Alcohol consumption and liver, pancreatic, head and neck cancers in Australia: Time-series analyses

JIANG, H., LIVINGSTON, M. & ROOM, R.
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Centre for Alcohol Policy Research
School of Psychology and Public Health

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Researcher affiliations

1. Heng (Jason) Jiang is a Research Fellow at the Centre for Alcohol Policy Research, La Trobe University.

2. Michael Livingston is a senior research fellow at the Centre for Alcohol Policy Research, La Trobe University.

3. Robin Room is Professor and Director of the Centre for Alcohol Policy Research, La Trobe University.

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Summary

This report examines the magnitude and distributions of the preventive effects from the reduction of population drinking on three types of cancer mortality across different gender and age groups in Australia between 1968 and 2011, controlling for the effects of smoking and health expenditure. The report extends our understanding of the role that alcohol plays with respect to liver, pancreatic, head and neck cancers in Australia at an aggregate level. Importantly, this report extends these findings by using time series method with an innovative lagged effects estimation and lag-length selection process. The report provides the first suggestive evidence that there could be significant preventive effects on liver, head and neck cancer deaths from reducing population drinking levels, particularly among men and older age groups.

Key findings

- Change in alcohol consumption per capita was significantly and positively associated with change in both male and female head and neck cancer mortality, particularly among males and females aged 50 and above.

- Change in alcohol consumption per capita was significantly and positively associated with change in male liver cancer mortality, particularly among males aged 50-69.

- No associations were found between alcohol consumption per capita and pancreatic cancer mortality.

- The results suggest that one litre decreases in annual alcohol consumption per capita were associated with reductions of 11.6 per cent in male and 7.3 per cent in female head and neck cancer mortality across a 20-year period.

- The results also suggest that one litre decreases in annual alcohol consumption per capita were associated with a reduction of male liver cancer mortality of 15.0 per cent across a 20-year period.

- In total, it is estimated from the analysis that about 6.5 per cent of male and 4.1 per cent of female head and neck cancer deaths were related to alcohol consumption in Australia between 1968 and 2011.

- Alcohol consumption was estimated to be responsible for 8.4 per cent of male liver cancer deaths in Australia in the last 50 years.

Introduction

Alcohol use and misuse can have numerous consequences for the health of the drinker. For example, a single occasion of heavy drinking can be associated with violence, traffic accidents and unintentional injuries; and long-term alcohol consumption can be associated with liver cirrhosis, mental disorders and cancers (Bagnardi et al., 2001a). There is significant individual-level evidence linking cancer mortality to alcohol consumption, particularly for liver, pancreatic, and head and neck cancers (oral cavity, pharynx and oesophagus) (Boffetta and Hashibe, 2006). But understanding whether or not mean population-level consumption is related to population-level cancer mortality is a crucial question for public health policy that is not answered by these individual-level studies. There is evidence for other conditions (for example liver disease) that changing per-capita consumption can affect mortality rates (Jiang et al., 2013), but there has been little research focussing on cancer.

Epidemiology of alcohol-related liver, pancreatic, head and neck cancers

Alcohol has been identified as a key factor responsible for increased risk of head and neck cancers in many countries, particularly in Europe (Bray et al., 2000); this causal relation has been noted since the 1950s (Haenel, 1989). The strength of association between alcohol and the various cancer types included in this heading are different, possibly due in part to the extent of physical contact between alcohol and the relevant tissue (Zeka et al., 2003). The concurrent effects of alcohol use and tobacco smoking were reported already in the 1970s, and the joint effect has become a paradigm of the interaction of two environmental factors in human carcinogenesis (Boffetta and Hashibe, 2006). Previous epidemiological studies have shown a consistent dose-response relation between alcohol consumption and the risk of head and neck cancer in non-smoking alcohol drinkers, but the results for different types of alcoholic beverages are inconsistent (Bosetti et al., 2002; Brennan and Boffetta, 2004).

A positive relationship between heavy alcohol consumption and risk of liver cancer or hepatocellular carcinoma (HCC) has been reported in a meta-analysis (Corrao et al., 2004), which reported that the heaviest drinkers (at least 100g pure alcohol per day) were 27 times as likely to have liver cancers. The relationship between alcoholic liver cirrhosis and the development of HCC has been widely discussed. Heavy alcohol consumption is a significant risk factor for cirrhosis, but HCC does not develop in all patients with liver cirrhosis because, once patients are confirmed as having cirrhosis or other liver conditions, they are likely to substantially decrease their alcohol consumption (La Vecchia, 2007). A Japanese study found that quitting or reducing heavy drinking can reduce the risk of primary liver cancer (Shimazu et al., 2012).

Although there is sufficient evidence on the causal links between alcohol consumption and liver, head and neck cancers, the link between alcohol consumption and pancreatic cancer is less clear (Pandeya et al., 2015). Epidemiological studies on alcohol and the risk of pancreatic cancer have been inconsistent, with different confounding variables presented in various investigations. No association between alcohol consumption and pancreatic cancer was reported by a meta-analysis of 17 studies (Bagnardi et al., 2001b). In contrast, one study suggests that in individuals who drink four or more standard drinks a day, the risk of pancreatic cancer is tripled (Zheng et al., 1993), while some other studies have found a negative association between alcohol and pancreatic cancer (Boffetta and Hashibe, 2006).

Reflecting the meta-analytic findings, burden of disease studies of alcohol's role as a risk factor attribute substantial portions of oral cavity and pharynx cancer deaths to alcohol, and some liver cancer deaths, but not pancreatic cancer deaths. A study of alcohol's role in the Australian burden of disease in 2010 postulated that 30 per cent of male and 8 per cent of female oral cavity and pharynx cancer deaths were alcohol-related, and attributed 15 per cent of male and 7 per cent of female liver cancer deaths to alcohol (Gao et al., 2014). Similarly, an Australian cancer epidemiology study suggested that alcohol was responsible for 38 per cent of male and 13 per cent of female oral cavity and pharynx cancer deaths, and 16 per cent of male and 5 per cent of female liver cancer deaths (Pandeya et al., 2015).

