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Pre-diagnosis alcohol intake and metachronous cancer risk in cancer survivors: a prospective cohort study

Running head: Long-term alcohol use and metachronous cancer risk

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Abbreviations: CI, confidence interval; HR, hazard ratio; ICD-O-3, International Classification of Diseases for Oncology; MCCS, Melbourne Collaborative Cohort Study; UADT, Upper aero-digestive tract

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Novelty and Impact

Alcohol consumption is a known cause of cancer, but its role in the etiology of second primary (metachronous) cancer is uncertain. Here, the authors studied the role of pre-diagnosis long-term alcohol intake in the etiology of metachronous cancer in nearly 10,000 cancer survivors and found positive associations for metachronous colorectal, upper aero-digestive tract and kidney cancer which were partly explained by effects of smoking. Findings have implications for preventing subsequent cancers in cancer survivors.

Abstract

Alcohol consumption is a known cause of cancer, but its role in the etiology of second primary (metachronous) cancer is uncertain. Associations between alcohol intake up until study enrollment (pre-diagnosis) and risk of metachronous cancer were examined in 9,435 participants in the Melbourne Collaborative Cohort Study who were diagnosed with their first invasive cancer after enrollment (1990-94). Follow-up was from date of first invasive cancer until diagnosis of metachronous cancer, death or censor date (February 2018), whichever came first. Alcohol intake for 10-year periods from age 20 until decade encompassing baseline using recalled beverage-specific frequency and quantity was used to calculate baseline and lifetime intakes, and group-based intake trajectories. We estimated hazard ratios (HR) and 95% confidence intervals (CI), adjusted for potential confounders. After a mean follow-up of 7 years, 1,512 metachronous cancers were identified. A 10 g/day increment in pre-diagnosis lifetime alcohol intake (HR=1.03, 95% CI:1.00-1.06;p_{value}=0.02) and an intake of ≥60 g/day (HR=1.32, 95% CI:1.01-1.73) were associated with increased metachronous cancer risk. We observed positive associations (per 10 g/day increment) for metachronous colorectal (HR=1.07, 95% CI:1.00-1.14), upper aero-digestive tract (UADT) (HR=1.16, 95% CI:1.00-1.34) and kidney cancer (HR=1.24, 95% CI:1.10-1.39). Although these findings were partly explained by effects of smoking, the association for kidney cancer remained unchanged when current smokers or obese individuals were excluded. Alcohol intake trajectories over the life course confirmed associations with metachronous cancer risk. Pre-diagnosis long-term alcohol intake, and particularly heavy drinking, may increase the risk of metachronous cancer, particularly of the colorectum, UADT and kidney.

Introduction

A combination of early detection, quality supportive care and effective treatment has led to enhanced survival following a diagnosis of cancer in recent decades.[1] As a result, ~5% of the population are estimated to be living with a diagnosis of cancer.[2, 3] Prolonged survival coupled with increasing cancer incidence have led to rising incidence of second primary cancers (hereafter referred to as metachronous cancers), but their etiology remains largely unknown.[4]

Metachronous cancer, which is a new primary cancer that is not a recurrence or a metastatic deposit of an initial lesion, may reflect late sequelae of treatment as well as effects of lifestyle-related, environmental and genetic factors and interactions between them.[4] Less than 10% of metachronous solid cancers in adults are caused by radiotherapy, the main treatment modality known to increase cancer risk, and chemotherapy (which could lead to leukemia) and targeted drug therapies (sometimes associated with squamous cell carcinomas of the skin) cause even fewer,[5] suggesting that the majority of second primary cancers result from other risk factors such as lifestyle or genetics.[6] Identifying modifiable risk factors for metachronous cancer could help target prevention and optimize surveillance whilst providing new insights into mechanisms involved in carcinogenesis.[6] Alcohol consumption could be an important risk factor as it is causally linked to several cancers.[7, 8] It caused an estimated 400,000 deaths from cancer worldwide (representing 4.2% of all cancer deaths) in 2016.[9]

In the present study, we aimed to estimate associations between pre-diagnosis alcohol use in cancer survivors and metachronous cancer risk, with emphasis on long-term intake.

Materials and Methods

Study Population

The Melbourne Collaborative Cohort Study (MCCS) is a prospective cohort study of 41,513 individuals (58.9% women; 99.2% aged 40-69 years at enrollment) recruited during 1990-94 in Melbourne, Australia.[10] A diagnosis of invasive cancer was identified for 11,309 participants during follow-up till February 2018 from whom we excluded individuals with an invasive cancer diagnosis at study enrollment (n=1,527), individuals who had died (n=79) or had a second cancer diagnosed on the date of first cancer diagnosis (n=79), and individuals missing covariate data (n=189), leaving 9,435 cases for this analysis (Supplementary Figure 1). The study protocol was approved by the Cancer Council Victoria Human Research Ethics Committee. Participants provided written informed consent.

Data Collection

Participants attended clinics at enrollment where demographic, lifestyle and dietary information (from a 121-item food frequency questionnaire)[11] were collected, and body weight and height were measured. Structured interview schedules were used to obtain information on lifestyle behaviors, including intake of alcoholic beverages and cigarette smoking.

Assessment of Alcohol Intake

Participants were asked at baseline if they had ever drunk at least 12 alcoholic drinks in a year. Those who had were then asked about their usual frequency of consumption and usual quantity consumed per drinking occasion for beer, wine and spirits separately during 10-year age periods commencing at age 20, up to the decade of their age at baseline attendance. Usual

alcohol intake within each age period in grams per day for each beverage type was calculated by multiplying beverage intake frequency by quantity and standard amount of alcohol per container using data from Australian food composition tables.[12] The alcohol intake for each age period in grams per day was calculated as the sum of intake from the three beverage types. The baseline alcohol intake in grams per day was defined as intake for the age period encompassing enrollment. Beverage-specific total intakes within age periods were summed to obtain total lifetime intakes in grams. The average lifetime alcohol intake in grams per day was derived by dividing the total lifetime intake by the total number of days within the age intervals up to enrollment.

