Br J Cancer*, 106:1881–1890. http://dx.doi.org/10.1038/bjc.2012.136 PMID:22516951
11. Cheng G, Xie L (2011). Alcohol intake and risk of renal cell carcinoma: a meta-analysis of published case-control studies. *Arch Med Sci*, 7:648–657. http://dx.doi.org/10.5114/aoms.2011.24135 PMID:22291801
12. Rothman KJ, Greenland S, Lash TL, eds (2008). *Modern Epidemiology*, 3rd ed. Philadelphia, PA: Lippincott Williams & Wilkins.
13. Shield KD, Parry C, Rehm J (2013). Chronic diseases and conditions related to alcohol use. *Alcohol Res*, (in press).
14. 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. http://dx.doi.org/10.1093/aje/kwp222 PMID:19745021
15. Rehm J, Taylor B, Mohapatra S *et al.* (2010). Alcohol as a risk factor for liver cirrhosis: a systematic review and meta-analysis. *Drug Alcohol Rev*, 29:437–445. http://dx.doi.org/10.1111/j.1465-3362.2009.00153.x PMID:20636661
16. Rehm J, Baliunas D, Borges GLG *et al.* (2010). The relation between different dimensions of alcohol consumption and burden of disease: an overview. *Addiction*, 105:817–843. http://dx.doi.org/10.1111/j.1360-0443.2010.02899.x PMID:20331573
17. Holmes J, Meier PS, Booth A *et al.* (2012). The temporal relationship between per capita alcohol consumption and harm: a systematic review of time lag specifications in aggregate time series analyses. *Drug Alcohol Depend*, 123:7–14. http://dx.doi.org/10.1016/j.drugalcdep.2011.12.005 PMID:22197480
18. Lachenmeier DW, Przybylski MC, Rehm J (2012). Comparative risk assessment of carcinogens in alcoholic beverages using the margin of exposure approach. *Int J Cancer*, 131:E995–E1003. http://dx.doi.org/10.1002/ijc.27553 PMID:22447328
19. Lachenmeier DW, Kanteres F, Rehm J (2009). Carcinogenicity of acetaldehyde in alcoholic beverages: risk assessment outside ethanol metabolism. *Addiction*, 104:533–550. http://dx.doi.org/10.1111/j.1360-0443.2009.02516.x PMID:19335652
20. Singletary KW, Gapstur SM (2001). Alcohol and breast cancer: review of epidemiologic and experimental evidence and potential mechanisms. *JAMA*, 286:2143–2151. http://dx.doi.org/10.1001/jama.286.17.2143 PMID:11694156
21. Babor T, Caetano R, Casswell S *et al.* (2010). *Alcohol: No Ordinary Commodity: Research and Public Policy*, 2nd ed. Oxford: Oxford University Press. http:dx.doi.org/10.1093/acprof:oso/9780199551149.001.0001
22. Rehm J, Shield KD, Gmel G *et al.* (2013). Modeling the impact of alcohol dependence on mortality burden and the effect of available treatment interventions in the European Union. *Eur Neuropsychopharmacol*, 23:89–97. http://dx.doi.org/10.1016/j.euroneuro.2012.08.001 PMID:22920734
23. Murray CJL, Ezzati M, Flaxman AD *et al.* (2012). GBD 2010: design, definitions, and metrics. *Lancet*, 380: 2063–2066. http://dx.doi.org/10.1016/S0140-6736(12)61899-6 PMID:23245602

Website

WHO Global Information System on Alcohol and Health: http://apps.who.int/ghodata/?theme=GISAH