The literature discussed above is fundamentally based on prospective or case-control epidemiological studies, relying on comparisons of the morbidity or mortality experience of individuals over time. To our knowledge there has been no previous estimation of alcohol-attributable fractions for cancers based on historical aggregate data. That is what is undertaken in this report. As Norström and Skog have argued (2001), such aggregate-level analysis is a useful convergent-validity test of individual-level findings, and its findings also relate more directly to the population level at which public health policies to reduce harmful effects of alcohol primarily operate.

Aims

Although long-term alcohol use has widely been recognised as a risk factor for cancer, and the relationship has been widely addressed in individual epidemiological studies, associations at the aggregate level of alcohol consumption and cancer mortality have rarely been examined, or investigated among different sub-population groups. This study aims to examine the magnitude and distributions of the preventive effects from the reduction of population drinking on three types of cancer mortality across different gender and age groups in Australia between 1968 and 2011, controlling for the effects of smoking and health expenditure. Four research questions are addressed, with respect to cancer mortality:

1. Is there an association between per-capita alcohol consumption and age and gender-specific head and neck cancer?

2. Is there an association between per-capita alcohol consumption and age and gender-specific liver cancer?

3. Is there an association between per-capita alcohol consumption and age and gender-specific pancreatic cancer?

4. If there are associations between per-capita alcohol consumption and different types of cancer, what are the alcohol-attributable fractions for these diagnoses?

A key technical sub-question for all of these analyses is the appropriate specification of a lag structure. The effects of changes in population consumption on cancer mortality will not be fully seen in the year in which the change occurs. Previous research on liver cirrhosis estimated that around 20-30 per cent of the effect of a change in per-capita consumption on cirrhosis mortality was found within a year, with the remaining effects gradually declining over past twenty-year period (Holmes et al., 2012). As noted by Holmes et al. (2012), there have been no previous aggregate-level studies of cancer mortality to inform the specification of the appropriate lag structures, and thus we explore specific approaches of lag selection in this preliminary analysis.

Data and method

Data

A proxy for per-capita alcohol consumption was constructed using data on the sale of alcohol sourced from the Australian Bureau of Statistics (ABS). From 1960 to 2011, data on alcohol consumption per person aged 15 and over is taken from a recent synthesis of historical data (ABS, 2015), while data from earlier years (1940-1960) were extracted manually from the relevant yearbooks (for example the Commonwealth Bureau of Census and Statistics (1960)), and converted from gallons or proof gallons to litres of pure alcohol. This was then converted to litres of pure alcohol per resident aged 15 and older, using population data provided by the Australian Institute of Health and Welfare (AIHW) (AIHW, 2016).

Age and gender-specific cancer mortality data (rate per 100,000 inhabitants), including overall head and neck, liver and pancreatic cancers, from 1968 to 2011 were collected from the AIHW, based on the International Classification of Diseases 10th Revision codes (see Table 1 for more details). The death rates were age-standardised for men and women separately and expressed per 100,000 population, using indirect standardisation to the 2001 population age structure. Per capita tobacco consumption and per capita health expenditure in Australia at the same time period were collected from Cancer Council Victoria (Scollo and Winstanley, 2015) and the Organisation for Economic Co-operation and Development (OECD, 2016), respectively. These data were included in the model to control for the impacts of tobacco consumption and health funding on the three types of cancer mortality in Australia.

Table 1 Description of three types of cancer mortality data

NAME AND ICD-10 CODES	DESCRIPTION	TIME PERIOD
Head and neck cancer; C00–C14, C30–C32,	Malignant neoplasms of lip, oral cavity and pharynx Malignant neoplasm of nasal cavity and middle ear Malignant neoplasm of accessory sinuses Malignant neoplasm of larynx	1968-2011
Liver cancer; C22	Malignant neoplasm of liver and intrahepatic bile ducts	1968-2011
Pancreatic cancer; C25	Malignant neoplasm of pancreas	1968-2011

Since annual alcohol consumption data are not available for specific gender or age groups in Australia, and analyses in this report will be based on total level of alcohol consumption and age and gender-specific cancer mortalities.

Time series models

The autoregressive integrated moving average (ARIMA) modelling technique was employed to estimate the association between per-capita alcohol consumption and three types of cancer mortalities. ARIMA models require stationary time series to reduce the risk of obtaining a spurious relation between two series that have common trends (Ramstedt, 2001). The Augmented Dickey-Fuller (ADF) unit root test is commonly used for testing for stationarity (Dickey and Fuller, 1979). Furthermore, the error term (which includes explanatory variables not considered in the model) is allowed to have a temporal structure that is modelled and estimated in terms of autoregressive or

moving average parameters (Stickley et al., 2011). In most cases, a differencing of the time series is sufficient to eliminate non-stationarily (Norström, 2001). In this study, a semi-log ARIMA model was selected, as the risk for chronic diseases is a convex function of alcohol intake (Norström and Ramstedt, 2005). The final model can be written as follows:

$$\Delta LnM_t = \alpha + \beta \Delta WA_t + \mu \Delta C_{i,t} + \Delta LnE_t$$

where Δ is the differencing operator, LnM_t is the natural logarithm of mortality rates from cancer diseases in Australia (15+) per 100,000 inhabitants, WA_t is lag weighted per-capita alcohol consumption, $C_{i,t}$ are the control variables considered in the estimation, i is number of control variables, μ is the coefficient values of the control variables, E_t is the error term including other causal factors, and α is the constant. The key coefficient value β indicates the proportional change in cancer mortality rate associated with a one litre change in weighted per-capita consumption. Therefore, a coefficient value of β means that a one litre increase in alcohol consumption is associated with an increase in the rate of cancer mortality of about $\left(e^{\beta} - 1\right) \times 100$.

In this study, two control variables were included in the models: tobacco consumption and health expenditure per capita. Epidemiologists have found smoking is one of the major risk factors for pancreatic, liver and head and neck cancer diseases (Boffetta and Hashibe, 2006). Health funding is central to public health planning and clinical practice, and higher cancer incidences have been found to be associated with lower health expenditure, and higher health expenditure to be correlated with longer cancer survival rates (Evans and Pritchard, 2000). The model fit was evaluated with the aid of the Box-Ljung portmanteau test of the first 10 autocorrelations, $Q(10)$. The model structures used are reported below, alongside the output of the models.

