Alcohol and Alcoholism, 2016, 51(3) 315–330
doi: 10.1093/alcalc/agv110
Advance Access Publication Date: 22 September 2015
Article

Article

Long-Term Alcohol Consumption and Breast, Upper Aero-Digestive Tract and Colorectal Cancer Risk: A Systematic Review and Meta-Analysis

Harindra Jayasekara[1,2,*], Robert J. MacInnis[1,3], Robin Room[4,5,6], and Dallas R. English[1,3]

[1]Centre for Epidemiology and Biostatistics, Melbourne School of Population and Global Health, The University of Melbourne, 207 Bouverie Street, Carlton, Victoria 3010, Australia, [2]Population Health, Murdoch Childrens Research Institute, Flemington Road, Parkville, Victoria 3052, Australia, [3]Cancer Epidemiology Centre, Cancer Council Victoria, 615 St Kilda Rd, Melbourne, Victoria 3004, Australia, [4]Centre for Alcohol Policy Research, La Trobe University, 215 Franklin St., Melbourne, Victoria 3000, Australia, [5]Centre for Health Equity, Melbourne School of Population and Global Health, The University of Melbourne, 207 Bouverie Street, Carlton, Victoria 3010, Australia, and [6]Centre for Social Research on Alcohol and Drugs, Stockholm University, SE - 106 91 Stockholm, Sweden

*Corresponding author: Level 3, 207 Bouverie Street, Centre for Epidemiology and Biostatistics, Melbourne School of Population and Global Health, The University of Melbourne, Carlton, Victoria 3010, Australia. Tel.: +61-4-33469782; Fax: +61-3-93495815; E-mail: harindra_jaya@yahoo.com

Received 9 April 2015; Revised 29 June 2015; Accepted 18 August 2015

Abstract

Aims: Cancers of female breast, upper aero-digestive tract (UADT) (oral cavity, pharynx, larynx, oesophagus) and colorectum are causally related to alcohol consumption. Although alcohol consumption is likely to vary during life, the few studies that have explicitly measured lifetime consumption or intake over time have not been summarised. We therefore conducted a systematic review and meta-analysis.

Methods: Studies were identified by searching the Medline, CINAHL (Cumulative Index to Nursing and Allied Health Literature) and Scopus databases through January 2015 using broad search criteria. Studies reporting relative risks (RR) for quantitatively defined categories of alcohol consumption over time for breast, UADT or colorectal cancer were eligible. A two-stage random-effects meta-analysis was used to estimate a dose–response relationship between alcohol intake and each cancer site. RRs were also calculated for the highest relative to the lowest intake category.

Results: Sixteen articles for breast, 16 for UADT and 7 for colorectal cancer met the eligibility criteria. We observed a weak non-linear dose–response relationship for breast cancer and positive linear dose–response relationships for UADT and colorectal cancer. The pooled RRs were 1.28 (95% confidence interval, CI: 1.07, 1.52) for breast, 2.83 (95% CI: 1.73, 4.62) for UADT, 4.84 (95% CI: 2.51, 9.32) for oral cavity and pharynx, 2.25 (95% CI: 1.49, 3.42) for larynx, 6.71 (95% CI: 4.21, 10.70) for oesophageal and 1.49 (95% CI: 1.27, 1.74) for colorectal cancer.

Conclusion: Our findings confirm dose-dependent associations between long-term alcohol intake and breast, UADT and colorectal cancer.

INTRODUCTION

Ethanol in alcoholic beverages is carcinogenic to humans (International Agency for Research on Cancer, 2010), and the occurrence of malignant tumours of the oral cavity, pharynx, larynx, oesophagus, liver, colon, rectum and female breast is causally related to alcohol consumption (Baan *et al.*, 2007). Many cohort and case-control studies have consistently provided evidence of the association between these cancers and alcohol consumption (World Cancer Research Fund/American Institute for Cancer Research, 2007). Although alcohol causes primary liver cancer, it has been difficult to quantify its effect due to conditions of the liver (e.g. cirrhosis) that precede liver cancer and which often result in reducing alcohol intake (Bagnardi *et al.*, 2001). Most studies that have quantified the effect of alcohol on the risk for cancers of the female breast, upper aero-digestive tract (UADT) (oral cavity, pharynx, larynx, oesophagus) and colorectum have captured only 'current' drinking (alcohol intake at beginning of follow-up in cohort studies and usually just before diagnosis in case-control studies) (Bagnardi *et al.*, 2001; Cho *et al.*, 2004; Moskal *et al.*, 2007; World Cancer Research Fund/American Institute for Cancer Research, 2007; Fedirko *et al.*, 2011). To our knowledge, the studies that have examined the associations of alcohol intake during the lifetime or over time with these cancers have not been summarised. Since alcohol consumption is likely to vary during the course of life (Johnstone *et al.*, 1996; Skog and Rossow, 2006), it is possible that consumption over a prolonged period of time could be linked more closely with biological processes having a chronic effect on health rather than drinking at a specific time point, which is associated more with acute alcohol effects (Russell *et al.*, 1998).

We conducted a systematic review and meta-analysis to quantify the effect of alcohol consumption over a long period of time on the risk for cancers of the female breast, UADT and colorectum.

METHODS

Literature search and selection

We used Medline, CINAHL (Cumulative Index to Nursing and Allied Health Literature) and SCOPUS to systematically search for potentially relevant original papers published through January 2015. Broad search criteria were used since lifetime alcohol consumption has not been measured uniformly. The following keywords and subject headings were used to identify relevant articles: (alcohol* or ethanol) AND (lifetime drinking or lifetime consumption or lifetime intake or cumulative drinking or cumulative consumption or cumulative intake or drinking over time or consumption over time or intake over time or change* in drinking or change* in consumption or change* in intake or drinking pattern) AND (cancer* or carcinoma* or malignancy or malignant or carcinogenesis or tumour*) AND (case or retrospective or cohort or prospective or longitudinal or follow or ratio* or risk*). The search was not restricted to publications in English, and titles and abstracts in English for articles in any language were searched. Informally published, written material such as reports were not included in the search. In addition, an extensive manual search of relevant articles from reference lists in papers selected electronically was conducted. Standard criteria for analysis and reporting the results were followed (Stroup *et al.*, 2000).