Ascertainment of Cancers and Deaths

Cancers and vital status were ascertained through the Victorian Cancer Registry, the Australian Cancer Database, the Victorian Registry of Births, Deaths and Marriages and the National Death Index. Incident diagnosis of cancer and deaths are identified by at least annual record linkage to the Victorian Cancer Registry and the Victorian Registry of Births, Deaths and Marriages, both of which are considered complete. Notification to the Victorian Cancer Registry of all cancers diagnosed in Victoria is mandated by legislation since 1981. These linkages are complemented by at least 2-yearly record linkage to the National Death Index and the Australian Cancer Database to capture cancers and deaths for participants who may have moved interstate. The follow-up ended on the day of the most recent complete cancer data linkage. Participants are also sent reminders to contact the study coordinator to update contact information and usually self-report when they have left Australia. Second primary invasive cancer diagnoses were defined as *metachronous cancers* and coded following the 3rd Revision of the International Classification of Diseases for Oncology (ICD-O-3). Metachronous cancers of the oral cavity, pharynx, larynx and esophagus (collectively

referred to as upper aero-digestive tract [UADT] cancer) (codes C01–C06, C09–C10, C13–C15, C32), breast (code C50) and colorectum (codes C180, C182-189, C199, C209) were considered *alcohol-related metachronous cancer* (liver cancers were rare, n=14).[7] Ascertainment of metachronous cancer followed the common set of rules proposed by the International Agency for Research on Cancer.[13]

Statistical Analysis

Cox regression, with time since diagnosis of the first cancer as the time axis,[14] was used to estimate hazard ratios (HR) and 95% confidence intervals (CI) for metachronous cancer incidence. Analysis time continued until diagnosis of metachronous cancer, death, date of leaving Australia or 28 February 2018, whichever came first. Baseline and lifetime alcohol intakes were modelled as continuous (per 10 g/day increment in intake) and categorical variables (abstainer, >0–19, 20-39, 40-59, ≥60 g/day). A causal diagram (directed acyclic graph) guided the inclusion of confounding variables in multivariable models. All models were adjusted for age at diagnosis of first cancer, sex and cigarette smoking status (never, former, current smokers),[15] and were stratified by birth cohort (year of birth <1925, 5-year categories from 1925 to 1955) and country of birth (Italy/Greece, Australia/New Zealand/United Kingdom). Models estimating HRs for baseline alcohol intake (continuous) were fit with an additional binary variable indicating former drinkers at baseline. We also performed an analysis for categories of baseline alcohol intake separating former drinkers from baseline non-drinkers. To account for the potential impact of death as a competing risk, we used the Poisson regression method of Fine and Gray[16] to evaluate the ratio of subdistribution hazards. The cumulative incidence of metachronous cancer was estimated, and trends over time were evaluated in competing-risk models,[16] with adjustment for the

effects of age at first cancer diagnosis, sex, country of birth, cigarette smoking and lifetime alcohol intake when appropriate.

To examine associations for alcohol intake trajectories, we used a semiparametric group-based trajectory model[17, 18] to identify latent homogeneity in participants' intake trajectories across age decades. This model is an application of finite mixture modelling which assumes the population is composed of a mixture of groups following homogenous developmental courses.[17] Longitudinal alcohol intake data were fitted as a mixture of several latent trajectories in a censored normal model, allowing for no intake and high intake (capped at 100 g/day) limits, with a polynomial function for age.[18] We used the Bayesian Information Criterion and the log Bayes factor to select optimal shapes and number of trajectory groups through a two-stage approach.[17] First, the number of groups was determined by comparing up to 6 groups, assuming all trajectory groups were cubic functions of age. Here, the model using 4 groups was found to be optimal. Second, the preferred order of the polynomial (i.e. quadratic or cubic) for each trajectory was determined, with the model assuming quadratic patterns for all groups demonstrated to have the best fit. Participants were assigned to the group for which their posterior predicted probability calculated from the final model was largest. We evaluated the adequacy of the final model using the following recommended diagnostic measures: average posterior probability of assignment for each group of 0.7 or higher; odds of correct classification of 5.0 or higher; and the proportion of a sample assigned to a certain group close to the proportion estimated from the model.[17] Alcohol intake reported for each age decade was considered as intake for the midpoint of that decade. Having alcohol intake data from at least three time points was a requirement for inclusion. We estimated HRs and 95% CIs for metachronous cancer incidence for trajectory groups using Cox regression.[14]

To test for heterogeneity in the HRs across groups of metachronous cancer (alcohol-related *versus* other; across 10 most common solid cancers), Cox regression models were fit

using a competing risks method,[19] treating death as a competing risk. Dose-response relations between lifetime alcohol intake (continuous) and metachronous cancer incidence were examined using restricted cubic splines (3 knots).[20] We fit *a priori*-defined interaction terms to test for effect modification by sex, smoking and type of first cancer (alcohol-related, other and smoking-related, other). We also assessed associations by follow-up time since first cancer (<5 and ≥5 years) to examine the possible impact of survival. Nested models were compared using the likelihood ratio test.

Sensitivity analyses were performed: (i) excluding 204 second primary cancers diagnosed <6 months after the first cancer and (ii) excluding 15 second primary cancers that had an identical ICD-O-3 topology to the first cancer, from the definition of metachronous cancer; (iii) excluding 125 participants diagnosed with their first cancer <6 months after baseline; (iv) excluding 1,687 participants diagnosed with their first cancer >20 years after baseline and (v) excluding 6,096 participants diagnosed with their first cancer >10 years after baseline, to assess possible impact of exposure misclassification; and (vi) further adjusting models for highest level of education (primary school, some high/technical school, completed high/technical school, completed tertiary degree/diploma), socioeconomic status (deciles of the Socio-Economic Indexes For Areas (SEIFA) based on residential postcodes), first-degree family history of cancer (yes, no), body mass index (continuous), physical activity (none, low, moderate, high), red meat intake (quartiles), energy from food not including alcoholic beverages (continuous), dietary fiber intake (continuous) and dietary folate intake (continuous) and (vii) excluding current smokers and obese individuals (as relevant), to limit further the possibility of residual confounding.

Each model was examined for outliers and influential points. Tests based on Schoenfeld residuals showed no evidence that proportional hazard assumptions were violated. All

statistical tests were two-sided. All statistical analyses were performed using Stata 16.1 (StataCorp, College Station, TX).

Results

Characteristics of participants are given in Table 1. For the 9,435 participants (4,605 women, 4,830 men) who were diagnosed with a first primary cancer, the mean age at the diagnosis of their first cancer was 70.4 years (standard deviation, 9.4). By the end of follow-up (mean, 7.0 years; median, 5.2 years), 1,512 incident cases of metachronous cancer were ascertained (660 women, 852 men), including 441 (29.1%) alcohol-related metachronous cancers. There were 3,596 deaths (2,142 due to cancer) by the end of follow-up.