Lag effect and lag weighted alcohol consumption

Previous epidemiological studies and meta-analysis suggest that, even where drinking has ceased, alcohol consumption in the past 15-20 years still contributes to risks of various cancer diseases, including head and neck, and liver cancers (Rehm et al., 2007; Marron et al., 2010; Heckley et al., 2011). These studies may suggest that 15-20 years lagged effects of alcohol consumption on head and neck and liver cancer. However, to the best of our knowledge, no specific lag structure or length has been discussed in previous aggregate analyses on alcohol and cancer mortalities (Holmes et al., 2012). In accordance with previous studies on alcohol as a risk factor for chronic diseases, such as liver cirrhosis (Ramstedt, 2001; Jiang et al., 2013), lag structures were applied in the time series models in this study in order to take into account not only present but also past drinking as potentially affecting the cancer mortality risk. Alternative truncations after a 15-year and after a 20-year lag were tested. Furthermore, a composite consumption measure was used that is a weighted sum of past and present observations based on the selected lag length. A geometrical lag scheme was used in the estimation with λ=0.8, as advocated by Norström and Skog (2001). This approach builds in the lagged effects of consumption, with higher weights placed on more recent years (shown in Figures 1 and 2) and these weights sum to 1 across the 15 or 20 year period.

Figure 1 Distribution of geometric lag effects of alcohol consumption in the past 20 years
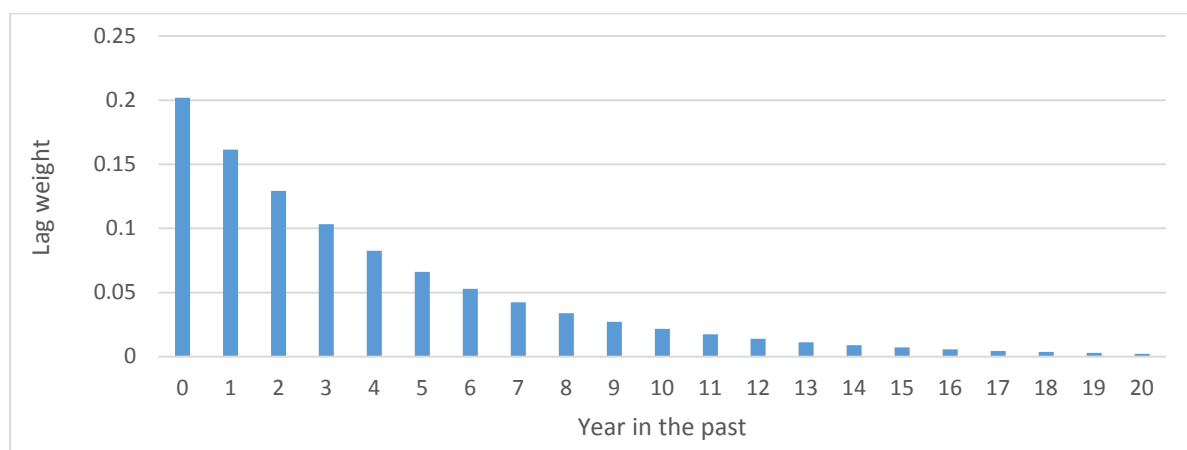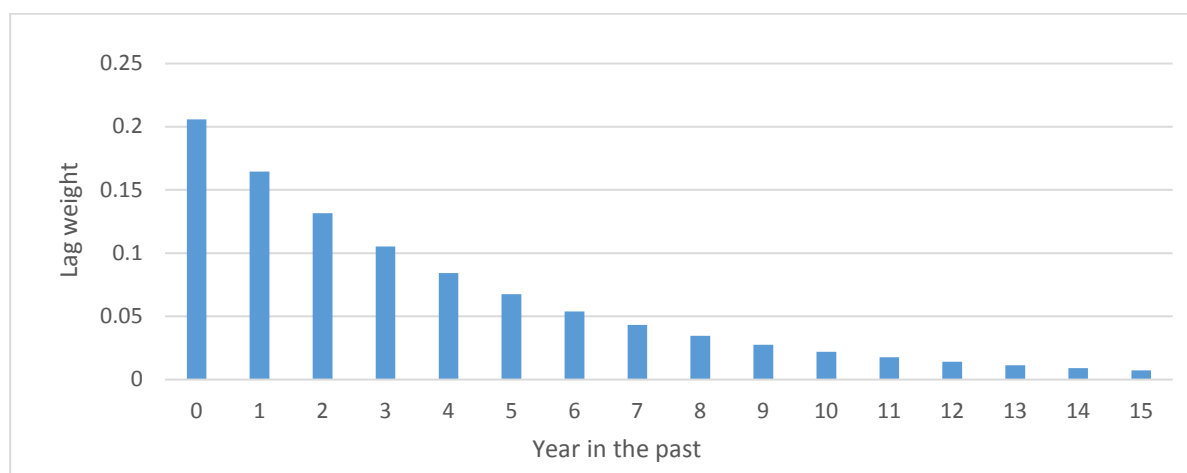

Figure 2 Distribution of geometric lag effects of alcohol consumption in the past 15 years

Given the uncertainty about the correct lag structure, we also conducted cross-correlation tests to explore the cross-correlation relationships between per capita alcohol consumption and rates of overall cancer mortality in Australia empirically. The results of the cross-correlation test between lag distributed alcohol and tobacco consumption and overall cancer mortality are presented in Table 2. The strongest positive correlation was found between overall cancer mortality and the drinking at the 10th year lag, and the results suggest that a 20 year lag on alcohol consumption could be applied in the cancer estimating models. The cross-correlation analyses also indicate that lag length for the associations between smoking and overall cancer mortality is 22 years and the highest lagged effects were at the 9th year.