Eligible articles included original publications (excluding letters, editorials, conference abstracts, reviews and commentaries) of cohort and case-control studies reporting hazard ratios, RR or odds ratios (referred to hereafter using the general term RR) and their 95% confidence intervals (CI) of the association between alcohol consumption over time (intake at two points in time, e.g. over a 10-year period) or during lifetime (intake from early adulthood, e.g. from age 20 years onwards) and breast, UADT or colorectal cancer. Alcohol intake had to be measured in terms of a single or multiple assessment/s of an individual's alcohol consumption history retrospectively for different periods of life based on age or more than one assessment of an individual's current alcohol consumption over time. Studies characterizing alcohol exposure qualitatively using such terms as 'problem drinkers' were excluded. If multiple publications from the same study cohort were available, the one with the most comprehensive data on alcohol consumption was included. Author H.J. performed the search and excluded studies at the first exclusion pass based on title and abstract. Relevant studies were identified from the remaining studies that reported any assessment of alcohol consumption over time and breast, UADT or colorectal cancer.

Case definition

Incidence of breast, UADT (individually as cancer of the oral cavity, pharynx, larynx or oesophagus, or as any combination of these) or colorectal (colon, rectal or colorectal) cancer were defined as the outcomes of interest, with outcomes based on registry data, medical records or reports accepted.

Data extraction

Information from the identified studies was extracted by H.J. with assistance from R.J.M. The following information was abstracted on each study included in the analysis using a standard pro forma: title, authors, year of publication, study name, study design, country, age, sex, sample size, % lost to follow-up, exposure and follow-up times, exposure assessment and the comparability of reference categories, end points, measures of association and covariates included in the multivariable analysis. The maximally adjusted RRs with corresponding 95% CIs were extracted for each category of alcohol consumption whenever possible.

Statistical analysis

A two-stage random-effects meta-analysis was used to examine a dose–response relationship for each cancer site (Orsini *et al.*, 2012). Alcohol consumption was modelled using restricted cubic splines with three knots at fixed percentiles (10, 50 and 90%) of the distribution (Harrell *et al.*, 1988). Restricted cubic spline models were initially computed for each study taking into account the within-study correlation, then afterwards, a random-effects meta-analysis was performed using the regression coefficients and the variance–covariance matrix from each individual study (Orsini *et al.*, 2006; Jackson *et al.*, 2010). For the dose–response meta-analysis, the median alcohol consumption in grams per day for each category of average intake was assigned to each corresponding RR. In order to calculate the median consumption for each intake category, we first converted their upper and lower boundaries into grams per day of alcohol from millilitres or standard drinks per day or week, based on the type of alcohol and the size of a standard drink in the study's country of origin (Stockwell and Chikritzhs, 2000).

In a separate analysis, we calculated pooled RRs for the highest category of alcohol intake over time, using DerSimonian–Laird random effects models (DerSimonian and Laird, 1986). The lowest intake category (usually nondrinking) was used as the reference category. For studies in which the lowest intake category was not the reference category, we recalculated RRs and CIs for the highest category of alcohol intake, making the lowest intake category the reference category.

Whenever individual studies reported more than one RR (e.g. for men and women, or by age group), separate within-study meta-analyses were performed to combine them into a single RR to be used in pooled analyses. When studies did not report RRs or CIs, we calculated crude estimates based on the number of cases and non-cases for each of the categories of alcohol intake.

The inconsistencies across studies and their impact on the analysis were quantified through the multivariate generalisation of the I^2 statistic (Higgins and Thompson, 2002). Two cutpoints of these I^2 values were considered, creating three groups: <30% (no between-study heterogeneity or marginal between-study heterogeneity), 30–75% (mild heterogeneity) and >75% (notable heterogeneity) (Higgins and Green, 2011). Publication bias was assessed by using Egger's regression test (Egger *et al.*, 1997). All statistical analyses were performed using Stata version 12.1 (StataCorp, College Station, TX, USA). *P*-values of <0.05 were considered statistically significant.

RESULTS

Characteristics of studies

The number of articles identified by the electronic search is given in Fig. 1. Fourteen full-text articles on breast cancer (Adami *et al.*, 1988; Colditz, 1993; Herrinton *et al.*, 1993; Freudenheim *et al.*, 1995; Longnecker *et al.*, 1995a,b; Swanson *et al.*, 1997; Männistö *et al.*, 2000; Tjonneland *et al.*, 2004; Terry *et al.*, 2006; Berstad *et al.*, 2008; Chen *et al.*, 2011; Chandran *et al.*, 2013; Weaver *et al.*, 2013), seven on UADT (Zheng *et al.*, 1990; Lopez-Abente *et al.*, 1992; Launoy *et al.*, 1997; Franceschi *et al.*, 2000; Thygesen *et al.*, 2007; Weikert *et al.*, 2009; Jayasekara *et al.*, 2015), six on colorectal cancer (Kune *et al.*, 1987; Freudenheim *et al.*, 1990; Riboli *et al.*, 1991; Lieberman *et al.*, 2003; Ferrari *et al.*, 2007; Thygesen *et al.*, 2008) and one on both UADT and colorectal cancer (Benedetti *et al.*, 2009) were selected after excluding the others based on their title or abstract. Of these, four on breast cancer (Adami *et al.*, 1988; Colditz, 1993; Herrinton *et al.*, 1993; Weaver *et al.*, 2013) and one on colorectal cancer (Lieberman *et al.*, 2003) were subsequently excluded as they did not report a measure of association between alcohol consumption over time and the endpoint. A manual search of reference lists added five more articles on breast cancer (Young, 1989; Katsouyanni *et al.*, 1994; Holmberg *et al.*, 1995; Lenz *et al.*, 2002; Liu *et al.*, 2013), seven more articles on UADT cancer (Victora *et al.*, 1987; Merletti *et al.*, 1989; De Stefani *et al.*, 1990; Castelletto *et al.*, 1994; Cheng *et al.*, 1995; Rolon *et al.*, 1995; Hayes *et al.*, 1999) and one more article on all three cancers (Williams and Horm, 1977). This left 16 articles that fulfilled the eligibility criteria for breast cancer (Table 1), 16 for UADT cancer (Table 2) and 7 for colorectal cancer (Table 3).

