Measuring the Impact of Alcohol on the Global Burden of Cancer

International analyses of alcohol-related cancers

Harriet Rumgay

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Measuring the Impact of Alcohol on the Global Burden of Cancer:
International analyses of alcohol-related cancers

De impact van alcohol op de wereldwijde kankerlast meten:
internationale analyses van aan alcohol-gerelateerde kankers

Thesis

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by

Harriet Jayne Rumgay
Born in Leeds, United Kingdom

Erasmus University Rotterdam

Doctoral Committee

Promotor
Prof. dr. V.E.P.P. Lemmens

Other members
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Table of Contents

1

Introduction

Chapter

General introduction

Population alcohol consumption

Nearly half (47%) of the world's adult population regularly consumes alcohol despite its many associated health risks and injuries.[1] In 2019, global alcohol consumption was 5.8 litres of pure alcohol per person aged 15 years and older, which is the equivalent of between one or two standard drinks of 10 grams of pure alcohol per day; if we only consider current drinkers, however, this increases by more than double.[2] There are large differences in the total volume of alcohol consumed by men and women globally, with men drinking nearly four times the volume of alcohol as women in 2019.[2] The amount of alcohol consumed also differs substantially between countries and regions of the world, resulting in major variation in consumption per capita.[2] On average, men in western, eastern, and northern Europe drink the most alcohol (more than 17 litres per capita in 2019), while the heaviest drinking levels among women are in western and northern Europe, and Australia and New Zealand (more than 5 litres per capita) (Figure 1). In contrast, northern Africa and western Asia have the lowest volumes of alcohol consumption per capita globally among both men and women.

The temporal trends of alcohol consumption also reveal variation in drinking patterns over time between world regions. European regions have historically outranked others by having the highest alcohol consumption globally (12.1 litres per capita in 1990), but alcohol use in Europe has dropped in recent years and decreased by 11% between 1990 and 2014 (to 10.7 litres per capita in 2014).[1,3] In several other regions including eastern and south-central Asia, total alcohol consumption has increased as the economic power of countries in these regions has grown; in some countries in eastern Asia, for example, the average volume of alcohol consumed among the population is now higher than in European countries.[1] Furthermore, economic development is often paralleled by an increase in alcohol consumption among women due to women taking on a larger share of paid employment and purchasing more alcohol with the disposable income. Consequently, the gap between male and female drinkers is predicted to fall by 2030 as more women take up drinking in countries under economic transition.[1] However, alcohol use has remained higher among men than women throughout the world which has led to a larger burden of alcohol-related disease among men than women.[4]

Considering drinking patterns by type of alcoholic beverage provides further insight into alcohol consumption trends. Alcoholic drinks can be categorised into six groups: beer, wine, spirits, fermented milks, mead, and cider. Globally, spirits are the most preferred beverage type, representing 44.8% of the total recorded volume of alcohol consumed in 2016.[5] But preference for type of beverage differs between populations; for example, of the European countries, beer made up more than half of recorded alcohol consumption per capita in Czechia, Austria, Poland, and Germany in 2019, whereas wine was the most popular alcoholic beverage in Italy, France, and Portugal.[6] Spirits and other types of alcoholic drinks are the most preferred types of alcohol in the south-east Asian and African regions of the World Health Organization (WHO) offices, respectively.[5] Regarding changes over time, beverage

type preferences have remained fairly stable since 2010, with a maximum difference of a 3% decline in the share of spirits consumed in Europe between 2010 and 2016.[5]

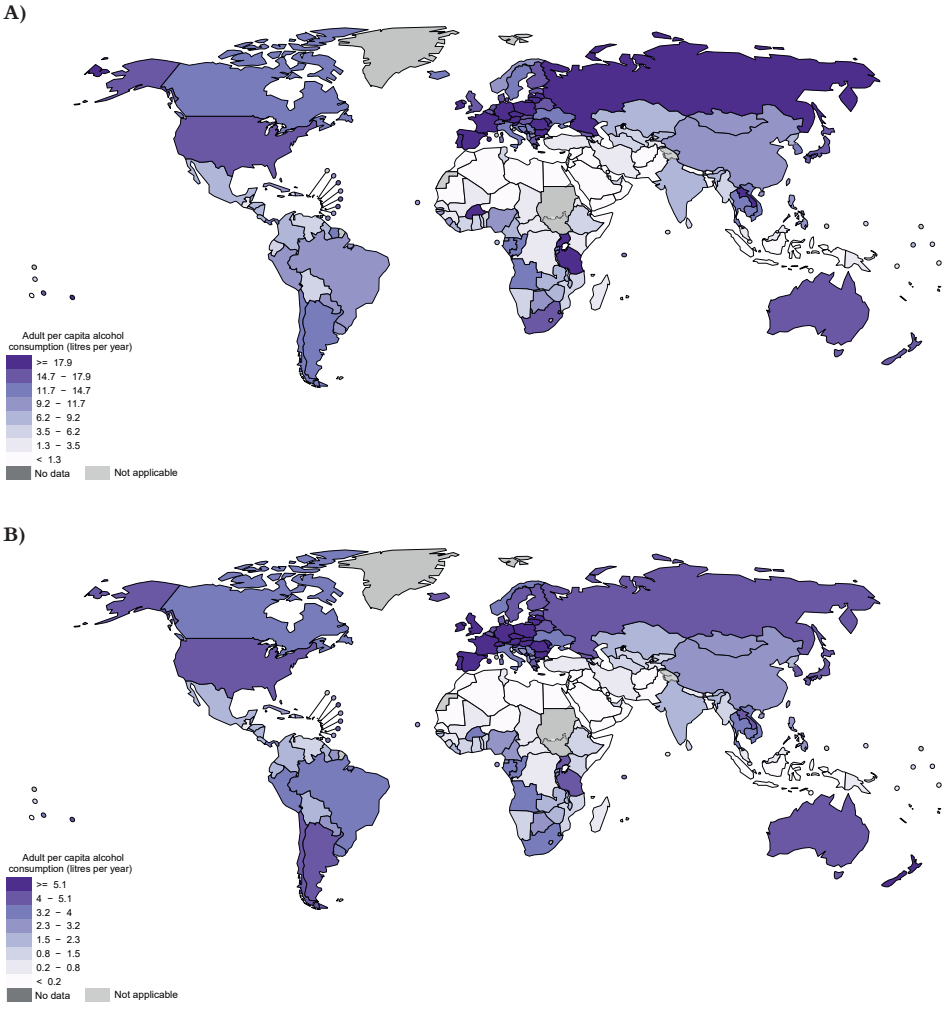

Figure 1. Total alcohol consumption per capita (15 years and older) in litres of pure alcohol among (A) men and (B) women in 2019. Source of data: WHO Global Health Observatory, 2021.

Causal link between alcohol and cancer

Drinking alcohol can increase the risk of over 200 injuries and diseases, including cancer.[7] As the cancer research agency of the WHO, the International Agency for Research on Cancer (IARC) first classified alcoholic beverages as a group 1 carcinogen in 1988 after reviewing the strength of the epidemiological and experimental evidence.[8] They concluded that alcohol consumption increases the risk of cancers of the oral cavity, pharynx, larynx, oesophagus,

and liver, later adding cancers of the colorectum and breast (among females) in subsequent Monographs.[9,10] The World Cancer Research Fund (WCRF) is a non-governmental body which also classifies the evidence on potential physical and dietary carcinogens. The WCRF base their classifications on the quality of epidemiological evidence and conduct meta-analyses as part of this review process which are presented in their most recent report on Diet, Nutrition, Physical Activity and Cancer.[11] In this report, WCRF concluded that there was strong evidence that consuming alcoholic drinks increased the risk of cancers of the mouth, pharynx and larynx, oesophagus (squamous cell carcinoma), liver, colorectum, and breast (postmenopausal), and that there was a probable increased risk of stomach cancer and premenopausal breast cancer (Figure 2).

ALCOHOLIC DRINKS AND THE RISK OF CANCER

WCRF/AICR GRADING		DECREASES RISK		INCREASES RISK	
		Exposure	Cancer site	Exposure	Cancer site
STRONG EVIDENCE	Convincing			Alcoholic drinks[1]	Mouth, pharynx and larynx 2018 Oesophagus (*squamous cell carcinoma*) 2016 Liver 2015[2] Colorectum 2017[3] Breast (postmenopause) 2017[4]
	Probable	Alcoholic drinks	Kidney 2015[5]	Alcoholic drinks	Stomach 2016[2] Breast (premenopause) 2017[4]
LIMITED EVIDENCE	Limited – suggestive			Alcoholic drinks	Lung 2017 Pancreas 2012[2] Skin (*basal cell carcinoma* and malignant *melanoma*) 2017
STRONG EVIDENCE	Substantial effect on risk unlikely	None identified			

1 Alcoholic drinks include beers, wines, spirits, fermented milks, mead and cider. The consumption of alcoholic drinks is graded by the International Agency for Research on Cancer as carcinogenic to humans (Group 1)[3].

2 The conclusions for alcoholic drinks and cancers of the liver, stomach and pancreas were based on evidence for alcohol intakes above approximately 45 grams of ethanol per day (about three drinks a day). No conclusions were possible for these cancers based on intakes below 45 grams of ethanol per day.

3 The conclusion for alcoholic drinks and colorectal cancer was based on alcohol intakes above approximately 30 grams of ethanol per day (about two drinks a day). No conclusion was possible based on intakes below 30 grams of ethanol per day.

4 No threshold level of alcohol intake was identified in the evidence for alcoholic drinks and breast cancer (pre and postmenopause).

5 The conclusion for alcoholic drinks and kidney cancer was based on alcohol intakes up to approximately 30 grams of ethanol per day (about two drinks a day). There was insufficient evidence to draw a conclusion for intakes above 30 grams of ethanol per day.

Figure 2. World Cancer Research Fund summary matrix on classifications of alcoholic drinks and the risk of cancer.[11] Source: World Cancer Research Fund, 2018.

It is widely accepted that alcohol consumption at any level increases the risk of cancer. This includes levels of consumption traditionally thought of as 'low', 'light', or 'moderate', including up to one or two alcoholic drinks per day. The risk relationship differs by cancer type, for example WCRF's dose-response meta-analysis of oral cavity cancer risk showed a 15% increase per 10 grams of alcohol per day, whereas the evidence for liver cancer suggests that the relationship is highly related to chronic alcohol consumption, with a probable threshold effect up to 45 grams of alcohol per day.[11] Yet, at least for cancers of the oral cavity, pharynx, larynx, oesophagus, and breast, an increase in risk is observed from the first alcoholic drink per day.[11,12]

Mechanistic evidence has shown that alcohol and its metabolite acetaldehyde can drive carcinogenesis through several pathways. These include through damaging DNA, blocking DNA synthesis and repair, and disrupting DNA methylation.[13] Ethanol can also induce inflammation and oxidative stress leading to further DNA damage and lipid peroxidation.[14] We discuss the biological pathways of alcohol-mediated carcinogenesis in further detail in Chapter 2.

Population impact of alcohol on cancer

Classifying the carcinogenic potential of risk factors is valuable but estimating the size of the impact of these factors on disease burden is key for public health strategy. A standard approach of measuring the impact of alcohol use on cancer burden, for example, is the use of population attributable fractions (PAFs). PAFs provide an estimate of the avoidable burden of disease by measuring the observed burden relative to the expected burden.[15] The methodology to calculate PAFs was conceived in the early 1950's and developed by Levin[16] and Doll[17] to estimate the occurrence of lung cancer attributable to cigarette smoking using data from case-control studies in the United States (US) and United Kingdom (UK), respectively. We can estimate PAFs through multiple methods, namely the 'literature-based' method and the 'low-risk' method.[18] The 'literature-based' method of calculating PAFs uses estimates of relative risk (RR) of developing disease due to exposure to a risk factor, and the public health importance of the risk factor i.e. the prevalence (P) among the population, in the following equation:

$$\mathrm{PAF} = \frac{P(\mathrm{RR}-1)}{P(\mathrm{RR}-1)+1}$$

The PAF estimates by Levin and Doll were the result of the 'low-risk' method which uses individual-level data from a low-risk cohort or case-control study. In cohort and case-control studies, information on multiple risk factors is collected from individuals; in analysing these data to estimate attributable risk for the study population or cohort, exposure to other risk factors can be adjusted for to give a best estimate of the risk attributable to a single risk factor. Whether from cohort or case-control studies, however, PAFs produced by the 'low-risk'

method are most relevant for the populations they represent and might not be applicable to wider populations. Nevertheless, by calculating the population impact of risk factors through either the 'low-risk' or 'literature-based' method, we can compare the effect of several risk factors and diseases. These comparisons enable prioritisation of resources to improve public health by targeting prevention of the factors which have the largest impact. To demonstrate this prioritisation in a cancer prevention setting, Figure 3 shows an infographic produced by Cancer Research UK, a large non-governmental organisation in the UK, to communicate the risk factors for cancer with the largest impact at the population level based on PAFs of cancer cases attributable to theoretically modifiable risk factors in the UK in 2015.[19]

Figure 3. Example of cancer population attributable fractions as a prioritisation tool for cancer prevention. Source: Cancer Research UK, 2019.

For alcohol consumption, PAFs of disease burden provide a valuable tool to quantify the absolute impact of alcohol use and are applied in setting alcohol control and disease prevention policies.[5] Alcohol PAFs are often calculated through the 'literature-based' method using a combination of estimates of population alcohol exposure, cancer risk from drinking different amounts of alcohol, and cancer burden.[4,20] The theoretical minimum risk for alcohol PAFs is usually lifetime abstention from alcohol consumption thus setting an ambitious target aiming to completely avoid alcohol use in the population. Other plausible minimum risks have also been used such as adhering to a government's alcohol guidelines[21] or eliminating heavy alcohol use.[22] In addition to being used as a tool for public health, alcohol PAFs can communicate health messages to the public to increase awareness of the health risks involved when drinking alcohol (example in Figure 4). By providing this information in absolute terms, PAFs might be easier for wider audiences understand than messaging using relative risks which are often harder to put into context.[23]

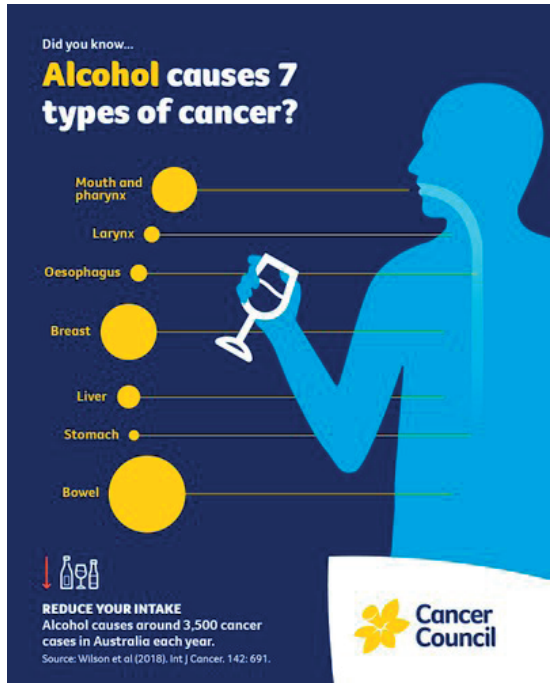

Figure 4. Example of alcohol population attributable fractions used in communication of cancer prevention messages to the public. Source: Cancer Council Australia, 2020.

PAFs for alcohol-attributable cancers are also used to quantify further implications of the impact of alcohol on cancer burden, such as through estimating the social and economic cost of alcohol-attributable cancers, as well as the effectiveness of certain alcohol control interventions. This type of monetary estimation can demonstrate the economic impact of the disease burden due to alcohol and might aid policymakers in weighing up the cost of alcohol-attributable disease versus the cost of alcohol control interventions i.e. the cost-effectiveness of reducing alcohol consumption among the population. Further, modelling the impact of alcohol control interventions on the incidence or mortality of cancer would provide evidence of the efficacy of policy solutions to reduce alcohol-attributable cancer burden.

Alcohol control policies

In order to assess ways of reducing population alcohol consumption, the WHO's list of so-called 'best buys' and other recommended interventions for the prevention and control of noncommunicable diseases provide the basis for effective alcohol control policies.[24] To be considered a 'best buy', the interventions must undergo cost-effectiveness analysis and result in a value of up to I$100 per disability-adjusted life year averted in low-and-middle income countries. The three 'best buys' to reduce alcohol use are: increasing excise taxes on

alcoholic beverages, banning alcohol advertising, and restricting the physical availability of retail alcohol products.[24] Similar to tobacco taxation policies, increasing the price of alcohol through excise taxes reduces affordability of alcohol products thus dissuading individuals from purchasing alcohol. This measure has markedly reduced the high levels of alcohol consumption in countries in eastern Europe such as Belarus and Moldova which previously had the highest alcohol consumption levels globally.[1] On advertising and marketing of alcohol products, the digital world poses new challenges to keep on top of advertising regulations, particularly concerning adolescents' exposure to alcohol marketing through social media.[25] Reducing the physical availability of alcohol products through restricting hours of sale and increasing the age to purchase alcohol provides a barrier to potential consumers; a further example of this physical barrier to purchasing alcohol includes the government monopolisation of off-premise alcohol sales in several provinces in Canada and states in the US where alcohol must be bought in dedicated liquor stores.[5]

Outside of WHO's 'best buys', other alcohol pricing policies include the introduction of minimum unit pricing (MUP). MUP has been implemented in several European countries and has already resulted in a reduction in alcohol-related mortality among males of working age in Russia.[26] Contrary to a blanket increase of excise taxes across all alcohol products, MUP primarily affects low-cost high-strength alcohol and has been shown to reduce alcohol consumption among heavy drinkers in lower socioeconomic groups.[27] Additional alcohol control policies currently being evaluated include the potential labelling of alcohol products with cancer warnings such as 'alcohol can cause cancer' (Figure 5).[28] Such labelling might put shoppers off from purchasing the product whilst also increasing public awareness of the

Figure 5. Warning labels placed on alcohol products during the Northern Territories Alcohol Label Study in 2017 in Yukon, Canada. Source: Canadian Institute for Substance Use Research, 2017.

association between alcohol and cancer which is currently low; for example, only a third of the population in several high-income countries lists alcohol as a risk factor for cancer.[29] In general, labelling along with the other alcohol control policies discussed are all 'upstream' approaches to alcohol prevention, but other 'midstream' and 'downstream' approaches include screening for excessive alcohol use and giving brief advice in primary care,[30] and individual-level education interventions such as mass media alcohol awareness campaigns.[31] All of these policies have the ultimate goal of reducing alcohol use among the population and thus avoiding alcohol harms.

Process of identifying alcohol-attributable cancer burden

Here we map out the step-by-step process of identifying alcohol-attributable cancer burden that we have used in this thesis (Figure 6). First, cancer registries collect data on cancer incidence and mortality in the population. Descriptive studies report the current burden of cancer and trends over time which enable hypotheses to be made around causes of the patterns observed such as risk factor changes and policy implementation. Observational studies produce evidence on the association between alcohol and cancer risk and their results are aggregated in systematic reviews and meta-analyses. The cancer types causally related to alcohol use are then identified and classified following peer-review and consensus among experts at Monograph meetings organised by IARC, Continuous Update Project review meetings by WCRF, and local meetings in different nations. After classifying the association between alcohol and cancer and expert review of the most appropriate cancer risk estimates and alcohol exposure data, PAFs can be estimated to quantify the population impact of alcohol on cancer burden. Using these PAFs, we can estimate the societal impact and cost of alcohol-attributable cancers and model the impact of changes in alcohol policy on the burden of alcohol-attributable cancers. These provide evidence of the best interventions to reduce alcohol use and the burden of cancer due to alcohol.

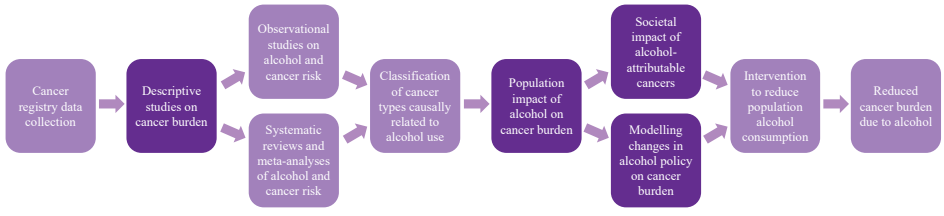

Figure 6. Simplified schema of the process of identifying alcohol-attributable cancer burden and the adaptation of alcohol control strategies to reduce alcohol-attributable cancer burden. Dark purple indicates the steps covered in this thesis.

Thesis aims and research questions

This thesis aims to measure the impact of population alcohol consumption on the burden of cancer globally, regionally, and in countries worldwide. Chapter 2 discusses the epidemiol-

ogy and mechanisms of alcohol-related cancers, and Chapters 3 to 9 include the research conducted for this thesis. These studies cover a range of steps in the process of identifying alcohol-attributable cancer burden, from describing the burden and trends of alcohol-related cancers (Part 2), to quantifying the number of cases of cancer attributable to alcohol and other risk factors (Part 3), and further expanding the use of these estimates to demonstrate the economic impact of alcohol-attributable cancer deaths and the effect of alcohol policy changes on alcohol-attributable cancer burden (Part 4).

Specifically, the research questions we addressed were:

1. What is the global burden of alcohol-related cancers and how have their trends evolved over time? (Part 2)
2. What proportion of cancer cases are due to alcohol and other modifiable risk factors globally and in the United Kingdom? (Part 3)
3. What is the societal and economic impact of alcohol-attributable cancer deaths and how can changes in alcohol policy affect cancer burden in Europe? (Part 4)

We conclude with a general discussion of the studies described in this thesis in Chapter 10 (Part 5).

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Chapter 2

Alcohol and cancer: epidemiology and biological mechanisms

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Ferrari P
Soerjomataram I

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ABSTRACT

Approximately 4% of cancers worldwide are caused by alcohol consumption. Drinking alcohol increases the risk of several cancer types, including cancers of the upper aerodigestive tract, liver, colorectum, and breast. In this review, we summarise the epidemiological evidence on alcohol and cancer risk and the mechanistic evidence of alcohol-mediated carcinogenesis. There are several mechanistic pathways by which the consumption of alcohol, as ethanol, is known to cause cancer, though some are still not fully understood. Ethanol's metabolite acetaldehyde can cause DNA damage and block DNA synthesis and repair, whilst both ethanol and acetaldehyde can disrupt DNA methylation. Ethanol can also induce inflammation and oxidative stress leading to lipid peroxidation and further DNA damage. One-carbon metabolism and folate levels are also impaired by ethanol. Other known mechanisms are discussed. Further understanding of the carcinogenic properties of alcohol and its metabolites will inform future research, but there is already a need for comprehensive alcohol control and cancer prevention strategies to reduce the burden of cancer attributable to alcohol.

1. INTRODUCTION

Approximately 4% of cancers worldwide are caused by alcohol consumption, equating to more than 740,000 cases of cancer globally in 2020.[1] The impact of alcohol consumption on cancer burden differs by cancer type, and cancers of the oesophagus, liver, and breast represent the most alcohol-attributable cases of cancer globally (Figure 1). Drinking alcohol even at lower levels of intake can increase the risk of cancer and we previously estimated that over 100,000 cases of cancer in 2020 were caused by light and moderate drinking of the equivalent of around one or two alcoholic drinks per day.[1] Despite this, there is low public awareness of the causal link between alcohol and cancer and alcohol use is growing in several regions of the world.[2,3]

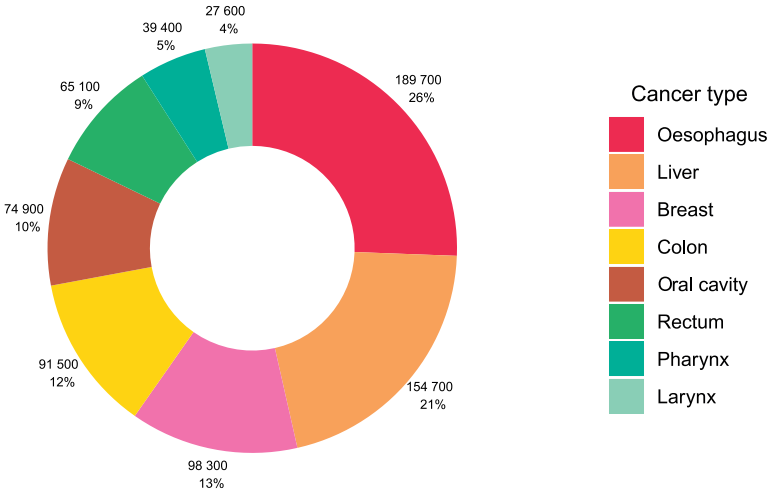

Figure 1. Global number and proportion of cancer cases attributable to alcohol consumption according to cancer type. Source of alcohol-attributable cases: Rumgay and colleagues.[1]

More than 30 years ago, in 1988, the International Agency for Research on Cancer (IARC) classified alcoholic beverages as a group 1 carcinogen, the most severe classification.[4] The IARC Monographs program aims to classify cancerous agents according to the strength of the available epidemiological and experimental evidence. Cancers of the oral cavity, pharynx, larynx, oesophagus, and liver were first classified as being causally related to the consumption of alcoholic beverages, and this was expanded to include cancers of the colorectum and female breast in the later monographs on alcoholic beverages in 2010 and 2012, with a positive association observed for cancer of the pancreas.[5,6]

The World Cancer Research Fund (WCRF) also conducts classification of physical and dietary components and their potential cancerous effects as part of their Continuous Update Project. The WCRF base their conclusions on the quality of epidemiological evidence and carry out meta-analyses of the association with cancer risk. In the most recent report on Diet,

Nutrition, Physical Activity and Cancer, WCRF concluded that there was strong evidence that alcohol consumption increased the risk of cancers of the mouth, pharynx and larynx, oesophagus (squamous cell carcinoma), liver, colorectum, and breast (postmenopausal), with a probable increased risk of stomach cancer and premenopausal breast cancer.[7]

In addition to associations from epidemiological studies, multiple mechanistic pathways through which alcohol can cause cancer have been proposed. In this review, we aim to summarise the epidemiological evidence on alcohol and cancer risk and the mechanistic evidence of alcohol-driven carcinogenesis. We searched the PubMed and Cochrane databases for reviews, umbrella reviews, meta-analyses, and Mendelian randomisation studies on total alcohol use and cancer risk and mechanisms of alcohol-related carcinogenesis published up until June 2021. We also searched the WCRF's Continuous Update Project reports for meta-analyses on alcohol consumption and cancer risk.

2. ALCOHOL AND CANCER RISK

The effects of alcohol consumption on cancer risk have been studied for many decades and an association with alcohol has been observed for multiple cancer sites. Here, we discuss evidence from large meta-analyses of observational studies and emerging evidence from Mendelian randomisation studies. Figure 2 and Figure 3 present the dose-response relationships for the risk of cancer at several sites per 10 g/day increase in alcohol consumption from the meta-analyses carried out in the WCRF Continuous Update Project,[7] and the risk of cancer at several sites according to three levels of alcohol intake [light (up to 12.5 g/day), moderate (12.5 to 50 g/day), and heavy (more than 50 g/day)] from a meta-analysis conducted by Bagnardi and colleagues,[8] both with respect to the reference category of alcohol non-drinkers.

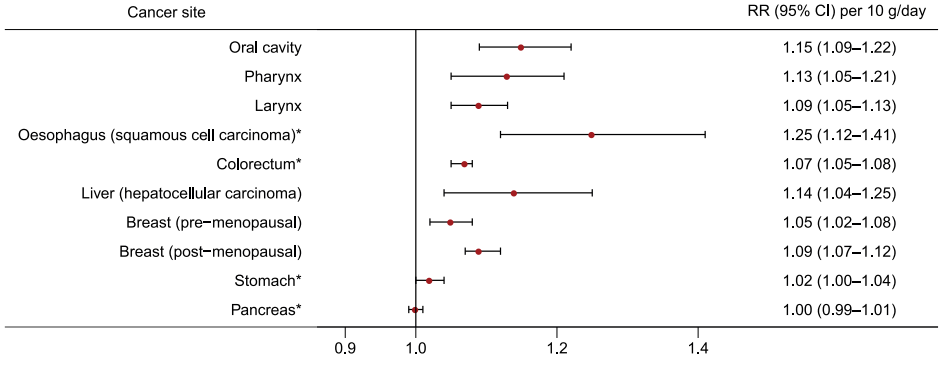

Figure 2. The dose-response relationship for the risk of cancer at different sites per 10 g/day increase in alcohol consumption. Source of relative risk estimates: WCRF Continuous Update Project.[7] RR = Relative risk; CI = Confidence interval. * Non-linear dose-response observed indicating threshold effect.

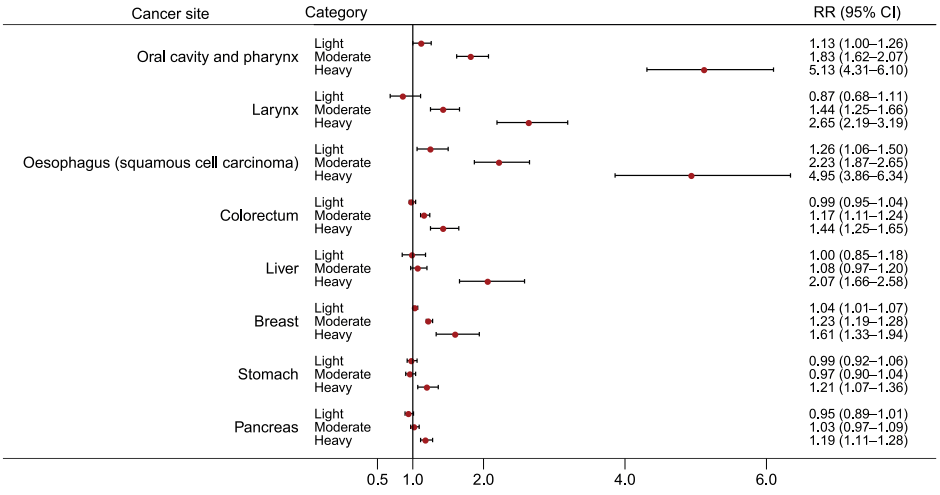

Figure 3. The dose-response relationship for the risk of cancer at different sites by three level of alcohol intake: light (up to 12.5 g/day), moderate (12.5 to 50 g/day), and heavy (more than 50 g/day). Source of relative risk estimates: Bagnardi and colleagues.[8] RR = Relative risk; CI = Confidence interval.

2.1. Oral Cavity Pharyngeal and Laryngeal Cancers

Drinking alcohol increases the risk of cancers of the upper aerodigestive tract. Consumption of 10 g alcohol per day was associated with a 15% increased risk of oral cavity cancer (RR 1.15 (95% CI 1.09–1.22)) in the most recent WCRF Continuous Update Project.[7] Pharyngeal cancer risk was also increased (RR 1.13 (95% CI 1.05–1.21) per 10 g alcohol per day).[7] In Bagnardi and colleagues' meta-analysis the RR of cancer of the oral cavity and pharynx was increased from 1.13 (95% CI 1.00–1.26) for current light drinking (up to 12.5 g alcohol per day) to 5.13 (95% CI 4.31–6.10) for heavy drinking (more than 50 g per day).[8] Cancers of the larynx were also observed to have an increased RR (1.09 (95% CI 1.05–1.13) per 10 g alcohol per day) in the WCRF meta-analysis.[7] Bagnardi and colleagues found significant increases in laryngeal cancer risk only in moderate and heavy drinking, with RRs of 1.44 (95% CI 1.25–1.66) and 2.65 (95% CI 2.19–3.19), respectively.[8]

2.2. Oesophageal Cancer

Drinking alcohol increases the risk of squamous cell carcinoma of the oesophagus which is the most common histological subtype of oesophageal cancer globally, and contributed the most cases of cancer in 2020 attributable to alcohol (189,700 cases).[1,9] An excess risk of oesophageal squamous cell carcinoma was found in the WCRF Continuous Update Project (RR 1.25 (95% CI 1.12–1.41) per 10 g alcohol per day),[7] and in Bagnardi and colleagues' meta-analysis, the pooled RR estimates for light and heavy drinking were 1.26 (95% CI 1.06–1.50) and 4.95 (95% CI 3.86–6.34), respectively.[8] There were differences in risk between geographic locations in both meta-analyses, with higher oesophageal squamous cell

carcinoma risk among drinkers in studies conducted in Asia than those in North America or Europe. This observation possibly reflects the elevated risk of oesophageal squamous cell carcinoma among carriers of the *ALDH2*2* polymorphism of the gene that codes the enzyme aldehyde dehydrogenase 2 (ALDH2).[10] The *ALDH2*2* variant allele is more common in Eastern Asian populations and confers nearly four times the risk of oesophageal cancer among drinkers compared with *ALDH2*1* carriers.[10] For oesophageal adenocarcinoma, the second most common histological subtype of oesophageal cancer, no increased risk was observed in the WCRF meta-analysis (RR 1.00 (95% CI 0.98–1.02) per 10 g per day) but an inverse association was found for oesophageal adenocarcinoma and gastric cardia cancer among light drinkers in the meta-analysis by Bagnardi and colleagues (RR 0.86 (95% CI 0.76–0.98)).[7,8]

Cancers of the upper aerodigestive tract can also be characterised as having a more than multiplicative increased risk when alcohol and tobacco are consumed together. This synergistic effect has been observed in several studies; for example a pooled analysis of 11,200 head and neck cancer cases and 16,200 controls found a 14 times risk of head and neck cancers among those who drank at least three alcoholic drinks per day and smoked more than 20 cigarettes per day, compared with never drinkers who had never smoked.[11] For oesophageal squamous cell carcinoma, a cohort study in the Netherlands observed an eight times risk among current smokers who drank 15 g alcohol or more per day, compared with never smokers who consumed less than 5 g alcohol per day.[12]

2.3. Colorectal Cancer

The meta-analysis conducted by WCRF found a 7% increased risk of colorectal cancer (RR 1.07 (95% CI 1.05–1.08)) per 10 g alcohol per day.[7] WCRF also found some evidence of a threshold effect around 20 g per day with a weaker association at lower intake levels.[7] The meta-analysis by Bagnardi and colleagues did not find an effect of alcohol on colorectal cancer risk among light drinkers, but the RR increased to 1.17 (95% CI 1.11–1.24) for moderate drinking, and 1.44 (95% CI 1.25–1.65) for heavy drinking.[8] Differences between subsites were minimal, with the risk of colon cancer (RR 1.07 95% CI 1.05–1.09) similar to rectal cancer (RR 1.08 95% CI 1.07–1.10).[7] Alcohol might also increase the risk of precancerous lesions in the colon, with a meta-analysis reporting a 27% increased risk of colorectal adenoma (RR 1.27 (95% CI 1.17–1.37)) per 25 g alcohol per day.[13]

2.4. Liver Cancer

The most common histological subtype of liver cancer is hepatocellular carcinoma (HCC) and around 154,700 cases of HCC in 2020 were attributable to alcohol consumption.[1] When restricted to HCC only, meta-analysis of WCRF sources resulted in a 14% increased risk of HCC (RR 1.14 (95% CI 1.04–1.25)) per 10 g alcohol per day.[7] However, a possible threshold effect was observed in the non-linear dose-response analysis by WCRF, where

less than 45 g alcohol per day did not significantly increase the risk of liver cancer. This was similar to the findings of Bagnardi and colleagues where light or moderate drinking did not significantly increase liver cancer risk but risk among heavy drinkers doubled (RR 2.07 (95% CI 1.66–2.58)).[8]

2.5. Breast Cancer

Female breast cancer is the most commonly diagnosed cancer globally and contributed the third largest number of alcohol-attributable cases in 2020 (98,300 cases).[1,14] The WCRF found a 7% increased risk of breast cancer per 10 g alcohol per day (95% CI 1.05–1.09).[7] Whether there is a difference in breast cancer risk by menopausal status is unclear, as risk of postmenopausal breast cancer overlapped with that of premenopausal breast cancer in the WCRF meta-analysis (RR 1.09 (95% CI 1.07–1.12) versus RR 1.05 (95% CI 1.02–1.08), respectively, per 10 g alcohol per day). It does, however, seem that risk of breast cancer among drinkers might be specific to hormone receptor status; the WCRF meta-analysis of post-menopausal women observed an excess risk of oestrogen-receptor-positive and progesterone receptor-positive (ER+PR+) tumours (RR 1.06 (95% CI 1.03–1.09)) and ER+PR– tumours (RR 1.12 (95% CI 1.01–1.24)) per 10 g alcohol per day, and no significant association was observed for ER–PR– tumours (RR 1.02 95% CI 0.98–1.06).[7] In a meta-analysis by Sun and colleagues, current drinkers had an increased risk of all hormone receptor status breast tumours compared with never drinkers, but RRs were higher for ER+PR+ tumours (RR 1.40 95% CI 1.30–1.51) and ER+PR– tumours (RR 1.39 95% CI 1.12–1.71) than ER–PR– tumours (RR 1.21 95% CI 1.02–1.43).[15]

2.6. Stomach Cancer

Alcohol consumption might increase the risk of stomach cancer. The linear dose-response meta-analysis by WCRF resulted in a non-significant RR of 1.02 (95% CI 1.00–1.04) per 10 g alcohol per day, but the non-linear dose-response analysis found an increase in stomach cancer risk for intakes over 45 g alcohol per day.[7] The meta-analysis by Bagnardi and colleagues observed a 21% increased risk in heavy drinking (RR 1.21 95% CI 1.07–1.36), and no significant increase in light or moderate drinking categories.[8]

2.7. Pancreatic Cancer

The meta-analysis by WCRF did not find an increased risk of pancreatic cancer per 10 g alcohol per day (RR 1.00 (95% CI 0.99–1.01)) but there was a possible threshold effect of increased risk for intakes of around 60 g per day (RR 1.17 (95% CI 1.05–1.29)).[7] This was a similar finding to the meta-analysis by Bagnardi and colleagues which found no increased risk at light or moderate drinking but a significant RR of 1.19 (95% 1.11–1.28) for heavy drinking.[8]

2.8. Other Cancer Types

The association between alcohol drinking and risk of other cancer types has been studied but without sufficient evidence to be classified in the IARC monographs or WCRF Continuous Update Project. Positive associations have been reported in some meta-analyses; for example, a 3% increase in lung cancer risk was observed per 10 g alcohol per day in the WCRF meta-analysis based on 28 studies (RR 1.03 (95% CI 1.01–1.04)) after excluding studies which did not control for smoking.[7] A positive association with lung cancer was only found for heavy drinkers in Bagnardi and colleagues' meta-analysis, but this was probably due to residual confounding from smoking because alcohol use did not increase the risk of lung cancer among non-smokers.[8] Little evidence of an association between alcohol consumption and gallbladder cancer was found in the WCRF Continuous Update Project, but Bagnardi and colleagues found an excess risk of gallbladder cancer among heavy drinkers (RR 2.64 (95% CI 1.62–4.30)). WCRF found an elevated risk of malignant melanoma per 10 g alcohol per day (RR 1.08 (95% CI 1.03–1.13)), but no effect on basal cell carcinoma (RR 1.04 (95% CI 0.99–1.10)) or squamous cell carcinoma (RR 1.03 (95% CI 0.97–1.09)) risk.[7] An increased risk of prostate cancer was observed for light and moderate drinking in Bagnardi and colleagues' meta-analysis but not in the dose-response analysis of one drink per day by WCRF.[7,8]

WCRF found an inverse association between alcohol consumption and kidney cancer risk (RR 0.92 (95% CI 0.86–0.97) per 10 g per day).[7] However, this association was restricted to light and moderate drinking in Bagnardi and colleagues' meta-analysis (RR 0.92 (95% CI 0.86–0.99) and 0.79 (95% CI 0.72–0.86), respectively).[8] The same meta-analysis also found significant inverse associations for the risk of thyroid cancer, Hodgkin lymphoma and non-Hodgkin lymphoma.[8]

2.9. Confirming the Causal Relation Reported in Observational Studies

Many observational studies have been conducted to identify and define the risks from drinking alcohol and cancer development. Some limitations in these studies have been identified, such as lack of sufficient adjustment of confounding factors, for example tobacco smoking and alcohol consumption are both common risk factors for oral cavity cancer. There are also concerns around reverse causality, with the reference categories of alcohol non-drinkers possibly including former drinkers who still have an elevated risk of cancer. There are other concerns over the accuracy of recording of alcohol exposure data where bias may be incorporated through non-participation of heavy drinkers in health studies, and under-reporting of alcohol consumption by the study subjects.

One method which might overcome some of the limitations in observational studies is Mendelian randomisation (MR), which uses genetic variants to explore the causal relationship between exposure and disease outcome. Assuming that analyses are conducted appropri-

ately, due to the random distribution of these genetic variants at birth, MR studies should be less prone to conventional confounding and reverse causality.

For oral and oropharyngeal cancer, an MR study using genetic data on 6000 oral or oropharyngeal cancer cases and 6600 controls found a positive causal effect of alcohol consumption independent of smoking.[16] The authors concluded that previous estimates of the association between alcohol and oral and oropharyngeal cancer from observational studies may have been underestimated.[16] Another MR study on UK Biobank data found that drinking alcohol, especially above the UK's low-risk guideline of up to 14 units per week, was causally related with head and neck cancers, but not breast cancer.[17] A further updated MR study using UK Biobank data did not find an association between alcohol exposure and cancer of any site, though they noted limitations of a lack of precision in their analyses due to low variance explained by the single nucleotide polymorphisms.[18] An MR analysis by Ong and colleagues found no significant increase in breast cancer risk per genetically predicted drink per day (odds ratio 1.00 (95% CI 0.93–1.08)).[19]

The future potential of MR studies is yet to be discovered but disclosing potential sources of biases and confounding in observational studies is necessary to obtain robust estimates of the causal relationship between alcohol consumption and cancer risk.

3. MECHANISMS OF ALCOHOL-DRIVEN CARCINOGENESIS

Following epidemiological evidence of the link between alcohol use and risk of cancer at multiple sites, several pathways have been investigated to explain the carcinogenic effects of alcohol. Here, we discuss the key mechanisms linking alcohol consumption to carcinogenesis, which are depicted in Figure 4.

3.1. Production of Acetaldehyde

Once consumed, alcohol is metabolised by enzymes including alcohol dehydrogenase (ADH), cytochrome P-450 2E1 (CYP2E1) and bacterial catalase, producing acetaldehyde.[20] Acetaldehyde is highly reactive towards DNA and has several carcinogenic and genotoxic properties.

As it is highly reactive towards DNA, acetaldehyde may bind to DNA to form DNA adducts which alter its physical shape and potentially block DNA synthesis and repair.[21] These DNA adducts are particularly genotoxic as they can induce DNA point mutations, double-strand breaks, sister chromatid exchanges, and structural changes to chromosomes.[21,22] The DNA adducts in question include N2-ethylidene-2′-deoxyguanosine, N2-ethyl-2′-deoxyguanosine, N2-propano-2′-deoxyguanosine (PdG), and N2-etheno-2′-deoxyguanosine.[23] The PdG adduct may form additional highly genotoxic structures such as DNA-protein cross-links

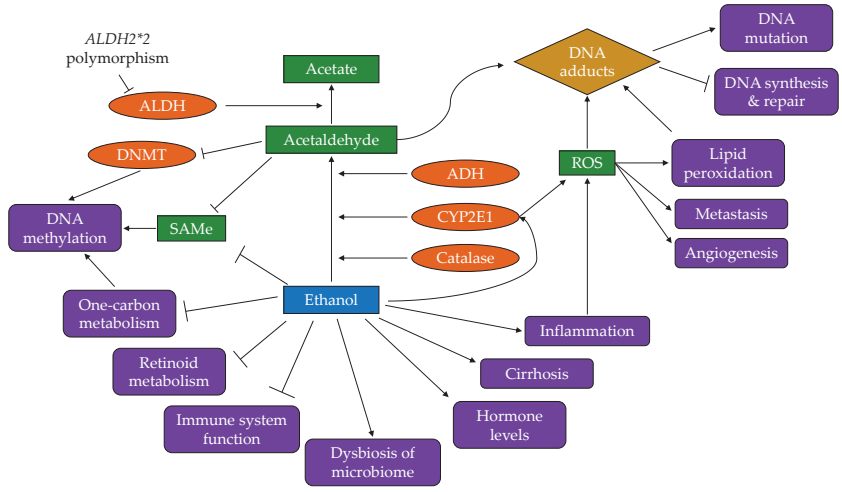

Figure 4. A simplification of the pathways by which alcohol, as ethanol, might drive carcinogenesis. The enzymes alcohol dehydrogenase (ADH), cytochrome P-450 2E1 (CYP2E1), and catalase metabolise ethanol to acetaldehyde; acetaldehyde dehydrogenase (ALDH) enzymes then metabolise acetaldehyde to acetate but common polymorphisms can reduce ALDH activity. Acetaldehyde forms DNA adducts causing mutations and blocking DNA synthesis and repair. Both ethanol and acetaldehyde can disrupt DNA methylation by inhibiting S-adenosyl-L-methionine (SAMe) synthesis and DNA methyltransferase (DNMT) activity, and ethanol can impair one-carbon metabolism. Cytochrome P-450 2E1 (CYP2E1) activity produces reactive oxygen species (ROS) leading to lipid peroxidation, metastasis, angiogenesis, and further formation of DNA adducts. Ethanol can also induce inflammation leading to production of ROS and their downstream effects. Retinoid metabolism and the normal function of the immune system are both impaired by ethanol, while ethanol may lead to increases in sex hormone levels, as well as dysbiosis of the microbiome and liver cirrhosis.

and DNA interstrand cross-links which may confer carcinogenesis.[24] As well as DNA-protein cross-links, acetaldehyde may also bind to proteins directly causing structural and functional changes;[21] these proteins include glutathione, a protein involved in reducing oxidative stress caused by alcohol, and enzymes which contribute to DNA repair and methylation, among others.

Both acetaldehyde and ethanol can impact DNA methylation which may lead to changes in the expression of oncogenes and tumour-suppressor genes.[21] Acetaldehyde can inhibit the activity of DNA methyltransferase (DNMT) which is essential for normal DNA methylation; acetaldehyde can also reduce DNMT mRNA levels leading to less production of DNMT.[25] Acetaldehyde and ethanol may also inhibit the synthesis of S-adenosyl-L-methionine (SAMe) which is essential to DNA methylation.[21]

Acetaldehyde is not the end-product of ethanol metabolism, however, as under normal conditions, acetaldehyde dehydrogenase (ALDH) enzymes convert acetaldehyde to acetate. The group of ALDH enzymes contains ALDH1A1, ALDH2, and ALDH1B1, with ALDH2 being responsible for the majority of acetaldehyde oxidation in the liver. A common poly-

morphism of this enzyme is the *ALDH2*2* variant allele which dramatically reduces the activity of ALDH2.[10] It is estimated that between 28% and 45% of East-Asian populations are carriers of the *ALDH2*2* allele,[10] while the proportion is considerably lower among Caucasians. In carriers of this polymorphism, acetaldehyde is not metabolised quickly enough, leading to an accumulation of acetaldehyde and thus the prolonged possibility to exert its described genotoxic effects. Evidence shows that alcohol drinkers who carry the *ALDH2*2* variant allele have a substantially increased risk of cancers of the oesophagus and the upper aerodigestive tract,[10] thus implicating the effects of acetaldehyde not only in the liver.

3.2. Induction of Oxidative Stress

Ethanol can also contribute to carcinogenesis through the induction of oxidative stress which is recognised as a key determinant of disease initiation.[26] Oxidative stress can be induced by activation of certain pathways which produce reactive oxygen species (ROS) such as superoxide anion and hydrogen peroxide. One pathway by which ethanol achieves this is through increased CYP2E1 activity which produces high quantities of ROS whilst oxidising ethanol to acetaldehyde.[27] Heavy alcohol use has been shown to increase CYP2E1 expression in the oesophagus.[27] Other sources of ROS during ethanol metabolism include the mitochondrial respiratory chain and some cytosolic enzymes.[28]

As ROS are highly reactive, their presence can lead to lipid peroxidation producing aldehydes which can bind to DNA forming etheno-DNA adducts.[29,30] These ethe-DNA adducts, namely 1,N6-ethenodeoxyadenosine and 3,N4-ethenodeoxycytidine, are highly mutagenic as they lead to mutations in several genes involved in key cell cycle regulation and tumour suppression.[21] Linhart and colleagues were able to demonstrate correlation between the amount of CYP2E1 and etheno-DNA adducts in cell, animal, and human tissue models, and highlighted their major importance in ethanol-mediated carcinogenesis in the liver, colorectum, and oesophagus, as well as other tissues.[30]

Presence of ROS can also lead to changes in cell cycle behaviour. ROS can act as messengers in intracellular signalling pathways to activate the transcription factor nuclear factor κB (NF-κB). ROS can further promote cell proliferation and metastasis by interfering with mitogen-activated protein kinase signalling pathways and upregulating vascular endothelial growth factor (VEGF) and monocyte chemotactic protein-1 (MCP-1) which can stimulate angiogenesis.[31] In HCC tissue samples from alcohol drinkers, ROS accumulation and increased synthesis of VEGF, MCP-1 and NF-κB were observed, indicating alcohol-driven promotion and progression of HCC.[32]

3.3. Increased Inflammation

Inflammation is a key pathway to cancer progression at several sites and is enhanced by alcohol use. Chronic alcohol consumption can recruit specific white blood cells (monocytes and macrophages) to the tumour microenvironment. These white blood cells produce pro-

inflammatory cytokines, such as tumour necrosis factor α (TNF-α) and the interleukins IL-1, IL-6, and IL-8,[31,33] which activate oxidant-generating enzymes leading to downstream formation of ROS.[30] NF-κB is also activated by these cytokines, stimulating further ROS-producing enzymes.

In addition to its involvement in downstream ROS-producing pathways, it is hypothesised that IL-8 contributes to further accumulation of white blood cells (neutrophils, specifically) in the liver leading to acute inflammation. Elevated IL-8 levels have been found in patients with acute liver injury such as alcoholic hepatitis.[34] Additionally, the cytokine IL-6 stimulates production of the anti-apoptotic protein Mcl-1, thus avoiding cell death and exposing the cell to further DNA damage.[35]

3.4. Disruption to One-Carbon Metabolism and Folate Absorption

There is mounting evidence that alcohol can negatively affect one-carbon metabolism which is essential for DNA methylation and DNA synthesis.[25] Ethanol and acetaldehyde can reduce the activity of enzymes involved in one-carbon metabolism that regulate DNA methylation, namely methionine synthase, methionine adenosyl transferase and DNMT, thus dysregulating epigenetic patterns and resulting in DNA hypomethylation.[20]

Lipotropic nutrients such as folate are key sources of the methyl groups necessary for DNA methylation and influence the availability of SAMe, which is also essential to DNA methylation.[25] Alcohol intake may deplete folate levels, or indeed be a cause of folate and vitamin B deficiency if alcohol constitutes the majority of calories consumed, as observed in malnourished alcoholics.[21,26] Folate deficiency affects the availability of nucleotides needed for DNA synthesis leading to accumulation of deoxyuridine monophosphate which is incorporated into new DNA molecules causing double-strand breaks and chromosomal damage.[25] Interestingly, there is evidence that higher folate intake among alcohol drinkers may attenuate the increased risk of liver cancer mortality compared with those with low folate intake.[36] This attenuation was also observed for risk of postmenopausal breast cancer among women who drink alcohol and have higher folate levels.[37] The effect of alcohol on one-carbon metabolism and folate might also be important in colorectal cancer development.[20]

3.5. Altered Retinoid Metabolism

Retinoids are important regulators against carcinogenesis as they can induce cell growth, cell differentiation, and apoptosis.[31] Alcohol can alter retinoid metabolism by inhibiting the oxidation of vitamin A to retinoic acid.[21] Alcohol increases CYP2E1 activity (Section 3.2) which also functions to metabolise retinoic acid resulting in the production of toxic metabolites.[21] This increased toxicity of retinoids may explain the observation of excess lung cancer risk in smokers who took β-carotene supplements and consumed 11 g or more of ethanol per day in the α-tocopherol, β-carotene cancer prevention study (ATBC trial) study.[21]

Chronic alcohol consumption has been linked with decreased levels of retinoids in the liver,[21] and low levels of retinol in the blood have been linked with higher risk of head and neck cancers.[31] Retinoids may also play a role in other signalling pathways implicated in cancer development, such as oestrogen and breast cancer.[31]

3.6. Changes to Oestrogen Regulation

Alcohol might interfere with oestrogen pathways by increasing hormone levels and enhancing the activity of ERs, important in breast carcinogenesis.[38] Sex hormone levels may be increased by alcohol through oxidative stress and through inhibition of the steroid degradation enzymes sulfotransferase and 2-hydroxylase.[39] Heavy use of alcohol has also been linked with increased circulating levels of oestrone and oestradiol as well as dehydroepiandrosterone sulphate (DHEAS).[39] DHEAS is metabolised to oestrogen by aromatase, the activity of which is also increased in chronic alcohol consumers.[40] A large cohort study found DHEAS levels 25% higher among women consuming at least 20 g alcohol per day compared with non-drinkers.[41] However, some of the associations among alcohol drinking premenopausal women were limited to those taking oral contraceptives.[40] Despite limited evidence of mediation of the association between alcohol and breast cancer by individual sex hormones, a case-control study nested within EPIC found that a hormonal signature reflecting lower levels of sex-hormone binding globulin and higher levels of sex hormones mediated 24% of the association, suggesting that an interplay of hormones may contribute to alcohol-mediated breast cancer development.[42]

ERs are important transcription factors within cells and may provide the main pathway by which alcohol promotes breast tumour growth.[40] Elevated concentrations of oestrogen due to alcohol use may lead to increased transcriptional activity of ER (up to 15 times higher than normal activity), resulting in proliferation of ER+ cells.[39]

3.7. Reduced Function of the Immune System

Alcohol has multiple negative effects on the host immune system. Firstly, alcohol can disrupt the production of proteins such as perforin and granzymes A and B, which are necessary for natural killer (NK) cells to function in targeting and destroying potentially cancerous cells.[33] Alcohol can block NK cells from being released from the bone marrow.[31] Alcohol can also activate NKT cells which are associated with liver injury and hepatocyte apoptosis.[33] Additionally, alcohol may suppress T cell immune responses therefore decreasing the anti-tumour regulation of the immune system.

With the immune system being compromised, alcohol consumption can exacerbate damage from viral infections such as hepatitis C virus, which is common among chronic alcoholic liver disease patients.[43] In addition, heavy episodic alcohol use might reduce the immune system's defence against infection by disrupting the production of pro-inflammatory cytokines and increasing the expression of anti-inflammatory cytokines.[33] This is contrary to

the increased expression of pro-inflammatory cytokines due to chronic alcohol exposure as discussed with other evidence on alcohol-induced inflammation (Section 3.3).

3.8. Dysbiosis of the Microbiome

Microbiota in the oral cavity metabolise ethanol to acetaldehyde by the enzyme catalase. However, these bacteria have limited capacity to break acetaldehyde down further into its non-harmful compound acetate, thus the oral epithelia are further exposed to acetaldehyde.[21,44] Acetaldehyde concentrations in the saliva of drinkers are between 10 and 100 times higher than in the blood; this is further doubled in smokers who drink alcohol as tobacco smoke contains high levels of acetaldehyde.[21]

Increased ethanol consumption can induce microbial dysbiosis and bacterial overgrowth in the intestine.[20] This heightened bacterial presence may compromise the intestinal barrier resulting in "gut leakiness" where the permeability of the intestinal lumen is high enough such that bacterial products including lipopolysaccharides and peptidoglycan move from the intestine into the blood.[20,45] Once in the blood these bacterial products easily reach the liver where a variety of cells are activated (endothelial cells, liver macrophages, stellate cells and hepatocytes) producing a chronic inflammatory environment,[33] which may confer an increased risk of liver cancer.[46]

3.9. Liver Cirrhosis

Liver cirrhosis is a well-recognised pathway to hepatocellular carcinoma development in heavy alcohol users and manifests as pre-neoplastic lesions in the liver.[47] Chronic alcohol exposure is associated with reduced expression of the cytokine interferon-γ which is an inhibitor of liver fibrosis.[33] Furthermore, ROS (Section 3.2) may trigger the production of pro-fibrotic cytokines and collagen in liver cells.[28]

3.10. Activation of Other Carcinogens

There is further hypothesis that alcohol consumption might activate the pathways of other carcinogenic agents; this could occur through the alcohol-induced activity of CYP2E1 which may metabolise pro-carcinogens in tobacco smoke and industrial chemicals.[21] It is also possible that ethanol might aid these carcinogens to penetrate cells, especially those of the mucosa of the upper aerodigestive tract,[21,48] where tobacco and alcohol have a synergistic effect on the risk of cancer.[11,12]

4. CONCLUSIONS

Alcohol and its metabolite acetaldehyde can drive cancer development through several pathways. Many of these pathways are interlinked and show the complexity and breadth

of alcohol's harmful potential. For example, inflammation can result in oxidative stress, but inflammation is a reaction by the immune system which is itself compromised by alcohol use. Furthermore, DNA damage can occur through exposure to acetaldehyde and ROS which are both produced through CYP2E1 activity, with acetaldehyde also a product of ADH activity. Other potential pathways have been proposed including the dysregulation of carnitine metabolism.[49] We have only covered carcinogenesis in this review, but alcohol likely alters, through these pathways and others, other functions in the body which render it more susceptible to other diseases and injuries, as discussed in other articles in this Special Issue.

Alcohol consumption is a well-established risk factor for cancer and has been linked to cancers of the oral cavity and pharynx, oesophagus, liver, colorectum and breast. While studies have provided evidence on alcohol's carcinogenic potential, further understanding of alcohol's pathways to cancer development will inform the direction of future research. This information is useful to corroborate existing evidence, develop chemoprevention strategies, and could improve cancer therapy, but there is already a wealth of evidence to support the need for further alcohol control and cancer prevention efforts. We have discussed evidence on mechanistic and epidemiological research in the field, and this information must be used to decrease the burden of cancers, as well as other diseases and injuries, attributable to alcohol.

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2

Describing the global burden of alcohol-related cancers

Chapter ٣

Global burden of primary liver cancer in 2020 and predictions to 2040

In press as:
Rumgay H
Arnold M
Ferlay J
Lesi O
Cabasag CJ
Vignat J
Laversanne M
McGlynn KA
Soerjomataram I

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ABSTRACT

Background & Aims: The burden of liver cancer varies across the world. Here, we present updated estimates of the current global burden of liver cancer incidence and mortality, and predictions to 2040.

Methods: We extracted primary liver cancer cases and deaths from the GLOBOCAN 2020 database for 185 countries worldwide. Age-standardised incidence and mortality rates (ASRs) per 100,000 person-years were calculated. Cases and deaths for the year 2040 were predicted based on incidence and mortality rates for 2020 and global demographic projections for 2040.

Results: In 2020, an estimated 905,700 people were diagnosed with, and 830,200 people died from, liver cancer globally. Global ASRs for liver cancer were 9.5 and 8.7 for new cases and deaths, respectively, per 100,000 people and were highest in eastern Asia (17.8 new cases, 16.1 deaths), northern Africa (15.2 new cases, 14.5 deaths), and South-eastern Asia (13.7 new cases, 13.2 deaths). Liver cancer was among the top three causes of cancer death in 46 countries and was among the top five causes of cancer death in 90 countries. ASRs of both incidence and mortality were higher among males than females in all world regions (Male:Female ASR ratio ranged between 1.2–3.6). The number of new cases of liver cancer per year is predicted to increase by 55.0% between 2020 and 2040, with a possible 1.4 million people diagnosed in 2040. A predicted 1.3 million people could die from liver cancer in 2040 (56.4% more than in 2020).

Conclusions: Liver cancer due to some causes is preventable if control efforts are prioritised. The predicted rise in cases may increase the need for resources to manage care of liver cancer patients.

INTRODUCTION

The global burden of liver cancer is substantial. According to 2020 estimates, liver cancer is the sixth most commonly diagnosed cancer and the third most common cause of cancer death.[1] Liver cancer also ranks as the second most common cause of premature death from cancer.[2] Incidence and mortality rates of liver cancer have dropped in some Eastern Asian countries including Japan, China, and the Republic of Korea, but rates have increased in many previously low-incidence countries across the world such as the United States (US), Australia, and several European countries.[3]

Risk factors for liver cancer include older age, sex (higher risk among males than females), and there are some differences in risk by ethnicity.[4] For example, in multi-ethnic populations such as the US, American Indians/Alaskan Natives, Hispanic persons, non-Hispanic Black persons and Asians/Pacific Islanders have higher rates than non-Hispanic White persons.[4] Although hepatitis B virus (HBV) and hepatitis C virus (HCV) infections constitute the most important exogenous risk factors for primary liver cancer, excessive alcohol consumption and the related conditions of metabolic syndrome, type 2 diabetes, obesity, and non-alcoholic fatty liver disease have also become prominent causes of primary liver cancer.[4,5] Further exogenous risk factors include cigarette smoking, ingestion of aflatoxin-contaminated food, and liver fluke infestation.[5] Recent studies suggest that approximately 56% of liver cancer is related to HBV and 20% is related to HCV.[6] A further 18% of liver cancer burden may be related to tobacco smoking,[7] and an estimated 17% of could be attributable to alcohol drinking globally,[8] with the possibility of multiple risk factors being attributed to the same cases or deaths.

An updated evaluation of the global burden of liver cancer incidence and mortality is warranted due to the disparities in burden across populations and the availability of more recent estimates. In this analysis, we describe where liver cancer ranks amongst all cancer types for cancer diagnoses and deaths in nations across the world. We also present predictions of the future liver cancer burden to 2040.

DATA SOURCES AND METHODS

The number of new cases of, and deaths from, primary liver cancer (International Classification of Disease, 10th revision [ICD-10] C22), were obtained from the GLOBOCAN 2020 database for 185 countries and territories, by sex and 18 age groups (0-4, 5-9, ..., 80-84, 85 and over),[1,2,9] Corresponding population data for 2020 were extracted from the United Nations (UN) website.[10] The data sources and hierarchy of methods used in compiling the cancer estimates have been described in detail elsewhere.[9] Briefly, the GLOBOCAN estimates are assembled at the national level using the best available sources of cancer incidence and mortality data within a given country.

We predicted the future number of primary liver cancer cases and deaths for the year 2040 based on the medium-variant UN population projections and the current global-level incidence and mortality rates of primary liver cancer for 2020. The predicted number of new cancer cases or deaths was computed by multiplying the age-specific incidence or mortality rates for the world for 2020 by the corresponding projected world population estimate. These expected populations differ from that of 2020 in term of age structure and size. The key assumption is that national rates, as estimated in 2020, will not change between 2020 and 2040 and thus changes in number of cases or deaths are solely due to the growth and aging of the population. To show the impact of changes in rates on the future primary liver cancer burden, we also predicted number of cases and deaths from seven scenarios of uniformly increasing or decreasing rates by 3%, 2%, and 1% annually from the baseline year of 2020 to 2040.

We present estimates of new cases and deaths and age-standardised incidence and mortality rates (ASR) per 100,000 person-years based on the 1966 Segi-Doll World standard population.[11,12] Male:Female ratios (M:F) of incidence and mortality ASRs are presented. Cases, deaths, and ASRs of primary liver cancer are presented by country, by 19 world regions based on UN definitions,[10] and by the UN's four-tier Human Development Index (HDI) in 2020,[13] the latter being a means to assess the burden, the strength of health systems, and the ability to report primary liver cancer cases and deaths at varying levels of development (low, medium, high and very high HDI). Rankings were based on number of new cancer cases and deaths by cancer type according to ICD-10 three-digit groupings and not including non-melanoma skin cancer (ICD-10 C44). For comparison of current liver cancer burden with the population prevalence of risk factors for liver cancer, the population attributable fractions of liver cancer due to HBV or HCV infection, alcohol consumption, and high body mass index were obtained from three global studies,[6-8] and are presented in Supplementary Figure 1.

RESULTS

Global burden of liver cancer incidence and mortality

An estimated 905,700 people were diagnosed with, and 830,200 people died from, liver cancer globally in 2020 (Table 1). This equated to total ASRs for liver cancer of 9.5 and 8.7 new cases and deaths, respectively, per 100,000 people. More than half of the world's estimated cases and deaths from liver cancer occurred in eastern Asia (54.3% and 54.1%, respectively), which was home to 21.5% of the world's population in 2020. China alone was home to 45.3% of the world's liver cancer cases and 47.1% of liver cancer deaths.

The ASRs of liver cancer incidence ranged six-fold between world regions, from 3.0 new cases per 100,000 people in South central Asia to 17.8 in eastern Asia. The pattern of mortal-

ity ASRs was similar. Eastern Asia had an ASR of 16.1 per 100,000 people compared with 2.8 in South central Asia, also resulting in a six-fold difference. Elevated ASRs for incidence and mortality were also found in northern Africa (15.2 new cases, 14.5 deaths) and South-eastern Asia (13.7 new cases, 13.2 deaths). Disparities by sex were apparent, with liver cancer incidence and mortality ASRs higher among males than females in all regions. The incidence M:F ratio ranged from 1.2 in central America to 3.3 in southern and western Europe, and Australia/New Zealand; the mortality M:F ratio was also lowest in central America (1.2), and was highest in southern Europe (3.2), western Europe, and eastern Asia (both 3.1).

At the national level, ASRs of liver cancer incidence were highest in Mongolia (85.6 new cases per 100,000 people), Egypt (34.1), Laos (24.4), and Cambodia (24.3), and lowest in Sri Lanka (1.2), Saint Lucia (1.3), Algeria (1.5), and Botswana (1.5) (Figure 1). Mortality ASRs showed a similar pattern as incidence. The full results for number of cases and deaths, and ASRs of liver cancer by country are available in Supplementary Table 1.

By HDI group, the largest burdens of liver cancer cases and deaths were in high HDI countries, representing 60.6% of new cases and 63.2% of deaths globally. The high HDI group also had the highest rates of incidence (14.0 new cases per 100,000 people) and mortality (13.3 deaths per 100,000 people). This large contribution to the world's liver cancer burden was not unexpected as the high HDI group includes some of the countries with the highest rates of liver cancer incidence and mortality, such as Mongolia, Egypt, and China. ASRs were similar across the remaining groups, ranging between 4.5 and 7.0. A correlation between a country's HDI and ASR for liver cancer incidence or mortality was not observed (Supplementary Figure 2).

Ranking of liver cancer diagnoses and deaths

Globally, liver cancer ranked as the sixth most commonly diagnosed cancer and the third most common cause of cancer death in 2020. At the national level, liver cancer was the most commonly diagnosed cancer in six countries (Cambodia, Egypt, Laos, Mongolia, Thailand, and Viet Nam) and was among the top three most commonly diagnosed cancers in a total of 18 countries (Figure 2). In terms of mortality, liver cancer was the most common cause of cancer death in 15 countries (Burkina Faso, Cambodia, Egypt, Gabon, The Gambia, Ghana, Guatemala, Laos, Mongolia, Nicaragua, Republic of Congo, Solomon Islands, Thailand, Vanuatu, and Viet Nam) and was among the top three causes of cancer death in a total of 46 countries worldwide. Liver cancer was among the top five causes of cancer death in 90 countries. Most of these countries were in eastern and South-eastern Asia, North and western Africa, and central America. However, liver cancer was also one of the top five causes of cancer mortality in some countries in Europe (Bosnia and Herzegovina, France, Italy, Republic of Moldova, and Romania) and western Asia (Iran, Saudi Arabia, Turkmenistan, and Uzbekistan).

Table 1. Estimated number of cases and deaths of primary liver cancer and age-standardised incidence and mortality rates per 100,000 persons in 2020, by world region and human development index

	Population		Incidence				Mortality			
	Total (thousands)	Percentage of world total (%)	Number of cases	Percentage of world total (%)	ASR	M:F	Number of deaths	Percentage of world total (%)	ASR	M:F
Eastern Africa	445,406	5.7	12,300	1.4	5.0	1.6	11,500	1.4	4.8	1.6
Middle Africa	179,595	2.3	6,100	0.7	6.1	2.3	5,700	0.7	5.9	2.3
Northern Africa	246,233	3.2	31,900	3.5	15.2	1.9	30,400	3.7	14.5	1.9
Southern Africa	67,504	0.9	2,600	0.3	4.6	2.2	2,400	0.3	4.3	2.3
Western Africa	401,861	5.2	17,600	1.9	8.4	2.0	16,900	2.0	8.2	2.0
Caribbean	43,532	0.6	3,400	0.4	5.5	1.6	3,200	0.4	5.0	1.6
Central America	179,670	2.3	11,800	1.3	6.3	1.2	11,200	1.4	5.9	1.2
South America	430,760	5.5	24,300	2.7	4.3	1.6	23,200	2.8	4.1	1.6
Northern America	368,870	4.7	46,600	5.1	6.8	2.7	34,800	4.2	4.7	2.4
Eastern Asia	1,678,090	21.5	491,700	54.3	17.8	3.0	449,500	54.1	16.1	3.1
China	1,447,470	18.6	410,000	45.3	18.2	3.1	391,200	47.1	17.2	3.0
South-Eastern Asia	668,620	8.6	99,300	11.0	13.7	3.0	95,700	11.5	13.2	3.0
South Central Asia	2,014,709	25.8	54,700	6.0	3.0	2.0	52,800	6.4	2.8	2.0
India	1,380,004	17.7	34,700	3.8	2.6	2.3	33,800	4.1	2.5	2.3
Western Asia	278,429	3.6	11,300	1.3	4.7	1.9	10,900	1.3	4.5	1.9
Central-Eastern Europe	293,013	3.8	24,800	2.7	4.3	2.6	23,000	2.8	3.9	2.6
Northern Europe	106,261	1.4	11,900	1.3	5.0	2.1	10,500	1.3	3.9	2.1
Southern Europe	153,423	2.0	24,800	2.7	6.7	3.3	21,200	2.6	5.1	3.2
Western Europe	196,146	2.5	26,100	2.9	5.4	3.3	23,700	2.8	4.5	3.1
Australia/New Zealand	30,322	0.4	3,300	0.4	6.1	3.3	2,500	0.3	4.1	2.7
Melanesia, Micronesia & Polynesia	12,356	0.2	1,100	0.1	11.3	1.7	1,000	0.1	11.2	1.7

Table 1. Estimated number of cases and deaths of primary liver cancer and age-standardised incidence and mortality rates per 100,000 persons in 2020, by world region and human development index (*continued*)

	Population		Incidence				Mortality			
	Total (thousands)	Percentage of world total (%)	Number of cases	Percentage of world total (%)	ASR	M:F	Number of deaths	Percentage of world total (%)	ASR	M:F
Low HDI	990,175	12.7	33,100	3.7	6.2	1.8	31,600	3.8	6.0	1.8
Medium HDI	2,327,556	29.9	100,000	11.0	4.7	2.3	95,900	11.5	4.5	2.3
High HDI	2,909,468	37.3	548,900	60.6	14.0	2.8	524,300	63.2	13.3	2.8
Very high HDI	1,564,286	20.1	223,300	24.7	7.0	2.8	178,100	21.5	5.1	2.8
World	7,794,799	100.0	905,700	100.0	9.5	2.7	830,200	100.0	8.7	2.7

ASR, age-standardised rate per 100,000; M:F, Male:Female ASR ratio; HDI, Human Development Index

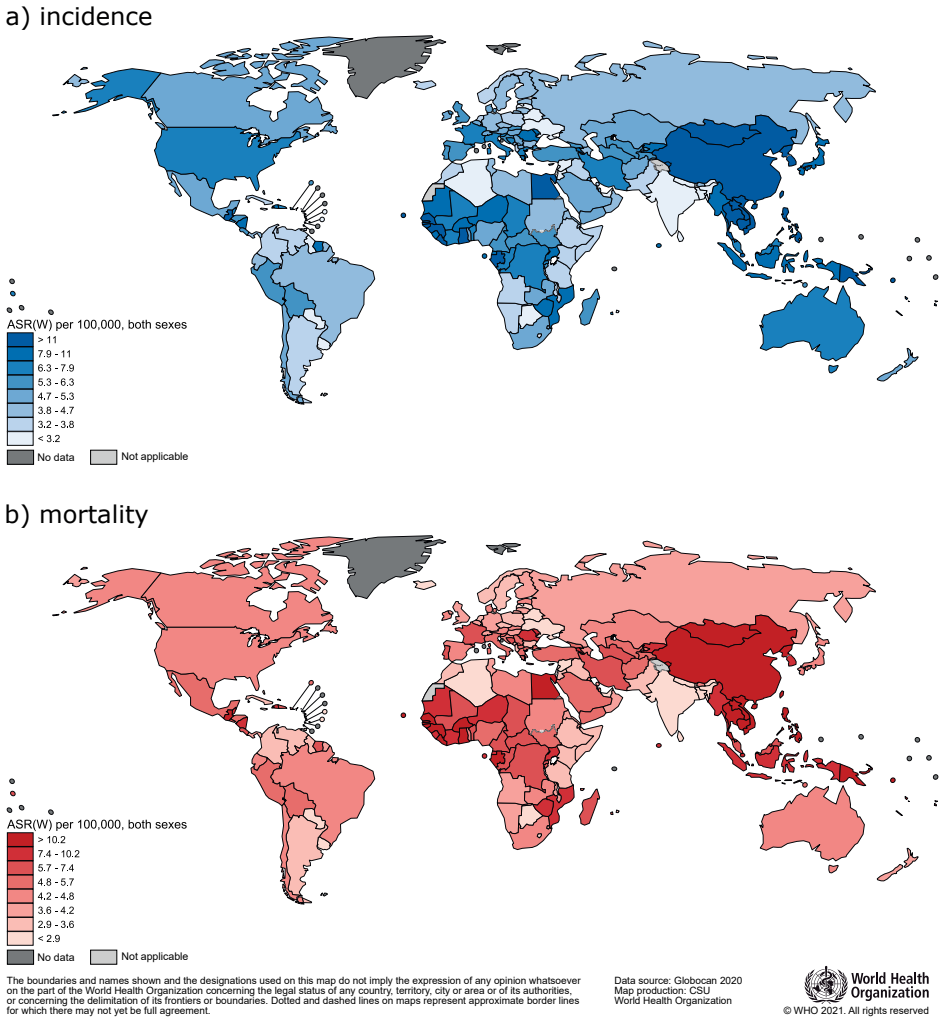

Figure 1. Age-standardised rate of primary liver cancer per 100,000 people in 2020, by country. (A) Age-standardised incidence rate. B) Age-standardised mortality rate.

Predicted number and percentage increase of cases and deaths from liver cancer

The number of new cases of liver cancer is predicted to increase by 55.0% between 2020 and 2040, with 1.4 million new diagnoses forecast for 2040 (Figure 3). An estimated 1.3 million deaths are predicted to occur in 2040, an increase of 56.4%. By HDI group, the highest absolute increase in cases and deaths could occur in high HDI countries, with 55.7% more cases (306,000 additional cases) and 57.6% more deaths (302,000 additional deaths) per year by 2040, reflecting the already elevated rates in the high HDI group and its large population which is predicted to continue to grow. However, the largest relative increases in

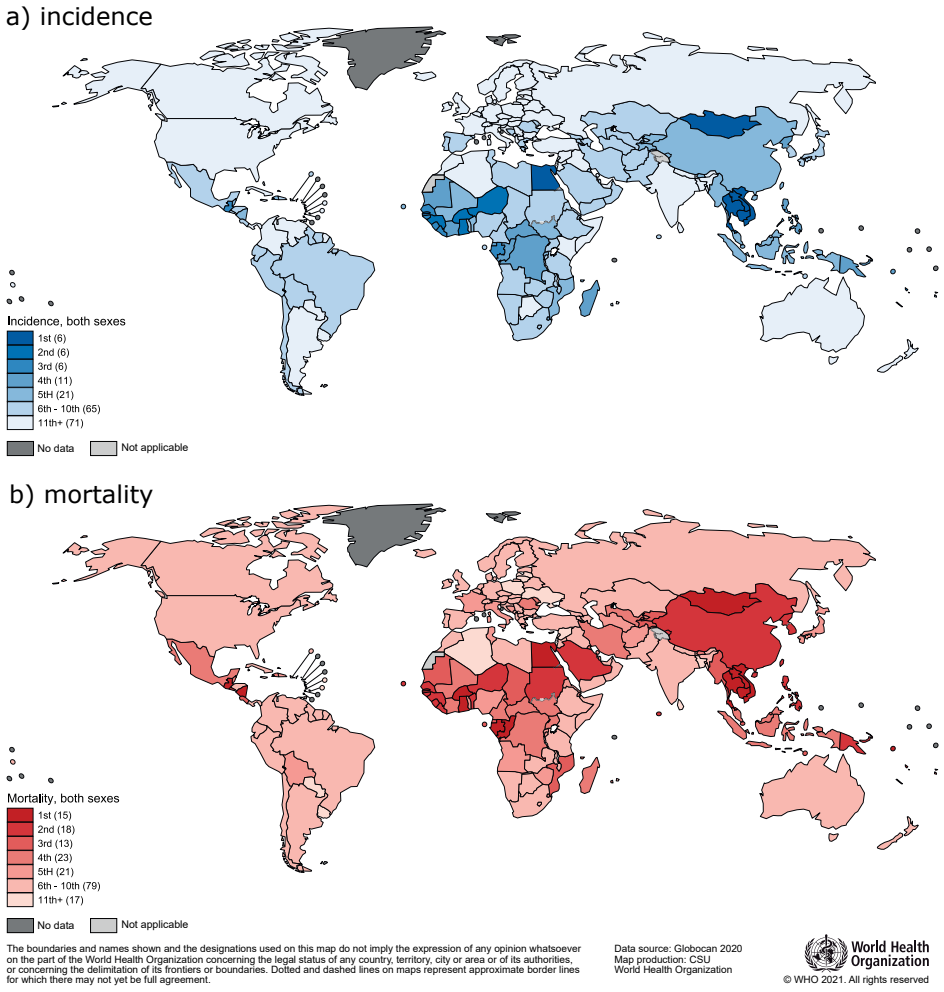

Figure 2. Ranking of primary liver cancer among 36 cancer types based on number of cases or deaths in 2020, by country. (A) Number of cases. (B) Number of deaths.

cases and deaths are predicted to occur in low HDI countries (99.9% and 101.0% increases, respectively) and medium HDI countries (69.2% and 68.8% increases, respectively), due to the predicted growth and aging of the population.

Predictions including annual changes in rates from seven scenarios (-3% to +3% annual change in ASR) showed a potential increase in the annual number of liver cancer cases and deaths by 2040 in all scenarios except the scenario in which a 3% decrease in ASR per year is achieved (Figure 4).