Table 2 Cross-correlation test between overall cancer mortality and alcohol and tobacco consumption per capita

OVERALL CANCER MORTALITY AND ALCOHOL (-t)	T	LAGGED EFFECTS	OVERALL CANCER MORTALITY AND TOBACCO (-t)	t	LAGGED EFFECTS
. |*** |	0	0.3138	. |****** |	0	0.2914
. |**** |	1	0.3581	. |****** |	1	0.3358
. |**** |	2	0.4158	. |****** |	2	0.3731
. |***** |	3	0.4923	. |****** |	3	0.4070
. |****** |	4	0.5704	. |****** |	4	0.4813
. |*******|	5	0.6496	. |****** |	5	0.5172
. |*******|	6	0.7204	. |******* |	6	0.5665
. |********|	7	0.7762	. |******* |	7	0.5743
. |********|	8	0.8111	. |******* |	8	0.5817
. |********|	9	0.8306	. |*******|	9	0.6217
. |********|	10	0.8348	. |******* |	10	0.6211
. |********|	11	0.8224	. |****** |	11	0.6059
. |********|	12	0.7926	. |****** |	12	0.5691
. |********|	13	0.7460	. |****** |	13	0.5674
. |*******|	14	0.6911	. |***** |	14	0.5216
. |****** |	15	0.6190	. |***** |	15	0.4997
. |***** |	16	0.5224	. |**** |	16	0.4725
. |**** |	17	0.4181	. |**** |	17	0.3923
. |*** |	18	0.3184	. |*** |	18	0.3244
. |**. |	19	0.2041	. |**. |	19	0.2685
. |* . |	20	0.0758	. |**. |	20	0.1908
			. |* . |	21	0.1453
			. | . |	22	0.0831

The estimated cross-correlation lags based on the alcohol consumption and overall cancer mortality rates were then used to build lagged alcohol and tobacco consumption series in order to measure the relationship between alcohol consumption and three specific types of cancer mortalities. Furthermore, three different lagged alcohol consumption models -- 15 and 20 years geometric lagged alcohol consumption and cross-correlation lagged consumption models -- were thus developed and compared based on the model fits (R-squares and standard error of regression) to identify the best model for the final estimation.

Computing alcohol attributable fraction

The calculation method of alcohol attributable fraction (AAF) for cancer mortality based on aggregate data analysis has been elaborated in previous studies (for example Ramstedt (2008) and Jiang et al. (2015)), and the equation can be presented as:

$$AAF = \frac{\text{AACP} * \text{E}}{\text{AM}}$$

Where AACP is the average alcohol consumption level during the observation period; E is the estimated annual mortality rate responsible for per litre alcohol consumption; and AM is the average mortality rate during the observation period. AAF will be calculated if there are significant associations between alcohol consumption and selected cancer mortality rates.

Results

Unit root test

The ADF unit root test is employed to test the stationarity of the time series in this study (shown in Table 3). The unit root test results suggest that alcohol consumption, tobacco consumption, health expenditure, and all types of cancer mortalities are non-stationary in data at the untransformed level, and become stationary after first differencing at the significance level of 0.05.

Table 3 Unit root test for stationarity of time series

	AUGMENTED DICKEY-FULLER TEST ON LEVEL DATA		AUGMENTED DICKEY-FULLER TEST ON FIRST DIFFERENCED DATA	
	T-STATISTICS	P-VALUE	T-STATISTICS	P-VALUE
Alcohol consumption per capita	-2.47	0.13	-2.28	0.02
Tobacco consumption per capita	0.67	0.99	-4.08	0.00
Health expenditure per capita	1.14	1.00	-5.52	0.00
Male head and neck cancer mortality	-1.04	0.73	-10.36	0.00
Female head and neck cancer mortality	-0.47	0.51	-11.26	0.00
Overall head and neck cancer mortality	-0.93	0.77	-10.43	0.00
Male liver cancer mortality	0.88	0.99	-11.29	0.00
Female liver cancer mortality	1.52	1.00	-8.69	0.00
Overall liver cancer mortality	1.54	1.00	-10.30	0.00
Male pancreatic cancer mortality	-1.61	0.47	-9.97	0.00
Female pancreatic cancer mortality	0.52	0.82	-8.17	0.00
Overall pancreatic cancer mortality	-2.16	0.22	-9.00	0.00

Alcohol and head and neck cancer mortality

Trends in alcohol and tobacco consumption per capita (aged 15 and over), and age and gender-specific head and neck cancer mortality rates per 100,000 inhabitants, are shown in Figures 3 and 4. Mortality of head and neck cancers among those aged 70 and over, and 50-69-year-olds was higher than in younger age groups. Per capita alcohol consumption increased significantly between 1950 and 1970, and there was an increase in head and neck cancer mortality among 50-69-year-old men between 1968 and 1986. Male and female head and neck cancer mortality rates decreased after the 1980s among people aged 50 and over. Tobacco consumption increased between 1950 and 1966 and decreased

steadily after that. The head and neck mortality rates among the youngest male and female age groups (0-29 years old) were small, and these age groups were thus excluded from further analysis.