Cumulative incidence of metachronous cancer and competing mortality. The cumulative incidence of metachronous cancer was higher in men than women (16% compared with 13% at 10 years post-diagnosis) (subdistribution HR = 1.22, 95% CI: 1.09-1.36, for men compared with women) (Figure 1A) while it did not differ appreciably by categories of age at diagnosis of first cancer (p_{trend} across age groups = 0.78) (Figure 1B) or lifetime alcohol intake (p_{trend} across intake categories = 0.20) (Figure 1D). The cumulative incidence was lower for individuals diagnosed with a first primary cancer in the period after 2005 (~13% at 10 years post-diagnosis) compared with those diagnosed before 1999 (>15% at 10 years post-diagnosis) (sub-distribution HR = 0.74, 95% CI: 0.65-0.85; p_{trend} across periods < 0.001) (Figure 1C). First cancer-specific mortality rose steeply with time since diagnosis of first cancer, before plateauing around 5 years post-diagnosis (Figure 1E), while mortality due to causes other than cancer was much lower and followed a gradual rise (Supplementary Figure 2). Cancer-specific mortality following metachronous cancer at 5 years post-diagnosis was approximately twice that for the first cancer (Figure 1F).

Alcohol intake and metachronous cancer incidence. Lifetime alcohol intake was associated with increased incidence of metachronous cancer (HR = 1.03 for a 10 g/day increment, 95% CI: 1.00-1.06) (Table 2). The HR for an average lifetime intake of ≥60 g/day compared with lifetime abstention was 1.32 (95% CI: 1.01-1.73; p_{trend} = 0.06). The respective HRs for lifetime intake for men and women were 1.04 (95% CI: 1.01-1.07) and 0.99 (95% CI: 0.92-1.08) for a 10 g/day increment; $p_{interaction}$ = 0.30. The strength of these associations was weaker for baseline intake compared with lifetime intake (Table 2); the HR for former drinkers compared with lifetime abstainers at baseline was 1.08 (95% CI: 0.90-1.31). In analyses of any metachronous cancer incidence allowing for death as a competing risk, the subdistribution HR for metachronous cancer for a 10 g/day increment in lifetime alcohol intake was attenuated (HR = 1.02, 95% CI: 0.99-1.05). There was little evidence that the estimated HR for alcohol (continuous) was higher for alcohol-related metachronous cancer compared with other cancers ($p_{homogeneity}$ = 0.42) (Table 2).

Alcohol intake trajectories and metachronous cancer incidence. Four patterns of alcohol intake over time, reflecting *low*, *light*, *moderate* and *heavy* intakes, were identified irrespective of sex, age at study enrollment and birth cohort (Supplementary Figure 3). Model adequacy diagnostics are presented in Supplementary Table 1. The female heavy drinkers drank relatively less alcohol than their male counterparts and the *low* intake trajectory included lifetime abstainers (Supplementary Figure 3). *Heavy* intake, compared with *low* intake, was associated with increased incidence of any (HR = 1.32, 95% CI: 1.02-1.71) and alcohol-related metachronous cancer (HR = 1.74, 95% CI: 1.08-2.81) while the evidence was suggestive that the association with other metachronous cancer was not dose-related ($p_{homogeneity}$ = 0.01) (Figure 2).

Alcohol intake and metachronous cancer incidence by metachronous cancer site. A 10 g/day increment in lifetime alcohol intake was associated with increased incidence of metachronous colorectal (HR = 1.07, 95% CI: 1.00-1.14; n = 242), kidney (HR = 1.24, 95% CI: 1.10-1.39; n = 35) and UADT (HR = 1.16, 95% CI: 1.00-1.34; n = 32) cancer; the HR for metachronous lung cancer was 1.08 (95% CI: 0.99-1.18; n = 112) (Table 2). Metachronous breast cancer incidence was not associated with lifetime alcohol intake (HR = 0.90 for a 10 g/day increment, 95% CI: 0.75-1.07; n = 167) (Table 2). Dose-response relations between lifetime alcohol intake and metachronous cancer incidence are shown in Figure 3. The only positive dose-dependent association evident for baseline alcohol intake with the most frequently observed metachronous cancers was with metachronous kidney cancer (HR = 1.13 for a 10 g/day increment, 95% CI: 1.01-1.28) (Table 2). In a stratified analysis, an association between lifetime alcohol intake and metachronous kidney cancer was evident for individuals with either alcohol-related or other first cancer (HR = 1.07, 95% CI: 1.04-1.10 and HR = 1.02, 95% CI: 1.00-1.04, respectively, for a 10 g/day increment).

Stratified analyses. There was evidence for an interaction between baseline alcohol intake and cigarette smoking ($p_{interaction} = 0.02$); the HR for metachronous cancer for current smokers was 1.09 (95% CI: 1.03-1.14) for a 10 g/day increment but a null association was seen in non-smokers (Table 3). Similar positive associations with baseline intake were observed for current smokers who smoked <20 or ≥20 cigarettes/day ($p_{interaction} = 0.09$ when using smoking intensity) (Table 3). The corresponding evidence for an interaction with smoking was weaker for lifetime alcohol intake ($p_{interaction} = 0.19$) (Table 3). In a sensitivity analysis excluding current smokers, HRs for any and alcohol-related metachronous cancer and for metachronous colorectal, lung and UADT cancer were attenuated; the positive association for metachronous

kidney cancer remained unchanged (Supplementary Table 2). The positive association for metachronous kidney cancer also remained unchanged when we excluded those with body mass index ≥30 kg/m^2 (results not shown). There was weak evidence that the association with a 10 g/day increment in lifetime alcohol intake was stronger during the first 5 years of follow-up ($p_{interaction}$ = 0.08) (Table 3).

Sensitivity analyses. Excluding second primary cancers diagnosed within six months of the first cancer or with an identical ICD-O-3 topology to the first one from the metachronous cancer definition; excluding participants diagnosed with their first cancer <6 months, >20 years or >10 years after baseline; or further adjusting the models for additional covariates, did not appreciably affect the HRs for metachronous cancer in relation to lifetime alcohol intake (Supplementary Table 3 and Supplementary Table 4).

Discussion

In this prospective cohort study, long-term pre-cancer alcohol intake was associated with increased risk of overall second primary cancer risk as well as increased risks of second primary colorectal, UADT and kidney cancers.

