Appendix

Methods used for estimating the number of alcohol-related cancer deaths and hospitalizations in Sweden

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1. Introduction

Alcohol consumption has been identified as causative for eight types of cancer: oral cancer, pharyngeal cancer, oesophageal cancer, stomach cancer, colorectal cancer, liver cancer, laryngeal cancer and breast cancer [1]. Recent studies have also have provided evidence that alcohol is possibly causative for pancreatic cancer and prostate cancer [2, 3].

2. Objective

The present study aims to estimate the burden of cancers (mortality and hospitalization) that are alcohol-attributable (AA) in Sweden in recent years.

3. Methods

Alcohol-related cancer deaths and cancer hospitalizations in Sweden were calculated using the steps described below. Each step was completed for six population subgroups, defined by gender (male, female) and age group (15 to 34, 35 to 64, 65 and older). We closely followed methods used in the WHO Global Burden of Disease study and gratefully acknowledge support and training in the latest methodology for this provided by Drs Jürgen Rehm and Kevin Shield (Centre for Addiction and Mental Health, Ontario, Canada). Minor variations from the standard methods are specified below.

3.1 Calculating total cancer mortality

Total cancer mortality for cancers which may be alcohol-related was identified by searching the Swedish Health and Welfare Database (accessed at http://www.socialstyrelsen.se/statistics/statisticaldatabase/causeofdeath). This database catalogues vital statistics in Sweden by calendar year and includes all those registered in Sweden at time of death. Persons who died on a temporary visit to Sweden, asylum seekers who had not obtained residence permits at the time of death, Swedes who have emigrated and stillborn births are not included. Alcohol-related cancers are identified by the use of ICD-10 codes, as shown in Table 1.

3.2 Calculating total cancer hospitalizations

The total number of inpatient hospitalizations for cancers which may be alcohol-related were requested and obtained from official Swedish National Board of Health and Welfare.

Counts were received by subgroup, year and four-digit ICD-10 code. Four-digit codes were rolled up to three-digit categories, as presented in Table 1.

Table 1: Three digit ICD-10 codes corresponding to alcohol-related cancers

Type of cancer	ICD-10 code
Oral	C00 to C09
Pharyngeal	C10 to C14
Oesophageal	C15
Stomach	C16
Liver	C22
Pancreatic	C25
Laryngeal	C32
Breast	C50
Prostate	C61

3.3 Estimating the distribution of alcohol consumption

Three pieces of information are needed to define drinking within a given population subgroup: the prevalence of lifetime abstainers, the prevalence of former drinkers and a continuous estimation of the average daily alcohol use among current drinkers. Following the methods used in WHO Global Burden of Disease study [4], lifetime abstainers are defined as those who have consumed no alcohol or less than one standard drink (SD) of alcohol in their lifetime but who have not done in the past year. Former drinkers are defined as those who have consumed alcohol within their lifetime but who have not consumed at least one SD of alcohol within the past year. Current drinkers are defined as those who have consumed at least one standard drink (SD) of alcohol in the past year.

The prevalence of abstainers and former drinkers was acquired for each population subgroup by Drs Mats Ramstedt and Thor Norstrom of CAN and the Karolinska Institutet. The data was collected within an EU project named Join Action on reducing Alcohol Related Harm (RARHA). The prevalence of current and binge drinkers was obtained using survey data from a national prospective study of substance use and harm in the general population (the NPSH). The distribution of current drinkers was calculated using the following multi-step process:

(i) Estimated per capita consumption for the Swedish population aged 15 and older was obtained from sales data (recorded consumption) and survey data (unrecorded consumption) and provided by the specialist Swedish research agency CAN.

(ii) Gender-specific per capita consumption was calculated using population weights and a defined gender consumption ratio from [4]

(iii) Gender- and age group-specific per capita consumption was calculated using population weights and a defined age-group consumption ratio from [4]

(iv) These subgroup-specific (by gender and age group) per capita consumption figures were used to define a continuous distribution of current drinkers, following the

methods proposed in [5]. The distribution is calculated using a one-parameter definition of the Gamma distribution, which requires as input only per capita consumption in a subgroup.

When estimating the distribution of alcohol consumption in each population sub-group we assumed a maximum level of consumption of 250g ethanol per day corresponding to the mean levels of consumption observed in street-involved groups of dependent drinkers in Canada (Stockwell et al, 2016). The standard WHO approach is to use a cut-off of 150g. Sensitivity analyses comparing the two assumptions showed there was a very small difference in final estimates of alcohol-attributable cancers. We selected 250g as reflecting evidence for the most appropriate upper level of alcohol consumption to assume in the general population.

3.4 Relative risk of cancer due to alcohol consumption

Cancer categories where alcohol consumption had a causal impact were identified via standardized methodology [6]. The relative risks (RRs) of cancers for former drinkers were obtained from World Health Organization methods [4] and a more recent study [3]. Relative risk functions for each type of cancer were based on the meta-analyses in [1] and obtained from Rehm et al., except for prostate cancer which was obtained from [3]. The functional forms of the cancer-specific relative risk functions are shown in Table 2.