Figure 3 Trends of alcohol and tobacco consumption per capita (aged 15 and over) and male age-specific head and neck cancer mortality rates per 100,000 inhabitants
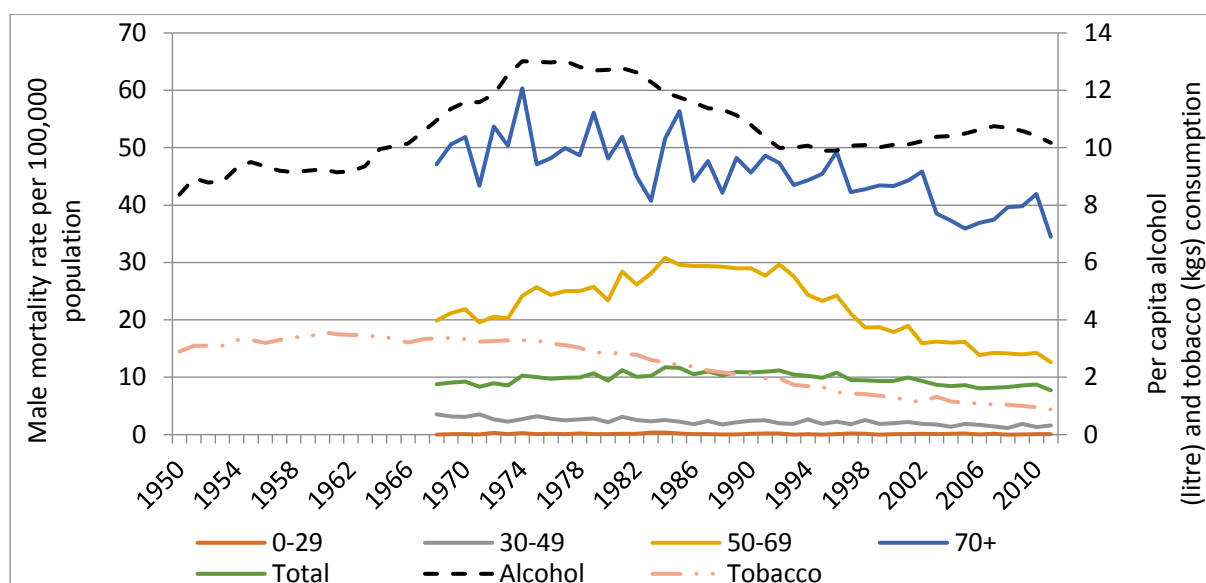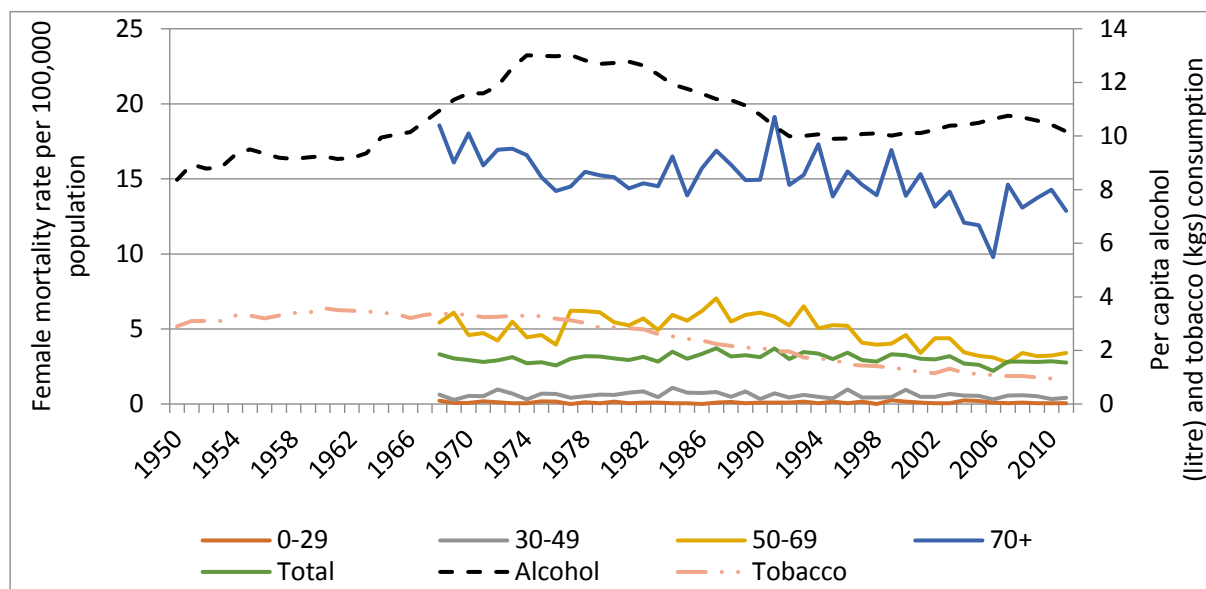

Figure 4 Trends of alcohol and tobacco consumption per capita (aged 15 and over) and female age-specific head and neck cancer mortality rate per 100,000 inhabitants

Three lagged alcohol consumption models were established, based on 15-year and 20-year geometric lagged weights and 20 years cross-correlation lagged weight. Comparing the three model outputs, presented in Table 4, the model with 20 years cross-correlation lagged alcohol consumption shows significant associations between alcohol consumption and head and neck mortality rates, while no significant associations were found in the two geometric lagged alcohol consumption models. The cross-correlation lagged consumption model achieved a higher R-square and lower standard error of

regression compared with two geometric lagged consumption models. Thus we chose the 20 years cross-correlation lagged alcohol consumption model to conduct age and gender-specific estimations.

Table 4 Semi-log ARIMA models on head and neck cancer mortality with different types of lag weighted alcohol consumption

	MALE ESTIMATE	S.E.	FEMALE ESTIMATE	S.E.	TOTAL ESTIMATE	S.E.
Model with 15 years geometric lagged alcohol consumption						
Alcohol	0.04	0.03	-0.02	0.03	0.02	0.03
Tobacco	0.05	0.05	0.03	0.02	0.04	0.02
Health spending	-0.03***	0.04	-0.02**	0.08	-0.03***	0.02
Constant	0.05**	0.02	0.05	0.03	0.05**	0.02
Model specification	*0,1,1*		*1,1,0*		*0,1,1*	
Q (lag 10)	*3.28, p=0.95*		*12.18, p=0.20*		*6. 407, p=0.70*	
R-square	*0.53*		*0.55*		*0.48*	
Model with 20 years geometric lagged alcohol consumption						
Alcohol	0.04	0.03	0.01	0.12	0.03	0.03
Tobacco	0.13	0.05	0.05	0.01	0.08	0.03
Health spending	-0.03***	0.05	-0.02*	0.10	-0.03***	0.05
Constant	0.02	0.02	0.01	0.03	0.03	0.02
Model specification	*0,1,1*		*1,1,0*		*0,1,1*	
Q (lag 10)	*3.01, p=0.96*		*11.71, p=0.23*		*6.94, p=0.64*	
R-square	*0.54*		*0.65*		*0.49*	
Model with 20 years cross-correlation lagged alcohol consumption						
Alcohol	0.11*	0.06	0.07*	0.09	0.09*	0.07
Tobacco	0.22*	0.38	0.13	0.60	0.18*	0.14
Health spending	-0.11*	0.06	-0.03*	0.06	-0.03*	0.07
Constant	0.02	0.33	-0.02	0.04	-0.02	0.18
Model specification	*0,1,1*		*0,1,1*		*1,1,1*	
Q (lag 10)	*5.57, p=0.78*		*11.41, p=0.25*		*4.95, p=0.76*	
R-square	*0.57*		*0.63*		*0.73*	

Note: ***p<0.001, **p<0.01, *p<0.05

The detailed age and gender-specific model outputs of the cross-correlation lagged alcohol consumption models are summarised in Table 5. The results suggest that a one litre decrease in per capita alcohol consumption can reduce male head and neck cancer mortality by 11.6 per cent [(e^-0.11-1)*100] and female by 7.3 per cent across a 20-year period, controlling for the trend of tobacco consumption and health expenditure per capita. Compared with other age groups, stronger and significant associations were found between per capita alcohol consumption and head and neck cancer mortality among both males and females aged 50 and above.