We observed a higher cumulative incidence of metachronous cancer in men compared with women in the present study, which is partially explained by their higher prevalence of unfavorable risk factors for cancer including smoking, alcohol intake and obesity in Australia.[3] Furthermore, the absence of an association with metachronous breast cancer in the present study potentially contributes to a HR that is close to null for the association between lifetime alcohol intake and metachronous cancer risk in women. One-fourth of the metachronous cancers seen in women were breast cancers. The 5-year second cancer-specific mortality was twice as high as the 5-year first cancer-specific mortality in our study, as has

been observed in the general population.[21] We have previously shown lower mortality with low alcohol intake and elevated mortality at higher intake levels for both men and women in the MCCS.[22] Our observation of a lower cumulative incidence of subsequent cancer in more recently diagnosed first cancer patients probably reflects recent successes of pre-cancer screening,[23] advanced testing[24] and targeted treatment,[25] as well as a relatively shorter period of follow-up.

Pre-diagnosis smoking[26] and body fatness[26-28] are known risk factors for metachronous cancer. The role of alcohol has not been studied broadly: it has been shown to increase slightly the risk of metachronous cancer in women with keratinocyte carcinoma in the Nurses' Health Study[29] and in patients with primary UADT cancer in a meta-analysis of 8 cohort and 11 case–control studies;[30] alcohol intake did not increase metachronous colorectal cancer risk in individuals with colorectal cancer in the Colon Cancer Family Registry;[31] and findings for patients with primary breast cancer were inconclusive.[32] The International Agency for Research on Cancer classified acetaldehyde, the first and most toxic metabolite of ethanol found in alcoholic beverages and produced in the liver, as carcinogenic to humans.[33] Although the precise mechanisms leading to alcohol-associated carcinogenesis are far from established, adverse effects on apoptosis,[34] the generation of oxygen free radicals,[35] and direct cellular injury and gene mutation[36] are postulated. We have previously shown evidence[37-39] suggestive of early initiation, during early adulthood, and chronic progression of carcinogenesis linked to alcohol and its metabolites.[40] The associations of metachronous cancer with alcohol using intake trajectories based on reported intake from age 20 to study enrollment and with lifetime alcohol intake compared with those observed for baseline intake in the present study corroborate findings that alcohol-induced carcinogenesis starts early in adult life. Nonetheless, our findings are partly due to effects of smoking and are suggestive of

a limited role for alcohol as an independent risk factor for metachronous cancer in the absence of smoking, consistent with existing evidence for cancer risk.[41]

We found a higher risk of metachronous kidney cancer for heavy drinkers compared with low drinkers. Kidney cancer incidence is rapidly increasing in Australia, Europe and North America.[1, 3] While its etiology is largely unknown,[42] tobacco smoking[43] and body fatness[44] are known to increase risk. Our result for metachronous kidney cancer is different to the current evidence on alcohol intake and first primary kidney cancer risk. The World Cancer Research Fund and American Institute for Cancer Research reported a lower risk of first primary kidney cancer for alcohol intakes up to 30 g/day but had insufficient evidence to draw conclusions for intakes higher than that.[8] Any plausible biological mechanisms as to why alcohol consumption may decrease risk of primary kidney cancer, however, are only speculative.[8, 42, 45] Although we found evidence of alcohol intake preceding first cancer as a potential risk factor for metachronous kidney cancer, independent of pre-diagnosis smoking and body fatness, we acknowledge that our finding could be due to chance.

The strengths of our study include the prospective design, comprehensive assessment of alcohol intake over the life course from age 20 until baseline, assessment of other health risk factors that preceded any cancer diagnosis, and the complete long-term follow-up with over 1,500 incident metachronous cancers which enabled the examination of associations for subgroups and common tumor sites.

Our study has several limitations. First, there was some chance of metachronous cancer misclassification. The Victorian Cancer Registry differentiates metachronous lesions from recurrences and metastatic deposits,[13] and in sensitivity analyses excluding second primary cancers diagnosed within 6 months of the first cancer or with an identical ICD-O-3 topology as the first cancer (~1%) from the definition of metachronous cancer, the overall association remained similar. Second, common to many observational studies,[26-28] information about the

first cancer treatment could not be included; therefore, we could not evaluate treatment as an effect modifier. Treatment, however, cannot be a confounder as it cannot be a common cause of pre-diagnosis alcohol intake.[46] Third, the use of self-reported alcohol intake, exposure misclassification and unmeasured residual confounding, particularly due to smoking habits and potential collider-stratification bias[47] in spite of adjustment for additional factors including an aggregate family history variable, may have influenced estimates of association. Lifestyle behaviors including alcohol intake following first cancer diagnosis were not assessed mainly due to limited availability of longitudinal data on covariates. This highlights the need for further research addressing the effectiveness of limiting alcohol intake as a preventive strategy in this group. Since the process of carcinogenesis takes many years, it is important, nonetheless, to assess long-term pre-diagnosis measurements which more accurately characterize long-term exposure and are less influenced by reverse causality due to first cancer. We also did not have information on alcohol intake prior to age 20.

Pre-diagnosis long-term alcohol intake, and particularly heavy drinking, may increase the risk of metachronous cancer, particularly of the colorectum, UADT and kidney. Our findings reaffirm the importance of proactively minimizing excessive exposure to alcohol, and the need for such guidelines.[48] These findings require replication by other prospective studies and using data on post-diagnosis behaviors.

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Contributors
HJ and RJM had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. HJ, RJM, RLM and GGG conceived and designed the study. HJ and RJM extracted the data. HJ carried out the statistical analysis with support from RJM. HJ produced an initial draft of the manuscript and subsequent revisions to it. All the authors critically revised the manuscript for important intellectual content. All the authors approved the final version of the manuscript. GGG obtained funding. HJ, RJM and RLM were responsible for administrative, technical, and material support. RJM was responsible for study supervision. HJ and RJM are guarantors. The authors assume full responsibility for analyses and interpretation of these data. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

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Competing interests
All authors declare: no support from any organization for the submitted work; no financial relationships with any organizations that might have an interest in the submitted work; and no other relationships or activities that could appear to have influenced the submitted work.

Ethical approval
The MCCS study protocol was approved by the Cancer Council Victoria Human Research Ethics Committee. Participants gave written informed consent to participate and for investigators to obtain access to their medical records.

Data availability
Statistical code is available from the lead/corresponding author. The MCCS data can be made available on request to pedigree@cancervic.org.au.