The variation in the age of study participants, the different methods of capturing exposure to alcohol, the different units used to measure intake and the covariates adjusted for are shown in Tables 1–3. The studies on breast cancer were published between 1977 and 2013, consisted of three cohort studies and 13 case-control studies and were conducted in North America (12 studies) and Europe (four studies) (Table 1). The studies on UADT cancer were published between 1977 and 2015, consisted of three cohort studies and 13 case-control studies, were conducted in Europe (six), South/Central America (five), Asia (two), North America (two) and Australia (one) and used cancer of the UADT, lip-tongue, gum-mouth, oral cavity and pharynx, larynx or oesophagus as the outcome of interest (Table 2). The studies on colorectal cancer were published between 1977 and 2009, consisted of two cohort studies and five case-control studies and were conducted in North America (four), Europe (two) and Australia (one) (Table 3). Individual studies had measured alcohol intake from early adulthood for different age periods (28 studies), for ≥2 age intervals (five) or relative to important life events (three) and had predominantly computed an average intake measure per unit time (e.g. grams/day, drinks/week) (28 studies) except some who had used drink-years (three) or total drinks during lifetime (five) (Tables 1–3).

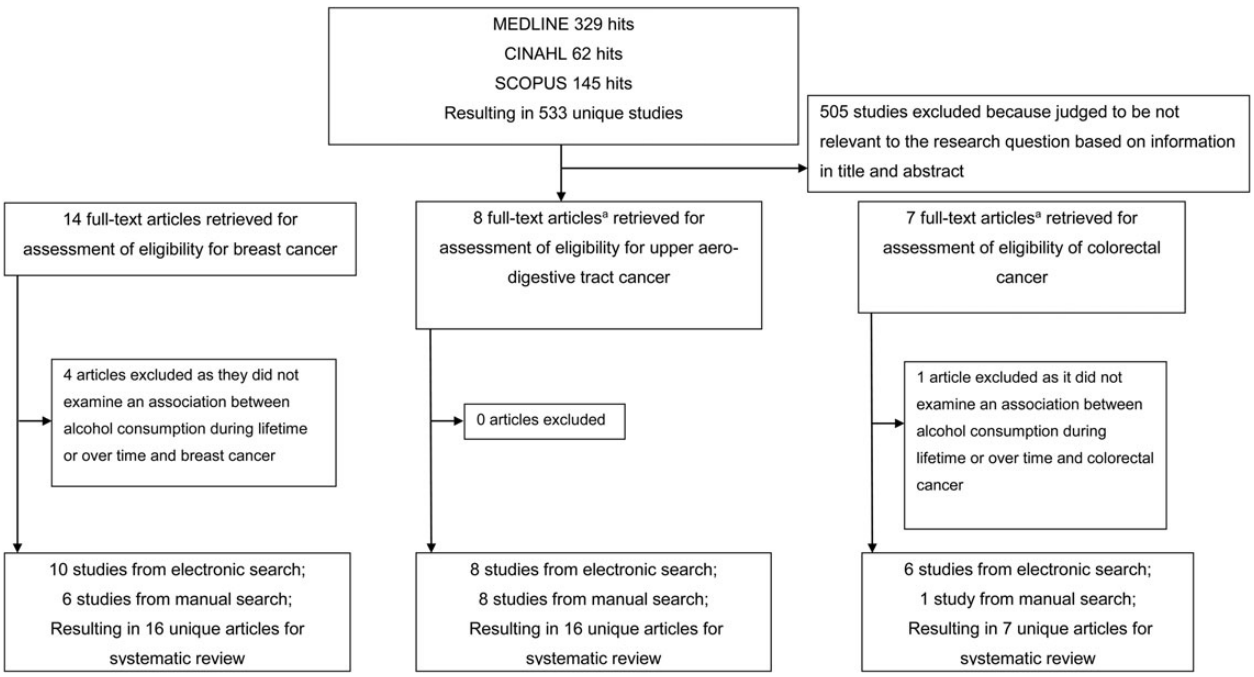

Fig. 1. Flow diagram describing selection of studies for inclusion in a systematic review of alcohol consumption over time and breast, UADT and colorectal cancer risk. [a]One article reported associations with both UADT and colorectal cancer.

Table 1. Characteristics of studies of alcohol intake over time and breast cancer risk

First author, year (reference)	Location	Study period	Study design	Age at baseline (years)	Exposure time assessed	Period of outcome ascertainment	Total number of cases	Sample		Unit of measurement for alcohol variable	Adjustment factors
								Population type	Number		
Williams, 1977 (Williams and Horm, 1977)	United States	1969–1971	Case-control	≥35	Lifetime history of alcohol use	N/A	7518 all cancers	Cases and Controls	Derived from within all cancers	'Ounce-years' of absolute alcohol consumption	Smoking, age, race
Young, 1989 (Young, 1989)	United States	1981–1982	Case-control	35–89	Alcohol intake for age <18, 18–35 and >35 years (excluding last 5 years)	N/A	277	Cases Controls -population -cancer	277 372 433	Drinks/week	Age, family history of breast cancer, body mass index, decaffeinated coffee (early age model only), salad consumption (later-age model only)
Katsouyanni, 1994 (Katsouyanni *et al.*, 1994)	Greece	1989–1991	Case-control	≥30	Alcohol intake for age <30, 30–50 and ≥50 years	N/A	820	Cases Controls	798 1528	Glasses/week	Age, place of birth, parity, age at first pregnancy, age at menarche, menopausal status, Quetelet index, total energy intake
Freudenheim, 1995 (Freudenheim *et al.*, 1995)	United States	1986–1991	Case-control	40–85	Index of intake in the past 20 years based on a weighted average of reported intakes for 210 and 20 years ago	N/A	740	Cases Controls	740 810	Total drinks	Age, education, menopausal status, age at menarche, age at 1st pregnancy, family history of breast cancer, previous benign breast disease, Quetelet index, intake of energy, fat, carotenoids, vitamin C, α-tocopherol, folic acid, dietary fibre, other types of alcohol
Holmberg, 1995 (Holmberg *et al.*, 1995)	Sweden	1987–1990	Case-control	40–75	Periodic alcohol intake for dietary periods since early life event	N/A	276	Cases Controls	276 452	Grams/day	Family history of breast cancer, parity, age at first birth, educational level, body mass index
Longnecker, 1995 (Longnecker *et al.*, 1995b)	United States	1987–1989	Case-control	55–64	Lifetime alcohol intake derived as average of intakes for ages 25 and 40 years, and recent intake	N/A	1425 invasive cancer and 161 *in situ* disease women	Cases Controls	1431 1431	Grams/day	Age at menarche, education, benign breast disease, family history, body mass index, parity, age at first full-term pregnancy, age at menopause, ethnicity
Longnecker, 1995 (Longnecker *et al.*, 1995a)	United States	1988–1991	Case-control	Average age 58.7	Average alcohol intake from age 16 to previous age interval	N/A	8579	Cases Controls	6163 8480	Grams/day	Age, state, age at first full-term pregnancy, parity, body mass index, age at menarche, education, benign breast disease, family history of breast cancer