About 5.1 per cent of total head and neck cancer deaths were alcohol-related. According to these results, alcohol is responsible overall for 6.5 per cent of male and 4.1 per cent of female head and neck cancer mortality in Australia, controlling for the effects of smoking and health spending.

Table 5 Associations between total per-capita (15 and over) alcohol consumption and head and neck cancer mortality among different gender and age groups
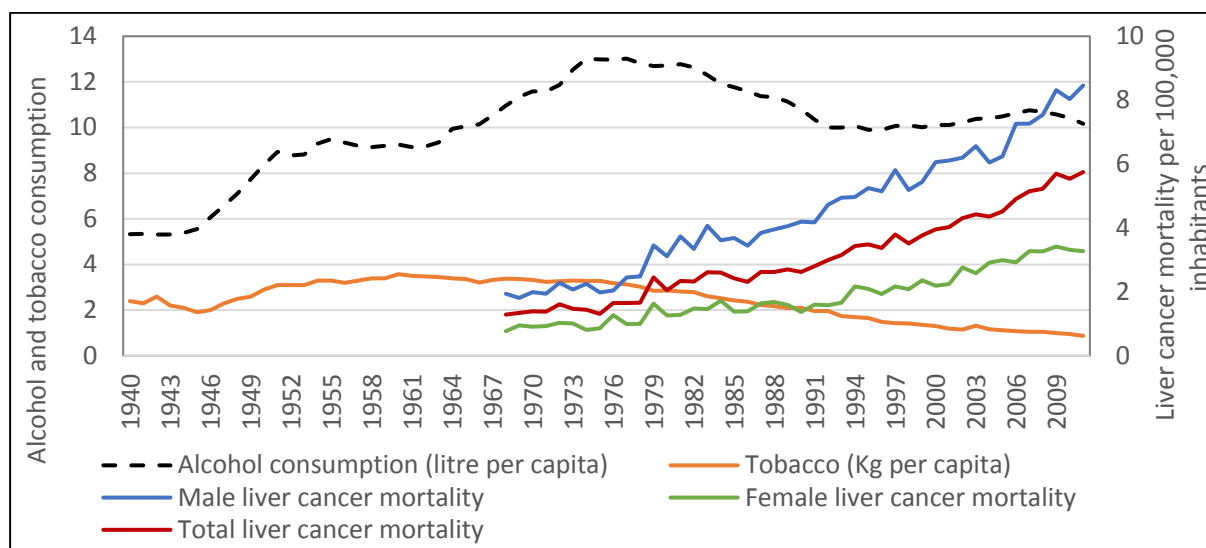
	ALCOHOL CONSUMPTION			
	ESTIMATE	S.E.	MODEL	Q (LAG 10)
Male				
30-49	-0.02	0.02	1,1,2	11.36, *p*=0.25
50-69	0.17**	0.08	0,1,1	10.90, *p*=0.28
70+	0.02(*)	0.10	0,1,1	13.81, *p*=0.13
Subtotal	0.11*	0.06	0,1,1	*5.57, p=0.78*
Female				
30-49	0.05	0.28	2,1,1	9.44, *p*=0.22
50-69	0.15**	0.14	0,1,1	11.7, *p*=0.23
70+	0.14(*)	0.15	0,1,1	3.75, *p*=0.93
subtotal	0.07*	0.09	0,1,1	*11.41, p=0.25*

Note: **p*<0.05, ***p*<0.01, ****p*<0.001, (*)*p*<0.10

Alcohol and liver cancer mortality

Figure 5 shows a dramatic increase in liver cancer mortality in Australia since 1968, from 2 to 5.5 deaths in 2011 per 100,000 population aged 15 and over. In contrast, in this period the trends of alcohol and tobacco consumption per capita are divergent from the trend of liver cancer mortality in Australia.

Figure 5 Trends in alcohol and tobacco consumption per capita (aged 15+), and in liver cancer mortality rate per 100,000 inhabitants

A cross-correlation weighted alcohol consumption model and two models with 15 years and 20 years geometric lagged alcohol consumption were estimated, controlling for the effects of smoking and of health spending; the estimates are presented in Table 6. A significant association was found only for females in the two geometric lagged alcohol distribution models. The model with cross-correlation lagged alcohol consumption suggests that alcohol consumption was only associated with male liver cancer mortality and provides a better R-square (0.56 vs 0.28) and model fit than the two geometric lagged models. Thus, we use the 20 years cross-correlation lag weighted model to estimate the age and gender-specific relation between alcohol consumption and liver cancer mortality.

Table 6 Semi-log ARIMA models on associations between liver cancer mortality and different types of lagged alcohol consumption

	MALE		FEMALE		TOTAL	
	ESTIMATE	S.E.	ESTIMATE	S.E.	ESTIMATE	S.E.
Model with 15 years geometric lagged alcohol consumption						
Alcohol	0.06	0.11	0.19*	0.08	0.08	0.09
Tobacco	-0.05	0.06	0.18*	0.06	-0.05	0.06
Health spending	-0.09	0.19	-0.13	0.07	0.01	0.13
Constant	0.01	0.04	-0.05	0.04	0.00	0.04
Model specification	*1,1,1*		*0,1,1*		*0,1,1*	
Q (lag 10)	*6.94, p=0.54*		*13.17, p=0.16*		*9.27, p=0.41*	
R-square	*0.37*		*0.51*		*0.28*	
Model with 20 years geometric lagged alcohol consumption						
Alcohol	0.11	0.13	0.22(*)	0.12	0.11	0.12
Tobacco	0.16	0.29	0.14	0.64	0.19	0.26
Health spending	-0.02	0.20	0.28	0.14	0.08	0.16
Constant	-0.01	0.05	-0.05	0.05	-0.01	0.04
Model specification	*1,1,0*		*0,1,1*		*0,1,1*	
Q (lag 10)	*9.92, p=0.36*		*12.65, p=0.18*		*10.26, p=0.33*	
R-square	*0.35*		*0.50*		*0.28*	
Model with 20 years cross-correlation lagged alcohol consumption						
Alcohol	0.14(*)	0.15	0.08	0.11	0.12	0.15
Tobacco	0.18	0.11	0.11	0.58	0.24	0.26
Health spending	-0.16	0.22	-0.10	0.11	-0.06	0.22
Constant	-0.02	0.05	0.03	0.04	0.01	0.05
Model specification	*1,1,1*		*0,1,1*		*1,1,0*	
Q (lag 10)	*7.48, p=0.49*		*10.99, p=0.28*		*3.99, p=0.912*	
R-square	*0.59*		*0.58*		*0.56*	