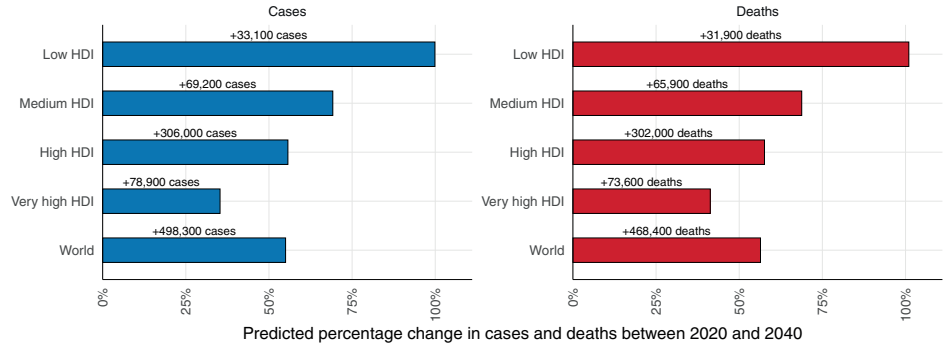

Figure 3. Predicted percentage change (absolute numbers are shown above bars) of new cases and deaths from primary liver cancer between 2020 and 2040, by Human Development Index.

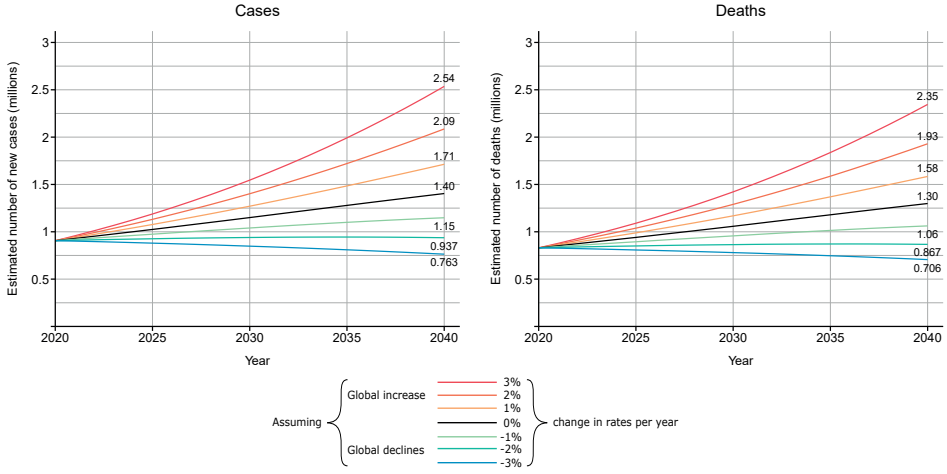

Figure 4. Predicted number of new cases and deaths from primary liver cancer assuming seven scenarios of annual change in global rates between 2020 and 2040.

DISCUSSION

Globally, in 2020, an estimated 900,000 people were diagnosed with, and 830,000 people died from liver cancer. Liver cancer incidence and mortality rates were highest in eastern Asia, northern Africa, and South-eastern Asia, and liver cancer was the most common cause of cancer death in 15 countries including several countries in South-eastern Asia and sub-Saharan Africa. The number of new cases and deaths from liver cancer are predicted to rise by more than 50% over the next 20 years, assuming current rates do not change, with the burden set to increase unless a 3% or greater annual decrease in rates is achieved.

Liver cancer was among the top three causes of cancer death in 46 countries, and among the top five in 90 countries in 2020, despite not being the most commonly diagnosed cancer

in the majority of countries across the world. Moreover, liver cancer was the second most common cause of premature death from cancer in 2020, after lung cancer, with more than 530,000 deaths among persons aged 30 to 69 years.[2] Survival from liver cancer remains poor even in high-income countries. A recent study of seven high-income countries reported that the highest 3-year net survival from liver cancer occurred in Australia (28%) and the lowest occurred in Denmark (17%) in 2012–2014.[14] The results of another study found that 5-year survival during 2010–2014 ranged from less than 10% in several European countries to 30% in Japan, and changed very little over a 20 year time-period.[15] With few improvements in survival in recent decades, primary prevention of liver cancer is key in reducing its burden globally.

Liver cancer due to some major risk factors with large attributable fractions is potentially preventable. For example, chronic HBV infection, which is responsible for more than half of liver cancer cases globally,[6] is most prevalent in sub-Saharan African countries, some South-East Asian countries, and central Asia[16] which is where the highest proportions of liver cancer attributable to HBV are found (Supplementary Figure 1a). HBV infection can be prevented by neonatal immunisation, which has now been introduced in 133 countries with global coverage of the full 3 vaccine doses estimated at 83% in 2020.[17] A modelling study estimated that 1.5 million liver cancer deaths could be avoided between 2015 and 2030 by scaling up the coverage of neonatal HBV vaccination to 80% of new-borns, as well as increasing coverage of infant HBV vaccination to 90% of infants, use of peripartum antivirals to 80% of HBV-positive mothers, and population-wide testing and treatment of 80% of eligible people.[18] Many countries now have data on the first cohorts which received the HBV vaccine in infancy as they reach young adulthood; studies in Taiwan and Shanghai reported an 80% and 50% reduction in liver cancer incidence, respectively, among young adults vaccinated in infancy compared with previous or unvaccinated cohorts,[19,20] and elimination of liver cancer has been achieved in Alaska Native children since 1999 following universal neonatal immunisation coupled with a child catch-up program.[21] Another major risk factor for liver cancer is chronic HCV infection which causes approximately 20% of liver cancer cases globally, and more than 50% of liver cancer cases are attributable to HCV in the most affected countries including Egypt, the US, and Pakistan[6] (Supplementary Figure 1b). There is no vaccine for HCV, but curative therapy of chronic infection can be achieved with direct-acting antivirals (DAAs), and strategies to reduce transmission are available worldwide.[22] A prospective study of patients with HCV infection and liver cirrhosis in France observed a 70% reduction in risk of liver cancer incidence after the treatment achieved a sustained viral response, and suggested that DAA therapy will have a substantial effect on liver cancer rates in the future.[23] This was further supported by a modelling study of chronic HCV patients in England which predicted an increase in liver cancer incidence unless there was a 115% increase in the number of eligible patients treated for HCV by 2018, which would have reduced the number of HCV-related liver cancer cases by 50% by 2020.[24] In response to

these trends, in 2016, the World Health Organization committed to reducing HBV infections by 90% and reducing HBV and HCV deaths by 65% by 2030, and highlighted the critical contribution of HBV immunisation and HCV curative therapy, for which universal health coverage and access to affordable medicines are essential.[25,26]

Contamination of crops by the fungi *Aspergillus flavus* also poses a threat to public health in tropical and subtropical areas that lie in the global aflatoxin belt.[27] Pre- and post-harvest strategies to decrease aflatoxin contamination including sorting crops and improving storage have been outlined,[28] but many regions in the aflatoxin belt have limited resources to implement control measures. It has been estimated that populations in sub-Saharan Africa, South-East Asia, and China have the highest burdens of liver cancer attributable to aflatoxin exposure, particularly as there is a synergistic effect between aflatoxin and HBV infection.[27] Additional causes of liver cancer must also be incorporated into planning for liver cancer control in various regions. For example, in Europe and North America excessive alcohol consumption was associated with an estimated 22% of liver cancer cases in 2020[8] (Supplementary Figure 1c), yet cost-effective policies exist to reduce consumption in the population.[29]

To explore the potential relationship between the development of a country and its rate of liver cancer incidence or mortality, we plotted HDI by liver cancer mortality rate and did not find a correlation. However, the current burden of liver cancer might be influenced by other demographic factors. For example, we found a strong male predominance for liver cancer across all world regions which has been reported previously and could be largely related to exposure to risk factors for liver cancer.[4] Ethnic disparities in liver cancer incidence have also been observed in studies using cancer registry data in the US, finding the highest rates among American Indians/Alaskan Natives, Hispanics, and Asians/Pacific Islanders.[4] Additional studies in three US states further disaggregated the ethnic groups and found the highest liver cancer incidence rates in California were among Vietnamese, Cambodian and Laotian groups,[30] and the most elevated liver cancer mortality rates among Vietnamese, Chinese and Korean groups in California, Florida, and New York.[31] Furthermore, migration has likely influenced rates of liver cancer among ethnic minorities in western countries, as observed in the US, Australia, Canada, and western Europe, where the highest incidence rates were among migrants from high-risk countries.[31-34] In addition, increasing age is directly correlated with liver cancer incidence in most populations,[4] and population ageing has already driven changes across the world such as in Shanghai, China, where demographic changes, largely attributed to the ageing population, accounted for 45% of the rise in liver cancer mortality between 1980 and 2019.[35] Based on population projections, population ageing will continue to drive the global burden of liver cancer.

As a baseline for control of liver cancer, we estimated the potential future number cases and deaths resulting from several scenarios of annual changes in rates. If current rates remain the same, we predict the largest increases in liver cancer burden could occur in high HDI countries, including China, due to ageing and growth of the population. The largest relative

increases could occur in low HDI countries, where we predict that the number of liver cancer cases and deaths per year could double by 2040. Considering these changes, public health officials must prepare for the predicted increase in demand for resources to manage the care of liver cancer patients throughout the cancer pathway, including improved access to palliative care. As our predictions are based on current rates and projected future populations, the impact of changes in risk factor exposure or national health programmes have not been taken into account despite advances in HBV and HCV control. Recent successes include high immunisation coverage, testing, and treatment for HBV, and a reduction in new HCV infections in some regions which were paralleled with a rise in the number of people receiving curative treatment for HCV infections.[36] While we would expect these promising achievements to result in a lower number of liver cancer cases in the future if current HBV and HCV control efforts are maintained, liver cancer incidence has increased over time in several areas with low HBV and HCV endemicity.[3,37] This might be due to the growing obesity and diabetes epidemics,[37] thus our baseline scenario of liver cancer predictions have possibly underestimated the future burden if diabetes treatment and primary prevention of obesity are not addressed. Furthermore, focus on liver cancer prevention efforts must continue during and after the COVID-19 pandemic. Approximately 43% of countries that responded to the WHO Pulse survey reported disruption in HBV and HCV diagnosis and treatment during June 2020 to March 2021 due to the COVID-19 pandemic response.[38] The impact of these disruptions could reverse some of the progress made in HBV and HCV control and might also be reflected in future liver cancer rates.

Our study provides a global snapshot of the estimated burden of liver cancer in 2020 and is an essential tool for planning of liver cancer control. The GLOBOCAN estimates presented here were compiled using national data from population-based cancer registries and vital registration systems wherever possible.[9] While the estimation of rates is an extensive process using validated techniques, there are large gaps in data availability which could lead to a major underestimation of the burden of liver cancer in underrepresented populations. For example, only 15% of the world population and only 1% of the population in Africa were covered by the population-based cancer registries included in the latest volume of Cancer Incidence in Five Continents (vol. XI), a compilation of quality-assessed cancer registry data.[39] The expansion of the African Cancer Registry Network has led to more accurate estimates of cancer burden in sub-Saharan Africa which were utilised in the GLOBOCAN methods, but data are still limited in many low- and middle-income countries.[40] The Global Burden of Disease (GBD) Study has also produced estimates of liver cancer incidence and mortality up to 2019 using similar sources of cancer registry and vital registration data, but applying a different modelling method to obtain estimates in areas with less reliable or missing data.[7] GBD estimated that, globally, 534,000 liver cancer cases and 485,000 liver cancer deaths occurred in 2019.[7,41] These estimates were considerably lower than the 905,700 cases and 830,200 deaths in 2020 obtained from GLOBOCAN. At the national level, GBD estimates were much lower

than GLOBOCAN for several of the countries which contributed the most cases and deaths to the global total; these included countries such as China which represented more than half of the difference between the GBD and GLOBOCAN estimates. For example, there were 187,700 liver cancer deaths in China according to GBD but 391,200 according to GLOBOCAN. Also, the crude rate of death from liver cancer in China according to GLOBOCAN was double that of GBD (27.0 versus 13.2 per 100,000). Two studies based on cancer registry data for China reported 422,1000 liver cancer deaths and a crude rate of 23.7 liver cancer deaths per 100,000 people in China in 2015.[42,43] Large differences were also noted for Viet Nam where GLOBOCAN estimated 25,300 liver cancer deaths in 2020 but GBD estimated 2,400 in 2019; the GLOBOCAN crude rate of death from liver cancer was also 10-times as high as the GBD estimate for Viet Nam (26.0 versus 2.5 per 100,000). Such discrepancies are the result of the differing modelling methods used by both studies to estimate cancer burden as well as potential differences in the data sources and the recency of the input data. As part of their modelling of all causes of death, the GBD also redistributed unspecified causes of death to produce additional deaths from cancer.[7,41] Furthermore, the GBD methodology is based on global patterns of disease burden and uses covariates such as the prevalence of risk factors for liver cancer e.g. Hepatitis B surface antigen seroprevalence to impute missing cancer data, whereas the GLOBOCAN developers use a data-based approach and review available data for each country with respect to the local context and, if necessary, using information from neighbouring countries while ensuring that locally collected data form the basis of this process.[9] We believe that producing cancer burden estimates based as closely as possible on the collected data is a priority, and that providing support and capacity building through such programs as the Global Initiative for Cancer Registry Development (https://gicr.iarc.fr/) is of utmost importance to ensure the sustainability and improved coverage of cancer registries which will in turn produce more accurate measures of cancer burden.

Limitations to our estimates of liver cancer burden include the reported change over time in methods of diagnosing liver cancer, with some areas of the world using imaging more commonly than biopsy, which might also be related to global variation in liver cancer diagnoses.[14,44,45] In addition, the liver is a common site for metastasis so there is potential for some misclassification.[46] Also, our 2040 predictions were not based on recent changes in liver cancer incidence and mortality rates or risk factor exposures and did not take into account heterogeneity in incidence and mortality trends between countries thus there is substantial uncertainty around our results. Finally, while our study estimated the total burden of liver cancer, distinct patterns are evident when examining liver cancer by histology.[47] The major histologic types are hepatocellular carcinoma and intrahepatic cholangiocarcinoma and trends in the incidence of these histologic types differ: rates of hepatocellular carcinoma declined in high-risk countries, but increased in South-Central Asia, Europe, and North America between 1978 and 2012,[37] with evidence of a decline in the US since 2015;[48] rates of intrahepatic cholangiocarcinoma, however, increased in most countries between 1992 and

2012.[49] It is estimated that hepatocellular carcinoma makes up 80% of liver cancer diagnoses globally, thus addressing risk factors for hepatocellular carcinoma in regions with increasing rates would have the biggest impact on liver cancer burden.[47]

In summary, while the burden of liver cancer varies greatly, it is among the top three causes of cancer death in 46 countries, and among the top five causes of cancer death in 90 countries worldwide. Furthermore, the number of cases and deaths from liver cancer are predicted to increase by more than 50% over the next 20 years if global rates do not change, and will increase unless a 3% or greater annual decrease in rates is achieved. Liver cancer due to some major risk factors is preventable if control efforts are prioritised. While the impact of HBV and HCV elimination efforts is only beginning to be reflected in the burden of liver cancer today, increasing prevalence of other risk factors might drive future changes in liver cancer incidence. Considering these changes, public health officials must prepare for an increase in demand for resources to manage the care of liver cancer patients throughout the cancer pathway.

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SUPPLEMENTARY MATERIALS

Supplementary Table 1. Estimated number of cases and deaths of primary liver cancer and age-standardised incidence and mortality rates per 100,000 persons in 2020, by country. Number of cases and deaths suppressed if less than five.

	Incidence			Mortality		
	Number of cases	ASR	M:F	Number of deaths	ASR	M:F
Eastern Africa						
Burundi	360	6.2	1.7	340	6.0	1.7
Comoros	30	5.6	1.7	30	5.6	1.7
Djibouti	30	3.8	2.3	30	3.8	2.3
Eritrea	90	4.1	1.7	90	3.9	1.7
Ethiopia	2,400	3.7	1.5	2,300	3.5	1.5
Kenya	920	3.3	1.2	860	3.1	1.3
La Reunion	120	7.6	2.2	100	6.3	2.0
Madagascar	1,100	6.0	1.6	980	5.8	1.6
Malawi	410	3.8	1.8	380	3.7	1.8
Mauritius	70	3.1	1.4	60	2.9	1.5
Mozambique	1,600	8.6	1.7	1,400	8.2	1.7
Rwanda	480	6.8	2.4	450	6.5	2.4
Somalia	280	3.6	1.4	280	3.6	1.4
South Sudan	360	5.4	1.7	350	5.2	1.7
Tanzania	1,000	3.3	1.3	1,000	3.2	1.3
Uganda	2,000	8.5	1.5	1,900	8.1	1.5
Zambia	400	4.8	1.8	370	4.6	1.8
Zimbabwe	680	9.0	1.6	650	8.8	1.6
Middle Africa						
Angola	610	3.8	2.0	580	3.7	2.0
Cameroon	1,000	6.3	2.9	960	6.0	2.9
Central African Republic	160	5.8	2.6	150	5.7	2.6
Chad	490	6.3	2.3	460	6.2	2.2
Democratic People Republic of Congo	3,300	6.5	2.3	3,100	6.2	2.3
Equatorial Guinea	70	8.5	1.6	70	8.4	1.6
Gabon	160	11.3	1.4	160	11.0	1.4
Republic of Congo	250	7.1	2.5	240	7.0	2.5
Sao Tome and Principe	10	8.2	7.0	10	8.2	7.0
Northern Africa						
Algeria	610	1.5	1.3	570	1.4	1.3
Egypt	27,900	34.1	2.0	26,500	32.5	2.0

Supplementary Table 1. Estimated number of cases and deaths of primary liver cancer and age-standardised incidence and mortality rates per 100,000 persons in 2020, by country. Number of cases and deaths suppressed if less than five. (*continued*)

	Incidence			Mortality		
	Number of cases	ASR	M:F	Number of deaths	ASR	M:F
Libya	230	4.4	1.9	210	4.2	1.9
Morocco	1,300	3.3	1.4	1,300	3.1	1.3
Sudan	1,200	4.4	1.9	1,100	4.3	1.9
Tunisia	630	4.3	1.2	600	4.0	1.2
Southern Africa						
Botswana	30	1.5	1.1	30	1.5	1.1
Eswatini	30	4.0	1.8	30	3.9	1.8
Lesotho	50	2.6	2.1	50	2.6	2.0
Namibia	60	3.8	1.9	60	3.7	1.9
South Africa	2,400	4.8	2.2	2,300	4.5	2.4
Western Africa						
Benin	500	7.2	2.2	470	6.9	2.2
Burkina Faso	1,200	10.9	1.8	1,200	10.6	1.8
Cape Verde	50	11.3	1.2	50	10.5	1.2
Cote d Ivoire	1,100	7.9	1.8	1,100	7.5	1.8
Ghana	3,500	16.9	2.4	3,200	16.0	2.4
Guinea	1,400	21.8	1.7	1,400	21.6	1.7
Guinea-Bissau	160	16.2	1.6	160	16.3	1.6
Liberia	460	15.3	1.7	450	15.2	1.7
Mali	730	7.5	1.9	680	7.2	1.9
Mauritania	260	9.8	1.8	260	9.6	1.8
Niger	1,100	9.9	2.0	1,000	9.5	2.0
Nigeria	5,200	5.2	2.5	5,000	5.1	2.5
Senegal	1,100	12.2	1.7	1,100	12.0	1.7
Sierra Leone	410	9.4	1.8	390	9.2	1.7
The Gambia	250	17.2	3.5	250	16.8	3.5
Togo	220	4.9	1.6	210	4.8	1.6
Caribbean						
Bahamas	20	3.2	2.8	20	3.2	2.8
Barbados	10	2.3	1.6	10	2.3	1.6
Cuba	870	3.8	1.5	810	3.3	1.5
Dominican Republic	890	7.6	1.3	830	7.0	1.3
Guadeloupe	40	4.0	2.5	40	3.7	2.5
Haiti	810	9.2	1.5	790	9.1	1.5
Jamaica	110	3.0	1.0	100	2.6	1.1

Supplementary Table 1. Estimated number of cases and deaths of primary liver cancer and age-standardised incidence and mortality rates per 100,000 persons in 2020, by country. Number of cases and deaths suppressed if less than five. (*continued*)

	Incidence			Mortality		
	Number of cases	ASR	M:F	Number of deaths	ASR	M:F
Martinique	40	3.8	2.0	30	2.8	1.9
Puerto Rico	430	6.1	4.1	400	5.3	3.8
Saint Lucia	<5	1.3	2.3	<5	1.3	2.0
Trinidad and Tobago	70	3.0	1.4	60	2.8	1.4
Central America						
Belize	20	7.8	2.8	20	7.8	2.8
Costa Rica	460	6.1	1.5	440	5.7	1.6
El Salvador	520	6.6	1.0	490	6.2	1.0
Guatemala	2,000	15.6	1.2	1,900	14.9	1.1
Honduras	460	6.0	2.5	420	5.6	2.4
Mexico	7,500	5.3	1.2	7,200	5.0	1.1
Nicaragua	600	10.6	1.3	580	10.2	1.3
Panama	230	4.3	0.9	220	3.9	0.9
South America						
Argentina	2,400	3.7	2.1	2,200	3.3	2.0
Bolivia	740	6.0	0.8	700	5.7	0.8
Brazil	12,700	4.5	1.9	12,100	4.3	1.9
Chile	1,600	4.8	1.6	1,500	4.5	1.6
Colombia	2,300	3.5	1.2	2,200	3.4	1.2
Ecuador	920	4.6	1.0	880	4.4	1.0
French Guyana	10	4.1	-	10	3.8	10.6
Guyana	30	3.1	1.1	30	3.2	1.1
Paraguay	180	2.7	1.0	180	2.6	1.0
Peru	2,200	5.4	1.0	2,100	5.1	1.0
Suriname	50	8.0	1.7	50	7.2	1.8
Uruguay	180	2.7	2.6	160	2.5	3.4
Venezuela	1,100	3.2	1.6	1,000	3.2	1.7
Northern America						
Canada	4,300	5.2	2.3	3,700	4.3	2.3
United States of America	42,300	7.0	2.8	31,100	4.7	2.4
Eastern Asia						
China	410,000	18.2	3.1	391,200	17.3	3.0
Democratic People Republic of Korea	5,600	15.5	2.8	5,200	14.4	3.0
Japan	45,700	10.4	3.0	28,200	4.8	3.4
Mongolia	2,200	85.7	1.5	2,100	80.6	1.6

Supplementary Table 1. Estimated number of cases and deaths of primary liver cancer and age-standardised incidence and mortality rates per 100,000 persons in 2020, by country. Number of cases and deaths suppressed if less than five. (*continued*)

	Incidence			Mortality		
	Number of cases	ASR	M:F	Number of deaths	ASR	M:F
Republic of Korea	14,800	14.3	3.5	11,200	9.9	3.8
South-Eastern Asia						
Brunei Darussalam	40	10.5	5.0	40	8.8	4.5
Cambodia	3,100	24.3	2.6	2,900	22.9	2.6
Indonesia	21,400	7.9	3.6	20,900	7.7	3.7
Lao People Democratic Republic	1,300	24.4	2.5	1,200	22.9	2.5
Malaysia	2,100	6.4	2.6	2,100	6.1	2.6
Myanmar	5,500	10.0	2.3	5,300	9.7	2.3
Philippines	10,600	11.4	2.9	10,000	10.8	2.9
Singapore	1,300	12.2	3.2	1,300	11.4	3.1
Thailand	27,400	22.6	2.6	26,700	21.9	2.7
Timor-Leste	50	5.5	3.2	50	5.2	3.3
Viet Nam	26,400	23.0	3.8	25,300	21.9	3.9
South-Central Asia						
Afghanistan	960	5.3	1.4	920	5.1	1.5
Bangladesh	3,300	2.2	3.1	3,100	2.2	3.3
Bhutan	30	4.7	3.2	30	4.5	3.0
India	34,700	2.6	2.3	33,800	2.5	2.3
Islamic Republic of Iran	5,700	6.8	1.2	5,300	6.4	1.2
Kazakhstan	1,000	4.9	2.1	990	4.6	2.2
Kyrgyzstan	480	9.3	2.4	470	9.1	2.4
Maldives	30	8.2	3.1	30	8.1	3.1
Nepal	520	2.1	4.1	500	2.0	4.4
Pakistan	5,300	3.5	1.2	5,100	3.3	1.2
Sri Lanka	350	1.2	3.2	340	1.1	2.8
Tajikistan	300	5.4	1.2	290	5.1	1.1
Turkmenistan	320	6.3	2.0	300	5.8	2.0
Uzbekistan	1,600	6.0	1.2	1,500	5.6	1.2
Western Asia						
Armenia	430	8.7	2.1	410	8.4	2.1
Azerbaijan	510	4.5	1.3	500	4.4	1.3
Bahrain	40	3.7	1.2	30	3.6	1.2
Georgia	420	5.9	4.4	400	5.6	4.3
Iraq	710	3.3	1.2	690	3.2	1.2
Israel	390	2.9	2.3	360	2.6	2.2

Supplementary Table 1. Estimated number of cases and deaths of primary liver cancer and age-standardised incidence and mortality rates per 100,000 persons in 2020, by country. Number of cases and deaths suppressed if less than five. (*continued*)

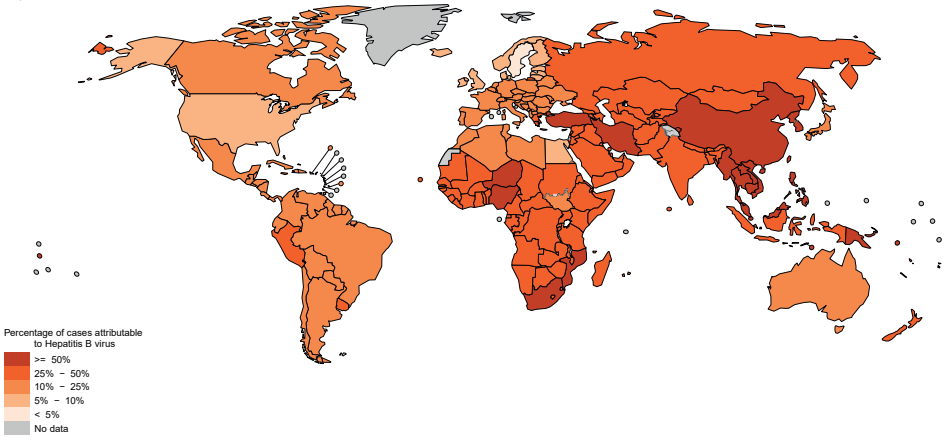
	Incidence			Mortality		
	Number of cases	ASR	M:F	Number of deaths	ASR	M:F
Jordan	200	3.0	1.4	200	3.0	1.4
Kuwait	130	5.0	1.3	120	4.7	1.3
Lebanon	170	2.3	1.2	170	2.2	1.1
Oman	130	4.4	2.3	120	4.1	2.3
Palestine	160	6.5	1.7	160	6.4	1.7
Qatar	60	5.0	1.4	50	4.9	1.5
Saudi Arabia	1,100	5.2	2.1	1,100	5.1	2.1
Syrian Arab Republic	380	2.9	1.3	360	2.8	1.3
Turkey	5,600	5.3	2.2	5,500	5.1	2.1
United Arab Emirates	80	2.9	0.9	80	2.8	0.8
Yemen	750	5.1	2.0	710	5.0	2.1
Central and Eastern Europe						
Belarus	540	3.2	3.4	510	2.9	4.0
Bulgaria	640	4.2	2.7	580	3.6	2.5
Czechia	1,000	3.9	2.4	870	3.3	2.3
Hungary	1,000	4.8	3.3	940	4.2	3.1
Moldova	580	9.2	3.4	560	8.6	3.5
Poland	2,800	3.5	2.0	2,500	2.9	2.0
Romania	3,600	8.8	2.8	3,400	8.1	2.8
Russian Federation	11,700	4.3	2.4	11,100	4.0	2.5
Slovakia	630	5.7	3.3	530	4.6	3.5
Ukraine	2,200	2.7	2.5	2,100	2.5	2.7
Northern Europe						
Denmark	650	4.9	2.2	630	4.5	2.0
Estonia	140	4.4	2.8	130	4.2	2.6
Finland	630	3.9	2.5	600	3.6	2.9
Iceland	20	3.2	2.6	20	2.8	2.6
Ireland	480	5.2	2.3	420	4.4	2.4
Latvia	150	3.2	2.7	130	2.9	3.2
Lithuania	280	4.2	3.2	250	4.1	3.4
Norway	410	3.7	2.5	390	3.3	2.9
Sweden	980	4.4	2.6	860	3.2	2.6
United Kingdom	8,200	5.3	1.9	7,100	4.1	1.9
Southern Europe						
Albania	170	3.4	1.8	160	3.0	1.8

Supplementary Table 1. Estimated number of cases and deaths of primary liver cancer and age-standardised incidence and mortality rates per 100,000 persons in 2020, by country. Number of cases and deaths suppressed if less than five. (*continued*)

	Incidence			Mortality		
	Number of cases	ASR	M:F	Number of deaths	ASR	M:F
Bosnia Herzegovina	540	7.2	1.6	520	6.8	1.6
Croatia	580	5.7	3.3	530	4.8	3.3
Cyprus	110	4.8	2.3	100	4.2	2.4
Greece	1,800	6.6	2.6	1,500	4.9	2.6
Italy	11,700	7.7	3.2	9,800	5.3	3.6
Malta	40	3.4	3.3	30	2.8	3.3
Montenegro	50	3.9	1.8	50	3.5	2.7
North Macedonia	190	5.1	2.3	190	4.9	2.2
Portugal	1,600	6.1	4.9	1,500	5.8	4.9
Serbia	1,000	5.2	1.7	960	4.9	1.7
Slovenia	330	6.3	3.5	310	5.6	3.3
Spain	6,600	6.3	4.2	5,600	4.6	3.6
Western Europe						
Austria	1,100	5.3	3.0	990	4.4	3.1
Belgium	1,300	5.2	3.2	1,100	3.8	2.9
France (metropolitan)	11,500	7.6	3.8	10,300	6.0	3.7
Germany	9,500	4.3	3.0	8,900	3.7	2.7
Luxembourg	70	5.6	2.1	50	3.8	3.0
Netherlands	1,500	3.6	2.1	1,400	3.3	2.2
Switzerland	1,100	5.2	3.2	910	4.0	3.0
Australia and New Zealand						
Australia	2,900	6.4	3.3	2,100	4.2	2.7
New Zealand	420	4.7	2.7	360	3.7	2.3
Melanesia, Micronesia & Polynesia						
Fiji	80	8.8	2.5	70	8.7	2.6
French Polynesia	30	8.9	3.3	30	8.5	3.1
Guam	30	14.5	4.8	30	11.9	3.8
New Caledonia	40	9.2	3.0	30	7.9	3.0
Papua New Guinea	750	11.7	1.3	730	12.0	1.4
Samoa	10	7.3	1.9	10	6.7	1.6
Solomon Islands	50	11.1	3.0	50	11.1	3.0
Vanuatu	30	13.2	3.9	30	13.2	3.9

ASR, age-standardised rate per 100,000; M:F, Male:Female ASR ratio.

A)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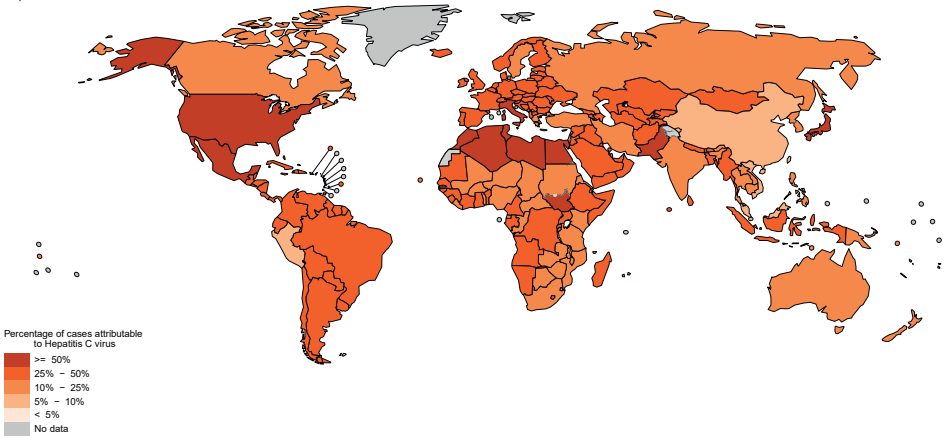
25% – 50%
10% – 25%
5% – 10%
< 5%
No data

B)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10% – 25%
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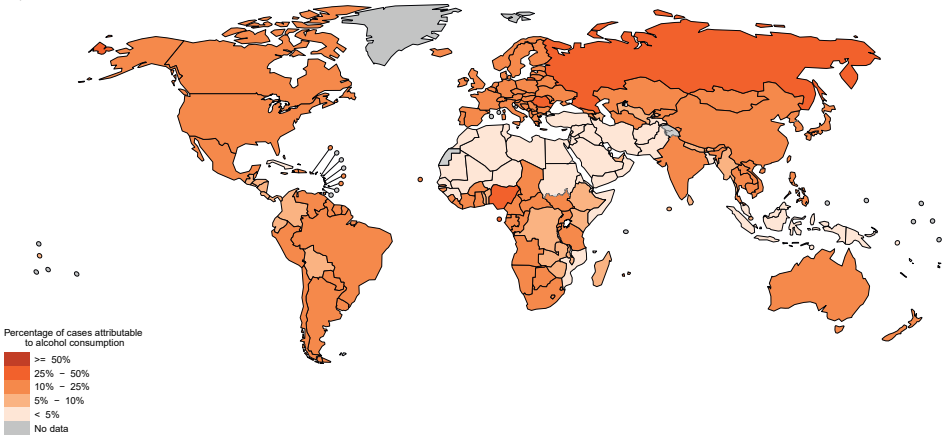
No data

C)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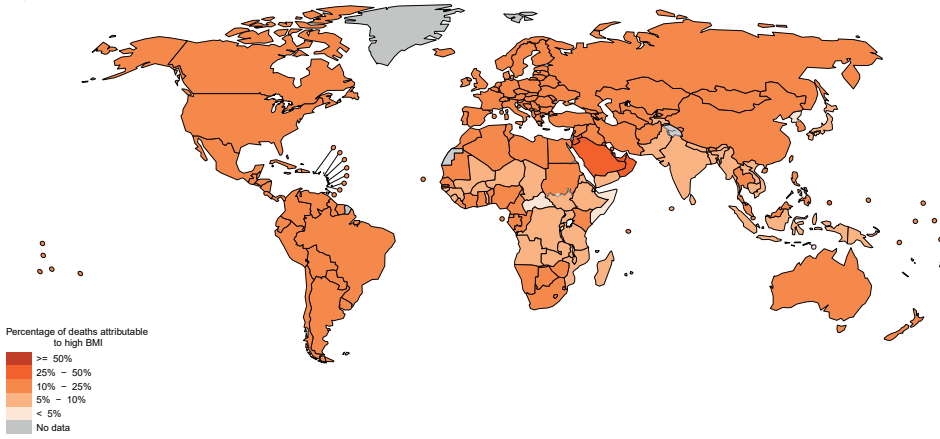
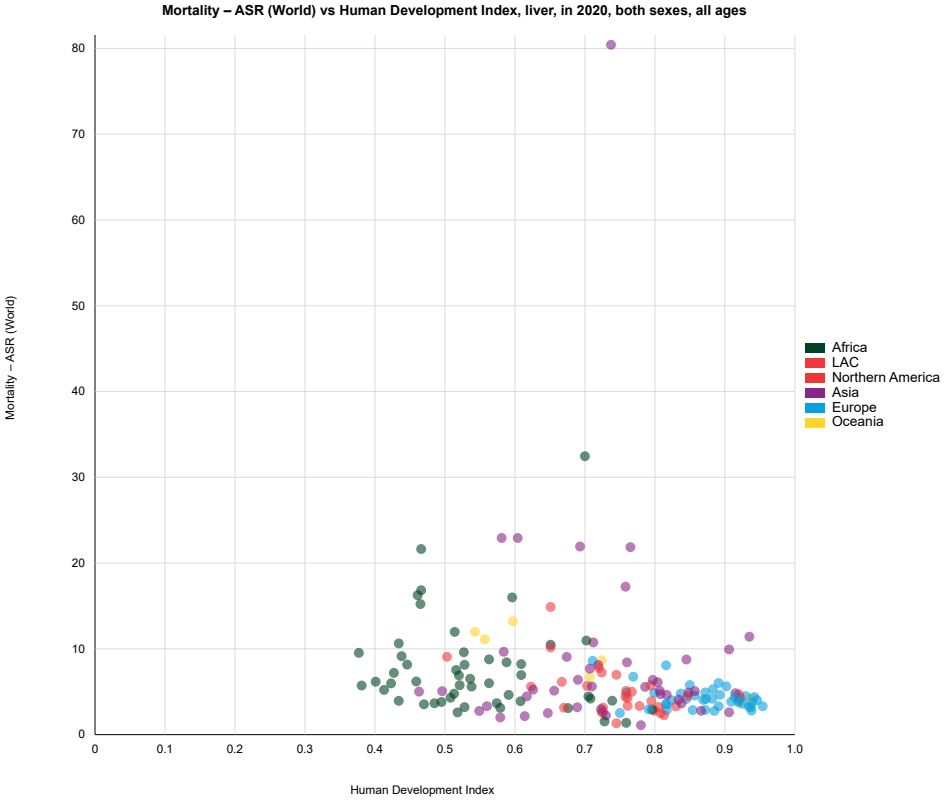
10% – 25%
5% – 10%
< 5%
No data

D)



Supplementary Figure 1. Population attributable fractions for liver cancer cases or deaths attributable to major risk factors. (A) Hepatitis B virus. (B) Hepatitis C virus. (C) Alcohol consumption. (D) High body mass index. Sources of data: Maucourt-Boulch et al. 2018 (hepatitis B and C virus),[1] Rumgay et al. 2021 (alcohol),[2] Murray et al. 2020 (high body mass index).[3]



Supplementary Figure 2. Relationship between country-specific Human Development Index and age-standardised liver cancer mortality rates per 100,000 persons in 2020.
ASR, age-standardised rate; LAC, Latin America and the Caribbean

SUPPLEMENTARY REFERENCES

1. Maucort-Boulch D, de Martel C, Franceschi S, Plummer M. Fraction and incidence of liver cancer attributable to hepatitis B and C viruses worldwide. *International Journal of Cancer* 2018; **142**(12): 2471-7.
2. Rumgay H, Shield K, Charvat H, et al. Global burden of cancer in 2020 attributable to alcohol consumption: a population-based study. *The Lancet Oncology* 2021; **22**(8): 1071-80.
3. Murray CJL, Aravkin AY, Zheng P, et al. Global burden of 87 risk factors in 204 countries and territories, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019. *The Lancet* 2020; **396**(10258): 1223-49.

Chapter 4

Global, regional and national burden of primary liver cancer by subtype

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Rumgay H
Ferlay J
de Martel C
Georges D
Ibrahim AS
Zheng R
Wei W,
Lemmens VEPP
Soerjomataram I

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ABSTRACT

Introduction: Hepatocellular carcinoma (HCC) and intrahepatic cholangiocarcinoma (iCCA) are the two main histological subtypes of primary liver cancer. Estimates of the burden of liver cancer by subtype are needed to facilitate development and evaluation of liver cancer control globally. We provide worldwide, regional and national estimates of HCC and iCCA incidence using high-quality data.

Methods: We used population-based cancer registry data on liver cancer cases by histological subtype from 95 countries to compute the sex- and country-specific distributions of HCC, iCCA and other specified histology. Subtype distributions were applied to estimates of total liver cancer cases for 2018 from the Global Cancer Observatory. Age-standardised incidence rates (ASRs) were calculated.

Results: There were an estimated 826,000 cases of liver cancer globally in 2018: 661,000 HCC (ASR 7.3 cases per 100,000); 123,000 iCCA (ASR 1.4) and 42,000 other specified histology (ASR 0.5). HCC contributed 80% of the world total liver cancer burden followed by iCCA (14.9%) and other specified histology (5.1%). HCC rates were highest in Eastern Asia (ASR 14.8), Northern Africa (ASR 13.2) and South-Eastern Asia (ASR 9.5). Rates of iCCA were highest in South-Eastern Asia (ASR 2.9), Eastern Asia (ASR 2.0), Northern Europe, the Caribbean and Central America and Oceania (ASR all 1.8).

Conclusion: We have shown the importance of uncovering the distinct patterns of the major subtypes of liver cancer. The use of these estimates is critical to further develop public health policy to reduce the burden of liver cancer and monitor progress in controlling HCC and iCCA globally.

1. INTRODUCTION

Liver cancer is the sixth most commonly diagnosed cancer worldwide and the third most common cause of cancer death.[1] The two most common histological subtypes of primary liver cancer differ in their aetiology and epidemiology; globally, the main risk factors for hepatocellular carcinoma (HCC) are infection with hepatitis B or hepatitis C viruses. In highly endemic areas, significant transmission of hepatitis B occurs from mother to infant during childbirth, and transmission of both hepatitis B and C viruses can occur through unsafe injections and medical procedures and less commonly through sexual contact. HCC can also be caused by heavy alcohol use, obesity, diabetes and ingestion of aflatoxins.[2] Meanwhile, intrahepatic cholangiocarcinoma (iCCA) develops in the bile ducts within the liver, and its most well-known preventable causes are the food-borne trematode parasites *Opisthorchis viverrini* and *Clonorchis sinensis*, which are found in specific endemic areas in Eastern Asia and the Russian Federation.[2] In these areas, the geographic pattern of liver fluke infection is very uneven, but high rates are more frequently seen in rural than urban environments, especially in wetlands and agricultural areas. In high endemic areas of liver fluke infection such as northern Thailand, iCCA is reported as the most commonly diagnosed liver cancer subtype.[3] Other established risk factors for iCCA include primary sclerosing cholangitis, Caroli's disease and hepatolithiasis.[4] Liver cancer subtypes that are less common include hepatoblastoma — a rare childhood cancer — and angiosarcoma which has been linked to historic occupational exposure to vinyl chloride, among other risk factors.[2]

Although it is estimated that HCC represents around 77% of liver cancer cases in the United States (US),[5] worldwide estimates of the burden of primary liver cancer by subtype based on high-quality data are not available. Here, we use population-based cancer registry (PBCR) data to provide global, regional and country level estimates of the burden of major subtypes of liver cancer, namely, HCC and iCCA, to facilitate development and evaluation of strategies to control the disease. This is discussed alongside differences in the distribution of potential causes of the major liver cancer subtypes which are expected to reflect regional heterogeneity in the occurrence of HCC and iCCA.

2. METHODS

2.1. Data sources

National estimates of primary liver cancer (International Classification of Diseases, 10th revision: C22) were taken from the Global Cancer Observatory (GLOBOCAN) 2018 database which includes estimates of incidence, mortality and prevalence for 185 countries by sex and five-year age group.[1] We obtained liver cancer cases by histological subtype from Cancer Incidence in Five Continents (CI5) Volumes IX, X and XI and other PBCRs selected for data

quality used to construct the GLOBOCAN estimates.[6–8] The histological subtype groupings were based on the International Classification of Diseases for Oncology, third edition (ICD-O-3) morphology codes for liver cancer (C22) as described in the CI5 volumes: HCC (8170–8175); iCCA (8050, 8140–8141, 8160–8161, 8260, 8440, 8480–8500 and 8570–8572) other specified histology (8010–8035, 8970, 9120–9133, 9161, 8800–8811, 8830, 8840–8921, 8990–8991, 9040–9044, 9150, 9170 and 9540–9581); and unspecified histology (8000–8005).

2.2. Subtype case estimation

Using the most recent data where possible, we excluded cancer registry data with 75% or more unspecified histology of liver cancer at the national level in CI5 Vol. IX, X or XI and with less than one case of HCC or iCCA per sex. After applying the exclusion criteria, national-level proportions of HCC, iCCA, other specified histology and unspecified histology cases were computed for 95 countries by sex. Proportions of unspecified cases at the regional level ranged from 6.2% of the total liver cancer cases in men in North America to 48.8% in women in Southern Europe (Supplementary Table 1). We assumed unspecified cases would be less likely to be other specified histology and so reallocated unspecified cases to HCC and iCCA as per their relative proportions; this assumption was based on two observations: higher proportions of microscopically verified cases in the other specified histology group compared with HCC or iCCA[9] and an in-depth analysis which showed most other specified histology cases were of 'carcinoma, not otherwise specified (NOS) (8010)' or 'combined hepatocellular and cholangiocarcinoma (8180)'. Country-specific proportions of HCC, iCCA and other specified histology by sex were applied to the total number of cases of liver cancer by sex and five-year age groups as per GLOBOCAN 2018.[1] For the remaining 90 countries where country-specific liver cancer data by subtype were unavailable or did not meet the inclusion criteria, subregional average proportions of HCC, iCCA and other specified histology were applied to the country-specific cases. Subregions were categorised using the United Nations definitions into 14 world regions: the Caribbean and Central America; Central and Eastern Europe; Eastern Asia, North America; northern Africa; Northern Europe; Oceania; South America; South-Central Asia; South-Eastern Asia; Southern Europe; sub-Saharan Africa; Western Asia and Western Europe.[10] Country-specific data were excluded from regional averages when the prevalence of hepatitis B and hepatitis C was in the highest category as per estimates by Schweitzer et al.[11] and the Polaris Observatory[12] and when liver flukes were reported as endemic as per the International Agency for Research on Cancer Monograph on Biological Agents.[13] More information on the data sources for each country is provided in Supplementary Table 2. The global and regional estimated numbers of liver cancers reported in this analysis are the sum of the individual countries and do not correspond exactly to the world total published in GLOBOCAN 2018 which includes some small country populations for which no estimates are provided.[1]

Age-standardised incidence rates (ASRs) of HCC, iCCA and other specified histology per 100,000 person-years were calculated by sex for 185 countries using the newly estimated cases for each sex and five-year age group and were age-adjusted to the Segi-Doll world standard population.[14] Male to female ASR ratios (M:F) were reported by subtype and world region.

2.3. Sensitivity analysis

Alternative scenarios of reallocation of the unspecified histology cases were carried out to compare the resulting proportions and cases of HCC, iCCA and other specified histology. The alternative reallocation scenarios were as follows:

- Alternative scenario 1: Assume unspecified cases are equally likely to be HCC, iCCA and other specified histology so reallocate unspecified cases to HCC, iCCA and other specified histology based on their relative proportions.
- Alternative scenario 2: Only use microscopically verified cases, excluding cases diagnosed through other methods. PBCRs register all cases diagnosed through microscopic verification (including histological and cytological examination) and clinical examination (including clinical observation and magnetic resonance imaging (MRI)/computed tomography (CT) scanning), as well as death certificate only. Around 42% of liver cancer cases included in the main analysis were diagnosed using microscopic verification.

3. RESULTS

3.1. Hepatocellular carcinoma and intrahepatic cholangiocarcinoma incidence by world regions

Of an estimated 826,000 cases of liver cancer in 2018, 661,000 (80.0%) were HCC, 123,000 (14.9%) were iCCA, and 42,000 (5.1%) were other specified histology (Table 1). In nearly all world regions, HCC was more common than iCCA, although the proportion of each subtype clearly varied by world region and sex (Figure 1, Supplementary Table 3). In men, large contributions of HCC to total liver cancer cases were found in northern Africa (94.9% of total cases), Eastern Asia (87.2%) and sub-Saharan Africa (85.9%), whereas relatively smaller proportions of HCC — owing to larger iCCA contributions — were found in Northern Europe (66.7%), the Caribbean and Central America (68.8%) and South-Central Asia (72.3%). A similar pattern was observed in women where the largest contributions of HCC to total liver cancer were found in northern Africa (89.2%), Eastern Asia (78.8%) and sub-Saharan Africa (74.3%), and the smallest proportions were in Northern Europe (35.9%), the Caribbean and Central America (50.5%) and Oceania (50.7%).

Table 1 Estimated number of cases and age-standardised incidence rate of liver cancer per 100,000 person-years by subtype and world region in 2018.

World Region	Men		Women		Total	
Subtype	**Cases**	**ASR**	**Cases**	**ASR**	**Cases**	**ASR**
Africa						
Northern Africa						
HCC	19,000	19.7	7,100	7.0	26,000	13.2
iCCA	700	0.7	600	0.5	1,200	0.6
Other	300	0.4	300	0.3	600	0.3
Sub-Saharan Africa						
HCC	20,000	7.3	9,800	3.2	30,000	5.1
iCCA	1,800	0.7	2,400	0.8	4,200	0.7
Other	1,600	0.6	1,000	0.3	2,500	0.4
Asia						
Eastern Asia						
HCC	291,000	23.1	94,000	6.7	385,000	14.8
iCCA	31,000	2.4	20,000	1.5	51,000	2.0
Other	12,000	1.0	4,900	0.4	17,000	0.7
South-Central Asia						
HCC	21,000	2.5	8,700	1.0	30,000	1.7
iCCA	4,700	0.6	4,300	0.5	9,000	0.5
Other	3,400	0.4	2,000	0.2	5,400	0.3
South-Eastern Asia						
HCC	50,000	16.1	13,000	3.7	64,000	9.5
iCCA	11,000	3.5	8,300	2.3	19,000	2.9
Other	4,200	1.3	2,000	0.6	6,200	0.9
Western Asia						
HCC	4,600	4.3	2,100	1.7	6,700	2.9
iCCA	700	0.7	900	0.8	1,600	0.7
Other	500	0.4	400	0.3	900	0.4
Europe						
Central and Eastern Europe						
HCC	11,000	4.8	6,200	1.7	17,000	3.0
iCCA	2,100	1.0	2,200	0.6	4,300	0.8
Other	900	0.4	600	0.2	1,500	0.3
Northern Europe						
HCC	4,700	4.4	1,400	1.1	6,100	2.7
iCCA	2,100	1.9	2,300	1.7	4,400	1.8
Other	300	0.3	200	0.2	500	0.2

Table 1 Estimated number of cases and age-standardised incidence rate of liver cancer per 100,000 person-years by subtype and world region in 2018. (*continued*)

World Region	Men		Women		Total	
Subtype	**Cases**	**ASR**	**Cases**	**ASR**	**Cases**	**ASR**
Southern Europe						
HCC	14,000	8.9	4,800	2.0	19,000	5.3
iCCA	2,500	1.6	2,200	0.9	4,700	1.2
Other	700	0.4	300	0.1	1,000	0.3
Western Europe						
HCC	14,000	6.7	3,500	1.3	17,000	3.9
iCCA	2,900	1.4	2,500	1.0	5,400	1.2
Other	700	0.3	400	0.2	1,000	0.2
Latin America and the Caribbean						
Caribbean and Central America						
HCC	4,900	4.5	3,500	2.8	8,400	3.6
iCCA	1,500	1.4	2,700	2.2	4,300	1.8
Other	700	0.7	700	0.5	1,400	0.6
South America						
HCC	10,000	4.4	6,300	2.1	17,000	3.2
iCCA	2,300	1.0	3,600	1.2	5,900	1.1
Other	900	0.4	800	0.3	1,700	0.3
North America						
North America						
HCC	25,000	8.5	7,600	2.2	33,000	5.2
iCCA	3,500	1.2	3,500	1.0	6,900	1.1
Other	1,400	0.5	800	0.2	2,300	0.4
Oceania						
Oceania						
HCC	2,100	7.8	600	1.9	2,700	4.8
iCCA	500	1.9	500	1.7	1,100	1.8
Other	<100	0.3	<100	0.2	100	0.2
World						
HCC	492,000	11.6	169,000	3.4	661,000	7.3
iCCA	67,000	1.6	56,000	1.2	123,000	1.4
Other	27,000	0.7	14,000	0.3	42,000	0.5

ASR, age-standardised rate; HCC, hepatocellular carcinoma; iCCA, intrahepatic cholangiocarcinoma.

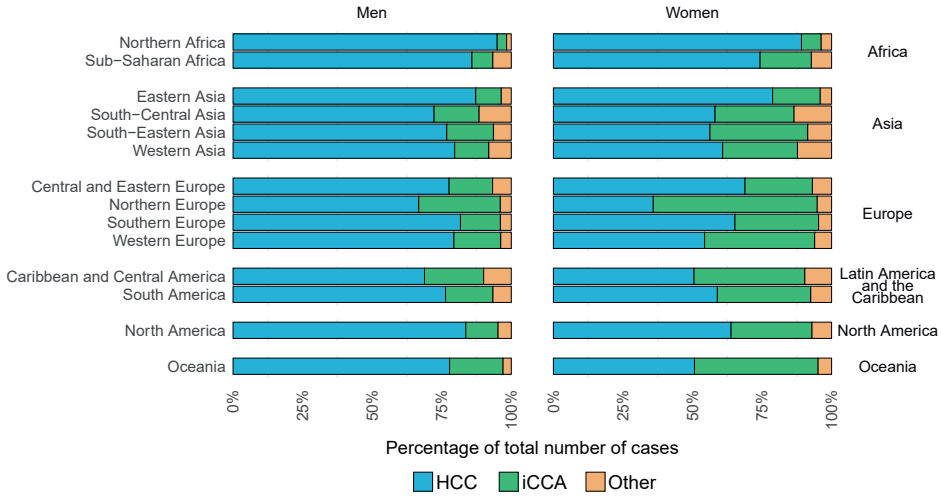

Figure 1. The proportion of liver cancer cases by histological subtype in 2018 in men and women. HCC, hepatocellular carcinoma; iCCA, intrahepatic cholangiocarcinoma.

Overall, larger proportions of iCCA — and thus smaller proportions of HCC — were seen in women compared with men within regions. This was observed particularly in Northern Europe where the proportion of iCCA was substantially larger in women (58.9%) than in men (29.3%). Other large differences in iCCA proportions between sexes were also observed in Oceania (44.4% and 19.2% in women and men, respectively) and Western Europe (39.6% and 16.8% in women and men, respectively).

3.2. Hepatocellular carcinoma incidence by country and world region

At the global level, the ASR of HCC was 7.3 cases per 100,000 person-years: 11.6 cases per 100,000 men and 3.4 per 100,000 women (Table 1). ASRs varied across world regions, with the highest incidence rates in Eastern Asia (14.8), northern Africa (13.2) and South-Eastern Asia (9.5). The region contributing the largest share of HCC cases was Eastern Asia, contributing 58.3% of all HCC cases; this was followed by South-Eastern Asia (9.6%), and North America (4.9%) (Figure 2). Overall, men showed higher rates of HCC compared with women, and the M:F ratio ranged from 1.6 in the Caribbean and Central America to 5.0 in Western Europe (Figure 3). Large M:F ratios were also found in Southern Europe (4.4) and South-Eastern Asia (4.3).

At the national level, ASRs of HCC in men were highest in Mongolia (105.9 cases per 100,000), Egypt (48.4), Vietnam (30.5) and the Gambia (30.3) (Figure 4, Supplementary Table 4). The highest ASRs of HCC in women were found in Mongolia (64.3 cases per 100,000), Egypt (16.2) and Guinea (10.9).

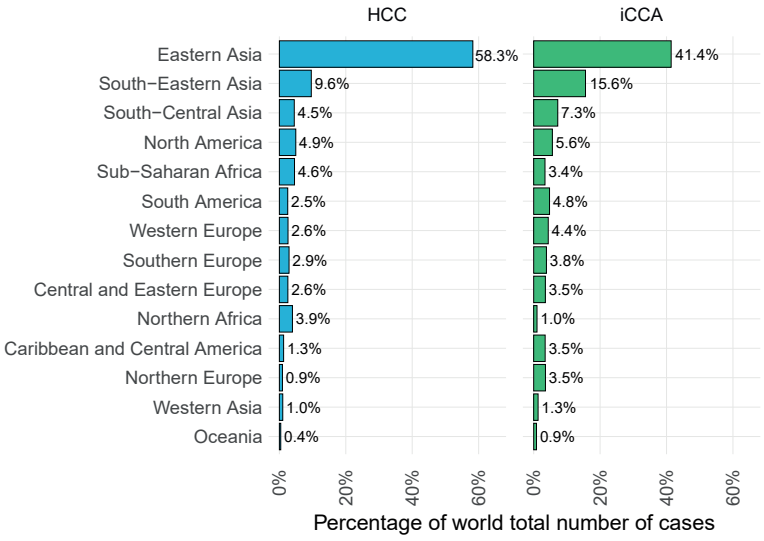

Figure 2. Regional distribution of estimated liver cancer cases by histological subtype in 2018 as the percentage of world total cases per subtype. HCC, hepatocellular carcinoma; iCCA, intrahepatic cholangiocarcinoma.

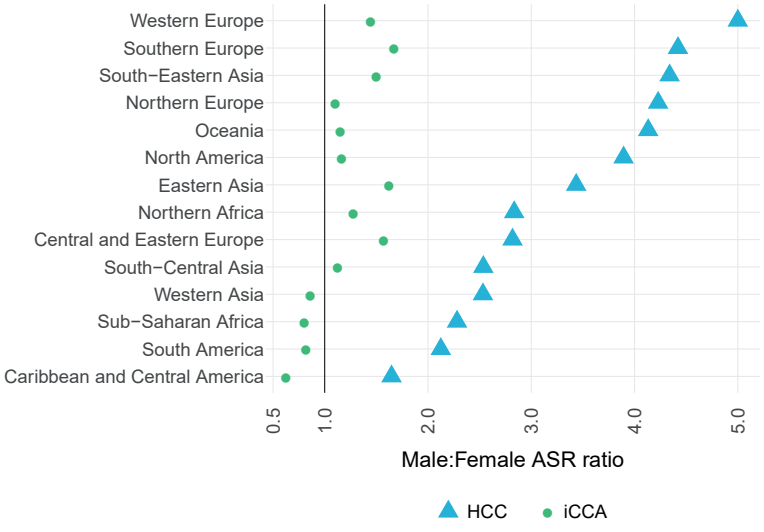

Figure 3. Male:Female ratio of age-standardised incidence rate (ASR) per 100,000 person-years in men and women by world region. HCC, hepatocellular carcinoma; iCCA, intrahepatic cholangiocarcinoma.

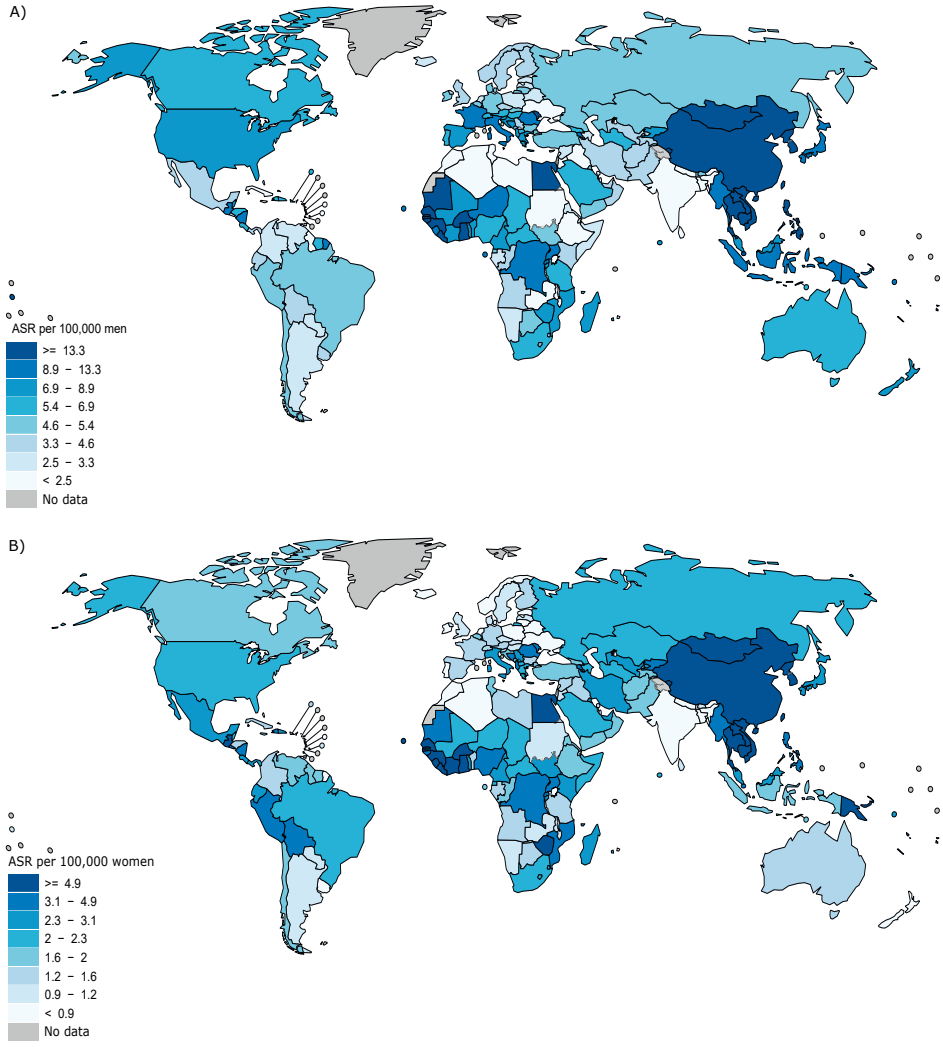

Figure 4. Age-standardised incidence rate (ASR) of hepatocellular carcinoma per 100,000 person-years in (A) men and (B) women.

3.3. Intrahepatic cholangiocarcinoma incidence by country and world region

The global ASR of iCCA was 1.4 cases per 100,000 person-years: 1.6 per 100,000 men and 1.2 per 100,000 women (Table 1). The highest rates of iCCA were in South-Eastern Asia (2.9), Eastern Asia (2.0), Northern Europe (1.8), the Caribbean and Central America (1.8) and Oceania (1.8). The region contributing the largest share of iCCA cases was Eastern Asia, with 41.4% of all iCCA cases globally; this was followed by South-Eastern Asia (15.6%) and South-Central Asia (7.3%) (Figure 2). Sex differences were observed in iCCA incidence

(Figure 3) with rates of iCCA in men in Southern Europe nearly double those of women (M:F ratio 1.7). On the other hand, in some world regions, reverse M:F ratios were observed, that is, rates of iCCA were higher among women than men in the Caribbean and Central America, sub-Saharan Africa, South America and Western Asia (M:F ratios 0.6, 0.8, 0.8 and 0.9, respectively).

At the national level, estimated iCCA ASRs in men were highest in Mongolia (8.5 cases per 100,000), Vietnam (6.2) and Thailand (6.1) (Figure 5, Supplementary Table 4). The highest ASRs of iCCA in women were found in Mongolia (7.7 cases per 100,000) and Guatemala (7.4).

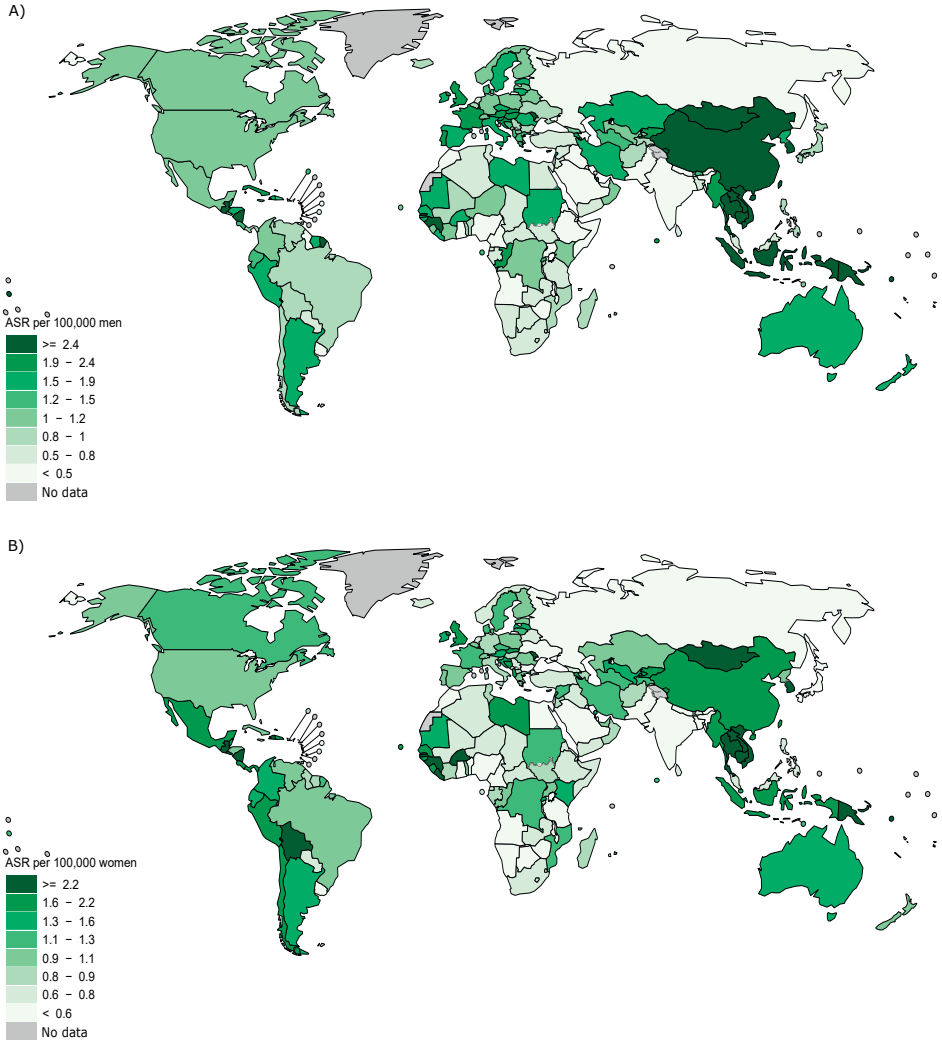

Figure 5. Age-standardised incidence rate (ASR) of intrahepatic cholangiocarcinoma per 100,000 person-years in (A) men and (B) women.

3.4. Sensitivity analysis

Moderate differences were observed in the percentages of HCC, iCCA and other specified histology when comparing the alternative scenarios to the main results (Supplementary Table 5, Supplementary Table 6, Supplementary Figure 1 and Supplementary Figure 2). Alternative scenario 1, where unspecified histology cases were re-allocated to HCC, iCCA and other specified histology, provided lower estimates of HCC and iCCA, that is, 626,000 cases of HCC (75.7%), 117,000 cases of iCCA (14.1%) and 84,000 cases of other specified histology (10.2%) versus 80.0%, 14.9% and 5.1%, respectively, in the main analysis (Supplementary Table 5). In alternative scenario 2, where we restricted to microscopically verified cases, there was a lower proportion of HCC with 591,000 cases of HCC (71.5%), 139,000 cases of iCCA (16.8%) and 96,000 cases of other specified histology (11.6%) (Supplementary Table 6).

4. DISCUSSION

There were an estimated 661,000 cases of HCC, 123,000 cases of iCCA and 42,000 cases of other specified histology among primary liver cancer diagnoses worldwide in 2018. Incidence rates of HCC were highest in Eastern Asia, northern Africa and South-Eastern Asia, and incidence of iCCA was highest in South-Eastern and Eastern Asia and Northern Europe. In addition to geographical patterns, we also saw differences by sex whereby proportions of HCC were much larger in men than women. HCC was more often diagnosed among men with regional rates ranging from 1.6 to 5.0 times higher among men than women, whereas the sex differences in iCCA rates were much smaller (M:F between 0.7 and 1.7). As such, the proportion of iCCA was overall larger in women compared with men, particularly in Northern and Western Europe and Oceania.

In our study, HCC and iCCA contributed 80% and 14.9% of the world total liver cancer burden, respectively, and these estimates largely agree with the existing literature. We cross-referenced our estimates with incidence data from the SEER-18 registries,[5] covering around 28% of the US population, which had recorded 77% of primary liver cancer cases in 2012—2016 as HCC, and 15% as iCCA when using the same morphology groupings as we used; in our study, we estimated 78% and 16% of primary liver cancers in the US in 2018 were HCC and iCCA, respectively. In another study, Baecker et al.[15] used rates of microscopically verified cases from CI5 Vol. X[7] to compute country-specific percentages of HCC and found overall lower proportions of HCC than the present study; this discrepancy is likely owing to use of the microscopically verified data set which would not include the large contribution of HCC and iCCA cases diagnosed through clinical examination and thus not microscopically verified. But when comparing our estimates from the sensitivity analysis using only microscopically verified cases (alternative scenario 2), the results were largely similar, for example, 80.0% (present study) versus 88.5% (Baecker et al.) in men in Egypt and 79.6%

versus 76.1% in men in Mongolia. Petrick et al.[16] conducted international trend analysis for HCC reporting ASRs from CI5 Vol. XI[8] which somewhat varied from ours; for example, the Republic of Korea had an ASR of 15.9 cases per 100,000, whereas we reported an ASR of 14.7. Florio et al.[17] conducted similar trend analysis for iCCA; some differences were noted between their observed ASRs and the estimated ASRs for iCCA in the present study, for example, 2.19 versus 5.2 cases per 100,000 in Thailand. The estimates in Florio et al. were also based on cancer registry data for 2008–2012 and did not consider unspecified histology cases, whereas we extrapolated the observed distribution of the subtypes to the estimated incidence of primary liver cancer as per GLOBOCAN 2018[1] after reallocating unspecified histology cases, which represented 79% of primary liver cancers recorded in CI5 Vol. XI[8] for the Thailand registries in 2008–2012. Differences in results between our study and those of Petrick et al.[17] and Florio et al.[18] might also be partially owing to the inclusion of different mixes of cancer registries for some countries that did not have complete population coverage by a single national registry.

We found the highest rates of HCC in Eastern and South-Eastern Asia and northern Africa which together represented 72% of the total world HCC incidence. This is a striking contribution considering that these regions only make up 33% of the world total population coverage (Supplementary Figure 3). A previous analysis estimated that 69% of liver cancer cases in Eastern Asia and 50% in sub-Saharan Africa were caused by hepatitis B virus infection.[18] In 2016, the World Health Assembly committed to eliminating viral hepatitis as a threat to public health by 2030 and highlighted the critical contribution of hepatitis B immunisation.[19] Global coverage of three doses of hepatitis B vaccine was estimated at 84% in 2018,[20] and this high immunisation coverage is expected to substantially reduce the future global burden of liver cancer. Hepatitis C virus infection further explains the high HCC rates in Eastern Asia and northern Africa. A report of 963 HCC cases in Mongolia found half (50%) of cases positive for hepatitis B surface antigen, more than a quarter (27%) positive for antibodies against hepatitis C virus (anti-HCV) and a fifth (21%) positive for both viruses.[21] In Egypt, another country with high rates of HCC, an estimated 84% of liver cancer cases in 2012 were caused by hepatitis C infection.[18] Use of direct-acting antivirals is effective in curing hepatitis C infection but requires vast resources to screen the population, treat those infected and manage virally caused cirrhosis, and risk of reinfection is not eliminated.[22] Primary prevention through screening of donated blood and safe injection practice is therefore key in hepatitis C control.

As hepatitis B and aflatoxin have a strong synergistic effect on the development of HCC, the ingestion of aflatoxins is an important contributor to the burden of HCC particularly in sub-Saharan Africa, Southeast Asia and China, where the prevalence of hepatitis B chronic carriers is highest.[23] A large proportion of maize and groundnut crops in Africa and Asia are located in regions where the climate is favourable for *Aspergillus flavus* and *Aspergillus parasiticus* proliferation.[23,24] Contamination with aflatoxins occurs through suboptimal field

practices and poor storage and drying of the harvested crops; rural populations are disproportionately affected as their diets consist of more maize and groundnut compared with urban populations who consume more diverse diets which are better controlled for contaminants.[23] Further studies are recommended to better understand the relationship between aflatoxins and hepatitis viruses especially in low and middle-income countries. In high-income countries such as those in Northern America and Western Europe, alcoholic cirrhosis was suggested as an important risk factor for HCC, and a recent study reported 22% of all liver cancer cases in Europe and North America in 2020 to be attributed to alcohol consumption.[25] Furthermore, HCC risk reportedly increases by 24% in those who are overweight and by 90% in those who are obese, compared with people with a healthy body weight.[26] As overweight and obesity have become more common among the global population, excess body fatness and type 2 diabetes may become more prominent risk factors for HCC.[27]

When exploring iCCA incidence, we found the highest rates in South-Eastern and Eastern Asia. The most preventable causes of iCCA are the parasitic liver flukes *O. viverrini* and *C. sinensis*,[2] which are endemic in northern Thailand, Laos, Cambodia, Malaysia and Vietnam, and parts of southern China, the Republic of Korea, Eastern Russia and Vietnam, respectively.[28] The presence of these parasites worldwide is mostly reflected in the pattern of iCCA in our study. But while liver flukes may explain some of the high burdens of iCCA in endemic regions, they do not provide a plausible reason for the relatively large contribution of iCCA in Northern and Western Europe or Oceania. Other risk factors for iCCA including primary sclerosing cholangitis, obesity and diabetes could explain this finding,[29] but further research into other causes and effective preventive measures of iCCA is warranted owing to the observed increases in iCCA incidence over time in most countries examined in a recent international trend analysis.[17]

To an extent, differences in the recording and classification of iCCA between cancer registries might have contributed to the patterns of iCCA incidence in our study. A specific type of cholangiocarcinoma — the hilar or 'Klatskin' tumour — is located at the hepatic duct bifurcation and can currently be classified as an intrahepatic (ICD-O-3 C22.1) or extrahepatic (ICD-O-3 C24.0) bile duct cancer.[30,31] In the first edition of ICD-O, coding of hilar tumours was not specified, and therefore could have been coded either as iCCA or extrahepatic cholangiocarcinoma (eCCA). However, in the following revision, ICD-O assigned a specific code to classify Klatskin tumours as extrahepatic, which was then removed in the third revision. These changes might have led to potential misclassification of some Klatskin tumours.[31] Under ICD-O-2, around 91% of Klatskin tumours in the US were coded as iCCA, resulting in a 13% overestimation of iCCA and 15% underestimation of eCCA.[30] Yet, the proportion of this cancer is small, ranging from 0.5% to 8% of total cholangiocarcinoma in the US and the United Kingdom between 1992 and 2000.[30,31] Still, as numbers of iCCA are low in regions without liver flukes, any difference in tumour classification could impact

reported rates; thus, an accurate and consistent practice of iCCA and eCCA classification is needed to achieve meaningful comparisons.

The strengths of our study include the use of population-based data from cancer registries in 95 countries to estimate the distribution of liver cancer by subtype. The absence of high-quality registry data from the remaining countries highlights the need for further investment to improve the quality of data from existing cancer registries and expand availability of registry coverage where it is not population-based. It is also important to note that although this study aims to quantify the burden of primary liver cancer by subtype, the cancer registry histology data have been extrapolated to GLOBOCAN cancer incidence estimates, which are themselves estimates extrapolated from cancer registries. Therefore, caution must be taken when using these results.

Regarding the reallocation of unspecified histology cases, in our main analysis, we assigned unspecified cases to HCC and iCCA as per their relative distributions. We also calculated the subtype distributions by reallocating unspecified cases to other specified histology as well as HCC and iCCA (alternative scenario 1). The overall proportion of HCC decreased from 80.0% to 75.7%, and the proportion of other specified histology doubled from 5.1% to 10.2%, which equated to differences of around 40,000 cases globally. Some may argue that restricting use to microscopically verified cases would be the most reliable approach to determine the true distribution of liver cancer cases by subtype; however, the proportion of HCC cases diagnosed through microscopic verification has decreased over time in many high-income countries,[9] and ultrasound, CT and MRI imaging (i.e. without microscopic verification) have become the main modes of diagnosis of HCC in Europe[32] and the US.[33] Cases diagnosed through these means would be considered unspecified histology if solely using microscopically verified cases, so the true burden of HCC would be underestimated. It is also possible that the cancer registry data included in the main analysis were already largely represented by microscopically verified cases, as 42% of all liver cancer cases being microscopically verified is still a substantial proportion considering reports of less than 10% in clinical practice. Therefore, there could be an overrepresentation of cases histologically confirmed through autopsy, for example, or an underrepresentation of cases diagnosed through imaging or clinical observation. In both of these instances, the burden of HCC would be underestimated further.

We have shown the importance of uncovering the distinct patterns of the major subtypes of liver cancer. In summary, HCC is estimated to constitute around four-fifths of liver cancer cases worldwide in 2018, and high rates of HCC in Eastern and South-Eastern Asia and northern Africa are likely driven by infection with hepatitis B and C viruses. Regarding iCCA, liver fluke infestation might have driven the high rates observed in South-Eastern Asia, but other risk factors or misclassification could have contributed to the high proportions of iCCA among women in Northern and Western Europe and Oceania. The impact of changes in diagnosis and registration practice on the distribution of liver cancer subtypes

in regions without liver flukes in particular should be assessed. In conclusion, the use of our estimates is critical to further develop public health policy to reduce the burden of liver cancer and monitor progress in controlling HCC and iCCA globally.

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SUPPLEMENTARY MATERIALS

Supplementary Table 1. Distribution of liver cancer subtypes as a percentage of total liver cancer cases, before reallocation of unspecified cases: Hepatocellular Carcinoma (HCC), intrahepatic Cholangiocarcinoma (iCCA), other specified histology, and unspecified according to sex and world region.

	Men				Women			
World Region	**HCC**	**iCCA**	**Other**	**Unspecified**	**HCC**	**iCCA**	**Other**	**Unspecified**
Africa								
Northern Africa	45.6%	4.7%	3.8%	45.9%	34.5%	11.6%	7.4%	46.5%
Sub-Saharan Africa	41.5%	3.9%	5.1%	49.6%	42.0%	8.0%	5.7%	44.3%
Asia								
Eastern Asia	51.8%	7.0%	3.1%	38.0%	46.2%	12.1%	3.5%	38.2%
South-Central Asia	42.6%	9.5%	14.7%	33.2%	29.2%	15.1%	16.5%	39.2%
South-Eastern Asia	39.5%	8.2%	5.5%	46.8%	28.6%	17.6%	7.3%	46.5%
Western Asia	69.4%	10.2%	7.1%	13.2%	49.8%	19.7%	10.8%	19.7%
Europe								
Central and Eastern Europe	39.2%	11.5%	9.3%	40.0%	29.5%	16.7%	10.8%	43.0%
Northern Europe	55.1%	24.8%	3.8%	16.2%	28.4%	47.4%	5.1%	19.1%
Southern Europe	47.1%	8.5%	4.0%	40.5%	32.4%	14.3%	4.4%	48.8%
Western Europe	63.8%	14.1%	4.6%	17.5%	42.5%	30.8%	6.9%	19.8%
Latin America and the Caribbean								
Caribbean and Central America	44.4%	11.1%	9.5%	35.1%	26.2%	19.2%	9.3%	45.3%
South America	46.6%	10.7%	6.6%	36.0%	31.3%	17.5%	7.8%	43.5%
North America								
North America	78.3%	10.7%	4.8%	6.2%	58.5%	26.1%	7.2%	8.3%
Oceania								
Oceania	67.2%	16.4%	3.0%	13.3%	43.1%	38.0%	4.7%	14.2%
World	57.2%	9.7%	4.3%	28.7%	43.6%	19.8%	5.8%	30.7%

International Classification of Diseases for Oncology (ICD-O-3) codes: hepatocellular carcinoma (8170-8175); cholangiocarcinoma (8050, 8140-8141, 8160-8161, 8260, 8440, 8480-8500, 8570-8572); other specified histology (8010-8035, 8970, 9120-9133, 9161, 8800-8811, 8830, 8840-8921, 8990-8991, 9040-9044, 9150, 9170, 9540-9581); and unspecified histology (8000-8005).