Swanson, 1997 (Swanson *et al.*, 1997)	United States	1990–1992	Case-control	20–44	Usual past intake relative to life events	N/A	1645	Cases Controls	1645 1497	Drinks/week	Age, study site, race, parity, oral contraceptive use
Männistö, 2000 (Männistö *et al.*, 2000)	Finland	1990–1995	Case-control	25–75	Past alcohol intake for periods defined by participants, and relative to life events	N/A	113 premenopausal and 188 postmenopausal women	Premenopausal Cases Controls Postmenopausal Cases Controls	 113 172 188 271	Grams/lifetime	Age, area, age at menarche, age at first full-term pregnancy, use of oral contraceptives, use of oestrogen replacement therapy, family history of breast cancer, history of benign breast disease, level of education, smoking, physical activity, body mass index, waist-to-hip ratio
Lenz, 2002 (Lenz *et al.*, 2002)	Canada	1996–1997	Case-control	50–75	Alcohol intake at age 20, 30, 40 and 50 years	N/A	556	Cases Controls	181 156	Drink-years	Age, family history, age at oophorectomy, education, marital status, ethnicity, age at menarche, oral contraception use, duration of hormone replacement therapy use, total duration of breast feeding, smoking status, body mass index, age at first full-term pregnancy, proxy respondent status
TjØnneland, 2004 (Tjonneland *et al.*, 2004)	Denmark	1993–2000	Cohort	50–64	Mean alcohol intake for 20–29, 30–39, 40–49 and 50-to current	3–7 years	423	Women	23, 683	Grams/day	Parous/nulliparous, number of births, age at first birth, previous benign breast tumour surgery, school education, use and duration of hormone replacement therapy, body mass index
Terry, 2006 (Terry *et al.*, 2006)	United States	1996–1997	Case-control	20–98	Weighted average of intake for age <20, 20–29, 30–39, 40–49, 50–59, ≥60 years	N/A	1508	Cases Controls	1508 1553	Grams/day	Age at diagnosis, race, education, body mass index
Berstad, 2008 (Berstad *et al.*, 2008)	United States	1998–2003	Case-control	20–49	Alcohol intake from age 15 years to reference age	N/A	1728	Cases Controls	1726 434	Drinks/week	Age, race, education, first-degree breast cancer family history, age at menarche, age at first full-term pregnancy, parity, breast feeding duration, smoking, body mass index

Continued

Table 1. Continued

First author, year (reference)	Location	Study period	Study design	Age at baseline (years)	Exposure time assessed	Period of outcome ascertainment	Total number of cases	Sample		Unit of measurement for alcohol variable	Adjustment factors
								Population type	Number		
Chen, 2011 (Chen *et al.*, 2011)	United States	1980–2008	Cohort	30–55	Repeated measures of alcohol intake over time	28 years	7690	women	84,630	Grams/day	Age, questionnaire year, ages at menarche and menopause, family history of breast cancer in first-degree relative, benign breast disease, body mass index, parity and age at first full-term birth, hormone therapy use, total duration of breast feeding, cigarette smoking
Liu, 2013 (Liu *et al.*, 2013)	United States	1989–2009	Cohort	25–44	Alcohol intake for period between menarche and first pregnancy, and period between first pregnancy and current age/ menopause using periodic recall	20	1609	Women	91,005	Grams/day	Age, questionnaire year, current body mass index, age at menarche, menopausal status, average body size between ages 5 and 10 years, family history of breast cancer in mother or sister, postmenopausal hormone use, total duration of breast feeding, parity and age at first pregnancy
Chandran, 2013 (Chandran *et al.*, 2013)	United States	2003–2012	Case-control	20–75	Lifetime alcohol intake using intake for age <20, 20–29, 30–39, 40–49, 50–59 and ≥60	N/A	803	Cases Controls	803 889	Total number of drinks during lifetime by African–American women	Age, ethnicity, country of origin, education, age at menarche, parity, age at first birth, breastfeeding status, menopausal status, family history of breast cancer, HRT use, OC use, history of benign breast disease, total energy intake and BMI

N/A, not applicable; N/R, not reported.

Table 2. Characteristics of studies of alcohol intake over time and UADT cancer risk

First author, year (reference)	Location	Study period (years)	Sex	Study design	Age range at baseline (years)	Exposure time assessed (years)	Period of outcome ascertainment (years)	Number of cases (by site)	Sample		Unit of measurement for alcohol variable	Adjustment factors
									Population type	Number		
Williams, 1977 (Williams and Horm, 1977)	United States	1969–1971	Men and women	Case-control	≥35	Lifetime history of alcohol use	N/A	7518 all cancers	Cases and Controls	Derived from within all cancers	'Ounce-years' of absolute alcohol consumption	Smoking, age, race
Victora, 1987 (Victora *et al.*, 1987)	Brazil	1985–1986	Men and women	Case-control	≤80	Recalled lifetime intake of *cachaca*	N/A	171 cases of oesophageal cancer	Cases Controls	171 342	Grams/day	Place of residence, smoking status, frequency of eating fruit, frequency of eating meat,
Merletti, 1989 (Merletti *et al.*, 1989)	Italy	1980–1984	Men and women	Case-control	Not specified	Lifelong drinking history	N/A	86 men and 36 women with cancer of oral cavity and oropharynx	Cases Controls	122 606	Grams/day	Age, educational level, area of birth, tobacco smoking habits, type of beverage
Zheng, 1990 (Zheng *et al.*, 1990)	China	1988–1989	Men and women	Case-control	18–80	Recalled lifetime intake (time variable)	N/A	248 oral cancer in men and 156 oral cancer in women	Cases Controls (age/sex-matched)	404 404	Kilo grams/lifetime	Age, years of education, smoking (risk assessed for men only)
De Stefani, 1990 (De Stefani *et al.*, 1990)	Uruguay	1985–1988	Men and women	Case-control	Not specified	Recalled lifetime alcohol intake	N/A	261 cases of oesophageal cancer	Cases Controls	261 522	Millilitres/day	Smoking
Lopez-Abente, 1992 (Lopez-Abente *et al.*, 1992)	Spain	1982–1985	Men	Case-control	≤80	Recalled lifetime beverage-specific intake	N/A	50 cases of cancer of larynx	Cases Controls	50 103	Grams/week	Age, packs of cigarettes/lifetime, occupation
Castelleto, 1994 (Castelletto *et al.*, 1994)	Argentina	1986–1989	Men and women	Case-control	Not specified	Recalled lifetime alcohol intake	N/A	131 cases of oesophageal cancer	Cases Controls	131 262	Millilitres/day	Age group, sex, hospital group, education, smoking, barbecue frequency, beef intake
Rolon, 1995 (Rolon *et al.*, 1995)	Paraguay	1988–1991	Men and women	Case-control	≤75	Recalled lifetime alcohol intake	N/A	131 cases of oesophageal cancer	Cases Controls	131 381	Litres/lifetime	Age group, sex, hospital group, lifetime cigarette consumption