Note: *$p<0.05$, **$p<0.01$, ***$p<0.001$, (*)$p<0.10$

Age and gender-specific model outputs of the 20 years cross-correlation lagged alcohol consumption model are summarised in Table 7, showing a significant association between alcohol consumption per capita and male liver cancer mortality at the 0.10 significance level. The models suggest that a one litre decrease in per capita alcohol consumption will reduce male liver cancer mortality by 15 per cent across a 20-year period. However, no significant association was found between alcohol consumption and female liver cancer mortality. The age and gender-specific estimations suggest that there is a significant positive association between alcohol consumption and liver cancer mortality only among males aged 50-69 years, with no associations found among males aged 30-49 or 70 and over. According to these results, about 8.4 per cent of male liver cancer deaths were alcohol attributable in Australia during the period 1968-2011.

Table 7 Associations between liver cancer mortality and 20 years cross-correlation lagged alcohol consumption among different gender and age groups
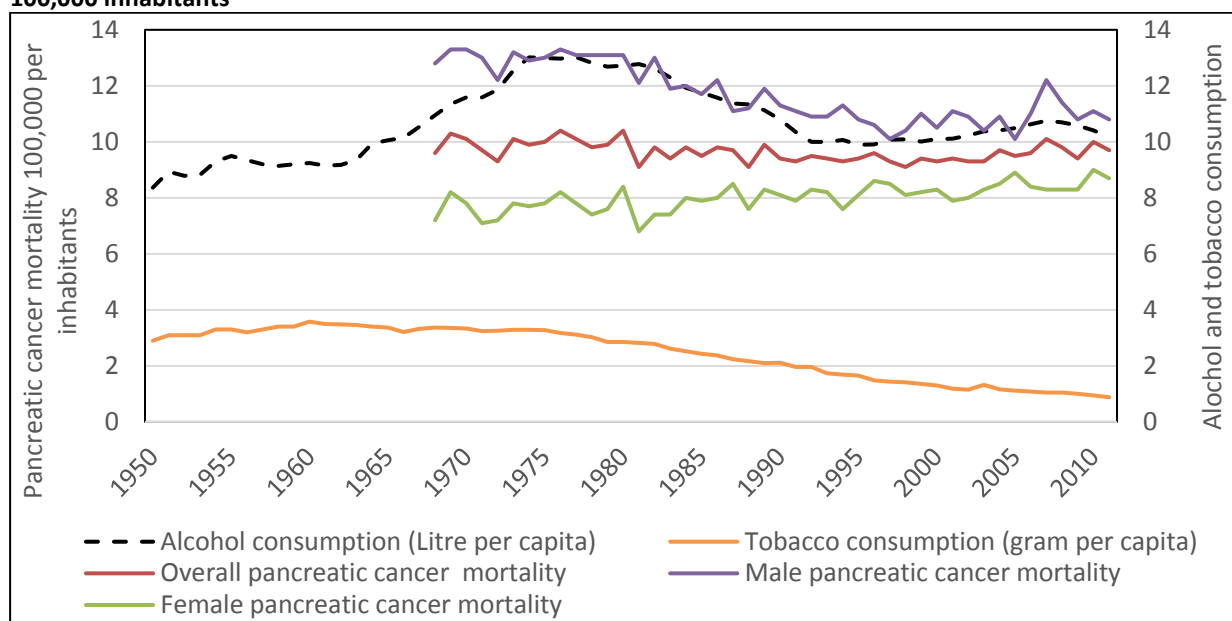
	ALCOHOL CONSUMPTION			
	ESTIMATE	S.E.	MODEL	Q (LAG 10)
Male				
30-49	0.24	0.96	1,1,1	7.99, *p*=0.43
50-69	0.25(*)	0.15	1,1,1	7.48, *p*=0.49
70+	0.05	0.24	1,1,1	10.73, *p*=0.22
Subtotal	0.14(*)	0.15	1,1,1	*7.48, p=0.49*
Female				
30-49	0.08	0.20	0,1,1	12.69, *p*=0.19
50-69	0.15	0.13	1,1,1	10.95, *p*=0.21
70+	0.06	0.47	3,1,1	13.49, *p*=0.10
Subtotal	0.08	0.11	0,1,1	10.99, *p*=0.28

Note: **p*<0.05, ***p*<0.01, ****p*<0.001, (*)*p*<0.10

Alcohol and pancreatic cancer mortality

Figure 6 shows trends in alcohol and tobacco consumption per capita (aged 15 and over), and pancreatic cancer mortality rate per 100,000 inhabitants. The total pancreatic cancer mortality remained at roughly the same level from 1968 to 2011, while female pancreatic cancer mortality increased slightly during this period. In contrast, male pancreatic cancer mortality seems to have broadly moved in line with the changes in per capita alcohol consumption.

Figure 6 Trends in alcohol and tobacco consumption per capita, and pancreatic cancer mortality rate per 100,000 inhabitants

Three lagged weighted alcohol consumption models were built: the 15 and 20 years geometric lag weighted models and the 20 years cross-correlation lag weighted computation model. The results of the three time series models are presented in Table 8. The results suggest that there are slightly positive but not statistically significant associations between pancreatic cancer mortality and per capita alcohol consumption in each of the three different lag structures.