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Figure legends

Figure 1. Cumulative incidence of metachronous cancer by sex (A), age at first cancer (B), period of diagnosis (C) and lifetime alcohol intake (D), and cancer-specific mortality following first (E) and second cancer (F).

Figure 2. Forest plots of adjusted hazard ratios (HR) and 95% confidence intervals (CI) for metachronous cancer according to alcohol intake pattern during lifetime.

Figure 3. Dose-response relations between lifetime alcohol intake and incidence of the most frequently observed metachronous cancers. UADT, upper aero-digestive tract; models for breast and prostate included only women and men, respectively. Dashed line, reference value (hazard ratio=1).

Table 1. Characteristics of participants diagnosed with a first primary cancer after enrollment in the Melbourne Collaborative Cohort Study

Characteristic	According to lifetime alcohol intake				All participants (N=9,435)
	Lifetime abstention (n=2,491)	>0–19 g/day (n=4,628)	20-39 g/day (n=1,410)	≥40 g/day (n=906)	
Age at recruitment (years), n (%)					
40-49	396 (15.9)	1,087 (23.5)	339 (24.0)	179 (19.8)	2,001 (21.2)
50-59	855 (34.3)	1,560 (33.7)	473 (33.6)	308 (34.0)	3,196 (33.9)
60-69	1,240 (49.8)	1,981 (42.8)	598 (42.4)	419 (46.2)	4,238 (44.9)
Mean (standard deviation)	58.7 (7.6)	57.1 (8.3)	56.9 (8.2)	57.8 (8.0)	57.5 (8.1)
Age at first primary cancer (years), n (%)					
<60	288 (11.6)	718 (15.5)	201 (14.3)	115 (12.7)	1,322 (14.0)
60-69	757 (30.4)	1,533 (33.6)	516 (36.6)	310 (34.2)	3,136 (33.2)
≥70	1,446 (58.0)	2,357 (50.9)	693 (49.1)	481 (53.1)	4,977 (52.8)
Mean (standard deviation)	71.6 (9.4)	70.0 (9.5)	69.7 (9.0)	70.6 (9.0)	70.4 (9.4)
Diagnosis period of first cancer, n (%)					
<1999	532 (21.4)	820 (17.7)	256 (18.1)	165 (18.2)	1,773 (18.8)
1999-2005	666 (26.7)	1,331 (28.8)	421 (29.9)	273 (30.1)	2,691 (28.5)
≥2006	1,293 (51.9)	2,477 (53.5)	733 (52.0)	468 (51.7)	4,971 (52.7)
Duration from enrollment to first primary diagnosis (years), n (%)					
<1	79 (3.2)	118 (2.6)	35 (2.5)	33 (3.6)	265 (2.8)
1-4	349 (14.0)	592 (12.8)	178 (12.6)	108 (11.9)	1,227 (13.0)
5-9	480 (19.3)	914 (19.7)	275 (19.5)	170 (18.8)	1,839 (19.5)
10-14	515 (20.7)	1,065 (23.0)	353 (25.0)	228 (25.2)	2,161 (22.9)
15-19	590 (23.7)	1,115 (24.1)	330 (23.4)	223 (24.6)	2,258 (23.9)
≥20	478 (19.2)	824 (17.8)	239 (17.0)	144 (15.9)	1,685 (17.9)
Mean (standard deviation)	12.9 (6.9)	12.9 (6.6)	12.8 (6.6)	12.8 (6.6)	12.9 (6.7)
Follow-up duration from first primary diagnosis (years), n (%)					
<1	464 (18.6)	738 (16.0)	245 (17.4)	198 (21.9)	1,645 (17.4)
1-4	765 (30.7)	1,480 (32.0)	446 (31.6)	295 (32.6)	2,986 (31.7)
5-9	568 (22.8)	1,025 (22.1)	313 (22.2)	198 (21.8)	2,104 (22.3)

10-14	331 (13.3)	715 (15.5)	226 (16.0)	126 (13.9)	1,398 (14.8)
15-19	219 (8.8)	423 (9.1)	116 (8.2)	63 (6.9)	821 (8.7)
≥20	144 (5.8)	247 (5.3)	64 (4.6)	26 (2.9)	481 (5.1)
Mean (standard deviation)	7.0 (6.5)	7.2 (6.4)	6.9 (6.2)	6.1 (5.8)	7.0 (6.3)
First primary cancer, n (%)					
Alcohol-related first primary cancer	950 (38.1)	1,493 (32.3)	329 (23.3)	198 (21.9)	2,970 (31.5)
Breast	538 (21.6)	761 (16.5)	110 (7.8)	25 (2.8)	1,434 (15.2)
Colorectum	361 (14.5)	631 (13.6)	186 (13.2)	145 (16.0)	1,323 (14.0)
Upper aero-digestive tract	51 (2.0)	101 (2.2)	33 (2.3)	28 (3.1)	213 (2.3)
Other first primary cancer	1,541 (61.9)	3,135 (67.7)	1,081 (76.7)	708 (78.1)	6,465 (68.5)
Prostate	260 (10.4)	883 (19.1)	432 (30.6)	301 (33.2)	1,876 (19.9)
Melanoma of skin	190 (7.6)	453 (9.8)	125 (8.9)	70 (7.7)	838 (8.9)
Sex, n (%)					
Male	684 (27.5)	2,204 (47.6)	1,108 (78.6)	834 (92.0)	4,830 (51.2)
Female	1,807 (72.5)	2,424 (52.4)	302 (21.4)	72 (8.0)	4,605 (48.8)
Country of birth, n (%)					
Australia/New Zealand/United Kingdom	1,770 (71.1)	3,927 (84.8)	1,073 (76.1)	625 (69.0)	7,395 (78.4)
Italy/Greece	721 (28.9)	701 (15.2)	337 (23.9)	281 (31.0)	2,040 (21.6)
Cigarette smoking, n (%)					
Never	1,869 (75.0)	2,455 (53.1)	462 (32.8)	175 (19.3)	4,961 (52.6)
Former	392 (15.8)	1,671 (36.1)	727 (51.5)	534 (59.0)	3,324 (35.2)
Current	230 (9.2)	502 (10.8)	221 (15.7)	197 (21.7)	1,150 (12.2)

Table 2. Hazard ratios (HR) and 95% confidence intervals (CI) for metachronous cancer incidence by alcohol intake