Continued

Table 2. Continued

First author, year (reference)	Location	Study period (years)	Sex	Study design	Age range at baseline (years)	Exposure time assessed (years)	Period of outcome ascertainment (years)	Number of cases (by site)	Sample		Unit of measurement for alcohol variable	Adjustment factors
									Population type	Number		
Cheng, 1995 (Cheng *et al.*, 1995)	Hong Kong	1989–1990	Men and women	Case-control	Not specified	Recalled lifetime beverage-specific intake	N/A	378 cases of cancer of oesophagus	Cases Controls	378 1567	Grams/week	Educational attainment, place of birth, meal pattern, consumption of fresh vegetables, citrus fruits, and pickled vegetables, tobacco smoking (average amount smoked per day and smoking status)
Launoy, 1997 (Launoy *et al.*, 1997)	France	1991–1994	Men	Case-control	<85	Recalled lifetime intake during up to four time periods	N/A	208 oesophageal cancer patients	Cases Controls	208 399	Grams/week	Interviewer, age, place of residence, occupation, education standard, life style, duration of tobacco consumption, years since stopping smoking
Hayes, 1999 (Hayes *et al.*, 1999)	Puerto Rico	1992–1995	Men and women	Case-control	21–79	Recalled lifetime intake	N/A	342 cases of cancer of oral cavity and pharynx (except nasopharynx)	Cases Controls	342 521	Drinks/week	Age, tobacco use
Franceschi, 2000 (Franceschi *et al.*, 2000)	Italy	1992–1997	Men and women	Case-control	<79	Recalled lifetime beverage-specific intake	N/A	754 cases of cancer of oral cavity and pharynx	Cases Controls	754 1775	Drinks/week	Age, gender, centre, interviewer, education, smoking habits, drinking status

Thygesen, 2007 (Thygesen *et al.*, 2007)	Denmark	1976–1983	Men and women	Cohort	20.6–93.2	Alcohol intake over time between 1976–1978 and 1981–1983	Until 31 December 2002	105 cases of UADT cancer	Men and women	11,135	Drinks/week	Age, initial alcohol intake, sex, changes in smoking
Benedetti, 2009 (Benedetti *et al.*, 2009)	Canada	Early 1980s	Men	Case-control	35–70	Recalled lifetime beverage-specific intake	N/A	78 cases of cancer of oesophagus	Cases Controls	78 507	Drinks/week	Age, smoking status, cigarette-year, respondent status, ethnicity, census tract income, years of schooling, time since quitting
Weikert, 2009 (Weikert *et al.*, 2009)	Europe	1992 to date	Men and women	Cohort	35–70	Lifetime intake based on beverage-specific intake at 20, 30, 40, 50 of years, and current intake	8.6 years/ person	279 men and 113 women with UADT cancer	Men Women	98,505 172,748	Grams/day	Duration and status of smoking, education, fruit and vegetable intake, body mass index
Jayasekara, 2015 (Jayasekara *et al.*, 2015)	Australia	1990–2010	Men and women	Cohort	40–69	Lifetime intake based on beverage-specific intake for 10-year age periods commencing at age 20 up to the decade of their baseline age	16.2 years/ person	57 men and 41 women with UADT cancer	Men and women	38,159	Grams/day	Age, sex, country of birth, education, socioeconomic status, smoking, fruit and vegetable consumption, body mass index, energy intake from food

N/A, not applicable.

Table 3. Characteristics of studies of alcohol intake over time and colorectal cancer risk

First author, year (reference)	Location	Study period (years)	Sex	Study design	Age range at baseline (years)	Exposure time assessed (years)	Period of outcome ascertainment (years)	Number of cases (by site)	Sample		Unit of measurement for alcohol variable	Adjustment factors
									Population type	Number		
Williams, 1977 (Williams and Horm, 1977)	United States	1969–1971	Men and women	Case-control	≥35	Lifetime history of alcohol use	N/A	7518 all cancers	Cases and Controls	Derived from within all cancers	'Ounce-years' of absolute alcohol consumption	Smoking, age, race
Kune, 1987 (Kune *et al.*, 1987)	Australia	Not given	Men and women	Case-control	Not given	Recalled lifetime beverage-specific intake	N/A	715 adenocarcinoma of the large bowel	Cases Controls	715 727	Grams/week	Beef, fat, milk, fibre, vegetables, vitamin C, pork, fish, vitamin supplements
Freudenheim, 1990 (Freudenheim *et al.*, 1990)	United States	1978–1986	Men and women	Case-control	≥40	Recalled lifetime beverage-specific intake	N/A	277 men and 145 women with rectal cancer	Cases men women Controls Men women	 277 145 277 145	Drink-years	Unadjusted (risk estimates adjusted for one dietary variable at a time for men similar to unadjusted risk estimates; adjusted risk estimates not reported for women)
Riboli, 1991 (Riboli *et al.*, 1991)	France	1979–1985	Men and women	Case-control	Mean ages 65.4 years for men and 65.9 years for women	Recalled lifetime intake defined by periods in life	N/A	389 cases of colorectal cancer	Cases Controls	389 641	Millilitres/day	Age, calories without calories for alcohol, fibre from vegetables and fruit
Ferrari, 2007 (Ferrari *et al.*, 2007)	Europe	1992 to date	Men and women	Cohort	35–70	Lifetime intake based on beverage-specific intake at 20, 30, 40, 50 of years, and current intake	6.2 years/person	1184 colon and 649 rectal cancer	478,732 participants		Grams/day	Centre, age, gender, duration of alcohol consumption, time since quitting alcohol consumption, drinking status, total physical activity index, smoking status, education level, weight, height, energy from non-alcohol sources
Thygesen, 2008 (Thygesen *et al.*, 2008)	United States	Enrolled in 1986	Men	Cohort	40–75	Repeated measures of average intake every 4 years	16 years	868 cases of colorectal cancer	47,432 men		Grams/day	Folate, methionine, vitamin D, calcium, total calories, multivitamin, processed and red meat, aspirin, smoking, physical activity, body mass index, colonoscopy, sigmoidoscopy, family history
Benedetti, 2009 (Benedetti *et al.*, 2009)	Canada	Early 1980s	Men	Case-control	35–70	Recalled lifetime beverage-specific intake	N/A	427 cases of cancer of colon and 239 cases of cancer of rectum	Cases colon rectal Controls	 427 239 507	Drinks/week	Age, smoking status, cigarette-year, respondent status, ethnicity, census tract income, years of schooling, time since quitting