Supplementary Table 2. Method used for country estimates – country-specific or regional average.

Country	Method	Location for method
Africa		
Algeria	Country-specific	Algeria
Angola	Region average	Sub-Saharan Africa
Benin	Region average	Sub-Saharan Africa
Botswana	Country-specific	Botswana
Burkina Faso	Region average	Sub-Saharan Africa
Burundi	Region average	Sub-Saharan Africa
Cameroon	Country-specific	Cameroon
Cape Verde	Region average	Sub-Saharan Africa
Central African Republic	Region average	Sub-Saharan Africa
Chad	Region average	Sub-Saharan Africa
Comoros	Region average	Sub-Saharan Africa
Congo, Democratic People Republic of	Region average	Sub-Saharan Africa
Congo, Republic of	Country-specific	Congo, Republic of
Cote d Ivoire	Country-specific	Cote d Ivoire
Djibouti	Region average	Sub-Saharan Africa
Egypt	Country-specific	Egypt
Equatorial Guinea	Region average	Sub-Saharan Africa
Eritrea	Region average	Sub-Saharan Africa
Ethiopia	Region average	Sub-Saharan Africa
France, La Reunion	Region average	Sub-Saharan Africa
Gabon	Country-specific	Gabon
Ghana	Country-specific	Ghana
Guinea	Region average	Sub-Saharan Africa
Guinea-Bissau	Region average	Sub-Saharan Africa
Kenya	Country-specific	Kenya
Lesotho	Region average	Sub-Saharan Africa
Liberia	Region average	Sub-Saharan Africa
Libya	Region average	Northern Africa
Madagascar	Region average	Sub-Saharan Africa
Malawi	Region average	Sub-Saharan Africa
Mali	Region average	Sub-Saharan Africa
Mauritania	Region average	Sub-Saharan Africa
Mauritius	Country-specific	Mauritius
Morocco	Country-specific	Morocco
Mozambique	Region average	Sub-Saharan Africa
Namibia	Country-specific	Namibia
Niger	Region average	Sub-Saharan Africa

Supplementary Table 2. Method used for country estimates – country-specific or regional average. (*continued*)

Country	Method	Location for method
Nigeria	Country-specific	Nigeria
Rwanda	Region average	Sub-Saharan Africa
Sao Tome and Principe	Region average	Sub-Saharan Africa
Senegal	Region average	Sub-Saharan Africa
Sierra Leone	Region average	Sub-Saharan Africa
Somalia	Region average	Sub-Saharan Africa
South Africa	Region average	Sub-Saharan Africa
South Sudan	Region average	Sub-Saharan Africa
Sudan	Region average	Northern Africa
Swaziland	Region average	Sub-Saharan Africa
Tanzania	Region average	Sub-Saharan Africa
The Gambia	Region average	Sub-Saharan Africa
Togo	Region average	Sub-Saharan Africa
Tunisia	Country-specific	Tunisia
Uganda	Country-specific	Uganda
Zambia	Country-specific	Zambia
Zimbabwe	Country-specific	Zimbabwe
Asia		
Afghanistan	Region average	South-Central Asia
Armenia	Region average	Western Asia
Azerbaijan	Region average	Western Asia
Bahrain	Country-specific	Bahrain
Bangladesh	Region average	South-Central Asia
Bhutan	Region average	South-Central Asia
Brunei Darussalam	Country-specific	Brunei Darussalam
Cambodia	Region average	South-Eastern Asia
China	Country-specific	China
Georgia	Region average	Western Asia
India	Country-specific	India
Indonesia	Country-specific	Indonesia
Iran, Islamic Republic of	Country-specific	Iran, Islamic Republic of
Iraq	Region average	Western Asia
Israel	Country-specific	Israel
Japan	Country-specific	Japan
Jordan	Country-specific	Jordan
Kazakhstan	Country-specific	Kazakhstan
Korea, Democratic People Republic of	Region average	Eastern Asia
Korea, Republic of	Country-specific	Korea, Republic of

Supplementary Table 2. Method used for country estimates – country-specific or regional average. (*continued*)

Country	Method	Location for method
Kuwait	Country-specific	Kuwait
Kyrgyzstan	Region average	South-Central Asia
Lao People Democratic Republic	Region average	South-Eastern Asia
Lebanon	Country-specific	Lebanon
Malaysia	Country-specific	Malaysia
Maldives	Region average	South-Central Asia
Mongolia	Region average	Eastern Asia
Myanmar	Region average	South-Eastern Asia
Nepal	Region average	South-Central Asia
Oman	Country-specific	Oman
Pakistan	Country-specific	Pakistan
Palestine	Region average	Western Asia
Philippines	Country-specific	Philippines
Qatar	Country-specific	Qatar
Saudi Arabia	Country-specific	Saudi Arabia
Singapore	Country-specific	Singapore
Sri Lanka	Region average	South-Central Asia
Syrian Arab Republic	Country-specific	Syrian Arab Republic
Tajikistan	Region average	South-Central Asia
Thailand	Country-specific	Thailand
Timor-Leste	Region average	South-Eastern Asia
Turkey	Country-specific	Turkey
Turkmenistan	Region average	South-Central Asia
United Arab Emirates	Region average	Western Asia
Uzbekistan	Region average	South-Central Asia
Viet Nam	Region average	South-Eastern Asia
Yemen	Region average	Western Asia
Europe		
Albania	Region average	Southern Europe
Austria	Country-specific	Austria
Belarus	Country-specific	Belarus
Belgium	Country-specific	Belgium
Bosnia Herzegovina	Region average	Southern Europe
Bulgaria	Country-specific	Bulgaria
Croatia	Country-specific	Croatia
Cyprus	Country-specific	Cyprus
Czechia	Country-specific	Czechia
Denmark	Country-specific	Denmark

Supplementary Table 2. Method used for country estimates – country-specific or regional average. (*continued*)

Country	Method	Location for method
Estonia	Country-specific	Estonia
Finland	Country-specific	Finland
France (metropolitan)	Country-specific	France (metropolitan)
Germany	Country-specific	Germany
Greece	Region average	Southern Europe
Hungary	Region average	Central and Eastern Europe
Iceland	Country-specific	Iceland
Ireland	Country-specific	Ireland
Italy	Country-specific	Italy
Latvia	Country-specific	Latvia
Lithuania	Country-specific	Lithuania
Luxembourg	Region average	Western Europe
Macedonia	Region average	Southern Europe
Malta	Country-specific	Malta
Moldova	Region average	Central and Eastern Europe
Montenegro	Region average	Southern Europe
Norway	Country-specific	Norway
Poland	Country-specific	Poland
Portugal	Country-specific	Portugal
Romania	Country-specific	Romania
Russian Federation	Country-specific	Russian Federation
Serbia	Country-specific	Serbia
Slovakia	Country-specific	Slovakia
Slovenia	Country-specific	Slovenia
Spain	Country-specific	Spain
Sweden	Country-specific	Sweden
Switzerland	Country-specific	Switzerland
The Netherlands	Country-specific	The Netherlands
Ukraine	Country-specific	Ukraine
United Kingdom	Country-specific	United Kingdom
Latin America and the Caribbean		
Argentina	Country-specific	Argentina
Bahamas	Region average	Caribbean and Central America
Barbados	Region average	Caribbean and Central America
Belize	Region average	Caribbean and Central America
Bolivia	Region average	South America
Brazil	Country-specific	Brazil
Chile	Country-specific	Chile

Supplementary Table 2. Method used for country estimates – country-specific or regional average. (*continued*)

Country	Method	Location for method
Colombia	Country-specific	Colombia
Costa Rica	Country-specific	Costa Rica
Cuba	Country-specific	Cuba
Dominican Republic	Region average	Caribbean and Central America
Ecuador	Country-specific	Ecuador
El Salvador	Region average	Caribbean and Central America
France, Guadeloupe	Country-specific	France, Guadeloupe
France, Martinique	Country-specific	France, Martinique
French Guyana	Country-specific	French Guyana
Guatemala	Country-specific	Guatemala
Guyana	Region average	South America
Haiti	Region average	Caribbean and Central America
Honduras	Region average	Caribbean and Central America
Jamaica	Country-specific	Jamaica
Mexico	Region average	Caribbean and Central America
Nicaragua	Region average	Caribbean and Central America
Panama	Region average	Caribbean and Central America
Paraguay	Region average	South America
Peru	Country-specific	Peru
Puerto Rico	Country-specific	Puerto Rico
Saint Lucia	Region average	Caribbean and Central America
Suriname	Region average	South America
Trinidad and Tobago	Region average	Caribbean and Central America
Uruguay	Country-specific	Uruguay
Venezuela	Region average	South America
North America		
Canada	Country-specific	Canada
United States of America	Country-specific	United States of America
Oceania		
Australia	Country-specific	Australia
Fiji	Region average	Oceania
France, New Caledonia	Country-specific	France, New Caledonia
French Polynesia	Country-specific	French Polynesia
Guam	Country-specific	Guam
New Zealand	Country-specific	New Zealand
Papua New Guinea	Region average	Oceania
Samoa	Region average	Oceania
Solomon Islands	Region average	Oceania
Vanuatu	Country-specific	Vanuatu

Supplementary Table 3. Distribution of liver cancer subtypes as a percentage of total liver cancer cases after reallocation of unspecified cases to Hepatocellular Carcinoma (HCC) and intrahepatic Cholangiocarcinoma (iCCA) only, according to sex and world region.

	Men			Women			Persons		
World Region	**HCC**	**iCCA**	**Other**	**HCC**	**iCCA**	**Other**	**HCC**	**iCCA**	**Other**
Africa									
Northern Africa	94.9%	3.4%	1.7%	89.2%	7.1%	3.7%	93.3%	4.5%	2.3%
Sub-Saharan Africa	85.9%	7.5%	6.6%	74.3%	18.4%	7.3%	81.7%	11.4%	6.9%
Asia									
Eastern Asia	87.2%	9.2%	3.6%	78.8%	17.1%	4.1%	85.0%	11.3%	3.7%
South-Central Asia	72.3%	16.2%	11.5%	58.1%	28.4%	13.5%	67.4%	20.3%	12.2%
South-Eastern Asia	76.8%	16.8%	6.4%	56.3%	35.2%	8.6%	71.4%	21.6%	7.0%
Western Asia	79.7%	12.3%	8.1%	60.8%	26.9%	12.3%	72.6%	17.8%	9.6%
Europe									
Central and Eastern Europe	77.7%	15.6%	6.7%	68.9%	24.2%	6.9%	74.2%	19.0%	6.8%
Northern Europe	66.7%	29.3%	3.9%	35.9%	58.9%	5.2%	55.8%	39.9%	4.4%
Southern Europe	81.7%	14.3%	3.9%	65.3%	30.1%	4.7%	76.9%	18.9%	4.1%
Western Europe	79.4%	16.8%	3.8%	54.4%	39.6%	6.1%	72.7%	22.9%	4.4%
Latin America and the Caribbean									
Caribbean and Central America	68.8%	21.3%	9.9%	50.5%	39.8%	9.6%	59.9%	30.4%	9.8%
South America	76.4%	17.1%	6.6%	58.9%	33.6%	7.5%	68.7%	24.3%	7.0%
North America									
North America	83.7%	11.6%	4.7%	63.9%	29.1%	7.0%	78.0%	16.6%	5.4%
Oceania									
Oceania	77.8%	19.2%	2.9%	50.7%	44.4%	4.8%	69.6%	26.8%	3.5%
World	83.9%	11.4%	4.7%	70.4%	23.5%	6.0%	80.0%	14.9%	5.1%

International Classification of Diseases for Oncology (ICD-O-3) codes: hepatocellular carcinoma (8170-8175); cholangiocarcinoma (8050, 8140-8141, 8160-8161, 8260, 8440, 8480-8500, 8570-8572); other specified histology (8010-8035, 8970, 9120-9133, 9161, 8800-8811, 8830, 8840-8921, 8990-8991, 9040-9044, 9150, 9170, 9540-9581).

Supplementary Table 4. Estimated age-standardised incidence rate per 100,000 person-years of liver cancer by subtype, sex and country in 2018.

	Men			Women			Both sexes		
	HCC	iCCA	Other	HCC	iCCA	Other	HCC	iCCA	Other
Africa									
Northern Africa									
Algeria	0.7	0.8	0.2	0.4	0.7	0.1	0.5	0.7	0.2
Egypt	48.4	0.5	0.1	16.2	0.2	0.3	31.6	0.4	0.2
Libya	2.0	1.5	0.9	1.4	1.7	0.7	1.7	1.6	0.8
Morocco	0.5	0.3	0.6	0.3	0.3	0.4	0.4	0.3	0.5
Sudan	2.2	1.6	1.0	1.0	1.3	0.5	1.6	1.4	0.7
Tunisia	1.8	0.6	0.2	1.6	0.9	0.2	1.7	0.7	0.2
Sub-Saharan Africa									
Angola	4.3	0.5	0.4	1.6	0.5	0.2	2.8	0.5	0.3
Benin	8.1	0.9	0.8	1.4	0.5	0.2	4.1	0.6	0.4
Botswana	4.7	0.7	1.0	1.4	0.5	0.5	2.7	0.5	0.7
Burkina Faso	15.9	1.8	1.5	6.5	2.2	1.0	10.6	2.0	1.2
Burundi	7.5	0.8	0.7	2.6	0.9	0.4	4.9	0.9	0.5
Cameroon	8.9	0.4	0.0	2.9	0.2	0.0	5.8	0.3	0.0
Cape Verde	9.4	1.1	0.9	6.2	2.1	0.9	8.0	1.8	1.0
Central African Republic	6.2	0.7	0.6	2.1	0.7	0.3	4.0	0.7	0.4
Chad	6.5	0.7	0.6	2.3	0.8	0.4	4.3	0.8	0.5
Comoros	6.3	0.7	0.6	2.7	0.9	0.4	4.4	0.8	0.5
Congo, Democratic People Republic of	9.6	1.1	0.9	3.3	1.1	0.5	6.2	1.1	0.7
Congo, Republic of	4.6	1.9	2.1	1.7	1.0	0.7	3.1	1.4	1.4
Cote d Ivoire	8.4	1.0	0.2	6.0	0.8	0.1	7.2	0.9	0.2
Djibouti	2.5	0.3	0.2	1.5	0.5	0.2	2.0	0.4	0.2
Equatorial Guinea	5.0	0.6	0.5	2.0	0.7	0.3	3.7	0.6	0.4
Eritrea	3.1	0.3	0.3	1.9	0.7	0.3	2.5	0.5	0.3
Ethiopia	2.2	0.2	0.2	1.9	0.6	0.3	2.0	0.4	0.2
France, La Reunion	7.5	0.8	0.7	2.2	0.7	0.3	4.7	0.8	0.5
Gabon	2.7	0.6	0.7	1.5	0.9	0.2	2.2	0.7	0.5
Ghana	23.2	0.3	0.9	7.3	0.1	0.1	14.7	0.2	0.5
Guinea	23.1	2.6	2.2	10.9	3.7	1.7	16.8	3.2	1.9
Guinea-Bissau	14.3	1.6	1.3	4.9	1.7	0.7	9.2	1.6	1.0
Kenya	4.6	1.2	0.4	2.7	1.3	0.5	3.6	1.2	0.5
Lesotho	5.4	0.6	0.5	2.0	0.7	0.3	3.3	0.6	0.4
Liberia	15.7	1.8	1.5	7.9	2.7	1.2	11.6	2.2	1.3
Madagascar	6.9	0.8	0.6	2.4	0.8	0.4	4.5	0.8	0.5
Malawi	2.0	0.2	0.2	1.2	0.4	0.2	1.6	0.3	0.2

Supplementary Table 4. Estimated age-standardised incidence rate per 100,000 person-years of liver cancer by subtype, sex and country in 2018. (*continued*)

	Men			Women			Both sexes		
	HCC	iCCA	Other	HCC	iCCA	Other	HCC	iCCA	Other
Mali	8.4	1.0	0.8	2.0	0.7	0.3	5.0	0.8	0.5
Mauritania	13.9	1.6	1.3	4.4	1.5	0.7	8.9	1.5	1.0
Mauritius	2.6	1.1	0.3	0.5	1.9	0.3	1.4	1.5	0.3
Mozambique	7.3	0.8	0.7	3.4	1.1	0.5	5.1	1.0	0.6
Namibia	3.1	0.7	0.3	1.2	0.6	0.1	2.0	0.6	0.2
Niger	9.6	1.1	0.9	2.2	0.7	0.3	5.8	0.9	0.6
Nigeria	5.5	0.0	0.3	4.0	0.3	0.0	4.8	0.2	0.2
Rwanda	12.2	1.4	1.1	4.4	1.5	0.7	7.8	1.4	0.9
Sao Tome and Principe	12.3	1.4	1.1	1.7	0.6	0.3	6.7	1.0	0.7
Senegal	14.9	1.7	1.4	5.7	1.9	0.9	9.7	1.8	1.1
Sierra Leone	10.4	1.2	1.0	5.1	1.7	0.8	7.7	1.5	0.9
Somalia	3.0	0.3	0.3	2.2	0.7	0.3	2.6	0.5	0.3
South Africa	6.3	0.7	0.6	2.2	0.7	0.3	3.9	0.7	0.4
South Sudan	5.4	0.6	0.5	2.5	0.9	0.4	3.9	0.7	0.4
Swaziland	4.2	0.5	0.4	2.2	0.7	0.3	3.0	0.6	0.4
Tanzania	6.7	0.8	0.6	1.5	0.5	0.2	3.9	0.6	0.4
The Gambia	30.3	3.4	2.8	8.0	2.7	1.2	18.9	3.0	2.0
Togo	8.0	0.9	0.8	2.9	1.0	0.4	5.4	0.9	0.6
Uganda	9.2	0.4	0.5	4.2	1.0	0.2	6.5	0.7	0.4
Zambia	1.7	0.6	0.6	1.1	0.6	0.1	1.3	0.6	0.3
Zimbabwe	8.3	0.2	0.2	5.3	0.3	0.1	6.6	0.2	0.2
Asia									
Eastern Asia									
China	24.0	2.5	1.0	7.1	1.6	0.4	15.5	2.1	0.7
Japan	11.1	0.9	0.3	3.1	0.4	0.1	6.8	0.6	0.2
Korea, Democratic People Republic of	23.0	1.8	0.6	7.8	0.9	0.3	14.7	1.4	0.4
Korea, Republic of	22.8	4.3	0.6	5.6	2.4	0.2	13.7	3.3	0.4
Mongolia	105.9	8.5	2.6	64.3	7.7	2.1	83.2	8.1	2.4
South-Central Asia									
Afghanistan	3.4	0.8	0.7	1.6	0.9	0.5	2.4	0.9	0.6
Bangladesh	2.3	0.6	0.5	0.6	0.3	0.2	1.4	0.4	0.3
Bhutan	5.3	1.3	1.2	1.2	0.7	0.4	3.5	1.0	0.8
India	2.2	0.5	0.4	0.8	0.4	0.2	1.5	0.5	0.3
Iran, Islamic Republic of	3.5	1.6	0.2	2.6	1.2	0.3	3.1	1.4	0.3
Kazakhstan	4.9	1.5	1.8	2.0	1.1	0.8	3.2	1.3	1.2
Kyrgyzstan	8.9	2.1	2.0	3.6	2.1	1.2	5.9	2.1	1.5
Maldives	8.4	2.0	1.9	2.0	1.1	0.6	5.4	1.6	1.3

Supplementary Table 4. Estimated age-standardised incidence rate per 100,000 person-years of liver cancer by subtype, sex and country in 2018. (*continued*)

	Men			Women			Both sexes		
	HCC	iCCA	Other	HCC	iCCA	Other	HCC	iCCA	Other
Nepal	1.1	0.3	0.2	0.4	0.3	0.1	0.7	0.3	0.2
Pakistan	3.4	0.1	0.2	1.9	0.2	0.2	2.7	0.2	0.2
Sri Lanka	2.5	0.6	0.6	1.0	0.6	0.3	1.7	0.6	0.4
Tajikistan	4.1	1.0	0.9	1.9	1.1	0.6	2.9	1.0	0.8
Turkmenistan	5.8	1.4	1.3	2.2	1.3	0.7	3.8	1.3	1.0
Uzbekistan	4.6	1.1	1.0	2.5	1.4	0.8	3.4	1.3	0.9
South-Eastern Asia									
Brunei Darussalam	13.0	1.9	2.1	1.7	1.3	0.2	7.2	1.6	1.1
Cambodia	27.1	5.5	2.0	7.4	4.4	0.9	15.6	4.9	1.4
Indonesia	9.2	2.9	0.3	1.6	1.6	0.1	5.2	2.2	0.2
Lao People Democratic Republic	26.1	5.3	2.0	7.6	4.5	0.9	16.1	4.9	1.4
Malaysia	8.5	0.6	0.5	2.3	0.7	0.2	5.4	0.6	0.3
Myanmar	11.4	2.3	0.9	3.6	2.2	0.4	7.2	2.2	0.6
Philippines	14.1	0.8	2.9	4.6	0.7	0.9	8.9	0.8	1.8
Singapore	17.1	2.0	0.4	4.2	1.4	0.3	10.3	1.7	0.3
Thailand	23.8	6.1	2.3	5.7	4.4	1.3	14.1	5.2	1.8
Timor-Leste	5.7	1.2	0.4	1.9	1.1	0.2	3.8	1.2	0.3
Viet Nam	30.5	6.2	2.3	5.6	3.3	0.7	17.1	4.7	1.4
Western Asia									
Armenia	11.0	1.6	1.0	4.4	1.8	0.8	7.2	1.7	0.8
Azerbaijan	3.3	0.5	0.3	2.1	0.8	0.4	2.6	0.7	0.3
Bahrain	2.9	0.6	0.4	1.0	1.4	0.4	2.0	1.0	0.4
Georgia	6.8	1.0	0.6	2.0	0.8	0.3	4.1	0.9	0.5
Iraq	2.5	0.4	0.2	1.5	0.6	0.3	1.9	0.5	0.2
Israel	2.9	0.5	0.1	1.1	0.5	0.1	1.9	0.5	0.1
Jordan	2.4	0.8	0.3	1.2	0.9	0.6	1.8	0.8	0.5
Kuwait	5.4	0.3	0.5	2.5	0.7	0.5	4.3	0.5	0.5
Lebanon	1.4	1.6	0.6	0.6	1.5	0.6	1.0	1.6	0.6
Oman	3.7	1.2	0.9	1.6	0.8	0.3	2.8	1.0	0.6
Palestine	2.0	0.3	0.2	0.8	0.3	0.1	1.4	0.3	0.2
Qatar	3.1	2.7	0.0	1.2	0.5	0.1	2.2	1.8	0.0
Saudi Arabia	5.5	0.4	0.3	2.0	0.3	0.2	3.9	0.3	0.2
Syrian Arab Republic	2.6	0.6	0.3	1.3	1.1	0.2	1.9	0.9	0.2
Turkey	5.3	0.7	0.6	1.7	0.7	0.4	3.3	0.7	0.5
United Arab Emirates	3.5	0.5	0.3	2.7	1.1	0.5	3.2	0.7	0.4
Yemen	5.1	0.8	0.5	1.7	0.7	0.3	3.3	0.7	0.4

Supplementary Table 4. Estimated age-standardised incidence rate per 100,000 person-years of liver cancer by subtype, sex and country in 2018. (*continued*)

	Men			Women			Both sexes		
	HCC	iCCA	Other	HCC	iCCA	Other	HCC	iCCA	Other
Europe									
Central and Eastern Europe									
Belarus	2.6	1.1	1.2	0.9	0.7	0.5	1.6	0.9	0.8
Bulgaria	4.7	0.9	0.2	1.2	0.5	0.1	2.8	0.7	0.1
Czechia	4.1	1.5	0.5	1.1	1.3	0.3	2.4	1.4	0.4
Hungary	6.1	2.1	1.0	1.2	0.9	0.3	3.3	1.4	0.6
Moldova	13.9	4.8	2.2	4.2	3.1	1.1	8.4	3.9	1.6
Poland	3.0	1.2	0.6	0.8	1.0	0.3	1.7	1.1	0.4
Romania	10.6	1.7	0.5	3.6	1.1	0.2	6.7	1.3	0.3
Russian Federation	5.3	0.5	0.2	2.1	0.3	0.1	3.4	0.4	0.1
Slovakia	5.2	2.3	0.2	1.2	1.6	0.1	2.9	1.9	0.2
Ukraine	1.9	0.9	0.4	0.8	0.5	0.2	1.3	0.7	0.3
Northern Europe									
Denmark	5.4	1.4	0.5	1.2	1.2	0.3	3.2	1.3	0.4
Estonia	3.3	1.5	0.4	0.8	1.1	0.2	1.8	1.2	0.2
Finland	3.9	1.2	0.1	1.3	1.0	0.1	2.5	1.1	0.1
Iceland	3.2	0.9	0.1	0.2	0.6	0.2	1.7	0.7	0.1
Ireland	5.0	1.6	0.3	0.6	1.3	0.1	2.7	1.4	0.2
Latvia	2.6	1.2	0.0	1.0	1.6	0.1	1.6	1.5	0.1
Lithuania	4.7	1.5	0.3	0.6	1.3	0.1	2.2	1.4	0.2
Norway	3.8	1.2	0.2	0.8	0.6	0.1	2.3	0.9	0.1
Sweden	4.3	1.7	0.5	1.2	1.1	0.3	2.7	1.4	0.4
United Kingdom	4.5	2.2	0.2	1.1	2.1	0.2	2.7	2.2	0.2
Southern Europe									
Albania	8.2	1.5	0.4	3.8	1.7	0.3	5.9	1.6	0.3
Bosnia Herzegovina	7.5	1.3	0.4	3.9	1.7	0.3	5.6	1.6	0.3
Croatia	7.7	2.0	0.3	1.8	1.5	0.1	4.5	1.7	0.2
Cyprus	2.6	2.2	0.2	0.7	1.2	0.1	1.6	1.7	0.1
Greece	7.0	1.3	0.3	2.2	1.0	0.2	4.4	1.1	0.2
Italy	10.9	1.5	0.5	2.5	0.8	0.1	6.5	1.1	0.3
Macedonia	5.8	1.0	0.3	2.0	0.9	0.1	3.8	1.0	0.2
Malta	1.3	1.7	0.6	0.2	0.6	0.1	0.7	1.1	0.3
Montenegro	4.7	0.8	0.2	1.7	0.7	0.1	3.0	0.8	0.2
Portugal	6.2	2.2	0.8	0.9	1.1	0.3	3.3	1.6	0.5
Serbia	4.5	0.9	0.4	2.5	0.6	0.2	3.4	0.8	0.3
Slovenia	7.7	1.8	0.2	1.3	1.0	0.1	4.3	1.4	0.1
Spain	8.8	1.8	0.4	1.4	1.0	0.1	4.9	1.4	0.2

Supplementary Table 4. Estimated age-standardised incidence rate per 100,000 person-years of liver cancer by subtype, sex and country in 2018. (*continued*)

	Men			Women			Both sexes		
	HCC	iCCA	Other	HCC	iCCA	Other	HCC	iCCA	Other
Western Europe									
Austria	5.7	1.9	0.6	1.3	1.5	0.3	3.3	1.7	0.4
Belgium	4.7	0.9	0.2	1.8	0.9	0.2	3.2	0.9	0.2
France (metropolitan)	10.8	2.2	0.3	1.5	1.1	0.1	5.9	1.6	0.2
Germany	5.0	1.1	0.3	1.3	0.8	0.2	3.1	1.0	0.2
Luxembourg	7.1	1.6	0.4	2.3	1.7	0.3	4.5	1.6	0.4
Switzerland	6.0	1.1	0.2	1.5	1.1	0.1	3.6	1.1	0.2
The Netherlands	2.6	0.7	0.2	0.9	0.7	0.1	1.7	0.7	0.2
Latin America and the Caribbean									
Caribbean and Central America									
Bahamas	2.8	0.7	0.4	0.6	0.4	0.1	1.6	0.6	0.2
Barbados	2.2	0.5	0.3	1.0	0.7	0.2	1.5	0.7	0.2
Belize	8.8	2.2	1.2	2.3	1.7	0.4	5.6	2.0	0.8
Costa Rica	6.1	1.3	0.5	2.7	1.7	0.4	4.3	1.5	0.4
Cuba	1.7	2.2	0.8	1.3	1.1	0.6	1.5	1.6	0.7
Dominican Republic	5.5	1.4	0.7	2.9	2.1	0.5	4.2	1.8	0.6
El Salvador	4.6	1.2	0.6	3.6	2.7	0.7	4.1	2.0	0.6
France, Guadeloupe	4.7	1.0	0.5	1.0	0.5	0.2	2.6	0.7	0.3
France, Martinique	5.2	0.2	0.5	2.0	0.4	0.3	3.4	0.3	0.4
Guatemala	9.8	4.5	1.6	5.5	7.4	1.2	7.4	6.1	1.4
Haiti	6.9	1.7	0.9	3.6	2.6	0.6	5.1	2.2	0.8
Honduras	6.7	1.7	0.9	1.4	1.1	0.3	3.9	1.3	0.5
Jamaica	1.6	1.4	0.0	2.0	0.8	0.0	1.8	1.1	0.0
Mexico	4.0	1.0	0.5	2.8	2.1	0.5	3.4	1.6	0.5
Nicaragua	9.8	2.5	1.3	4.2	3.1	0.8	6.7	2.8	1.0
Panama	3.6	0.9	0.5	2.5	1.8	0.4	3.0	1.4	0.5
Puerto Rico	6.7	1.3	0.9	1.3	0.8	0.2	3.7	1.0	0.5
Saint Lucia	1.6	0.4	0.2	0.4	0.3	0.1	1.0	0.4	0.1
Trinidad and Tobago	2.8	0.7	0.4	1.5	1.1	0.3	2.1	0.9	0.3
South America									
Argentina	3.0	1.5	0.5	1.0	1.3	0.2	1.9	1.4	0.3
Bolivia	4.2	1.0	0.4	4.0	2.2	0.5	4.0	1.6	0.5
Brazil	5.2	0.8	0.3	2.3	0.9	0.2	3.6	0.9	0.3
Chile	5.1	0.8	1.0	1.8	1.8	0.5	3.3	1.4	0.7
Colombia	3.2	1.2	0.3	1.5	1.6	0.3	2.3	1.4	0.3
Ecuador	4.0	1.3	0.4	3.1	1.4	0.4	3.5	1.4	0.4
French Guyana	11.1	3.7	0.7	0.9	1.3	0.2	5.7	2.4	0.4

Supplementary Table 4. Estimated age-standardised incidence rate per 100,000 person-years of liver cancer by subtype, sex and country in 2018. (*continued*)

	Men			Women			Both sexes		
	HCC	iCCA	Other	HCC	iCCA	Other	HCC	iCCA	Other
Guyana	2.0	0.5	0.2	1.6	0.9	0.2	1.8	0.7	0.2
Paraguay	2.8	0.7	0.2	1.2	0.7	0.2	2.0	0.7	0.2
Peru	4.7	1.5	0.6	3.9	1.8	0.7	4.2	1.7	0.7
Suriname	6.9	1.6	0.6	1.6	0.9	0.2	4.0	1.2	0.4
Uruguay	4.0	0.3	0.1	0.9	0.3	0.1	2.2	0.3	0.1
Venezuela	3.3	0.8	0.3	1.8	1.0	0.2	2.5	0.9	0.3
North America									
Canada	6.2	1.1	0.3	1.8	1.2	0.1	3.9	1.2	0.2
United States of America	8.7	1.2	0.5	2.2	1.0	0.3	5.4	1.1	0.4
Oceania									
Australia	6.6	1.8	0.3	1.5	1.3	0.1	4.0	1.5	0.2
Fiji	9.5	2.4	0.4	2.4	2.2	0.2	5.8	2.3	0.3
France, New Caledonia	13.3	1.0	0.0	5.7	0.4	0.8	9.3	0.7	0.4
French Polynesia	11.7	1.1	0.6	4.3	0.5	0.9	8.0	0.8	0.7
Guam	21.0	0.4	3.1	4.0	0.5	0.7	12.4	0.5	1.9
New Zealand	8.1	1.7	0.2	0.9	1.1	0.1	4.3	1.4	0.1
Papua New Guinea	10.8	2.7	0.4	5.0	4.5	0.5	7.8	3.7	0.5
Samoa	13.4	3.4	0.5	1.2	1.1	0.1	7.3	2.2	0.3
Solomon Islands	12.0	3.0	0.5	2.5	2.3	0.2	7.3	2.7	0.4
Vanuatu	17.7	1.5	1.0	5.0	0.9	0.2	11.3	1.2	0.6
World	11.6	1.6	0.7	3.4	1.2	0.3	7.3	1.4	0.5

International Classification of Diseases for Oncology (ICD-O-3) codes: hepatocellular carcinoma (8170-8175); cholangiocarcinoma (8050, 8140-8141, 8160-8161, 8260, 8440, 8480-8500, 8570-8572); other specified histology (8010-8035, 8970, 9120-9133, 9161, 8800-8811, 8830, 8840-8921, 8990-8991, 9040-9044, 9150, 9170, 9540-9581).

Supplementary Table 5. Distribution of liver cancer subtypes as a percentage of total liver cancer cases by sex and world region, alternative scenario 1: reallocate unspecified cases to Hepatocellular Carcinoma (HCC), intrahepatic Cholangiocarcinoma (iCCA) and other specified histology.

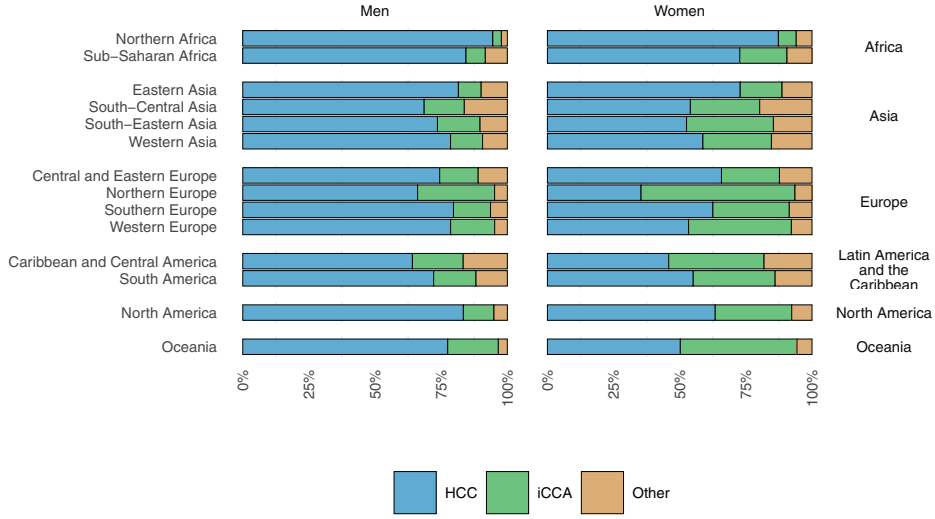
	Men			Women			Persons		
World Region	**HCC**	**iCCA**	**Other**	**HCC**	**iCCA**	**Other**	**HCC**	**iCCA**	**Other**
Africa									
Northern Africa	94.5%	3.3%	2.2%	87.3%	6.7%	6.0%	92.4%	4.3%	3.3%
Sub-Saharan Africa	84.4%	7.3%	8.3%	72.7%	17.8%	9.5%	80.2%	11.1%	8.7%
Asia									
Eastern Asia	81.5%	8.6%	9.9%	72.9%	15.8%	11.3%	79.2%	10.5%	10.3%
South-Central Asia	68.6%	15.2%	16.3%	54.0%	26.2%	19.8%	63.6%	18.9%	17.5%
South-Eastern Asia	73.6%	16.1%	10.3%	52.6%	32.8%	14.6%	68.0%	20.5%	11.4%
Western Asia	78.5%	12.1%	9.4%	58.8%	25.9%	15.3%	71.1%	17.3%	11.6%
Europe									
Central and Eastern Europe	74.4%	14.5%	11.0%	65.8%	21.9%	12.3%	71.0%	17.5%	11.5%
Northern Europe	66.1%	29.1%	4.8%	35.4%	58.2%	6.4%	55.2%	39.4%	5.4%
Southern Europe	79.6%	14.0%	6.4%	62.5%	28.9%	8.6%	74.6%	18.3%	7.0%
Western Europe	78.6%	16.7%	4.8%	53.4%	38.8%	7.8%	71.8%	22.6%	5.6%
Latin America and the Caribbean									
Caribbean and Central America	64.1%	19.2%	16.7%	45.8%	36.0%	18.1%	55.2%	27.5%	17.4%
South America	72.2%	16.0%	11.8%	55.1%	30.9%	13.9%	64.6%	22.6%	12.8%
North America									
North America	83.4%	11.6%	5.1%	63.4%	28.9%	7.7%	77.7%	16.5%	5.8%
Oceania									
Oceania	77.5%	19.1%	3.4%	50.2%	44.1%	5.7%	69.2%	26.7%	4.1%
World	79.7%	10.9%	9.5%	66.1%	22.1%	11.8%	75.7%	14.1%	10.2%

International Classification of Diseases for Oncology (ICD-O-3) codes: hepatocellular carcinoma (8170-8175); cholangiocarcinoma (8050, 8140-8141, 8160-8161, 8260, 8440, 8480-8500, 8570-8572); other specified histology (8010-8035, 8970, 9120-9133, 9161, 8800-8811, 8830, 8840-8921, 8990-8991, 9040-9044, 9150, 9170, 9540-9581).

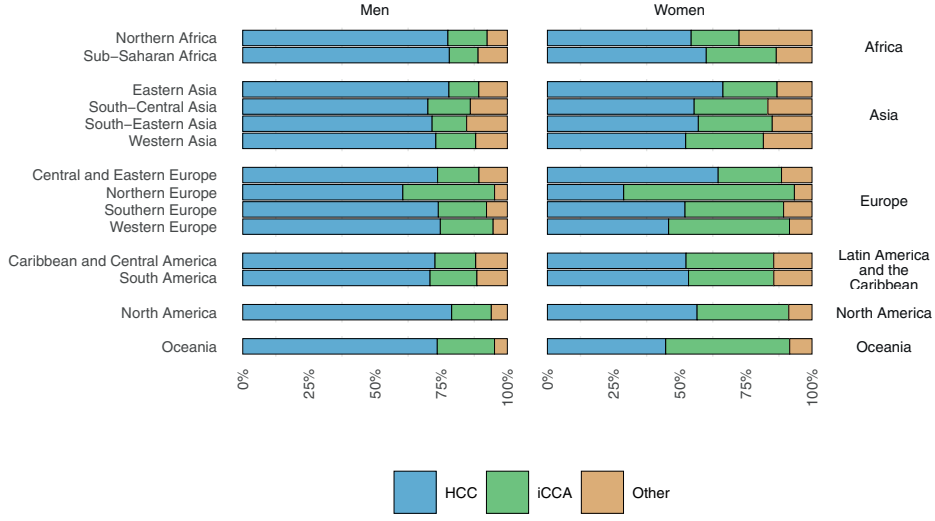
Supplementary Table 6. Distribution of liver cancer subtypes as a percentage of total liver cancer cases by sex and world region, alternative scenario 2: Use of microscopically verified cases only.

	Men			Women			Persons		
World Region	**HCC**	**iCCA**	**Other**	**HCC**	**iCCA**	**Other**	**HCC**	**iCCA**	**Other**
Africa									
Northern Africa	77.5%	14.8%	7.6%	54.3%	18.1%	27.6%	70.9%	15.8%	13.4%
Sub-Saharan Africa	78.1%	10.9%	11.1%	60.0%	26.5%	13.5%	71.6%	16.5%	11.9%
Asia									
Eastern Asia	77.9%	11.3%	10.8%	66.3%	20.4%	13.2%	74.9%	13.7%	11.4%
South-Central Asia	70.0%	16.0%	14.0%	55.5%	27.9%	16.7%	65.0%	20.1%	14.9%
South-Eastern Asia	71.6%	13.0%	15.4%	57.0%	27.9%	15.0%	67.7%	17.0%	15.3%
Western Asia	73.0%	15.1%	12.0%	52.3%	29.4%	18.4%	65.2%	20.4%	14.4%
Europe									
Central and Eastern Europe	73.6%	15.6%	10.7%	64.5%	23.9%	11.5%	70.0%	18.9%	11.0%
Northern Europe	60.5%	34.7%	4.8%	28.8%	64.5%	6.7%	49.2%	45.3%	5.5%
Southern Europe	73.9%	18.2%	7.9%	52.0%	37.2%	10.7%	67.5%	23.8%	8.7%
Western Europe	74.7%	20.0%	5.4%	45.8%	45.7%	8.5%	66.9%	26.9%	6.2%
Latin America and the Caribbean									
Caribbean and Central America	72.7%	15.4%	12.0%	52.4%	33.1%	14.5%	62.7%	24.1%	13.2%
South America	70.8%	17.7%	11.5%	53.3%	32.2%	14.4%	63.1%	24.1%	12.8%
North America									
North America	79.0%	15.0%	6.1%	56.6%	34.6%	8.8%	72.6%	20.6%	6.8%
Oceania									
Oceania	73.5%	21.6%	4.8%	44.7%	46.9%	8.4%	64.8%	29.2%	5.9%
World	76.0%	13.2%	10.8%	60.6%	25.8%	13.7%	71.5%	16.8%	11.6%

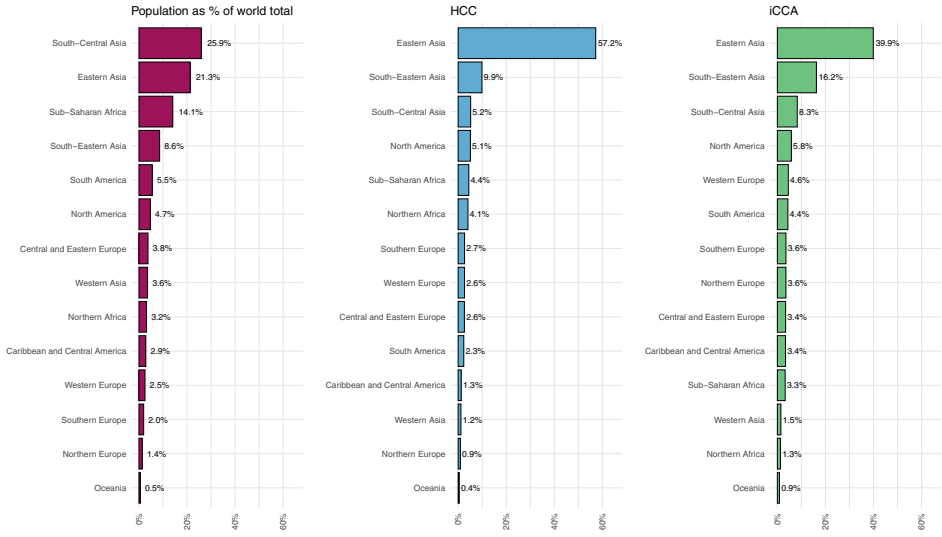
International Classification of Diseases for Oncology (ICD-O-3) codes: hepatocellular carcinoma (8170-8175); cholangiocarcinoma (8050, 8140-8141, 8160-8161, 8260, 8440, 8480-8500, 8570-8572); other specified histology (8010-8035, 8970, 9120-9133, 9161, 8800-8811, 8830, 8840-8921, 8990-8991, 9040-9044, 9150, 9170, 9540-9581).



Supplementary Figure 1. Distribution of liver cancer subtypes as a percentage of total liver cancer cases by sex and world region, alternative scenario 1: reallocate unspecified cases to Hepatocellular Carcinoma (HCC), intrahepatic Cholangiocarcinoma (iCCA) and other specified histology.



Supplementary Figure 2. Distribution of liver cancer subtypes as a percentage of total liver cancer cases by sex and world region, alternative scenario 2: Use of microscopically verified cases only. HCC, Hepatocellular Carcinoma; iCCA, intrahepatic Cholangiocarcinoma.



Supplementary Figure 3. Regional distribution of world total population and estimated liver cancer cases by histological subtype in 2018 as the percentage of world total cases per subtype. HCC, hepatocellular carcinoma; iCCA, intrahepatic cholangiocarcinoma.

Chapter 5

International trends in oesophageal squamous cell carcinoma and adenocarcinoma incidence

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Rumgay H
Arnold M
Laversanne M
Whiteman DC
Thrift AP
Wei W
Lemmens VEPP
Soerjomataram I

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ABSTRACT

Introduction: We aimed to improve our understanding of the epidemiology of squamous cell carcinoma and adenocarcinoma of the esophagus.

Methods: We estimated average annual percent change and analyzed age-period-cohort trends on population-based cancer data.

Results: We found decreases in squamous cell carcinoma incidence in half of male populations (largest decrease in US black males [average annual percent change −7.6]) and increases in adenocarcinoma incidence in nearly a third of populations. Trends may be associated with a mix of birth cohort and period effects.

Discussion: More complete data and evidence are needed to conclude the reasons for the observed trends.

INTRODUCTION

In 2018, esophageal cancer was the seventh most common cancer globally and the sixth most common cause of cancer death.[1] Around 75% of the global burden of new cases and deaths from esophageal cancer occurs in Eastern and South Central Asia.[1] Squamous cell carcinoma (SCC) and adenocarcinoma (AC) are the 2 most common histological subtypes of esophageal cancer, with SCC being the most commonly diagnosed subtype globally (84% of total esophageal cancer were SCC vs 15% AC).[2] Yet, studies have reported that in many highly developed countries, incidence rates of AC have surpassed those of SCC and are predicted to increase further.[3] By assessing recent trends and generational effects of esophageal SCC and AC incidence internationally, we aimed to improve our understanding of the epidemiology of the 2 subtypes to provide perspective on the current burden.

METHODS

New cases of invasive esophageal cancer by calendar year, sex, 5-year age group, and histological subtype (SCC, AC, other, unspecified) were obtained from the *Cancer Incidence in Five Continents Plus* database for the years 1975–2012.[4] We included a total of 70 of 104 registries in 28 populations (detailed data source and methods provided in Supplementary Materials). The populations included are presented in Supplementary Table 1 with the average annual population size, cases of each subtype, proportion of total esophageal cancer, age-standardized incidence rate (ASR), and male-to-female ASR ratio for 2008–2012.

We calculated average annual percent change (AAPC) in ASRs (per 100,000) and corresponding 95% confidence intervals (95% CIs) for the 10 most recent years of data using Joinpoint regression.[5] We assessed long-term trends by birth cohort and period of diagnosis.[6] Because of the low number of cases among females, age-period-cohort modeling was restricted to male populations. Six male populations are presented here, and the remaining male populations are presented in Supplementary Figure 1.

RESULTS

Over the most recent 10 years (2003–2012), we found significant decreases in SCC incidence in half (14) of the male populations analyzed (Table 1). The largest decreases were found in US black males (AAPC −7.6, 95% CI −9.6 to −5.6, 2003–2012), followed by India (AAPC −6.2, 95% CI −9.4 to −2.8, 2003–2012) and Turkey (AAPC −5.1, 95% CI −7.7 to −2.3, 2003–2012). Males in Lithuania and Japan experienced a significant increase in SCC incidence (AAPC 2.5, 95% CI 0.8–4.2, 2003–2012 [Lithuania], AAPC 2.4, 95% CI 1.8–3.0,

2001–2010 [Japan]). Among females, SCC incidence trends showed significant decreases in fewer populations (US black, India, China, Canada, and England) and significant increases in more populations (Czechia, Japan, and Spain) than in males (Table 1).

We observed significant increases in AC incidence in 8 male populations (Table 1). The largest increases were found among males in Germany (AAPC 7.9, 95% CI 5.2–10.6, 2003–2012), Japan (AAPC 6.4, 95% CI 1.7–11.2, 2001–2010), and Czechia (AAPC 4.3, 95% CI 2.3–6.3, 2003–2012). We observed smaller increases in Norway, Canada, the Netherlands, England, and Australia. Significant increases in female AC incidence were observed in similar populations as in males (Canada, Czechia, Germany, England, and the Netherlands), as well as Austria, France, and Northern Ireland. Significant decreases in AC were observed among females in China and Slovakia.

In long-term trend analysis, we observed generational decreases in SCC incidence in male populations in North America, Northern, Southern and Western Europe, and Oceania (see Supplementary Figure 1a). A decline was observed as early as cohorts born in 1905 in US whites and born after 1920 in US blacks. In Japan, SCC rates increased over time in older age groups with a period effect observed around 2003 in males aged 55 years and older; but a decrease was observed around 1998 in males younger than 50 years. A mix of cohort and period effects were observed in the remaining male populations (see Supplementary Figure 1a).

We observed increases in AC incidence across birth cohorts in males in North America, Northern and Western Europe, and Oceania (see Supplementary Figure 1b). These increases attenuated in men aged 50 years and older in the US white population from around 2000, and in Australia from around 2005, suggestive of a period effect in these age groups. Birth cohort and period effect analysis did not show distinct patterns in populations with few cases of AC or shorter duration of data availability (see Supplementary Figure 1b).

Table 1 Average Annual Percent Change Trends With 95% CIs (UCI and LCI)

	Males						Females					
	Adenocarcinoma			Squamous cell carcinoma			Adenocarcinoma			Squamous cell carcinoma		
Population	AAPC (%)	LCI (%)	UCI (%)	AAPC (%)	LCI (%)	UCI (%)	AAPC (%)	LCI (%)	UCI (%)	AAPC (%)	LCI (%)	UCI (%)
North America												
Canada	**3.4**	**2.5**	**4.2**	**-1.1**	**-2.1**	**-0.2**	**4.2**	**1.6**	**6.8**	**-2.0**	**-3.7**	**-0.3**
US black	4.3	-0.7	9.7	**-7.6**	**-9.6**	**-5.6**	1.7	-12.8	18.6	**-6.7**	**-10.5**	**-2.7**
US white	0.5	-0.6	1.6	**-2.5**	**-3.6**	**-1.4**	1.1	-0.5	2.8	-2.1	-4.9	0.8
Eastern Asia												
China	-3.6	-8.6	1.7	0.3	-1.7	2.3	**-6.0**	**-11.1**	**-0.6**	**-4.1**	**-6.8**	**-1.3**
Japan	**6.4**	**1.7**	**11.2**	**2.4**	**1.8**	**3.0**	4.0	-5.2	14.2	**5.0**	**3.6**	**6.5**
Republic of Korea	-1.3	-5.5	3.1	-0.2	-1.4	0.9	-3.5	-19.8	16.2	0.0	-3.2	3.3
South-Central and Western Asia												
India	-0.6	-6.0	5.1	**-6.2**	**-9.4**	**-2.8**	1.8	-15.3	22.4	**-4.8**	**-6.7**	**-2.9**
Turkey	3.4	-2.8	10.1	**-5.1**	**-7.7**	**-2.3**	-5.0	-26.8	23.2	-1.2	-4.8	2.4
Central and Eastern Europe												
Czechia	**4.3**	**2.3**	**6.3**	0.2	-1.7	2.2	**7.0**	**1.0**	**13.4**	**6.5**	**1.7**	**11.5**
Slovakia	1.4	-3.6	6.7	0.7	-1.5	3.0	**-6.5**	**-12.5**	**-0.1**	2.3	-5.3	10.5
Northern Europe												
Denmark	3.6	-0.5	7.8	1.6	-1.1	4.3	4.1	-1.8	10.3	0.9	-0.9	2.6
Ireland	1.2	-1.2	3.7	-1.7	-4.3	1.0	1.0	-1.5	3.5	-1.3	-3.3	0.8
Lithuania	-1.8	-8.8	5.8	**2.5**	**0.8**	**4.2**	-	-	-	3.0	-4.2	10.6
Norway	**3.9**	**1.7**	**6.2**	-1.4	-4.5	1.8	2.1	-4.9	9.7	0.9	-2.8	4.7
UK - England	**2.0**	**1.0**	**3.0**	**-0.9**	**-1.4**	**-0.4**	**2.4**	**1.4**	**3.4**	**-1.1**	**-1.6**	**-0.6**
UK - Northern Ireland	2.4	-0.6	5.4	1.5	-2.3	5.4	**4.9**	**1.3**	**8.6**	-	-	-
UK - Scotland	0.9	-0.3	2.1	**-2.9**	**-4.4**	**-1.4**	0.3	-1.8	2.4	-1.4	-3.3	0.6
Southern Europe												
Croatia	2.7	-0.8	6.3	**-4.9**	**-6.7**	**-3.0**	-	-	-	-2.6	-8.4	3.5
Italy	2.8	-2.0	7.8	**-4.8**	**-7.0**	**-2.5**	-0.3	-5.5	5.3	-1.6	-5.2	2.1
Slovenia	-0.1	-4.7	4.8	**-3.5**	**-6.0**	**-1.0**	-	-	-	-0.7	-6.4	5.3
Spain	1.5	-1.8	4.9	**-3.5**	**-4.9**	**-2.1**	3.6	-0.5	7.9	**4.2**	**1.1**	**7.4**
Western Europe												
Austria	0.1	-2.7	2.9	-1.6	-5.2	2.2	**4.3**	**0.0**	**8.7**	0.9	-4.0	6.0
France	2.6	-0.3	5.6	**-3.9**	**-4.9**	**-2.8**	**6.2**	**0.2**	**12.6**	1.2	-2.1	4.6
Germany	**7.9**	**5.2**	**10.6**	-1.1	-3.9	1.8	**15.5**	**7.8**	**23.7**	-1.4	-6.7	4.3
Netherlands	**3.3**	**2.6**	**4.1**	-0.3	-1.4	0.7	**4.6**	**2.9**	**6.2**	0.1	-1.6	1.8
Switzerland	-0.8	-4.3	2.9	**-3.5**	**-5.6**	**-1.3**	5.2	-0.8	11.5	-0.9	-5.9	4.3
Oceania												
Australia	**1.7**	**0.6**	**2.9**	**-1.8**	**-3.1**	**-0.5**	0.7	-2.0	3.6	-2.7	-7.1	1.8
New Zealand	0.2	-1.1	1.5	-0.2	-4.7	4.5	-1.0	-7.0	5.3	-0.4	-4.1	3.4

AAPC, Average Annual Percent Change; LCI, Lower Confidence Interval; UCI, Upper Confidence Interval; US, United States of America; UK, United Kingdom

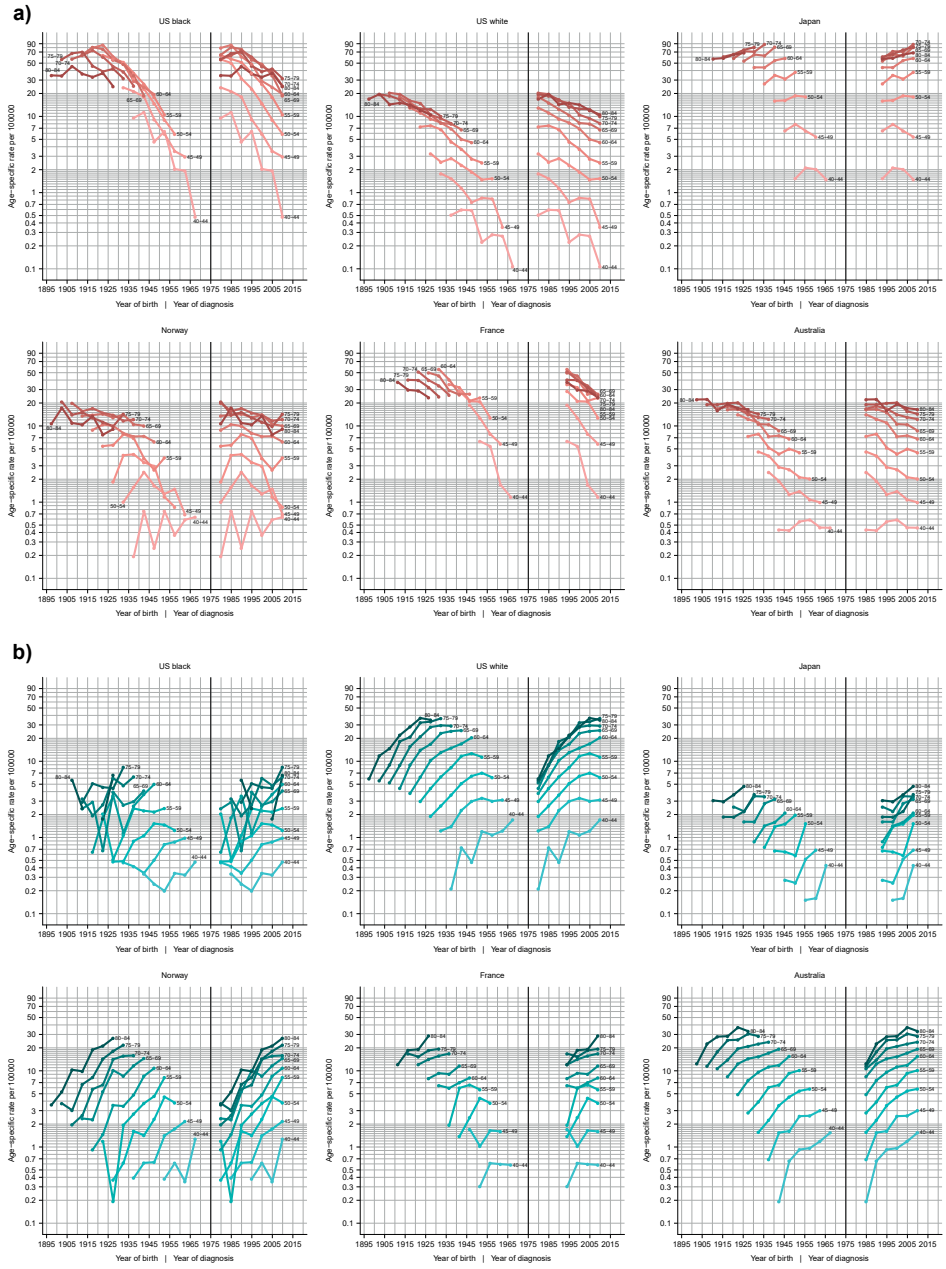

Figure 1 Age-specific incidence rates of esophageal squamous cell carcinoma (a) and adenocarcinoma (b) by year of birth (cohort) and year of diagnosis (period) for men in 6 populations. Rates are displayed on a semilog plot.

DISCUSSION

We observed significant declines in esophageal SCC incidence rates over the most recent decade in several world regions. AC incidence rates increased significantly in nearly a third of populations studied. Long-term trends in SCC and AC incidence may be associated with a mix of birth cohort and period effects.

US black males experienced the largest decline in recent SCC rates, yet SCC incidence remains higher in US black males than US white males. Brown et al.[7,8] estimated that 92% of the excess SCC incidence in US blacks compared with whites could be attributed to tobacco smoking and heavy alcohol use; they also suggested that US blacks may have a higher genetic susceptibility to alcohol-associated esophageal SCC. Further research is needed to understand the complex links between alcohol, ethnicity, and the influence of socioeconomic status on observed disparities.

Previous studies suggest that the increases observed in SCC incidence in Japan were induced by a considerable rise in alcohol consumption in the Japanese population.[9,10] We did not find similar recent increases and cohort effects in SCC incidence in China despite recorded increases in alcohol use.[11] When pooled, the registries in this study only covered 0.7% of the total population in China and thus may not be nationally representative. Trend analysis by subtype should be explored using high-quality cancer incidence data covering a considerably larger part of the population, especially considering China holds approximately half of the global burden of esophageal cancer.[1]

There is some debate around the reasons behind the observed increases in esophageal AC: Increases in the prevalence of AC risk factors such as gastroesophageal reflux disease and Barrett's esophagus in the presence of abdominal obesity have been paralleled by a reduction of *Helicobacter pylori* prevalence over time.[12–14] Nevertheless, we found a strong male predominance for esophageal AC in all populations; thus, additional studies on the potential impact of risk-reduction interventions in high-risk individuals, e.g., men with high waist circumference, are warranted.

The strengths of our study include use of high-quality data from population-based cancer registries to ensure comparability and validity. Because of missing information on tumor histology, many available cancer registries were excluded from this study. We acknowledge that the inclusion criteria for this study still allow a large proportion of unspecified cases which may impact changes in the recorded specificity of esophageal SCC and AC classification over time. Interpretation of SCC and AC trends should be performed with caution in the relevant populations.

Furthermore, there is a notable lack of sufficient incidence trend data from Asian, African, and South American countries where many of the highest rates of esophageal SCC incidence are found (2). A number of risk factors other than tobacco and alcohol are also at play in the "esophageal cancer belt" in Asia and the "East African corridor".[15,16] Improved data

availability in these parts of the world would be invaluable to gain a more complete picture of the global epidemiology of esophageal cancer.

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SUPPLEMENTARY MATERIALS

Detailed data source and methods

Data source

New cases of invasive esophageal cancer (International Statistical Classification of Diseases and Related Health Problems, 10th revision [ICD-10]: C15) by calendar year, sex, five-year age group and histological subtype were extracted from the *Cancer Incidence in Five Continents Plus* (CI5plus) database of population-based cancer registry data.[1] Cases were categorized into four histology groups according to the International Classification of Diseases for Oncology, Third edition (ICD-O-3), morphology codes: SCC (8050-8078, 8083-8084); AC (8140-8141, 8143-8145, 8190-8231, 8260-8265, 8310, 8401, 8480-8490, 8550-8552, 8570-8574, 8576); sarcoma, other specified carcinoma, other specified malignant neoplasm and unspecified carcinoma (8010-8011,8800-8811, 8830, 8840-8921, 8990-8991, 9040-9044, 9120-9133, 9150, 9540-9581); and unspecified malignant neoplasm (8000-8005).

Population-based cancer registries with 15 or more consecutive years of data were included, and multiple subnational cancer registries in the same countries were aggregated to obtain a national proxy. We excluded countries with population coverage of less than 500,000 people, countries which recorded less than five cases of either SCC or AC annually, countries with more than 30% of esophageal cancer cases assigned unspecified histology unless more than 90% of the remaining cases were specified as either SCC or AC per year in the most recent 10 years. Using these criteria, we included a total of 70 out of 104 registries to examine incidence patterns in 28 populations in 27 countries; we kept United States (US) blacks and whites as separate populations, as well as the nations in the United Kingdom (England, Northern Ireland and Scotland [no data for Wales]). Esophageal cancer incidence in these populations is presented in Supplementary Table 1 for years 2003-2012.

Statistical analysis

Age-standardized incidence rates (ASR) per 100,000 person-years were calculated by sex and subtype for all ages combined using the 1960 Segi–Doll world standard population.[2] Male to female (M:F) incidence rate ratios were calculated using sex-specific ASRs. We calculated average annual percent change (AAPC) and corresponding 95% confidence intervals (95% CI) for the 10 most recent years of data using Joinpoint regression.[3] This approach uses the Monte Carlo Permutation to test for a significant change in trend; AAPC was calculated as the weighted average of the annual percent changes from the joinpoint model of the time period selected. The minimum and maximum numbers of joinpoints were set to 0 and 3, respectively.

We assessed long-term trends by birth cohorts, which indicate changes in the prevalence of exposure to risk factors across successive generations, and by period of diagnosis, an indicator

of changes linked to diagnostic methods or classification of disease that influence multiple age groups at a point in time.[4] Birth cohorts were obtained by subtracting the midpoint of the five-year age-group from the midpoint of the five-year period of diagnosis, assuming incidence rates were constant within five-year age groups. Data management and plotting were carried out using the *Rcan*[5] package in R version 3.5.1.[6]

Supplementary Table 1. Average annual population, cases, proportion of total cases, age-standardized incidence rate and male to female rate ratio (M:F) by population and esophageal cancer subtype 2003-2012.

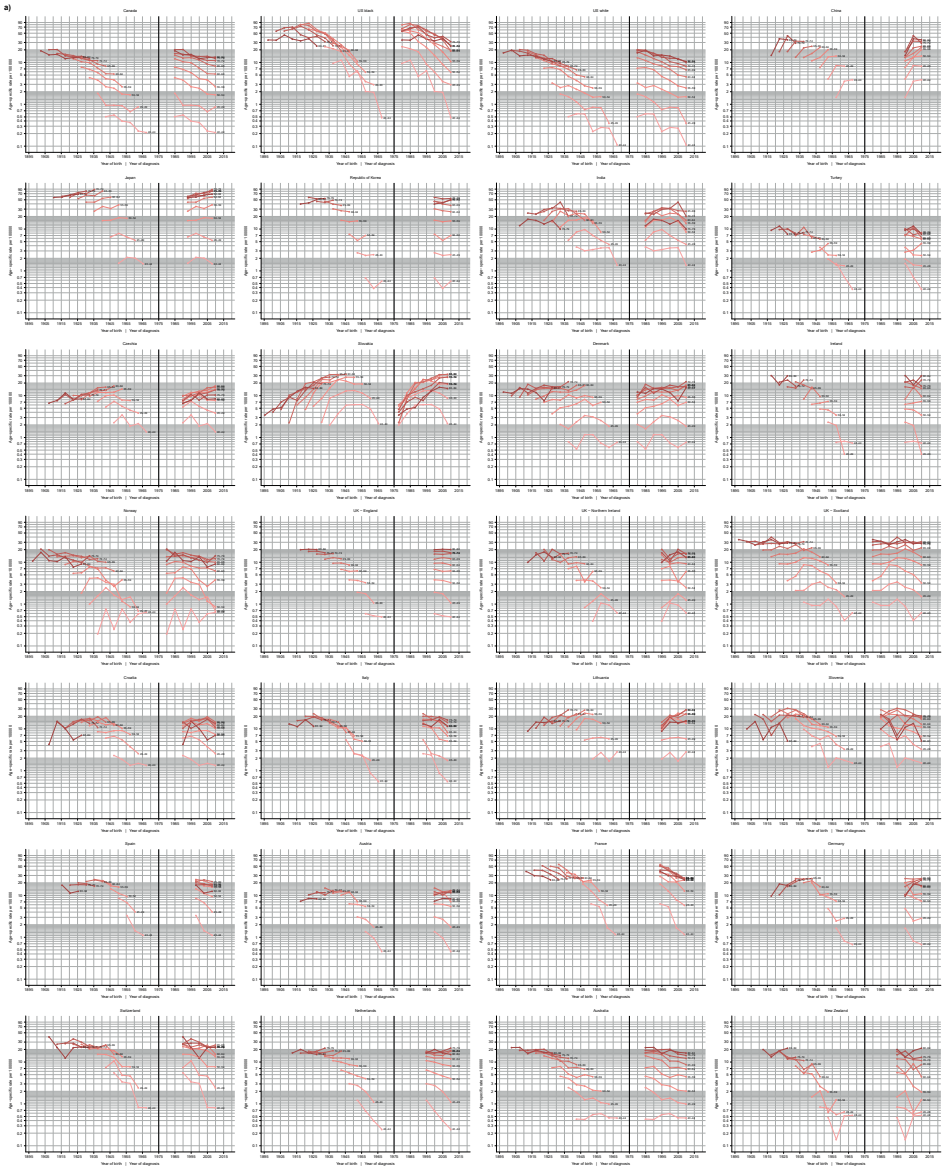
					Adenocarcinoma				Squamous cell carcinoma				Other specified				Unspecified			
Population	**Year from**	**Year to**	**N. Years**	**Population (millions)**	**Cases**	**Proportion of total cases (%)**	**ASR**	**M:F**	**Cases**	**Proportion of total cases (%)**	**ASR**	**M:F**	**Cases**	**Proportion of total cases (%)**	**ASR**	**M:F**	**Cases**	**Proportion of total cases (%)**	**ASR**	**M:F**
North America																				
Canada*	1983	2012	30	25.3	705	55%	1.7	7.0	418	33%	0.9	2.0	89	7%	0.2	3.3	61	5%	0.1	2.5
US black*	1978	2012	35	3.6	17	11%	0.4	4.3	100	65%	2.6	2.7	27	18%	0.7	1.7	9	6%	0.2	2.5
US white*	1978	2012	35	21.1	739	54%	2.1	7.9	280	21%	0.8	2.0	252	18%	0.7	3.8	92	7%	0.2	2.9
Eastern Asia																				
China*	1998	2012	15	9.0	35	4%	0.2	4.0	497	59%	3.0	5.4	14	2%	0.1	4.2	295	35%	1.5	3.7
Japan*	1988	2010	23	12.7	71	4%	0.3	8.7	1537	78%	5.6	6.3	71	4%	0.2	4.8	299	15%	0.9	6.2
Republic of Korea*	1998	2012	15	17.8	22	3%	0.1	6.1	547	86%	2.5	15.4	21	3%	0.1	7.4	49	8%	0.2	6.8
South-Central and Western Asia																				
India*	1983	2012	30	4.6	14	6%	0.3	2.4	153	65%	3.6	1.6	15	7%	0.4	1.4	54	23%	1.3	1.6
Turkey	1998	2012	15	5.6	18	17%	0.3	4.1	69	66%	1.1	1.3	6	6%	0.1	2.6	11	11%	0.2	1.3
Central and Eastern Europe																				
Czechia	1988	2012	25	10.4	181	33%	1.0	9.1	275	50%	1.6	5.7	34	6%	0.2	6.3	54	10%	0.3	4.6
Slovakia	1971	2010	40	5.4	33	11%	0.4	7.9	221	77%	3.0	13.2	10	4%	0.1	12.2	24	8%	0.3	6.6
Northern Europe																				
Denmark	1953	2012	60	5.5	201	46%	1.8	5.2	192	44%	1.9	2.1	30	7%	0.3	3.0	16	4%	0.1	2.9
Ireland	1994	2012	19	4.4	175	48%	2.7	4.9	147	40%	2.3	1.2	22	6%	0.3	2.2	20	5%	0.2	1.8

Lithuania	1993	2012	20	3.3	17	9%	0.3	7.7	109	59%	2.1	12.5	5	3%	0.1	9.8	54	29%	1.0	6.9
Norway	1953	2012	60	4.8	110	52%	1.3	5.5	80	37%	0.9	2.3	15	7%	0.2	2.8	8	4%	0.1	2.5
UK - England*	1995	2012	18	51.6	3734	56%	3.6	5.2	1978	30%	1.9	1.1	769	12%	0.6	2.2	190	3%	0.1	2.0
UK - Northern Ireland	1993	2012	20	1.8	97	54%	3.3	4.5	54	30%	1.7	1.3	13	7%	0.4	2.4	15	9%	0.4	3.2
UK - Scotland	1978	2012	35	5.2	452	53%	4.2	4.7	302	36%	2.8	1.3	64	7%	0.5	2.0	30	4%	0.2	2.3
Southern Europe																				
Croatia	1988	2012	25	4.4	26	12%	0.3	9.2	112	51%	1.5	9.0	17	8%	0.2	7.1	66	30%	0.7	5.0
Italy*	1991	2010	20	4.9	53	22%	0.5	7.3	142	60%	1.4	4.0	14	6%	0.1	3.5	28	12%	0.2	3.0
Slovenia	1983	2012	30	2.0	14	16%	0.4	10.7	61	70%	1.7	6.4	6	6%	0.2	3.3	7	8%	0.1	5.3
Spain*	1993	2010	18	8.6	106	24%	0.7	8.4	273	63%	2.1	7.4	24	6%	0.2	8.9	29	7%	0.2	4.8
Western Europe																				
Austria	1998	2012	15	8.3	118	30%	0.8	7.2	178	45%	1.3	4.7	43	11%	0.3	6.1	55	14%	0.3	4.2
France (Metropolitan)*	1988	2011	24	5.8	114	26%	1.0	8.1	284	65%	3.0	5.2	24	6%	0.2	5.2	13	3%	0.1	5.0
Germany*	1998	2012	15	2.8	85	34%	1.5	6.1	117	47%	2.2	3.2	41	17%	0.7	3.3	4	2%	0.1	8.1
Switzerland*	1988	2012	25	1.8	48	35%	1.4	7.4	78	57%	2.5	2.7	7	5%	0.2	5.3	5	4%	0.1	4.1
The Netherlands	1989	2012	24	16.5	1097	62%	3.6	5.6	558	31%	1.9	1.7	97	5%	0.3	2.6	24	1%	0.1	2.5
Oceania																				
Australia*	1983	2012	30	16.8	514	50%	1.8	6.6	395	38%	1.3	1.5	73	7%	0.2	2.5	53	5%	0.1	1.9
New Zealand	1983	2012	30	4.2	137	51%	1.9	6.3	91	34%	1.2	1.1	16	6%	0.2	1.8	27	10%	0.3	3.0

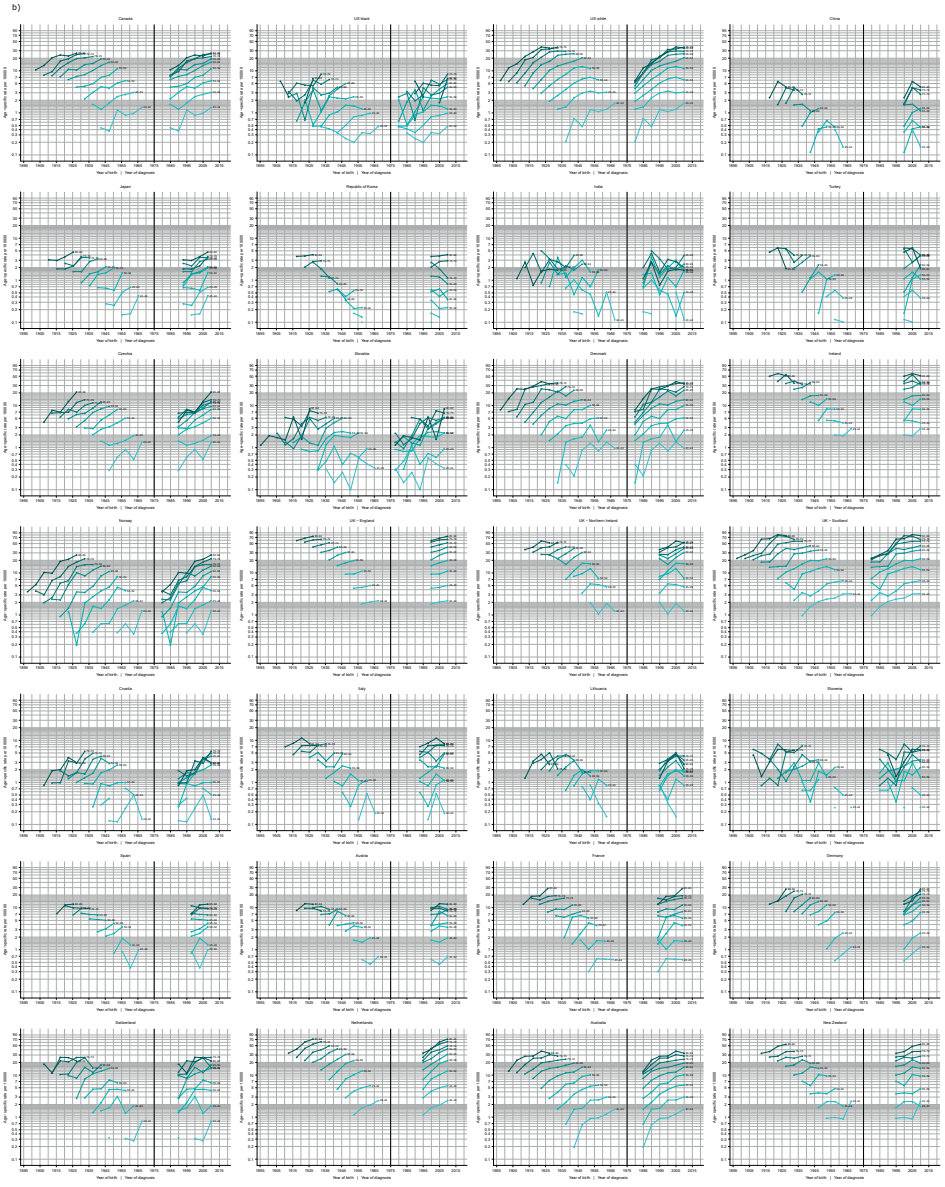
* Country-level aggregates compiled from the following regional registries: Canada - Alberta, British Columbia, Manitoba, New Brunswick, Newfoundland and Labrador, Northwest Territories, Nova Scotia, Ontario, Prince Edward Island, Saskatchewan; US - Georgia, Greater California, Idaho, Kentucky, Louisiana, Massachusetts, New York, Utah, Wisconsin (SEER-9); China - Harbin, Jiashan, Shanghai, Zhongshan; Japan - Miyagi, Nagasaki, Osaka; Republic of Korea - Busan, Gwangju, Incheon, Seoul; India - Chennai; UK - England - East Midlands, East of England, London, North East, North West, South East, South West, West Midlands, Yorkshire; Italy - Modena, Parma, Ragusa, Romagna, Veneto; Spain - Albacete, Basque Country, Canary-Islands, Cuenca, Girona, Granada, Murcia, Navarra, Tarragona; France - Bas-Rhin, Calvados, Doubs, Haut-Rhin, Herault, Isere, Somme; Germany - Hamburg, Saarland; Switzerland - Geneva, Neuchatel, St Gall-Appenzell, Vaud; Australia - New South Wales Australian Capital Territory, South Australia, Tasmania, Victoria, Western Australia

US, United States of America; UK, United Kingdom; ASR, Age-standardised rate; M:F, Male to Female ratio of ASR

A)


a)
Canada
US black
US white
China
Japan
Republic of Korea
India
Turkey
Czechia
Slovakia
Denmark
Ireland
Norway
UK – England
UK – Northern Ireland
UK – Scotland
Croatia
Italy
Lithuania
Slovenia
Spain
Austria
France
Germany
Switzerland
Netherlands
Australia
New Zealand

B)



Supplementary Figure 1. Age-specific incidence rates of esophageal squamous cell carcinoma (A) and adenocarcinoma (B) by year of birth (cohort) and year of diagnosis (period) for men in all 28 populations. Rates are displayed on a semi-log plot.

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3

Estimating the proportion of cancer cases due to alcohol and other modifiable risk factors globally and in the United Kingdom

Chapter 9

Global burden of cancer in 2020 attributable to alcohol consumption: a population-based study

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Global burden of cancer in 2020 attributable to alcohol consumption: a population-based study.

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SUMMARY

Background: Alcohol use is causally linked to multiple cancers. We present global, regional, and national estimates of alcohol-attributable cancer burden in 2020 to inform alcohol policy and cancer control across different settings globally.

Methods: In this population-based study, population attributable fractions (PAFs) calculated using a theoretical minimum-risk exposure of lifetime abstention and 2010 alcohol consumption estimates from the Global Information System on Alcohol and Health (assuming a 10-year latency period between alcohol consumption and cancer diagnosis), combined with corresponding relative risk estimates from systematic literature reviews as part of the WCRF Continuous Update Project, were applied to cancer incidence data from GLOBOCAN 2020 to estimate new cancer cases attributable to alcohol. We also calculated the contribution of moderate (<20 g per day), risky (20–60 g per day), and heavy (>60 g per day) drinking to the total alcohol-attributable cancer burden, as well as the contribution by 10 g per day increment (up to a maximum of 150 g). 95% uncertainty intervals (UIs) were estimated using a Monte Carlo-like approach.