	Baseline alcohol intake					Lifetime alcohol intake				
	No.	**Events, n (%)**	**HR (95% CI)[a]**	***P* value[b]**	**$P_{homogeneity}$[c]**	**No.**	**Events, n (%)**	**HR (95% CI)[a]**	***P* value[b]**	**$P_{homogeneity}$[c]**
Any metachronous cancer										
Per 10 g/day increment	9,435	1,512 (100)	1.02 (0.99 to 1.04)	0.22		9,435	1,512 (100)	1.03 (1.00 to 1.06)	0.02	
Intake categories				0.55					0.06	
Abstention	3,507	528 (34.9)	1.00			2,491	363 (23.9)	1.00		
>0–19	3,813	625 (41.3)	1.00 (0.89 to 1.13)			4,628	745 (49.1)	1.03 (0.90 to 1.18)		
20-39	1,277	217 (14.4)	1.04 (0.88 to 1.23)			1,410	239 (15.7)	1.06 (0.89 to 1.27)		
40-59	450	72 (4.8)	1.00 (0.78 to 1.29)			564	96 (6.3)	1.12 (0.88 to 1.42)		
≥60	388	70 (4.6)	1.09 (0.85 to 1.41)			342	69 (4.6)	1.32 (1.01 to 1.73)		
Alcohol-related versus other metachronous cancer (per 10 g/day increment)					0.57					0.42
Alcohol-related metachronous cancer[d]	9,435	441 (100)	1.03 (0.98 to 1.08)	0.22		9,435	441 (100)	1.06 (1.00 to 1.12)	0.03	
Other metachronous cancer	9,435	1,071 (100)	1.00 (0.97 to 1.03)	0.99		9,435	1,071 (100)	1.02 (0.99 to 1.05)	0.24	
Most frequently observed metachronous cancer (per 10 g/day increment)										
Colorectum (C180, 182-189, 199, 209)	9,435	242 (16.0)	1.03 (0.98 to 1.10)	0.26		9,435	242 (16.0)	1.07 (1.00 to 1.14)	0.04	
Melanoma of skin (ICD-10 C43 and morphology codes¶)	9,435	186 (12.3)	0.96 (0.89 to 1.04)	0.33		9,435	186 (12.3)	1.05 (0.98 to 1.12)	0.21	
Breast (C50)‡	4,605	167 (25.3)	0.97 (0.85 to 1.10)	0.61		4,605	167 (25.3)	0.90 (0.75 to 1.07)	0.23	
Prostate (C61)‼	4,830	151 (17.7)	0.99 (0.92 to 1.06)	0.78		4,830	151 (17.7)	0.97 (0.90 to 1.05)	0.50	
Lung (C34)	9,435	112 (7.4)	1.06 (0.97 to 1.15)	0.18		9,435	112 (7.4)	1.08 (0.99 to 1.18)	0.09	
Pancreas (C25 excluding C25.4)	9,435	41 (2.7)	0.93 (0.78 to 1.11)	0.43		9,435	41 (2.7)	1.03 (0.87 to 1.21)	0.76	
Bladder (C67)	9,435	40 (2.6)	0.96 (0.82 to 1.11)	0.56		9,435	40 (2.6)	0.92 (0.77 to 1.09)	0.34	
Stomach (C16)	9,435	38 (2.5)	1.05 (0.92 to 1.20)	0.46		9,435	38 (2.5)	1.05 (0.90 to 1.22)	0.54	
Kidney (C64)	9,435	35 (2.3)	1.13 (1.01 to 1.28)	0.04		9,435	35 (2.3)	1.24 (1.10 to 1.39)	<0.001	
Upper aero-digestive tract (C01–C06, 09–10, 13–15, 32)	9,435	32 (2.1)	1.11 (0.97 to 1.26)	0.15		9,435	32 (2.1)	1.16 (1.00 to 1.34)	0.046	

[a]Adjusted for age, sex and smoking status (never, former, current), and stratified by birth cohort (year of birth <1925, 5-year categories for 1925 to 1955) and country of birth (Australia/New Zealand/United Kingdom, Italy/Greece); additional indicator variable for former drinkers fit in models using baseline alcohol intake; additionally, interaction term also fit for sex in competing risks models.

[b]Wald test from Cox regression models assessing linear trends for a 10 g/day increment in alcohol intake or intake categories fit as a continuous variable.

[c]Test of homogeneity.

[d]Alcohol-related metachronous cancers include cancers of the upper aero-digestive tract, breast and colorectum.

¶International Classification of Diseases (ICD)-10 code C43 and morphology codes 8720, 8721, 8723, 8730, 8740, 8742-8745, 8770-8774 and 8780.

‡From model that included only women.

‼From model that included only men.

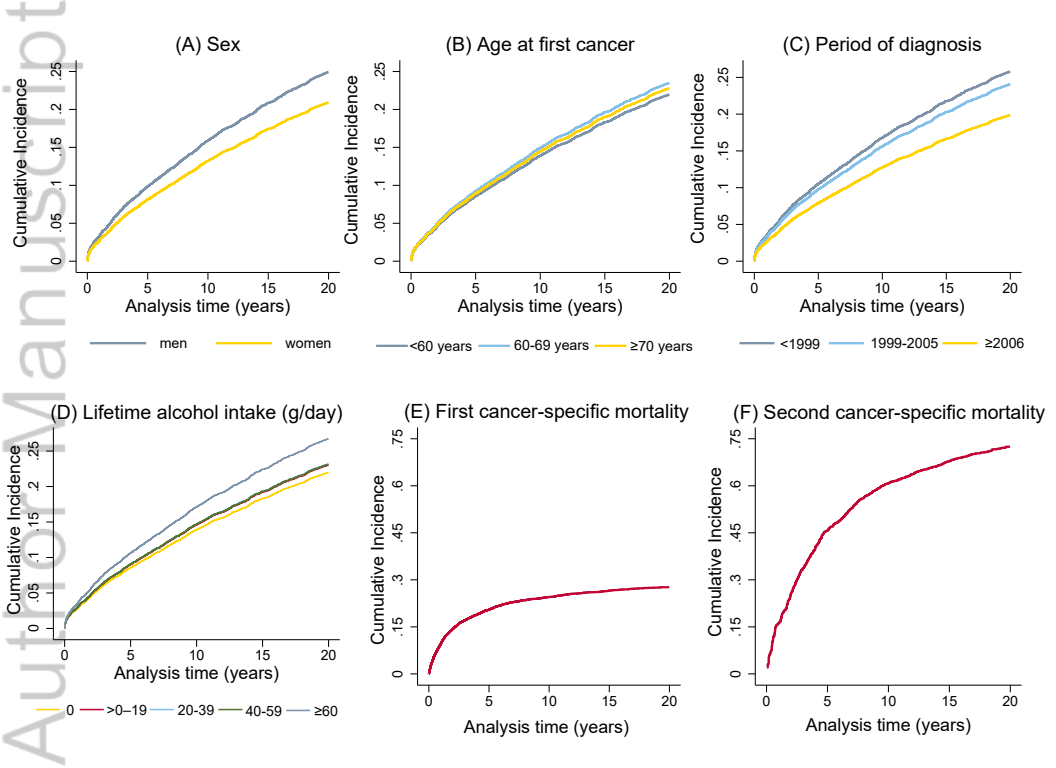
Table 3. Hazard ratios (HR) and 95% confidence intervals (CI) for metachronous cancer incidence for a 10 g/day increment in alcohol intake by subgroup