N/A, not applicable.

Breast cancer

A relatively weak, positive, non-linear (*P*-value for nonlinearity = 0.02) dose–response relationship between alcohol intake during lifetime or over time and breast cancer incidence is shown in Fig. 2A. Between-study heterogeneity of study-specific trends was mild, I^2 = 59% and 35% for coefficients of first and second spline transformations of alcohol consumption, respectively.

The RR for the highest versus lowest category of alcohol intake were elevated: pooled RR = 1.28 (95% CI: 1.07, 1.52) for all studies; 1.48 (95% CI: 1.33, 1.64) for cohort studies; 1.25 (95% CI: 0.99, 1.57) for case-control studies (Fig. 3). There was mild between-study heterogeneity between case-control studies (I^2 = 73.9%) (Fig. 3) but no evidence of publication bias (Egger's test *P*-value = 0.62). The RR for case-control studies changed only slightly when the study by Chandran *et al.* (2013), which included only African–American women was excluded: pooled RR = 1.31 (95% CI: 1.05, 1.65); I^2 = 68.0%; Egger's test *P*-value = 0.98.

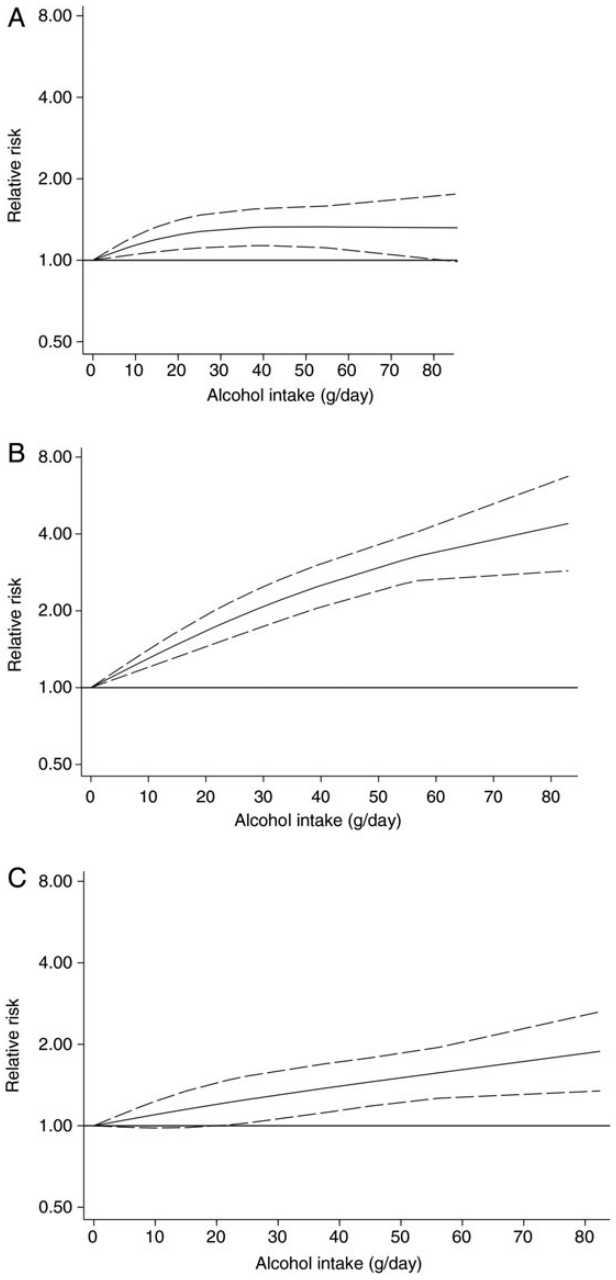

Fig. 2. Adjusted RR of cancer sites associated with average alcohol consumption during lifetime/over time in a meta-analysis of published studies. (**A**) breast cancer; (**B**) cancers of oral cavity, pharynx, larynx or oesophagus individually or as any combination; (**C**) colorectal cancer. The vertical axis is on a log scale. Bold line, spline model; long dashed lines, upper and lower confidence limits of spline model. Reference line, RR = 1.

In addition to the reported RRs for categories of alcohol intake, RRs for a 10 g/day increment in alcohol intake were reported by Tjonneland *et al.* (RR = 1.02; 95% CI: 0.99, 1.05) (Tjonneland *et al.*, 2004), Chen *et al.* (RR = 1.10; 95% CI: 1.07, 1.12) (Chen *et al.*, 2011) and Liu *et al.* (RR = 1.13; 95% CI: 1.03, 1.24 for intake from menarche to first pregnancy and RR = 1.11; 95% CI: 0.99, 1.24 for intake from first pregnancy onwards) (Liu *et al.*, 2013).

Upper aero-digestive tract cancer

A positive, linear (*P*-value for nonlinearity = 0.10) dose–response relationship between alcohol intake during lifetime or over time and cancers of the UADT was clearly observed (Fig. 2B). Between-study heterogeneity of study-specific trends was marginal to mild, I^2 = 15% and 58% for coefficients of first and second spline transformations of alcohol consumption, respectively.

RRs for the highest versus lowest category of alcohol intake during lifetime or over time were elevated for the UADT (pooled RR = 2.83; 95% CI: 1.73, 4.62; I^2 = 0.0%) using data from cohort studies, and for oral cavity and pharynx (pooled RR = 4.84; 95% CI: 2.51, 9.32; I^2 = 73.4%), larynx (pooled RR = 2.25; 95% CI: 1.49, 3.42; I^2 = 0.0%) and oesophagus pooled RR = 6.71; 95% CI: 4.21, 10.70; I^2 = 62.4%) using data from case-control studies (Fig. 4). Egger's test showed no evidence of publication bias (*P*-value ≥ 0.18 for cancers of the UADT, oral cavity and pharynx and oesophagus).