Findings: Globally, an estimated 741,300 (95% UI 558,500–951,200), or 4.1% (3.1–5.3), of all new cases of cancer in 2020 were attributable to alcohol consumption. Males accounted for 568,700 (76.7%; 95% UI 422,500–731,100) of total alcohol-attributable cancer cases, and cancers of the oesophagus (189,700 cases [110,900–274,600]), liver (154,700 cases [43,700–281,500]), and breast (98,300 cases [68,200–130,500]) contributed the most cases. PAFs were lowest in northern Africa (0.3% [95% UI 0.1–3.3]) and western Asia (0.7% [0.5–1.2]), and highest in eastern Asia (5.7% [3.6–7.9]) and central and eastern Europe (5.6% [4.6–6.6]). The largest burden of alcohol-attributable cancers was represented by heavy drinking (346,400 [46.7%; 95% UI 227,900–489,400] cases) and risky drinking (291,800 [39.4%; 227,700–333,100] cases), whereas moderate drinking contributed 103,100 (13.9%; 82,600–207,200) cases, and drinking up to 10 g per day contributed 41,300 (35,400–145,800) cases.

Interpretation: Our findings highlight the need for effective policy and interventions to increase awareness of cancer risks associated with alcohol use and decrease overall alcohol consumption to prevent the burden of alcohol-attributable cancers.

Funding: None.

INTRODUCTION

Alcohol use is associated with a vast range of injuries and diseases, including cancer, and is a leading risk factor for the global burden of disease.[1,2] The consumption of alcoholic beverages is causally linked to cancers of the upper aerodigestive tract (oral cavity, pharynx, larynx, and oesophagus) and cancers of the colon, rectum, liver, and female breast.[3] Together, these cancers contributed 6.3 million cases and 3.3 million deaths globally in 2020 (data from the GLOBOCAN 2020 database).

Previous estimates of the contribution of alcohol to the burden of cancer have been published,[2,4,5] but patterns of alcohol consumption continue to change over time across world regions.[6] Alcohol consumption per capita has decreased in many European countries, especially those in eastern Europe, whereas alcohol use is on the rise in Asian countries, such as China, India, and Vietnam, and in many countries in sub-Saharan Africa.[6] With these changes in alcohol consumption and more recent cancer incidence data, new estimates of the alcohol-attributable burden of cancer are warranted. We updated previous global estimates by using cancer incidence for 2020, recent relative risk estimates from the scientific literature, and alcohol consumption figures from multiple sources to calculate alcohol-attributable cancer burden. We also quantified the contribution of moderate, risky, and heavy drinking to the total burden of alcohol-attributable cancers. The overall and sex-specific world-level, regional-level, and country-level results from our study can be used to inform alcohol policy and cancer control across different settings globally.

METHODS

Study design and data sources

In this population-based study, we used the most recent International Agency for Research on Cancer (IARC) monograph on personal habits to select cancer types with sufficient evidence of a causal relationship with the consumption of alcoholic beverages (Supplementary Table 1).[3] Country-specific estimates of incident cancer cases were extracted from the GLOBOCAN 2020 database for lip and oral cavity cancer, pharyngeal cancer, oesophageal cancer, colon cancer, rectal cancer, liver cancer, laryngeal cancer, breast cancer (female only), and all cancers combined, excluding non-melanoma skin cancer (defined using International Classification of Diseases, tenth revision; Supplemental methods). Due to the specific causality with hepatocellular carcinoma and oesophageal squamous cell carcinoma, estimates of these cancers were obtained from two studies that have estimated the distributions of the histological subtypes of liver and oesophageal cancer using cancer registry data[7] (hepatocellular carcinoma estimates: Rumgay H, unpublished). Hepatocellular carcinoma and oesophageal squamous cell carcinoma were defined according to International Classification

of Diseases for Oncology (third edition; Supplemental methods). We included cancers of the stomach and pancreas in sensitivity analysis due to evidence suggesting a causal association with alcohol consumption in World Cancer Research Fund (WCRF) classifications, but an absence of sufficient evidence in the IARC monograph classification (Supplementary Table 1).[3,8] In our aim to quantify the burden of avoidable cancers, we did not include the potential reduction in kidney cancer incidence despite probable evidence of a protective effect from alcohol intake of up to 30 g per day.[8] Details on the cancer site selection and incidence estimates are shown in the Supplemental methods.

Relative risk estimates for current drinking were obtained from the systematic literature reviews done as part of the WCRF Continuous Update Project (Supplemental methods, Supplementary Table 2).[8] Former drinking, defined as lifetime alcohol use but not in the past 12 months, was included in sensitivity analysis using sex-specific relative risks from multiple sources, as detailed in the Supplemental methods and Supplementary Table 2.

Assuming a 10-year latency period between exposure and cancer diagnosis (Supplemental methods), alcohol consumption estimates for 2010 were obtained from the Global Information System on Alcohol and Health as adult per capita alcohol consumption in litres of alcohol per year by country disaggregated by age (15–19, 20–24, 25–34, 35–49, 50–64, and 65 years and older) and sex.[9]

We then converted the alcohol consumption estimates to grams of alcohol per day. To minimise the effect of bias in reporting of alcohol use, the per capita alcohol consumption data (ie, population-level alcohol exposure data) were derived from multiple sources: recorded, unrecorded, and tourist per capita alcohol consumption. Details on the sources of the alcohol consumption data and the methods to estimate the distribution of population alcohol use are summarised in the Supplemental methods.

Statistical analysis

We calculated the effect of alcohol consumption on the incidence of cancer worldwide in 2020 using a Levin-based population attributable fraction (PAF) method[10] adapted from Shield and colleagues[5] and based on a theoretical minimum-risk exposure of lifetime abstention from alcohol consumption (Supplemental methods). We calculated PAFs for each age, sex, country, and cancer site by combining the age-specific, sex-specific, and country-specific prevalence of current drinking (P_{CD}) with the cancer relative risks of current drinking (RR_{CD}) using the following formula:

$$\mathrm{PAF} = \frac{\int_{0.1}^{150} P_{CD}(x)(\mathrm{RR}_{CD}(x) - 1)\mathrm{d}x}{\int_{0.1}^{150} P_{CD}(x)(\mathrm{RR}_{CD}(x) - 1)\mathrm{d}x + 1}$$

Amount of alcohol consumed for current drinking (x) was modelled with an upper integration limit of 150 g per day. We modelled the contribution of different levels of alcohol

consumption by splitting alcohol prevalence into three categories: moderate drinking (<20 g per day, the equivalent of up to two alcoholic drinks per day), risky drinking (20–60 g per day, the equivalent of between two and six alcoholic drinks per day), and heavy drinking (>60 g per day, the equivalent of more than six alcoholic drinks per day). We also stratified alcohol consumption by 10 g per day increments from less than 10 g per day to 140–150 g per day. Details on the estimation of PAF by drinking category and former drinking are included in the Supplemental methods.

Using the age-specific PAFs for each country, sex, and cancer site, we derived the number of cancer cases attributable to alcohol consumption for each country, sex, and cancer site (Supplemental methods). Alcohol-attributable age-standardised incidence rates per 100,000 people were calculated using the age-specific, sex-specific, and country-specific number of alcohol-attributable cases. Countries were categorised into 17 world regions based on UN definitions. Alcohol PAFs for ten countries with missing alcohol prevalence data were imputed using the average age-specific, sex-specific, and cancer-specific PAFs from each world region in which they were located. World region totals were subsequently recalculated including the imputed estimates of alcohol-attributable cases. We also grouped countries into the Human Development Index categories using the UN Development Programme human development data for 2019. More details on the country groupings are described in the Supplemental methods.

Estimates of uncertainty were modelled using a Monte Carlo-like approach where 1,000 estimates of the drinking status, mean, and SD of the alcohol consumption estimates and relative risks were randomly simulated based on their respective uncertainty distributions (Supplemental methods). The 2.5th and 97.5th percentiles were taken from the 1,000 modelled PAF estimates to construct the 95% uncertainty intervals (UIs). All analyses were carried out using R (version 3.6.1).

Role of the funding source

There was no funding source for this study.

RESULTS

Globally, an estimated 741,300 (95% UI 558,500–951,200; PAF 4.1% [3.1–5.3]) of all new cases of cancer in 2020 were attributable to alcohol consumption. In males, there were 568,700 (76.7%; 95% UI 422,500–731,100; PAF 6.1% [4.6–7.9]) alcohol-attributable cancer cases, and in females there were 172,600 (23.3%; 135,900–220,100; 2.0% [1.6–2.5]) alcohol-attributable cancer cases (table). The global age-standardised incidence rate was 8.4 (95% UI 6.2–10.9) alcohol-attributable cancer cases per 100,000 people: 13.4 (10.0–17.4) cases per 100,000 males and 3.7 (2.7–5.0) cancer cases per 100,000 females. The cancers with the

Table. Global number of alcohol-attributable cancer cases, population attributable fraction, and age-standardised incidence rate of alcohol-attributable cases in 2020, by cancer site and sex

	Males			Females			Total		
	Alcohol-attributable cases	**Population attributable fraction**	**Age-standardised incidence rate per 100 000 males**	**Alcohol-attributable cases**	**Population attributable fraction**	**Age-standardised incidence rate per 100 000 females**	**Alcohol-attributable cases**	**Population attributable fraction**	**Age-standardised incidence rate per 100 000 people**
Lip and oral cavity cancer (C00–C06)	66,700 (40,000–105,300)	25.9% (15.6%–40.9%)	1.6 (0.9–2.5)	8,200 (4,600–14,300)	7.3% (4.1%–12.7%)	0.2 (0.1–0.3)	74,900 (44,600–119,600)	20.2% (12.1%–32.3%)	0.9 (0.5–1.4)
Pharyngeal cancer (C09–C10, C12–C13)	37,000 (15,200–63,400)	25.3% (10.4%–43.4%)	1.8 (0.7–3.1)	2,500 (940–4,400)	7.4% (2.8%–13.4%)	0.1 (0.0–0.2)	39,400 (16,100–67,800)	22.0% (9.0%–37.8%)	0.5 (0.4–1.6)
Oesophageal cancer (C15)*	163,100 (94,200–231,000)	39.2% (22.7%–55.6%)	3.9 (2.2–5.5)	26,600 (16,700–43,700)	14.3% (9.0%–23.5%)	0.6 (0.4–0.9)	189,700 (110,900–274,600)	31.6% (18.4%–45.7%)	2.1 (1.3–3.1)
Colon cancer (C18)	76,900 (57,700–95,400)	13.0% (9.7%–16.1%)	1.8 (1.3–2.2)	14,600 (10,600–19,100)	2.7% (1.9%–3.5%)	0.3 (0.2–0.4)	91,500 (68,300–114,500)	8.1% (6.0%–10.1%)	1.0 (0.7–1.2)
Rectal cancer (C19–C20)	57,300 (42,700–71,800)	13.0% (9.7%–16.3%)	1.4 (1.0–1.7)	7,800 (5,800–10,300)	2.7% (2.0%–3.6%)	0.2 (0.1–0.2)	65,100 (48,500–82,000)	9.0% (6.7%–11.3%)	0.7 (0.5–0.9)
Liver cancer (C22)†	141,300 (39,600–255,000)	22.7% (6.4%–40.9%)	3.3 (0.9–6.0)	13,400 (4,100–26,400)	5.0% (1.5%–9.8%)	0.3 (0.1–0.5)	154,700 (43,700–281,500)	17.3% (4.9%–31.6%)	1.7 (0.5–3.2)

Laryngeal cancer (C32)	26,400 (15,100–41,600)	16.6% (9.5%–26.1%)	0.6 (0.4–1.0)	1,200 (620–1,700)	4.7% (2.5%–7.0%)	0.0 (0.0–0.0)	27,600 (15,700–43,300)	15.0% (8.6%–23.6%)	0.3 (0.2–0.5)
Breast cancer (C50)	..	..	..	98,300 (68,200–130,500)	4.4% (3.0%–5.8%)	2.2 (1.3–3.2)	98,300 (68,200–130,500)	4.4% (3.0%–5.8%)	1.1 (0.7–1.6)
All sites excluding non-melanoma skin cancer (C00–C97 excluding C44)	568,700 (422,500–731,100)	6.1% (4.6%–7.9%)	13.4 (10.0–17.4)	172,600 (135,900–220,100)	2.0% (1.6%–2.5%)	3.7 (2.7–5.0)	741,300 (558,500–951,200)	4.1% (3.1%–5.3%)	8.4 (6.2–10.9)

Data in parentheses are 95% uncertainty intervals. Cancer types were defined according to International Classification of Diseases (tenth revision; ICD-10) and International Classification of Diseases for Oncology (third edition; ICD-O-3).

* Alcohol-attributable cases of oesophageal cancer calculated as estimates of squamous cell carcinoma (ICD-10 code C15; ICD-O-3 codes 8050–8078, 8083–8084); the population attributable fraction is of all oesophageal cancer cases (ICD-10 code C15). † Alcohol-attributable cases of liver cancer calculated as estimates of hepatocellular carcinoma (ICD-10 code C22; ICD-O-3 code, 8170–8175); the population attributable fraction is of all liver cancer cases (ICD-10 code C22).

highest PAFs were cancers of the oesophagus (31.6% [95% UI 18.4–45.7]), pharynx (22.0% [9.0–37.8]), and lip and oral cavity (20.2% [12.1–32.3]), with considerable differences by sex; for example, 39.2% (22.7–55.6) of oesophageal cancers in males were attributable to alcohol, compared with 14.3% (9.0–23.5) in females. The cancer sites that contributed the most attributable cases were cancers of the oesophagus (189,700 cases [95% UI 110,900–274,600]), liver (154,700 cases [43,700–281,500]), and breast (98,300 cases [68,200–130,500]; table). For distribution of cancer sites according to world region, see Supplementary Figure 5.

The highest PAFs of all new cases of cancer were observed in Mongolia, China, Moldova, and Romania, which are reflected at the regional level where eastern Asia and central and eastern Europe had the highest PAFs (5.7% [95% UI 3.6–7.9] and 5.6% [4.6–6.6], respectively; Supplementary Tables 3 and 4); we found the lowest PAFs in northern African (0.3% [0.1–3.3]) and western Asian (0.7% [0.5–1.2]) countries, including Kuwait, Libya, and Saudi Arabia (Supplementary Table 4). The national and regional patterns in males were similar to the average for both sexes combined, with the largest PAFs found in eastern Asia and central and eastern Europe (Figure 1, Figure 2; Supplementary Table 3). Among females, the largest PAFs were found in central and eastern Europe—driven by the highest national PAFs in females in Belarus, Moldova, Romania, and Russia—as well as in Australia and New Zealand and western Europe (Figure 1, Figure 3; Supplementary Tables 3 and 4). For all country-specific estimates, see Supplementary Table 4.

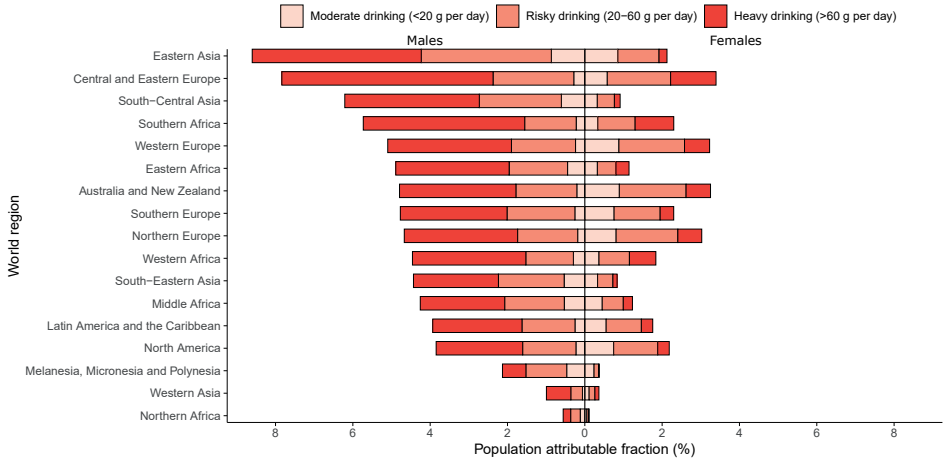

Figure 1. Population attributable fractions, by alcohol consumption category, sex, and world region

The global and regional patterns of age-standardised incidence rates differed slightly to those of the PAFs: at the national level, many central and eastern European countries, including Moldova, Slovakia, and Romania, had the highest age-standardised incidence rates in males, which is reflected in the region having the highest age-standardised incidence rate

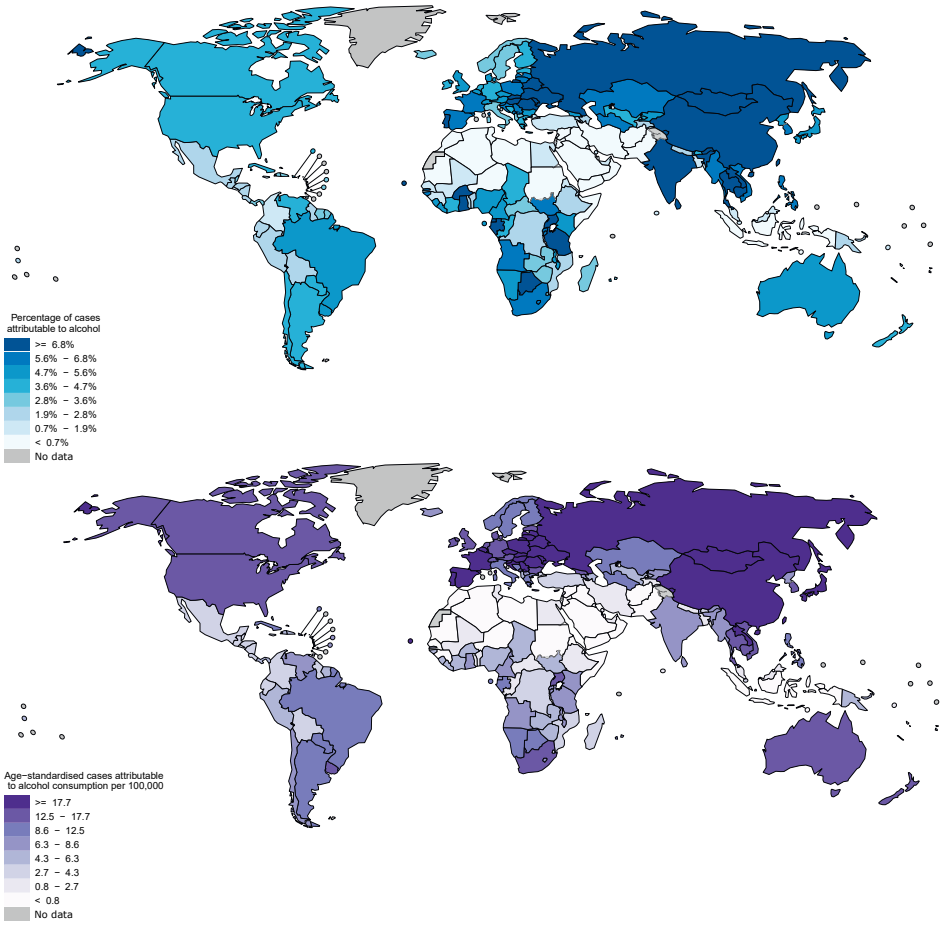

Figure 2. Population attributable fraction and age-standardised incidence rate of alcohol-attributable cancer cases in males in 2020, by country

(23.1 [95% UI 19.0–26.6] per 100,000 males; Figure 2; Supplementary Tables 3 and 4); the next highest regional age-standardised incidence rates were found in eastern Asia (21.5 [13.4–29.6] per 100,000 males), followed by western Europe (17.3 [13.8–20.4] per 100,000 males) and Australia and New Zealand (17.0 [12.7–20.7] per 100,000 males; Supplementary Table 3). Among females, the highest national-level age-standardised incidence rates were in northern and western European countries, including Belgium, France, and Ireland (Figure 3; Supplementary Table 4), but at the regional level, the age-standardised incidence rate was highest in females in Australia and New Zealand (10.2 [95% UI 6.3–15.2] per 100,000 females), followed by western Europe (9.4 [6.2–12.8] per 100,000 females) and northern Europe (9.1 [5.9–12.8] per 100,000 females; Supplementary Table 3). In every world region, the age-standardised incidence rate was higher in males than in females; the smallest relative

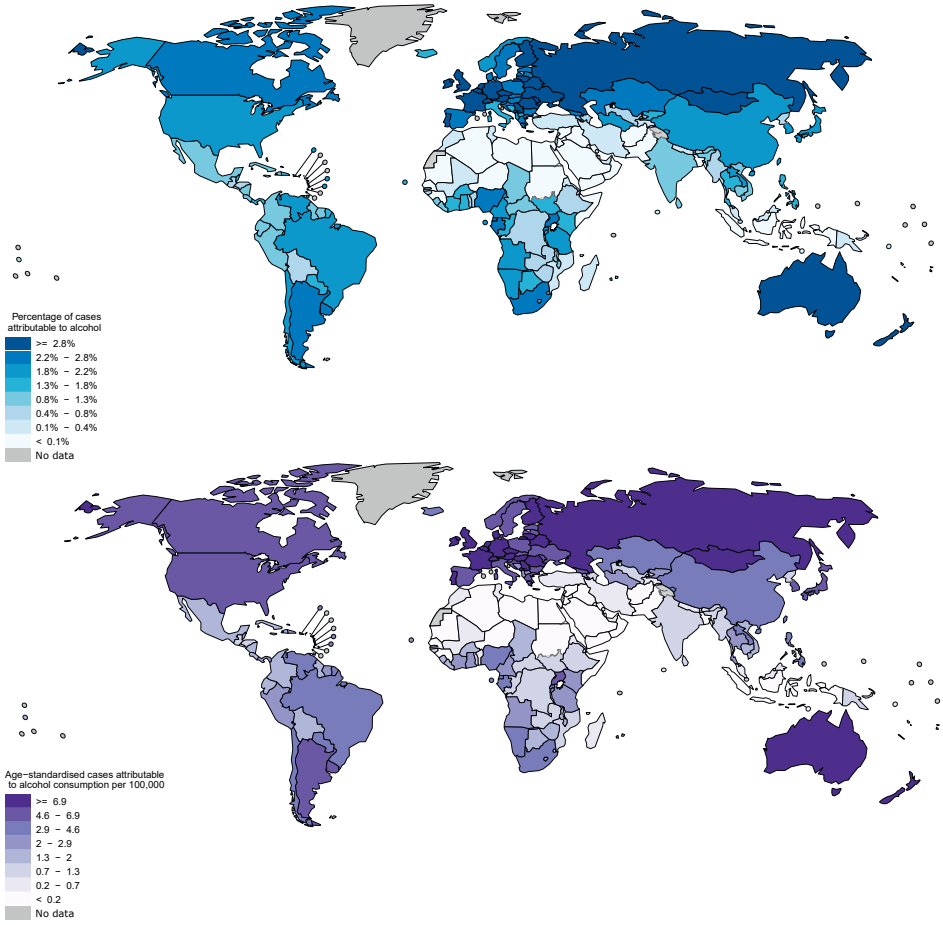

Figure 3. Population attributable fraction and age-standardised incidence rate of alcohol-attributable cancer cases in females in 2020, by country

differences between males and females were found in Australia and New Zealand, northern Europe, and western Europe (male-to-female ratios 1.7, 1.7, and 1.8, respectively), whereas the largest relative differences were observed in south-central and southeastern Asia, where males had a 5.6–6.8 times higher rate than females.

Of 741,300 cases, when separated into drinking categories, moderate drinking (<20 g per day) contributed 103,100 (13.9%; 95% UI 82,600–207,200) cases of alcohol-attributable cancer, risky drinking (20–60 g per day) contributed 291,800 (39.4%; 227,700–333,100) cases, and heavy drinking (>60 g per day) contributed 346,400 cases (46.7%; 227,900–489,400; Supplementary Table 5). The proportion of cases of cancer attributable to heavy drinking in males was highest in the following regions: southern Africa (2,100 [72.9%] of 2,800) and central and eastern Europe (34,800 [69.7%] of 49,900); in females, it was highest

in the following regions: southern Africa (590 [43.4%] of 1,400) and western Africa (990 [37.2%] of 2,700; Figure 1; Supplementary Table 5). For regional estimates by consumption category, see Supplementary Table 5. After further stratifying alcohol consumption into 10 g per day increments, drinking up to 10 g per day contributed 41,300 (95% UI 35,400–145,800) alcohol-attributable cancer cases: 16,700 (14,300–75,400) cases were found in males and 24,600 (21,100–70,400) in females (16,700 [2.9%] of 568,700 and 24,600 [14.3%] of 172,600 alcohol-attributable cases among males and females, respectively), although the highest frequencies of alcohol-attributable cancers were in males drinking from 30 to less than 40 g per day and 40 to less than 50 g per day and in females drinking from 10 to less than 20 g per day and 20 to less than 30 g per day (Figure 4; Supplementary Table 6).

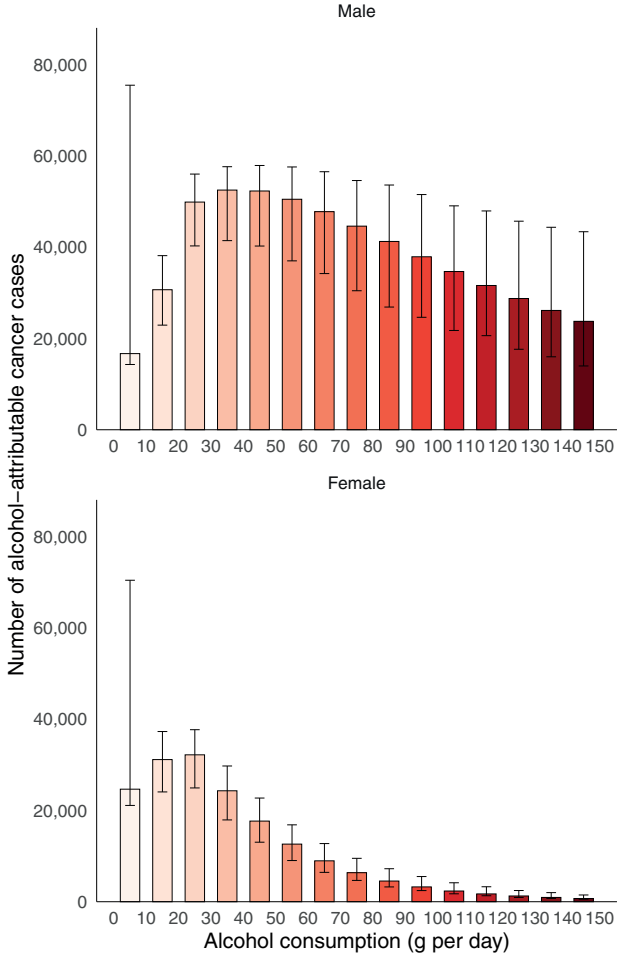

Figure 4. Global number of alcohol-attributable cancer cases, by 10 g per day increase in alcohol consumption and sex

In a sensitivity analysis, when stomach and pancreatic cancers were included, the total alcohol-attributable cases reached 808,700 (95% UI 616,300–1,034,800; PAF 4.5% [3.4–5.8]; age-standardised incidence rate 9.1 [6.8–11.8]) from 50,000 (13,200–95,900; PAF 10.1% [2.7–19.4], age-standardised incidence rate 0.5 [0.1–1.0]) pancreatic cancer cases and 17,400 (810–36,900; PAF 1.6% [0.1–3.4], age-standardised incidence rate 0.2 [0.0–0.4]) stomach cancer cases (data not shown). Furthermore, sensitivity analysis, in which former drinking was included, added an additional 135,000 (95% UI 102,200–171,900) cases, which increased the total number of cases to 925,900 (705,900–1,187,500; 713,200 [543,600–910,400] in males and 212,700 [162,400–277,100] in females), the world total PAF to 5.2% (3.9–6.6; males 7.7% [5.9–9.8], females 2.4% [1.9–3.2]), and the age-standardised incidence rate to 10.3 (7.7–13.4) cases per 100,000 people (16.7 [12.7–21.4] per 100,000 males, 4.5 [3.2–6.1] per 100,000 females; data not shown).

DISCUSSION

Globally, about 741,000, or 4.1%, of all new cases of cancer in 2020 were attributable to alcohol consumption. About three-quarters of alcohol-attributable cancer cases were in males, and the cancer sites contributing the most attributable cases were oesophageal, liver, and breast (in females). PAFs were lowest in northern Africa and western Asia in both sexes, and highest among males in eastern Asia and central and eastern Europe, and among females in central and eastern Europe, Australia and New Zealand, and western Europe. Risky and heavy drinking contributed most to the burden of alcohol-attributable cancers; however, moderate drinking still contributed one in seven alcohol-attributable cases and more than 100,000 cancer cases worldwide.

Our estimated global PAF was lower than the previous global estimates of 5.5% of cancer cases in 2012,[4] 4.8% of cancer deaths in 2016,[5] and 4.9% of cancer deaths in 2019.[2] This difference could be due to genuine decreases in consumption of alcohol in several world regions, such as in southern Europe and central and eastern Europe, as Shield and colleagues reported a 5.5% decrease in the global alcohol-attributable age-standardised rate of death from cancer between 2000 and 2016.[5] Furthermore, there were differences in the numbers of included cancer sites; in all previous studies,[2, 4, 5] total liver cancer was used, whereas in the current study we used hepatocellular carcinoma-specific incidence, which represents 80% of total primary liver cancers (Rumgay H, unpublished). Praud and colleagues also included pancreatic and gallbladder cancers in their main analysis, accounting for about 40,000 alcohol-attributable cases.[4] Shield and colleagues incorporated former drinking into their main analysis,[5] and inclusion of former drinking in our sensitivity analysis resulted in a more similar PAF. One of the major differences, however, is that the previous studies estimated cancer mortality attributable to alcohol, whereas our study covered cancer

incidence only. The previous studies assumed that the increased risk from drinking alcohol was the same for both cancer incidence and mortality and that the latency period between alcohol exposure and cancer mortality did not change. For breast cancer and colorectal cancer, which have much lower mortality rates than incidence in many populations, the burden of alcohol-attributable deaths was much lower than alcohol-attributable cases in the study by Praud and colleagues.[4] Despite differences in the relative risks used and source of alcohol consumption data, our country-specific estimates were consistent with those of previous national studies, including those done in Chile, the UK, and the USA.[11, 12, 13] Due to the consistent methodology and data sources used in our study, we consider our results to provide the most comparable estimates between countries and world regions.

There are several biological pathways by which the consumption of alcohol, as ethanol, can lead to cancer development, including DNA, protein, and lipid alterations or damage by acetaldehyde, the carcinogenic metabolite of ethanol;[14] oxidative stress;[15] and alterations to the regulation of hormones such as oestrogens and androgens.[16] Ethanol might also promote cancer development indirectly by acting as a solvent for other carcinogenic agents such as chemicals in tobacco.[17] Evidence shows that humans who carry the aldehyde dehydrogenase-2*2 (*ALDH2*2*) variant allele of ALDH2—the main enzyme that metabolises acetaldehyde—have a substantially increased risk for development of cancers of the upper aerodigestive tract.[18]

It is estimated that between 28% and 45% of eastern Asian populations are carriers of the *ALDH2*2* polymorphism;[18] therefore, a proportion of the alcohol-associated cancers in eastern Asian populations in our study could be due to the increased risk from this genetic variant. However, it is thought that some self-selection takes place whereby people who are slow metabolisers of acetaldehyde experience a flushing reaction that might be unpleasant for the individual and they might prefer to avoid drinking alcohol;[18] this hypothesis is in contrast with the observed increase in alcohol use in a number of eastern Asian populations.[6]

Consistent with patterns of alcohol per capita consumption, PAFs were lowest in countries such as Saudi Arabia and Kuwait, where religious-based policies have ensured that population alcohol consumption remains low and lifetime abstention rates remain high.[6] On the other end of the spectrum, alcohol consumption in central and eastern Europe has historically outranked that of other world regions, but has decreased in recent years,[6] whereas increases in alcohol consumption, linked with countries' economic development, are projected in Asian countries such as China and India. With regard to the effect of social and economic development, increases in alcohol consumption in women have been reported as women have taken on a larger share of paid employment.[6] This finding is clearly reflected in countries highly indexed in development, where we saw the highest burden of alcohol-attributable cancers in women and the most similar male-to-female ratios of alcohol-attributable cancer rates; in these regions, breast cancer was the main driver of the high alcohol-attributable cancer incidence rates among women. Global changes in alcohol drinking patterns by region and

sex alongside demographic changes and a growing cancer burden might mark an increase in alcohol-attributable cases in several world regions,[19] such as eastern and south-central Asia, which should be countered by comprehensive national cancer control plans that cover cancer prevention.

There is low awareness of the link between alcohol and cancer risk among the general public, but adding cancer warnings to alcohol labels, similar to those used on tobacco products, might deter people from purchasing alcohol products and increase awareness of the causal link with cancer,[20] which could then confer increased public support for alcohol policies.[21] WHO developed its list of so-called best buys for tackling non-communicable diseases, and for alcohol these involve policies to increase taxation, limit purchasing availability, and reduce marketing of alcohol brands to the public;[22] yet their effective implementation relies on enforcement and regulation—processes that are not always available in low-income or middle-income settings. In such settings, there is also a scarcity of research into effective alcohol policies: for example, in the sub-Saharan African regions where heavy drinking had the largest contribution to alcohol-attributable cases, only 16 of 46 countries have national or subnational alcohol strategies.[23] A good understanding of the local context is essential for successful policy implementation and is paramount in reducing the alcohol-attributable burden of cancer.

We believe that the main results of our study are conservative estimates; we only included cancer sites with sufficient evidence of a causal link according to the most recent IARC monograph.[3] We also only considered current drinking in our main analysis, with inclusion of former drinking in the sensitivity analysis. Other strengths of our study include the use of meta-analyses of risk estimates from cohort studies of the highest quality, and the specific model used to estimate alcohol prevalence, which corrects for under-reporting of alcohol consumption in survey data using population data on per capita consumption of alcohol, as described by Shield and colleagues.[5] However, this method of adjustment does not account for differential degrees of under-reporting by age and sex, and changes in alcohol consumption before and after 2010, and it does not address survey biases that lead to an under estimation of the prevalence of former drinkers. Furthermore, variations in the quality of data on per capita consumption of alcohol and surveys exist between countries. In particular, data from countries with a high volume of unrecorded alcohol consumption and data from countries that do not have high-quality nationally representative surveys are more susceptible to biases.

Another limitation of our study is that we did not consider the synergistic effect between alcohol and tobacco, which is reported as a true interaction for most upper aerodigestive tract cancers. It is possible that some alcohol-attributable cases in our study could have been caused by tobacco due to residual confounding in the current and former drinking relative risks used. Similarly, a proportion of alcohol-attributable liver cancers could be the result of synergism with hepatitis B or hepatitis C virus infection or aflatoxin exposure. This could

have been the case in Mongolia, where hepatitis B and hepatitis C viruses were estimated to have caused around 44% and 46% of liver cancer cases, respectively, in 2012.[24] Another cofactor that we did not consider was obesity, despite some evidence of an interaction between alcohol and obesity on liver disease and risk of hepatocellular carcinoma.[25] Along with alcohol, the cofactors discussed are associated with social inequalities both between and within countries, and the determinants of these inequalities should be explored further to understand the observed disparities. In addition, by not using population-specific relative risks, we might have underestimated the alcohol-attributable cancer burden in populations in which a higher risk is observed, such as in people with a history of cancer, and in eastern Asian populations carrying the *ALDH2*2* allele. Furthermore, high-quality prospective aetiological studies in low-income and middle-income settings are scarce, so differences in risk are still largely unknown. High-quality estimates of risk in different populations and ethnicities would further define the true global picture of the alcohol-attributable burden of cancer.

It is also important to consider the impact of the global COVID-19 pandemic when estimating health outcomes for the year 2020.[26] The cancer incidence estimates for 2020 used in our study do not account for changes in the reporting of cancer due to disruptions caused by health system closures and the concerns of individuals, among other reasons. One study in the Netherlands reported a 27% decrease in cancer diagnoses in the early phase of the pandemic response, with some evidence of this returning to pre-pandemic rates.[27] The COVID-19 pandemic could have also affected individuals' total consumption of alcohol, as shown by a reported increase in the proportion of the UK population binge drinking or drinking four or more times a week observed during national lockdowns in the UK.[28] However, any changes in drinking patterns among individuals are not yet evident for current cancer rates, but could be reflected in the next decades.

In summary, we found that alcohol use causes a substantial burden of cancer, a burden that could potentially be avoided through cost-effective policy and interventions to increase awareness of the risk of alcohol and decrease overall alcohol consumption. General population strategies, such as WHO's best buys, include a reduction of availability, an increase in price via taxation, and a ban on marketing, and are most effective for an outcome such as alcohol-attributable cancer, where even lower levels of drinking can increase the risk of cancer.[22] With increases in alcohol consumption predicted until at least 2030 in several world regions, action must be taken to reduce the avoidable burden of cancer attributable to alcohol.

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SUPPLEMENTARY MATERIALS

Supplemental methods

Study design

In this population-based study we calculated the impact of alcohol consumption on the incidence of cancer worldwide in 2020 using a Levin-based population attributable fraction (PAF) method[1] adapted from Shield et al. 2020[2], and based on a theoretical minimum-risk exposure of lifetime abstention from alcohol consumption. PAFs were estimated by combining data on alcohol consumption and the relative risk (RR) of developing cancer. Due to a delay between alcohol consumption and possible development of cancer, it is necessary to factor in a latency period between the year of alcohol exposure data and the year of cancer outcome. A 10-year latency period between exposure and cancer diagnosis was chosen based on an observed approximate latency period of 11 to 12 years for breast, colorectal, oral cavity, oesophageal (squamous cell carcinoma) and pharyngeal cancers and 8 to 9 years for laryngeal and liver cancers in a previous Canadian study,[3] and has been used in other PAF studies.[2,4]

Selection of cancer sites and national incidence estimates

The selection of cancers included in this study was based on the most recent International Agency for Research on Cancer (IARC) monograph on personal habits for cancer types with sufficient evidence of a causal relationship with the consumption of alcoholic beverages (Supplementary Table 1).[5] The underlying cancer incidence estimates were taken from the GLOBOCAN 2020 database which models global burden of primary cancers based on data from several sources;[6] high-quality cancer registry data, new sources in sub-Saharan Africa retrieved through the African Cancer Registry Network, targeted searches for new registry data online, and the most recent mortality data from the WHO.[7] For countries where high-quality population-based cancer registry data were lacking, complex methods incorporating other data sources such as national mortality records and averages from neighbouring countries were used.

Country-specific estimates of cancer cases for 2020 by sex and five-year age group (from 0–4 to 85 years of age and over) were obtained for: lip and oral cavity cancer (International Statistical Classification of Diseases and Related Health Problems, 10th revision [ICD-10] C00-06); pharyngeal cancer (C09-10, C12-C13); oesophageal cancer (C15); colon cancer (C18); rectal cancer (C19-20); liver cancer (C22); laryngeal cancer (C32); breast cancer (C50, only female); and all cancers combined excluding non-melanoma skin cancer (C00-C97 excl. C44). Due to the specific causality with hepatocellular carcinoma (HCC) and oesophageal squamous cell carcinoma (SCC), estimates of HCC (International Classification of Diseases for Oncology, 3rd edition [ICD-O-3] morphology codes 8170-8175) and oesophageal SCC (ICD-O-3 8050-8078, 8083-8084) were obtained from two studies that have estimated

cases based on observed distributions of the histological subtypes of liver and oesophageal cancer using cancer registry data (liver cancer results: Rumgay H, unpublished).[8] We included cancers of the stomach (C16) and pancreas (C25) in sensitivity analysis due to evidence suggesting a causal association with alcohol consumption in World Cancer Research Fund (WCRF) classifications but a lack of sufficient evidence in the IARC monograph classification (Supplementary Table 1).[5,9] In our aim to quantify the burden of avoidable cancers we did not include the potential reduction in kidney cancer incidence despite probable evidence of a protective effect from alcohol intake of up to 30 g/day.[9]

Cancer risks related to alcohol consumption

For each cancer type included we took risk estimates for the association with alcohol consumption (measured per 10 grams increase in alcohol [as ethanol] consumed per day) from the systematic literature reviews conducted as part of the WCRF Continuous Update Project (Supplementary Table 2).[9] To obtain the HCC-specific risk estimate we conducted a random-effects meta-analysis selecting the RRs from studies with HCC as the outcome which were presented in the liver cancer systematic literature review (Supplementary Figure 1).[10] The variance of the linear RRs was calculated from their 95% confidence intervals. Due to the presence of a non-linear dose-response curve for oesophageal SCC, the RR function and variance-covariance matrix for oesophageal SCC risk were taken from Shield et al.,[2] originally obtained from Bagnardi et al. 2015.[11] The risks of colon and rectum cancers were modelled for alcohol consumption above 20 g per day based on the non-linear dose-response curve showing no significant increased risk of colorectal cancer at less than 20 g per day in the WCRF Continuous Update Project systematic review for colorectal cancer.[12] Similarly, the risks of pancreatic cancer and stomach cancer were modelled for alcohol consumption above 45 g per day only due to the decision made by WCRF that conclusions below this intake were not possible.[9] Former drinking was included in sensitivity analysis using sex-specific RRs from the WCRF Continuous Update Project report[10] for liver cancer, Schütze et al.[13] for colon and rectal cancer, Marron et al.[14] for upper aerodigestive cancers, and Corrao et al.[15] for pancreas and stomach cancers, as previously described by Shield and colleagues.[2]

In terms of cancer risk by type of alcoholic beverage, there is little-to-no observed difference in the risk of cancer between consumption of beers, wines or spirits.[9] With regards to differences by drinking patterns and the potential effect of heavy episodic drinking or binge drinking on cancer risk, it is believed that it is the total average intake of alcohol which is most at play with no difference whether this is spread over several occasions or consumed all at once.[16] Further on drinking patterns, the risk of cancer may vary by changes in patterns of drinking over the life-course, or alcohol consumption trajectory, in individuals; a cohort study in Thailand with more than 30 years of follow-up observed double the cancer mortality in those who were consistent-regular drinkers throughout their life compared with consistent-occasional drinkers,[17] but the risk of cancer among former heavy drinkers was not

discussed. Cancer risk among former drinkers may vary by intensity and duration of past drinking. In our analysis we were not able to distinguish these discrepancies in the alcohol consumption data, although there is evidence that the elevated risk of head and neck cancer in former drinkers reduces back to that of lifetime abstainers after 20 years of quitting.[14]

Global prevalence of alcohol consumption

Alcohol consumption estimates for 2010 were obtained from the Global Information System on Alcohol and Health as adult per capita alcohol consumption in litres of alcohol per year by country disaggregated by age (15–19, 20–24, 25–34, 35–49, 50–64, and 65 years of age and older) and sex.[18] The per capita alcohol consumption data, i.e. population level alcohol exposure data, were derived from three sources: recorded, unrecorded, and tourist per capita alcohol consumption. Recorded per capita data were based on production, sales, and taxation statistics;[19] unrecorded per capita data were based on population surveys and expert opinion (measured through Delphi analysis);[20] and tourist per capita data were derived based on data from the World Tourism Organization. Per capita alcohol consumption estimates were corrected by a factor of 0.8 to take into account alcohol not consumed (wastage) and the under-reporting of alcohol consumption from population-based surveys being larger than that in risk relations studies;[21] this correction factor of 0.8 was found to be appropriate by a recent systematic review of coverage of per capita alcohol consumption recorded in population surveys compared with that recorded in risk relations studies.[22]

The distribution of daily adult alcohol consumption among past year drinkers was estimated using the methodology developed by Rehm and colleagues,[23] and Kehoe and colleagues,[24] whereby alcohol consumption distributions can be modelled using a Gamma distribution. This method assumes that there is a strong correlation between the mean and the standard deviation of the Gamma distribution where the standard deviation of the Gamma distribution for alcohol consumption can be accurately estimated based on the mean of the Gamma distribution. We then estimated the scale and the shape parameter from the mean (μ) and the standard deviation (σ) of the Gamma distribution using Formula 1.

Formula 1

$$\sigma = (1.171 + 0.087 * sex) * \mu$$

In Formula 1, the coefficient of sex is 1 for women and 0 for men.

Estimation of population attributable fraction

PAFs were calculated for each age, sex, country, and cancer site by combining the age-, sex- and country-specific prevalence of current drinking (P_{CD}) with the cancer RRs (RR). Amount of alcohol consumed for current drinking (χ) was modelled with an upper integration limit of 150 g per day based on the observation that intakes greater than 150 g of alcohol per day are not sustained for a long period of time.[25] We modelled the contribution of

different levels of alcohol consumption by splitting alcohol prevalence into three categories: moderate drinking (0.1 to 20 g per day, the equivalent of up to two alcoholic drinks per day), risky drinking (20 to 60 g per day, the equivalent of between two and six alcoholic drinks per day), and heavy drinking (>60 g per day, the equivalent more than six alcoholic drinks per day). We also split alcohol consumption by 10g per day increment from 0.1 to 10 g per day up to 140 to 150 g per day. Formula 2 was used to calculate PAFs for total current drinking and Formula 3 was used to estimate PAFs by the three categories of alcohol consumption and by 10 g increment by changing the lower and upper integration limits in the numerator appropriately, where y is the lower bound of the category and z is the upper bound.

Formula 2

$$\mathrm{PAF} = \frac{\int_{0.1}^{150} P_{CD}(x)(\mathrm{RR}_{CD}(x) - 1)\mathrm{d}x}{\int_{0.1}^{150} P_{CD}(x)(\mathrm{RR}_{CD}(x) - 1)\mathrm{d}x + 1}$$

Formula 3

$$\mathrm{PAF}_{Category} = \frac{\int_{y}^{z} P_{CD}(x)(\mathrm{RR}_{CD}(x) - 1)\mathrm{d}x}{\int_{0.1}^{150} P_{CD}(x)(\mathrm{RR}_{CD}(x) - 1)\mathrm{d}x + 1}$$

Former alcohol consumers have an elevated risk of cancer based on their lifetime alcohol consumption.[9] However, the increase in cancer risk is thought to be heterogenous by country due to differences in alcohol consumption trajectories.[26] Accordingly, as country specific former drinker cancer risks are unknown, the elevated risk of cancer among former drinkers was not incorporated into the main analysis. As sensitivity analysis, the risk of cancer among former drinkers (P_{FD}) was calculated using Formula 4, and the PAF from current drinking and formerly drinking was subsequently re-calculated using Formula 5.

Formula 4

$$\mathrm{PAF}_{FD} = \frac{P_{FD}(\mathrm{RR}_{FD} - 1)}{P_{FD}(\mathrm{RR}_{FD} - 1) + \int_{0.1}^{150} P_{CD}(x)(\mathrm{RR}_{CD}(x) - 1)\mathrm{d}x + 1}$$

Formula 5

$$\mathrm{PAF}_{CD+FD} = \frac{P_{FD}(\mathrm{RR}_{FD} - 1) + \int_{0.1}^{150} P_{CD}(x)(\mathrm{RR}_{CD}(x) - 1)\mathrm{d}x}{P_{FD}(\mathrm{RR}_{FD} - 1) + \int_{0.1}^{150} P_{CD}(x)(\mathrm{RR}_{CD}(x) - 1)\mathrm{d}x + 1}$$

To obtain estimates of alcohol-attributable cases the age-specific PAFs for each country, sex, and cancer site were applied to the cases of cancer in each five-year age group while factoring in the 10-year latency period; e.g. the PAF for laryngeal cancer in males for the 25–34 age group was applied to the number of cases of laryngeal cancer in males in the 35–39 and 40–44 age groups in each country. The PAFs for each cancer site and sex were calculated by summing the alcohol-attributable cases across all age groups then dividing by the total number of cases for all age groups combined. The total number of liver cancer cases was used

as the denominator for the HCC calculations to obtain the PAF of total liver cancer, and the total number of oesophageal cancer cases was used as the denominator for the oesophageal SCC calculations.

Alcohol-attributable age-standardised incidence rates (ASIR) per 100,000 people were calculated using the age-, sex-, and country-specific number of alcohol-attributable cases in 2020, population estimates, and the Segi-Doll world standard.[6,27] Countries were categorised into 17 world regions based on the United Nations definitions: Australia and New Zealand, Central and Eastern Europe, Eastern Africa, Eastern Asia, Latin America and the Caribbean, Melanesia, Micronesia and Polynesia, Middle Africa, North America, Northern Africa, Northern Europe, South-Central Asia, South-Eastern Asia, Southern Africa, Southern Europe, Western Africa, Western Asia, and Western Europe. Alcohol PAFs for 10 countries with missing alcohol prevalence data (French Guiana, French Polynesia, the State of Palestine, Guadeloupe, Guam, Martinique, New Caledonia, Puerto Rico, Reunion, and South Sudan) were imputed using the average age-, sex- and cancer-specific PAFs from each prementioned subregion they are located in. Subregion totals were subsequently recalculated including the imputed estimates of alcohol-attributable cases. We also grouped countries into the Human Development Index categories using the UN Development Programme human development data for 2019 (UNDP http://www.hdr.undp.org/en/indicators/137506).

Estimates of uncertainty

Ninety five percent uncertainty intervals (95% UIs) were modelled using a Monte Carlo-like approach where 1,000 estimates of the drinking status, mean, and standard deviation of the alcohol consumption estimates and RRs were randomly simulated based on their respective uncertainty distributions. The methods explaining the creation of the variance and random samples of each parameter are further detailed by Gmel and colleagues.[28] These simulated estimates were used to create 1,000 PAF estimates using the formulae previously described. The 2.5th and 97.5th percentiles were taken from the 1,000 modelled PAF estimates to construct the 95% UIs.[29]

Supplementary Table 1. Summary of the classifications of evidence for a causal relationship between alcohol consumption and the risk of cancer by cancer site and organisation.

	Classification	
Cancer site	**International Agency for Research on Cancer[5]**	**World Cancer Research Fund (Continuous Update Project)[9]**
Oral cavity	Sufficient evidence	Convincing
Pharynx	Sufficient evidence	Convincing
Oesophagus	Sufficient evidence	-
Oesophagus - adenocarcinoma		Limited - no conclusion
Oesophagus - squamous cell carcinoma		Convincing
Colorectum	Sufficient evidence	Convincing*
Liver		Convincing**
Liver - hepatocellular carcinoma	Sufficient evidence	
Larynx	Sufficient evidence	Convincing
Breast (female)	Sufficient evidence	
Breast - pre-menopausal		Convincing
Breast - post-menopausal		Probable
Stomach		Probable**
Pancreas	Limited evidence	Limited - suggestive**

*WCRF conclusion for colorectal cancer was based on consumption above 30 g ethanol per day

**WCRF conclusions for liver, stomach and pancreatic cancers were based on consumption above 45 g ethanol per day

Supplementary Table 2. Relative risks and variance used for the alcohol-attributable fraction calculations

Linear dose-response per 10 g ethanol/day						
Cancer site	**RR**	**LCI**	**UCI**	**Variance**	**Notes**	**Source**
Oral cavity	1.15	1.09	1.22	0.002874315370003^2		WCRF 2016[30]
Pharynx	1.13	1.05	1.21	0.003618117230592^2		WCRF 2016[30]
Colon	1.07	1.05	1.08	0.000718644820579^2	Modelled above 20 g/day	WCRF 2017[12]
Rectum	1.07	1.05	1.08	0.000718644820579^2	Modelled above 20 g/day	WCRF 2017[12]
Liver - HCC	1.14	1.04	1.25	0.004691909136758^2		WCRF 2015[10]
Larynx	1.09	1.05	1.13	0.001873149708031^2		WCRF 2016[30]
Breast - pre-menopausal	1.04	1.01	1.08	0.001709456894973^2	Adjusted estimates only★	WCRF 2017[31]
Breast - post-menopausal	1.08	1.05	1.1	0.001186735092727^2	Adjusted estimates only★	WCRF 2017[31]
Pancreas	1.17	1.05	1.29	0.003500885275581^2	Modelled above 45 g/day	WCRF 2012[32]
Stomach	1.02	1.00	1.04	0.001000528396767^2	Modelled above 45 g/day	WCRF 2015[33]
Non-linear dose-response per 10 g ethanol/day						
Cancer site	**RR function**			**Variance-covariance matrix**		**Source**
Oesophagus - SCC	exp(ß1x + ß2x*ln(x))	ß1 = 0.05593	ß2 = -0.00789	0.00006500	-0.00001000	Shield 2018 (France),[34] originally from Bagnardi 2015[11]
				-0.00001000	0.00000264	
Former drinkers						
	Males		**Females**			**Source**
Cancer site	**RR**	**Variance**	**RR**	**Variance**		
Oral cavity	1.2	0.330343005747873^2	1.2	0.330343005747873^2		Shield 2020,[2] originally from Marron et al., 2010[14]

Supplementary Table 2. Relative risks and variance used for the alcohol-attributable fraction calculations (*continued*)

Pharynx	1.2	0.330343005747873^2	1.2	0.330343005747873^2	Shield 2020,[2] originally from Marron et al., 2010[14]
Larynx	1.18	0.288991189^2	1.18	0.288991189^2	Shield 2020,[2] originally from Marron et al., 2010[14]
Oesophagus	1.16	0.243480229040442^2	1.16	0.243480229040442^2	Shield 2020,[2] originally from Marron et al., 2010[14]
Colon	2.19	0.0465106^2	1.05	0.145968002587317^2	Shield 2020,[2] originally from Schütze et al., 2011[13]
Rectum	2.19	0.0465106^2	1.05	0.145968002587317^2	Shield 2020,[2] originally from Schütze et al., 2011[13]
Liver	2.23	0.259097757^2	2.68	0.272560609^2	WCRF 2015[10]
Breast	-	-	1	0	Shield 2020, originally from Schütze et al., 2011[13]
Pancreas	1.21	0.0465106^2	1.44	0.0585138^2	Corrao 2004[15]
Stomach	1.21	0.0465106^2	1.44	0.0585138^2	Corrao 2004[15]

*Only estimates which adjusted for age, BMI and reproductive factors

Supplementary Table 3. Global number of alcohol-attributable cancer cases, population attributable fraction, and age-standardised incidence rate of alcohol-attributable cases in 2020, by world region, Human Development Index, and sex

	Males			Females			Total		
World Region	Alcohol-attributable cases	PAF	ASIR per 100,000	Alcohol-attributable cases	PAF	ASIR per 100,000	Alcohol-attributable cases	PAF	ASIR per 100,000
Africa									
Eastern Africa	6,000	4.9%	5.9	2,300	1.1%	1.9	8,300	2.6%	3.8
	(4,200–7,900)	(3.4%–6.4%)	(4.0–7.8)	(1,700–3,100)	(0.8%–1.6%)	(1.3–2.7)	(5,800–11,100)	(1.8%–3.4%)	(2.6–5.1)
Middle Africa	1,900	4.3%	4.6	740	1.2%	1.6	2,600	2.5%	3.0
	(1,200–2,600)	(2.8%–5.8%)	(3.0–6.3)	(510–1,000)	(0.8%–1.7%)	(1.0–2.3)	(1,700–3,700)	(1.7%–3.5%)	(1.9–4.2)
Northern Africa	820	0.6%	0.8	180	0.1%	0.2	990	0.3%	0.5
	(350–9,500)	(0.2%–6.5%)	(0.3–12.8)	(80–370)	(0.0%–0.2%)	(0.1–0.4)	(420–9,800)	(0.1%–3.3%)	(0.2–6.4)
Southern Africa	2,800	5.7%	12.6	1,400	2.3%	4.4	4,200	3.9%	7.8
	(2,100–3,500)	(4.2%–7.0%)	(9.1–15.7)	(830–1,900)	(1.4%–3.3%)	(2.5–6.6)	(2,900–5,400)	(2.7%–5.0%)	(5.3–10.3)
Western Africa	4,400	4.5%	4.6	2,700	1.8%	2.5	7,000	2.9%	3.5
	(2,500–6,300)	(2.6%–6.5%)	(2.7–6.8)	(1,900–3,700)	(1.3%–2.6%)	(1.6–3.7)	(4,300–10,100)	(1.8%–4.2%)	(2.1–5.2)
Asia									
Eastern Asia	275,900	8.6%	21.5	56,300	2.1%	4.3	332,100	5.7%	12.7
	(172,600–378,400)	(5.4%–11.8%)	(13.4–29.6)	(36,200–81,900)	(1.4%–3.1%)	(2.5–6.6)	(208,800–460,200)	(3.6%–7.9%)	(7.9–17.9)
South-Central Asia	59,200	6.2%	6.7	8,900	0.9%	1.0	68,100	3.5%	3.8
	(33,200–114,800)	(3.5%–12.0%)	(3.7–13.3)	(4,800–19,000)	(0.5%–1.9%)	(0.5–2.2)	(37,900–133,800)	(2.0%–6.9%)	(2.1–7.7)
South-Eastern Asia	23,000	4.4%	7.4	4,700	0.8%	1.3	27,700	2.6%	4.1
	(14,100–33,400)	(2.7%–6.4%)	(4.5–10.8)	(3,300–6,400)	(0.6%–1.1%)	(0.9–1.9)	(17,500–39,700)	(1.6%–3.7%)	(2.6–6.0)
Western Asia	2,300	1.0%	2.1	750	0.4%	0.6	3,000	0.7%	1.3
	(1,500–3,900)	(0.7%–1.7%)	(1.4–3.8)	(480–1,300)	(0.2%–0.6%)	(0.4–1.2)	(2,000–5,200)	(0.5%–1.2%)	(0.8–2.4)

Supplementary Table 3. Global number of alcohol-attributable cancer cases, population attributable fraction, and age-standardised incidence rate of alcohol-attributable cases in 2020, by world region, Human Development Index, and sex (*continued*)

	Males			Females			Total		
World Region	**Alcohol-attributable cases**	**PAF**	**ASIR per 100,000**	**Alcohol-attributable cases**	**PAF**	**ASIR per 100,000**	**Alcohol-attributable cases**	**PAF**	**ASIR per 100,000**
Europe									
Central and Eastern Europe	49,900	7.8%	23.1	21,500	3.4%	7.4	71,400	5.6%	14.0
	(41,100–57,300)	(6.5%–9.0%)	(19.0–26.6)	(16,700–26,900)	(2.6%–4.3%)	(5.1–10.0)	(57,800–84,200)	(4.6%–6.6%)	(10.9–16.9)
Northern Europe	15,600	4.7%	15.6	9,200	3.0%	9.1	24,800	3.9%	12.2
	(12,600–18,300)	(3.8%–5.5%)	(12.4–18.3)	(6,600–12,100)	(2.2%–4.0%)	(5.9–12.8)	(19,200–30,300)	(3.0%–4.8%)	(9.0–15.3)
Southern Europe	23,100	4.8%	14.9	9,300	2.3%	5.9	32,400	3.6%	10.1
	(18,300–27,400)	(3.8%–5.7%)	(11.7–17.7)	(6,900–12,000)	(1.7%–3.0%)	(3.7–8.2)	(25,200–39,400)	(2.8%–4.4%)	(7.5–12.6)
Western Europe	34,400	5.1%	17.3	18,400	3.2%	9.4	52,800	4.2%	13.1
	(27,500–40,300)	(4.1%–6.0%)	(13.8–20.4)	(13,800–23,200)	(2.4%–4.1%)	(6.2–12.8)	(41,300–63,500)	(3.3%–5.1%)	(9.8–16.3)
Latin America and the Caribbean									
Latin America and the Caribbean	26,800	3.9%	8.0	12,600	1.8%	3.3	39,300	2.8%	5.4
	(20,600–32,300)	(3.0%–4.7%)	(6.0–9.7)	(9,100–17,100)	(1.3%–2.4%)	(2.1–4.7)	(29,600–49,400)	(2.1%–3.5%)	(3.9–7.0)
North America									
North America	38,500	3.8%	12.7	21,200	2.2%	6.7	59,600	3.0%	9.5
	(27,000–48,400)	(2.7%–4.8%)	(8.8–16.0)	(13,500–29,400)	(1.4%–3.0%)	(3.8–10.1)	(40,600–77,800)	(2.1%–4.0%)	(6.2–12.9)
Oceania									
Australia and New Zealand	4,200	4.8%	17.0	2,600	3.3%	10.2	6,800	4.1%	13.5
	(3,200–5,100)	(3.7%–5.8%)	(12.7–20.7)	(1,700–3,500)	(2.2%–4.4%)	(6.3–15.2)	(5,000–8,600)	(3.0%–5.1%)	(9.4–17.8)
Melanesia, Micronesia and Polynesia	160	2.1%	4.2	30	0.4%	0.8	190	1.2%	2.4
	(30–310)	(0.4%–4.1%)	(0.8–8.1)	(10–60)	(0.1%–0.7%)	(0.2–1.4)	(40–370)	(0.2%–2.2%)	(0.5–4.5)

Supplementary Table 3. Global number of alcohol-attributable cancer cases, population attributable fraction, and age-standardised incidence rate of alcohol-attributable cases in 2020, by world region, Human Development Index, and sex (*continued*)

	Males			Females			Total		
World Region	**Alcohol-attributable cases**	**PAF**	**ASIR per 100,000**	**Alcohol-attributable cases**	**PAF**	**ASIR per 100,000**	**Alcohol-attributable cases**	**PAF**	**ASIR per 100,000**
HDI									
Very high HDI	203,100	4.9%	15.4	92,600	2.5%	6.6	295,700	3.8%	10.7
	(161,700–236,700)	(3.9%–5.7%)	(12.3–18.0)	(71,600–114,400)	(1.9%–3.1%)	(4.5–8.9)	(233,300–351,100)	(3.0%–4.5%)	(8.1–13.0)
High HDI	291,500	7.6%	16.1	65,100	1.9%	3.4	356,500	4.9%	9.5
	(188,800–398,200)	(4.9%–10.4%)	(10.4–22.0)	(44,100–91,100)	(1.3%–2.6%)	(2.1–5.0)	(232,900–489,300)	(3.2%–6.7%)	(6.1–13.2)
Medium HDI	63,000	6.2%	6.8	9,900	0.9%	1.0	72,900	3.5%	3.9
	(36,700–118,900)	(3.6%–11.8%)	(3.8–13.1)	(5,600–19,700)	(0.5%–1.8%)	(0.6–2.2)	(42,300–138,700)	(2.0%–6.6%)	(2.2–7.6)
Low HDI	9,400	4.0%	4.3	4,600	1.3%	1.8	14,000	2.4%	3.0
	(6,500–13,600)	(2.8%–5.7%)	(3.0–6.2)	(3,500–6,300)	(1.0%–1.8%)	(1.3–2.7)	(10,000–19,800)	(1.7%–3.3%)	(2.1–4.3)
Missing	1,800	4.1%	7.7	380	0.8%	1.4	2,100	2.4%	4.2
	(1,000–2,800)	(2.4%–6.5%)	(4.5–12.2)	(260–600)	(0.5%–1.3%)	(0.8–2.3)	(1,300–3,400)	(1.4%–3.8%)	(2.4–6.7)
World	568,700	6.1%	13.4	172,600	2.0%	3.7	741,300	4.1%	8.4
	(422,500–731,100)	(4.6%–7.9%)	(10.0–17.4)	(135,900–220,100)	(1.6%–2.5%)	(2.7–5.0)	(558,500–951,200)	(3.1%–5.3%)	(6.2–10.9)

Numbers in parentheses are 95% Uncertainty Intervals. Cases may not sum due to rounding. PAF, Population-attributable Fraction; ASIR, Age-standardised incidence rate of alcohol-attributable cases; HDI, Human Development Index

Missing HDI assigned to the following countries: French Guiana, French Polynesia, Guadeloupe, Guam, Korea (the Democratic People's Republic of), Martinique, New Caledonia, Puerto Rico, Reunion, and Somalia.

Supplementary Table 4. Number of alcohol-attributable cancer cases, population attributable fraction, and age-standardised incidence rate of alcohol-attributable cases in 2020, by country and sex. Number of cases suppressed if less than five.

				Males		
Continent	Region	Human Development Index	Country	Alcohol-attributable cases	PAF	ASIR per 100,000
Africa	Eastern Africa	Low HDI	Burundi	220 (130–300)	6.8% (4.2%–9.2%)	8.3 (5.1–11.4)
Africa	Eastern Africa	Medium HDI	Comoros	<5 (<5–40)	0.6% (0.1%–19.8%)	0.6 (0.1–18.9)
Africa	Eastern Africa	Low HDI	Djibouti	<5 (<5–20)	1.0% (0.0%–5.5%)	0.8 (0.0–2.3)
Africa	Eastern Africa	Low HDI	Eritrea	10 (<5–20)	1.1% (0.0%–2.6%)	0.7 (0.0–1.8)
Africa	Eastern Africa	Low HDI	Ethiopia	700 (200–1,100)	2.7% (0.8%–4.2%)	2.5 (0.7–4.0)
Africa	Eastern Africa	Missing	France, La Réunion	70 (50–90)	4.0% (3.0%–5.2%)	11.1 (8.3–14.6)
Africa	Eastern Africa	Medium HDI	Kenya	820 (390–1,200)	5.3% (2.6%–7.7%)	7.6 (3.6–11.1)
Africa	Eastern Africa	Low HDI	Madagascar	230 (40–430)	2.9% (0.5%–5.4%)	3.5 (0.6–6.6)
Africa	Eastern Africa	Low HDI	Malawi	350 (130–550)	5.3% (2.0%–8.4%)	8.4 (3.2–13.4)
Africa	Eastern Africa	Very high HDI	Mauritius	40 (20–60)	3.0% (1.4%–4.6%)	4.4 (2.0–7.0)
Africa	Eastern Africa	Low HDI	Mozambique	200 (30–410)	2.1% (0.3%–4.2%)	2.9 (0.5–5.8)
Africa	Eastern Africa	Low HDI	Rwanda	240 (160–310)	6.5% (4.4%–8.6%)	7.7 (5.1–10.3)
Africa	Eastern Africa	Missing	Somalia	20 (<5–330)	0.6% (0.1%–9.1%)	0.6 (0.1–10.0)
Africa	Eastern Africa	Low HDI	South Sudan	150 (100–200)	5.7% (3.8%–7.4%)	4.4 (2.9–5.7)
Africa	Eastern Africa	Low HDI	Tanzania, United Republic of	1,200 (770–1,600)	8.2% (5.2%–10.7%)	8.6 (5.4–11.3)
Africa	Eastern Africa	Low HDI	Uganda	1,400 (940–1,800)	9.7% (6.6%–12.3%)	17.7 (11.9–22.4)
Africa	Eastern Africa	Medium HDI	Zambia	180 (100–260)	3.0% (1.6%–4.4%)	5.3 (2.9–7.6)
Africa	Eastern Africa	Medium HDI	Zimbabwe	200 (100–300)	3.6% (1.7%–5.4%)	6.2 (2.9–9.4)

Females			Total		
Alcohol-attributable cases	PAF	ASIR per 100,000	Alcohol-attributable cases	PAF	ASIR per 100,000
70 (40–100)	1.4% (0.8%–2.2%)	2.3 (1.2–3.6)	280 (170–400)	3.6% (2.2%–5.1%)	5.2 (3.1–7.3)
<5 (<5–20)	0.0% (0.0%–4.8%)	0.1 (0.0–7.1)	<5 (<5–60)	0.3% (0.0%–10.3%)	0.3 (0.0–12.7)
<5 (<5–2)	0.1% (0.0%–0.4%)	0.2 (0.0–0.5)	<5 (<5–20)	0.5% (0.0%–2.3%)	0.5 (0.0–1.3)
<5 (<5–9)	0.3% (0.0%–0.6%)	0.3 (0.0–0.6)	10 (<5–30)	0.6% (0.0%–1.3%)	0.5 (0.0–1.1)
360 (110–650)	0.7% (0.2%–1.3%)	1.1 (0.3–2.1)	1,100 (310–1,700)	1.4% (0.4%–2.3%)	1.8 (0.5–3.0)
10 (10–20)	1.1% (0.8%–1.4%)	2.1 (1.3–2.9)	80 (60–110)	2.8% (2.0%–3.6%)	6.4 (4.6–8.4)
360 (150–610)	1.4% (0.6%–2.3%)	2.7 (1.1–4.8)	1,200 (550–1,800)	2.8% (1.3%–4.3%)	4.9 (2.2–7.6)
50 (9–100)	0.4% (0.1%–0.8%)	0.6 (0.1–1.3)	280 (50–520)	1.4% (0.2%–2.6%)	2.0 (0.3–3.8)
100 (30–170)	0.9% (0.3%–1.6%)	1.8 (0.7–3.3)	440 (170–730)	2.5% (0.9%–4.1%)	4.8 (1.8–7.8)
20 (7–30)	1.0% (0.5%–1.7%)	1.7 (0.7–3.0)	60 (30–90)	1.9% (0.9%–3.0%)	2.9 (1.3–4.8)
70 (10–130)	0.4% (0.1%–0.9%)	0.7 (0.1–1.5)	270 (50–540)	1.1% (0.2%–2.2%)	1.7 (0.3–3.4)
110 (70–160)	2.2% (1.4%–3.1%)	2.9 (1.7–4.4)	350 (230–470)	4.0% (2.6%–5.4%)	5.1 (3.3–7.1)
9 (<5–180)	0.1% (0.0%–2.9%)	0.2 (0.0–5.4)	30 (<5–510)	0.3% (0.0%–5.2%)	0.4 (0.1–7.7)
50 (40–70)	1.4% (1.0%–1.9%)	1.3 (0.9–1.8)	200 (130–260)	3.2% (2.2%–4.2%)	2.8 (1.8–3.7)
440 (260–640)	1.8% (1.1%–2.6%)	2.8 (1.6–4.3)	1,700 (1,000–2,200)	4.2% (2.6%–5.7%)	5.5 (3.4–7.6)
540 (360–770)	2.8% (1.9%–4.0%)	5.7 (3.7–8.3)	1,900 (1,300–2,500)	5.7% (3.9%–7.5%)	11.1 (7.4–14.6)
50 (20–80)	0.6% (0.3%–1.1%)	1.2 (0.5–2.0)	230 (120–340)	1.7% (0.9%–2.5%)	3.0 (1.6–4.5)
70 (30–120)	0.7% (0.3%–1.2%)	1.5 (0.6–2.8)	270 (120–420)	1.7% (0.8%–2.7%)	3.5 (1.6–5.6)

Supplementary Table 4. Number of alcohol-attributable cancer cases, population attributable fraction, and age-standardised incidence rate of alcohol-attributable cases in 2020, by country and sex. Number of cases suppressed if less than five. (*continued*)

				Males		
Continent	Region	Human Development Index	Country	Alcohol-attributable cases	PAF	ASIR per 100,000
Africa	Middle Africa	Medium HDI	Angola	540 (380–670)	6.5% (4.6%–8.1%)	8.4 (5.8–10.5)
Africa	Middle Africa	Medium HDI	Cameroon	470 (280–660)	5.6% (3.4%–7.9%)	6.9 (4.2–9.7)
Africa	Middle Africa	Low HDI	Central African Republic	30 (10–60)	3.3% (1.1%–5.6%)	2.7 (0.9–4.6)
Africa	Middle Africa	Low HDI	Chad	140 (60–210)	4.2% (1.9%–6.4%)	4.3 (1.9–6.6)
Africa	Middle Africa	Low HDI	Congo, Democratic Republic of	570 (200–1,000)	2.7% (0.9%–4.8%)	2.8 (1.0–5.0)
Africa	Middle Africa	Medium HDI	Congo, Republic of	40 (20–60)	3.6% (1.7%–5.8%)	2.5 (1.2–4.0)
Africa	Middle Africa	Medium HDI	Equatorial Guinea	30 (20–40)	7.8% (4.7%–10.6%)	7.5 (4.7–10.2)
Africa	Middle Africa	High HDI	Gabon	70 (50–90)	9.9% (6.6%–12.6%)	9.6 (6.4–12.5)
Africa	Middle Africa	Medium HDI	Sao Tome and Principe	<5 (<5–6)	5.1% (2.5%–7.6%)	9.8 (4.6–14.8)
Africa	Northern Africa	High HDI	Algeria	80 (<5–350)	0.3% (0.0%–1.3%)	0.4 (0.0–1.1)
Africa	Northern Africa	High HDI	Egypt	470 (<5–8,900)	0.7% (0.0%–13.6%)	1.2 (0.0–28.9)
Africa	Northern Africa	High HDI	Libya	<5 (<5–270)	0.0% (0.0%–7.3%)	0.0 (0.0–12.1)
Africa	Northern Africa	Medium HDI	Morocco	140 (10–1,800)	0.5% (0.0%–6.1%)	0.8 (0.0–11.0)
Africa	Northern Africa	Low HDI	Sudan	60 (<5–1,000)	0.5% (0.0%–9.6%)	0.5 (0.0–9.8)
Africa	Northern Africa	High HDI	Tunisia	70 (20–110)	0.7% (0.2%–1.1%)	1.1 (0.2–1.7)
Africa	Southern Africa	High HDI	Botswana	70 (50–90)	8.5% (5.8%–11.0%)	10.3 (6.8–13.7)
Africa	Southern Africa	Medium HDI	Eswatini	10 (7–20)	3.5% (2.2%–5.0%)	3.8 (2.2–5.4)

Females			Total		
Alcohol-attributable cases	PAF	ASIR per 100,000	Alcohol-attributable cases	PAF	ASIR per 100,000
230 (140–320)	2.0% (1.2%–2.8%)	2.8 (1.6–4.2)	770 (520–990)	3.9% (2.7%–5.1%)	5.4 (3.5–7.1)
220 (120–360)	1.8% (1.0%–3.0%)	2.9 (1.3–4.8)	690 (400–1,000)	3.4% (1.9%–5.0%)	4.8 (2.7–7.1)
10 (5–30)	0.9% (0.3%–1.7%)	1.0 (0.3–1.9)	50 (20–90)	1.9% (0.6%–3.2%)	1.8 (0.6–3.2)
50 (20–100)	1.0% (0.4%–1.9%)	1.4 (0.5–2.6)	190 (80–310)	2.3% (1.0%–3.7%)	2.8 (1.2–4.5)
170 (60–300)	0.6% (0.2%–1.1%)	0.7 (0.3–1.3)	740 (260–1,300)	1.5% (0.5%–2.8%)	1.7 (0.6–3.1)
20 (10–30)	1.5% (0.8%–2.4%)	1.2 (0.6–2.1)	60 (30–100)	2.4% (1.2%–3.9%)	1.9 (0.9–3.0)
10 (7–20)	2.3% (1.3%–3.6%)	3.3 (1.6–5.3)	40 (30–60)	4.8% (2.8%–6.7%)	5.6 (3.3–7.9)
30 (20–40)	2.6% (1.6%–3.8%)	3.7 (2.0–5.7)	100 (60–130)	5.6% (3.6%–7.4%)	6.7 (4.3–9.1)
<5 (<5–<5)	2.2% (1.3%–3.1%)	3.0 (1.7–4.7)	6 (<5–8)	3.7% (2.0%–5.5%)	6.1 (2.9–9.2)
30 (<5–90)	0.1% (0.0%–0.3%)	0.1 (0.0–0.5)	110 (<5–440)	0.2% (0.0%–0.8%)	0.3 (0.0–0.8)
60 (<5–220)	0.1% (0.0%–0.3%)	0.1 (0.0–0.5)	530 (<5–9,100)	0.4% (0.0%–6.9%)	0.7 (0.0–14.1)
<5 (<5–<5)	0.0% (0.0%–0.1%)	0.0 (0.0–0.1)	<5 (<5–270)	0.0% (0.0%–3.6%)	0.0 (0.0–5.7)
50 (<5–120)	0.2% (0.0%–0.4%)	0.3 (0.0–0.7)	200 (10–1,900)	0.3% (0.0%–3.2%)	0.5 (0.0–5.6)
20 (<5–60)	0.1% (0.0%–0.4%)	0.1 (0.0–0.5)	70 (<5–1,100)	0.3% (0.0%–4.0%)	0.3 (0.0–4.9)
20 (<5–40)	0.2% (0.0%–0.5%)	0.3 (0.0–0.6)	90 (20–150)	0.5% (0.1%–0.8%)	0.7 (0.1–1.2)
20 (10–20)	1.4% (0.8%–2.2%)	1.8 (1.0–2.8)	80 (60–110)	4.4% (2.9%–5.8%)	5.4 (3.5–7.4)
<5 (<5–7)	0.7% (0.4%–1.1%)	1.0 (0.5–1.6)	20 (10–20)	1.7% (1.0%–2.4%)	2.1 (1.2–3.1)

Supplementary Table 4. Number of alcohol-attributable cancer cases, population attributable fraction, and age-standardised incidence rate of alcohol-attributable cases in 2020, by country and sex. Number of cases suppressed if less than five. (*continued*)

				Males		
Continent	Region	Human Development Index	Country	Alcohol-attributable cases	PAF	ASIR per 100,000
Africa	Southern Africa	Low HDI	Lesotho	40 (30–60)	6.8% (4.3%–9.1%)	8.1 (5.1–10.9)
Africa	Southern Africa	Medium HDI	Namibia	70 (50–90)	5.2% (4.0%–6.5%)	10.7 (7.9–13.4)
Africa	Southern Africa	High HDI	South Africa	2,600 (1,900–3,200)	5.7% (4.2%–7.0%)	13.0 (9.4–16.2)
Africa	Western Africa	Low HDI	Côte d'Ivoire	340 (170–510)	4.6% (2.3%–7.0%)	4.8 (2.4–7.2)
Africa	Western Africa	Low HDI	Benin	70 (20–130)	2.3% (0.6%–4.4%)	2.5 (0.6–4.8)
Africa	Western Africa	Low HDI	Burkina Faso	310 (160–480)	7.3% (3.8%–11.3%)	6.3 (3.2–9.8)
Africa	Western Africa	Medium HDI	Cabo Verde	40 (20–50)	10.3% (6.2%–13.4%)	22.5 (13.4–29.6)
Africa	Western Africa	Medium HDI	Ghana	730 (230–1,300)	7.5% (2.4%–13.2%)	8.1 (2.8–14.2)
Africa	Western Africa	Low HDI	Guinea	30 (<5–110)	1.1% (0.0%–4.2%)	0.8 (0.0–3.3)
Africa	Western Africa	Low HDI	Guinea-Bissau	20 (8–40)	5.7% (2.0%–10.4%)	4.7 (1.6–8.5)
Africa	Western Africa	Low HDI	Liberia	70 (30–120)	5.2% (2.0%–9.0%)	5.8 (2.2–9.9)
Africa	Western Africa	Low HDI	Mali	60 (<5–130)	1.1% (0.0%–2.5%)	1.4 (0.0–3.1)
Africa	Western Africa	Low HDI	Mauritania	<5 (<5–200)	0.1% (0.0%–16.9%)	0.1 (0.0–16.3)
Africa	Western Africa	Low HDI	Niger	20 (<5–80)	0.4% (0.0%–2.0%)	0.3 (0.0–1.5)
Africa	Western Africa	Low HDI	Nigeria	2,500 (1,500–3,400)	4.9% (3.1%–6.8%)	5.4 (3.3–7.5)
Africa	Western Africa	Low HDI	Senegal	30 (<5–100)	0.7% (0.0%–2.5%)	0.8 (0.0–2.6)
Africa	Western Africa	Low HDI	Sierra Leone	90 (40–150)	5.0% (2.4%–8.3%)	4.9 (2.4–8.1)
Africa	Western Africa	Low HDI	The Republic of the Gambia	30 (9–60)	6.7% (2.0%–13.3%)	5.4 (1.7–10.7)