Table 8 Semi-log ARIMA models on associations between liver cancer mortality and different types of lagged alcohol consumption

	MALE		FEMALE		TOTAL	
	ESTIMATE	S.E.	ESTIMATE	S.E.	ESTIMATE	S.E.
Model with 15 years geometric lagged alcohol consumption						
Alcohol	0.04	0.03	0.01	0.03	0.01	0.02
Tobacco	0.07	0.19	0.08	0.21	0.11	0.10
Health spending	-0.09	0.03	-0.02	0.03	-0.06	0.01
Constant	-0.02	0.01	-0.02	0.01	-0.02	0.01
Model specification	*0,1,1*		*0,1,1*		*1,1,1*	
Q (lag 10)	*4.95, p=0.84*		*8.39, p=0.50*		*8.78, p=0.36*	
R-square	*0.53*		*0.51*		*0.69*	
Model with 20 years geometric lagged alcohol consumption						
Alcohol	0.04	0.04	0.06	0.05	0.02	0.02
Tobacco	0.03	0.22	0.03	0.26	0.16	0.11
Health spending	-0.12*	0.05	-0.09	0.06	-0.04	0.03
Constant	0.01	0.02	0.03	0.02	0.01	0.01
Model specification	*0,1,1*		*0,1,1*		*1,1,1*	
Q (lag 10)	*5.24, p=0.81*		*9.38, p=0.40*		*9.15, p=0.33*	
R-square	*0.51*		*0.52*		*0.70*	
Model with 20 years cross-correlation lagged alcohol consumption						
Alcohol	0.02	0.01	0.01	0.05	0.01	0.01
Tobacco	0.18*	0.08	0.03	0.33	0.05	0.01
Health spending	-0.16**	0.04	-0.01	0.05	-0.09**	0.01
Constant	0.02	0.00	0.00	0.02	-0.01	0.00
Model specification	*0,1,1*		*0,1,1*		*1,1,1*	
Q (lag 10)	*4.44, p=0.88*		*6.68, p=0.67*		*7.90, p=0.44*	
R-square	*0.42*		*0.50*		*0.68*	

Note: *****$p<0.05$, ******$p<0.01$, *******$p<0.001$, ^(*)$p<0.10$

Discussion

The study provides the first evidence from an aggregate-level analysis that a decrease in population level drinking could lead to a reduction in head and neck cancer mortality in Australia, particularly among 50-69-year males and females. Decreasing alcohol consumption may also reduce male liver cancer mortality, particularly among males aged 50-69. Taken at face value, the results would suggest that between 1968 and 2011, about 6.5 per cent of male and 4.1 per cent of female head and neck cancer deaths and 8.4 per cent of male liver cancer deaths were alcohol-related.

The consistent results between our aggregate analyses and Australian epidemiological and burden of disease studies on alcohol and head and neck cancer (or oral cavity and pharynx cancer), suggest that reducing alcohol consumption at the population level could have higher preventive impacts on head and neck cancer mortality for males than for females. In substantial part, this no doubt reflects that males account for considerably more than females of the total alcohol consumption. Our analyses suggests that, with respect to liver cancer, reducing alcohol consumption per capita will only reduce male mortality significantly, with no effects on female liver cancer. These findings are consistent with the epidemiological literature, which suggests a higher alcohol-attributed fraction for male liver cancer mortality, but a significant effect also for females.

The associations between alcohol consumption per capita and liver, head and neck cancer mortality were found only among older age groups, particularly among those aged 50-69. This can be seen as

reflecting the long-term effects of alcohol consumption on the development of malignant neoplasms in the human body, although as noted more work is needed to specify the appropriate lag structures to reflect the time lag between changes in consumption, incidence of cancer and mortality. With people aged 70 and above, competing causes of death, such as from injuries from falls, may reduce the toll from these cancers (Taylor et al., 2010; Jiang et al., 2015).

We found no associations between alcohol consumption and pancreatic cancer mortality rates. This is in line with results in most previous clinical and epidemiology studies (Boffetta and Hashibe, 2006).

The Australian Guidelines to Reduce Health Risk from Drinking Alcohol released by the National Health and Medical Research Council in 2009 suggest that an adult should drink no more than two standard drinks on any day to reduce the lifetime risk of harm attributed to alcohol, such as cancer, cardiovascular diseases and mental disorders. If more of the population followed this drinking guideline, this would reduce the risk of developing alcohol-related cancers. Furthermore, public health policies on alcohol, such as reducing affordability by increasing alcohol prices, increasing control of alcohol availability, providing brief interventions for heavy drinkers to moderate their drinking, and health promotion for quitting long-term drinking, are among the means by which the toll of cancer diseases can be reduced in Australia.

Limitations

We use overall alcohol and tobacco consumption per person aged 15 and over in the estimation, since no age or gender-specific annual consumption per capita data is available in Australia. These could affect our estimates of how much gender or age-specific cancer mortality could be reduced by a decrease in overall alcohol consumption, especially where there have been changes in the relative contribution to total consumption of different age and sex sub-groups. Besides alcohol and tobacco consumption, there are many other factors which could affect rates of head and neck cancer, liver cancer, and pancreatic cancer, such as infectious diseases (for example HPV), poor oral and dental hygiene, environmental or occupational inhalants and so on, and these factors were not considered in our study. Nevertheless, the use of differenced data in the ARIMA models reduces the risk of this kind of confounding, unless change in the unmeasured variable is correlated with change in both per-capita alcohol consumption and mortality. The effects of the patterning of the drinking – on dimensions such as frequency of drinking occasions and whether there are heavy drinking bouts – or the magnitude of dose-response effects cannot, of course, be estimated from our aggregate analyses.

It should be noted that the analyses presented here use innovative lag-structure approaches to attempt to account for the temporal delays between alcohol consumption and cancer mortality. The results of the modelling were sensitive to the specification of these lag structures, meaning all relationships should be interpreted with caution. More research is needed to confirm the effects identified here.

Conclusion

Substantial epidemiological evidence has been provided in the last several decades to show that alcohol contributes to the development of a number of types of cancers, though many of the mechanisms underlying alcohol-related cancer development remain unclear. This study extends our understanding of the role that alcohol plays with respect to liver, pancreatic, head and neck cancers in Australia in the last 50 years from an aggregate perspective, using time series methods with an innovative lagged effects estimation and lag-length selection process. In large part, the findings from

these aggregate analyses are convergent with the results from individual-level longitudinal studies. The policy implications of the report are that there would be significant preventive effects on liver, head and neck cancer deaths, particularly among older age groups, from reducing population drinking levels.

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