In addition, Weikert *et al.* reported the following RRs for a 10 g/day increment in lifetime intake: 1.10 (95% CI: 1.08, 1.13) for UADT cancer, 1.09 (95% CI: 1.06, 1.12) for cancer of oral cavity and pharynx, 1.08 (95% CI: 1.05, 1.12) for cancer of larynx and 1.18 (95% CI: 1.10, 1.27) for cancer of oesophagus, in men; 1.29 (95% CI: 1.16, 1.43) for UADT cancer, 1.26 (95% CI: 1.07, 1.49) for cancer of oral cavity and pharynx, 1.32 (95% CI: 0.93, 1.89) for cancer of larynx and 1.35 (95% CI: 1.13, 1.60) for cancer of oesophagus, in women (Weikert *et al.*, 2009). Jayasekara *et al.* reported a RR of 1.16 (95% CI: 1.06, 1.28) for a 10 g/day increment in lifetime alcohol intake for both men and women combined (Jayasekara *et al.*, 2015).

Colorectal cancer

An increasing risk of colorectal cancer incidence associated with increasing alcohol intake during lifetime or over time was observed (*P*-value for nonlinearity = 0.78) (Fig. 2C). Between-study heterogeneity of study-specific trends was marginal, I^2 = 24% and 20% for coefficients of first and second spline transformations of alcohol consumption, respectively.

The RR for the highest versus lowest category of alcohol intake during lifetime or over time was elevated: pooled RR = 1.49 (95% CI: 1.27, 1.74); I^2 = 33.5% for all studies; pooled RR = 1.86 (95% CI: 1.47, 2.36) for cohort studies; pooled RR = 1.35 (95% CI: 1.17, 1.57) for case-control studies (Fig. 5). Egger's test did not show evidence of publication bias (*P* = 0.84 for all studies; *P* = 0.41 for case-control studies). The pooled estimates changed only slightly when the study by Freudenheim *et al.* (1990), which included only rectal cancer was excluded: pooled RR = 1.45 (95% CI: 1.22, 1.71); I^2 = 35.2%; Egger's test *P*-value = 0.96.

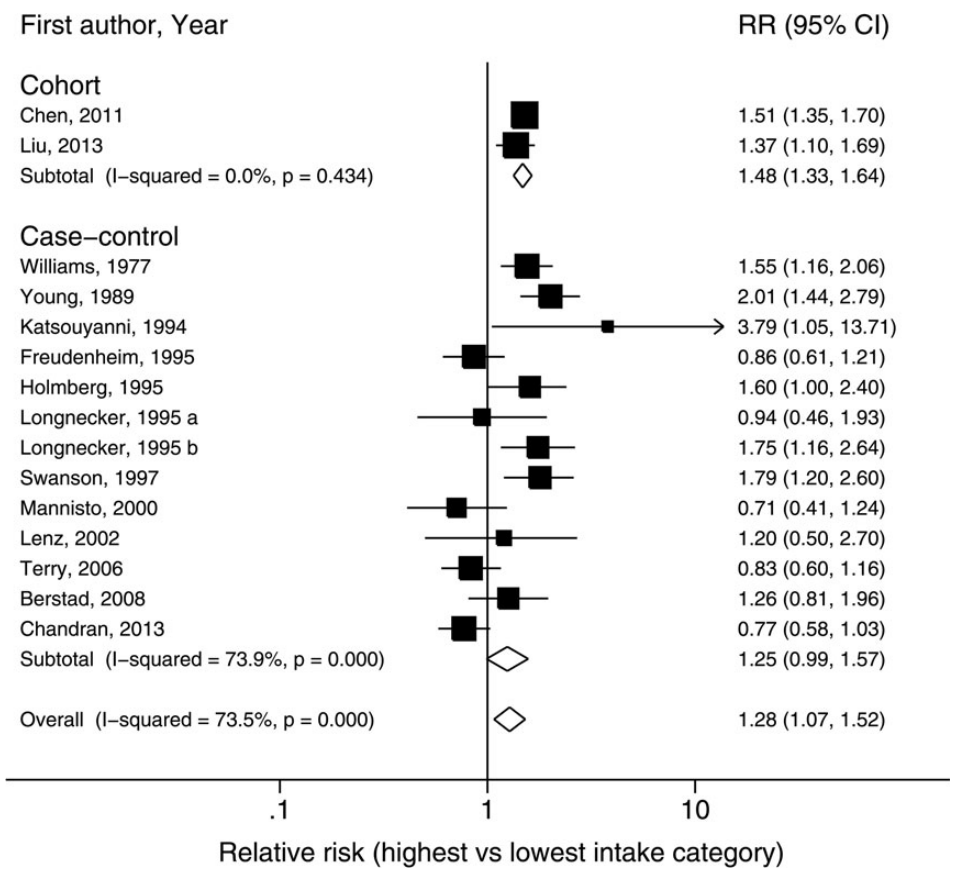

Fig. 3. Forest plot displaying meta-analysis of reported RRs for the association between alcohol consumption measured during lifetime/over time and breast cancer. Midpoint of box representing each study indicates RR, and area of box indicates weight given to the study (inverse of the sum of the individual sampling variance and the between-study variance); diamonds, pooled RR. RR, relative risk; CI, confidence interval. Separate RRs reported by Liu *et al.* (2013) for pre-pregnant and post-pregnant intake, Young (1989) for early and later age and Männistö *et al.* (2000) for premenopausal and postmenopausal women were internally pooled. Williams and Horm (1977) did not report CIs, which we calculated using raw data.

Ferrari *et al.* reported the following RRs for a 15 g/day increment in lifetime intake: 1.08 (95% CI: 1.04, 1.12) for colorectal cancer, 1.05 (95% CI: 1.00, 1.11) for colon cancer and 1.12 (95% CI: 1.06, 1.18) for rectal cancer (Ferrari *et al.*, 2007). Thygesen *et al.* reported a RR of 1.08 (95% CI: 1.03, 1.13) for a 10 g/day increment in intake over time for colorectal cancer (Thygesen *et al.*, 2008).