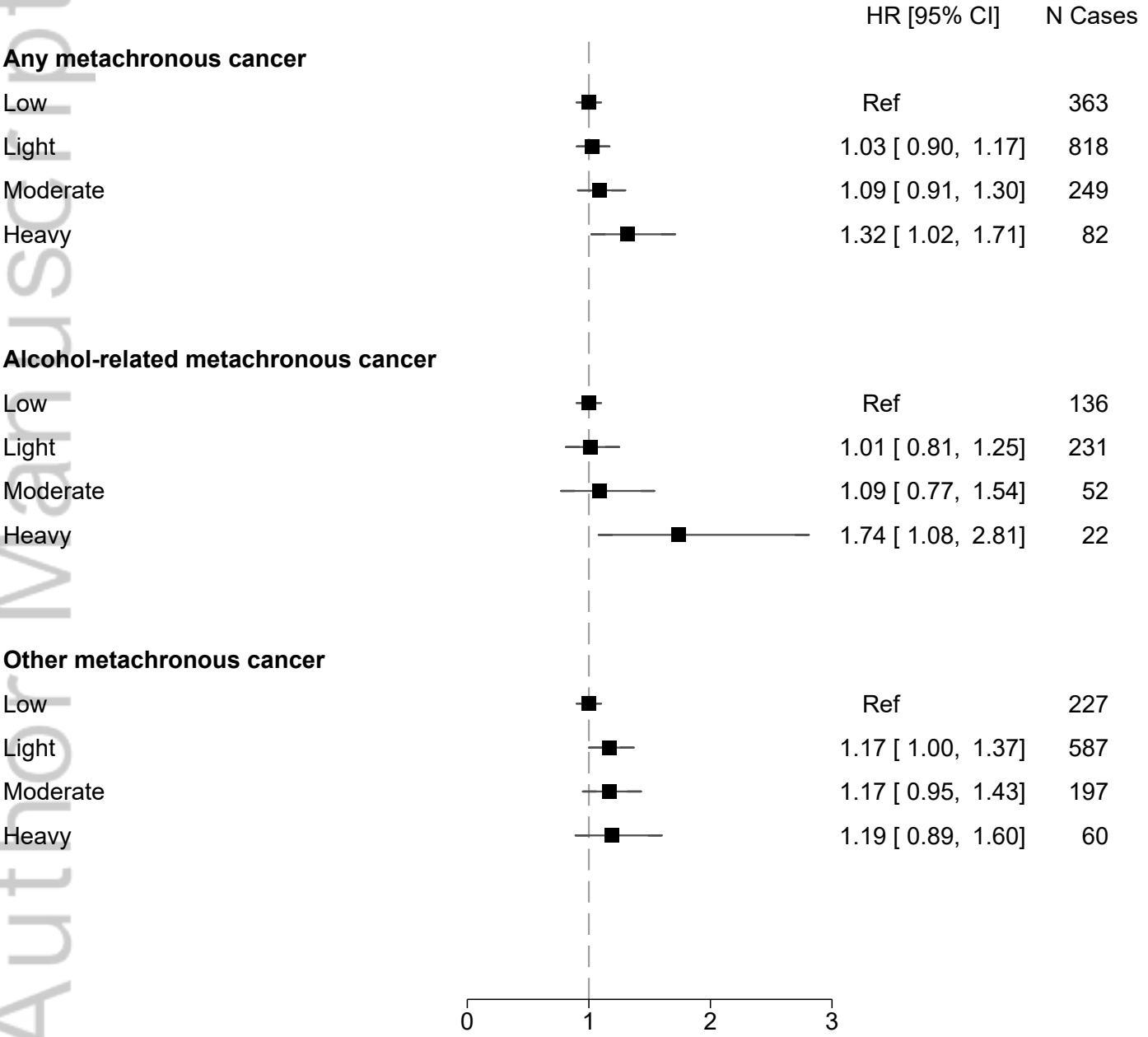
	Baseline alcohol intake					Lifetime alcohol intake				
	No.	**Events, n (%)**	**HR (95% CI)[a]**	***P* value[b]**	***P*$_{interaction}$**	**No.**	**Events, n (%)**	**HR (95% CI)[a]**	***P* value[b]**	***P*$_{interaction}$**
By sex					0.10					0.30
Men	4,830	852 (56.4)	1.03 (1.00 to 1.06)	0.07		4,830	852 (56.4)	1.04 (1.01 to 1.07)	0.01	
Women	4,605	660 (43.7)	0.97 (0.91 to 1.03)	0.34		4,605	660 (43.6)	0.99 (0.92 to 1.08)	0.88	
By smoking status					0.02					0.19
Never	4,961	758 (50.2)	1.00 (0.95 to 1.05)	0.93		4,961	758 (50.2)	1.03 (0.98 to 1.08)	0.31	
Former	3,324	575 (38.0)	1.00 (0.96 to 1.03)	0.89		3,324	575 (38.0)	1.02 (0.98 to 1.06)	0.34	
Current	1,150	179 (11.8)	1.09 (1.03 to 1.14)	0.001		1,150	179 (11.8)	1.09 (1.02 to 1.16)	0.006	
By smoking status (never and former combined)					0.008					0.11
Never or former	8,285	1,333 (88.2)	1.00 (0.97 to 1.03)	0.84		8,285	1,333 (88.2)	1.03 (1.00 to 1.06)	0.07	
Current	1,150	179 (11.8)	1.09 (1.03 to 1.14)	0.001		1,150	179 (11.8)	1.09 (1.02 to 1.15)	0.007	
By smoking intensity					0.09					0.51
Never	4,961	758 (50.2)	1.00 (0.95 to 1.05)	0.91		4,961	758 (50.2)	1.03 (0.98 to 1.08)	0.31	
Former ≥20 years since quitting	1,163	219 (14.5)	0.99 (0.94 to 1.06)	0.86		1,163	219 (14.5)	1.05 (0.99 to 1.11)	0.14	
Former 11-19 years since quitting	972	168 (11.1)	1.02 (0.96 to 1.08)	0.47		972	168 (11.1)	1.00 (0.93 to 1.07)	0.98	
Former ≤10 years since quitting	1,159	187 (12.4)	0.96 (0.89 to 1.03)	0.23		1,159	187 (12.4)	1.00 (0.93 to 1.07)	0.99	
Current <20 cigarettes/day	645	108 (7.1)	1.10 (1.00 to 1.20)	0.05		645	108 (7.1)	1.07 (0.96 to 1.19)	0.25	
Current ≥20 cigarettes/day	499	70 (4.6)	1.07 (1.01 to 1.14)	0.02		499	70 (4.6)	1.09 (1.01 to 1.17)	0.02	
Incomplete	36	2 (0.1)	-			36	2 (0.1)	-		
By first primary cancer status (alcohol)					0.09					0.11
Alcohol-related first primary cancer[c]	2,970	509 (33.7)	0.98 (0.94 to 1.03)	0.48		2,970	509 (33.7)	1.00 (0.94 to 1.05)	0.90	
Other first primary cancer	6,465	1.003 (66.3)	1.03 (1.00 to 1.06)	0.06		6,465	1.003 (66.3)	1.04 (1.01 to 1.08)	0.006	
By first primary cancer status (smoking)					0.57					0.53
Smoking-related first primary cancer[d]	3,085	404 (26.7)	1.03 (0.98 to 1.07)	0.23		3,085	404 (26.7)	1.04 (1.00 to 1.09)	0.06	
Other first primary cancer	6,350	1,108 (73.3)	1.01 (0.98 to 1.04)	0.49		6,350	1,108 (73.3)	1.03 (0.99 to 1.06)	0.12	
By follow-up time since first cancer					0.65					0.08
<5 years	9,435	805 (53.2)	1.02 (0.99 to 1.06)	0.21		9,435	805 (53.2)	1.05 (1.02 to 1.09)	0.003	
≥5 years	4,804	707 (46.8)	1.01 (0.97 to 1.05)	0.62		4,804	707 (46.8)	1.01 (0.96 to 1.05)	0.80	