Females			Total		
Alcohol-attributable cases	PAF	ASIR per 100,000	Alcohol-attributable cases	PAF	ASIR per 100,000
20 (9–30)	1.4% (0.8%–2.4%)	2.1 (1.1–3.5)	60 (40–90)	3.3% (2.0%–4.8%)	4.4 (2.7–6.4)
40 (30–60)	2.2% (1.4%–3.2%)	4.5 (2.5–6.7)	110 (80–140)	3.5% (2.5%–4.6%)	7.1 (4.8–9.5)
1,300 (760–1,800)	2.4% (1.4%–3.4%)	4.6 (2.5–6.9)	3,900 (2,700–5,100)	3.9% (2.7%–5.0%)	8.1 (5.4–10.7)
170 (90–260)	1.7% (0.9%–2.7%)	2.6 (1.3–4.1)	500 (260–770)	3.0% (1.5%–4.5%)	3.7 (1.9–5.8)
20 (6–40)	0.6% (0.2%–1.2%)	0.6 (0.2–1.2)	90 (20–180)	1.4% (0.4%–2.7%)	1.5 (0.4–2.8)
100 (60–160)	1.4% (0.8%–2.2%)	1.9 (1.0–3.2)	420 (220–640)	3.5% (1.9%–5.5%)	3.9 (2.0–6.2)
6 (<5–9)	1.4% (0.7%–2.2%)	2.7 (1.3–4.5)	50 (30–60)	5.8% (3.4%–7.7%)	11.6 (6.7–15.8)
210 (100–370)	1.5% (0.7%–2.6%)	2.1 (0.9–3.8)	940 (330–1,700)	4.0% (1.4%–7.0%)	4.9 (1.8–8.7)
5 (<5–20)	0.1% (0.0%–0.3%)	0.1 (0.0–0.4)	30 (<5–130)	0.5% (0.0%–1.7%)	0.5 (0.0–1.8)
6 (<5–10)	0.8% (0.4%–1.5%)	1.0 (0.4–1.9)	30 (10–50)	2.6% (0.9%–4.7%)	2.7 (1.0–5.0)
20 (10–40)	1.1% (0.5%–1.8%)	1.6 (0.7–2.8)	100 (40–160)	2.8% (1.1%–4.7%)	3.6 (1.4–6.2)
20 (<5–40)	0.2% (0.0%–0.4%)	0.3 (0.0–0.8)	70 (<5–160)	0.5% (0.0%–1.2%)	0.8 (0.0–1.8)
<5 (<5–10)	0.0% (0.0%–0.5%)	0.0 (0.0–0.2)	<5 (<5–210)	0.0% (0.0%–6.9%)	0.0 (0.0–7.7)
<5 (<5–10)	0.0% (0.0%–0.2%)	0.0 (0.0–0.2)	20 (<5–90)	0.2% (0.0%–0.9%)	0.2 (0.0–0.8)
2,000 (1,300–2,900)	2.8% (1.9%–4.0%)	3.8 (2.2–5.8)	4,500 (2,900–6,300)	3.7% (2.4%–5.2%)	4.6 (2.8–6.6)
6 (<5–20)	0.1% (0.0%–0.3%)	0.1 (0.0–0.4)	40 (<5–120)	0.3% (0.0%–1.1%)	0.4 (0.0–1.4)
30 (20–50)	1.1% (0.5%–1.8%)	1.4 (0.7–2.5)	120 (60–200)	2.6% (1.2%–4.3%)	3.1 (1.5–5.2)
<5 (<5–6)	0.5% (0.2%–1.0%)	0.5 (0.2–1.0)	30 (10–70)	3.3% (1.0%–6.5%)	2.9 (0.9–5.7)

Supplementary Table 4. Number of alcohol-attributable cancer cases, population attributable fraction, and age-standardised incidence rate of alcohol-attributable cases in 2020, by country and sex. Number of cases suppressed if less than five. (*continued*)

				Males		
Continent	Region	Human Development Index	Country	Alcohol-attributable cases	PAF	ASIR per 100,000
Africa	Western Africa	Low HDI	Togo	50 (10–90)	2.3% (0.6%–4.2%)	2.7 (0.7–4.9)
Asia	Eastern Asia	High HDI	China	236,100 (142,300–329,200)	9.6% (5.8%–13.4%)	21.9 (13.1–30.7)
Asia	Eastern Asia	Very high HDI	Japan	30,100 (19,300–40,500)	5.1% (3.3%–6.8%)	18.3 (11.8–24.6)
Asia	Eastern Asia	Missing	Korea, Democratic Republic of	1,300 (590–2,200)	4.8% (2.2%–8.2%)	8.6 (3.9–14.7)
Asia	Eastern Asia	Very high HDI	Korea, Republic of	7,800 (5,000–10,700)	6.5% (4.1%–8.9%)	17.7 (10.9–24.4)
Asia	Eastern Asia	High HDI	Mongolia	450 (180–720)	15.0% (5.9%–24.1%)	41.6 (17.3–67.2)
Asia	South-Central Asia	Low HDI	Afghanistan	40 (<5–1,800)	0.4% (0.0%–17.5%)	0.5 (0.0–22.4)
Asia	South-Central Asia	Medium HDI	Bangladesh	860 (<5–37,700)	1.0% (0.0%–43.1%)	1.2 (0.0–53.5)
Asia	South-Central Asia	Medium HDI	Bhutan	10 (<5–20)	4.0% (1.0%–7.2%)	3.4 (0.8–6.2)
Asia	South-Central Asia	Medium HDI	India	54,400 (23,500–78,100)	8.5% (3.7%–12.2%)	8.5 (3.6–12.5)
Asia	South-Central Asia	High HDI	Iran, Islamic Republic of	350 (60–5,100)	0.5% (0.1%–7.5%)	0.9 (0.1–15.3)
Asia	South-Central Asia	Very high HDI	Kazakhstan	990 (720–1,200)	6.2% (4.5%–7.5%)	12.5 (9.1–15.4)
Asia	South-Central Asia	Medium HDI	Kyrgyzstan	170 (110–230)	5.2% (3.4%–7.3%)	8.4 (5.4–11.7)
Asia	South-Central Asia	High HDI	Maldives	<5 (<5–6)	1.4% (0.5%–2.4%)	2.0 (0.6–3.4)
Asia	South-Central Asia	Medium HDI	Nepal	190 (9–380)	2.1% (0.1%–4.2%)	1.6 (0.1–3.3)
Asia	South-Central Asia	Medium HDI	Pakistan	370 (40–23,000)	0.4% (0.0%–26.9%)	0.5 (0.1–31.6)
Asia	South-Central Asia	High HDI	Sri Lanka	1,100 (480–1,700)	7.6% (3.4%–11.9%)	8.3 (3.7–13.0)
Asia	South-Central Asia	Medium HDI	Tajikistan	50 (10–90)	2.1% (0.4%–3.4%)	1.9 (0.4–3.2)

Females			Total		
Alcohol-attributable cases	**PAF**	**ASIR per 100,000**	**Alcohol-attributable cases**	**PAF**	**ASIR per 100,000**
20 (5–30)	0.6% (0.2%–1.1%)	0.8 (0.2–1.5)	70 (20–120)	1.3% (0.3%–2.5%)	1.7 (0.4–3.1)
46,200 (26,600–70,600)	2.2% (1.3%–3.4%)	4.3 (2.3–6.8)	282,300 (168,900–399,800)	6.2% (3.7%–8.8%)	13.0 (7.7–18.6)
7,400 (4,500–11,200)	1.8% (1.1%–2.6%)	5.0 (2.6–8.1)	37,600 (23,900–51,600)	3.7% (2.3%–5.1%)	11.2 (6.9–15.8)
200 (90–350)	0.7% (0.3%–1.2%)	1.1 (0.4–1.9)	1,500 (680–2,600)	2.6% (1.2%–4.5%)	4.3 (1.9–7.5)
2,400 (1,500–3,400)	2.2% (1.4%–3.2%)	5.2 (2.7–8.6)	10,200 (6,500–14,100)	4.5% (2.8%–6.2%)	10.9 (6.5–15.7)
110 (50–190)	4.0% (2.0%–7.0%)	8.3 (4.1–14.8)	560 (230–910)	9.8% (4.1%–16.1%)	23.0 (9.9–37.9)
5 (<5–430)	0.0% (0.0%–3.6%)	0.1 (0.0–6.4)	50 (<5–2,200)	0.2% (0.0%–10.0%)	0.3 (0.0–14.2)
60 (<5–250)	0.1% (0.0%–0.4%)	0.1 (0.0–0.4)	920 (<5–38,000)	0.6% (0.0%–24.4%)	0.6 (0.0–27.2)
<5 (<5–<5)	0.7% (0.2%–1.3%)	0.6 (0.2–1.1)	10 (<5–30)	2.5% (0.6%–4.5%)	2.1 (0.5–3.9)
7,800 (3,100–13,600)	1.1% (0.5%–2.0%)	1.2 (0.5–2.1)	62,100 (26,600–91,700)	4.7% (2.0%–7.0%)	4.8 (2.0–7.3)
100 (9–710)	0.2% (0.0%–1.2%)	0.3 (0.0–2.7)	450 (70–5,800)	0.4% (0.1%–4.6%)	0.6 (0.1–9.1)
430 (260–630)	2.4% (1.4%–3.5%)	3.8 (2.1–5.7)	1,400 (980–1,800)	4.2% (2.9%–5.4%)	7.3 (4.9–9.5)
60 (40–80)	1.6% (1.0%–2.2%)	2.1 (1.3–3.2)	220 (150–320)	3.3% (2.1%–4.6%)	4.8 (3.0–6.8)
<5 (<5–<5)	0.3% (0.1%–0.5%)	0.4 (0.1–0.8)	<5 (<5–7)	0.9% (0.3%–1.5%)	1.2 (0.4–2.2)
30 (<5–70)	0.3% (0.0%–0.7%)	0.3 (0.0–0.6)	220 (10–450)	1.1% (0.1%–2.2%)	0.9 (0.0–1.8)
50 (7–7,800)	0.1% (0.0%–8.8%)	0.1 (0.0–11.3)	430 (40–30,800)	0.2% (0.0%–17.7%)	0.3 (0.0–21.6)
200 (90–330)	1.3% (0.6%–2.2%)	1.3 (0.6–2.3)	1,300 (560–2,000)	4.3% (1.9%–6.8%)	4.5 (2.0–7.2)
10 (<5–30)	0.4% (0.1%–0.9%)	0.4 (0.1–0.8)	70 (10–110)	1.2% (0.2%–2.0%)	1.1 (0.2–1.9)

Supplementary Table 4. Number of alcohol-attributable cancer cases, population attributable fraction, and age-standardised incidence rate of alcohol-attributable cases in 2020, by country and sex. Number of cases suppressed if less than five. (*continued*)

				Males		
Continent	Region	Human Development Index	Country	Alcohol-attributable cases	PAF	ASIR per 100,000
Asia	South-Central Asia	High HDI	Turkmenistan	190 (120–260)	6.6% (4.2%–9.0%)	9.7 (6.1–13.4)
Asia	South-Central Asia	High HDI	Uzbekistan	510 (240–720)	3.6% (1.7%–5.1%)	4.4 (2.1–6.3)
Asia	South-Eastern Asia	Very high HDI	Brunei	<5 (<5–<5)	0.3% (0.0%–0.6%)	0.7 (0.1–1.6)
Asia	South-Eastern Asia	Medium HDI	Cambodia	730 (300–1,200)	8.8% (3.6%–14.2%)	14.0 (5.7–22.7)
Asia	South-Eastern Asia	High HDI	Indonesia	910 (<5–3,200)	0.5% (0.0%–1.8%)	0.8 (0.0–2.7)
Asia	South-Eastern Asia	Medium HDI	Lao People's Democratic Republic	450 (250–650)	10.0% (5.6%–14.6%)	19.8 (11.0–29.1)
Asia	South-Eastern Asia	Very high HDI	Malaysia	230 (<5–570)	1.0% (0.0%–2.5%)	1.5 (0.0–3.8)
Asia	South-Eastern Asia	Medium HDI	Myanmar	1,900 (570–3,300)	5.8% (1.7%–9.8%)	7.8 (2.3–13.4)
Asia	South-Eastern Asia	High HDI	Philippines	3,900 (2,100–5,600)	5.8% (3.1%–8.4%)	10.1 (5.6–14.6)
Asia	South-Eastern Asia	Very high HDI	Singapore	170 (50–310)	1.4% (0.4%–2.6%)	3.3 (0.9–6.4)
Asia	South-Eastern Asia	High HDI	Thailand	8,200 (4,600–12,000)	8.9% (5.0%–13.1%)	16.1 (9.0–23.7)
Asia	South-Eastern Asia	Medium HDI	Timor-Leste	<5 (<5–<5)	0.2% (0.0%–0.7%)	0.2 (0.0–0.7)
Asia	South-Eastern Asia	High HDI	Viet Nam	6,500 (2,900–10,800)	6.6% (3.0%–11.0%)	13.3 (5.8–22.0)
Asia	Western Asia	High HDI	Armenia	130 (70–190)	2.8% (1.4%–4.0%)	7.4 (3.7–10.8)
Asia	Western Asia	High HDI	Azerbaijan	220 (100–330)	2.7% (1.2%–4.2%)	4.6 (2.0–7.2)
Asia	Western Asia	Very high HDI	Bahrain	<5 (<5–10)	0.9% (0.3%–1.7%)	1.0 (0.2–2.1)
Asia	Western Asia	High HDI	Gaza Strip and West Bank	20 (20–40)	1.1% (0.7%–1.9%)	1.9 (1.2–3.7)
Asia	Western Asia	Very high HDI	Georgia	360 (250–440)	5.5% (3.9%–6.9%)	12.9 (9.0–16.1)

Females			Total		
Alcohol-attributable cases	PAF	ASIR per 100,000	Alcohol-attributable cases	PAF	ASIR per 100,000
70 (40–110)	1.9% (1.0%–3.0%)	2.6 (1.3–4.4)	260 (160–370)	4.0% (2.4%–5.7%)	5.7 (3.4–8.3)
130 (50–250)	0.8% (0.3%–1.4%)	0.9 (0.3–1.7)	640 (290–970)	2.0% (0.9%–3.1%)	2.5 (1.1–3.8)
<5 (<5–<5)	0.1% (0.0%–0.2%)	0.3 (0.0–0.6)	<5 (<5–<5)	0.2% (0.0%–0.4%)	0.5 (0.1–1.1)
130 (50–220)	1.3% (0.5%–2.2%)	1.8 (0.7–3.2)	850 (350–1,400)	4.7% (1.9%–7.7%)	6.9 (2.8–11.4)
190 (<5–600)	0.1% (0.0%–0.3%)	0.1 (0.0–0.5)	1,100 (<5–3,800)	0.3% (0.0%–1.0%)	0.4 (0.0–1.5)
80 (40–130)	1.8% (1.0%–2.8%)	3.1 (1.6–5.1)	530 (300–780)	5.9% (3.3%–8.7%)	10.9 (6.0–16.2)
70 (<5–160)	0.3% (0.0%–0.6%)	0.4 (0.0–1.0)	290 (<5–730)	0.6% (0.0%–1.5%)	1.0 (0.0–2.4)
240 (70–430)	0.6% (0.2%–1.1%)	0.8 (0.2–1.6)	2,200 (650–3,700)	3.0% (0.9%–5.1%)	4.0 (1.2–7.0)
1,400 (740–2,200)	1.6% (0.9%–2.6%)	3.1 (1.5–5.1)	5,300 (2,800–7,800)	3.5% (1.8%–5.1%)	6.2 (3.3–9.3)
70 (20–110)	0.6% (0.2%–1.0%)	1.3 (0.4–2.4)	230 (70–420)	1.0% (0.3%–1.8%)	2.2 (0.6–4.3)
1,700 (930–2,500)	1.8% (1.0%–2.6%)	2.9 (1.5–4.6)	9,900 (5,500–14,500)	5.3% (2.9%–7.7%)	8.9 (4.9–13.3)
<5 (<5–<5)	0.1% (0.0%–0.2%)	0.1 (0.0–0.2)	<5 (<5–<5)	0.1% (0.0%–0.4%)	0.1 (0.0–0.5)
850 (390–1,500)	1.0% (0.5%–1.8%)	1.4 (0.6–2.6)	7,400 (3,300–12,300)	4.1% (1.8%–6.8%)	6.8 (3.0–11.4)
60 (30–90)	1.3% (0.7%–2.2%)	2.3 (1.1–4.0)	190 (100–290)	2.1% (1.1%–3.1%)	4.4 (2.2–6.8)
60 (30–110)	0.8% (0.3%–1.4%)	1.0 (0.4–2.0)	280 (120–450)	1.8% (0.8%–2.8%)	2.6 (1.1–4.3)
<5 (<5–<5)	0.3% (0.1%–0.6%)	0.4 (0.1–0.9)	7 (<5–10)	0.6% (0.2%–1.1%)	0.7 (0.2–1.6)
10 (6–10)	0.4% (0.2%–0.6%)	0.7 (0.4–1.2)	30 (20–60)	0.7% (0.5%–1.2%)	1.3 (0.8–2.4)
160 (100–230)	2.6% (1.6%–3.7%)	4.6 (2.4–7.2)	520 (350–680)	4.1% (2.8%–5.3%)	8.1 (5.2–10.9)

Supplementary Table 4. Number of alcohol-attributable cancer cases, population attributable fraction, and age-standardised incidence rate of alcohol-attributable cases in 2020, by country and sex. Number of cases suppressed if less than five. (*continued*)

				Males		
Continent	**Region**	**Human Development Index**	**Country**	**Alcohol-attributable cases**	**PAF**	**ASIR per 100,000**
Asia	Western Asia	Medium HDI	Iraq	40 (<5–570)	0.3% (0.0%–4.1%)	0.4 (0.0–8.6)
Asia	Western Asia	Very high HDI	Israel	110 (30–210)	0.8% (0.2%–1.5%)	2.0 (0.6–3.8)
Asia	Western Asia	High HDI	Jordan	20 (<5–110)	0.4% (0.0%–2.2%)	0.6 (0.0–1.5)
Asia	Western Asia	Very high HDI	Kuwait	<5 (<5–150)	0.0% (0.0%–8.4%)	0.0 (0.0–9.5)
Asia	Western Asia	High HDI	Lebanon	40 (7–70)	0.7% (0.1%–1.2%)	1.1 (0.2–2.1)
Asia	Western Asia	Very high HDI	Oman	6 (<5–20)	0.3% (0.0%–0.8%)	0.3 (0.0–1.0)
Asia	Western Asia	Very high HDI	Qatar	6 (<5–10)	0.7% (0.1%–1.5%)	0.9 (0.1–2.3)
Asia	Western Asia	Very high HDI	Saudi Arabia	10 (<5–1,200)	0.1% (0.0%–8.3%)	0.1 (0.0–9.9)
Asia	Western Asia	Medium HDI	Syrian Arab Republic	20 (8–120)	0.2% (0.1%–1.3%)	0.3 (0.1–2.0)
Asia	Western Asia	Very high HDI	Turkey	1,200 (430–1,800)	0.9% (0.3%–1.4%)	2.9 (0.9–4.4)
Asia	Western Asia	Very high HDI	United Arab Emirates	30 (8–50)	1.4% (0.4%–2.2%)	1.0 (0.2–1.9)
Asia	Western Asia	Low HDI	Yemen	20 (<5–660)	0.3% (0.0%–9.4%)	0.4 (0.0–11.3)
Europe	Central and Eastern Europe	Very high HDI	Belarus	1,800 (1,500–2,100)	8.6% (6.8%–10.0%)	27.8 (21.7–32.4)
Europe	Central and Eastern Europe	Very high HDI	Bulgaria	1,000 (790–1,200)	5.3% (4.1%–6.3%)	15.3 (11.4–18.5)
Europe	Central and Eastern Europe	Very high HDI	Czechia	1,900 (1,500–2,200)	5.5% (4.4%–6.4%)	18.8 (14.6–22.2)
Europe	Central and Eastern Europe	Very high HDI	Hungary	2,200 (1,700–2,600)	7.0% (5.4%–8.4%)	26.9 (20.4–32.7)

Females			Total		
Alcohol-attributable cases	PAF	ASIR per 100,000	Alcohol-attributable cases	PAF	ASIR per 100,000
20 (<5–50)	0.1% (0.0%–0.3%)	0.1 (0.0–0.5)	50 (<5–620)	0.2% (0.0%–1.8%)	0.2 (0.0–4.2)
90 (40–150)	0.6% (0.3%–1.0%)	1.6 (0.6–2.8)	200 (70–350)	0.7% (0.2%–1.2%)	1.8 (0.6–3.3)
7 (<5–20)	0.1% (0.0%–0.3%)	0.2 (0.0–0.6)	30 (<5–130)	0.2% (0.0%–1.2%)	0.4 (0.0–1.0)
<5 (<5–<5)	0.0% (0.0%–0.2%)	0.0 (0.0–0.8)	<5 (<5–160)	0.0% (0.0%–4.1%)	0.0 (0.0–6.1)
20 (5–40)	0.3% (0.1%–0.7%)	0.6 (0.1–1.5)	60 (10–110)	0.5% (0.1%–0.9%)	0.9 (0.1–1.8)
<5 (<5–<5)	0.1% (0.0%–0.3%)	0.1 (0.0–0.4)	8 (<5–20)	0.2% (0.0%–0.6%)	0.3 (0.0–0.8)
<5 (<5–<5)	0.2% (0.0%–0.5%)	0.3 (0.1–1.0)	7 (<5–20)	0.5% (0.1%–1.1%)	0.7 (0.1–1.7)
<5 (<5–10)	0.0% (0.0%–0.1%)	0.0 (0.0–0.1)	10 (<5–1,200)	0.1% (0.0%–4.3%)	0.1 (0.0–5.7)
10 (<5–30)	0.1% (0.0%–0.3%)	0.2 (0.0–0.5)	40 (10–150)	0.2% (0.1%–0.7%)	0.3 (0.1–1.2)
300 (70–530)	0.3% (0.1%–0.5%)	0.6 (0.1–1.2)	1,500 (500–2,300)	0.7% (0.2%–1.0%)	1.6 (0.5–2.6)
9 (<5–20)	0.3% (0.1%–0.7%)	0.6 (0.1–1.5)	40 (10–70)	0.8% (0.2%–1.4%)	0.9 (0.2–1.7)
7 (<5–300)	0.1% (0.0%–3.3%)	0.1 (0.0–4.1)	30 (<5–960)	0.2% (0.0%–5.9%)	0.2 (0.0–7.5)
800 (550–1,100)	4.2% (2.9%–5.5%)	8.3 (4.9–12.0)	2,600 (2,000–3,200)	6.5% (4.9%–7.9%)	16.3 (11.8–20.3)
420 (270–580)	2.8% (1.8%–3.8%)	5.8 (3.2–8.7)	1,500 (1,100–1,800)	4.2% (3.1%–5.2%)	10.0 (6.9–13.0)
970 (650–1,300)	3.3% (2.2%–4.5%)	8.7 (5.2–12.7)	2,900 (2,200–3,500)	4.5% (3.4%–5.6%)	13.2 (9.5–16.9)
870 (600–1,200)	2.8% (1.9%–3.9%)	8.5 (5.1–12.6)	3,100 (2,300–3,800)	4.9% (3.7%–6.1%)	16.5 (11.8–21.2)

Supplementary Table 4. Number of alcohol-attributable cancer cases, population attributable fraction, and age-standardised incidence rate of alcohol-attributable cases in 2020, by country and sex. Number of cases suppressed if less than five. (*continued*)

				Males		
Continent	**Region**	**Human Development Index**	**Country**	**Alcohol-attributable cases**	**PAF**	**ASIR per 100,000**
Europe	Central and Eastern Europe	Very high HDI	Poland	6,300 (4,700–7,500)	6.3% (4.8%–7.6%)	19.6 (14.5–23.7)
Europe	Central and Eastern Europe	High HDI	Republic of Moldova	800 (630–940)	11.1% (8.6%–12.9%)	30.8 (23.7–36.3)
Europe	Central and Eastern Europe	Very high HDI	Romania	4,700 (3,500–5,700)	9.2% (6.8%–10.9%)	29.1 (21.6–34.8)
Europe	Central and Eastern Europe	Very high HDI	Russian Federation	23,200 (18,600–26,900)	8.4% (6.7%–9.7%)	23.8 (18.9–27.7)
Europe	Central and Eastern Europe	Very high HDI	Slovakia	1,300 (960–1,500)	7.8% (6.0%–9.4%)	29.1 (21.9–35.3)
Europe	Central and Eastern Europe	High HDI	Ukraine	6,600 (5,100–7,700)	8.5% (6.5%–9.9%)	21.1 (16.0–24.9)
Europe	Northern Europe	Very high HDI	Denmark	980 (710–1,200)	4.7% (3.4%–5.9%)	16.7 (12.0–20.9)
Europe	Northern Europe	Very high HDI	Estonia	170 (130–200)	4.2% (3.3%–5.0%)	15.3 (11.7–18.4)
Europe	Northern Europe	Very high HDI	Finland	700 (520–850)	4.0% (3.0%–4.8%)	11.3 (8.4–13.8)
Europe	Northern Europe	Very high HDI	Iceland	20 (10–30)	2.9% (1.8%–3.8%)	8.0 (4.8–10.7)
Europe	Northern Europe	Very high HDI	Ireland	670 (510–790)	4.6% (3.6%–5.5%)	16.7 (12.8–20.1)
Europe	Northern Europe	Very high HDI	Latvia	370 (280–430)	6.1% (4.5%–7.1%)	23.7 (17.7–28.1)
Europe	Northern Europe	Very high HDI	Lithuania	530 (430–610)	6.3% (5.1%–7.3%)	22.9 (18.2–26.8)
Europe	Northern Europe	Very high HDI	Norway	610 (400–800)	3.4% (2.3%–4.5%)	11.9 (7.6–15.6)
Europe	Northern Europe	Very high HDI	Sweden	990 (660–1,300)	3.2% (2.2%–4.1%)	9.5 (6.3–12.3)
Europe	Northern Europe	Very high HDI	United Kingdom	10,600 (8,100–12,600)	4.9% (3.8%–5.9%)	16.5 (12.6–19.9)

Females			Total		
Alcohol-attributable cases	PAF	ASIR per 100,000	Alcohol-attributable cases	PAF	ASIR per 100,000
2,400 (1,600–3,500)	2.5% (1.6%–3.6%)	6.4 (3.6–9.8)	8,700 (6,300–11,000)	4.4% (3.2%–5.6%)	12.2 (8.4–15.9)
240 (160–340)	4.1% (2.6%–5.7%)	6.9 (4.0–10.4)	1,000 (780–1,300)	7.9% (5.9%–9.7%)	17.1 (12.5–21.4)
1,700 (1,100–2,400)	3.9% (2.5%–5.5%)	8.7 (5.1–13.0)	6,500 (4,600–8,000)	6.8% (4.9%–8.4%)	18.0 (12.6–22.9)
11,200 (7,800–14,900)	3.7% (2.6%–5.0%)	8.0 (5.1–11.3)	34,400 (26,400–41,800)	6.0% (4.6%–7.3%)	14.3 (10.6–17.8)
350 (230–490)	2.6% (1.7%–3.6%)	6.7 (3.9–9.9)	1,600 (1,200–2,000)	5.4% (4.0%–6.8%)	16.7 (12.0–21.3)
2,500 (1,600–3,500)	3.1% (2.0%–4.4%)	5.6 (3.2–8.5)	9,100 (6,700–11,200)	5.8% (4.3%–7.1%)	11.9 (8.4–15.2)
520 (340–720)	2.7% (1.8%–3.7%)	9.4 (5.6–13.9)	1,500 (1,100–1,900)	3.8% (2.6%–4.8%)	12.9 (8.6–17.2)
100 (70–130)	2.6% (1.8%–3.6%)	6.6 (3.8–10.1)	270 (200–340)	3.5% (2.6%–4.4%)	10.0 (7.0–13.2)
560 (370–790)	3.5% (2.3%–4.9%)	9.3 (5.5–14.0)	1,300 (890–1,600)	3.8% (2.6%–4.9%)	10.1 (6.8–13.7)
10 (7–20)	1.6% (1.0%–2.5%)	4.3 (2.2–7.1)	40 (20–50)	2.3% (1.4%–3.2%)	6.1 (3.5–8.8)
380 (260–520)	3.0% (2.1%–4.1%)	9.9 (5.9–14.3)	1,000 (780–1,300)	3.9% (2.9%–4.8%)	13.1 (9.2–17.0)
140 (90–200)	2.4% (1.6%–3.3%)	6.6 (3.6–10.0)	510 (370–630)	4.3% (3.1%–5.2%)	13.4 (9.3–17.1)
260 (180–350)	3.2% (2.2%–4.3%)	8.2 (4.7–11.9)	790 (610–970)	4.8% (3.7%–5.8%)	14.2 (10.3–17.8)
310 (170–460)	2.1% (1.2%–3.1%)	6.6 (3.4–10.5)	920 (570–1,300)	2.8% (1.8%–3.8%)	9.1 (5.4–12.9)
620 (350–920)	2.3% (1.3%–3.5%)	6.6 (3.4–10.3)	1,600 (1,000–2,200)	2.8% (1.8%–3.8%)	8.0 (4.8–11.2)
6,300 (4,100–8,700)	3.2% (2.1%–4.4%)	9.8 (5.8–14.4)	16,800 (12,200–21,300)	4.1% (3.0%–5.2%)	13.0 (9.1–16.9)

Supplementary Table 4. Number of alcohol-attributable cancer cases, population attributable fraction, and age-standardised incidence rate of alcohol-attributable cases in 2020, by country and sex. Number of cases suppressed if less than five. (*continued*)

				Males		
Continent	**Region**	**Human Development Index**	**Country**	**Alcohol-attributable cases**	**PAF**	**ASIR per 100,000**
Europe	Southern Europe	High HDI	Albania	120 (70–150)	2.9% (1.8%–3.8%)	4.9 (3.0–6.5)
Europe	Southern Europe	High HDI	Bosnia and Herzegovina	350 (210–450)	4.4% (2.7%–5.9%)	11.4 (7.0–15.0)
Europe	Southern Europe	Very high HDI	Croatia	800 (620–940)	5.9% (4.6%–7.0%)	20.0 (15.2–24.0)
Europe	Southern Europe	Very high HDI	Cyprus	110 (80–130)	3.9% (3.0%–4.7%)	11.3 (8.6–13.8)
Europe	Southern Europe	Very high HDI	Greece	1,500 (1,000–1,900)	4.2% (3.0%–5.4%)	12.4 (8.7–15.7)
Europe	Southern Europe	Very high HDI	Italy	6,900 (4,100–9,200)	3.4% (2.1%–4.6%)	10.6 (6.4–14.3)
Europe	Southern Europe	Very high HDI	Malta	40 (20–50)	2.8% (1.9%–3.6%)	7.6 (5.0–9.9)
Europe	Southern Europe	Very high HDI	Montenegro	90 (70–110)	6.0% (4.4%–7.2%)	17.2 (12.3–21.1)
Europe	Southern Europe	Very high HDI	Portugal	2,700 (2,100–3,100)	8.2% (6.4%–9.6%)	26.6 (20.8–31.4)
Europe	Southern Europe	Very high HDI	Serbia	1,500 (1,200–1,800)	6.3% (4.8%–7.4%)	20.1 (15.1–24.1)
Europe	Southern Europe	Very high HDI	Slovenia	450 (340–550)	5.8% (4.4%–7.1%)	21.6 (16.0–26.6)
Europe	Southern Europe	Very high HDI	Spain	8,500 (6,100–10,500)	5.7% (4.1%–7.0%)	18.5 (13.2–22.9)
Europe	Southern Europe	High HDI	The former Yugoslav Republic of Macedonia	130 (70–180)	3.2% (1.8%–4.3%)	8.1 (4.4–11.1)
Europe	Western Europe	Very high HDI	Austria	1,100 (860–1,400)	4.9% (3.7%–5.9%)	13.2 (10.0–16.1)
Europe	Western Europe	Very high HDI	Belgium	2,100 (1,600–2,500)	5.2% (4.0%–6.3%)	19.0 (14.2–23.2)
Europe	Western Europe	Very high HDI	France	13,500 (10,300–16,600)	5.8% (4.4%–7.1%)	21.8 (16.4–26.8)
Europe	Western Europe	Very high HDI	Germany	13,600 (10,400–16,400)	4.7% (3.6%–5.7%)	15.1 (11.5–18.2)

Females			Total		
Alcohol-attributable cases	PAF	ASIR per 100,000	Alcohol-attributable cases	PAF	ASIR per 100,000
50 (30–80)	1.8% (1.0%–2.9%)	2.2 (1.0–3.9)	170 (100–230)	2.5% (1.5%–3.4%)	3.5 (2.0–5.1)
90 (50–140)	1.4% (0.8%–2.2%)	2.9 (1.4–4.8)	440 (260–600)	3.1% (1.8%–4.2%)	6.8 (4.0–9.4)
290 (190–400)	2.5% (1.7%–3.5%)	6.5 (3.7–9.7)	1,100 (810–1,300)	4.3% (3.2%–5.3%)	12.6 (8.9–16.0)
60 (40–90)	2.7% (1.8%–3.8%)	6.7 (3.8–10.2)	170 (120–210)	3.3% (2.4%–4.3%)	8.8 (6.0–11.8)
680 (430–990)	2.5% (1.6%–3.6%)	5.6 (3.1–8.8)	2,200 (1,500–2,900)	3.5% (2.4%–4.6%)	8.8 (5.7–11.9)
3,200 (1,900–4,700)	1.8% (1.0%–2.6%)	4.9 (2.5–7.8)	10,100 (6,000–14,000)	2.6% (1.6%–3.6%)	7.6 (4.4–10.8)
20 (10–30)	1.8% (1.1%–2.5%)	4.5 (2.4–6.9)	60 (40–70)	2.3% (1.5%–3.1%)	5.9 (3.6–8.2)
40 (20–50)	2.9% (1.8%–4.1%)	7.1 (3.9–10.9)	130 (90–160)	4.5% (3.2%–5.8%)	11.8 (7.8–15.6)
880 (580–1,200)	3.5% (2.3%–4.8%)	7.9 (4.6–11.7)	3,500 (2,700–4,300)	6.1% (4.6%–7.5%)	16.4 (12.0–20.7)
680 (440–960)	3.0% (1.9%–4.2%)	8.4 (4.7–12.9)	2,200 (1,600–2,800)	4.7% (3.4%–5.9%)	13.7 (9.5–17.9)
150 (100–200)	2.5% (1.7%–3.4%)	6.8 (4.0–10.1)	590 (440–750)	4.4% (3.2%–5.5%)	13.8 (9.7–17.9)
3,100 (1,900–4,400)	2.8% (1.8%–4.0%)	6.6 (3.6–10.1)	11,600 (8,000–14,900)	4.4% (3.1%–5.7%)	12.2 (8.2–16.0)
50 (20–70)	1.4% (0.6%–2.2%)	2.7 (1.1–4.8)	180 (90–250)	2.4% (1.3%–3.4%)	5.2 (2.7–7.7)
620 (410–870)	3.0% (2.0%–4.1%)	7.1 (4.2–10.5)	1,800 (1,300–2,300)	4.0% (2.9%–5.1%)	9.9 (6.9–13.0)
1,200 (780–1,600)	3.4% (2.2%–4.7%)	10.9 (6.4–16.2)	3,200 (2,300–4,100)	4.4% (3.2%–5.6%)	14.7 (10.1–19.4)
6,400 (4,300–8,700)	3.4% (2.3%–4.6%)	10.5 (6.3–15.3)	20,000 (14,700–25,200)	4.7% (3.5%–6.0%)	15.8 (11.1–20.6)
7,900 (5,300–10,700)	3.2% (2.1%–4.3%)	8.9 (5.3–12.9)	21,500 (15,700–27,100)	4.0% (2.9%–5.0%)	11.8 (8.3–15.3)

Supplementary Table 4. Number of alcohol-attributable cancer cases, population attributable fraction, and age-standardised incidence rate of alcohol-attributable cases in 2020, by country and sex. Number of cases suppressed if less than five. (*continued*)

				Males		
Continent	**Region**	**Human Development Index**	**Country**	**Alcohol-attributable cases**	**PAF**	**ASIR per 100,000**
Europe	Western Europe	Very high HDI	Luxembourg	80 (60–100)	5.0% (3.7%–6.2%)	15.7 (11.1–19.8)
Europe	Western Europe	Very high HDI	Switzerland	1,200 (880–1,500)	4.8% (3.5%–5.9%)	14.1 (10.2–17.4)
Europe	Western Europe	Very high HDI	The Netherlands	2,700 (2,000–3,400)	4.4% (3.3%–5.4%)	14.8 (11.1–18.4)
Latin America and the Caribbean	Latin America and the Caribbean	Very high HDI	Argentina	2,700 (1,900–3,400)	4.5% (3.2%–5.6%)	10.2 (7.1–12.9)
Latin America and the Caribbean	Latin America and the Caribbean	Very high HDI	Bahamas	8 (5–10)	1.9% (1.2%–2.6%)	3.5 (2.2–4.9)
Latin America and the Caribbean	Latin America and the Caribbean	Very high HDI	Barbados	20 (10–20)	3.5% (2.5%–4.4%)	8.4 (5.6–10.9)
Latin America and the Caribbean	Latin America and the Caribbean	High HDI	Belize	5 (<5–8)	3.2% (1.7%–5.0%)	4.3 (1.9–7.0)
Latin America and the Caribbean	Latin America and the Caribbean	High HDI	Bolivia, Plurinational State of	160 (80–240)	2.4% (1.3%–3.6%)	3.2 (1.6–4.8)
Latin America and the Caribbean	Latin America and the Caribbean	High HDI	Brazil	14,500 (10,100–17,900)	5.2% (3.6%–6.4%)	12.5 (8.6–15.7)
Latin America and the Caribbean	Latin America and the Caribbean	Very high HDI	Chile	980 (670–1,300)	3.6% (2.4%–4.6%)	7.8 (5.2–10.0)
Latin America and the Caribbean	Latin America and the Caribbean	High HDI	Colombia	980 (510–1,400)	1.9% (1.0%–2.7%)	3.8 (1.9–5.4)
Latin America and the Caribbean	Latin America and the Caribbean	Very high HDI	Costa Rica	120 (60–180)	2.0% (1.0%–3.1%)	3.8 (1.8–6.0)
Latin America and the Caribbean	Latin America and the Caribbean	High HDI	Cuba	920 (490–1,300)	4.0% (2.1%–5.6%)	9.2 (4.9–13.0)

Females			Total		
Alcohol-attributable cases	PAF	ASIR per 100,000	Alcohol-attributable cases	PAF	ASIR per 100,000
50 (30–70)	3.5% (2.2%–4.9%)	9.9 (5.4–15.4)	130 (90–170)	4.3% (3.0%–5.6%)	12.5 (8.1–17.3)
690 (450–980)	3.1% (2.0%–4.3%)	8.2 (4.8–12.3)	1,900 (1,300–2,500)	4.0% (2.8%–5.2%)	11.0 (7.4–14.7)
1,500 (980–2,100)	2.8% (1.9%–4.1%)	9.0 (5.2–13.8)	4,200 (3,000–5,500)	3.7% (2.6%–4.8%)	11.8 (8.0–15.9)
1,700 (1,100–2,400)	2.5% (1.6%–3.6%)	5.6 (3.1–8.7)	4,400 (3,000–5,800)	3.4% (2.3%–4.6%)	7.6 (4.9–10.4)
<5 (<5–6)	0.9% (0.6%–1.4%)	1.5 (0.7–2.5)	10 (8–20)	1.4% (0.9%–2.0%)	2.3 (1.4–3.5)
10 (6–20)	1.8% (1.0%–2.6%)	4.1 (1.9–6.8)	30 (20–40)	2.6% (1.8%–3.5%)	6.0 (3.6–8.5)
<5 (<5–5)	1.7% (1.0%–2.7%)	2.4 (1.2–4.0)	9 (5–10)	2.4% (1.3%–3.8%)	3.4 (1.5–5.5)
70 (30–120)	0.8% (0.4%–1.4%)	1.4 (0.6–2.5)	230 (120–350)	1.5% (0.8%–2.3%)	2.2 (1.1–3.6)
6,000 (3,500–9,200)	2.2% (1.3%–3.3%)	4.4 (2.2–7.2)	20,500 (13,700–27,100)	3.7% (2.5%–4.9%)	8.0 (5.1–11.0)
500 (300–720)	2.1% (1.2%–3.0%)	3.5 (1.9–5.4)	1,500 (960–2,000)	2.9% (1.9%–3.8%)	5.4 (3.3–7.4)
530 (260–820)	0.9% (0.4%–1.4%)	1.7 (0.7–2.9)	1,500 (760–2,200)	1.4% (0.7%–2.0%)	2.6 (1.3–4.0)
50 (20–80)	0.8% (0.4%–1.4%)	1.6 (0.7–2.8)	170 (80–270)	1.4% (0.7%–2.2%)	2.6 (1.2–4.3)
200 (90–320)	1.0% (0.4%–1.6%)	1.9 (0.8–3.2)	1,100 (590–1,600)	2.6% (1.4%–3.7%)	5.4 (2.8–8.0)

Supplementary Table 4. Number of alcohol-attributable cancer cases, population attributable fraction, and age-standardised incidence rate of alcohol-attributable cases in 2020, by country and sex. Number of cases suppressed if less than five. (*continued*)

				Males		
Continent	**Region**	**Human Development Index**	**Country**	**Alcohol-attributable cases**	**PAF**	**ASIR per 100,000**
Latin America and the Caribbean	Latin America and the Caribbean	High HDI	Dominican Republic	310 (190–420)	3.0% (1.9%–4.2%)	6.0 (3.8–8.3)
Latin America and the Caribbean	Latin America and the Caribbean	High HDI	Ecuador	270 (140–390)	2.1% (1.1%–3.1%)	3.2 (1.6–4.8)
Latin America and the Caribbean	Latin America and the Caribbean	Medium HDI	El Salvador	60 (20–110)	1.6% (0.6%–2.7%)	2.1 (0.8–3.6)
Latin America and the Caribbean	Latin America and the Caribbean	Missing	France, Guadeloupe	40 (30–50)	3.1% (2.5%–3.9%)	10.1 (8.0–12.9)
Latin America and the Caribbean	Latin America and the Caribbean	Missing	France, Martinique	30 (30–40)	2.8% (2.2%–3.4%)	9.0 (7.0–11.3)
Latin America and the Caribbean	Latin America and the Caribbean	Missing	French Guyana	10 (8–10)	3.6% (2.7%–4.3%)	8.7 (6.1–10.9)
Latin America and the Caribbean	Latin America and the Caribbean	Medium HDI	Guatemala	150 (50–280)	2.0% (0.6%–3.8%)	2.9 (0.9–5.5)
Latin America and the Caribbean	Latin America and the Caribbean	Medium HDI	Guyana	10 (7–20)	2.5% (1.4%–3.3%)	3.7 (2.1–5.2)
Latin America and the Caribbean	Latin America and the Caribbean	Low HDI	Haiti	200 (120–290)	3.3% (1.9%–4.7%)	5.3 (3.1–7.8)
Latin America and the Caribbean	Latin America and the Caribbean	Medium HDI	Honduras	100 (50–160)	2.0% (0.9%–3.2%)	3.4 (1.5–5.4)
Latin America and the Caribbean	Latin America and the Caribbean	High HDI	Jamaica	60 (30–90)	1.7% (0.7%–2.6%)	3.5 (1.4–5.4)
Latin America and the Caribbean	Latin America and the Caribbean	High HDI	Mexico	2,200 (1,400–3,000)	2.6% (1.6%–3.6%)	3.7 (2.2–5.1)

Females			Total		
Alcohol-attributable cases	PAF	ASIR per 100,000	Alcohol-attributable cases	PAF	ASIR per 100,000
160 (90–240)	1.7% (1.0%–2.6%)	2.9 (1.5–4.7)	470 (280–660)	2.4% (1.5%–3.4%)	4.4 (2.6–6.4)
160 (80–260)	1.0% (0.5%–1.7%)	1.8 (0.8–3.3)	430 (220–650)	1.5% (0.8%–2.3%)	2.5 (1.2–3.9)
40 (10–60)	0.7% (0.3%–1.1%)	1.0 (0.3–1.8)	100 (40–170)	1.0% (0.4%–1.8%)	1.4 (0.5–2.6)
10 (10–20)	1.9% (1.3%–2.6%)	3.3 (1.9–4.9)	50 (40–70)	2.6% (2.0%–3.4%)	6.3 (4.6–8.4)
20 (10–20)	2.1% (1.4%–2.8%)	4.4 (2.6–6.5)	50 (40–70)	2.5% (1.9%–3.2%)	6.5 (4.5–8.7)
<5 (<5–5)	1.7% (1.1%–2.3%)	3.0 (1.7–4.4)	10 (10–20)	2.7% (2.0%–3.4%)	5.8 (3.9–7.6)
60 (20–110)	0.7% (0.3%–1.2%)	1.0 (0.3–1.8)	210 (70–390)	1.3% (0.4%–2.4%)	1.8 (0.6–3.4)
7 (<5–10)	1.1% (0.6%–1.7%)	1.8 (0.8–3.1)	20 (10–30)	1.7% (1.0%–2.4%)	2.7 (1.4–4.0)
80 (50–120)	1.3% (0.7%–2.0%)	1.8 (1.0–2.9)	280 (160–410)	2.3% (1.3%–3.3%)	3.4 (1.9–5.1)
30 (20–60)	0.6% (0.3%–1.0%)	0.9 (0.4–1.6)	140 (60–220)	1.3% (0.6%–2.1%)	2.0 (0.9–3.3)
30 (10–50)	0.8% (0.4%–1.5%)	1.7 (0.6–3.1)	90 (40–150)	1.3% (0.5%–2.0%)	2.5 (1.0–4.2)
1,400 (740–2,100)	1.3% (0.7%–2.1%)	2.0 (1.0–3.4)	3,600 (2,100–5,200)	1.9% (1.1%–2.8%)	2.8 (1.6–4.2)

Supplementary Table 4. Number of alcohol-attributable cancer cases, population attributable fraction, and age-standardised incidence rate of alcohol-attributable cases in 2020, by country and sex. Number of cases suppressed if less than five. (*continued*)

				Males		
Continent	**Region**	**Human Development Index**	**Country**	**Alcohol-attributable cases**	**PAF**	**ASIR per 100,000**
Latin America and the Caribbean	Latin America and the Caribbean	Medium HDI	Nicaragua	90 (40–150)	2.6% (1.2%–4.2%)	3.9 (1.8–6.3)
Latin America and the Caribbean	Latin America and the Caribbean	Very high HDI	Panama	110 (70–130)	2.8% (2.0%–3.5%)	4.7 (3.3–6.1)
Latin America and the Caribbean	Latin America and the Caribbean	High HDI	Paraguay	260 (180–320)	4.1% (2.9%–5.2%)	8.6 (5.9–11.0)
Latin America and the Caribbean	Latin America and the Caribbean	High HDI	Peru	750 (450–1,000)	2.4% (1.5%–3.2%)	4.7 (2.7–6.4)
Latin America and the Caribbean	Latin America and the Caribbean	Missing	Puerto Rico	290 (230–360)	4.4% (3.4%–5.4%)	10.5 (7.9–13.1)
Latin America and the Caribbean	Latin America and the Caribbean	High HDI	Saint Lucia	9 (7–10)	3.5% (2.7%–4.3%)	8.5 (5.9–11.0)
Latin America and the Caribbean	Latin America and the Caribbean	High HDI	Suriname	20 (9–20)	3.1% (1.8%–4.4%)	5.8 (3.2–8.3)
Latin America and the Caribbean	Latin America and the Caribbean	High HDI	Trinidad and Tobago	50 (30–70)	2.6% (1.6%–3.4%)	5.8 (3.5–7.8)
Latin America and the Caribbean	Latin America and the Caribbean	Very high HDI	Uruguay	380 (260–460)	4.8% (3.4%–5.9%)	15.0 (10.5–18.4)
Latin America and the Caribbean	Latin America and the Caribbean	High HDI	Venezuela, Bolivarian Republic of	950 (670–1,200)	3.8% (2.7%–4.8%)	6.4 (4.4–8.1)
North America	North America	Very high HDI	Canada	4,600 (3,300–5,600)	4.2% (3.0%–5.1%)	12.9 (9.3–16.0)
North America	North America	Very high HDI	United States of America	33,900 (22,900–43,300)	3.8% (2.6%–4.9%)	12.6 (8.4–16.2)
Oceania	Australia and New Zealand	Very high HDI	Australia	3,700 (2,800–4,500)	4.9% (3.7%–6.0%)	17.6 (12.9–21.7)
Oceania	Australia and New Zealand	Very high HDI	New Zealand	570 (410–700)	4.2% (3.1%–5.2%)	13.8 (9.7–17.0)

Females			Total		
Alcohol-attributable cases	PAF	ASIR per 100,000	Alcohol-attributable cases	PAF	ASIR per 100,000
40 (20–70)	0.9% (0.4%–1.5%)	1.4 (0.6–2.4)	130 (60–210)	1.7% (0.8%–2.7%)	2.5 (1.1–4.1)
60 (40–90)	1.5% (1.0%–2.4%)	2.4 (1.3–4.0)	160 (110–220)	2.2% (1.5%–3.0%)	3.5 (2.2–5.0)
100 (60–160)	1.7% (1.0%–2.5%)	3.4 (1.6–5.7)	360 (240–480)	2.9% (1.9%–3.8%)	6.0 (3.7–8.3)
480 (270–710)	1.3% (0.7%–2.0%)	2.7 (1.3–4.4)	1,200 (720–1,700)	1.8% (1.1%–2.6%)	3.6 (2.0–5.3)
120 (80–160)	2.1% (1.5%–2.8%)	3.7 (2.3–5.3)	410 (310–520)	3.3% (2.5%–4.2%)	6.7 (4.8–8.7)
<5 (<5–6)	2.2% (1.4%–3.2%)	3.4 (1.7–5.3)	10 (10–20)	3.0% (2.2%–3.8%)	5.8 (3.7–8.0)
7 (<5–10)	1.3% (0.7%–2.0%)	2.1 (1.0–3.5)	20 (10–30)	2.2% (1.2%–3.2%)	3.7 (1.9–5.6)
30 (20–40)	1.4% (0.8%–2.1%)	2.7 (1.4–4.4)	80 (50–110)	2.0% (1.2%–2.8%)	4.1 (2.4–5.9)
170 (100–250)	2.4% (1.4%–3.5%)	5.6 (3.0–8.8)	550 (370–710)	3.7% (2.5%–4.8%)	9.7 (6.3–12.9)
520 (290–770)	1.8% (1.0%–2.6%)	3.0 (1.6–4.8)	1,500 (960–2,000)	2.7% (1.8%–3.6%)	4.6 (2.9–6.3)
2,400 (1,500–3,400)	2.3% (1.5%–3.3%)	6.9 (4.0–10.4)	7,000 (4,900–9,000)	3.3% (2.3%–4.2%)	9.8 (6.5–13.0)
18,800 (11,500–26,800)	2.2% (1.3%–3.1%)	6.7 (3.7–10.3)	52,700 (34,400–70,100)	3.0% (2.0%–4.0%)	9.5 (5.9–13.1)
2,200 (1,400–3,100)	3.3% (2.2%–4.6%)	10.5 (6.1–15.9)	5,800 (4,200–7,500)	4.1% (3.0%–5.3%)	13.9 (9.4–18.7)
370 (230–530)	3.1% (1.9%–4.3%)	9.1 (5.1–14.0)	940 (640–1,200)	3.7% (2.5%–4.8%)	11.3 (7.3–15.4)

Supplementary Table 4. Number of alcohol-attributable cancer cases, population attributable fraction, and age-standardised incidence rate of alcohol-attributable cases in 2020, by country and sex. Number of cases suppressed if less than five. (*continued*)

				Males		
Continent	**Region**	**Human Development Index**	**Country**	**Alcohol-attributable cases**	**PAF**	**ASIR per 100,000**
Oceania	Melanesia, Micronesia and Polynesia	High HDI	Fiji	10 (5–20)	2.3% (0.8%–4.0%)	3.0 (1.1–5.4)
Oceania	Melanesia, Micronesia and Polynesia	Missing	France, New Caledonia	7 (<5–10)	1.1% (0.2%–1.6%)	3.7 (0.8–5.7)
Oceania	Melanesia, Micronesia and Polynesia	Missing	French Polynesia	5 (<5–8)	1.1% (0.2%–1.6%)	3.0 (0.6–4.6)
Oceania	Melanesia, Micronesia and Polynesia	Missing	Guam	<5 (1–6)	1.7% (0.4%–2.7%)	3.6 (0.8–6.0)
Oceania	Melanesia, Micronesia and Polynesia	Medium HDI	Papua New Guinea	120 (6–260)	2.4% (0.1%–5.2%)	4.8 (0.2–10.3)
Oceania	Melanesia, Micronesia and Polynesia	High HDI	Samoa	<5 (<5–5)	2.1% (0.9%–3.1%)	4.6 (2.0–7.2)
Oceania	Melanesia, Micronesia and Polynesia	Medium HDI	Solomon Islands	<5 (<5–8)	1.3% (0.1%–3.1%)	1.6 (0.2–4.1)
Oceania	Melanesia, Micronesia and Polynesia	Medium HDI	Vanuatu	<5 (<5–<5)	1.2% (0.2%–3.0%)	1.2 (0.1–3.2)

Numbers in parentheses are 95% Uncertainty Intervals. Cases may not sum due to rounding.
PAF, Population-attributable Fraction; ASIR, Age-standardised incidence rate of alcohol-attributable cases.

Females			Total		
Alcohol-attributable cases	**PAF**	**ASIR per 100,000**	**Alcohol-attributable cases**	**PAF**	**ASIR per 100,000**
5 (<5–9)	0.6% (0.2%–1.0%)	1.1 (0.4–2.0)	20 (7–30)	1.2% (0.5%–2.2%)	2.0 (0.7–3.6)
<5 (<5–<5)	0.3% (0.1%–0.5%)	1.0 (0.3–1.5)	8 (<5–10)	0.7% (0.2%–1.1%)	2.3 (0.5–3.6)
<5 (<5–<5)	0.3% (0.1%–0.4%)	0.6 (0.2–1.0)	6 (<5–9)	0.7% (0.2%–1.1%)	1.8 (0.4–2.8)
<5 (<5–<5)	0.3% (0.1%–0.4%)	0.5 (0.1–0.8)	<5 (<5–7)	1.0% (0.2%–1.6%)	2.0 (0.4–3.4)
20 (2–50)	0.4% (0.0%–0.7%)	0.7 (0.1–1.5)	140 (8–310)	1.3% (0.1%–2.7%)	2.6 (0.1–5.6)
<5 (<5–<5)	0.6% (0.2%–1.0%)	1.4 (0.5–2.5)	5 (<5–7)	1.3% (0.5%–2.0%)	2.9 (1.2–4.8)
<5 (<5–<5)	0.3% (0.0%–0.6%)	0.4 (0.1–1.0)	<5 (<5–10)	0.7% (0.1%–1.6%)	1.0 (0.1–2.5)
<5 (<5–<5)	0.2% (0.0%–0.4%)	0.2 (0.0–0.5)	<5 (<5–<5)	0.7% (0.1%–1.7%)	0.7 (0.1–1.8)

Supplementary Table 5. Global number of alcohol-attributable cancer cases in 2020, by alcohol consumption category, world region, Human Development Index, and sex. Number of cases suppressed if less than five.

		Alcohol-attributable cases			Percentage of total alcohol-attributable cases		
World Region	**Level of alcohol consumption (grams ethanol per day)**	**Males**	**Females**	**Total**	**Males**	**Females**	**Total**
Africa							
Eastern Africa	Moderate (<20 g)	550	650	1,200	9.1%	28.4%	14.4%
		(430–1,100)	(490–3,000)	(920–4,000)			
	Risky (20-60 g)	1,900	960	2,800	30.9%	42.0%	34.0%
		(1,400–2,100)	(640–1,300)	(2,000–3,400)			
	Heavy (>60 g)	3,600	680	4,300	60.0%	29.5%	51.6%
		(2,200–5,400)	(420–1,200)	(2,600–6,600)			
Middle Africa	Moderate (<20 g)	240	270	510	12.5%	36.6%	19.2%
		(150–300)	(170–350)	(330–640)			
	Risky (20-60 g)	690	330	1,000	36.2%	44.2%	38.4%
		(420–870)	(210–470)	(630–1,300)			
	Heavy (>60 g)	980	140	1,100	51.3%	19.2%	42.3%
		(600–1,500)	(70–260)	(670–1,800)			
Northern Africa	Moderate (<20 g)	170	80	260	21.2%	46.8%	25.8%
		(30–9,200)	(20–560)	(50–9,800)			
	Risky (20-60 g)	360	70	430	44.2%	37.0%	42.9%
		(70–710)	(30–160)	(100–870)			
	Heavy (>60 g)	280	30	310	34.6%	16.1%	31.3%
		(80–1,400)	(10–120)	(90–1,600)			

Supplementary Table 5. Global number of alcohol-attributable cancer cases in 2020, by alcohol consumption category, world region, Human Development Index, and sex. Number of cases suppressed if less than five. (*continued*)

		Alcohol-attributable cases			Percentage of total alcohol-attributable cases		
World Region	**Level of alcohol consumption (grams ethanol per day)**	**Males**	**Females**	**Total**	**Males**	**Females**	**Total**
Southern Africa	Moderate (<20 g)	110	200	310	3.9%	14.6%	7.4%
		(80–150)	(150–260)	(230–400)			
	Risky (20-60 g)	660	570	1,200	23.2%	42.0%	29.3%
		(550–740)	(400–710)	(960–1,400)			
	Heavy (>60 g)	2,100	590	2,700	72.9%	43.4%	63.4%
		(1,400–2,700)	(230–1,000)	(1,600–3,700)			
Western Africa	Moderate (<20 g)	290	530	820	6.6%	20.0%	11.7%
		(170–540)	(380–730)	(550–1,300)			
	Risky (20-60 g)	1,200	1,100	2,300	27.6%	42.8%	33.4%
		(750–1,500)	(830–1,500)	(1,600–2,900)			
	Heavy (>60 g)	2,900	990	3,900	65.8%	37.2%	55.0%
		(1,600–4,500)	(520–1,600)	(2,100–6,100)			
Asia							
Eastern Asia	Moderate (<20 g)	27,800	22,600	50,400	10.1%	40.2%	15.2%
		(18,000–38,800)	(17,300–27,400)	(35,300–66,100)			
	Risky (20-60 g)	107,900	28,200	136,100	39.1%	50.1%	41.0%
		(79,900–122,400)	(14,400–41,600)	(94,300–164,000)			
	Heavy (>60 g)	140,200	5,400	145,700	50.8%	9.7%	43.9%
		(54,900–231,600)	(1,100–16,900)	(56,000–248,500)			

Supplementary Table 5. Global number of alcohol-attributable cancer cases in 2020, by alcohol consumption category, world region, Human Development Index, and sex. Number of cases suppressed if less than five. (*continued*)

		Alcohol-attributable cases			Percentage of total alcohol-attributable cases		
World Region	**Level of alcohol consumption (grams ethanol per day)**	**Males**	**Females**	**Total**	**Males**	**Females**	**Total**
South-Central Asia	Moderate (<20 g)	5,800	3,200	8,900	9.8%	35.4%	13.1%
		(4,300–63,900)	(2,500–45,700)	(6,800–109,600)			
	Risky (20-60 g)	20,200	4,300	24,500	34.2%	48.4%	36.0%
		(12,800–23,300)	(1,200–6,600)	(13,900–29,900)			
	Heavy (>60 g)	33,200	1,400	34,600	56.1%	16.2%	50.8%
		(6,300–58,200)	(330–5,000)	(6,600–63,200)			
South-Eastern Asia	Moderate (<20 g)	2,800	1,900	4,600	12.1%	39.6%	16.8%
		(1,700–3,500)	(1,300–2,300)	(3,000–5,800)			
	Risky (20-60 g)	8,800	2,200	11,100	38.4%	47.5%	39.9%
		(5,800–11,100)	(1,500–3,100)	(7,300–14,200)			
	Heavy (>60 g)	11,400	610	12,000	49.6%	12.9%	43.3%
		(5,900–19,300)	(250–1,400)	(6,200–20,600)			
Western Asia	Moderate (<20 g)	140	230	370	6.2%	30.6%	12.3%
		(110–2,000)	(170–5,000)	(280–7,000)			
	Risky (20-60 g)	680	310	990	30.3%	41.1%	33.0%
		(500–820)	(190–410)	(690–1,200)			
	Heavy (>60 g)	1,400	210	1,600	63.5%	28.3%	54.7%
		(700–2,100)	(70–440)	(770–2,600)			
Europe							

Supplementary Table 5. Global number of alcohol-attributable cancer cases in 2020, by alcohol consumption category, world region, Human Development Index, and sex. Number of cases suppressed if less than five. (*continued*)

		Alcohol-attributable cases			Percentage of total alcohol-attributable cases		
World Region	**Level of alcohol consumption (grams ethanol per day)**	**Males**	**Females**	**Total**	**Males**	**Females**	**Total**
Central and Eastern Europe	Moderate (<20 g)	1,800	3,700	5,500	3.6%	17.1%	7.7%
		(1,500–2,100)	(2,800–4,500)	(4,300–6,600)			
	Risky (20-60 g)	13,300	10,400	23,700	26.6%	48.3%	33.1%
		(11,700–14,300)	(8,400–12,100)	(20,000–26,400)			
	Heavy (>60 g)	34,800	7,400	42,200	69.7%	34.6%	59.2%
		(27,700–40,900)	(4,800–10,800)	(32,400–51,700)			
Northern Europe	Moderate (<20 g)	620	2,500	3,100	4.0%	26.8%	12.4%
		(480–740)	(1,900–3,000)	(2,300–3,700)			
	Risky (20-60 g)	5,200	4,800	10,000	33.3%	52.8%	40.5%
		(4,500–5,600)	(3,600–6,000)	(8,000–11,700)			
	Heavy (>60 g)	9,800	1,900	11,700	62.8%	20.4%	47.1%
		(7,200–12,200)	(960–3,400)	(8,200–15,600)			
Southern Europe	Moderate (<20 g)	1,200	3,100	4,300	5.4%	33.0%	13.3%
		(910–1,500)	(2,300–3,800)	(3,200–5,300)			
	Risky (20-60 g)	8,500	4,800	13,300	36.8%	51.8%	41.1%
		(7,000–9,400)	(3,400–6,200)	(10,400–15,600)			
	Heavy (>60 g)	13,400	1,400	14,800	57.8%	15.2%	45.6%
		(9,600–17,200)	(850–2,400)	(10,500–19,700)			
Western Europe	Moderate (<20 g)	1,600	5,000	6,700	4.7%	27.3%	12.6%

Supplementary Table 5. Global number of alcohol-attributable cancer cases in 2020, by alcohol consumption category, world region, Human Development Index, and sex. Number of cases suppressed if less than five. (*continued*)

		Alcohol-attributable cases			Percentage of total alcohol-attributable cases		
World Region	**Level of alcohol consumption (grams ethanol per day)**	**Males**	**Females**	**Total**	**Males**	**Females**	**Total**
		(1,200–1,900)	(3,900–6,100)	(5,100–8,000)			
	Risky (20-60 g)	11,200	9,700	20,900	32.5%	52.6%	39.5%
		(9,600–12,100)	(7,600–11,900)	(17,200–24,000)			
	Heavy (>60 g)	21,600	3,700	25,300	62.8%	20.1%	47.9%
		(16,100–26,700)	(2,100–6,000)	(18,200–32,700)			
Latin America and the Caribbean							
Latin America and the Caribbean	Moderate (<20 g)	1,700	4,000	5,700	6.5%	31.4%	14.4%
		(1,300–2,100)	(2,900–5,000)	(4,300–7,100)			
	Risky (20-60 g)	9,300	6,500	15,800	34.9%	51.8%	40.3%
		(7,800–10,300)	(4,600–8,400)	(12,400–18,600)			
	Heavy (>60 g)	15,700	2,100	17,800	58.7%	16.7%	45.3%
		(10,500–20,700)	(1,100–4,200)	(11,500–24,900)			
North America							
North America	Moderate (<20 g)	2,300	7,200	9,500	6.0%	34.2%	16.0%
		(1,600–2,900)	(5,400–9,000)	(7,100–11,900)			
	Risky (20-60 g)	13,800	11,000	24,800	35.8%	52.1%	41.6%
		(11,200–15,200)	(6,500–15,200)	(17,700–30,400)			
	Heavy (>60 g)	22,400	2,900	25,300	58.2%	13.7%	42.4%
		(12,800–31,500)	(850–6,800)	(13,700–38,300)			

Supplementary Table 5. Global number of alcohol-attributable cancer cases in 2020, by alcohol consumption category, world region, Human Development Index, and sex. Number of cases suppressed if less than five. (*continued*)

		Alcohol-attributable cases			Percentage of total alcohol-attributable cases		
World Region	**Level of alcohol consumption (grams ethanol per day)**	**Males**	**Females**	**Total**	**Males**	**Females**	**Total**
Oceania							
Australia and New Zealand	Moderate (<20 g)	180	700	880	4.3%	27.5%	13.0%
		(130–220)	(530–870)	(660–1,100)			
	Risky (20-60 g)	1,400	1,400	2,700	32.9%	53.1%	40.5%
		(1,200–1,500)	(940–1,800)	(2,100–3,300)			
	Heavy (>60 g)	2,700	500	3,200	62.8%	19.4%	46.4%
		(1,800–3,400)	(190–1,000)	(1,900–4,400)			
Melanesia, Micronesia and Polynesia	Moderate (<20 g)	30	20	60	22.0%	64.7%	29.5%
		(10–40)	(10–30)	(10–70)			
	Risky (20-60 g)	80	10	90	49.6%	32.9%	46.7%
		(10–110)	(<5–30)	(10–140)			
	Heavy (>60 g)	40	<5	50	28.4%	2.4%	23.9%
		(10–180)	(<5–10)	(10–190)			
HDI							
Very high HDI	Moderate (<20 g)	12,500	27,400	39,900	6.2%	29.6%	13.5%
		(9,700–14,700)	(21,300–33,900)	(31,000–48,500)			
	Risky (20-60 g)	71,100	47,100	118,300	35.0%	50.9%	40.0%
		(59,600–77,900)	(36,800–56,500)	(96,400–134,400)			
	Heavy (>60 g)	119,500	18,100	137,500	58.8%	19.5%	46.5%

Supplementary Table 5. Global number of alcohol-attributable cancer cases in 2020, by alcohol consumption category, world region, Human Development Index, and sex. Number of cases suppressed if less than five. (*continued*)

		Alcohol-attributable cases			Percentage of total alcohol-attributable cases		
World Region	**Level of alcohol consumption (grams ethanol per day)**	**Males**	**Females**	**Total**	**Males**	**Females**	**Total**
		(91,000–147,100)	(13,600–26,100)	(104,600–173,100)			
High HDI	Moderate (<20 g)	27,300	23,500	50,800	9.4%	36.0%	14.2%
		(18,100–40,700)	(18,200–36,500)	(36,300–77,200)			
	Risky (20-60 g)	108,500	32,700	141,200	37.2%	50.3%	39.6%
		(80,600–123,100)	(18,600–45,900)	(99,200–169,000)			
	Heavy (>60 g)	155,600	8,900	164,500	53.4%	13.6%	46.1%
		(69,900–247,400)	(4,500–21,000)	(74,400–268,400)			
Medium HDI	Moderate (<20 g)	6,400	3,700	10,100	10.2%	36.8%	13.8%
		(4,900–62,700)	(2,800–43,200)	(7,700–105,900)			
	Risky (20-60 g)	21,900	4,800	26,700	34.8%	48.3%	36.6%
		(14,400–25,000)	(1,600–7,200)	(16,100–32,200)			
	Heavy (>60 g)	34,700	1,500	36,200	55.0%	14.9%	49.6%
		(7,600–59,800)	(390–5,200)	(8,000–65,000)			
Low HDI	Moderate (<20 g)	810	1,100	1,900	8.6%	23.2%	13.4%
		(630–3,800)	(820–7,900)	(1,400–11,600)			
	Risky (20-60 g)	2,800	1,900	4,600	29.3%	41.3%	33.2%
		(2,000–3,200)	(1,400–2,400)	(3,400–5,600)			
	Heavy (>60 g)	5,800	1,600	7,500	62.1%	35.5%	53.4%
		(3,800–8,400)	(1,000–2,500)	(4,800–10,900)			

Supplementary Table 5. Global number of alcohol-attributable cancer cases in 2020, by alcohol consumption category, world region, Human Development Index, and sex. Number of cases suppressed if less than five. (*continued*)

		Alcohol-attributable cases			Percentage of total alcohol-attributable cases		
World Region	**Level of alcohol consumption (grams ethanol per day)**	**Males**	**Females**	**Total**	**Males**	**Females**	**Total**
Missing	Moderate (<20 g)	280	180	460	16.0%	46.5%	21.3%
		(170–750)	(120–2,400)	(290–3,100)			
	Risky (20-60 g)	820	160	980	46.4%	43.4%	45.8%
		(450–1,100)	(90–270)	(540–1,300)			
	Heavy (>60 g)	670	40	710	37.7%	10.1%	32.8%
		(300–1,300)	(20–80)	(320–1,400)			
World	Moderate (<20 g)	47,300	55,800	103,100	8.3%	32.3%	13.9%
		(37,200–103,600)	(45,400–103,600)	(82,600–207,200)			
	Risky (20-60 g)	205,100	86,700	291,800	36.1%	50.3%	39.4%
		(161,700–226,700)	(66,000–106,400)	(227,700–333,100)			
	Heavy (>60 g)	316,300	30,100	346,400	55.6%	17.4%	46.7%
		(205,200–442,400)	(22,700–47,000)	(227,900–489,400)			

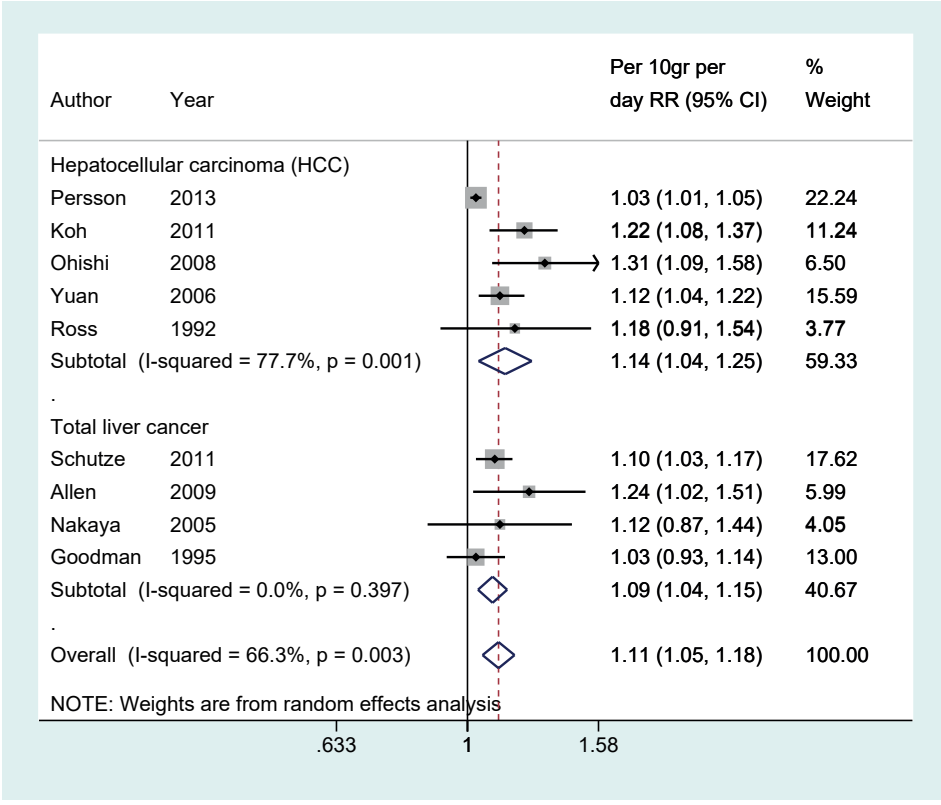
Numbers in parentheses are 95% Uncertainty Intervals. Cases and percentages may not sum due to rounding. HDI, Human Development Index

Missing HDI assigned to the following countries: French Guiana, French Polynesia, Guadeloupe, Guam, Korea (the Democratic People's Republic of), Martinique, New Caledonia, Puerto Rico, Reunion, and Somalia.

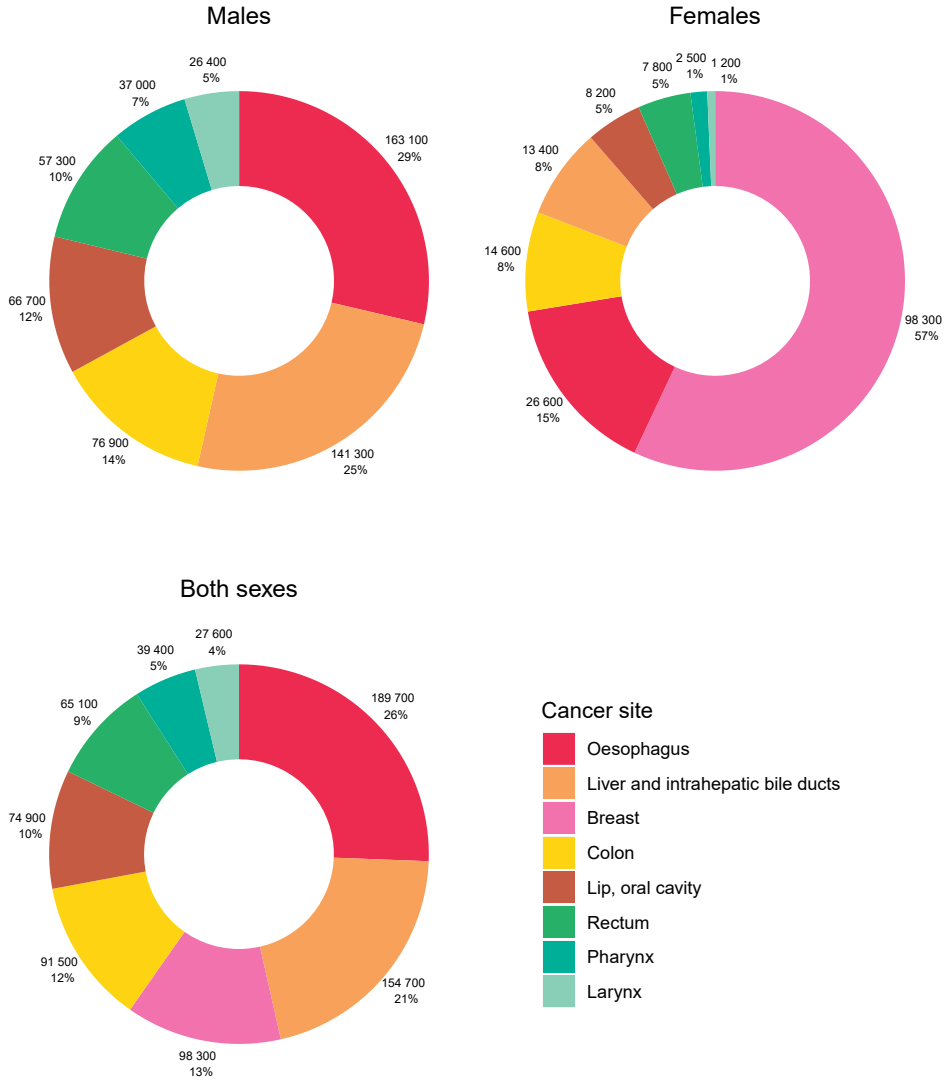
Supplementary Table 6. Global number of alcohol-attributable cancer cases, by 10 g per day increase in alcohol consumption and sex.

Level of alcohol consumption (grams ethanol per day)	Alcohol-attributable cases			Percentage of total alcohol-attributable cases		
	Males	Females	Total	Males	Females	Total
<10	16,700	24,600	41,300	2.9%	14.3%	5.6%
	(14,300–75,400)	(21,100–70,400)	(35,400–145,800)			
10-20	30,700	31,100	61,800	5.4%	18.0%	8.3%
	(22,900–38,100)	(24,000–37,300)	(47,000–75,400)			
20-30	49,900	32,200	82,000	8.8%	18.6%	11.1%
	(40,300–56,000)	(24,900–37,700)	(65,200–93,700)			
30-40	52,500	24,300	76,800	9.2%	14.1%	10.4%
	(41,400–57,600)	(17,900–29,700)	(59,300–87,300)			
40-50	52,300	17,700	69,900	9.2%	10.2%	9.4%
	(40,200–57,900)	(13,000–22,700)	(53,300–80,600)			
50-60	50,500	12,600	63,100	8.9%	7.3%	8.5%
	(37,000–57,500)	(9,000–16,800)	(46,000–74,400)			
60-70	47,800	9,000	56,700	8.4%	5.2%	7.7%
	(34,200–56,500)	(6,400–12,700)	(40,600–69,200)			
70-80	44,600	6,400	50,900	7.8%	3.7%	6.9%
	(30,400–54,600)	(4,700–9,500)	(35,100–64,100)			
80-90	41,200	4,500	45,800	7.3%	2.6%	6.2%
	(26,900–53,600)	(3,200–7,200)	(30,100–60,800)			
90-100	37,900	3,200	41,100	6.7%	1.9%	5.5%
	(24,600–51,500)	(2,400–5,500)	(27,100–57,000)			
100-110	34,600	2,300	37,000	6.1%	1.4%	5.0%
	(21,700–49,000)	(1,700–4,100)	(23,500–53,200)			
110-120	31,600	1,700	33,300	5.6%	1.0%	4.5%
	(20,600–47,900)	(1,300–3,300)	(21,900–51,200)			
120-130	28,700	1,300	30,000	5.1%	0.7%	4.0%
	(17,600–45,700)	(930–2,500)	(18,600–48,100)			
130-140	26,100	940	27,100	4.6%	0.5%	3.7%
	(16,000–44,300)	(720–2,000)	(16,700–46,300)			
140-150	23,700	710	24,400	4.2%	0.4%	3.3%
	(14,000–43,400)	(550–1,500)	(14,500–44,800)			

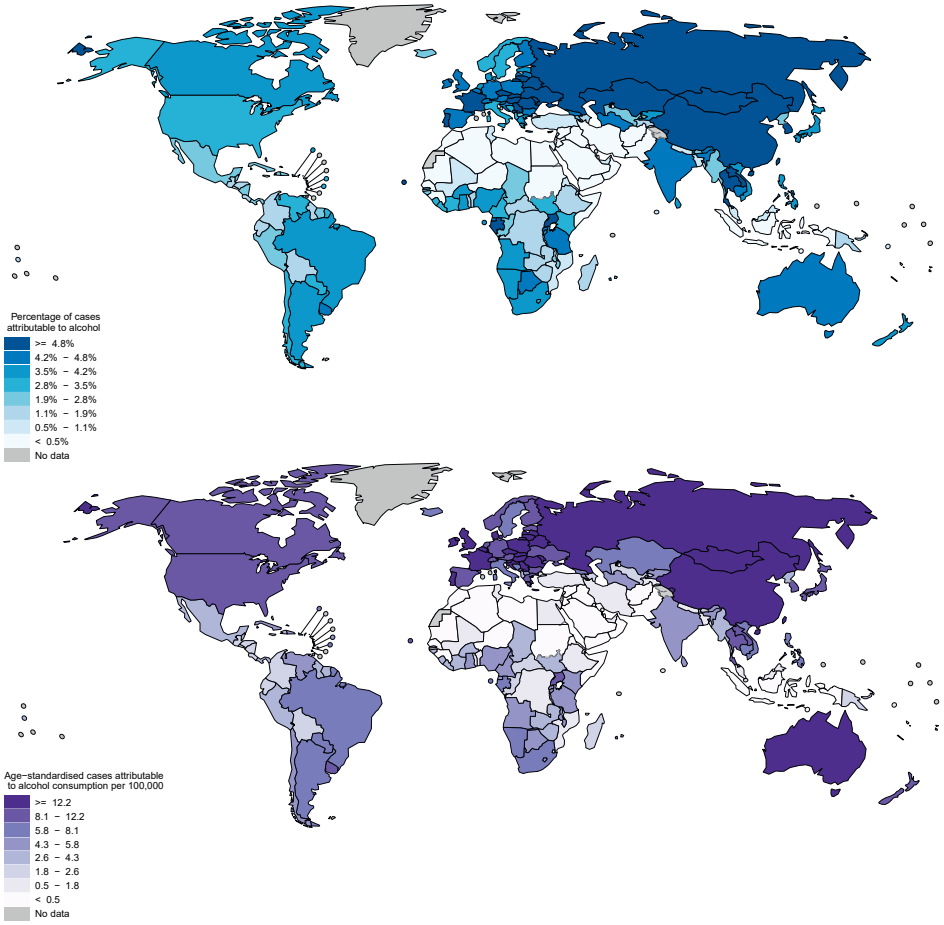
Numbers in parentheses are 95% Uncertainty Intervals. Cases and percentages may not sum due to rounding.