Table 2: Functional forms of cancer- and gender-specific relative risk curves

Type of cancer	Gender	β_1	β_2	β_3	β_4
Oral	Both	0.0000000000	0.0270986007	-0.0000918620	0.0000000738
Pharyngeal	Both	0.0000000000	0.0270986007	-0.0000918620	0.0000000738
Oesophagus	Both	0.0000000000	0.0132063596	0.0000000000	-0.0000000415
Colorectal	Both	0.0000000000	0.0062790000	0.0000000000	0.0000000000
Liver	Both	0.0000000000	0.0074294915	-0.0000148593	0.0000000000
Laryngeal	Both	0.0000000000	0.0142200000	0.0000000000	-0.0000000730
Pancreatic	Both	0.0000000000	0.0000961884	-0.0000151899	0.0000000000
Prostate	Male	0.0000000000	0.0022000000	0.0000000000	0.0000000000
Breast	Male	0.0000000000	0.0000000000	0.0000000000	0.0000000000
	Female	0.0000000000	0.0087900000	0.0000000000	0.0000000000
Stomach	Male	Defined as step function: {=0 when 0<x<=36 {=1.20 when 36<x<=250			
	Female	Defined as step function: {=0 when 0<x<=36 {=3.23 when 36<x<=150			

All RR functions, except for stomach cancer and pancreatic cancer, are defined as third-order polynomials with coefficients in the table above, according to the formula

$$\ln RR = \beta_1 + \beta_2 x + \beta_3 x^2 + \beta_4 x^3$$

For example, the functional form for oral cancer is given by the following equation:

$$\ln RR_{oralcancer} = 0.0270986007\text{x} - 0.0000918620\text{x}^2 + 0.0000000738\text{x}^3$$

There is a different functional form for pancreatic cancer, which takes the following form:

$$\ln RR_{pancreaticcancer} = \beta_2\text{x}^2 + \beta_3(\ln(\text{x}))\text{x}^2.$$

3.5 Calculating alcohol-attributable fractions (AAFs)

Using the results from subsections 3.1 to 3.4, we were then able to calculated alcohol-attributable fractions for each type of cancer, for each of the six subgroups, for each calendar year. An AAF is the proportion of cancers for a given time period that would theoretically have not occurred in the absence of an exposure (in this case, the consumption of alcohol). It compares the observed prevalence of consumption with an alternate state wherein everyone in the population is at the theoretical minimum risk; with respect to alcohol use, this is a lifetime abstainer.

To calculate AAFs, we use the general formula for calculating population attributable fractions and apply certain alcohol-specific cut-offs, modified from [5]. This formula becomes:

$$AAF = \frac{P_f[RR_f - 1] + \int_0^{250} P(x)[RR(x) - 1]\,dx}{P_f[RR_f - 1] + \int_0^{250} P(x)[RR(x) - 1]\,dx + 1}$$

where P_f is the prevalence of former drinkers, $RR_f$is the relative risk of former drinkers, P(x) is the prevalence of drinkers at daily consumption level *x* and is calculating using the Gamma distribution, RR(x) is the disease-specific relative risk at daily consumption level *x* and 250g is an assumed maximum daily consumption level. This formula is a modification of that shown in [5] and the 250g is based on Canadian data regarding typical drinking levels of alcohol dependent drinkers.

3.6. Statistical analysis

We used R 3.3.1 to perform the data analysis to calculate AAFs for cancers. The R codes were originally written by Shield and Rehm for the GBD project. We revised the R codes to include the analysis on prostate cancer. We used SAS 9.3 to calculate the number of deaths and hospitalizations that are attributable to alcohol consumption by applying the estimates of AAFs for cancers.

References

1. Corrao G, Bagnardi V, Zambon A, La Vecchia C: **A meta-analysis of alcohol consumption and the risk of 15 diseases**. *Preventive medicine* 2004, **38**(5):613-619.
2. Bagnardi V, Rota M, Botteri E, Tramacere I, Islami F, Fedirko V, Scotti L, Jenab M, Turati F, Pasquali E *et al*: **Alcohol consumption and site-specific cancer risk: a comprehensive dose-response meta-analysis**. *Br J Cancer* 2015, **112**(3):580-593.
3. Zhao J, Stockwell T, Roemer A, Chikritzhs T: **Is alcohol consumption a risk factor for prostate cancer? A systematic review and meta-analysis.** in press.

4. World Health O: **Global status report on alcohol and health. Retreived from**. In. Geneva, Switzerland: WHO Press; 2011.
5. Kehoe T, Gmel G, Shield KD, Gmel G, Rehm J: **Determining the best population-level alcohol consumption model and its impact on estimates of alcohol-attributable harms**. *Population health metrics* 2012, **10**(1):1.
6. Rehm J, Baliunas D, Borges GLG, Graham K, Irving H, Kehoe T, Parry CD, Patra J, Popova S, Poznyak V *et al*: **The relation between different dimensions of alcohol consumption and burden of disease: an overview**. *Addiction* 2010, **105**(5):817-843.