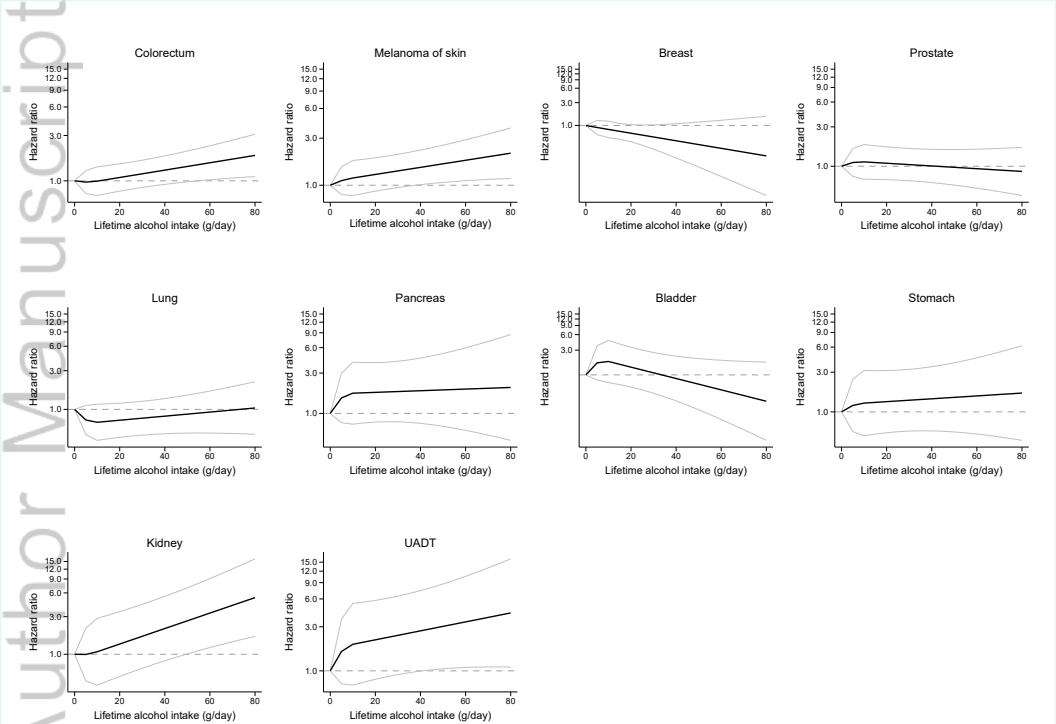
[a]Adjusted for age, sex and smoking status (never, former, current), and stratified by birth cohort (year of birth <1925, 5-year categories for 1925 to 1955) and country of birth (Australia/New Zealand/United Kingdom, Italy/Greece); additional indicator variable for former drinkers fit in models using baseline alcohol intake.

[b]Wald test from Cox regression models assessing linear trends for a 10 g/day increment in alcohol intake.

[c]Alcohol-related metachronous cancers include cancers of the upper aero-digestive tract, breast and colorectum.
[d]Smoking-related metachronous cancers include cancers of the lung, esophagus, larynx, mouth, throat, kidney, bladder, liver, pancreas, stomach, cervix, colon, and rectum, as well as acute myeloid leukemia.







Novelty & Impact Statement: IJC-20-3277.R1

Alcohol consumption is an important risk factor for certain cancer types. Whether alcohol also influences the development of second primary tumors known as metachronous cancers, which occur at least six months after first primary tumors, however, is uncertain. Here, investigation of pre-diagnosis long-term alcohol intake and metachronous cancer in nearly 10,000 cancer survivors reveals associations between consumption of 60 or more grams of alcohol per day and metachronous cancers of the colorectum, upper aero-digestive tract, and kidney. The associations were modified by smoking behavior. The findings offer new insight into risk factors for subsequent cancers in cancer survivors.