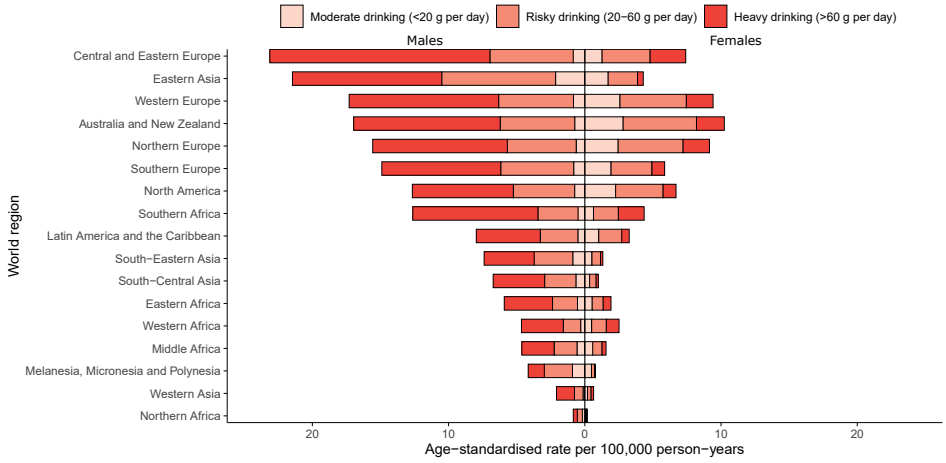
Supplementary Figure 1. Dose-response meta-analysis per 10 g per day of alcohol intake and liver cancer stratified by hepatocellular carcinoma (HCC) or total liver cancer.



Supplementary Figure 2. Cancers attributable to alcohol consumption according to cancer site in males, females, and both sexes combined, in 2020.



Supplementary Figure 3. Population attributable fraction and age-standardised incidence rate of alcohol-attributable cancer cases in both sexes combined in 2020, by country.



Supplementary Figure 4. Age-standardised incidence rate (ASIR) of alcohol-attributable cancer cases by alcohol consumption category, sex, and world region.

Supplementary Figure 5. Cancers attributable to alcohol consumption according to cancer site and region, both sexes combined, in 2020.

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Chapter 1

The fraction of cancer attributable to modifiable risk factors in England, Wales, Scotland, Northern Ireland, and the United Kingdom in 2015

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Parkin DM

The fraction of cancer attributable to modifiable risk factors in England, Wales, Scotland, Northern Ireland, and the United Kingdom in 2015.

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ABSTRACT

Background: Changing population-level exposure to modifiable risk factors is a key driver of changing cancer incidence. Understanding these changes is therefore vital when prioritising risk-reduction policies, in order to have the biggest impact on reducing cancer incidence. UK figures on the number of risk factor-attributable cancers are updated here to reflect changing behaviour as assessed in representative national surveys, and new epidemiological evidence. Figures are also presented by UK constituent country because prevalence of risk factor exposure varies between them.

Methods: Population attributable fractions (PAFs) were calculated for combinations of risk factor and cancer type with sufficient/convincing evidence of a causal association. Relative risks (RRs) were drawn from meta-analyses of cohort studies where possible. Prevalence of exposure to risk factors was obtained from nationally representative population surveys. Cancer incidence data for 2015 were sourced from national data releases and, where needed, personal communications. PAF calculations were stratified by age, sex and risk factor exposure level and then combined to create summary PAFs by cancer type, sex and country.

Results: Nearly four in ten (37.7%) cancer cases in 2015 in the UK were attributable to known risk factors. The proportion was around two percentage points higher in UK males (38.6%) than in UK females (36.8%). Comparing UK countries, the attributable proportion was highest in Scotland (41.5% for persons) and lowest in England (37.3% for persons). Tobacco smoking contributed by far the largest proportion of attributable cancer cases, followed by overweight/obesity, accounting for 15.1% and 6.3%, respectively, of all cases in the UK in 2015. For 10 cancer types, including two of the five most common cancer types in the UK (lung cancer and melanoma skin cancer), more than 70% of UK cancer cases were attributable to known risk factors.

Conclusion: Tobacco and overweight/obesity remain the top contributors of attributable cancer cases. Tobacco smoking has the highest PAF because it greatly increases cancer risk and has a large number of cancer types associated with it. Overweight/obesity has the second-highest PAF because it affects a high proportion of the UK population and is also linked with many cancer types. Public health policy may seek to mitigate the level of harm associated with exposure or reduce exposure levels—both approaches may effectively impact cancer incidence. Differences in PAFs between countries and sexes are primarily due to varying prevalence of exposure to risk factors and varying proportions of specific cancer types. This variation in turn is affected by socio-demographic differences which drive differences in exposure to theoretically avoidable 'lifestyle' factors. PAFs at UK country level have not been available previously and they should be used by policymakers in devolved nations. PAFs are estimates based on the best available data, limitations in those data would generally bias toward underestimation of PAFs. Regular collection of risk factor exposure prevalence data

which corresponds with epidemiological evidence is vital for analyses like this and should remain a priority for the UK Government and devolved Administrations.

INTRODUCTION

Over the last decade, age-standardised incidence rates for all cancers combined (International Classification of Diseases version 10 [ICD-10][1] C00-C97 excluding C44) have increased by 7% in the UK, with a larger increase in females (8%) than in males (3%).[2,3] Over the next two decades, incidence rates for all cancers combined are projected to rise by 2% in the UK; this slower pace of increase is in part due to falling smoking rates since the 1970s, the impact of which will be seen most clearly in future decades.[4] Changes in exposure to risk factors are key drivers of changes in cancer incidence, with improvements in cancer diagnosis and data capture contributing to a lesser extent. Quantifying the contribution of these risk factors indicates the reduction in cancer incidence, which could be achieved through risk exposure reduction or removal.

Efforts to reduce exposure to theoretically modifiable cancer risk factors at individual and societal level may be hampered by the breadth of factors implicated (and possibly limited awareness of some of those factors),[2,3] and a lack of clarity on which factors have the most impact on cancer risk, and therefore which to prioritise. Risk factors which contribute the most cases to the overall cancer burden are either those with the highest relative risks associated with exposure, those with the highest exposure prevalence in the population, those with the largest number of associated common cancer types, or combinations thereof. Parkin et al.[5] published novel data on the burden of theoretically avoidable cancer in the UK in 2010. These have informed tobacco, alcohol and obesity policy in the UK, as well as inspiring similar work internationally.[6]

International versions of Parkin[5,7] work demonstrate how nations differ markedly in the population attributable fractions (PAFs) for specific cancer types and risk factors, and for all cancers and risk factors combined. Several factors underpin true variation between countries. Prevalence of exposure to risk factors varies both with time period and geography. Age and sex profile of cancer cases may vary, often due to different availability of and eligible ages for screening programmes. Morphology breakdowns of individual cancer types (e.g. oesophageal squamous cell carcinoma and adenocarcinoma) vary with risk factor prevalence. Proportions of individual cancer types contributing to the total number of cancers vary due to screening availability and risk factor prevalence. Methodological differences also contribute to PAF differences, for example the relative risks used, calculation methods, and choice of risk factors included.

It is not ideal therefore to use whole-UK PAFs to describe the burden in individual UK countries when many of these factors, most importantly the prevalence of risk factor exposure, is known to vary between them.[8] It is also important to regularly update widely used figures such as these, to incorporate changes over time in risk factor exposure prevalence, new high-quality evidence on relative risks, changes in the demography of cancer patients, and changes in official classifications of risk factor evidence strength (by the International Agency for Research on Cancer [IARC] and World Cancer Research Fund [WCRF]).[9,10]

This update builds on the methodology devised by Parkin et al.[5] to provide 2015 PAFs by cancer type and risk factor for the UK overall and for each constituent country. Differences in methodology compared with Parkin et al.[5] mainly reflect updates to evidence and classifications, and availability and quality of UK country-level exposure prevalence data.

MATERIALS AND METHODS

Risk factors included

Combinations of risk factor and cancer type were included in the analysis if they were, at the time of the literature search for the analysis (April 2017), classified by IARC or WCRF as having 'sufficient' (IARC) or 'convincing' (WCRF) evidence of a causal association.[9,10,11] If both IARC and WCRF had issued a classification on a combination of risk factor and cancer type, then the most recently issued classification was used; the source of each classification used is shown in Supplementary Material A. Cancer types with no risk factors classified as having 'sufficient' or 'convincing' evidence of a causal association (e.g. prostate and testicular cancers) were not included in any PAF calculations, but were included in the all cancers combined total. For oral contraceptives, which increase risk for some cancer types but decrease risk for others, PAFs were calculated only for the cancer types where risk is increased, as the aim of this study is to quantify cancers caused, not the net effect. Ethics approval was not required and the study was performed in accordance with the Declaration of Helsinki.

PAF formula

For most risk factors, PAFs were calculated using the standard formula described by Parkin et al.[7]

$$\frac{(p_1 \times \mathrm{ERR}_1) + (p_2 \times \mathrm{ERR}_2) + (p_3 \times \mathrm{ERR}_3) \ldots + (p_n \times \mathrm{ERR}_n)}{1 + (p_1 \times \mathrm{ERR}_1) + (p_2 \times \mathrm{ERR}_2) + (p_3 \times \mathrm{ERR}_3) \ldots + (p_n \times \mathrm{ERR}_n)}$$

where p_1 is the proportion of the population in exposure level 1 (and so on) and ERR_1 is the excess relative risk (relative risk − 1) at exposure level 1 (and so on).

Where relative risk (RR) was provided for the presence of/increase in a risk factor when the PAF was to be calculated for the absence of/decrease in that risk factor, ERR was calculated as the natural logarithm of the reciprocal of the RR (ln(1/RR)). Where RR was provided for multiple units when the calculation required ERR per unit, ERR for x units was divided by x to obtain ERR per unit.

For some risk factors PAFs were obtained from other published studies, as was the case in Parkin et al.[5] This applied to PAFs for Epstein–Barr virus,[12] human papillomavirus (HPV),[13,14] Kaposi sarcoma herpesvirus/human herpesvirus 8 (KSHV/HHV8),[15] and diagnostic radiation.[16]

Where IARC/WCRF classifications were specific to cancer type subsites, morphological types, or patient age groups (Supplementary Material C), the number of attributable cases was calculated using only those specific attributes, and the PAF used those specific cases as the numerator and the total cases of that overall cancer type as the denominator. For example, the overweight/obesity PAF for stomach cancer uses the attributable cases of gastric cardia stomach cancer, within the total cases of stomach cancer overall. This applied to meningioma and postmenopausal breast cancer for overweight/obesity (denominators were brain tumours and breast cancers); non-cardia stomach cancer and mucosa-associated lymphoid tissue lymphoma for *Helicobacter pylori* (denominators were stomach cancer and non-Hodgkin lymphoma); conjunctiva for HIV (denominator was eye cancer); salivary gland and all leukaemias excluding chronic lymphocytic leukaemia for ionising radiation (denominators were oral cavity cancer and all leukaemias combined); and mucinous ovarian cancer and acute myeloid leukaemia for tobacco (denominators were ovarian cancer and all leukaemias combined).

Relative risks

RRs were identified through systematic PubMed searches (search terms are shown in Supplementary Material B, selected relative risks and sources are shown in Supplementary Material C). Meta-analyses were the preferred source of RRs, followed by pooled analyses and cohort studies, with case–control studies selected only when no other sources could be found. Within meta- and pooled analyses where multiple analyses were reported, or where more than one meta- or pooled analysis was available, RRs were selected based on characteristics most relevant to the evidence. For example, where statistically significant variation between pooled estimates for different world regions was observed, the Europe/UK estimate was preferred; where there was statistically significant male versus female variation, sex-specific RRs were used; and where confounding was a particular concern, RRs with the most comprehensive adjustment for confounders were selected. Sample size and compatibility with the format of exposure prevalence data were also considered in these decisions, for example, tobacco exposure prevalence was usually defined as cigarette smoking rather than use of other tobacco products, so RRs for cigarettes rather than all tobacco products were used where available. The relative risk of leukaemia associated with ionising radiation exposure was calculated using the formula presented by Parkin et al.[5]

Risk factor exposure prevalence

For the majority of risk factors analysed, cancer risk increases with higher exposure, the optimum exposure level is nil, and the reference category in the RR sources is 'unexposed' (Supplementary Material D). For fibre, physical activity and breastfeeding, increased cancer risk is associated with lower exposure. Fibre exposure prevalence was calculated as deficit against UK Government recommended levels at the time the PAFs were calculated (30 g per day of fibre).[17] Physical activity exposure prevalence was calculated as deficit against the

reference category in the RR source (600 metabolic equivalent [MET]-minutes, or 150 min of moderate-intensity activity per week), because the latest evidence indicates that significant reductions in bowel cancer risk are only achieved at higher physical activity levels than the UK Government recommends.[18] Breastfeeding exposure prevalence was calculated as absence of the behaviour. While the World Health Organization recommendation (based on benefits to the child) is to breastfeed for 6 months,[19] the prevalence data available are insufficient to accurately gauge duration of breastfeeding across all the UK countries. For factors where UK Government recommendations are maximum rather than minimum intake (alcohol and processed meat),[20,21] the optimum exposure was defined as nil.

Prevalence of exposure to risk factors was generally obtained from nationally representative population surveys (Supplementary Material D), at as granular a breakdown of age and sex as the data allowed. Where UK- or Great Britain-wide surveys with a country breakdown provided an adequate sample size for each constituent nation, these were used to afford direct comparability between countries; however, in most cases a separate survey (e.g. national health surveys, which are powered for devolved nations' analysis) was used for each country. Data were obtained for 2005 for each country wherever possible, providing a ten-year lag between risk exposure and cancer incidence. In some cases it was not possible to match years across countries. Conversions or imputations were made where exposure prevalence data were not available for all cohorts required. These calculations are described in Supplementary Material E; where no calculations are described the data were lifted directly from source with no conversion or imputation required. References are provided in the Supplementary Materials.

Incidence

Cancer incidence data for 2015 were obtained for each of the UK constituent countries mainly from their routine annual publications.[22,23,24,25] Generally these publications provided data at the ICD-10 3-digit level. A small number of calculations required incidence data not routinely published: by 4-digit ICD-10 code (e.g. brain, other central nervous system and intracranial tumours), by morphology (e.g. oesophageal squamous cell carcinoma and adenocarcinoma), or for rarer cancer types (e.g. gallbladder and sinonasal cancers). For these calculations, the UK countries' cancer registries kindly provided appropriate data (Information Services Division Scotland, September 2016, Scotland 2012–2014 incidence data for oesophageal adenocarcinoma, oesophageal squamous cell carcinoma, and mucinous ovarian carcinoma, personal communication; Northern Ireland Cancer Registry, November 2016, Northern Ireland 2010–14 incidence data for oesophageal adenocarcinoma, oesophageal squamous cell carcinoma, and mucinous ovarian carcinoma, personal communication; Office for National Statistics, September 2016, England 2014 incidence data for oesophageal adenocarcinoma, oesophageal squamous cell carcinoma, and mucinous ovarian carcinoma, personal communication; Welsh Cancer Intelligence and Surveillance Unit, June 2016, Wales 2012-2014 incidence data for oesophageal adenocarcinoma, oesophageal squamous cell carcinoma, and mucinous ovarian carcinoma, personal communication).

Combining PAFs

PAFs for all risk factors combined, for each cancer type and for all cancers combined, were obtained by first applying the first relevant PAF in the sequence shown in Table 1 to the total number of observed cases, to obtain the number of cases attributable to that factor only. The order of risk factors within the sequence does not affect the result of the sum, the order in Table 1 runs from highest to lowest UK PAF within males, females and persons separately. Each subsequent PAF in the sequence was applied only to the number of observed cases not yet explained by the risk factors earlier in the sequence, as described by Parkin et al.[26] Though the RRs used in the PAFs calculations are generally adjusted and therefore should represent only the effect of the specific risk factor in isolation, residual confounding remains possible. This aggregation method avoids overestimating PAFs for all risk factors combined but does not account for cases caused by exposure to risk factors in combination, e.g. the synergistic effect of tobacco and alcohol on oesophageal cancer risk, or of HPV and tobacco smoking on cervical cancer risk.

RESULTS

Summary results are presented in Tables 1 and 2. More detailed results by risk factor–cancer type combination, cancer type, sex and country are presented in Supplementary Material F (available at https://www.nature.com/articles/s41416-018-0029-6#MOESM1).

Table 1 Summary population attributable fractions and attributable cases, by risk factor, sex and country, 2015

	All cancers excluding non-melanoma skin cancer (ICD-10 C00-C97 excluding C44), 2015									
	England		Scotland		Wales		Northern Ireland		UK	
	PAF (%)	Attrib. cases	PAF (%)	Attrib. cases	PAF (%)	Attrib. cases	PAF (%)	Attrib. cases	PAF (%)	Attrib. cases
Males										
Cancer incidence		152,891		15,184		9,837		4,650		182,562
Tobacco smoking	17.3	26,375	21.1	3,204	18.6	1,832	17.8	830	17.7	32,242
Overweight and obesity	5.2	7,960	6.0	909	4.6	450	5.3	248	5.2	9,567
Occupation	4.9	7,458	5.8	875	5.3	520	5.0	234	5.0	9,087
Radiation—UV	3.9	5,899	3.9	587	3.7	364	3.8	174	3.8	7,025
Insufficient fibre	3.1	4,713	3.5	529	3.3	322	3.7	171	3.1	5,735
Alcohol	3.0	4,634	3.8	572	3.2	319	3.5	164	3.1	5,689

Table 1 Summary population attributable fractions and attributable cases, by risk factor, sex and country, 2015 (*continued*)

	All cancers excluding non-melanoma skin cancer (ICD-10 C00-C97 excluding C44), 2015									
	England		Scotland		Wales		Northern Ireland		UK	
	PAF (%)	Attrib. cases	PAF (%)	Attrib. cases	PAF (%)	Attrib. cases	PAF (%)	Attrib. cases	PAF (%)	Attrib. cases
Infections	3.0	4,539	4.0	608	2.8	279	3.8	178	3.1	5,605
Processed meat	2.0	3,096	2.3	346	2.1	204	2.4	112	2.1	3,758
Radiation—ionising	1.7	2,675	1.6	239	2.0	196	1.7	80	1.7	3,190
Air pollution	1.1	1,636	1.0	146	0.8	82	0.8	38	1.0	1,901
Insufficient physical activity	0.5	794	0.6	85	0.5	51	0.6	27	0.5	957
All of the above	38.0	58,141	43.3	6,567	39.0	3,838	39.9	1,856	38.6	70,425
Females										
Cancer incidence		146,862		16,266		9,251		4,606		176,985
Tobacco smoking	12.1	17,738	15.6	2,532	13.4	1,241	11.3	519	12.4	22,029
Overweight and obesity	7.5	11,036	7.6	1,244	6.4	590	7.0	324	7.5	13,194
Infections	4.0	6,083	5.1	832	3.9	364	4.4	202	4.2	7,481
Radiation—UV	3.8	5,541	3.5	570	3.4	311	3.4	157	3.7	6,579
Alcohol	3.5	5,202	3.3	538	3.3	301	3.5	163	3.5	6,205
Insufficient fibre	3.3	4,917	3.5	564	3.4	316	3.5	161	3.4	5,958
Occupation	2.4	3,528	2.8	462	2.6	241	2.5	114	2.5	4,338
Radiation—ionising	2.1	3,128	1.9	314	2.4	221	2.2	100	2.1	3,764
Not breastfeeding	1.4	2,117	1.5	248	1.4	132	1.9	86	1.5	2,582
Air pollution	1.0	1,442	0.9	142	0.8	74	0.7	32	1.0	1,690
Processed meat	0.9	1,330	0.9	145	0.8	73	1.0	46	0.9	1,594
Postmenopausal hormones	0.7	1,089	0.8	132	1.2	107	0.9	43	0.8	1,371
Insufficient physical activity	0.5	801	0.5	86	0.5	49	0.5	25	0.5	959
Oral contraceptives	0.5	667	0.5	79	0.3	32	0.7	30	0.5	807
All of the above	36.4	53,480	39.7	6,455	36.5	3,373	36.1	1,663	36.8	65,130
Persons										
Cancer incidence		299,753		31,450		19,088		9,256		359,547
Tobacco smoking	14.7	44,113	18.2	5,736	16.1	3,073	14.6%	1,349	15.1	54,271
Overweight and obesity	6.3	18,996	6.8	2,153	5.4%	1,040	6.2	572	6.3	22,761
Radiation—UV	3.8	11,440	3.7	1,157	3.5	675	3.6	332	3.8	13,604
Occupation	3.7	11,078	4.4	1,373	4.0	765	3.8	353	3.8	13,558
Infections	3.5	10,622	4.6	1,441	3.4	643	4.1	380	3.6	13,086
Alcohol	3.3	9,836	3.5	1,110	3.3	621	3.5	327	3.3	11,894

Table 1 Summary population attributable fractions and attributable cases, by risk factor, sex and country, 2015 (*continued*)

	All cancers excluding non-melanoma skin cancer (ICD-10 C00-C97 excluding C44), 2015									
	England		Scotland		Wales		Northern Ireland		UK	
	PAF (%)	Attrib. cases	PAF (%)	Attrib. cases	PAF (%)	Attrib. cases	PAF (%)	Attrib. cases	PAF (%)	Attrib. cases
Insufficient fibre	3.2	9,630	3.5	1,093	3.3	638	3.6	332	3.3	11,693
Radiation—ionising	1.9	5,803	1.8	553	2.2	417	1.9	180	1.9	6,954
Processed meat	1.5	4,426	1.6	490	1.4	276	1.7	159	1.5	5,352
Air pollution	1.0	3,078	0.9	288	0.8	156	0.8	70	1.0	3,591
Not breastfeeding	0.7	2,117	0.8	248	0.7	132	0.9	86	0.7	2,582
Insufficient physical activity	0.5	1,595	0.5	171	0.5	100	0.6	51	0.5	1,917
Postmenopausal hormones	0.4	1,089	0.4	132	0.6	107	0.5	43	0.4	1,371
Oral contraceptives	0.2	667	0.2	79	0.2	32	0.3	30	0.2	807
All of the above	37.3	111,722	41.5	13,038	37.8	7,207	38.0	3,519	37.7	135,507

UK

Nearly four in ten (37.7%) cancer cases in 2015 in the UK were attributable to known risk factors. The proportion was around two percentage points higher in UK males (38.6%) than in UK females (36.8%). Excluding sex-specific cancer types (cervix, ovary, uterus, vagina, vulva, penis [prostate and testicular have no risk factor-attributable cases in these calculations]) and breast cancer, the proportion was much higher in UK males (36.4%) than in UK females (25.6%).

The attributable proportion for all cancers combined was highest in Scotland (41.5% for persons) and lowest in England (37.3% for persons). Between-country variation was marginally larger for males than for females, with around five (males) and four (females) percentage points between highest and lowest.

Tobacco smoking contributed by far the largest proportion of attributable cancer cases, accounting for 15.1% of all cases in the UK in 2015. Smoking had the highest PAF in all the UK countries. The proportion was higher in UK males (17.7%) than in UK females (12.4%), reflecting higher smoking prevalence in males in 2005. The tobacco smoking-attributable proportion of cancer cases was highest in Scotland (18.2% for persons) and lowest in Northern Ireland (14.6% for persons). The cancer types with the highest PAFs for tobacco smoking were lung (72.2% for UK persons) and larynx (64.0% for UK persons).

Overweight and obesity was the second-largest preventable cause of cancer in the UK and accounted for 6.3% of all cases in the UK in 2015. This factor was second-highest in all

Table 2 Summary population attributable fractions and attributable cases, by cancer type, sex and country, 2015

Cancer type and ICD-10 code		All risk factors combined														
		England			Scotland			Wales			Northern Ireland			UK		
		M	*F*	*P*	*M*	*F*	*P*	*M*	*F*	*P*	*M*	*F*	*P*	*M*	*F*	*P*
Oral cavity (C00–C06)	PAF (%)	52.9	34.3	46.3	53.3	32.8	46.2	53.3	32.0	46.4	52.9	32.3	46.8	52.9	34.0	46.3
	Attrib. cases	1,422	515	1,941	188	63	251	44	27	77	22	13	38	1,676	618	2,308
Nasopharynx (C11)	PAF (%)	85.3	84.3	84.9	85.1	84.5	84.9	85.9	85.0	85.8	85.7	84.6	85.5	85.3	84.3	85.0
	Attrib. cases	101	51	153	20	6	25	13	2	15	4	1	5	138	60	198
Pharynx (C09, C10, C12–C14)	PAF (%)	90.2	81.4	88.3	90.5	82.2	88.6	90.5	81.5	88.9	90.4	80.4	88.4	90.2	81.5	88.4
	Attrib. cases	1,621	472	2,100	218	67	286	112	26	139	65	18	84	2,017	584	2,609
Oesophagus (C15)	PAF (%)	60.9	54.4	58.7	61.0	55.2	58.9	59.3	52.3	56.9	55.9	54.9	55.4	60.7	54.4	58.6
	Attrib. cases	3,068	1,306	4,367	363	179	542	188	85	273	72	41	113	3,691	1,612	5,295
Stomach (C16)	PAF (%)	56.4	47.5	53.1	67.6	57.4	64.0	51.3	43.7	48.2	66.0	63.8	65.0	57.3	48.6	54.2
	Attrib. cases	2,009	921	2,925	260	129	390	137	68	203	90	41	130	2,496	1,159	3,649
Bowel (C18-C20)	PAF (%)	57.0	50.8	54.1	59.3	52.3	56.0	56.7	50.1	53.8	58.8	51.5	55.6	57.2	50.9	54.3
	Attrib. cases	10,923	7,895	18,796	1,170	887	2,056	724	492	1,215	375	249	624	13,193	9,523	22,691
Anus (C21)	PAF (%)	88.7	92.5	91.3	88.7	92.5	91.2	88.7	92.5	90.9	88.7	92.5	91.5	88.7	92.5	91.3
	Attrib. cases	357	789	1,146	43	87	130	23	34	57	5	15	20	428	925	1,353
Liver (C22)	PAF (%)	53.0	39.3	48.3	55.7	44.9	52.2	51.7	35.3	47.0	51.0	36.9	45.6	53.2	39.6	48.5
	Attrib. cases	1,579	666	2,255	220	90	311	115	34	150	41	20	61	1,955	811	2,778
Pancreas (C25)	PAF (%)	33.9	28.5	31.2	36.2	31.8	34.0	35.5	29.2	32.2	35.0	27.0	31.3	34.2	28.7	31.5
	Attrib. cases	1,415	1,179	2,596	144	131	276	85	79	164	51	34	86	1,694	1,424	3,120
Gallbladder (C23)	PAF (%)	12.5	23.0	19.9	13.7	24.7	21.8	9.6	18.1	15.5	12.7	21.1	20.7	12.4	22.8	19.9
	Attrib. cases	31	140	171	3	14	17	1	5	7	0	4	4	35	163	198
Larynx (C32)	PAF (%)	73.4	66.0	72.1	74.9	69.8	73.9	76.7	67.3	75.0	74.2	63.0	72.4	73.8	66.5	72.5
	Attrib. cases	1,120	238	1,360	177	40	217	97	20	117	51	9	61	1,444	308	1,754

Table 2 Summary population attributable fractions and attributable cases, by cancer type, sex and country, 2015 (*continued*)

Cancer type and ICD-10 code		All risk factors combined														
		England			Scotland			Wales			Northern Ireland			UK		
		M	*F*	*P*	*M*	*F*	*P*	*M*	*F*	*P*	*M*	*F*	*P*	*M*	*F*	*P*
Lung (C33–C34)	PAF (%)	81.8	74.8	78.8	81.7	76.7	79.4	83.8	77.0	80.8	80.6	68.4	75.4	81.9	75.0	78.9
	Attrib. cases	16,369	13,184	29,631	2,068	1,890	3,969	1,081	907	1,993	541	389	935	20,060	16,372	36,532
Mesothelioma (C45)	PAF (%)	97.0	82.5	94.4	97.0	82.5	94.4	97.0	82.5	94.4	97.0	82.5	94.4	97.0	82.5	94.4
	Attrib. cases	1,895	321	2,212	180	18	196	110	9	117	35	5	40	2,220	353	2,565
Melanoma (C43)	PAF (%)	88.6	84.8	86.8	83.0	83.0	84.9	91.0	81.0	86.1	83.5	81.4	82.5	88.5	84.4	86.5
	Attrib. cases	5,899	5,541	11,440	561	570	1157	364	311	675	174	157	332	7025	6579	13,604
Kaposi sarcoma (C46.1)	PAF (%)	100.0	100.0	100.0	100.0	0.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0
	Attrib. cases	125	17	142	7	0	7	2	1	3	3	1	4	137	19	156
Breast (C50)	PAF (%)	0.0	23.0	22.9	0.1	24.0	24.0	0.1	23.0	22.9	0.0	24.5	24.4	0.0	23.1	23.0
	Attrib. cases	—	10,523	10,523	—	1,139	1,139	—	641	641	—	357	357	—	12,659	12,659
Vulva (C51)	PAF (%)	0.0	68.8	68.8	0.0	68.8	68.8	0.0	68.8	68.8	0.0	68.8	68.8	0.0	68.8	68.8
	Attrib. cases	—	744	744	—	97	97	—	55	55	—	25	25	—	921	921
Vagina (C52)	PAF (%)	0.0	75.0	75.0	0.0	75.0	75.0	0.0	75.0	75.0	0.0	75.0	75.0	0.0	75.0	75.0
	Attrib. cases	—	148	148	—	16	16	—	5	5	—	6	6	—	174	174
Cervix (C53)	PAF (%)	0.0	99.8	99.8	0.0	99.8	99.8	0.0	99.8	99.8	0.0	99.8	99.8	0.0	99.8	99.8
	Attrib. cases	—	2511	2511	—	378	378	—	149	149	—	81	81	—	3119	3119
Uterus (C54–C55)	PAF (%)	0.0	34.4	34.4	0.0	34.9	34.9	0.0	30.1	30.1	0.0	28.4	28.4	0.0	34.0	34.0
	Attrib. cases	—	2561	2561	—	279	279	—	145	145	—	70	70	—	3056	3056
Ovary (C56)	PAF (%)	0.0	11.1	11.1	0.0	12.1	12.1	0.0	11.2	11.2	0.0	12.6	12.6	0.0	11.2	11.2
	Attrib. cases	—	641	641	—	69	69	—	40	40	—	17	17	—	766	766
Penis (C60)	PAF (%)	63.3	0.0	63.3	63.3	0.0	63.3	63.3	0.0	63.3	63.3	0.0	63.3	63.3	0.0	63.3
	Attrib. cases	329	—	329	45	—	45	18	—	18	13	—	13	404	—	404

Table 2 Summary population attributable fractions and attributable cases, by cancer type, sex and country, 2015 (*continued*)

Cancer type and ICD-10 code		All risk factors combined														
		England			Scotland			Wales			Northern Ireland			UK		
		M	*F*	*P*	*M*	*F*	*P*	*M*	*F*	*P*	*M*	*F*	*P*	*M*	*F*	*P*
Bladder (C67)	PAF (%)	50.6	43.2	48.6	51.7	47.1	50.4	54.0	46.2	51.9	48.7	37.1	45.2	50.8	43.6	48.9
	Attrib. cases	3,112	1,007	4,125	285	131	417	241	84	326	70	26	96	3,708	1,247	4,964
Kidney (C64-C66, C68)	PAF (%)	32.1	36.1	33.5	32.9	38.1	34.8	30.7	33.1	31.5	31.7	33.5	32.2	32.1	36.1	33.5
	Attrib. cases	2,068	1,404	3,467	231	154	385	111	68	179	72	40	112	2,483	1,666	4,142
Thyroid (C73)	PAF (%)	9.8	8.8	9.1	10.0	9.6	9.7	8.5	7.8	8.1	11.0	8.1	8.9	9.8	8.8	9.1
	Attrib. cases	80	197	278	8	19	27	3	6	9	3	4	7	94	227	321
Myeloma (C90)	PAF (%)	15.8	10.5	13.6	16.8	11.5	14.6	13.8	8.8	11.4	16.3	9.9	13.4	15.8	10.5	13.6
	Attrib. cases	425	205	630	47	22	69	21	12	33	13	6	19	505	246	751
Hodgkin lymphoma (C81)	PAF (%)	40.1	40.7	40.3	41.2	40.1	40.7	43.0	40.0	41.6	41.8	37.4	39.9	40.4	40.5	40.4
	Attrib. cases	414	305	719	30	30	60	27	23	49	15	10	25	486	367	853
Non-Hodgkin lymphoma (C82–C85, C96)	PAF (%)	3.4	3.3	3.4	4.2	4.8	4.5	3.4	3.3	3.4	3.9	3.8	3.8	3.5	3.4	3.5
	Attrib. cases	122	64	185	22	24	46	12	10	22	7	6	12	260	211	472
Leukaemia (C91-C95)	PAF (%)	11.3	12.9	12.0	13.0	15.7	14.0	11.0	12.5	11.5	12.9	13.5	13.2	11.5	13.1	12.1
	Attrib. cases	567	444	1,009	47	38	85	43	29	72	16	14	30	673	525	1195
Brain & other central nervous system (C70–C72)	PAF (%)	0.0	4.8	2.5	0.1	6.3	3.5	0.1	3.5	2.0	0.0	4.9	2.6	0.0	4.8	2.5
	Attrib. cases	2	228	230	0	34	34	0	16	17	0	10	10	3	288	291
All excl non-melanoma skin cancer (C00–C97 excl C44)	PAF (%)	38.0	36.4	37.3	43.3	39.7	41.5	39.0	36.5	37.8	39.9	36.1	38.0	38.6	36.8	37.7
	Attrib. cases	58,141	53,480	111,722	6,567	6,455	13,038	3,838	3,373	7,207	1,856	1,663	3,519	70,425	65,130	135,507

the UK constituent countries. The proportion was higher in UK females (7.5%) than in UK males (5.2%), and was highest in Scotland (6.8% for persons) and lowest in Wales (5.4% for persons). The cancer types with the highest PAFs for overweight and obesity were uterine for females (34.0% for UK females) and oesophagus for males (31.3% for UK males).

UV radiation and occupational risks contributed the next-highest proportions of attributable cases (both 3.8% in UK persons), both with less than one percentage point difference in PAFs between highest (Scotland for occupation, England for UV) and lowest (England for occupation, Wales for UV) countries.

Exposure to infections, alcohol drinking and insufficient dietary fibre each contributed 2–4% of attributable cancer cases in UK persons. The remaining factors contributed less than 2% each.

For 10 cancer types, including two female-specific sites, more than 70% of cases in UK persons were attributable to known risk factors: Kaposi sarcoma (100%), cervical (99.8%), mesothelioma (94.4%), anal (91.3%), pharyngeal (88.4%), nasopharyngeal (85.0%), melanoma (86.5%), lung (78.9%), vaginal (75.0%) and laryngeal (72.5%).

England

Almost four in ten (37.3%) cancer cases in 2015 in England were attributable to known risk factors. The proportion differed only marginally between England males (38.0%) and females (36.4%), in contrast to the other UK countries where the sex difference was larger. The overall PAF was lowest in England males and second-lowest in England females, when comparing between countries.

Tobacco smoking contributed the largest proportion of England's attributable cancer cases (14.7%). This was the second-lowest tobacco smoking-attributable proportion among the UK countries. Overweight and obesity contributed the second-highest proportion of cases in England (6.3%) and this proportion was second-highest among the UK countries.

England had the joint-largest (with Scotland) sex difference in the UK in alcohol PAFs, with a lower PAF for males (3.0%) than for females (3.5%).

Among the UK countries, England had the highest PAFs for UV radiation and air pollution. England had the lowest or joint-lowest PAF among the UK countries for a number of risk factors, including alcohol drinking, insufficient dietary fibre and occupational risks.

These PAF differences reflect risk factor exposure prevalence, for example England's current smoking prevalence was the lowest in the UK in 2005, and its overweight and obesity prevalence was the highest in the UK in 2005.

Scotland

Around four in ten (41.5%) cancer cases in 2015 in Scotland were attributable to known risk factors. The proportion was nearly four percentage points higher in Scotland males (43.3%)

than in females (39.7%). The overall PAF was the highest among the UK countries for both males and females.

These PAF differences reflect risk factor exposure prevalence, but also proportion of specific cancer types in the all cancers combined total. For example, 2005 smoking prevalence is not markedly higher in Scotland than in the other UK countries, but Scotland has a higher proportion of lung cancer cases in its all cancer combined total.

Tobacco smoking contributed the largest proportion of attributable cancer cases in Scotland (18.2%). This was by far the largest tobacco smoking-attributable proportion among the UK countries, around two percentage points higher than the next-highest country. Overweight and obesity contributed the second-highest proportion of cases (6.8%) and again this proportion was highest among the UK countries, though the between-country variation here was smaller.

Scotland had the joint-largest (with England) sex difference in the UK in alcohol PAFs, but in the opposite direction to England with a higher PAF in males (3.8%) than in females (3.3%).

Scotland had the lowest PAF in the UK for only one risk factor: ionising radiation. For all other risk factors Scotland had the highest or second-highest PAF in the UK.

Wales

Nearly four in ten (37.8%) cancer cases in 2015 in Wales were attributable to known risk factors. The proportion was more than two percentage points higher in Wales males (39.0%) than in females (36.5%). The overall females PAF was second-highest among the UK countries.

Tobacco smoking and overweight and obesity contributed the highest proportions of cases (16.1% and 5.4% respectively). The overweight and obesity PAF was lowest in Wales compared with the other UK countries.

Wales had the highest PAFs in the UK for ionising radiation and postmenopausal hormones, and the lowest or joint-lowest PAFs in the UK for processed meat, infections, UV radiation, alcohol, physical activity, air pollution and not breastfeeding.

Risk factor exposure prevalence again underpins these results: Wales had particularly low obesity prevalence in 2004/2005 (although overweight prevalence was similar to other UK countries), and radon levels are slightly higher in Wales than elsewhere in the UK.

Northern Ireland

Nearly four in ten (38.0%) cancer cases in 2015 in Northern Ireland were attributable to known risk factors. The proportion was nearly four percentage points higher in Northern Ireland males (39.9%) than in females (36.1%).

Northern Ireland's tobacco PAF was the lowest among the UK countries for males and females combined, though this was mainly driven by the between-country pattern in females.

Northern Ireland had the largest sex difference in the UK in tobacco smoking PAFs, with the PAF around 50% higher in males (17.8%) than in females (11.3%).

Tobacco smoking and overweight and obesity contributed the highest proportions of cases in Northern Ireland (14.6% and 6.2% respectively).

Northern Ireland had the highest or joint-highest PAFs in the UK for processed meat, insufficient dietary fibre, insufficient physical activity, oral contraceptives, not breastfeeding, and alcohol—though for all these factors the difference was very small. It had the joint-lowest (with Wales) PAF in the UK for air pollution.

Prevalence of diet and physical activity risk factors was higher in Northern Ireland in 2005 compared with the other UK countries. Although Northern Ireland's air pollution concentrations were second-lowest to Scotland, the higher proportion of lung cancer in Scotland meant more air pollution-attributable cases there.

DISCUSSION

Variation by sex and country

Variation by UK country and sex was generally only a few percentage points, so these differences should be interpreted cautiously.

Males have higher prevalence of exposure to risk factors than do females, across almost all risk factors and UK countries. Tobacco smoking, overweight and obesity, meat-eating, and alcohol drinking are more common and/or at higher levels in men than in women[27,28,29,30]). Fibre is a notable exception, with lower intake, and accordingly higher PAFs, in females than in males. The male excess in risk factor exposure is generally not offset by the female-only cancer types, with the exceptions of overweight and obesity, infections, and ionising radiation, where PAFs are higher in females than in males mainly because of sex-specific cancers, some of which have high PAFs. Nor is men's higher risk factor exposure offset by female-only risk factors such as exogenous hormone use and non-breastfeeding.

The relative risk of cancer associated with risk factor exposure is often higher in males than in females (although this may relate to sample size and statistical power, discussed in more detail below), so even where exposure levels are similar, the estimated population impact is higher in males than in females. The all cancers combined total in males comprises a higher proportion of tobacco smoking-associated cancer types with high individual PAFs, while in females some of the largest contributors to the all cancers combined total have reasonably low individual PAFs (e.g. 23.0% for breast cancer). Sex-specific cancers contribute much more to the total PAF for females than for males, with breast cancer accounting for most of the difference.

Differences between countries in the all cancers combined PAFs are due to a combination of two related factors: risk factor exposure prevalence and proportions of specific cancer

types. Differences in risk factor exposure prevalence between countries are to some extent a reflection of data availability and quality in each nation, and comparisons between countries' PAFs should be made with this in mind. Any true differences probably reflect demographic differences which drive those 'lifestyle' differences. For example, areas with higher levels of socioeconomic deprivation have higher tobacco smoking rates[31]; areas with larger populations which eschew alcohol for faith reasons have lower alcohol-drinking rates.[32] Further, many lifestyle 'choices' are driven by environmental/societal factors such as food pricing and availability, and susceptibility to these factors varies with socioeconomic position.[33] Differences in risk factor exposure prevalence between countries are generally not large, with the exception of *H. pylori* which may reflect both differing deprivation levels across the UK and artefact due to differing data periods.[34] Factors beyond individual-level control also vary between countries, for example, the predominant occupation groups and air pollution levels. Geographical variation, for example, in radon and UV exposure levels is not controllable (although individuals and Government can take steps to ameliorate the risk associated with those factors). Similarly, having a higher proportion of workers in 'cancer risk' industries may not translate to a higher proportion of occupation-related cancers, as employers and Government can implement risk-reduction policies; however, the country-specific occupation PAFs presented here account only for variation in workforce size, not for possible variation in workplace safety.

Variation by risk factor

Risk factors with the largest PAFs are either those with the highest relative risks associated with exposure, those with the highest exposure prevalence in the population, those with the largest number of associated common cancer types, or combinations thereof. For example, tobacco smoking rates are lower than alcohol drinking rates but tobacco smoking has a much greater impact on cancer risk, and a much larger number of cancer types associated with it, leading to a much higher PAF.

Comparison with other relevant studies

The results reported here are overall in line with those from similar studies, though methodological differences—different groups of risk factors used, different time periods and different relative risk sources—preclude direct comparisons. For all modifiable risk factors and all cancers combined where the UK 2015 PAF was 37.7%, other reported PAFs include 42.0% in the US in 2014;[35] 40.8% in Alberta, Canada in 2012;[36] and 31.9% in Australia in 2010.[37] In all these studies the preventable proportion was higher in males than in females, with the gap widest in Canada (3.7 percentage points) and smallest in the US (1.0 percentage points), in line with the 1.8 percentage point sex difference reported here. Tobacco contributed the highest proportion of preventable cases across the board (PAFs ranging from 19.0% in the US 2014 to 13.4% in Australia 2010; 15.1% in the UK 2015), with between-country varia-

tion reflecting method differences and, arguably, temporal changes in smoking prevalence worldwide. Overweight and obesity was the second-biggest cause of cancer after tobacco in the US 2014 (PAF 7.8%) and UK 2015 (PAF 6.3%), and ranked third in Canada 2012 (PAF 4.3%) and fourth in Australia 2010 (PAF 3.4%). Between-country variation here mainly reflects geographical and temporal differences in overweight/obesity prevalence, and is in line with Arnold and colleagues' global overweight/obesity PAFs calculations for 2012,[38] reinforcing their conclusion that the UK has among the highest proportion of overweight/obesity-associated cancers in the world.

The obvious reference point for this work is the UK PAFs published by Parkin and colleagues in 2011.[5] The all cancers combined PAF for UK persons presented here (37.7%) is almost five percentage points lower than the equivalent figure obtained by Parkin et al. (42.7%).[26] This does not represent a direct temporal change: changes in risk factor prevalence, cancer incidence and study methodology have all contributed to this difference.

This study has built on Parkin et al.[5] Risk factors with probable/limited evidence for associations with specific cancer types were included by Parkin et al.,[5] but have not been included in this study. The difference in inclusion criteria for risk factor–cancer type combinations partly explains the lower PAFs seen here compared with Parkin et al.'s[5] work, though this effect is reduced by the addition of new combinations which have been classified as sufficient/convincing over the last 6 years.

This study has used specific cancer type subsites, morphological types and patient age groups where evidence of causality was specific to those attributes, where Parkin et al.[5] often used entire cancer types in their calculations.

The evidence base on relative cancer risk for specific risk factor–cancer type associations has improved since Parkin et al.'s[5] study, with many more meta-analyses available now. These gold standard evidence syntheses have been used in preference to single studies wherever possible in this work. The meta-analyses used in this study typically report lower relative risks than the single studies used by Parkin et al.,[5] and this is an important explanation for the difference in PAFs between the studies.

Risk factor exposure prevalence is different in this study compared with Parkin et al.,[5] and this explains a large part of the difference in PAFs obtained. Risk factor exposure prevalence changed between 2000 (ref. [5]) and 2005. In this period shifts both towards optimal population prevalence (e.g. reduction in smoking prevalence) and away from it (e.g. increase in overweight and obesity prevalence). This study used risk factor exposure prevalence data from each UK constituent country where available, where Parkin et al.[5] typically used England or Great Britain as a proxy for the whole UK.

In Parkin et al.'s[5] estimated 2010 cancer incidence data, smoking-related cancers contributed 52% of the males all cancers combined total, and 43% of the females all cancers combined total. In this study's observed 2015 cancer incidence data, these proportions were 50% and 42%. Therefore even if the 2015 cancer type PAFs were identical to the 2010 cancer

type PAFs, the all cancers combined PAF would be lower simply because the proportion of smoking-related cancers in the all cancers combined denominator is lower.

The largest methodological difference between Parkin et al.[5] and the current work is in tobacco smoking—but method differences apart, tobacco smoking PAFs have fallen over this time because of reductions in smoking prevalence. Calculating the 2010 tobacco PAF using 2000 smoking prevalence with the same method as in this study produces PAFs of 19.9%, 12.2% and 16.1% for UK males, females and persons respectively—markedly higher than the corresponding 2015 PAFs of 17.7%, 12.4% and 15.1%.

Differences in methodology do also contribute to the different PAFs between studies. Here, lower RRs from meta-analyses have been used, while Parkin et al.[5] used higher RRs mainly from single studies, and this is a key driver of the PAF differences. The use of survey-reported smoking prevalence rather than notional smoking prevalence as used by Parkin et al.5 made a smaller difference. The main benefit of using notional prevalence is that latency between smoking and cancer does not need to be defined,[39,40] and the choice of latency in the current work is almost certainly too short for tobacco smoking. To use a different lag for smoking than for the other risk factors would not have been systematic, given the similarly sparse data on latency for smoking and for the other risk factors included in this work. Aside from this latency-related benefit, using notional in incidence PAF calculations across multiple cancer types is problematic because it represents a substantial deviation from the original purpose of the method and therefore requires many assumptions which were not considered reliable enough for use in the current study.

There are other methodological differences between this study and Parkin et al.[5] which influenced the PAFs, but these are relatively small. The UV radiation PAF was calculated using several theoretically UV-unexposed/less UV-exposed groups rather than the single less-exposed birth cohort used in the original project, in an effort to reduce the impact of overdiagnosis in skin cancer which is thought to have increased over time.[41] However these PAFs probably reflect increased diagnosis as well as true increased incidence, and the relative contribution of each is impossible to assess. Alcohol consumption and breastfeeding prevalence were calculated as categorical rather than continuous variables, in order to minimise the amount of manipulation and assumption around the exposure prevalence data and to better match the sources of relative risks. Moderate physical activity was defined as 4 METs rather than 6 METs as used by Parkin et al.,[5] again to better match the source of relative risks and reflect the World Health Organization definition of moderate physical activity.[42] The optimum level of physical activity was defined as exceeding, rather than just reaching, 10 MET-hours per week, because recent evidence suggests bowel cancer risk is only reduced at substantially higher levels.[18] Meat pies and pastries and other meat and meat products were included with processed meat in this study where they were excluded from meat calculations in Parkin et al.,[5] because the definition of these categories places them fairly clearly in the processed category and they make up a sizeable proportion of processed meat intake. The

optimum fibre intake was defined as 30 g/day rather than 23 g/day to reflect the current guidelines which form the context for policymakers' use of the current study's results. Cases caused by oral contraceptive use were included in the all cancers combined PAF where oral contraceptives were excluded altogether from the all cancers combined PAF in ref. [5] because of the net protective effect of oral contraceptive use. A net protective effect was observed in the current study (around 4,400 cases prevented and around 800 cases caused), but there is a burden of preventable cases nonetheless and the aim of this work was to quantify preventable cases. The effect of including the causal effect of oral contraceptives in the overall PAF is minimal: omitting oral contraceptives entirely from the UK persons all cancers combined PAF would reduce that PAF by only 0.2 percentage points.

Strengths and limitations

This work provides UK and constituent country-level PAF estimates for the full compendium of risk factors where evidence of a causal role in cancer development is sufficient/convincing. PAFs at this level have not been available previously and they will be useful for policymakers in devolved nations. Further, at a UK level this work updates the original evidence from Parkin et al.,[5] and this update is timely given changes in risk factor exposure prevalence and developments in epidemiological evidence.

The PAFs presented here are estimates based on the best available data; therefore, the PAFs should be interpreted with the limitations of the source data (and the limitations of the calculations made on those data) in mind. Most of these limitations would bias toward underestimation of PAFs in the current work. Traditional confidence intervals cannot be provided due to the multiple components in the PAF calculation. Sensitivity analyses—using the upper and lower confidence intervals of the RR and risk factor exposure prevalence data to calculate the highest- and lowest-possible PAFs—were conducted for most risk factor-cancer type combinations, as colleagues using the same PAF calculation method have done.[5,6] However, as in these colleagues' work, the results of those analyses are not reported here lest they be misleading, the ranges implying precision though they do not take into account all the possible biases operating on the components of the PAF calculations.[43]

Restricting to risk factors with IARC/WCRF-classified sufficient/convincing evidence of a causal link with cancer is likely to underestimate the true PAF, as genuine risk factor-cancer type combinations may not yet be clear. For example, evidence is mounting for a causal association between obesity and risk of advanced prostate cancer,[44,45] and were this risk factor–cancer type combination to be included in the present calculations, the overall PAF for males would increase slightly. For some risk factor–site–sex combinations, the association is not statistically significant in the latest evidence, so the RR has been set to 1 in the PAF calculations (Supplementary Material C) resulting in no attributable cases. This may in some cases reflect lack of statistical power (particularly for rarer cancer types and less prevalent

behaviours) rather than a genuine lack of association. Excluding all non-significant RRs has almost certainly resulted in conservative PAFs.

Comparison between risk factors is only as reliable as the relative risk evidence available, and in most cases confounding cannot be completely ruled out. For example, the alcohol PAFs are likely to be underestimates as 'unexposed' reference groups in this literature often include ex- and occasional drinkers, which dilutes the observed effect of alcohol drinking on cancer risk.[46] The relative risk figures used were identified and selected systematically but different choices here would influence the PAFs.

Perhaps one of the most vexed issues in PAF calculation is latency, and the results presented here are certainly affected by using a blanket ten-year latency period across all risk factors. PAF calculations are limited by the availability of relative risk and exposure prevalence data for the relevant period. There would be bias in calculating a PAF assuming 30-year latency, with poor exposure prevalence data and relative risk from a study with only a ten-year follow-up, just as there is in calculating a PAF using good exposure prevalence and appropriate relative risk data assuming a 10-year latency which is too short. Clear data on latency between exposure and cancer development are lacking, moreso for some cancer types than others, and using bespoke lags for each cancer type in this study would have been unsystematic and reduced comparability between risk factors. Tobacco smoking has the most evidence for a longer latency and as tobacco smoking prevalence is falling, the tobacco smoking PAF is almost certainly an underestimate. Despite this, calculating the UK 2015 PAF for tobacco smoking using a 20-year latency produces only a 1 percentage point increase compared with the 10-year latency 2015 PAF, therefore supporting the use of a shorter latency with higher quality data for the UK countries.

PAFs for individual risk factor–cancer type combinations represent the fraction of that cancer attributable to that risk factor in isolation, when the effect of other risk factors has been controlled for in the relative risk figure. Control for confounding is easier for some risk factors and cancer types than others. The method of summing individual PAFs to reach the all factors combined total for each risk factor avoids overestimation by applying PAFs sequentially only to the cases not attributed for by factors earlier in the sequence. The issue of cancer cases with more than one cause is distinct from that of cancer cases caused by the synergistic effects of risk factors in combination. For example, the effect of tobacco smoking and alcohol drinking together on oesophageal cancer risk,[47] or on radon and smoking together on lung cancer risk,[48] is several times greater than the effects of these factors individually. Synergistic effects have not been included in the calculations reported here for several reasons. National survey data on prevalence of combined risk factor exposure are not sufficiently detailed for use in PAF calculations, and IARC and WCRF do not comment explicitly on synergistic effects so those cancer type-risk factor combinations cannot be evaluated against our inclusion criteria. Further, there is a strong possibility of double-counting if synergistic effects are included: residual confounding in the RRs for

individual risk factors (a particular concern for alcohol RRs being confounded by tobacco) would mean that some of the 'alcohol-only' cases actually do reflect alcohol and tobacco in combination; adding 'official' alcohol and tobacco synergy cases to this would arguably risk overestimating the PAF.

Risk factor exposure prevalence data from surveys is prone to self-reporting errors, particularly underestimation of exposure.[49] Throughout the analysis some datapoints for specific countries or time periods were not available, and so imputation, estimation and extrapolation (see Supplementary Material E) were required to fill those gaps. This has particularly affected the devolved nations' results, and this project demonstrates the value of collecting risk factor exposure prevalence data consistently across countries, regularly, and in a format which facilitates linkage with epidemiological data in order to calculate the most accurate PAFs.

Operationalising overweight and obesity prevalence, alcohol consumption, and breastfeeding prevalence as categorical rather than continuous variables is likely to have overestimated the PAFs for these risk factors. However, available exposure prevalence and relative risk data were overwhelmingly categorical, so converting to continuous data would have introduced further uncertainty. RRs comparing categories of people will overestimate the effect for those very near to the category boundary and underestimate the effect for those furthest away from it. If the exposure prevalence distribution is left-skewed (more people near the boundary with optimum exposure), as is the case for overweight and obesity, then the PAF is likely to be an overestimate. This is less of a concern if the within-category distribution is similar in the RR source and the exposure prevalence. However, this information is rarely reported and so the risk of PAF overestimation on this basis cannot be quantified. More accurate PAFs could be calculated if relative risks and exposure prevalence were reported continuously rather than categorically.

The physical activity PAF may be an overestimate as those people achieving 600 + MET-min in less than 5 days were classified as inadequately active. Exposure prevalence data were provided as days when 30 + min moderate physical activity was achieved, rather than total minutes per week. Exposure prevalence data are collected in a format matching the current UK Government physical activity guidelines but the latest evidence shows that these guidelines need to be exceeded quite substantially to impact bowel cancer risk.

Air pollution PAFs are based on exposure prevalence in 2010, although outdoor air pollution levels have decreased markedly over past decades.[50] However in the absence of firm evidence on latency in this area, erring toward underestimating the PAF was preferred.

The occupation chapter in the original UK attributable cancers project was based on a large separate piece of work and it was beyond the scope of this update to re-create that work. The method used to derive country-level PAFs for occupation here is crude but the results are not unexpected: Among the UK countries Scotland and Wales have the highest overall occupation PAFs and those countries have the highest proportions of the workforce in industries with the highest exposure to cancer risk factors (construction and manufac-

turing, specifically mining). Removing shiftwork and non-melanoma skin cancer from the PAF estimates in the original attributable cancers project report was offset by adjusting for country-specific occupational exposure levels, so the all cancers combined occupation PAF for the UK has remained similar to the original estimate.

Oral contraceptives calculations use the most recent freely available data with appropriate age breakdowns, from 2010 to 2012. These were assumed accurate for 'current' use in 2015 (as the RRs are for current use at the time of cancer diagnosis). The validity of this assumption cannot be checked with freely available data, but marked change is unlikely in 3–5 years. For the exogenous hormones calculations there were no freely available data on prevalence of use by preparation type or duration of use, which necessitated a simplified (and arguably weaker) methodology in comparison to Parkin et al.[5] The relative risks used in the calculations are not preparation or duration-specific and are from a UK population, so the distribution of preparation types and use durations in the exposure prevalence data are expected to be close to that in the relative risk data.

Calculations for ionising radiation may overestimate radon-attributable cases as radon prevalence at country level was taken from recent Public Health England data which focuses on high-radon areas rather than a random sample;[51] however, it is unlikely that the magnitude of overestimation varies between countries.

Expectations for future years' PAFs in the UK

Tobacco smoking currently contributes by far the largest proportion of UK cancer cases attributable to risk factor exposure, and as prevalence of this behaviour is falling, so the tobacco PAF is expected to fall in future. This assumes that tobacco smoking prevalence will continue to fall in future, but this is not guaranteed; progress to date in this area is thanks to public health initiatives, including mass media cessation campaigns, Stop Smoking Services, smoke free legislation and plain packaging for tobacco products.[52] Despite this, a wide disparity in smoking rates exists between different societal groups, for example, rates remain very high among those with mental health conditions.[53] Some groups will need more support to quit so effective smoking cessation interventions should continue to be provided by the government and the NHS to maintain the current momentum and address health inequalities.[54]

Overweight and obesity contributes the second-highest proportion of attributable cases and prevalence of this risk factor is rising, so this PAF is expected to rise in future. Evidence for the impact of high BMI on cancer risk is still growing, so more cancer types could also be classified as having strong evidence for an association with BMI, which would also increase the PAF. The PAF gap between tobacco and overweight and obesity will shrink in future if current overweight and obesity prevalence trends continue. Current initiatives, including the UK Government's Soft Drinks Industry Levy and Sugar Reduction programme, may slow the increase, but a more comprehensive approach as seen in tobacco may be necessary

to significantly reduce prevalence.[55] This should include recommendations made by Public Health England such as restrictions to the advertising of foods high in fat, sugar, and salt.[56]

Factors not included in these calculations may impact on PAFs by affecting the mix of cancer types in the all cancers combined total. Screening for bowel, cervical and breast cancer, and HPV vaccination, may reduce the proportion of cancer types which contribute a large number of preventable cases in the current calculations, reducing the overall PAF. Introduction of further screening programmes would also affect the overall PAFs.[57,58,59] In addition, incidence could fall for some cancers in the future with more conservative testing practice—for example, if prostate cancer incidence falls with more conservative use of PSA testing in future, the proportion of non-risk-factor-attributable cancer cases in the all cancers combined total will be reduced, increasing the overall PAF.

CONCLUSION

Known risk factors are responsible for a substantial proportion of UK cancer cases. Prevention efforts which focus on smoking and overweight and obesity are likely to have the largest population-level impact. Between-country variation likely reflects population demographics; deprived communities across the UK require additional support to reduce their cancer risk. Evidence from this study should be used to focus efforts on reducing the number and proportions of cancers attributable to preventable risk factors across the countries of the UK Department of Health.[20]

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SUPPLEMENTARY MATERIALS

Supplementary Material A: Combinations of risk factor and cancer type included, with classification source

	Oral cavity (C00-C06)	Nasopharynx (C11)	Pharynx (C09, C10, C12-C14)	Oesophagus (C15)	Stomach (C16)	Bowel (C18-C20)	Anus (C21)	Liver (C22)	Pancreas (C25)	Gallbladder (C23)	Sino-nasal (C30-C31)	Larynx (C32)	Lung (C33-C34)	Bone (C40-41)
Tobacco	I 12	I 12	I 12	I 12	I 12	I 12		I 12	I 12		I 12	I 12	I 12	
Overweight and obesity				I 16	I 16	I 16		I 16	I 16	I 16				
Radiation - UV														
Occupation		I 04 – 17			I 04 – 17			I 04 – 17		I 04 – 17	I 04 – 17	I 04 – 17	I 04 – 17	
Infections	I 12	I 12	I 12		I 12		I 12	I 12						
Alcohol	I 12		I 12	W 16		I 12		W 15				I 12		
Fibre						W 17								
Radiation - ionising	I 12			I 12	I 12	I 12					I 12			I 12
Processed meat						W 17								
Air pollution													I 16	
Not breastfeeding														
Insufficient physical activity						W 17								
Post-menopausal hormones						I 12								
Oral contraceptives						I 12								

I = International Agency for Research on Cancer (IARC) classification.

W = World cancer Research Fund (WCRF) classification.

Numbers are the year in which the classification was published.

	Mesothelioma (C45)	Melanoma (C43)	Kaposi sarcoma (C46)	Breast (C50)	Vulva (C51)	Vagina (C52)	Cervix (C53)	Uterus (C54-C55)	Ovary (C56)	Penis (C60)	Bladder (C67)	Kidney (C64-C66, C68)	Eye (C69)	Thyroid (C73)	Myeloma (C90)	Hodgkin lymphoma (C81)	NHL (C82-C85, C96)	Leukaemia (C91-C95)	Brain and CNS (C70-C72)
							I 12		I 12		I 12	I 12						I 12	
				I 16				I 16	I 16			I 16		I 16	I 16				I 16
		I 12																	
	I 04 – 17	I 04 – 17							I 04 – 17		I 04 – 17	I 04 – 17	I 04 – 17					I 04 – 17	
			I 12		I 12	I 12	I 12			I 12			I 12			I 12	I 12		
				W 17															
		I 12		I 12							I 12	I 12		I 12				I 12	I 12
				W 10															
				I 12				I 12	I 12										
				I 12			I 12	I 12	I 12										

Supplementary Material B: Search terms for identifying relative risks

Combinations of cancer type and risk factor search strings were made using AND. Searches were made in PubMed, and were supplemented using Google Scholar and scrutiny of reference lists in other relevant papers.

Cancer type	Search string
Melanoma skin cancer	melanoma OR skin AND (cancer OR tumour)
Oral cavity cancer	(oral OR mouth) AND (cancer OR tumour)
Nasopharyngeal cancer	(nasopharynx OR nasopharyngeal) AND (cancer OR tumour)
Pharyngeal cancer	(oropharynx OR oropharyngeal OR pharynx OR pharyngeal) AND (cancer OR tumour)
Oesophageal cancer	(oesophagus OR oesophageal) AND (cancer OR adenocarcinoma OR squamous cell AND (cancer OR tumour)
Stomach cancer	(stomach OR gastric OR cardia) AND (cancer OR adenocarcinoma OR tumour)
Bowel cancer	(colorectum OR colorectal OR colon OR rectum OR rectal OR bowel) AND (cancer OR tumour)
Anal cancer	(anus OR anal) AND (cancer OR tumour)
Liver cancer	(liver OR hepatic OR hepatocellular) AND (cancer OR carcinoma OR tumour)
Pancreatic cancer	(pancreas OR pancreatic) AND (cancer OR adenocarcinoma OR tumour)
Gallbladder cancer	Gallbladder AND (cancer OR tumour)
Laryngeal cancer	(larynx OR laryngeal) AND (cancer OR tumour)
Lung cancer	lung AND (cancer OR adenocarcinoma OR squamous cell carcinoma OR tumour)
Mesothelioma	mesothelioma
Kaposi sarcoma	kaposi sarcoma
Breast cancer	breast AND (cancer OR carcinoma OR tumour)
Vulval cancer	(vulva OR vulval) AND (cancer OR tumour)
Vaginal cancer	(vagina OR vaginal) AND (cancer OR tumour)
Cervical cancer	(cervix OR cervical) AND (cancer OR tumour)
Uterine cancer	(uterus OR uterine OR endometrium OR endometrial) AND (cancer OR carcinoma OR tumour)
Ovarian cancer	(ovary OR ovarian) AND (cancer OR carcinoma OR tumour)
Penile cancer	(penis OR penile) AND (cancer OR carcinoma OR tumour)
Prostate cancer	(prostate OR prostatic) AND (cancer OR carcinoma OR tumour)
Bladder cancer	(bladder OR urothelium OR urothelial) AND (cancer OR carcinoma OR tumour)

Kidney cancer	(kidney OR renal OR renal cell) AND (cancer OR carcinoma OR tumour)
Thyroid cancer	thyroid (cancer OR tumour)
Myeloma	myeloma
Hodgkin lymphoma	Hodgkin lymphoma OR Hodgkin's disease
Non-Hodgkin lymphoma	non-Hodgkin lymphoma
Leukaemia	leukaemia OR leukemia
Brain and other central nervous system tumours	(brain OR nervous system OR spinal cord OR glioma OR meningioma) AND (cancer OR tumour)

Risk factor	**Search string**
Tobacco	tobacco OR cigarette OR smoking OR environmental tobacco smoke OR secondhand smoke
Overweight and obesity	weight OR BMI OR body mass index OR obesity OR obese OR overweight OR adiposity OR body size
Radiation - UV	(ultraviolet OR UV OR solar) AND radiation
Occupation	Not sought – used Rushton et al 2010
Infections	hepatitis B virus OR HBV hepatitis C virus OR HCV human papillomavirus OR HPV human immunodeficiency virus OR HIV OR acquired immune deficiency syndrome OR AIDS Helicobacter pylori OR H. pylori Epstein Barr virus OR EBV Kaposi sarcoma herpesvirus OR KSHV OR human herpesvirus 8 OR HHV8
Alcohol	alcohol OR alcoholic OR ethanol
Insufficient fibre	fibre OR fiber
Radiation - ionising	radon x-ray nuclear medicine OR radio-isotopes therapy radiotherapy
Processed meat	Meat OR bacon OR ham OR sausages OR jerky OR salami OR cured OR salted
Air pollution	(air OR environment OR outdoor) AND pollution
Not breastfeeding	breastfeeding OR breastfed OR lactation
Insufficient physical activity	physical OR activity OR exercise OR physically active OR sedentary
Post-menopausal hormones	hormone replacement therapy OR ((menopausal OR menopause) AND hormone therapy) OR
Oral contraceptives	(oral AND (contraceptive OR contraception)) OR birth control pill

Supplementary Material C: Relative risk figures used

Risk factor[a]	Cancer type																											
	Lung	Oral cavity[j]	Nasopharynx	Pharynx	Oesophageal AC	Oesophageal SCC	Stomach[e]	Liver	Pancreas	Colon	Rectum	Larynx	Cervix	Ovary[b]	Bladder	Kidney	Leukaemia[c]	Breast[d]	Uterus	Gallbladder	Brain[f]	Thyroid	Myeloma	Non-Hodgkin Lymphoma[g]	Other cancer types[h]
Tobacco (cigarette) smoking [1 2 3 4 5 6 7 8 9 10 11 12 13 14 15]																												
Current vs never																												
Males	8.96	1.91	1.95	3.43	2.32	4.21	1.62	1.61	2.20	1.11	1.44	7.01			3.44	1.35	1.47											
Females	8.96	1.91	1.95	3.43	2.32	4.21	1.20	1.86	2.20	1.11	1.44	7.01	1.83	1.49	3.56	1.35	1.47											
Former vs never																												
Males	3.85	1	1.39	1	1.62	2.18	1.34	1.47	1.17	1.15	1.11	2.37			1.92	1.22	1											
Females	3.85	1	1.39	1	1.62	2.18	1	1	1.17	1.15	1.11	2.37	1.26	1	2.04	1.22	1											
Secondhand exposed vs unexposed																												
Males	1.23																											
Females	1.37																											
Overweight and obesity [16 17 18 19 20 21 22 23 24 25 26 27 28]																												
Overweight vs healthy weight (BMI 25<30 vs BMI 18.5<25)																												
Males					1.87		1.22	1.18	1.15	1.17	1.17					1.22				1	1	1.1	1.17					
Females					1.87		1.22	1.18	1.12	1.07	1.07			1.08		1.38		1.13	1.34	1.22	1	1.1	1.12					

Supplementary Material C: Relative risk figures used (*continued*)

Risk factor[a]	Cancer type																										
	Lung	Oral cavity[i]	Nasopharynx	Pharynx	Oesophageal AC	Oesophageal SCC	Stomach[e]	Liver	Pancreas	Colon	Rectum	Larynx	Cervix	Ovary[b]	Bladder	Kidney	Leukaemia[c]	Breast[d]	Uterus	Gallbladder	Brain[f]	Thyroid	Myeloma	Non-Hodgkin Lymphoma[g]	Other cancer types[h]
Obese vs healthy weight (BMI 30+ vs BMI 18.5<25)																									
Males					2.73		1.61	1.83	1.20	1.38	1.38					1.63				1.54	1	1.27	1.23		
Females					2.73		1.61	1.83	1.15	1.17	1.17			1.11		1.95		1.20	2.54	1.75	1.60	1.27	1.15		
Infections																									
Helicobacter pylori (H. pylori) [29]																									
Persons							5.90																	6.30	
Hep B [30]																									
Persons								20.3																	
Hep C [30 31]																									
Persons								23.8																2.03	
HIV [32 33]																									
Persons																								10.6	8.06
Alcohol [34]																									

Supplementary Material C: Relative risk figures used (*continued*)

Risk factor[a]	Cancer type																										
	Lung	Oral cavity[i]	Nasopharynx	Pharynx	Oesophageal AC	Oesophageal SCC	Stomach[e]	Liver	Pancreas	Colon	Rectum	Larynx	Cervix	Ovary[b]	Bladder	Kidney	Leukaemia[c]	Breast[d]	Uterus	Gallbladder	Brain[f]	Thyroid	Myeloma	Non-Hodgkin Lymphoma[g]	Other cancer types[h]
Light (median daily ≤12.5g ethanol) vs never																											
Persons		1		1		1.34		1		1	1	1						1.04									
Moderate (median daily 12.5-50g ethanol) vs never																											
Persons		1.81		1.81		2.56		1		1.17	1.17	1.49						1.23									
Heavy (median daily 50g+ ethanol) vs never																											
Persons		5.07		5.07		5.45		2.16		1.33	1.33	2.39						1.60									
Fibre (per 1g deficit per day) [35]																											
Persons										1.03	1.03																
Ionising radiation																											
Background radiation (cosmic, gamma, internal, per Sv)[l] [36]																											
Persons	1.02	1.03			1.02		1.01			1.02	1				1.02	1	<1.2	1.02			1.02	1.02			1.03		
Radon (per 100 Bq/m^3) [37]																											
Persons	1.16																										

Supplementary Material C: Relative risk figures used (*continued*)

Risk factor[a]	Cancer type																										
	Lung	Oral cavity[i]	Nasopharynx	Pharynx	Oesophageal AC	Oesophageal SCC	Stomach[e]	Liver	Pancreas	Colon	Rectum	Larynx	Cervix	Ovary[b]	Bladder	Kidney	Leukaemia[c]	Breast[d]	Uterus	Gallbladder	Brain[f]	Thyroid	Myeloma	Non-Hodgkin Lymphoma[g]	Other cancer types[h]
Processed meat (per 50g per day) [38]																									
Persons										1.13	1.13														
Air pollution [39]																									
Anthropogenic $PM_{2.5}$, per μg m^3																									
Persons	1.09																								
Anthropogenic PM_{10}, per μg m^3																									
Persons	1																								
Breastfeeding (never vs ever) [40]																									
Females																		1.08							
Physical activity (*600-3999 vs <600 MET-minutes per week*[j]) [41]																									
Persons										0.90															

Supplementary Material C: Relative risk figures used (*continued*)

Risk factor[a]	Cancer type																											
	Lung	Oral cavity[i]	Nasopharynx	Pharynx	Oesophageal AC	Oesophageal SCC	Stomach[e]	Liver	Pancreas	Colon	Rectum	Larynx	Cervix	Ovary[b]	Bladder	Kidney	Leukaemia[c]	Breast[d]	Uterus	Gallbladder	Brain[f]	Thyroid	Myeloma	Non-Hodgkin Lymphoma[g]	Other cancer types[h]
Post-menopausal hormones [42 43]																												
Ex- (5+ years use, 5+ years since use) vs never-users																												
Females														1.10				1										
Current (5+ years use) vs never-users																												
Females														1.41				1.66										
Oral contraceptives (current- vs never-users [k]) [44 45]																												
Females													1.90					1.21										

[a] Relative risks obtained only for cancer type-risk factor combinations classified by IARC as 'sufficient' or WCRF as 'convincing'; blank cells indicate no RR was sought as the combination is not classified as above. RR = 1 if cancer type-risk factor association is not significant in the source evidence chosen. No RRs shown for Epstein-Barr virus, Human Papillomavirus (HPV), Kaposi Sarcoma Herpesvirus/Human Herpesvirus 8 (KSHV/HHV8), and diagnostic radiation, because for these factors PAFs were identified in the literature rather than being calculated within this project

[b] Mucinous ovarian cancer only for tobacco (cigarette) smoking

[c] Acute myeloid leukaemia only for tobacco (cigarette) smoking, all leukaemia excluding chronic lymphocytic for ionising radiation (RR varies with age, dose, sex, age at and time since exposure so RR given is upper bound)

[d] Postmenopausal breast cancer only for overweight and obesity, female breast cancer only for alcohol

[e] Gastric cardia cancer only for overweight and obesity, non-cardia only for *H. pylori*

[f] Meningioma only for overweight and obesity; brain, other central nervous system and intracranial tumours (malignant, benign and uncertain or unknown behaviour) for ionising radiation

[g] Mucosa-associated lymphoid tissue (MALT) lymphoma only for *H. pylori*

[h] Conjunctiva for HIV; bone and 'all other solid cancers' for ionising radiation (background radiation)

[i] Salivary gland for ionising radiation (background radiation)

[j] RR = 0.0022

[k] 0-5 years since last use (breast), 'current' and 5+ years use (cervix)

[l] Relative risks converted from percent per Sievert and used in calculations as excess relative risk per mSv, e.g. risks shown in this table are for much higher exposure levels than seen in UK population

Supplementary Material D: Summary prevalence of exposure to risk factors, by country and sex

Risk factor	England	Scotland	Wales	Northern Ireland	Optimum exposure
Tobacco (cigarette) smoking (%) [46 47 48 49]					
Data years	2005	2005	2004/05	2004/05	Nil
Current					
Males 16+	27	28	29	27	
Females 16+	24	24	30	25	
Former					
Males 16+	28	27	26	23	
Females 16+	20	21	24	13	
Exposure to secondhand smoke (%) [a 46 47 48 49]					
Data years	2005	2003	2004	GB average	Nil
Some exposure					
Males 16-75	58	63	73	65	
Females 16-75	48	57	67	57	
Overweight and obesity (%) [46 47 48 50]					
Data years	2005	2005	2004/05	2005/06	BMI 18<25
Overweight (BMI 25<30)					
Males 16+	43	41	42	39	
Females 16+	32	31	32	30	
Obese (BMI 30+)					
Males 16+	22	22	18	25	
Females 16+	24	23	18	23	
Occupation (industry sectors with highest PAFs)% of total jobs) [51]					
Data years	1982	1982	1982	1982	Nil
Manufacturing	23	21	21	22	
Construction	5	7	6	6	
Transport and storage	5	5	4	3	
Infections (%)					
Data years	2005	2005	2005	2005	Nil
H. pylori [f 52 53 54]	17	61	17	57	
Hep [B 55]	0.5	0.5	0.5	0.5	
Hep C [g 56 57 58 59]	0.4	0.7	0.4	0.2	
HIV [60 61]					
Males 15-59	0.22	0.01	0	0	
Males 60+	0.02	0	0	0	
Females 15-59	0.01	0.01	0	0	
Females 60+	0.02	0	0	0	
Alcohol drinking (%) [62]					

Supplementary Material D: Summary prevalence of exposure to risk factors, by country and sex (*continued*)

Risk factor	England	Scotland	Wales	Northern Ireland	Optimum exposure
Data years	2005	2005	2005	GB average	Nil
Light (median daily intake ≤12.5g ethanol)					
Males 16+	44	42	45	44	
Females 16+	54	58	57	56	
Moderate (median daily intake 12.5-50g ethanol)					
Males 16+	34	35	38	36	
Females 16+	26	24	24	25	
Heavy (median daily intake 50g+ ethanol)					
Males 16+	12	11	10	11	
Females 16+	2	1	2	2	
Fibre (g per day) [d 64 65 66 67]					
Data years	2000/01	2000/01	2000/01	2000/01	30g/day
Males 19+	20	19	19	18	
Females 19+	16	15	16	15	
Ionising radiation (average mSv per year) [63]					
Data years	2010	2010	2010	2010	Nil
Background radiation [h]	0.94	0.99	0.95	0.94	
Radon	1.49	0.84	1.9	1.23	
Processed meat (g per day) [c 64 65 66 67]					
Data years	2000/01	2000/01	2000/01	2000/01	Nil
Males 19+	74	77	68	80	
Females 19+	37	36	34	42	
Air pollution (mean annual concentration of anthropogenic $PM_{2.5}$ μg m^3) [68]					
Data years	2010	2010	2010	2010	Nil
Persons	9.9	6.8	7.5	6.9	
Breastfeeding (% never breastfed) [69 70 71 72 73 74 75 76]					
Data years	2016	2016	2016	2016	Ever-br'stfed
Females 30-89	52	58	52	66	
Physical activity (% achieving 150+ minutes moderate physical activity per week) [46 47 48 50]					
Data years	2005	2005	2004/05	2005/06	150+ mins/week
Males 16+	39	43	36	33	
Females 16+	27	31	23	28	
Post-menopausal hormones (%) [e 77 78]					
Data years	2010-12	2010-12	2010-12	GB average	Nil
Current use					
Females 16-74	2	2	3	2	
Females 75+	0	0	0	0	

Supplementary Material D: Summary prevalence of exposure to risk factors, by country and sex (*continued*)

Risk factor	England	Scotland	Wales	Northern Ireland	Optimum exposure
Past use					
Females 16-74	10	10	10	10	
Females 75+	22	25	19	22	
Oral contraceptives (%) [77 78]					
Data years	2010-12	2010-12	2010-12	ROI 2010	Nil
Current use (in last year)					
Females 16-74	0-41	0-44	0-44	1-61	
Females 75+	0	0	0	0	

[a] Responded anything other than 'never' when asked 'how many hours are you exposed to other people's smoke'

[b] Beef, veal and dishes; lamb and dishes; pork and dishes; liver, liver products and dishes

[c] Bacon and ham; burgers and kebabs; sausages; meat pies and pastries; other meat and meat products

[d] Data were provided as non-starch polysaccharides (NSP) grams per day and converted to fibre assuming 1g NSP = 1.28g fibre

[e] specific postmenopausal hormone preparation not reported in survey data

[f] *H. pylori* data from 1996 for England and Wales, 1992 for Scotland, 1986-87 for Northern Ireland

[g] England is figure for white/other ethnicity non-IDUs only; from the cited paper

[h] Cosmic, gamma, internal

Supplementary Material E: Calculations on relative risk or exposure prevalence data

Tobacco smoking

PAFs were calculated for 2015 and 2010, with the 2010 calculations to afford comparison with Parkin et al. The same RRs were used for both 2015 calculations. Both calculations used survey-reported smoking prevalence.[46 47 48 49]

Secondhand smoke

Data were available only for England, Scotland and Wales so the averages of these countries were used for the Northern Ireland figures. Scotland data on exposure to other people's smoke were only collected in 2003 and 2008, but the Scotland public smoking ban came into force in 2006,[79] so a linear trend was assumed unlikely and the 2003 data were used in the analysis.

Overweight and obesity

Scotland data on body mass index were collected only in 2003 and 2008, so 2005 data were imputed assuming a linear trend between those two survey years.

UV radiation

UV PAFs were calculated using ratios of expected (in less UV-unexposed persons, and UV-unrelated melanoma morphologies) versus observed (in typically UV-exposed persons, and UV-related melanoma morphologies) melanoma skin cancer cases. Less-UV exposed was operationalised in several ways, in line with previous work,[80] and the final PAF was an average of the PAFs obtained using each of these definitions. Less UV-exposed persons were those in the 1918 birth cohort, whose expected melanoma skin cancer rates were calculated using an age-period-cohort model. Acral lentiginous melanoma was considered UV-unrelated.[80]

Occupation

Recalculating PAFs by cancer type for each UK country was not possible with publicly available occupation data, so the all cancers combined occupation PAF from the original UK attributable cancers project was converted to country-specific all cancers combined occupation PAFs, with no further breakdown by cancer type.[81] The breakdown of total jobs in 1982 by industry group was calculated for each country and for Great Britain. [51] The ratio of those percentages (e.g. Scotland:Great Britain) was applied to the Great Britain all cancers combined PAF (persons) for each industry, to obtain PAFs by industry by country. For example, manufacturing was 23% of total jobs in Great Britain, and 21% of total jobs in Scotland, so the Scotland PAF for manufacturing was 0.92 × the Great Britain PAF for manufacturing. Within these calculations non-melanoma skin cancer (NMSC) cases and shiftwork-attributable cancer cases were excluded; these were included in the original PAFs

by industry but NMSC registration is insufficiently complete to include in PAFs,[82] and there is not sufficient evidence that shiftwork causes cancer in humans, according to IARC.[83] PAFs by industry and country were summed cumulatively to obtain PAFs for all industries and all cancers combined, by country. To obtain male and female PAFs, ratios (male to persons and female to persons) from the original UK attributable cancers project report were applied to the persons PAF.[81]

Infections

Data on *H. pylori* prevalence were available only for a subset of age bands for the devolved nations compared with England, so missing values were imputed by applying the average percentage difference between all observed age points to the age point at each end of the observed range, and then applying that same percentage change to those imputed age points, and so on. Data on Hepatitis B prevalence was available only for the UK overall, so the same prevalence rate was assumed to apply across all UK countries and the age breakdown for hepatitis C was applied to these data, because the risk factors are similar for both infections.[84] Data on hepatitis C prevalence in devolved nations were extrapolated from England data, by applying the age breakdown observed in the England data to the total population reported prevalence for Scotland and Wales, and by applying to the England data a conversion factor derived from first-time blood donors for Northern Ireland. Data on HIV prevalence were available for the UK only in the most appropriate data year, so that UK prevalence was broken down by country according to the percentages of UK total new HIV diagnoses in 2005 contributed by each UK country.

Alcohol

Prevalence of alcohol use was provided in units per week but the RRs were defined as grams of ethanol per day. Units per week was converted to grams of ethanol per day (units per week divided by 7, multiplied by 8g ethanol per unit),[85] and this was mapped to low, moderate and high daily alcohol consumption as defined in grams of ethanol per day in the source of the alcohol RRs. Data were available only for England, Scotland and Wales so the averages of these countries were used for the Northern Ireland figures.

Processed meat and fibre

Prevalence of processed meat and fibre consumption was provided for Great Britain only, in the survey period most suited to the ten-year lag (2000/01). To obtain UK country breakdowns, ratios of processed meat and fibre intake in the UK overall versus each UK country were calculated from the same survey in a more recent data period (2008-12),[86] and applied to the Great Britain figures from 2000/01.

Ionising radiation

Data on radon exposure were provided in average millisieverts (mSv) per year but the RRs were defined in becquerels per metre cubed (Bq m^3). mSv per year were converted to Bq m^3 assuming that exposure to an average indoor radon concentration in air of 20 Bq m^3 results in an effective dose of about 1 mSv per year.[87] Data on the prevalence of radiotherapy use by cancer type was obtained from the original UK attributable cancers project report,[88] but the prevalence of cancer survivors was updated.[89] Data on background radiation were obtained for 2010, allowing a 5-year lag against incidence as in the original attributable cancers project.

Breastfeeding

Prevalence of ever-breastfeeding was calculated by identifying the median year in which each birth cohort had their first baby, and the percentage of women giving birth in that year who breastfed initially, then applying that percentage to the percentage of women who were parous by age 45. Data on median year of first birth (calculated from median age at first birth per cohort) was available for birth cohorts 1920-1986 for England & Wales, for birth cohorts 1951-1981 (at 5-year intervals) for Scotland, and for birth cohorts 1960-1986 for Northern Ireland. Data on percentage who breastfed initially was available for birth cohorts 1944-1980/81 (at around 5-year intervals though this varied depending on median year at first birth) for all UK countries, and earlier data was derived from publications describing the general state of UK breastfeeding in the early 20th century. Data on percentage parous by age 45 (defined as percentage not childless by age 45 per cohort) was available for birth cohorts 1920-1970 for England & Wales, for birth cohorts 1930-1955 (at 5-year intervals) for Scotland, and for birth cohorts 1940-1965 (at 5-year intervals) for Northern Ireland.

Missing data in the middle of the series (e.g. where data were available in 5-year intervals) were imputed by assuming linear change between the bookending datapoints. Missing data at either end of the series were typically imputed by applying the average England & Wales versus Scotland/Northern Ireland ratio from existing datapoints, to England & Wales data for the missing datapoints (this was done for Scotland and Northern Ireland percentage parous, and Northern Ireland median year of first birth). Missing data at either end of the series for Scotland median year of first birth were replaced with England & Wales data because the ratios in the existing datapoints were inconsistent. Missing data at the end of the series for England & Wales percentage parous and for all countries' percentage initially breastfeeding was replaced with the value at the end of the existing datapoints.

Physical activity

Prevalence of physical activity was provided as days per week on which at least 30 minutes of moderate physical activity was completed but the RRs were defined as metabolic-equivalent hours (MET-hours) per week. Days per week were converted to MET-hours per week as-

suming one hour of moderate activity is equal to four MET-hours, as defined in the source of the physical activity RRs and by the World Health Organization.[90] Using this conversion at least 5 days of 30+ minutes activity were required to exceed the reference category in the RR source (600 MET-minutes per week). It was not possible to identify people achieving 600+ MET-minutes in less than 5 days (e.g. 1 hour of moderate physical activity on 3 days per week).

Scotland data on physical activity were collected only in 2003 and 2008, so 2005 data were imputed assuming a linear trend between those two survey years.

Postmenopausal hormones

Prevalence of postmenopausal hormone use was provided as ever-use or current use, but the RRs were defined as current use or past use. Past use was calculated as the proportion who have ever used these products minus the proportion currently using them. Prevalence data did not specify which hormonal preparation was used (e.g. oestrogen-progestogen or oestrogen-only) so RRs for all preparations combined were used. Data were available only for England, Scotland and Wales so the averages of these countries were used for the Northern Ireland figures. Data on use of postmenopausal hormones were collected only for women up to age 74, so to impute figures for women aged 75+, ratios of use in women aged 65-74 versus women aged 75+ were calculated from a more recent survey,[91] and applied to the figures for women aged 65-74.

Postmenopausal hormones are associated with increased risk of some cancer types and decreased risk of others. As the outcome of interest in this project is attributable cases only, the cases theoretically avoided by use of postmenopausal hormones are not reported here. However as in the original UK attributable cancers project, it is likely that the net effect of postmenopausal use on cancer incidence in the UK is very small.

Oral contraceptives

Data on oral contraceptive use were not available for Northern Ireland so Republic of Ireland data were used as they were considered more representative of Northern Ireland than a GB average would be, given differences around contraception and abortion between Great Britain and Northern Ireland.[92] Data on use of oral contraceptives were collected only for women up to age 74, so to impute figures for women aged 75+, ratios of use in women aged 65-74 versus women aged 75+ were calculated from a more recent survey,91 and applied to the figures for women aged 65-74.

Oral contraceptives are also associated with increased risk of some cancer types and decreased risk of others, the cases theoretically avoided by their use are not reported here, and it is likely that the net effect of their use is very small.

Supplementary Material F: Results by country, risk factor and cancer type combinations.

Available at https://www.nature.com/articles/s41416-018-0029-6#MOESM1.

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4

Quantifying the societal and economic impact of alcohol-attributable cancer deaths and the effect of alcohol policy changes on cancer burden in Europe

Chapter

The cost of premature death from alcohol-attributable cancer: productivity losses in Europe in 2018

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Rumgay H
Ortega-Ortega M
Sharp L
Lunet N
Soerjomataram I

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Chapter 9

Fewer cancer cases in 4 countries of the WHO European Region in 2018 through increased alcohol excise taxation: a modelling study

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ABSTRACT

Introduction: Prevention of cancer has been identified as a major public health priority for Europe, and alcohol is a leading risk factor for various types of cancer. This contribution estimates the number of cancer cases that could have potentially been averted in 2018 in 4 European countries if an increase in alcohol excise taxation had been applied.

Methods: Current country and beverage-specific excise taxation of 4 member states of the WHO European Region (Germany, Italy, Kazakhstan, and Sweden) was used as a baseline, and the potential impacts of increases of 20, 50, and 100% to current excise duties were modelled. A sensitivity analysis was performed, replacing the current tax rates in the 4 countries by those levied in Finland. The resulting increase in tax was assumed to be fully incorporated into the consumer price, and beverage-specific price elasticities of demand were obtained from meta-analyses, assuming less elasticity for heavy drinkers. Model estimates were applied to cancer incidence rates for the year 2018.

Results: In the 4 countries, >35,000 cancer cases in 2018 were caused by alcohol consumption, with the highest rate of alcohol-attributable cancers recorded in Germany and the lowest in Sweden. An increase in excise duties on alcohol would have significantly reduced these numbers, with between 3 and 7% of all alcohol-attributable cancer cases being averted if taxation had been increased by 100%. If the 4 countries were to adopt an excise taxation level equivalent to the one currently imposed in Finland, an even higher proportion of alcohol-attributable cancers could be avoided, with Germany alone experiencing 1,600 fewer cancer cases in 1 year.

Discussion/Conclusion: Increasing excise duties can markedly reduce cancer incidence in European countries.

INTRODUCTION

Reducing the health burden caused by cancer is a top European health priority. Indeed, the European Union (EU) issued a European plan to fight cancer,[1] which stressed prevention as one of its 4 pillars. Similarly, the World Health Organization (WHO) Regional Office for Europe, whose member states also include Eastern European countries outside of the EU and Central Asian countries, has established the prevention and control of non-communicable diseases, especially cancer, as a public health priority.[2,3] Further, numerous key organizations of the European Public Health Alliance issued a joint statement in 2020 placing prevention at the heart of Europe's Beating Cancer Plan.[4]

Alcohol use is one of the major causes of cancer,[5,6] particularly in Europe, which has the highest level of alcohol consumption globally[7] (for the alcohol-attributable cancer burden, see [8,9]). In a comprehensive study comparing the impact of different risk factors on the incidence of cancer, alcohol was found to be the second leading cause of cancer in France after tobacco smoking.[10]

Effective and cost-effective alcohol control policies can decrease the burden of disease caused by alcohol use.[11,12] Increasing the price of alcoholic beverages by increasing alcohol-specific taxation is the most effective such policy in terms of costs involved and the time required for implementation. Accordingly, this study estimated the effect of increasing excise taxation by 20, 50, and 100% on cancer incidence in 4 member states of the WHO European Region: Germany, Italy, Kazakhstan, and Sweden.

MATERIALS AND METHODS

Selection of Countries

Four countries were selected to assess the effects of increasing excise taxes on cancer incidence based on their differing levels and patterns of alcohol consumption and alcohol policies. The 4 countries include Germany, Italy, Kazakhstan, and Sweden.

Germany, a high-income country, where beer is the most consumed beverage[13] was selected since it has one of the highest levels of alcohol use globally[7] (level of alcohol use is usually expressed in adult alcohol consumption per capita – APC – in litres pure alcohol)[14] and liberal alcohol control policies, including low taxation rates,[15] resulting in high affordability of alcoholic beverages.[16]

Italy, another high-income country, where wine is the most frequently consumed beverage,[13] was selected due to its relatively liberal alcohol control policies similar to Germany's[15] but in combination with a much lower APC compared to Germany. The current lower levels of alcohol use resulted after several decades of continued decrease, related to industrialization,

globalization, and social measures of control, which, among other causes, have reduced the tradition of consuming alcohol with both lunch and dinner on the same day.[17]

Kazakhstan, an upper middle-income country, was selected due to its large Muslim population (about 70% Muslims)[18] and therefore its high prevalence of abstainers.[7] However, similar to Eastern European countries, the volume of alcohol consumed by drinkers is relatively high, and the preferred beverage is spirits.[13] Furthermore, within the last decade, several of the WHO "best buy" policies for alcohol control have been implemented in Kazakhstan, resulting in relatively high rates of taxation (see below and [15]).

Sweden, a high-income country, was selected due to its relatively low APC (lower than the average EU country) and due to a switch in patterns of drinking in the last decades from spirits to wine as the preferred beverage.[13] Sweden traditionally has restrictive alcohol policies.[15] An overview of alcohol indicators for the 4 selected countries is provided in Appendix Table A1.

Building Different Taxation Scenarios

Since the main objective of this study is to see how many cancer cases could have been averted by increasing excise taxes on alcohol, the first step was to obtain information on the current taxation policies and the mean price per litre of each alcohol beverage type, to determine the percentage of the price represented by tax. For the 3 countries that are part of the EU, the current duties for alcohol are available at [19] and the data on the mean price have been obtained from the Statista webpage.[20] For Kazakhstan, we relied on government data, from the national taxation plan, for the level of excise duties[21] and for a number of sources for current prices (see Appendix). An overview of all data and procedures can be found in the Appendix.

Alcoholic beverages were categorized into 3 major groups: beer, wine, and spirits. In order to evaluate the mean proportion of the alcohol tax for each type of alcohol beverage, the mean percentage of pure alcohol for each beverage was assumed to be 5, 12.5, and 40% for beer, wine, and spirits, respectively (same assumptions as in [13]). Alcohol excise taxation statistics, by country and beverage type, are outlined in Table 1.

Table 1. Percentage of excise duty over the mean price per litre of the finished product for each alcoholic beverage type

Country	Beer		Wine		Spirits	
	mean price (€/L)	% tax	mean price (€/L)	% tax	mean price (€/L)	% tax
Germany	2.34	4.0	7.01	0	16.47	31.7
Italy	3.34	10.7	10.92	0	16.85	24.6
Kazakhstan[a]	0.93	12.2	5.19	1.4	5.84	35.0
Sweden	5.68	16.5	23.25	10.4	65.67	29.1

[a] Exchange course: 1 € = 500 KZH (July 31 2020).

In this study, 3 different scenarios were simulated to determine the effects after excise taxes for each of 3 main alcoholic beverage types are increased by 20, 50, and 100% (for similar analyses, see [11,12]). To apply an increase in excise duties to wine for Germany and Italy, where there is currently no such taxation (Table 1), the same tax percentage as for beer was assumed (i.e., a cheap taxation rate was applied).

Producers were assumed to pass the cost of the tax increase directly on to the consumer by increasing their alcoholic beverage prices by exactly that amount.[22] The price change (ΔP) will therefore increase by Ti*0.2, Ti*0.5, and Ti*1, respectively, where Ti is the current tax.

After estimating the impact of price increases on consumption, the impact of consumption on cancer was modelled. The relationship between the former parameters is usually called price elasticity (Formula (1); see [23], for a definition). Price elasticity is an economic measure of the change in the quantity demanded or purchased of a product in relation to its price change, which is mathematically described in Formula (1):

$$E = \frac{\Delta Q}{\Delta P}$$

where E = elasticity, Q = quantity of a product demanded or purchased; and P = price.

This formula expresses the proportion of consumption change given a price change. Thus, a value of −0.5 in our context indicates that for a proportional increase in price of 10%, consumption will decrease by 5%. We have obtained the values for price elasticity, which tend to vary based on beverage type, from previous meta-analyses.[24,25]

Prior meta-analyses have shown that price elasticities tend to be similar.[25–27] As indicated above, however, they appear to differ by beverage type, which seems to be caused by beverage preference (Table 2). The price elasticities assumed here are −1.2 (95% CI: −1.44, −0.96), −0.6 (95% CI: −0.72, −0.48), and −0.36 (95% CI: −0.48, −0.24) from the least-preferred to the most-preferred beverage type in a country (based on [24,25]). From economic theory, it is plausible that the most-preferred beverage should be more inelastic than others, that is, it should change to a lesser degree and its values should therefore be closer to zero.

Price elasticity for heavier drinkers – including but not limited to people with alcohol use disorders[28] – have also been shown to be lower,[26] in part because their inability to stop drinking is one of the defining characteristics of alcohol use disorders.[29] For heavy drinkers (defined here as men drinking >60 g pure alcohol/day and women >40 g/day), we applied the same price elasticity to all cases: −0.28 (95% CI: −0.37, −0.19; based on a meta-analysis).[26]

We have simulated the number of cancers that could have been averted in 2018 via increasing the duties on alcohol. For this reason, we applied the percentage of changes in exposure to 2008, since the lag time between exposure and cancer incidence must be taken into account.[30] Exposure data have been extracted from Manthey et al.[7]

In order to distinguish the heavy drinkers from other drinkers, we have simulated the distribution of level of drinking in each country with the gamma distribution.[31,32] In simulating this distribution, we can determine the percentage of alcohol consumed by heavy drinkers

Table 2. Percentage of preference for each alcoholic beverage type and modelled price elasticity for non-heavy drinkers

Country	Beer		Wine		Spirits	
	% preference	elasticity	% preference	elasticity	% preference	elasticity
Germany	54.1	-0.36 (-0.48 to -0.24)	27.6	-0.60 (-0.72 to -0.48)	18.4	-1.20 (-1.40 to -1.00)
Italy	21.5	-0.60 (-0.72 to -0.48)	68.0	-0.36 (-0.48 to -0.24)	10.5	-1.20 (-1.44 to -0.96)
Kazakhstan	37.9	-0.60 (-0.72 to -0.48)	3.6	-1.20 (-1.44 to -0.96)	58.5	-0.36 (-0.48 to -0.24)
Sweden	38.2	-0.60 (-0.72 to -0.48)	45.6	-0.36 (-0.48 to -0.24)	16.2	-1.20 (-1.44 to -0.96)

Values given in parentheses are 95% confidence intervals.

(see Supplementary Table 1 for results). Based on the drinking distribution, the distribution of beverage preference, and price elasticities, the decrease in APC following increases in excise duty can be calculated. For non-heavy drinkers, the decrease in consumption can be calculated as shown in Formula (2):

$$\mathrm{APC} - \mathrm{APC} \times \%B \times \%Qb - \mathrm{APC} \times \%W \times \%Qw - \mathrm{APC} \times \%S \times \%Qs$$
$$= \mathrm{APC}(1 - \%B\%Qb - \%W\%Qw - \%S\%Qs)$$

where %B, %W, and %S are the percentages of consumption of beer, wine, and spirits, respectively. The %Qb, %Qw, and %Qs are the percentages of change in beer, wine, and spirits consumption, respectively. For heavy drinkers, the formula is less complicated, since there are no differences in elasticities by beverage type (see Formula (3)):

$$\mathrm{APC} - \mathrm{APC} * \%Qa = APC(1 - \%Qa)$$

where %Qa is the difference in consumption for all drinks.

The overall results of applying the price elasticities on indicators of consumption can be seen in Supplementary Table 2.

Sensitivity Analyses

In addition to modelling taxation increases based on the current taxation system, we included an Arcadian normal,[33] where we modelled all 4 countries based on the current proportion of excise taxes on price from Finland, representing the highest levels of taxation for the most prevalent beverage in the WHO European Region, beer (for level of taxation, see [19]; for a distribution of beverage types in the WHO European Region, see [15]).

Deriving Alcohol-Attributable Fractions and Applying Them to Cancer Incidence

Based on the reduced alcohol use, we determined alcohol-attributable fractions for each cancer type and compared them to the alcohol-attributable fractions in the baseline scenario. These comparisons were made separately by sex and age for all 4 different scenarios (taxation increases of 20, 50, and 100%, assuming the taxation level in Finland), for all cancer types, which are causally related to alcohol. The latter were based on the classification of the International Agency for Research on Cancer, taking only cancer types with sufficient evidence for having a causal impact of alcohol:[5,34]

- Lip and oral cavity cancer (ICD-10 codes: C00-06)
- Oropharyngeal cancers (ICD-10 codes: C09-10)
- Oesophagus cancer (ICD-10 codes: C15)
- Colon and rectum cancers (ICD-10 codes: C18-20)
- Liver cancer (ICD-10 codes: C22)
- Female breast cancer (ICD-10 codes: C50)
- Larynx cancer (ICD-10 codes: C32)

The risk functions used for the calculation of the alcohol-attributable fractions were extracted from the World Cancer Research Fund (WCRF) Continuous Update Project Expert Report[35] and Shield et al.,[6] and the data for the total number of incident cancers came from the GLOBOCAN 2018 database in the Global Cancer Observatory.[36]

RESULTS

Alcohol is a major risk factor for cancer in Europe (see above and [37]) and alcohol-attributable cancer cases were estimated at 21,980, 10,006, 1,655, and 1,416 for Germany, Italy, Kazakhstan, and Sweden, respectively. Table 3 gives details about the alcohol-attributable incident cancers for the 4 countries in 2018, that is, the cancer cases that would not occur in a world without any alcohol use. As expected, Germany, the country with the highest level of alcohol consumption (Supplementary Table 1) had the highest rate of alcohol-attributable cancer for both sexes.

In Supplementary Table 3, the total numbers of incident cancer cases averted for each country are presented after applying the 3 different scenarios of increasing taxation (20, 50, and 100%; see above and Supplementary Materials for details). In case of a 100% increase in the alcohol excise taxes, 673, 480, 59, and 100 new cancer cases would be avoided in Germany, Italy, Kazakhstan, and Sweden, respectively. Obviously, the number of incident cancer cases averted depends substantially on the population size of the country, on the prevalence of drinking, and on the level of taxation before the increase. However, in a single country like Germany, if the current very low excise duties were increased, a substantial number of

Table 3. Alcohol-attributable incident cancers in 4 European countries in 2018 (based on [36])

Country	Women		Men		Total	
	number	rate per 1,000,000[a]	number	rate per 1,000,000[a]	number	rate per 1,000,000[a]
Germany	9,146	101.68	12,834	140.89	21,980	119.53
Italy	3,719	56.79	6,287	94.70	10,006	74.21
Kazakhstan	637	55.35	1,019	126.87	1,655	83.37
Sweden	661	70.51	754	71.91	1,416	70.59
All 4 countries combined	14,162	79.58	20,894	118.87	35,057	97.47

[a] Age-standardized rates based on Doll et al.[55]

new cancer cases could potentially be averted (673 in case of an increase in excise duties by 100%; see Supplementary Table 3).

However, it is difficult to contextualize and interpret these absolute number of potential cases averted due to different taxation scenarios. For this reason, in Table 4 and Figure 1, we present estimates of the percentages they represent out of all the cancer alcohol-attributable cases (i.e., cancers due to alcohol as presented in Table 3) and of all cancer cases for cancer types whose risk is increased by alcohol consumption.

Table 4. Proportion of cancer cases averted in 2018 in each country for different increases in excise duties for alcohol

Country	Increasing current excise duties by 20%		Increasing current excise duties by 50%		Increasing current excise duties by 100%	
	% alcohol-attributable cancers averted	% cancers averted / all cancers[a]	% alcohol-attributable cancers averted	% cancers averted / all cancers[a]	% alcohol-attributable cancers averted	% cancers averted / all cancers[a]
Germany	0.60 (0.50–0.72)	0.08 (0.07–0.10)	1.52 (1.26–1.81)	0.21 (0.17–0.25)	3.06 (2.55–3.67)	0.42 (0.35–0.51)
Italy	0.95 (0.81–1.10)	0.07 (0.06–0.09)	2.38 (2.04–2.76)	0.19 (0.16–0.22)	4.80 (4.10–5.56)	0.37 (0.32–0.43)
Kazakhstan	0.70 (0.56–0.91)	0.10 (0.08–0.14)	1.76 (1.42–2.29)	0.26 (0.21–0.34)	3.57 (2.87–4.67)	0.53 (0.43–0.70)
Sweden	1.38 (1.18–1.65)	0.12 (0.10–0.14)	3.48 (2.97–4.16)	0.29 (0.25–0.35)	7.03 (6.00–8.44)	0.60 (0.51–0.71)

Values given in parentheses are 95% confidence intervals. [a] The proportion here denotes the cases averted of all cancers from the following categories: lip and oral cavity, oropharynx, oesophagus, colon and rectum, liver, female breast, and larynx cancers.

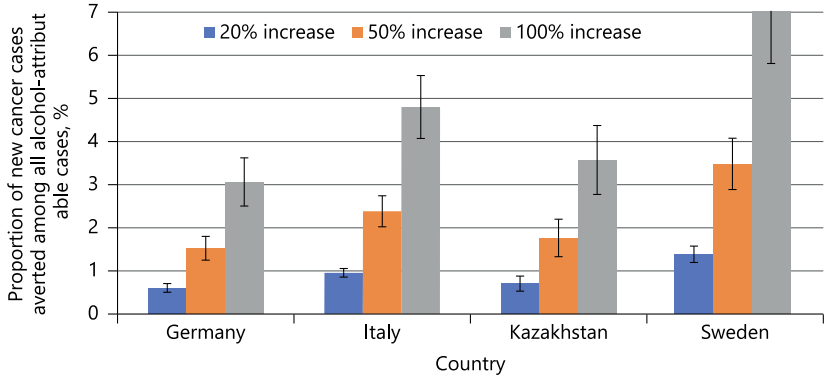

Figure 1. Proportion of new cancer cases averted of all alcohol-attributable cases in 2018 (in %) based on different increases of excise taxation for alcohol

According to this table, since we did proportional increases, the countries in which a higher percentage of cancer cases due to alcohol could have been averted are those where the current taxation rate is the highest. Out of the 4 countries under study, the first such country is Sweden and the second Italy. Germany is lowest, given its low overall excise taxation level. If we analyse the percentages of cancers averted over all cancers, again Sweden is highest, followed by Kazakhstan.

Table 5 gives the results of the sensitivity analyses and demonstrates what would happen if all 4 countries implemented the same excise taxation for alcoholic beverages as implemented in Finland (for the derivation of the proportions of consumer price for alcoholic beverage, which are determined by excise taxes, see Supplementary Materials): beer, 41.2%; wine, 14.5%; and spirits, 42.6%.

Table 5. Cancer cases averted in 2018 if each country had implemented the proportion of excise duties to consumer prices currently used in Finland

Country	Number of cancers averted	% Alcohol-attributable cancers averted	% Cancers averted / all cancers[a]
Germany	1,616 (1,284–1,941)	7.35 (5.84–8.83)	1.02 (0.81–1.22)
Italy	791 (697–914)	7.91 (6.79–9.13)	0.62 (0.53–0.71)
Kazakhstan	80 (63–99)	4.85 (3.81–5.97)	0.72 (0.57–0.89)
Sweden	92 (78–108)	6.49 (5.49–7.62)	0.55 (0.46–0.64)

Values given in parentheses are 95% confidence intervals. [a] The proportion here denotes the cases averted of all cancers from the following categories: lip and oral cavity, oropharynx, oesophagus, colon and rectum, liver, female breast, and larynx cancers.

The results show that marked numbers of incident cancers could been averted if the Finnish level of alcohol-specific taxes had been implemented. In Germany, for example, >1,600 cancer cases could have been averted in 2018 alone.

DISCUSSION/CONCLUSION

We have shown that raising prices of alcoholic beverages via increased taxation can reduce alcohol use and thus potentially avert significant numbers of new cancer cases. For example, in the scenario with highest increase in excise duties modelled, between 3 and 7% of all alcohol-attributable cancer cases were averted, which translated for Germany, the country with the lowest taxation rates at baseline, into 673 cancer cases averted in 2018 (see Supplementary Table 3). If Germany were to implement the Finnish level of excise taxes, >1,600 new cancer cases could have been averted in 2018. These numbers clearly signal a matter of public health importance, even more so as other alcohol-attributable morbidity and mortality will be averted as well (for an overview of alcohol-attributable mortality, see [6]). Obviously, the absolute number of cancer cases averted will depend mainly on the size of the population, the drinking level, and the distribution of cancers in the respective countries, but the relative sizes in achievable reduction are similar. Before we discuss the results further, we would like to point out the limitations of our approach.

As for all modelling studies, the major limitation lies with the assumptions underlying the model. While we did model the impact of alcohol use on cancer in a dose-dependent manner, separated by sex and age groups, 2 parameters were not available by sex or age: first, we did not have the distribution of beverage types by sex and age, and second, we assumed that elasticities were the same for all groups, defined by sex and age. Modelling these 2 parameters as though they were universal may have introduced some error. Another point is that the main scenarios were modelled as proportional increases based on current levels of excise taxation. This would lead to higher proportions averted for countries with higher levels of excise taxation.

As for elasticities, we only differentiated according to beverage preference and level of consumption. While this seems justified based on the literature – where major reviews and meta-analyses found similar elasticities[24-28,38] – this also may have introduced some bias. Another potential bias of our modelling was the lack of modelling cross-elasticities between alcoholic beverages or between alcohol and other substances such as cannabis. However, such cross-elasticities often are found to be small.[39] An additional difficulty here is the potential increase in unrecorded consumption[40] as an unintended consequence of taxation increases. While this argument has been frequently made in past discussions, often by the alcohol industry,[41] recent experiences in Europe do not seem to indicate a marked increase in unrecorded consumption as a consequence of taxation increases (e.g., in Russia or in Kazakhstan).[42,43] To avoid such unintended consequences, a stepwise implementation of taxation and cross-border treaties with neighbouring countries – to avoid large differences in the price of alcoholic beverages – might help.

Alcohol use data seem to have relatively few biases in this region, where the majority is based on recorded consumption (maybe with the exception of the level of unrecorded

consumption in Kazakhstan, which is part of a region with a traditionally high level of unrecorded consumption).[40] However, considerations of sex- and age-specific estimates relied on survey data and hence might have been influenced by underreporting and other biases.[44] Finally, the dose-response curves between level of alcohol use and cancer risk seem to be relatively stable as well in the different meta-analyses.

Alcohol prices can be raised not only through excise rates but also through other non-alcohol-specific taxes such as value-added taxes or via minimum unit pricing. What is important is the reduction of financial affordability of alcohol at the population level, and this can be achieved through different kinds of taxation schemes (for further discussion, see [23]). Affordability needs to remain low over time, and thus, adjustment for inflation of all taxation relating to alcoholic beverages is needed – otherwise, alcohol becomes relatively cheaper over time.

Kazakhstan is an interesting case here, as rates of excise duties and minimum unit prices have, in combination, increased over time, making alcohol steadily less affordable.[43] This strategy has been proven to be effective in reducing mortality, especially mortality of working-age males in Russia and Belarus in the past,[42,45,46] and there is evidence to suggest that the same reductions in mortality were achieved in Kazakhstan at least partially through higher alcohol prices.[47] However, this reduction cannot be attributed to pricing interventions alone, as several alcohol control measures were recently introduced in this country.[48] As for value-added taxes, while affecting the price, it should be noted that such taxes usually apply to all foods and thus would not recover the economic costs related specifically to alcohol use. As found in all major studies on the economic costs of alcohol use, alcohol-attributable costs not only comprise expenses for the healthcare system but also the costs of the legal system (e.g., drink-driving and alcohol-attributable aggression), as well as productivity losses.[49,50] Based on traditional economic theory (e.g., the concept of Pigouvian tax), all additional costs incurred by alcohol use (i.e., the so-called externalities[27]) should be recovered by the state via specific taxation, and value-added taxes on all consumer goods do not contribute here. Minimum unit prices are another measure to increase prices at the lower end of the price scale. This intervention has recently been shown to affect heavy drinkers in lower socioeconomic strata especially.[51] As a consequence, adequately set minimum unit prices are important in the alcohol policy mix but not specifically for cancer, as this disease category is mainly related to overall volume of alcohol use and not to irregular heavy drinking occasions, with relatively flat risk-relation curves.[52]

The main result of our analyses is, however, that more is possible in the prevention of alcohol-attributable cancers. More than 4 million people are diagnosed with cancer in the WHO European Region each year,[36] and thousands of such cancers could be averted, if all countries in this region adopted more stringent systems in excise taxation, or if the EU increased their minimum excise tax levels (which are as low as 0 EUR for wine).

In Germany, for example, the government could not only avoid over 1,600 new cancers per year, it could also increase their tax revenue if they implemented the same level of excise duties as Finland. And Finland is not an Arcadian utopia: it is a member of the EU with similar standards of healthcare and economic power.[53] Implementing Finnish rates for alcohol excise duties would not only decrease the number of new cancer cases, and subsequently cancer mortality, but also reduce many other health burdens related to alcohol,[52,54] and thus would contribute to a reduction in all-cause mortality and to an increase in life expectancy.

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SUPPLEMENTARY MATERIALS

Taxation structure by country

Based on the following sources unless otherwise specified:

European Commission Directorate-General Taxation and Customs Union. Excise duty tables. 2020;[1] Statista platform for business data,[2] data used for 2020.

Finland

Standard rates only

Alcoholic beverage	Duty per hectolitre	VAT
Beer	36.50 EUR per °alc per hectolitre	24%
Still wine	397.00 EUR per hectolitre of the finished product	24%
Ethyl alcohol	4,880.0 EUR per hectolitre pure alcohol	24%

Average % of taxation on the price:

1) Beer: Given an average price of 4.35 EUR per litre beer in 2020[3] and assuming an average alcohol content of 5 Vol% pure alcohol, the proportion of the alcohol tax on the beer price is 41.2%.
   Calculation: (36.5 EUR * 5 °Alc) / (4.35 EUR * 100) = 0.4195
2) Wine: Given an average price of 27.48 EUR per litre wine in 2020[3] and assuming an average alcohol content of 12.5 Vol% pure alcohol, the proportion of the alcohol tax on the wine price is 14.5%.
   Calculation: 397.0 EUR / (27.48 EUR * 100) = 0.1445
3) Spirits: Given an average price of 45.80 EUR per litre spirits in 2020[3] and assuming an average alcohol content of 40 Vol% pure alcohol, the proportion of the alcohol tax on the spirits price is 42.6%.
   Calculation: (4,880.0 EUR* 0.4) / (45.80 EUR* 100) = 0.4262

Germany

Standard rates only (excluding reduced rates for independent small breweries)

Alcoholic beverage	Duty	VAT
Beer	0.787 EUR per °Plato per hectolitre	19%
Still wine	0.00 EUR	19%
Ethyl alcohol	1,303 EUR per hectolitre pure alcohol)	19%

Average % of taxation on the price:

1) Beer: Given an average price of 2.34 EUR per litre beer in 2020[3] and assuming an average alcohol content of 5 Vol% pure alcohol and an average gravity of 12°Plato, the proportion of the alcohol tax on the beer price is 4.0%.

Calculation: 0.787 EUR * 12 Plato / (2.34 EUR * 100) = 0.0404

2) Wine: Excise duty for wine is 0 EUR per hectolitre, thus, there is no tax for wine in Germany.

3) Spirits: Given an average price of 16.47 EUR per litre spirits in 2020[3] and assuming an average alcohol content of 40 Vol% pure alcohol, the proportion of the alcohol tax on the spirits price is 31.7%.

Calculation: (1,303 EUR * 0.4) / (16.47 EUR * 100) = 0.3165

Italy

Standard rates only

Alcoholic beverage	Duty	VAT
Beer	2.99 EUR per °Plato per hectolitre	22%
Still wine	0.00 EUR	-
Ethyl alcohol	1,035.52 EUR per hectolitre of pure alcohol	22%

Average % of taxation on the price:

1) Beer: Given an average price of 3.34 EUR per litre beer in 2020[3] and assuming an average alcohol content of 5 Vol% pure alcohol and an average gravity of 12°Plato, the proportion of the alcohol tax on the beer price is 10.7%.
   Calculation: 2.99 EUR * 12 °Plato / (3.34 EUR * 100) = 0.1074
2) Wine: Excise duty for wine is 0 EUR per hectolitre, thus, there is no tax for wine in Italy.
3) Spirits: Given an average price of 16.85 EUR per litre spirits in 2020[3] and assuming an average alcohol content of 40 Vol% pure alcohol, the proportion of the alcohol tax on the spirits price is 24.6%.
   Calculation: (1,035.52 EUR * 0.4) / (16.85 EUR * 100) = 0.2458

Kazakhstan

Alcoholic beverage	Duty	VAT
Beer	57 KZT per litre of the finished product	12%
Wines	35 KZT per litre of the finished product	12%
Alcohol (including vodka)	2,550 KZT per litre of pure alcohol	12%

Exchange course: 1 € = 500 KZH (31/07/2020).

Average % of taxation on the price:

1) Beer: Given an average price of 466 KZT per litre beer in 2020[4] the proportion of the alcohol tax on the beer price is 12.2%.

Calculation: 57 KZT/466 KZT = 0.122318

2) Wine: Given an average price of 2,593 KZT per litre wine in 2020[5] and assuming an average alcohol content of 12.5 Vol% pure alcohol in wine, the proportion of the alcohol tax on the wine price is 1.4%.
   Calculation: 35 KZT/2,593 KZT = 0.013498
3) Spirits: Given an average price of 2,918 KZT per litre spirits in 2020[5] and assuming an average alcohol content of 40 Vol% pure alcohol in spirits, the proportion of the alcohol tax on the spirits price is 35.0%.
   Calculation: (2,550 KZT * 0.4) / 2,918 KZT = 0.349554

Sweden

Standard rates only

Alcoholic beverage	Duty	VAT
Beer	18.6963 EUR °alc per hectolitre	25%
Still wine	242.3109 EUR per hectolitre of the finished product	25%
Ethyl alcohol	4,781.3371 EUR per hectolitre of the pure alcohol	25%

Average % of taxation on the price:

1) Beer: Given an average price of 5.68 EUR per litre beer in 2020[3] and assuming an average alcohol content of 5 Vol% pure alcohol, the proportion of the alcohol tax on the beer price is 16.5%.
   Calculation: (18.6963 EUR * 5 °alc) / (5.68 EUR * 100) = 0.1646
2) Wine: Given an average price of 23.25 EUR per litre wine in 2020[3] and assuming an average alcohol content of 12.5 Vol% pure alcohol, the proportion of the alcohol tax on the wine price is 10.4%.
   Calculation: 242.3109 EUR / (23.25 EUR * 100) = 0.1042
3) Spirits: Given an average price of 65.67 EUR per litre spirits in 2020[3] and assuming an average alcohol content of 40 Vol% pure alcohol, the proportion of the alcohol tax on the spirits price is 29.1%.
   Calculation: (4,781.3371 EUR * 0.4) / (65.67 EUR * 100) = 0.2912

Supplementary Table 1. Alcohol use indicators for 2008

Country	Alcohol *per capita* consumption (APC) *				Percentage of current drinkers in the population			Percentage of heavy drinkers (men > 60g/day; women > 40g/day) in the population		
	Beer	Wine	Spirits	Total	Women	Men	Total	Women	Men	Total
Germany	6.35	3.24	2.16	13.26	74.51%	87.91%	81.02%	9.74%	21.24%	15.33%
Italy	1.47	4.65	0.72	7.23	63.88%	81.75%	72.48%	3.04%	11.19%	6.97%
Kazakhstan	2.81	0.29	4.33	10.30	38.90%	58.99%	48.37%	7.25%	16.37%	11.55%
Sweden	2.60	3.10	1.10	9.22	68.43%	83.95%	76.09%	5.14%	14.77%	9.89%

* The APC of beer, wine and spirits do not add up to total APC as beverage type is only known for recorded consumption.

Supplementary Table 2. Alcohol indicators for each different taxation scenario

Country	Taxation	Alcohol *per capita* consumption (APC) *				Percentage of current drinkers in the population			Percentage of heavy drinkers (men > 60g/day; women > 40g/day) in the population		
		Beer	Wine	Spirits	Total	Women	Men	Total	Women	Men	Total
Germany	+20%	6.33	3.23	2.06	13.14	74.51%	87.91%	81.02%	9.70%	21.05%	15.22%
Germany	+50%	6.31	3.21	1.91	12.97	74.51%	87.91%	81.02%	9.47%	20.83%	14.99%
Germany	+100%	6.27	3.18	1.67	12.68	74.51%	87.91%	81.02%	9.08%	20.47%	14.61%
Germany	Finnish Taxation	5.60	3.04	1.99	11.78	74.51%	87.91%	81.02%	8.08%	19.16%	13.47%
Italy	+20%	1.45	4.62	0.69	7.15	63.88%	81.75%	72.48%	3.03%	11.11%	6.92%
Italy	+50%	1.43	4.57	0.64	7.04	63.88%	81.75%	72.48%	2.89%	10.84%	6.72%
Italy	+100%	1.39	4.48	0.56	6.84	63.88%	81.75%	72.48%	2.66%	10.40%	6.39%
Italy	Finnish Taxation	1.25	4.43	0.60	6.56	63.88%	81.75%	72.48%	2.41%	9.73%	5.93%
Kazakhstan	+20%	2.78	0.29	4.24	10.18	38.90%	58.99%	48.37%	7.23%	16.38%	11.55%
Kazakhstan	+50%	2.74	0.29	4.09	9.99	38.90%	58.99%	48.37%	7.06%	16.19%	11.37%
Kazakhstan	+100%	2.67	0.29	3.86	9.68	38.90%	58.99%	48.37%	6.77%	15.87%	11.06%
Kazakhstan	Finnish Taxation	2.48	0.27	4.23	9.44	38.90%	58.99%	48.37%	6.58%	15.59%	10.82%
Sweden	+20%	2.56	3.05	1.08	9.07	68.43%	83.95%	76.09%	5.04%	14.55%	9.74%
Sweden	+50%	2.50	2.97	1.05	8.84	68.43%	83.95%	76.09%	4.74%	14.13%	9.38%
Sweden	+100%	2.40	2.83	1.00	8.47	68.43%	83.95%	76.09%	4.27%	13.41%	8.78%
Sweden	Finnish Taxation	2.30	3.00	1.05	8.49	68.43%	83.95%	76.09%	4.36%	13.43%	8.84%

* The APC of beer , wine and spirits do not add up to total APC, as beverage type is only known for recorded consumption.

Supplementary Table 3. Number of incident cancer cases which could have been averted in 2018 in each country for each different taxation scenario

Country	Increasing the excise duties by 20%	Increasing the excise duties by 50%	Increasing the excise duties by 100%
Germany	132 (114-158)	334 (277-398)	673 (560-807)
Italy	95 (81-110)	238 (204-276)	480 (410-556)
Kazakhstan	12 (9-15)	29 (24-38)	59 (47-77)
Sweden	20 (17-23)	49 (42-59)	100 (85-120)

Supplementary Table 4. Proportion of incident cancer cases averted in 2018 in each country for different increases in excise duties applying the Finnish taxation rates (see Table 5 for baseline results)

Country	% Alcohol-attributable cancer cases averted		
	Increasing current excise duties by 20%	Increasing current excise duties by 50%	Increasing current excise duties by 100%
Germany	1.98 (1.65-2.34)	5.06 (4.19-5.99)	10.47 (8.64-12.46)
Italy	2.22 (1.88-2.52)	5.60 (4.74-6.36)	11.42 (9.65-12.97)
Kazakhstan	1.64 (1.34-2.01)	4.21 (3.42-5.17)	8.75 (7.06-10.84)
Sweden	2.67 (2.29-3.13)	6.76 (5.80-7.95)	13.83 (11.86-16.26)

SUPPLEMENTARY REFERENCES

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5

Discussion

Chapter 01

General discussion

In this thesis, we have assessed several aspects of the burden of cancer attributable to alcohol use which we presented in four parts. To provide background on the link between alcohol drinking and cancer, in Part 1 we introduced the topics covered in this thesis and summarised the epidemiology and molecular mechanisms of alcohol-driven carcinogenesis. In Part 2 we described the burden of liver cancer globally and by subtype, and analysed oesophageal cancer incidence trends by histological subtype. We quantified the global burden of cancer attributable to alcohol use and the burden of cancer in the United Kingdom (UK) attributable to a range of modifiable risk factors, including alcohol, in Part 3. Expanding on these estimates of burden, in Part 4 we quantified the economic impact of alcohol-attributable cancer deaths and the effect of alcohol policy changes on cancer burden in Europe.

In this final chapter, Part 5, we address the research questions posed in Part 1 based on the main findings from Parts 2 to 4 set in the context of the current literature. We then discuss the methodological considerations and limitations of the studies presented. Finally, we suggest directions for future research and provide our conclusions and recommendations from the information presented in this thesis.

RESEARCH QUESTIONS AND MAIN FINDINGS

1. What is the global burden of alcohol-related cancers and how have their trends evolved over time?

More than 900,000 people were diagnosed with, and 830,000 people died from, primary liver cancer globally in 2020. Incidence and mortality rates of liver cancer are highest in eastern Asia, northern Africa, and south-eastern Asia, and liver cancer is among the top three causes of cancer death in 46 countries worldwide.

Primary liver cancer is causally related to alcohol use. In Chapter 3 we assessed the global burden of liver cancer in a descriptive evaluation of patterns of incidence and mortality rates by world region, country, and sex based on estimates from the GLOBOCAN 2020 database. More than 900,000 people were diagnosed with, and 830,000 people died from, liver cancer globally in 2020.[1] Among the world regions, the highest rates of liver cancer incidence and mortality were found in eastern Asia, northern Africa, and south-eastern Asia, and liver cancer was the most common cause of cancer death in 15 countries including several countries in south-eastern Asia and sub-Saharan Africa. The most prominent modifiable risk factors for liver cancer are infection with hepatitis B and C viruses which were attributable for approximately 56% and 20% of liver cancer cases worldwide, respectively, in 2018.[2] Ingestion of aflatoxin-contaminated crops also contributes to liver cancer burden in tropical and subtropical areas.[3] In countries with low endemicity of hepatitis B and C virus infection and less exposure to aflatoxins, alcohol consumption is suggested as a driving factor

of liver cancer rates.[4,5] Additional liver cancer risk factors include metabolic syndrome, type 2 diabetes, obesity, and non-alcoholic fatty liver disease, cigarette smoking, and liver fluke infestation.[6]

In Chapter 3 we noted that liver cancer was among the top three causes of cancer death in a total of 46 countries worldwide and was within the top five causes of cancer death in 90 countries. Considering the low survival from liver cancer even in high-income countries (e.g. 3-year net-survival of 28% in Australia in 2012-2014),[7] we recommended that public health officials prioritise prevention of liver cancer risk factors. Studies have also shown that several causes of liver cancer are subtype-specific, thus it would be valuable to investigate the patterns of the subtypes of liver cancer by sex and country to inform research and policy priorities in different settings. Furthermore, assessing the burden of liver cancer by subtype would enable us to produce more reliable estimates of the population impact of risk factors and prioritise prevention strategies targeted at the major subtypes.

Hepatocellular carcinoma is the major subtype of liver cancer and represented an estimated 80% of liver cancer cases globally in 2018. Hepatocellular carcinoma is the subtype of liver cancer which is causally related to alcohol consumption.

Alcohol consumption specifically increases the risk of hepatocellular carcinoma (HCC) which is a subtype of liver cancer. To assess the geographical patterns of HCC incidence, in Chapter 4 we estimated the number of cases of the major subtypes of liver cancer. To do this we used population-based cancer registry (PBCR) data by histological subtype to estimate their distribution in countries across the world. We estimated the proportion of HCC, intrahepatic cholangiocarcinoma (iCCA), and other subtypes using data from national and subnational registries and applied these proportions to national estimates of liver cancer incidence from the GLOBOCAN 2018 database. We found that HCC contributed 80% of the world total liver cancer burden followed by iCCA (15%), and other specified histology (5%), and uncovered distinct patterns in the incidence of the major subtypes by world region. Incidence rates of HCC were highest in eastern Asia, northern Africa, and south-eastern Asia, and iCCA rates were highest in south-eastern and eastern Asia, and northern Europe. These results will enable public health officials to identify the specific mix of subtypes in their region to apply tailored measures to reduce the burden of HCC and iCCA, including alcohol control for HCC prevention, in their settings.

This work also brought methodological insight to estimating liver cancer burden by subtype at the national level. Due to a large proportion of cases of liver cancer recorded with unspecified histology (ranging from 6% of registered cases in North America to 50% in sub-Saharan Africa in 2008-2012),[8] we proposed three scenarios to redistribute unspecified liver cancer cases based on several hypotheses: 1) the scenario used in the main analysis which redistributed unspecified cases according to the relative distribution of HCC and iCCA, assuming that any unspecified cases are not likely to be any other specified histological

subtype; 2) an alternative scenario which assumed unspecified cases were equally likely to be HCC, iCCA, or other specified histological subtype; and 3) another alternative scenario which used only cases of liver cancer which had been microscopically verified. Regarding the third scenario, restricting the number of cases of liver cancer to those microscopically verified is problematic because the proportion of HCC cases diagnosed through microscopic verification has decreased over time,[7] and many cases of liver cancer are diagnosed through means which do not require such verification, such as through ultrasound, CT and MRI imaging.[9,10] The data that we used were based on cases diagnosed mainly between 2008 and 2012; 42% of the cases were microscopically verified, and this differed largely between world regions and histology groups. For example, the largest proportion of microscopically verified cases was in south-central Asia and northern Africa, with 98% of iCCA microscopically verified as opposed to 20% and 37% of HCC cases in northern Africa and northern Europe, respectively. For the second scenario, assuming that unspecified cases could include subtypes other than HCC and iCCA might overestimate the incidence of other specified subtypes because these other subtypes are more likely to be diagnosed through microscopic verification than HCC and iCCA and thus less likely to be unspecified.[7] It is also important to note that we made extrapolations which have distanced our estimates further from the observed cancer registry data including the use of GLOBOCAN estimates which are themselves extrapolations based on the best available registry data.[11] We therefore advised that caution is necessary when interpreting our findings.

Incidence rates of oesophageal squamous cell carcinoma decreased in half of male populations analysed, and oesophageal adenocarcinoma incidence rates increased in nearly a third of populations (both sexes) analysed over the most recent decade. Oesophageal squamous cell carcinoma is the subtype of oesophageal cancer which is causally related to alcohol consumption.

The major subtypes of oesophageal cancer have distinct differences in their aetiology and epidemiology. Alcohol consumption and cigarette smoking increase the risk of oesophageal squamous cell carcinoma (SCC) which is the most common subtype of oesophageal cancer globally (84% of cases);[12,13] meanwhile, risk factors for oesophageal adenocarcinoma (AC) include gastro-oesophageal reflux disease, Barrett's oesophagus, abdominal obesity, and, to a lesser extent than oesophageal SCC, cigarette smoking.[12,14] In Chapter 5, we explored recent trends in incidence rates of oesophageal SCC and AC by estimating average annual percent change by sex and country, and assessed long-term trends using age-period-cohort analysis. Exploring long-term trends by birth cohort and calendar period allowed us to postulate the effects of changes in prevalence of risk factor exposure between generations (cohort effect), or changes in diagnostic methods and classification of disease (period effect).[15]

We found decreasing rates of oesophageal SCC in the majority of the male populations analysed, which we suggested were driven by a cohort effect. This cohort effect could be due

to tobacco and alcohol use changing from one generation to the next, but we were not able to conclude this hypothesis from the analysis conducted. We observed increases in oesophageal SCC incidence in Japan which might have been due to a mix of cohort and period effects; previous studies have attributed these increases to a rise in alcohol consumption in Japan over recent decades.[16,17] We did not, however, observe similar increases in oesophageal SCC rates in the male population from China despite similar increases in alcohol use,[18] but we noted that the Chinese registries in our study represented less than 1% of the total population of China. For that reason, we suggested that further trend analysis by subtype should be carried out using a larger and more representative population from China, especially considering that China holds more than half of the world's total burden of oesophageal cancer.[1] Furthermore, whilst our analysis used PBCR data from 28 populations across a range of world regions, we acknowledged that we did not obtain sufficient cancer registry trend data from countries where the highest rates of oesophageal SCC are found, such as in some Asian, sub-Saharan African, and south American countries.[13]

For the second major subtype of oesophageal cancer, AC incidence rates increased in a third of the male and female populations we analysed. In age-period-cohort analysis, changes in male rates were driven by a mix of both cohort and period effects with conflicting hypotheses for the causes of these trends: increases in the prevalence of oesophageal AC risk factors such as gastroesophageal reflux disease and Barrett's oesophagus in the presence of abdominal obesity have been paralleled by a reduction in *Helicobacter pylori* prevalence over time.[19–21] Despite the inability to draw conclusions around the causes leading to our observations, our study showed the value in investigating cancer trends by histological subtype to uncover differing patterns. Also, as alcohol use increases the risk of oesophageal SCC, understanding its epidemiology is essential before analysing the burden potentially attributable to alcohol.

2. What proportion of cancer cases are due to alcohol and other modifiable risk factors globally and in the United Kingdom?

Alcohol consumption was attributable for 4% of cancer cases globally in 2020, totalling more than 740,000 cases. Heavier drinking patterns contributed most to the global burden of alcohol-attributable cancers, but we estimated that moderate drinking of the equivalent of around one or two alcoholic drinks per day was responsible for more than 100,000 cases of cancer in 2020.

In Chapter 6 we quantified the global impact of alcohol consumption on cancer. To do this, we calculated population attributable fractions (PAFs) using estimates of alcohol prevalence, relative risk of cancer from drinking alcohol, and cancer incidence. Previous studies have estimated the global burden of cancer attributable to alcohol,[5,22,23] but patterns of alcohol use have changed over time and updated estimates of relative risk of cancer and cancer incidence were available. As a novel addition to our study, we quantified the contribution of three levels

of alcohol consumption (moderate, risky, and heavy) to demonstrate their respective impact on cancer burden.

We estimated that 741,300, or 4.1%, of all new cases of cancer globally in 2020 were attributable to alcohol consumption. Our results confirmed the higher burden of alcohol-attributable cancers among males who accounted for three quarters of the total alcohol-attributable cancer cases. Further, cancers of the oesophagus and liver contributed the most cases attributable to alcohol, followed by (female) breast cancer. This highlighted that even though alcohol-attributable cancer is a predominantly male disease, in settings where the incidence of breast cancer among women is high, this female disease is placed among the top causes of alcohol-attributable cancers. For example, in France more than a fifth (21.9%) of the total number of alcohol-attributable cancer cases among both sexes was breast cancer. In terms of level of consumption, risky and heavy drinking of 20 to 60 grams alcohol per day (two to six alcoholic drinks) and more than 60 grams alcohol per day (more than six alcoholic drinks), respectively, represented the largest burden of alcohol-attributable cancers (86% of the total attributable cases). But we found that moderate drinking of up to 20 grams per day (one or two alcoholic drinks) was accountable for more than 100,000 cases of cancer in 2020, providing evidence of the harmful effects of drinking alcohol even at lower levels of consumption. Additional subgroup analysis showed that moderate drinking had a larger impact among women (32.3% of alcohol-attributable cancers among women) compared with men (8.3%), which was largely driven by differences in drinking patterns between both sexes.

In addition to differences by sex and by level of intake, we found disparities in the alcohol-attributable burden of cancer between regions of the world which reflected differences in population alcohol consumption. With increases in alcohol consumption predicted until at least 2030 in countries in several world regions including south-central and eastern Asia, we recommended the implementation of alcohol control policies such as the World Health Organization's (WHO) list of so-called 'best buys'.[24] The WHO's 'best buys' are interventions which have undergone cost-effectiveness analysis and resulted in a value of up to I$100 per disability-adjusted life year (DALY) averted in low- and middle-income countries.[24] These policies comprise of increasing excise taxes on alcoholic beverages, banning alcohol advertising, and restricting the physical availability of retail alcohol products.[24] In Chapter 6 we also highlighted that public awareness of the causal link between alcohol and cancer is low in many populations.[25,26] Although not formally evaluated, the release of our findings might have increased public awareness through outreach of a range of media outputs including articles in several news outlets and social media platforms as well as dissemination of the infographics presented in Figures 1 and 2, Preliminary results from this study were also used to create a policy document on alcohol and cancer in the WHO European Region in collaboration with the WHO Regional Office for Europe to increase awareness of the link

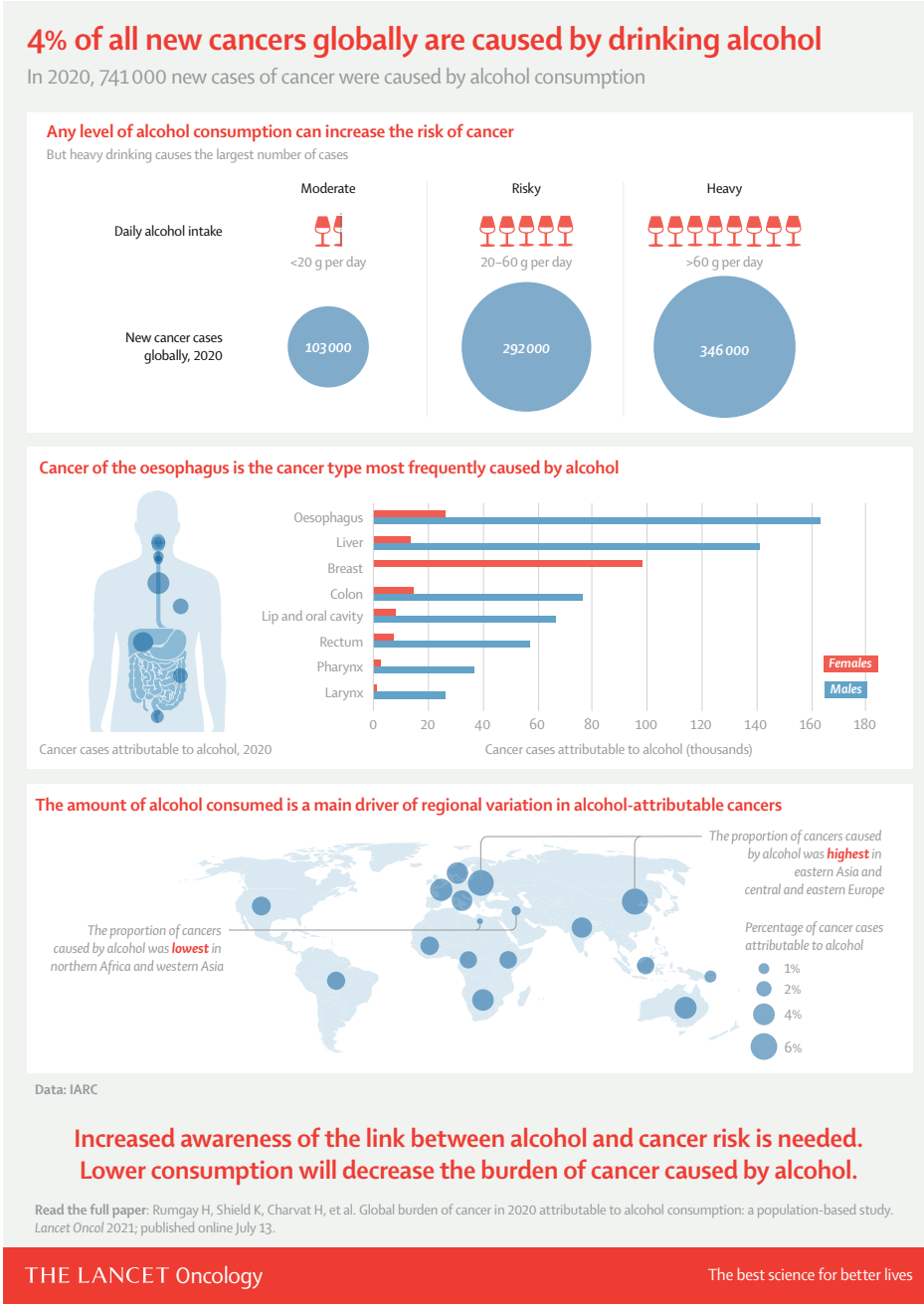

Figure 1. Infographic of main results from Chapter 6. Source: The Lancet Oncology, 2021.

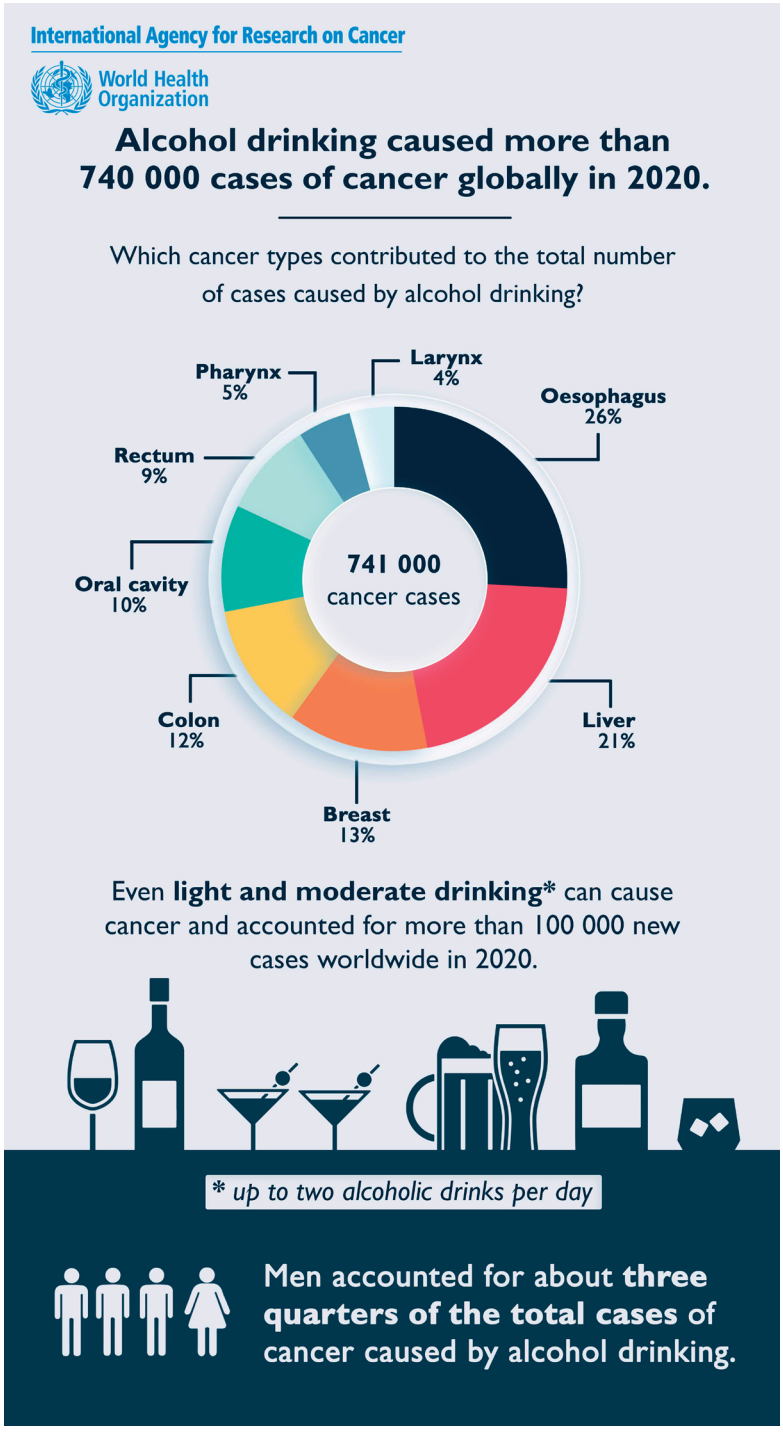

Figure 2. Infographic of main results from Chapter 6. Source: IARC, 2021.

between alcohol and cancer among policymakers and to provide policy solutions based on the WHO's 'best buys'.[27]

Overall, nearly four in ten cancer cases in the United Kingdom in 2015 were attributable to known modifiable risk factors. Alcohol consumption was attributable for 3% of cancer cases. The risk factors contributing more cases than alcohol were tobacco smoking, overweight and obesity, ultraviolet radiation, occupational exposures, and infections.

While quantifying the burden of cancer attributable to alcohol enables comparisons between cancer types and countries, it is also helpful to compare alcohol PAFs with other known modifiable risk factors. In Chapter 7 we conducted a comprehensive estimation of cancer PAFs for 14 risk factors in the UK and its constituent countries in 2015, updating and expanding on a previous analysis in the UK for 2010.[28] We found that alcohol use was attributable for 3.3% of cancer cases in the UK in 2015, ranging from 3.0% of cancer cases among men in England to 3.8% of cancer cases among men in Scotland. At the UK level, tobacco smoking, overweight and obesity, ultraviolet radiation, occupational exposures, and infections all contributed a larger proportion of cancer cases than alcohol (15.1%, 6.3%, 3.8%, 3.8%, 3.6%, respectively), and thus prevention efforts which focus on smoking and overweight and obesity were deemed as those most likely to have the largest population-level impact on cancer incidence in the UK. Combining all 14 risk factors, including some dietary factors and air pollution, produced a total PAF of 37.7% (135,500 preventable cancer cases) in the UK, although the country-specific PAFs were highest in Scotland (41.5%) and lowest in England (37.3%). This disparity in PAF was partly due to sociodemographic differences between the UK nations which have driven variation in exposure to the theoretically avoidable risk factors such as cigarette smoking which is more prevalent in Scotland, Wales, and Northern Ireland than England.[29,30] In Chapter 7 we also called for prioritisation of the regular collection of risk factor exposure prevalence data which is vital for conducting future PAF analyses and monitoring changes to inform and evaluate cancer control planning.

Through our study, we demonstrated the value of producing cancer PAFs at country level in the UK for several modifiable risk factors and cancer types. Our findings have steered the cancer prevention strategy of Cancer Research UK which is the world's largest independent cancer charity;[31] these results have also been cited in several policy documents within the UK such as the Scottish Government's diet and healthy weight delivery plan,[32] as well as the European Parliament's cancer control recommendations.[33]

3. What is the societal and economic impact of alcohol-attributable cancer deaths and how can changes in alcohol policy affect cancer burden in Europe?

Around 23,300 cancer deaths among people aged less than 65 in Europe in 2018 were attributable to alcohol consumption, equating to €4.58 billion in total productivity losses in the region. Premature cancer deaths from drinking alcohol cost 0.027% of the European Gross Domestic Product in 2018.

Although alcohol ranked as the sixth largest preventable cause of cancer in the UK in 2015, Europe consumes more alcohol per capita than any other world region.[34] This elevated level of consumption is likely to produce a substantial societal and economic cost in terms of alcohol-related disease, including cancer. In Chapter 8 we therefore calculated the societal impact by means of estimating the cost of premature death due to alcohol-attributable cancer in the 27 European Union (EU) countries plus Iceland, Norway, Switzerland, and the UK in 2018 using alcohol PAFs and estimates of productivity losses. We found that at least €4.58 billion in Europe in 2018 were lost to premature death from alcohol-attributable cancers, equating to 0.027% of the combined Gross Domestic Product (GDP) of the European countries. This represents a huge loss to society which should not be ignored. At the regional level, the largest total cost of productivity lost was in western Europe (€2.37 billion, 47% of which was from Germany alone [€1.12 billion]), but some countries in northern Europe and central and eastern Europe had the highest rate of premature mortality from alcohol-attributable cancer (14.3, 14.2, 13.2, 12.6 deaths per 100,000 people in Romania, Hungary, Lithuania, and Latvia, respectively) and the largest productivity losses in terms of the share of their national GDP (0.069%, 0.058%, 0.049%, and 0.055% of national GDP, respectively).

From this study we concluded that reporting both total cost and cost as a share of national GDP is important when presenting costs of alcohol-attributable cancers, as those with larger relative burden might not necessarily be those with the highest total cost. This is partly because countries with the most elevated population alcohol consumption, and thus burden of alcohol-attributable cancers, were also those with the lowest average income at the population level, so productivity losses as a share of GDP were disproportionately higher;[35] the reverse situation was true of countries with the highest income and often lower levels of alcohol consumption. This further demonstrates socioeconomic inequalities between countries in Europe, and the disproportionate effect of alcohol harms among populations with fewer resources.[36] An aspect that we did not analyse in this study was the total cost from other indirect measures, such as the loss of productivity from disease morbidity including time off work or reduced capacity due to illness, as well as direct costs of health expenditure on care and management of alcohol-attributable cancers, and costs of informal care by relatives and friends. These three factors contributed 10%, 52%, and 13% of the total economic cost of cancer in Europe in 2018,[37] respectively, therefore we certainly underestimated the full economic and societal impact of alcohol-attributable cancers. Nevertheless, we believed that

by providing this economic perspective on the alcohol-attributable burden of cancer we have added further evidence to assist priority setting for alcohol control and cancer prevention.

Increasing excise duties can reduce the number of cancer cases attributable to alcohol in European countries. In Germany, Italy, Kazakhstan, and Sweden, more than 35,000 cancer cases in 2018 were attributable to alcohol consumption. A 100% increase in excise duties on alcohol would have resulted in a reduction of between 3% and 7% of all alcohol-attributable cancer cases.

To provide evidence of policy changes to reduce alcohol-attributable cancer burden, in Chapter 9 we modelled the impact of increasing alcohol excise taxes on cases of cancer in four European countries selected for their differing alcohol excise tax compositions and population alcohol consumption. By considering the preferred type of alcoholic beverage consumed in each country and assigning price elasticities according to beverage preference, we modelled a reduction in consumption following three increments of increases in excise tax (20%, 50%, and 100% increase). We estimated that in Germany, Italy, Kazakhstan, and Sweden together, more than 35,000 cancer cases in 2018 were caused by alcohol consumption, which was 3.5% of all cancer cases in the four countries. A 100% increase in excise duties on alcohol could have avoided between 3% and 7% of all alcohol-attributable cancer cases. Sweden had the largest relative proportion of alcohol-attributable cancer cases potentially avoided in all three scenarios due to its already high alcohol taxation rates; Sweden's alcohol taxation rates comprised of a 16.5% excise duty on beer, 10.4% on wine, and 29.1% on spirits out of the mean price per litre of each beverage type.[38] The modelled increases in excise tax then resulted in an even higher level of tax in Sweden which, when paired with the elasticities described, would have had the largest relative impact on cancer cases of the four countries. On the other hand, Germany had the smallest relative proportion of cancer cases avoided given its low overall excise taxation of a 4% excise duty on beer, 0% on wine, and 31.7% on spirits. But Germany has the most to gain from increasing alcohol taxes as it had the highest rates of alcohol-attributable cancer incidence among the four countries (12.0 cases per 100,000 people) compared with the lowest rates in Sweden (7.1 per 100,000) in 2018. In our sensitivity analysis, increasing the proportion of excise duties to the same level as Finland (41.2% on beer, 14.5% on wine, 42.6% on spirits) – chosen because it is the country with the highest levels of taxation on the most prevalent beverage in the WHO European Region (beer) – would have avoided the most cancer cases in Germany (1,600 cases, 7.4% of alcohol-attributable cases) and Italy (790 cases, 7.9%).

Effective alcohol control policies can decrease the burden of disease and harms caused by alcohol use. Increasing the price of alcoholic beverages by increasing alcohol-specific taxation is the most cost-effective policy in terms of the costs and time required for implementation.[39] Thousands of cancer cases and deaths in Europe could be avoided if all countries in this region adopted stricter alcohol taxation systems such as ones which tax based on the

volume of pure alcohol in each beverage, or if the WHO or EU recommended a minimum level of tax in the final consumer price of alcohol (which is currently as low as €0 for wine).[40,41] As evidence of the impact of alcohol control on cancer burden, the findings from this study were incorporated into a document on alcohol and cancer for policymakers which was produced in collaboration with the WHO Regional Office for Europe.[27] The analyses were also expanded to include all the countries in the WHO European Region in a recent publication estimating the impact of increasing excise taxes on cancer cases and cancer deaths attributable to drinking alcohol in the Region.[42]

METHODOLOGICAL CONSIDERATIONS AND LIMITATIONS

This thesis covers a range of descriptive epidemiology methods and applications of PAFs, but there are several limitations to the data sources and methodology we have used.

Availability of high-quality population-based cancer data

Regarding cancer data, all the studies in this thesis relied on national estimates of cancer incidence or cancer mortality. In the estimation of liver cancer subtype distribution (Chapter 4), the oesophageal cancer trend analysis (Chapter 5), and the UK attributable fractions (Chapter 7), population-level data were obtained from cancer registries either from the Cancer Incidence in Five Continents (CI5) volumes compiled by the International Agency for Research on Cancer (IARC) or the registries themselves (the case for the UK registries).[43-45] PBCRs are the gold-standard for providing representative cancer burden estimates because they routinely collect data on cancer diagnoses for the population under their coverage area from multiple sources including pathologic laboratories, clinical diagnostic centres, vital statistics departments, and hospitals.[46] Often, when PBCRs are not available, hospital-based, pathological-based, or specialist cancer registries provide alternative cancer burden estimates; however, these registries are restricted either in terms of the population or the diseases that they cover.[46] Data from PBCRs give us the most accurate estimates of the burden of cancer in a population but are not available in many low-resource settings. This is most apparent in South America, Asia and Africa where less than 10% of the population is covered by PBCRs likely due to shortages in human, financial, or structural resources.[45,46]

When data are submitted to the CI5 editors, they undergo thorough quality assessment to ensure they are of a sufficiently high standard for comparison between registries and countries.[45] In addition to comparability, this review process evaluates the completeness and validity of the cancer registry data, with many registries not meeting the strict criteria; for example, data from 140 out of 483 registries were excluded in the most recent volume of CI5 (2008–2012).[45] Consequently, 85% of the world's population was not represented by the

CI5 data we used in the relevant chapters,[45] which has led to large gaps in our assessment of cancer burden where we have not captured the situation in populations most at risk. In Chapter 5, we noted that oesophageal cancer incidence trend data by histology were not available for some populations which have reported the highest rates of oesophageal SCC globally.[13] Also, many registries have sizeable proportions of their cancer cases recorded with unspecified histology, so there is still some uncertainty regarding the true burden of these subtypes. Large proportions of cancer cases recorded with unspecified histology could be due to lack of pathological verification through case ascertainment from death certificate only where histology is not available, or due to under-use of the International Classification of Diseases for Oncology (ICD-O) system. Improving the rate of histological verification by promoting the use of ICD-O would enable and enrich research in these areas. Furthermore, assessing cancer burden by histological subtype is key to uncovering otherwise masked patterns.

In addition to cancer registry data in Chapters 5 and 7, in Chapters 3, 4, 6, 8 and 9 we used estimates of cancer burden from the GLOBOCAN database. These GLOBOCAN estimates are limited especially for countries where they are an extrapolation of cancer registry data from subnational PBCRs, from national mortality data, or from neighbouring countries if no national or subnational data were available.[11,47] In the interest of using comparable estimates based on the best available methods, we have therefore assumed that the GLOBOCAN estimates are representative of the burden of cancer in each country but have advised that our findings must be interpreted with caution.

Sources of population alcohol consumption data

In Chapters 6 to 9 we used estimates of population alcohol consumption when calculating alcohol-attributable fractions of cancer incidence and mortality. Several limitations exist with these data: firstly, most population alcohol use statistics are collected through national surveys which ask subjects to report their personal consumption.[48] Collecting information through face-to-face interviews might lead to underreporting of an individual's alcohol use and thus underestimation at the population level due to social desirability bias.[49] Underestimating the total volume of alcohol consumed in a population might also occur in surveys due to inaccurate recall of the amount consumed by an individual or through under-representation of groups which might consume alcohol at the highest levels, such as the homeless and institutionalised.[48,50]

To attempt to correct for these biases, the alcohol consumption estimates produced by the Global Information System on Alcohol and Health — those we used in Chapters 6, 8, and 9 — were compiled through triangulation of estimates from national surveys with statistics on alcohol production, sales, and taxation.[51] The estimates were also supplemented with data on tourist alcohol consumption from the United Nations' World Tourism Organization, combining the number of tourists with average length of stay and the overall alcohol

consumption in the tourists' countries of origin.[51] In addition to recorded alcohol use and tourist consumption, unrecorded alcohol intake through home-brewed beverages (as in Figure 3), privately imported alcohol, and alcohol not intended for human consumption, was also incorporated into the estimations of population alcohol use.[52] Unrecorded alcohol consumption accounted for a quarter of the world total volume of alcohol consumed in 2015, with large variation between country income groups.[53] It is therefore important to in-

Figure 3. Example of alcohol home-brewing that contributes to unrecorded alcohol consumption in Cape Clear, Malawi. Information on consumption of the locally produced kachasu was collected as part of the Oesophageal Squamous Cell Carcinoma African Prevention research (ESCCAPE) consortium. Source:Valerie McCormack, 2018.

corporate measures of unrecorded alcohol use in population alcohol estimates; such information on unrecorded alcohol consumption was collected and modelled using expert opinion and population surveys by the Centre for Addiction and Mental Health (CAMH), Canada, and combined with the data on recorded and tourist consumption.[53] Through compiling these estimates, colleagues at CAMH found that the distribution of average daily alcohol consumption among current drinkers in a population could be predicted using a Gamma distribution based on the mean and standard deviation of per capita alcohol consumption.[54,55] Due to this modelling technique and the alcohol use estimates derived from multiple sources, we believe that the alcohol consumption data we used were the most reliable and comparable international estimates available.

Alcohol exposure in observational studies: impact on risk estimates

Similar to the limitations in population alcohol consumption data, there are often concerns with the information collected on alcohol intake in observational studies. Estimates of the magnitude of the association between alcohol drinking and cancer are usually from large cohort and case-control studies which collect nutritional and anthropometric information from their cohort or cases (patients), often through surveys and food-frequency questionnaires.[56] Social desirability biases are, again, applicable if assessment of a participant's alcohol consumption is reported by the individual; this is also true of information on other risk factors which might be confounders of the association, such as tobacco use or excess body weight. The coverage of alcohol consumption in cohort studies is higher than in population surveys but was still only 62% of per capita consumption according to a study by Stockwell and colleagues,[50] with about half of this under-coverage due to non-response bias. In the PAF studies in Chapters 6, 8, and 9 we corrected for this under-coverage based on the findings of Stockwell et al. Furthermore, as with national surveys, prospective studies are somewhat limited by participation bias and the 'healthy entrant' effect, where the group of participants in a longitudinal cohort study are of better health on average than the general population.[57]

One possible approach to avoiding bias in reporting of alcohol use by study participants might be through the collection of biomarkers such as phosphatidylethanol, which is a phospholipid formed in the presence of ethanol in the body.[58] This could also allow more accurate classification of former drinkers rather than grouping them with lifetime abstainers if both are grouped as 'non-drinkers'. Grouping both together should be avoided due to the possibility of reverse causality in cancer risk estimates, particularly if those who gave up drinking alcohol did so for health reasons which could give rise to the so-called 'sick-quitter' effect.[59] In our analysis we were not able to distinguish these discrepancies in the alcohol consumption data, although there is evidence that the elevated risk of head and neck cancer in former drinkers reduces back to that of lifetime abstainers after 20 years of quitting.[60] Biomarkers are, however, often short-lived in the body and are limited to providing information on products recently consumed; for example, the half-life of phosphatidylethanol is only four days.[58] This might not be most relevant for exposures which are accumulated over the life-course unless regular measurements are taken. Estimates of lifetime alcohol use and cancer risk could be more appropriate measures for alcohol PAFs as drinking patterns often change over the life-course and might influence cancer risk differently. A cohort study in Thailand with more than 30 years of follow-up observed double the cancer mortality in those who were consistent-regular drinkers throughout their life compared with consistent occasional drinkers;[61] and a case-control study in Spain suggested that women who moved from moderate alcohol consumption in adolescence to the highest consumption in adulthood (≥15 g/day) had double the risk of cancer compared with women whose alcohol consumption remained low (<5 g/day) throughout their lifetime, and that heavy consump-

tion in adolescence was strongly associated with breast cancer risk.[62] Nevertheless, if studies collect reliable, unbiased data to more accurately estimate cancer risk and causality then we will be able to obtain a clearer picture of the true impact of risk factors on cancer burden.

Estimating population attributable fractions

There are inherent assumptions in the PAF calculations which we address here. PAFs calculated through the 'literature-based' method (based on survey data and existing relative risk estimates) assume that estimates of risk factor prevalence are representative of the population and that the measures of cancer risk are appropriately matched to the risk factor prevalence and disease outcome. There are several considerations to take into account when matching these elements. Using alcohol PAFs as our example, population measures of alcohol use are often published as number of drinks per week, grams of alcohol per day, litres of alcohol per year, and drinking frequency per week.[34,63] In Chapters 6, 8, and 9 we used the continuous measure of grams of alcohol consumption per day for both the data on population-level alcohol consumption and cancer risk estimates. In the analysis of UK cancer PAFs (Chapter 7) we converted UK units of alcohol per week to grams of alcohol per day categorised into three levels of consumption to match the categorised risk estimates from a meta-analysis on alcohol and cancer risk.[64] Furthermore, in all of our PAF studies, we used a 10-year latency period between the year of alcohol exposure data and year of cancer incidence or mortality. The use of a latency period is important as current cancer rates do not reflect current risk factor exposure, and instead reflect past exposure.[65] We chose an interval of 10 years after reviewing the follow-up periods between the baseline measurement in cohort (observational) studies on alcohol exposure and cancer outcome. A study in Canada observed an approximate latency period of 11 to 12 years for breast, colorectal, oral cavity, oesophageal, and pharyngeal cancers, and 8 to 9 years for laryngeal and liver cancers between baseline and end of follow-up.[66] We did not test for effects on alcohol PAFs using other data years but as alcohol prevalence does not change a large amount year-on-year we would expect these results to be robust to at least the preceding and proceeding few years. Furthermore, in a sensitivity analysis as part of Chapter 7 we calculated the PAF of tobacco smoking with a 20-year latency instead of 10-year and found only a 1% (absolute) change in PAF (16.1% versus 15.1% of cancer cases).[67]

One of the more influential factors in calculating PAF through the 'literature-based' method is the choice of relative risk estimates i.e. the 'literature'. For most of our PAF estimates we used relative risks from meta-analyses of studies in different world regions produced by the World Cancer Research Fund (WCRF) Continuous Update Project.[68] One might argue that these relative risks are not representative of some populations which have significantly increased risks of cancer from drinking alcohol, such as in eastern Asian populations which have a substantially higher risk of upper aerodigestive cancers due to the prevalence of the *ALDH2*2* gene polymorphism,[69] or populations with low representation in observational

studies. However, when reviewing the results of the WCRF meta-analyses by subgroup, we prioritised the combined number of studies and total cases over possible heterogeneity in risk between subgroups to ensure that the estimates we used were based on the largest sample of cases. For example, the most heterogeneity was found between populations for oesophageal SCC where the RR per 10 gram increase in alcohol consumption per day was 1.34 (95% CI 1.19–1.51) based on four studies in Asia compared with 1.23 (1.07–1.42) in Europe (four studies) and 1.26 (1.12–1.41) in North America (one study).[70] There were also some small differences in colorectal cancer risk by sex, with a RR of 1.08 (1.06–1.10) for men (14 studies) and 1.04 (1.00–1.08) for women (10 studies), compared with the total for both sexes combined 1.07 (1.05–1.09) based on 16 studies.[71] Yet, deciding on the most appropriate relative risk estimates would not be a limitation if using the second commonly used method of estimating PAF — the 'low-risk' method (individual-level data from a low-risk cohort) — because the PAF is calculated using relative risks derived from the cohort's own risk factor exposure and cancer outcome data. Other advantages to the 'low-risk' method include closer alignment with the individual-level data and the ability to better adjust for confounders. With this information it is also possible to produce PAFs of combined risk factors such as alcohol and tobacco which are often discussed together in terms of cancer risk due to their synergistic effect on cancer risk.[72] However, PAF estimates from the 'low-risk' method might only be applicable to the cohort represented and have less power in statistical analysis than a large, global population-based analysis due to being based on a smaller number of cases. Running the case-control or cohort study would also require substantially more resources than for the 'literature-based' method which largely uses secondary data. Nevertheless, comparisons of PAF between our studies in Chapters 6 and 7 and attributable fractions from other studies gave similar estimates: Australian PAFs from a pooled consortium of seven cohorts taking into account competing risk of death and risk factor interdependence found that drinking more than two alcoholic drinks per day explained 6% of the burden of cancers causally related to both alcohol and tobacco;[73] this compared favourably with our estimate of 4% of all cancers in Australia from Chapter 6. Comparison with alcohol PAFs from a low-resource setting were more variable: we estimated that the fractions of oesophageal SCC attributable to alcohol were 40%, 35%, and 53% among men in Malawi, Kenya, and Tanzania, respectively, and 12%, 10%, and 21% among women; results from a large multicentre case-control study (the Oesophageal Squamous Cell Carcinoma African Prevention research [ESCCAPE] consortium) estimated PAFs of 65% and 56% among men in Kenya and Tanzania, respectively, and 9%, 23%, and 5% and among women in Malawi, Kenya, and Tanzania (with no estimate for men in Malawi).[74] Further, a comparative study on colorectal cancer in the US found minimal differences in the total fractions of colorectal cancer cases attributable to multiple risk factors between the 'literature-based' method and the 'low-risk' method using the Health Professional and National Health Study cohorts ('literature-based

method': 65% and 53%, and 'low-risk' method: 62% and 49% of CRC cases for males and females, respectively).[75]

Another aspect of PAF calculations is that they assume a causal relationship between risk factor exposure and disease outcome. We must therefore decide which risk factors or cancer types to include and this selection might impact the overall PAF for each cancer and for all cancers combined. In the global study in Chapter 6 and the UK study in Chapter 7, we restricted our selection criteria to use only cancer type-risk factor combinations with sufficient evidence according to the IARC Monographs and with convincing evidence according to the WCRF Continuous Update Project.[12,68] We were therefore conservative in this approach to avoid overestimating the attributable risk. If including cancer sites with limited (IARC) or probable (WCRF) associations in the global study in Chapter 6, the addition of stomach and pancreatic cancers increased the number of alcohol-attributable cancer cases from 741,300 to 808,700 cases globally in 2020, or from 4.1% to 4.5% of cases of all cancers combined.[76] This consideration was also necessary for former drinking, where we did not include former drinkers in the main analysis due to limitations in the available risk estimates compared with those for current drinking despite a likely sustained excess risk of cancer from previously drinking.[77] However, when former drinking was included with current drinking in the sensitivity analysis in Chapter 6, the number of alcohol-attributable cases increased to 925,900 or 5.2% (versus 4.1%) of cases of all cancers combined. Overall, considering the efforts made to not overestimate the fractions of cancers attributable to alcohol and other modifiable risk factors, we believe our findings provided unbiased estimates of cancer preventability.

Quantification of impact beyond cancer burden: economic cost

In Chapter 8, we estimated the impact of alcohol consumption in terms of productivity losses due to premature death from alcohol-attributable cancer in Europe. While giving an additional perspective on the impact of alcohol on cancer through a societal lens, limitations to this approach relate to the main assumptions of the methodological approach chosen. Assuming that people aged 65 and over would stop contributing to society clearly underestimated productivity from people beyond age 64; Ortega-Ortega and colleagues estimated that productivity losses from premature cancer death in Europe in 2018 would have increased by 19% and 29% if the retirement age rose to 67 and 68 years, respectively, due in part to large contributions from unpaid work.[78] Contributions to society through unpaid work take the form of tasks such as household jobs, family care, and volunteering, and are predominantly carried out by women whose role is therefore undervalued if only incorporating economic productivity. Loss of unpaid work due to premature mortality from cancer was estimated to account for €51.7 billion in Europe in 2018, or nearly half (49%) of total lost productivity,[78] thus we would expect our estimates of productivity losses due to alcohol-attributable cancer to potentially double if encompassing unpaid and informal work. Also, while we aimed to estimate the cost of productivity lost due to premature mortality,

we did not cover other sources of indirect cost such as time off work or reduced working hours, nor did we cover direct costs of cancer diagnosis and care. After incorporating these sources of cost, Hofmarcher and colleagues found that cancer cost a total of €199 billion in Europe in 2018 which composed of €103 billion from health expenditure on cancer care, €26.4 billion from informal care, and €70 billion in productivity losses (€49.6 billion from premature mortality, €20.4 billion from work absenteeism).[37] The full economic cost of alcohol-attributable cancer including cost of healthcare could therefore be much higher than that estimated through productivity losses from premature mortality. Finally, in Chapter 8 we used the human capital approach to estimate productivity lost but other methods are available such as the friction cost approach which assumes the economy replaces those who die or are unable to work.[79] Because the friction cost method only values the time when the work isn't carried out, estimates of productivity lost using this approach are much lower than those valued using human capital.[80] For example, productivity losses due to head and neck cancer in Ireland were valued at €253,800 using the human capital approach but were €6,800 through the friction cost or only 3% of the cost through human capital.[81] There is some debate around which approach is most appropriate but it is generally recognised that human capital — which is far more commonly used — best represents cost to society, and friction cost represents cost from an employer's perspective.[81]

Alcohol taxation to reduce cancer burden

We applied our alcohol PAFs to a policy setting in Chapter 9 to model the potential change in population alcohol consumption and alcohol-attributable cancers from increases in alcohol excise taxes. Limitations to this method include the assumptions that the price elasticities of different beverage types based on consumption preference did not differ by sex, age, economic status, or country where price elasticities among some groups might be higher than others, thus rendering the consumers more sensitive to price changes.[82] Price elasticities are most likely to differ for those with heavier drinking patterns and alcohol use disorders; to account for this in our analysis we assigned the lowest elasticity and thus the least likelihood of a reduction in consumption to men who drink more than 60 grams alcohol per day and women who drink over 40 grams alcohol per day.[38] Further, we did not look into cross-elasticities between beverage types or alcohol and other substances whereby consumers might be likely to replace the product which has had a price increase with a different beverage type or substance instead.[83] However, this theory of replacement does not seem to be so problematic as Meng and colleagues found that cross-price elasticities were small compared to own-price elasticities in a modelling study of on-trade and off-trade sales of different beverages in the UK.[83] Moreover, we did not measure the effect of increases in excise duties on changes in unrecorded alcohol consumption which contributed around one fifth of total alcohol consumed in the WHO European Region in 2015.[53] But recent studies in Russia and Kazakhstan did not indicate a marked increase in unrecorded alcohol consumption after

taxation increases because these regulations were introduced along with monitoring and restrictions on the production of surrogate alcohol.[84-86] Furthermore, our study assumed an immediate impact of increased taxes on alcohol consumption among the population therefore implying a direct behavioural change due to price increases. Although these parameters were based on price elasticities obtained from modelling studies, we acknowledge that implementing interventions which achieve sustained behavioural changes is far from easy.[87] However, we also note that policy measures that increase the price of alcohol have been shown to be among the most effective in reducing population alcohol consumption: it is generally accepted that a 1% increase in price of alcohol translates to a 0.5% reduction in alcohol consumption.[88] Alcohol taxation is one of the most cost-effective measures to reduce alcohol consumption and harms, but is one of the least implemented policy options in the WHO European Region. We therefore believe that alcohol pricing policies should form the basis of a successful whole-systems approach to reducing alcohol-related disease burden and harms.[89]

FUTURE RESEARCH

Considering the points discussed in this thesis, we suggest several directions for future research on alcohol-attributable cancers.

Additional measures of alcohol-attributable cancer burden

Firstly, when estimating cancer burden attributable to alcohol it would be valuable to compute additional measures such as DALYs. DALYs combine years of life lost (YLLs) due to premature mortality and years of healthy life lost due to disability (YLDs).[90] DALYs are therefore useful to compare the avoidable mortality of disease relative to the predicted life expectancy of the population, as well as summarising the impact in terms of time lived in states of less than full health due to the disease or disability. This broad inclusion of measures enables comparison across disease entities including illnesses with lower impact on life expectancy but many implications on quality of life and the well-being of individuals.[90] YLLs, YLDs, and DALYs are already estimated by the Institute for Health Metrics and Evaluation (IHME) through the Global Burden of Disease study, which found that around 93.0 million DALYs in 2019 were attributable to alcohol use, of which 13.0 million were from alcohol-attributable cancers consisting mainly of YLLs (12.6 million).[23] While IHME provides useful estimates of these indicators, their findings must be validated using other input data and methods, such as those we have used. In order to compute YLDs and DALYs we would need to obtain further variables on the prevalence and disability weights of alcohol-attributable cancers as well as cure rates and the proportion and duration of patient treatment.[91] Moreover, by producing estimates of YLLs, YLDs, and DALYs we would gain a better insight as to the full impact of

alcohol-attributable cancers on the population and be able to compare between other cancer risk factors and diseases.

Broader societal and economic impact of alcohol-attributable cancer

Another measure of burden which we explored in Chapter 8 was the economic impact of alcohol-attributable cancers in Europe through productivity losses of paid employment up to the statutory age of retirement in European countries. Future studies could encompass unpaid employment to provide information on the loss of unpaid production such as household work, family care, and volunteering. Using Ortega-Ortega's findings as an example, we could expect unpaid employment to double the productivity losses from alcohol-attributable cancers.[78] We also see value in conducting economic studies which explore additional measures such as other indirect costs through absenteeism from work or reduced productivity, and direct costs estimating that of health care in diagnosing and treating alcohol-attributable cancers. Other types of societal impact could include intersectional measures such as family financial ruin due to out-of-pocket expenses on care of cancer caused by alcohol, or inability of the main income provider to continue to work. This could also encompass the impact on the well-being of family and friends of cancer patients and the burden of orphans due to parental death from alcohol-attributable cancer. Exploring these aspects would add further societal and economic perspective for policymakers to fully comprehend the broad impact of alcohol-attributable cancers and could be compared with societal gains in increasing and expanding implementation of alcohol control policies.

Uncovering the influence of socioeconomic status on alcohol-attributable cancer

The alcohol-harm paradox is a well-known observation where the least deprived individuals are likely to drink more alcohol than others, yet those who are most deprived experience disproportionately greater alcohol-related harms.[92,93] Within this observation there are several themes which should be unpicked, such as the deep-rooted behaviour of drinking among those with higher socioeconomic status and the predicted increases in alcohol use in nations which undergo economic development.[18] In addition, the most deprived communities in high-income countries generally have the lowest overall levels of alcohol consumption but the highest levels of addiction and alcohol use disorders among those who drink.[93] Exploring the impact of these differences on cancer burden could inform the potential for policy to reduce social inequalities in cancer. This could involve aspects to determine whether improving access to alcohol cessation services outside of primary care,[94] or eliminating barriers which lower socioeconomic groups face in doing so, can reduce alcohol-related cancer burden in these groups. Further, we could estimate how premature death from alcohol-attributable cancer contributes to a broader range of inequalities between socioeconomic groups.

Exposure to other cancer risk factors such as cigarette smoking or weight gain might also accompany alcohol use, thus their combined effect on cancer risk could be an area for future research. Cigarette smoking, excess body weight, and infection with hepatitis B and C viruses are associated with social inequalities both within and between countries. Interaction among these factors might therefore further exacerbate socioeconomic disparities in alcohol-related cancers.

Modelling alcohol control policy impact beyond taxation

While quantifying the economic burden of alcohol-attributable cancer is important to estimate alcohol's impact on society, we should demonstrate how changes in various cancer policies will impact cancer rates to ultimately reduce the burden of cancer attributable to alcohol. In Chapter 9 we modelled the effect of increases in alcohol excise taxes on the number of cancer cases in four countries in Europe, expanding to 40 countries in the WHO European Region in a further study.[42] We predicted that the largest decreases in alcohol-attributable cancers would occur if alcohol excise taxes were at least doubled, but these results might differ in other world regions with varying tax structures. For example, excise rates on wine vary greatly across Organisation for Economic Co-operation and Development (OECD) countries, from US$0 per litre in Spain to more than US$6 per litre in Norway.[95] Excise on beer varies even more so, from less than US$5 per hectolitre in Czech Republic, Germany, Luxembourg, Slovakia, and Turkey, up to more than US$20 per hectolitre in Finland, Ireland, Israel, New Zealand, Sweden, and the UK. Our findings in Chapter 5 highlighted the elevated burden of alcohol-attributable cancers in eastern Asia as well as central and eastern Europe. These findings provide reason for conducting policy impact assessments in settings which are most affected or that have predicted increases in population alcohol consumption, as is the case for eastern Asia.[18] Exploring the potential impact of other policy changes on population alcohol intake and cancer burden would also be valuable; for example, an evaluation determining which alcohol policies among WHO's 'best buys' (increasing excise taxes on alcoholic beverages, banning alcohol advertising, and restricting the physical availability of retail alcohol products),[24] or which combinations of them and at what levels of implementation, could provide the biggest benefits in terms of reduction of alcohol-attributable cancers. Other alcohol policy strategies not yet recommended as WHO's cost-effective 'best buys' include minimum unit pricing,[96] adding cancer warning labels to alcohol products,[97] and giving brief advice to patients in primary care[98] (although several barriers to giving brief advice were identified in a survey of UK GPs and practice nurses and could increase inequalities between socioeconomic groups).[94,99] We could therefore model the impact of these policies on cancer burden as part of a comprehensive review of the most effective cancer control policies for policymakers to implement in their settings with regards to the specific patterns of alcohol consumption and alcohol-attributable cancer burden in their countries. This could be further complemented with recommendations on the best ways

of implementing these measures in different contexts, including suggested combinations of policies that countries with fewer resources for implementation could introduce.

Conclusions and recommendations

Regarding the findings of this thesis we conclude that:

- Liver cancer contributes a major burden of disease globally and was among the top three causes of cancer death in 46 countries worldwide in 2020.
- The most common subtype of liver cancer, hepatocellular carcinoma, represented 80% of liver cancer cases globally in 2018. To control liver cancer globally, public health officials should prioritise primary prevention of hepatocellular carcinoma risk factors, including hepatitis B and C virus infection and alcohol consumption.
- Alcohol use is an established risk factor for oesophageal squamous cell carcinoma. Incidence rates of oesophageal squamous cell carcinoma decreased in the majority of male populations analysed which we suggested was driven by changes in the prevalence of tobacco and alcohol use from one generation to the next.
- Alcohol consumption caused an estimated 741,000 cases of cancer, or 4% of all cancer cases, globally in 2020. While heavier drinking patterns contributed most to the global burden of alcohol-attributable cancers, moderate drinking of the equivalent of one or two alcoholic drinks per day contributed more than 100,000 cases of cancer in 2020. This demonstrated the impact of alcohol on cancer at lower levels of consumption.
- Nearly four in ten (38%) cancer cases in the UK in 2015 were attributable to known modifiable risk factors including alcohol use. The country-specific proportions of preventable cancer cases ranged from 37% in England to 42% in Scotland — the resulting disparity is partly due to sociodemographic differences which have driven variation in exposure to the theoretically avoidable risk factors.
- At least €4.58 billion were lost to premature death from alcohol-attributable cancers in Europe in 2018, equating to 0.027% of the combined GDP of the European countries. This economic perspective adds further evidence to assist priority setting for alcohol prevention and cancer control.
- Increasing alcohol excise duties can reduce the burden of cancer attributable to alcohol in European countries. A 100% increase in excise duties on alcohol could have avoided between 3% and 7% of all alcohol-attributable cancer cases in Germany, Italy, Kazakhstan, and Sweden in 2018.
- Policy measures that increase the price of alcohol are among the most effective and cost-effective policies to reduce population alcohol consumption and ultimately alcohol-attributable cancer burden.

Based on the results and conclusions of this thesis, we recommend the following:

- Regular collection of information on risk factor exposure is vital to carry out cancer preventability estimates, plan prevention strategies, monitor changes in risk factor prevalence, and evaluate the effectiveness of prevention interventions. Data collection should therefore be considered a fundamental function to improve public health in countries worldwide. To increase reliability, statistics could be compiled using risk factor exposure data from multiple sources.
- To improve the quality of data from cancer registries, increased histological verification through promotion of the use of ICD-O classification would enable and enrich research in areas which currently have limited information on histological subtypes.
- With improved availability and quality of cancer registry data, further trend analysis of oesophageal cancer by histological subtype should be carried out covering populations which have the most elevated rates of oesophageal cancer e.g. some Asian, sub-Saharan African, and South American countries.
- Country-level estimates of cancer burden attributable to risk factors should be used as key tools to drive cancer prevention and control strategies.
- Future economic studies on alcohol-attributable cancer could include loss of unpaid employment as well as additional costs of reduced productivity, and diagnosis and treatment of alcohol-attributable cancers.
- While quantifying the societal and economic burden of alcohol-attributable cancer is important, we should demonstrate how various alcohol control policies can ultimately reduce the burden of cancer attributable to alcohol.
- Alcohol pricing policies are the most cost-effective measure to decrease population alcohol consumption and should form the basis of a successful whole-systems approach to reducing alcohol harms including cancer burden.

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Summary

Part 1. Introduction

Nearly half of the world's adult population regularly consumes alcohol despite its many associated health risks and injuries. In 2019, global alcohol consumption was equal to 5.8 litres of pure alcohol per person aged 15 years and older — the equivalent of between one and two standard alcoholic drinks per day. At the global level, men drank around four times the volume of alcohol as women in 2019. Drinking patterns also differ substantially between world regions. The highest average consumption among men was in western Europe, eastern Europe, and northern Europe, while the highest average consumption among women was in western and northern Europe, and Australia and New Zealand. In contrast, northern Africa and western Asia have the lowest volumes of alcohol consumption per person globally among both men and women.

Alcohol consumption increases the risk of seven different cancer types including cancers of the oral cavity, pharynx, larynx, oesophagus, liver, colorectum, and breast. The International Agency for Research on Cancer has classified alcoholic beverages as a group 1 carcinogen since 1988 yet public awareness of the causal link between alcohol and cancer remains low. Alcohol consumption at any level increases the risk of cancer. This includes levels of consumption traditionally thought of as 'low', 'light', or 'moderate' drinking of the equivalent of up to one or two alcoholic drinks per day.

This thesis aimed to measure the impact of population alcohol consumption on the burden of cancer globally, regionally, and in countries worldwide. We have assessed several aspects of the burden of cancer attributable to alcohol use which we presented in four parts. To provide background on the link between alcohol drinking and cancer, in Part 1 we introduced the topics covered in this thesis and summarised the epidemiology and biological mechanisms of alcohol-driven carcinogenesis. In Part 2 we described the burden of liver cancer globally and by subtype, and analysed oesophageal cancer incidence trends by subtype. We quantified the global burden of cancer attributable to alcohol use and the burden of cancer in the UK attributable to a range of modifiable risk factors, including alcohol, in Part 3. Expanding on these estimates of burden, in Part 4 we quantified the economic impact of alcohol-attributable cancer deaths and the effect of alcohol policy changes on cancer burden in Europe.

Part 2. Describing the global burden of alcohol-related cancers

As primary liver cancer is causally related to alcohol use (Part 1, Chapter 2), in Chapter 3 we assessed the global burden of liver cancer in a descriptive evaluation of incidence and mortality rates by world region. More than 900,000 people were diagnosed with, and 830,000 people died from, liver cancer globally in 2020. We found that the highest rates of liver cancer incidence and mortality were in eastern Asia, northern Africa, and south-eastern Asia. Furthermore, liver cancer was among the top three causes of cancer death in a total of 46 countries worldwide and was within the top five causes of cancer death in 90 countries. Considering the low survival from liver cancer, we recommended that public health officials

prioritise primary prevention of liver cancer risk factors. Several causes of liver cancer vary by subtype thus we suggested that investigating the specific patterns of the subtypes of liver cancer by sex and country could better inform research and policy priorities in different settings.

To explore liver cancer patterns by subtype, in Chapter 4 we estimated the number of cases of the major subtypes of liver cancer. Hepatocellular carcinoma was the most common subtype of liver cancer and represented an estimated 80% of liver cancer cases globally in 2018. Hepatocellular carcinoma is also the subtype of liver cancer which is causally related to alcohol consumption. The second most common subtype of liver cancer, intrahepatic cholangiocarcinoma, represented 15% of liver cancer cases in 2018, while liver cancer cases of other specified histology groups represented 5%. By assessing liver cancer burden by subtype, we uncovered distinct patterns in the incidence of the major subtypes by world region. The findings from this chapter will enable public health officials to identify the specific mix of liver cancer subtypes in their region and to apply tailored measures to reduce the burden of hepatocellular carcinoma and intrahepatic cholangiocarcinoma, including alcohol control for hepatocellular carcinoma prevention. Also, assessing the burden of liver cancer by subtype shows the importance of improving cancer data to allow for more reliable estimates of the population impact of cancer risk factors.

Oesophageal cancer also has distinct subtypes which differ in their aetiology and epidemiology. Alcohol consumption increases the risk of oesophageal squamous cell carcinoma which is the most common subtype of oesophageal cancer globally, whereas drinking alcohol has not been classified as causally linked to oesophageal adenocarcinoma. In Chapter 5 we explored recent trends in incidence rates of the two major subtypes of oesophageal cancer and assessed long-term trends by birth cohort and calendar period. Assessing long-term trends allowed us to postulate the effects of changes in risk factor prevalence between generations, or changes in diagnostic methods or classification of disease. We found decreases in oesophageal squamous cell carcinoma incidence rates in half of male populations analysed and increases in oesophageal adenocarcinoma incidence rates in nearly a third of male and female populations analysed over the most recent decade. Considering these results, our study showed the value in investigating cancer trends by histological subtype to uncover differing patterns. Also, as alcohol use increases the risk of oesophageal squamous cell carcinoma, understanding its epidemiology is valuable to estimate and assess the proportion of oesophageal cancer burden attributable to alcohol.

Part 3. Estimating the proportion of cancer cases due to alcohol and other modifiable risk factors globally and in the United Kingdom

In Chapter 6 we quantified the global impact of alcohol consumption on cancer. We found that more than 740,000, or 4%, of all new cases of cancer globally in 2020 were attributable

to alcohol consumption. Our results confirmed the higher burden of alcohol-attributable cancers among males who accounted for three quarters of total number of alcohol-attributable cancer cases. Further, cancers of the oesophagus and liver contributed the most cases of cancer attributable to alcohol, followed by breast cancer. In terms of level of consumption, risky and heavy drinking of more than two alcoholic drinks per day represented the largest burden of alcohol-attributable cancers (86% of the total attributable cases). But we found that moderate drinking of up to one or two alcoholic drinks per day was accountable for more than 100,000 cases of cancer in 2020, providing evidence of the harmful effects of drinking alcohol at lower levels of consumption. In addition to differences by sex and by level of intake, we found disparities in the alcohol-attributable burden of cancer between regions of the world which largely reflected differences in population alcohol consumption. To tackle this burden, we recommended the implementation of alcohol control policies such as those recommended by the World Health Organization (WHO). These include increasing excise taxes on alcoholic beverages, banning alcohol advertising, and restricting the physical availability of retail alcohol products.

While quantifying the burden of cancer attributable to alcohol allows for comparisons between cancer types and countries, it is also worthwhile comparing this burden with that of other known modifiable risk factors. In Chapter 7 we conducted a comprehensive estimation of population attributable fractions (PAFs) for cancer incidence in the United Kingdom (UK) and its constituent countries in 2015. Overall, nearly four in ten (38%) cancer cases in the UK in 2015 were attributable to known modifiable risk factors. Alcohol consumption was the sixth largest preventable cause of cancer in the UK, behind tobacco smoking, overweight and obesity, UV radiation, occupational exposures, and infections. There were some disparities in PAFs between the UK countries which were partly due to sociodemographic differences driving variation in exposure to the theoretically avoidable risk factors. Due to this variation, our findings demonstrated the value of producing cancer PAFs at country level in the UK for several modifiable risk factors and cancer types.

Part 4. Quantifying the societal and economic impact of alcohol-attributable cancer deaths and the effect of alcohol policy changes on cancer burden in Europe

Europe consumes more alcohol per person than any other world region. This elevated level of consumption is likely to produce a substantial societal and economic cost in terms of alcohol-related disease, including cancer. In Chapter 8 we therefore calculated part of the societal impact of alcohol-attributable cancer by estimating the cost of premature death due to alcohol-attributable cancer in the 27 European Union (EU) countries plus Iceland, Norway, Switzerland, and the UK in 2018. We found that at least €4.58 billion in Europe in 2018 were lost to premature death from alcohol-attributable cancers, equating to 0.027% of the combined Gross Domestic Product of the European countries. This represents a huge

loss to society which should not be ignored and we believe that by providing this economic perspective on the alcohol-attributable burden of cancer we have added further evidence to assist priority setting for alcohol prevention and cancer control.

To provide evidence of policy changes to reduce alcohol-attributable cancer burden, in Chapter 9 we modelled the impact of increasing alcohol excise taxes on cases of cancer in four European countries. We estimated that in Germany, Italy, Kazakhstan, and Sweden, together, more than 35,000 cancer cases in 2018 were caused by alcohol consumption, which was 3.5% of all cancer cases in the four countries. A 100% increase in excise duties on alcohol could have avoided between 3% and 7% of all alcohol-attributable cancer cases in the four countries. Our findings suggest that thousands of cancer cases and deaths in Europe could be avoided if all countries in the region adopted stricter alcohol taxation systems such as ones which tax based on the volume of pure alcohol in each beverage, or if the WHO or EU recommended a minimum level of tax in the final consumer price of alcohol (which is currently as low as €0 for wine).

Conclusions and recommendations

Regarding the findings of this thesis we conclude that:

- Liver cancer contributes a major burden of disease globally and was among the top three causes of cancer death in 46 countries worldwide in 2020.
- The most common subtype of liver cancer, hepatocellular carcinoma, represented 80% of liver cancer cases globally in 2018. To control liver cancer globally, public health officials should prioritise primary prevention of hepatocellular carcinoma risk factors, including hepatitis B and C virus infection and alcohol consumption.
- Alcohol use is an established risk factor for oesophageal squamous cell carcinoma. Incidence rates of oesophageal squamous cell carcinoma decreased in the majority of male populations analysed which we suggested was driven by changes in the prevalence of tobacco and alcohol use from one generation to the next.
- Alcohol consumption caused an estimated 741,000 cases of cancer, or 4% of all cancer cases, globally in 2020. While heavier drinking patterns contributed most to the global burden of alcohol-attributable cancers, moderate drinking of the equivalent of one or two alcoholic drinks per day contributed more than 100,000 cases of cancer in 2020. This demonstrated the impact of alcohol on cancer at lower levels of consumption.
- Nearly four in ten (38%) cancer cases in the UK in 2015 were attributable to known modifiable risk factors including alcohol use. The country-specific proportions of preventable cancer cases ranged from 37% in England to 42% in Scotland — the resulting disparity is partly due to sociodemographic differences which have driven variation in exposure to the theoretically avoidable risk factors.
- At least €4.58 billion were lost to premature death from alcohol-attributable cancers in Europe in 2018, equating to 0.027% of the combined GDP of the European countries.

This economic perspective adds further evidence to assist priority setting for alcohol prevention and cancer control.

- Increasing alcohol excise duties can reduce the burden of cancer attributable to alcohol in European countries. A 100% increase in excise duties on alcohol could have avoided between 3% and 7% of all alcohol-attributable cancer cases in Germany, Italy, Kazakhstan, and Sweden in 2018.
- Policy measures that increase the price of alcohol are among the most effective and cost-effective policies to reduce population alcohol consumption and ultimately alcohol-attributable cancer burden.

Based on the results and conclusions of this thesis, we recommend the following:

- Regular collection of information on risk factor exposure is vital to carry out cancer preventability estimates, plan prevention strategies, monitor changes in risk factor prevalence, and evaluate the effectiveness of prevention interventions. Data collection should therefore be considered a fundamental function to improve public health in countries worldwide. To increase reliability, statistics could be compiled using risk factor exposure data from multiple sources.
- To improve the quality of data from cancer registries, increased histological verification through promotion of the use of ICD-O classification would enable and enrich research in areas which currently have limited information on histological subtypes.
- With improved availability and quality of cancer registry data, further trend analysis of oesophageal cancer by histological subtype should be carried out covering populations which have the most elevated rates of oesophageal cancer e.g. some Asian, sub-Saharan African, and South American countries.
- Country-level estimates of cancer burden attributable to risk factors should be used as key tools to drive cancer prevention and control strategies.
- Future economic studies on alcohol-attributable cancer could include loss of unpaid employment as well as additional costs of reduced productivity, and diagnosis and treatment of alcohol-attributable cancers.
- While quantifying the societal and economic burden of alcohol-attributable cancer is important, we should demonstrate how various alcohol control policies can ultimately reduce the burden of cancer attributable to alcohol.
- Alcohol pricing policies are the most cost-effective measure to decrease population alcohol consumption and should form the basis of a successful whole-systems approach to reducing alcohol harms including cancer burden.

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Samenvatting

Deel 1. Introductie

Bijna de helft van de volwassen wereldbevolking consumeert regelmatig alcohol ondanks de vele bijbehorende gezondheidsrisico's en kans op verwondingen. Uit data van WHO blijkt dat in 2019 de wereldwijde gemiddelde alcoholconsumptie bij mensen van 15 jaar en ouder 5,8 liter pure alcohol per persoon was - wat gelijk staat aan één tot twee standaardglazen per dag. Mannen consumeren ongeveer vier keer meer alcohol dan vrouwen. Alcoholgebruik verschilt ook aanzienlijk per regio. Onder mannen wordt hoogste alcoholgebruik gezien in West-, Oost- en Noord-Europa, onder vrouwen in West- en Noord-Europa, Australië en Nieuw-Zeeland. Noord-Afrika en West-Azië hebben daarentegen wereldwijd de laagste hoeveelheid alcoholgebruik per persoon.

Alcoholconsumptie verhoogt het risico op zeven verschillende soorten kanker, waaronder kanker van de mond, keelholte, strottenhoofd, slokdarm, lever, darm en borst. Sinds 1988 heeft de International Agency for Research on Cancer (IARC) alcoholische dranken geclassificeerd als groep 1 kankerverwekkende stoffen, maar het publieke bewustzijn van het oorzakelijk verband tussen alcohol en kanker blijft laag. Alcoholconsumptie op elk niveau verhoogt het risico op kanker. Dit omvat ook consumptieniveaus die traditioneel gezien worden als 'laag alcoholgebruik', en 'licht' of 'matig' drinken, wat gelijk staat aan maximaal één of twee alcoholische dranken per dag.

Dit proefschrift heeft als doel om wereldwijd, regionaal en landelijk de impact van alcoholgebruik op de ziektelast van kanker in de algemene bevolking te bepalen. We hebben verschillende aspecten van de ziektelast van kanker die toe te schrijven zijn aan alcoholgebruik beoordeeld. De resultaten hiervan presenteerden we in vier delen. Om de achtergrond te schetsen over het verband tussen alcoholgebruik en kanker, hebben we in Deel 1 de onderwerpen geïntroduceerd die in dit proefschrift worden behandeld, en de epidemiologie en biologische mechanismen van door alcohol gedreven carcinogenese samengevat. In Deel 2 beschreven we de ziektelast van leverkanker wereldwijd en per subtype, en analyseerden we de trends van slokdarmkankerincidentie per subtype. In Deel 3 kwantificeerden we de wereldwijde ziektelast van kanker veroorzaakt door alcoholgebruik en de ziektelast van kanker in het Verenigd Koninkrijk veroorzaakt door verschillende risicofactoren, waaronder alcohol. Voortbouwend op deze schattingen van ziektelast, hebben we in Deel 4 de economische impact van alcoholgerelateerde kankersterfte en het effect van veranderingen in alcoholbeleid op de ziektelast van kanker in Europa gekwantificeerd.

Deel 2. Beschrijving van de wereldwijde ziektelast van alcoholgerelateerde kanker

Aangezien primaire leverkanker causaal gerelateerd isaan alcoholgebruik (Deel 1, hoofdstuk 2), hebben we de wereldwijde ziektelast van leverkanker beoordeeld in een descriptieve evaluatie van incidentie en sterfte per regio. In 2020 werden meer dan 900.000 mensen gediagnosticeerd met, en stierven 830.000 mensen aan, leverkanker wereldwijd. We von-

den de hoogste incidentie en mortaliteit van leverkanker in Oost-Azië, Noord-Afrika en Zuidoost-Azië. Bovendien behoorde leverkanker tot de top drie van kanker-doodsoorzaken in een totaal van 46 landen wereldwijd en stond het in de top vijf van kanker-doodsoorzaken in 90 landen. Gezien de lage overlevingskans van leverkanker hebben we beleidsmakers aanbevolen om prioriteit te geven aan primaire preventie van leverkanker. De oorzaken van leverkanker variëren per subtype, dus we onderzochten de specifieke patronen van de subtypen van leverkanker naar geslacht en land, om onderzoek en beleidsprioriteiten in verschillende settings te bevorderen.

Om de patronen van leverkanker per subtype te onderzoeken, hebben we in hoofdstuk 4 het aantal nieuwe gevallen van de belangrijkste subtypen van leverkanker geschat. Hepatocellulair carcinoom was het meest voorkomende subtype van leverkanker en vertegenwoordigde naar schatting 80% van de nieuwe gevallen van leverkanker wereldwijd in 2018. Hepatocellulair carcinoom is ook het subtype van leverkanker dat causaal verband heeft met alcoholgebruik. Het tweede meest voorkomende subtype van leverkanker, intrahepatisch cholangiocarcinoom, vertegenwoordigde 15% van de nieuwe gevallen van leverkanker in 2018, terwijl leverkankergevallen van andere gespecificeerde histologiegroepen 5% vertegenwoordigden. Door de ziektelast van leverkanker per subtype te bepalen, ontdekten we verschillende patronen in de incidentie van de belangrijkste subtypen per regio. De bevindingen van dit hoofdstuk zullen beleidsmakers in staat stellen de specifieke combinatie van leverkankersubtypen in hun land te identificeren en maatregelen op maat toe te passen om de ziektelast van hepatocellulair carcinoom en intrahepatisch cholangiocarcinoom te verminderen. Het beoordelen van de ziektelast van leverkanker per subtype benadrukt ook het belang van het vergroten van de kwaliteit en beschikbaarheid van data om betrouwbaardere schattingen van de populatie-impact van risicofactoren voor kanker mogelijk te maken.

Ook slokdarmkanker heeft verschillende subtypen die verschillen in hun etiologie en epidemiologie. Alcoholgebruik verhoogt het risico op plaveiselcelcarcinoom van de slokdarm, het meest voorkomende subtype van slokdarmkanker wereldwijd, terwijl het drinken van alcohol niet is geclassificeerd als een veroorzaker van adenocarcinoom van de slokdarm. In hoofdstuk 5 onderzochten we de recente trends in de incidentie van de twee belangrijkste subtypen van slokdarmkanker en beoordeelden we langetermijntrends per geboortecohort en kalenderperiode. Het beoordelen van de langetermijntrends stelde ons in staat om de effecten van veranderingen in de prevalentie van risicofactoren tussen generaties, of veranderingen in diagnostische methoden of classificatie van ziekten te bestuderen. We vonden dalende plaveiselcelcarcinoom- incidentiecijfers in de helft van de geanalyseerde mannenpopulaties, en toenames in adenocarcinoom-diagnoses in bijna een derde van de geanalyseerde populaties in het afgelopen decennium. Op basis van deze resultaten liet onze studie zien wat de waarde is van het onderzoeken van kankertrends per histologisch subtype met betrekking tot het ontdekken van verschillende patronen. Omdat alcoholgebruik het risico op plaveiselcelcarcinoom van de slokdarm verhoogt, is het begrijpen van de epidemi-

ologie ervan waardevol voor het schatten en beoordelen van het aandeel van de ziektelast van slokdarmkanker dat toe te schrijven is aan alcohol.

Deel 3. Schatting van het aandeel kankergevallen als gevolg van alcohol en andere modificeerbare risicofactoren wereldwijd en in het Verenigd Koninkrijk

In hoofdstuk 6 hebben we de wereldwijde impact van alcoholgebruik op kanker gekwantificeerd. We ontdekten dat meer dan 740.000(of 4% van alle nieuwe) gevallen van kanker wereldwijd in 2020 toe te schrijven zijn aan alcoholgebruik. Onze resultaten bevestigden de hogere ziektelast van alcohol-gerelateerde kankers bij mannen, die bijdragen aan driekwart van het totale aantal aan alcohol toe te schrijven kankergevallen. Verder droegen slokdarmkanker en leverkanker bij aan de meeste gevallen van kanker die toe te schrijven zijn aan alcohol, gevolgd door borstkanker. In termen van consumptieniveau vertegenwoordigde risicovol en overmatig drinken (meer dan twee alcoholische dranken per dag) de grootste ziektelast door alcohol veroorzaakte kanker (86% van het totaal aantal toerekenbare nieuwe kankergevallen). Maar we ontdekten ook dat matig drinken van maximaal één of twee alcoholische dranken per dag verantwoordelijk was voor meer dan 100.000 gevallen van kanker in 2020, wat bewijs levert van de schadelijke effecten van alcoholgebruik zelfs bij lagere consumptieniveaus. Naast verschillen per geslacht en per consumptieniveau, vonden we verschillen in de alcohol gerelateerde ziektelast van kanker tussen regio's, dat grotendeels de verschillen in alcoholgebruik van de bevolking weerspiegelde. Om deze ziektelast aan te pakken hebben we aanbevolen om een alcoholpreventiebeleid in te voeren zoals aanbevolen door de WHO. Dit omvat het verhogen van accijnzen op alcoholische dranken, het verbieden van alcoholreclame en het beperken van de beschikbaarheid van alcoholproducten in winkels.

Hoewel het kwantificeren van de aantallen van kanker die toe te schrijven zijn aan alcohol het mogelijk maakt om kankersoorten en landen te vergelijken, is het ook de moeite waard om het aantal kankergevallen als gevolg van alcohol te vergelijken met die van andere modificeerbare risicofactoren. In hoofdstuk 7 hebben we een uitgebreide schatting uitgevoerd van populatie attributieve fracties (PAFs) voor de incidentie van kanker in het Verenigd Koninkrijk (VK) en de samenstellende landen in 2015. Over het algemeen waren bijna vier op de tien (38%) kankergevallen in het VK in 2015 toe te schrijven aan bekende modificeerbare risicofactoren. Alcoholgebruik was de zesde belangrijkste vermijdbare oorzaak van kanker in het Verenigd Koninkrijk, na roken, overgewicht en obesitas, UV-straling, beroepsmatige blootstelling en infecties. Er waren enkele verschillen in PAFs tussen de verschillende Britse landen die deels te wijten waren aan socio-demografische verschillen die variatie in blootstelling aan de theoretisch vermijdbare risicofactoren veroorzaakten. Vanwege deze variatie toonden onze bevindingen de waarde aan van het uitrekenen van PAFs gerelateerd

aan kanker op landniveau in het VK voor verschillende modificeerbare risicofactoren en kankertypen.

Deel 4. Kwantificering van de maatschappelijke en economische gevolgen van overlijden aan alcoholgerelateerde kanker en het effect van veranderingen in het alcoholbeleid op de sterfte aan kanker in Europa

In Europa is de alcoholconsumptie per persoon hoger dan in andere regio's in de wereld. Dit verhoogde consumptieniveau brengt waarschijnlijk aanzienlijke maatschappelijke en economische kosten met zich mee in termen van alcoholgerelateerde ziekten, waaronder kanker. In hoofdstuk 8 hebben we daarom een deel van de maatschappelijke impact van alcohol-attributieve fractie in kanker berekend door de kosten van vroegtijdig overlijden als gevolg van aan alcohol-attributieve kanker in de 27 landen van de Europese Unie (EU) plus IJsland, Noorwegen, Zwitserland en het VK in 2018 te schatten. We ontdekten dat ten minste € 4,58 miljard in Europa in 2018 verloren ging aan vroegtijdig overlijden aan alcoholgerelateerde kanker, wat overeenkomt met 0,027% van het gecombineerde bruto binnenlands product (BBP) van de Europese landen. We geloven sterk dat door dit economische perspectief van de aan alcohol toe te schrijven aantallen van kanker weer te geven, we verder bewijs hebben geleverd voor de prioritering van preventiemaatregelen op het gebied van alcoholgebruik in relatie tot kanker .

Om bewijs te leveren van de effectiviteit van beleidswijzigingen om de aan alcohol toe te schrijven kankeraantallen te verminderen, hebben we in hoofdstuk 9 de impact van het verhogen van alcohol-belasting/alcoholaccijnzen op het aantal gevallen van kanker in vier Europese landen gemodelleerd. We schatten dat in Duitsland, Italië, Kazachstan en Zweden samen meer dan 35.000 gevallen van kanker in 2018 werden veroorzaakt door alcoholgebruik, 3,5% van de totale kankersterfte in die vier landen. Een verhoging van de accijns op alcohol met 100% had 3% tot 7% van alle kankergevallen die aan alcohol zijn toe te schrijven in de vier landen kunnen voorkomen. Onze bevindingen suggereren dat duizenden gevallen van kanker en sterfte in Europa kunnen worden voorkomen wanneer strengere alcoholbelastingsystemen zouden worden geimplementeerd, zoals die welke belasting heffen op basis van het volume pure alcohol in drank, of zoals de WHO en de EU adviseren, een minimumbelastingniveau in de consumentenprijs van alcohol (momenteel € 0 voor wijn bv.).

Conclusies en aanbevelingen

Op basis van de bevindingen van dit proefschrift trekken we de volgende conclusies:

- Leverkanker leidt wereldwijd tot grote ziektelast en behoorde in 2020 tot de top-drie kankergerelateerde doodsoorzaken in 46 landen wereldwijd.

- Het meest voorkomende subtype van leverkanker, het hepatocellulair carcinoom, vertegenwoordigde 80% van de gevallen van leverkanker wereldwijd in 2018. Om leverkanker wereldwijd onder controle te houden, moeten beleidsmakers prioriteit geven aan primaire preventie van blootstelling aan de risicofactoren voor hepatocellulair carcinoom, waaronder hepatitis B- en C-virusinfecties en alcoholgebruik.
- Alcoholgebruik is een vastgestelde risicofactor voor plaveiselcelcarcinoom van de slokdarm. De incidentie van het plaveiselcelcarcinoom van de slokdarm daalde in de meerderheid van de geanalyseerde mannelijke populaties. Wij denken dat dit werd veroorzaakt door veranderingen in de gebruik van tabak- en alcohol.
- Alcoholgebruik veroorzaakte naar schatting 741.000 gevallen van alle kankers wereldwijd in 2020, wat gelijk staat aan 4% van alle kankergevallen. Overmatig alcoholgebruik droeg het meest bij aan de wereldwijde ziektelast van aan alcohol toe te schrijven kanker. Desondanks droeg matig gebruik van alcohol, het equivalent van maximaal één of twee alcoholische dranken per dag, bij aan meer dan 100.000 gevallen van kanker in 2020. Dit toont de impact van alcohol op de kankerincidentie aan, zelfs bij lagere consumptieniveaus.
- Bijna vier op de tien (38%) kankergevallen in het Verenigd Koninkrijk in 2015 waren toe te schrijven aan bekende modificeerbare risicofactoren, waaronder alcoholgebruik, de zesde belangrijkste vermijdbare oorzaak van kanker. De percentages van vermijdbare kankergevallen varieerden van 37% in Engeland tot 42% in Schotland - deels te wijten aan socio-demografische verschillen leidend tot verschillen in blootstelling aan theoretisch vermijdbare risicofactoren.
- In 2018 ging in Europa ten minste 4,58 miljard euro verloren aan vroegtijdig overlijden aan alcoholgerelateerde kanker, wat overeenkomt met 0,027% van het gecombineerde BBP Europa. Dit economische perspectief levert verder bewijs voor de importantie van het prioriteren van alcohol- en de daaraan gerelateerde kankerbestrijding.
- Het verhogen van de alcoholaccijns kan het aantal door alcohol veroorzaakte kankergevallen in Europa verminderen. Een verhoging van de accijns op alcohol met 100% zou in 2018 tussen de 3% en 7% van alle aan alcohol toe te schrijven gevallen van kanker in Duitsland, Italië, Kazachstan en Zweden hebben kunnen voorkomen.
- Beleidsmaatregelen die de prijs van alcohol verhogen behoren tot de meest effectieve en kosteneffectieve beleidsmaatregelen om het alcoholgebruik van de bevolking te verminderen en uiteindelijk het aantal alcoholgerelateerde kankergevallen te verminderen.

Op basis van de resultaten en conclusies van dit proefschrift doen wij de volgende aanbevelingen:

- Het verzamelen van informatie over blootstelling aan risicofactoren is van belang om schattingen van de vermijdbaarheid van kanker uit te rekenen, preventiestrategieën te plannen, veranderingen in de prevalentie van risicofactoren te monitoren en de ef-

fectiviteit van interventies te evalueren. Het verzamelen van dat soort gegevens moet daarom worden beschouwd als een fundamentele voorwaarde om de te verbeteren. Om de betrouwbaarheid van schattingen en berekeningen te vergroten, zouden statistieken van gegevens over blootstelling aan risicofactoren uit meerdere bronnen kunnen worden samengesteld.

- Om de kwaliteit van de gegevens uit kankerregisters te verbeteren, zou histologische verificatie door het bevorderen van het gebruik van de ICD-O-classificatie onderzoek faciliteren.Verder zou dat het wetenschappelijk onderzoek kunnen verrijken in gebieden waar momenteel beperkte informatie over histologische subtypen bestaat.
- Met een betere beschikbaarheid en kwaliteit van kankerregistratiegegevens kan een verdere trendanalyse van slokdarmkanker per histologisch subtype worden uitgevoerd voor populaties met het meest verhoogde risico op slokdarmkanker, bijvoorbeeld bepaalde landen in Azië, Sub-Sahara-Afrika en Zuid-Amerika.
- De relatie tussen anker en blootstelling aan risicofactoren moet actiever worden ingezet als belangrijke instrument om strategieën voor kankerpreventie en -bestrijding te ontwikkelen en te stimuleren.
- Toekomstige economische studies over aan alcohol toe te schrijven kanker kunnen verlies van onbetaald werk omvatten, evenals extra kosten van verminderde productiviteit, en diagnose en behandeling van alcohol-attributieve kanker.
- Hoewel het kwantificeren van de maatschappelijke en economische last van aan alcohol toe te schrijven kanker belangrijk is, moeten we vooral aantonen hoe verschillende maatregelen uiteindelijk de ziektelast van kanker die aan alcohol te wijten is, kunnen verminderen.
- Alcoholprijsbeleid is de meest kosteneffectieve maatregel om het alcoholgebruik te verminderen en moet de basis vormen voor een succesvolle aanpak van het huidige systeem om alcoholschade, waaronder kanker, te verminderen.

R

Résumé

Partie 1. Introduction

Près de la moitié de la population adulte mondiale consomme régulièrement de l'alcool malgré les nombreux risques et blessures qui y sont associés. En 2019, la consommation mondiale d'alcool était égale à 5,8 litres d'alcool pur par personne âgée de 15 ans et plus, soit l'équivalent d'un ou deux verres standards d'alcool par jour. Au niveau mondial, les hommes ont bu environ quatre fois plus d'alcool que les femmes en 2019. Également, les habitudes de consommation diffèrent considérablement d'une région du monde à l'autre. La consommation moyenne la plus élevée chez les hommes se situait en Europe de l'Ouest, en Europe de l'Est, et en Europe du Nord, et la consommation moyenne la plus élevée chez les femmes se situait en Europe de l'Ouest et du Nord, ainsi qu'en Australie et en Nouvelle-Zélande. En revanche, l'Afrique du Nord et l'Asie occidentale ont les volumes de consommation d'alcool par personne les plus faibles au monde, parmi les hommes et les femmes.

La consommation d'alcool augmente le risque de sept types de cancer différents, notamment les cancers de la cavité buccale, du pharynx, du larynx, de l'œsophage, du foie, du côlon et du rectum, et du sein. Le Centre International de Recherche sur le Cancer classe les boissons alcoolisées comme cancérogène du groupe 1 depuis 1988, mais la sensibilisation du public au lien entre l'alcool et le cancer reste faible. La consommation d'alcool à n'importe quel niveau augmente le risque de cancer. Cela inclut les niveaux de consommation traditionnellement considérés comme une consommation « faible », « légère » ou « modérée » de l'équivalent d'une ou deux boissons alcoolisées par jour.

Cette thèse visait à mesurer l'impact de la consommation d'alcool dans la population sur le taux de cancer aux échelles mondiale, régionale, et nationale. Nous avons évalué plusieurs aspects du nombre total de cancer attribuable à la consommation d'alcool que nous avons présentés en quatre parties. Pour fournir des informations sur le lien entre la consommation d'alcool et le cancer, dans la partie 1, nous avons présenté les sujets couverts dans cette thèse et nous avons résumé l'épidémiologie et les mécanismes biologiques de la carcinogenèse induite par l'alcool. Dans la partie 2, nous avons décrit le nombre total de cancer du foie à l'échelle mondiale et par sous-type, et nous avons analysé les tendances de l'incidence du cancer de l'œsophage par sous-type. Nous avons quantifié la charge mondiale du cancer attribuable à la consommation d'alcool et le nombre de cas de cancer au Royaume-Uni attribuables à une série de facteurs modifiables de risque, y compris l'alcool, dans la partie 3. En développant ces estimations, dans la partie 4, nous avons quantifié l'impact économique des décès par cancer attribuables à l'alcool et l'effet des changements de politique en matière d'alcool sur le nombre total de cancer en Europe.

Partie 2. Description du taux mondial de cancers liés à l'alcool

La consommation d'alcool est une cause du cancer primitif du foie (partie 1, chapitre 2), nous avons évalué au chapitre 3 la charge mondiale du cancer du foie dans une évaluation descriptive des taux d'incidence et de mortalité par région du monde. Plus de 900 000

personnes ont reçu un diagnostic de cancer du foie et 830 000 personnes en sont décédées dans le monde en 2020. Nous avons constaté que les taux les plus élevés d'incidence et de mortalité par cancer du foie se trouvaient en Asie de l'Est, en Afrique du Nord et en Asie du Sud-Est. En outre, le cancer du foie figurait parmi les trois principales causes de décès par cancer dans un total de 46 pays à travers le monde et figurait parmi les cinq principales causes de décès par cancer dans 90 pays. Compte tenu du faible taux de survie au cancer du foie, nous avons recommandé aux responsables de la santé publique de donner la priorité à la prévention primaire des facteurs de risque du cancer du foie. Plusieurs causes de ce cancer varient selon le sous-type. Nous avons donc suggéré que l'étude des schémas spécifiques des sous-types de cancer du foie par sexe et par pays pourrait mieux éclairer les priorités de recherche et de politique dans différents contextes.

Pour explorer les schémas de cancer du foie par sous-type, au chapitre 4, nous avons estimé le nombre de cas des principaux sous-types de cancer du foie. Le carcinome hépatocellulaire était le sous-type de cancer du foie le plus courant et représentait environ 80 % des cas de cancer du foie dans le monde en 2018. Le carcinome hépatocellulaire est également le sous-type de cancer du foie qui est causalement lié à la consommation d'alcool. Le deuxième sous-type de cancer du foie le plus courant, le cholangiocarcinome intrahépatique, représentait 15 % des cas de cancer du foie en 2018, tandis que les cas de cancer du foie d'autres groupes histologiques spécifiés représentaient 5 %. En évaluant le nombre total de cancer du foie par sous-type, nous avons découvert des tendances distinctes dans l'incidence des principaux sous-types par région du monde. Les résultats de ce chapitre permettront aux responsables de la santé publique d'identifier le mélange spécifique de sous-types de cancer du foie dans leur région et d'appliquer des mesures adaptées pour réduire le poids du carcinome hépatocellulaire et du cholangiocarcinome intrahépatique, y compris le contrôle de l'alcool pour la prévention du carcinome hépatocellulaire. De plus, l'évaluation du cancer du foie par sous-type montre l'importance d'améliorer les données sur le cancer pour permettre des estimations plus fiables de l'impact des facteurs de risque de cancer sur la population.

Le cancer de l'œsophage a également des sous-types distincts qui diffèrent par leur étiologie et leur épidémiologie. La consommation d'alcool augmente le risque de carcinome épidermoïde de l'œsophage, qui est le sous-type le plus courant de cancer de l'œsophage dans le monde, alors que la consommation d'alcool n'a pas été classée comme causalement liée à l'adénocarcinome de l'œsophage. Au chapitre 5, nous avons exploré les tendances récentes des taux d'incidence des deux principaux sous-types de cancer de l'œsophage et évalué les tendances à long terme par cohorte de naissance et par période calendaire. L'évaluation des tendances à long terme nous a permis de postuler les effets des changements dans la prévalence des facteurs de risque entre les générations, ou des changements dans les méthodes de diagnostic ou la classification des maladies. Nous avons constaté des diminutions des taux d'incidence des carcinomes épidermoïdes de l'œsophage dans la moitié des populations masculines analysées et des augmentations des taux d'incidence des adénocarcinomes de

l'œsophage dans près d'un tiers des populations masculines et féminines analysées au cours de la dernière décennie. Compte tenu de ces résultats, notre étude a montré l'intérêt d'étudier les tendances du cancer par sous-type histologique pour découvrir des modèles différents. De plus, comme la consommation d'alcool augmente le risque de carcinome épidermoïde de l'œsophage, la compréhension de son épidémiologie est précieuse pour estimer et évaluer la proportion des cas de cancer de l'œsophage attribuable à l'alcool.

Partie 3. Estimation de la proportion de cas de cancer dus à l'alcool et à d'autres facteurs de risque modifiables dans le monde et au Royaume-Uni

Au chapitre 6, nous avons quantifié l'impact global de la consommation d'alcool sur le cancer. Nous avons constaté que plus de 740 000, soit 4%, de tous les nouveaux cas de cancer dans le monde en 2020 étaient attribuables à la consommation d'alcool. Nos résultats ont confirmé le taux élevé des cancers attribuables à l'alcool chez les hommes, qui représentaient les trois quarts du nombre total de cas de cancer attribuables à l'alcool. De plus, les cancers de l'œsophage et du foie ont contribué à la plupart des cas de cancer attribuables à l'alcool, suivis du cancer du sein. En termes de niveau de consommation, la consommation à risque et excessive de plus de deux verres d'alcool par jour représentait le poids le plus important des cancers attribuables à l'alcool (86 % du nombre total de cas attribuables). Mais nous avons constaté qu'une consommation modérée allant jusqu'à une ou deux boissons alcoolisées par jour était responsable de plus de 100 000 cas de cancer en 2020, ce qui prouve les effets nocifs de la consommation d'alcool à des niveaux de consommation inférieurs. En plus des différences selon le sexe et le niveau de consommation, nous avons constaté des disparités dans la charge de cancer attribuable à l'alcool entre les régions du monde, qui reflétaient largement les différences de consommation d'alcool dans la population. Pour faire face à ce total, nous avons recommandé la mise en œuvre de politiques de contrôle de l'alcool telles que celles recommandées par l'Organisation Mondiale de la Santé (OMS). Celles-ci comprennent l'augmentation des taxes d'accise sur les boissons alcoolisées, l'interdiction de la publicité pour l'alcool et la restriction de la disponibilité physique des produits alcoolisés au détail.

Si la quantification du nombre total de cancer attribuable à l'alcool permet des comparaisons entre les types de cancer et les pays, il est également intéressant de comparer ce taux avec celui d'autres facteurs de risque modifiables connus. Dans le chapitre 7, nous avons effectué une estimation complète des fractions attribuables à la population (FAP) pour l'incidence du cancer au Royaume-Uni et dans ses pays constitutifs en 2015. Dans l'ensemble, près de quatre cas de cancer sur dix (38 %) au Royaume-Uni en 2015 étaient attribuables à des facteurs de risque modifiables connus. La consommation d'alcool était la sixième cause évitable de cancer au Royaume-Uni, derrière le tabagisme, le surpoids et l'obésité, les rayons UV, les expositions professionnelles et les infections. Il y avait quelques disparités dans les FAP entre

les pays du Royaume-Uni, qui étaient en partie dues aux différences sociodémographiques entraînant une variation de l'exposition aux facteurs de risque théoriquement évitables. En raison de cette variation, nos résultats ont démontré la valeur de la production de FAP de cancer au niveau national au Royaume-Uni pour plusieurs facteurs de risque modifiables et types de cancer.

Partie 4. Quantifier l'impact sociétal et économique des décès par cancer attribuables à l'alcool et l'effet des changements de politique en matière d'alcool sur le taux de cancers en Europe

L'Europe consomme plus d'alcool par personne que toute autre région du monde. Ce niveau élevé de consommation est susceptible de produire un coût sociétal et économique substantiel en termes de maladies liées à l'alcool, y compris le cancer. Dans le chapitre 8, nous avons donc calculé une partie de l'impact sociétal du cancer attribuable à l'alcool en estimant le coût des décès prématurés dus aux cancers attribuables à l'alcool dans les 27 pays de l'Union européenne (UE) plus l'Islande, la Norvège, la Suisse et le Royaume-Uni en 2018. Nous avons constaté qu'au moins 4,58 milliards d'euros en Europe en 2018 ont été perdus en raison de décès prématurés dus à des cancers attribuables à l'alcool, ce qui équivaut à 0,027 % du produit intérieur brut combiné des pays européens. Cela représente une perte énorme pour la société qui ne doit pas être ignorée et nous pensons qu'en fournissant cette perspective économique sur le poids du cancer attribuable à l'alcool, nous avons ajouté des preuves supplémentaires pour aider à établir des priorités pour la prévention de l'alcool et la lutte contre le cancer.

Pour fournir des preuves des changements de politique visant à réduire le nombre total de cancers attribuables à l'alcool, nous avons modélisé au chapitre 9 l'impact de l'augmentation des taxes d'accise sur l'alcool sur les cas de cancer dans quatre pays européens. Nous avons estimé qu'en Allemagne, en Italie, au Kazakhstan et en Suède, ensemble, plus de 35 000 cas de cancer en 2018 étaient dus à la consommation d'alcool, soit 3,5 % de tous les cas de cancer dans les quatre pays. Une augmentation de 100% des droits d'accise sur l'alcool aurait pu éviter entre 3 % et 7 % de tous les cas de cancers attribuables à l'alcool dans les quatre pays. Nos résultats suggèrent que des milliers de cas de cancer et de décès en Europe pourraient être évités si tous les pays de la région adoptaient des systèmes de taxation de l'alcool plus stricts, tels que ceux qui taxent en fonction du volume d'alcool pur dans chaque boisson, ou si l'OMS ou l'UE recommandaient un niveau minimum de taxation dans le prix final à la consommation de l'alcool (qui est actuellement aussi bas que 0€ pour le vin).

Conclusions et recommandations

En ce qui concerne les résultats de cette thèse, nous concluons que :

- Le cancer du foie représente une proportion de maladies majeure dans le monde et figurait parmi les trois principales causes de décès par cancer dans 46 pays du monde en 2020.
- Le sous-type de cancer du foie le plus courant, le carcinome hépatocellulaire, représentait 80 % des cas de cancer du foie dans le monde en 2018. Pour contrôler le cancer du foie à l'échelle mondiale, les responsables de la santé publique devraient donner la priorité à la prévention primaire des facteurs de risque du carcinome hépatocellulaire, y compris l'infection par les virus de l'hépatite B et C et consommation d'alcool.
- La consommation d'alcool est un facteur de risque établi pour le carcinome épidermoïde de l'œsophage. Les taux d'incidence du carcinome épidermoïde de l'œsophage ont diminué dans la majorité des populations masculines analysées, ce qui, selon nous, était dû aux changements dans la prévalence de la consommation de tabac et d'alcool d'une génération à l'autre.
- La consommation d'alcool a causé environ 741 000 cas de cancer, soit 4 % de tous les cas de cancer, dans le monde en 2020. Bien que les habitudes de consommation excessive contribuent le plus au nombre total mondial des cancers attribuables à l'alcool, une consommation modérée de l'équivalent d'une ou deux consommations d'alcool par jour a contribué à plus de 100 000 cas de cancer en 2020. Cela démontre l'impact de l'alcool sur le cancer à des niveaux de consommation plus faibles.
- Près de quatre cas de cancer sur dix (38 %) au Royaume-Uni en 2015 étaient attribuables à des facteurs de risque modifiables connus, dont la consommation d'alcool. Les proportions de cas de cancer évitables par pays variaient de 37% en Angleterre à 42% en Écosse - la disparité qui en résulte est en partie due aux différences sociodémographiques qui ont entraîné une variation de l'exposition aux facteurs de risque théoriquement évitables.
- Au moins 4,58 milliards d'euros ont été perdus en raison de décès prématurés dus à des cancers attribuables à l'alcool en Europe en 2018, ce qui équivaut à 0,027 % du PIB combiné des pays européens. Cette perspective économique ajoute des preuves supplémentaires pour aider à établir des priorités en matière de prévention de l'alcool et de lutte contre le cancer.
- L'augmentation des droits d'accise sur l'alcool peut réduire le poids du cancer attribuable à l'alcool dans les pays européens. Une augmentation de 100 % des droits d'accise sur l'alcool aurait pu éviter entre 3% et 7% de tous les cas de cancer attribuables à l'alcool en Allemagne, en Italie, au Kazakhstan et en Suède en 2018.
- Les mesures politiques qui augmentent le prix de l'alcool sont parmi les politiques les plus efficaces et les plus rentables pour réduire la consommation d'alcool dans la population et, en fin de compte, le taux de cancer attribuable à l'alcool.

Sur la base des résultats et des conclusions de cette thèse, nous recommandons :

- La collecte régulière d'informations sur l'exposition aux facteurs de risque est essentielle pour effectuer des estimations de la prévention du cancer, planifier des stratégies de prévention, surveiller les changements dans la prévalence des facteurs de risque et évaluer l'efficacité des interventions de prévention. La collecte de données doit donc être considérée comme une fonction fondamentale pour améliorer la santé publique dans les pays du monde entier. Pour accroître la fiabilité, des statistiques pourraient être compilées à l'aide de données sur l'exposition aux facteurs de risque provenant de sources multiples.
- Pour améliorer la qualité des données des registres du cancer, une vérification histologique accrue par la promotion de l'utilisation de la classification ICD-O permettrait et enrichirait la recherche dans des domaines qui disposent actuellement d'informations limitées sur les sous-types histologiques.
- Avec l'amélioration de la disponibilité et de la qualité des données des registres du cancer, une analyse plus approfondie des tendances du cancer de l'œsophage par sous-type histologique devrait être effectuée en couvrant les populations qui présentent les taux les plus élevés de cancer de l'œsophage, par exemple certains pays d'Asie, d'Afrique subsaharienne et d'Amérique du Sud.
- Les estimations nationales du cancer attribuable aux facteurs de risque doivent être utilisées comme des outils clés pour piloter les stratégies de prévention et de lutte contre le cancer.
- Les futures études économiques sur le cancer attribuable à l'alcool pourraient inclure la perte d'emplois non rémunérés ainsi que les coûts supplémentaires de productivité réduite, et le diagnostic et le traitement des cancers attribuables à l'alcool.
- Bien qu'il soit important de quantifier le poids sociétal et économique du cancer attribuable à l'alcool, nous devrions démontrer comment diverses politiques de contrôle de l'alcool peuvent finalement réduire le nombre total de cancers attribuable à l'alcool.
- Les politiques de tarification de l'alcool sont la mesure la plus rentable pour réduire la consommation d'alcool de la population et devraient constituer la base d'une approche systémique réussie pour réduire les méfaits de l'alcool, y compris le taux de cancer.

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About the author

CURRICULUM VITAE

Harriet Jayne Rumgay was born on 26 December 1991 in Leeds, United Kingdom (UK). Growing up in Yorkshire, Harriet became fond of learning and started to pursue her interests in life sciences. She started an undergraduate degree in Biology with French for Sciences at Imperial College London in 2011. After graduating with a BSc, Hons in Biology in 2014, Harriet took up a volunteering internship at Cancer Research UK (CRUK).

Harriet started working in the Statistical Information Team (now the Cancer Intelligence Team) at CRUK in 2015 where her interests in cancer epidemiology grew while developing her data analysis and research skills. Over the following three and a half years, Harriet's projects focused more on cancer risk factors, cancer prevention, and lifetime risk of cancer, and Harriet became one of the key contributors to the updated estimates of preventable cancers in the UK with Dr Katrina Brown. It was thanks to this experience and the generosity of Dr Isabelle Soerjomataram and Professor Dr Valery Lemmens that Harriet was offered the position of Doctoral Student in the Cancer Surveillance Branch at the International Agency for Research on Cancer (IARC) in Lyon, France.

At IARC, under the supervision of Dr Soerjomataram, Harriet has led various projects on alcohol-related cancers which have included estimating the global burden of cancer attributable to alcohol and analysing the descriptive epidemiology of liver and oesophageal cancers. The results of these projects are presented in this thesis.

LIST OF PUBLICATIONS

In this thesis

Rumgay H, Murphy N, Ferrari P, Soerjomataram I. Alcohol and Cancer: Epidemiology and Biological Mechanisms. *Nutrients*. 2021 Sep 11;13(9):3173. doi: 10.3390/nu13093173.

Rumgay H, Arnold M, Ferlay J, Lesi O, Cabasag CJ, Vignat J, Laversanne M, McGlynn KA, Soerjomataram I. Global burden of primary liver cancer in 2020 and predictions to 2040. In press. *Journal of Hepatology*.

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Other publications

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Arnold M, Morgan E, **Rumgay H**, Mafra A, Singh D, Laversanne M, Vignat J, Gralow JR, Cardoso F, Siesling S, Soerjomataram I. Current and future burden of breast cancer: global statistics for 2020 and 2040. *Breast*. 2022 Sep 2;66:15-23. doi: 10.1016/j.breast.2022.08.010.

Morgan E, Soerjomataram I, **Rumgay H**, Coleman HG, Thrift AP, Vignat J, Laversanne M, Ferlay J, Arnold M. The Global Landscape of Esophageal Squamous Cell Carcinoma and

Esophageal Adenocarcinoma Incidence and Mortality in 2020 and Projections to 2040: New Estimates From GLOBOCAN 2020. *Gastroenterology*. 2022 Jun 4:S0016-5085(22)00608-4. doi: 10.1053/j.gastro.2022.05.054.

Kilian C, Rovira P, Neufeld M, Ferreira-Borges C, **Rumgay H**, Soerjomataram I, Rehm J. Modelling the impact of increased alcohol taxation on alcohol-attributable cancers in the WHO European Region. *The Lancet Regional Health-Europe*. 2021 Sep 15:100225. doi: 10.1016/j.lanepe.2021.100225.

Birch JM, Critchlow N, Calman L, Petty R, Rosenberg G, **Rumgay H**, Vohra J. The Frequency and Content of Discussions About Alcohol Use in Primary Care and Application of the Chief Medical Officer's Low-Risk Drinking Guidelines: A Cross-Sectional Survey of General Practitioners and Practice Nurses in the UK. *Alcohol and Alcoholism*. 2021 Jun 29;56(4):433-442. doi: 10.1093/alcalc/agaa120.

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Rumgay H, Ryan M, Smith N, Brown K. Excess body weight as a risk factor for skin cancer: a meta-analysis. Submitted.

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Ferrari P, **Rumgay H**, Weiderpass E, Soerjomataram I. "Alcohol and Cancer: The Epidemiological Evidence" in Alcoholism and Alcohol-related disorders, edited by Mueller S and Heilig M. Submitted.

P

PhD Portfolio

PhD candidate	Harriet Rumgay		
PhD Period	2018–2022		
Erasmus MC department	Public Health		
Promotor	Professor Dr. Valery E.P.P. Lemmens		
Co-promotor	Dr. Isabelle Soerjomataram		
		Year	**Workload (ECTS)**
Courses and workshops			
Erasmus MC			
Introduction to Global Public Health		2021	0.7
Methods of Public Health Research		2021	0.7
Fundamentals of Medical Decision Making		2021	0.7
Social Epidemiology		2021	0.7
Scientific Integrity		2022	0.3
IARC			
GICR masterclass courses: Quality Control in Cancer Registration		2018	0.2
Introduction to Cancer Epidemiology		2019	2.9
Implementing Cancer Prevention and Early Detection		2019	1.5
SURVMARK coding and classifications workshop		2019	0.2
Library use, PubMed, systematic review, networking		2019	0.4
Statistics training: Modelling the effect of variables, Linear regression, logistic regression, confidence intervals, variance and covariance		2018–2019	0.2
ECSA career and training workshops		2020–2022	0.2
Science Communication		2022	0.3
Other			
WEON conference, pre-conference course: Economic evaluation		2019	0.2
Presentations			
Oral presentations			
Public Health England Cancer Services, Data and Outcomes Conference, Manchester		2018	0.5
IARC Early Career Scientific Week, online		2021	0.5
WHO/Europe NCD Office Seminar Series for Early Career Researchers, online		2021	0.5
European Public Health Conference, online		2021	0.5
IARC Cancer Surveillance Branch Scientific Review, online		2022	0.5
IARC Cancer Surveillance Branch meetings, Lyon & online		2018–2022	1.2

Poster presentations		
Public Health England Cancer Services, Data and Outcomes Conference, Manchester	2018	0.5
WEON conference, Groningen	2019	0.5
IARC ECSA Scientific Day, Lyon	2019	0.5
NCI Annual Symposium on Global Cancer Research (2 posters), online	2021	1.0

Communication		
Media interviews (incl. Sky News, The Guardian, BBC Mundo, Radio Canada, Medscape, NPR, Domingo Espetacular)	2021–2022	2.1
Podcast recordings (The Lancet Oncology, The Institute for Alcohol Studies)	2021	0.6
Developing infographics and YouTube videos	2020–2021	1.2
Managing Global Cancer Observatory Twitter account	2020–2022	2.9

Conferences		
IARC Early Career Scientific Day, Lyon	2019	0.3
WEON conference, Groningen	2019	0.6
NCI 9th Annual Symposium on Global Cancer Research, online	2021	0.3
IARC Early Career Scientific Week, online	2021	0.3
Symposium 10 ans Prévention Cancer Environnement, online	2021	0.3
Early Career Alcohol Research Symposium, online	2021	0.6
Global Alcohol Policy Alliance Virtual Event, online	2021	0.4
IACR 2021 Scientific Conference, online	2021	0.2
European Public Health Conference, online	2021	0.9
NCI 10th Annual Symposium on Global Cancer Research, online	2022	0.3

Meetings, seminars, and webinars		
IARC Monograph meeting on shift work (IARC secretariat), Lyon	2019	2.0
IARC Cancer Surveillance Branch research meetings, Lyon & online	2018–2022	2.9
IARC Seminars, Lyon & online	2018–2022	2.2
Webinars on current topics in public health and cancer control, online	2018–2022	2.1

Peer-review activities		
International Journal of Hygiene and Environmental Health, Lung Cancer, International Journal of Cancer, Cancer Epidemiology, Scientific Reports	2018–2021	1.5

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I also wouldn't be in this position without the mentorship and friendship of Dr Katrina Brown. I remember Katrina suggesting that I look into doing a PhD during one of our career conversations and me taking a very short amount of time to say that it wasn't the path for me and that I would rather look for something else. Are you happy now, Katrina? Just kidding. But genuinely, you saw this path for me before I saw it for myself, and I am hugely grateful for the opportunities you gave to me while at CRUK which led me to this PhD at IARC.

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Compiling the articles in this thesis would not have been possible without the valuable input from my co-authors who I have had the privilege to collaborate with over the past few years. Thank you so much for your contributions and I hope we can work together in the future. Thank you also to my assessment committee for the time you have given to reviewing this thesis.

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And finally, to the family members lost to cancer and other causes along the way. I have dedicated my work to you since starting my studies at Imperial College London. This one's for you.

I'm sure it's no coincidence that the three people who believed I could do this PhD before I did are three brilliant, strong, smart women: Isabelle, Katrina, and Lesley. Perhaps behind every woman in science there is at least a trio of brilliant women encouraging them to achieve their potential.

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