DISCUSSION

There was wide variation in terms of study design, the age of study participants, the methods used to capture exposure to alcohol, the units of alcohol measurement and intake categories used and the covariates adjusted for in multivariate models. Nevertheless, we observed an increased cancer risk associated with a higher intake of alcohol over time or during lifetime: a 28% higher risk of breast cancer, approximately a 3-fold higher risk of UADT cancer, a 5-fold higher risk of cancer of oral cavity and pharynx, a 2-fold higher risk of cancer of larynx, a 7-fold higher risk of oesophageal cancer and a 49% higher risk of colorectal cancer, for the highest intake category compared with the lowest. Monotonic dose–response relationships were also observed.

The strength of association between alcohol intake (predominantly using current intake) and breast cancer from previous pooled data- and meta-analyses is modest: approximately a 7–8% increase in risk for an increase in intake of 10 g/day (Smith-Warner *et al.*, 1998; Ellison *et al.*, 2001; World Cancer Research Fund/American Institute for Cancer Research, 2007); pooled RRs of 1.07 (95% CI: 0.89, 1.29) for cohort studies and 1.05 (95% CI: 1.03, 1.07) for case-control studies for an intake of five times/week (World Cancer Research Fund/American Institute for Cancer Research, 2007); pooled RRs of 1.41 (95% CI: 1.18, 1.69) for an intake of 30–59 g/day and 1.31 (95% CI: 0.86, 1.98) for an intake of ≥60 g/day compared with non-drinkers (Smith-Warner *et al.*, 1998). In contrast, previous meta-analyses predominantly using current drinking have reported a strong association between alcohol and UADT cancer: RR 1.24 (95% CI: 1.18, 1.30) for cohort studies and 1.03 (95% CI: 1.02, 1.04) for case-control studies per drink/week for mouth, pharynx and larynx combined (World Cancer Research Fund/American Institute for Cancer Research, 2007); 6.01 (95% CI: 5.46, 6.62) for oral cavity and pharynx, 3.95 (95% CI: 3.43, 4.57) for larynx and 4.23 (95% CI: 3.91, 4.59) for oesophagus for an intake of 100 g/day (Bagnardi *et al.*, 2001); 1.04 (95% CI: 1.03, 1.05) for case-control studies per drink/week for oesophagus (World Cancer Research Fund/American Institute for Cancer Research, 2007). Previously reported pooled RRs for the association between current drinking and colorectal cancer are as follows: 1.41 (95% CI: 1.16, 1.72) for colorectal cancer for an intake of ≥45 g/day compared with abstention (Cho *et al.*, 2004); 1.50 (95% CI: 1.25, 1.79) for colon cancer and 1.63 (95%

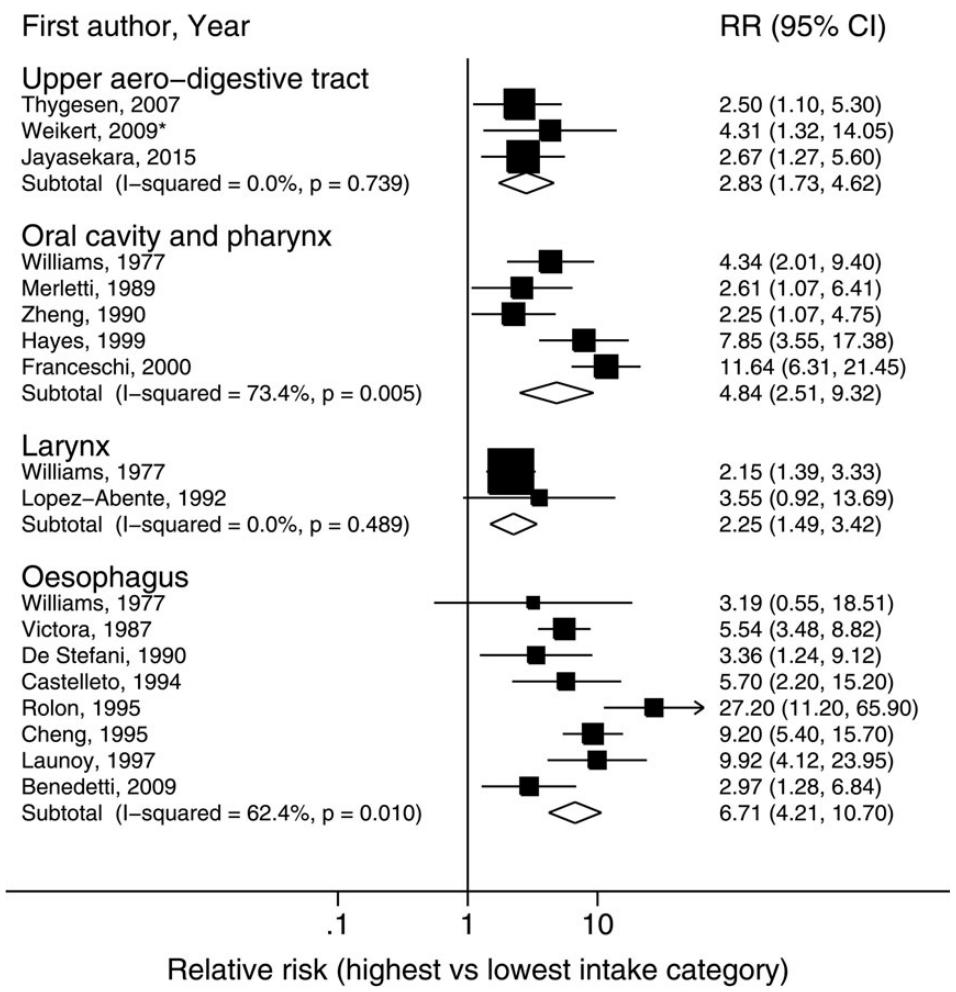

Fig. 4. Forest plot displaying meta-analysis of reported RRs for the associations of alcohol consumption measured during lifetime/over time with cancers of the UADT, oral cavity and pharynx and oesophagus. Midpoint of box representing each study indicates RR, and area of box indicates weight given to the study (inverse of the sum of the individual sampling variance and the between-study variance); diamonds, pooled RR. RR, relative risk; CI, confidence interval. Thygesen *et al.* (2007), Weikert *et al.* (2009) and Jayasekara *et al.* (2015) cohort studies; others case-control studies. *RR and CIs recalculated for the highest category of alcohol intake making the lowest intake category the reference category. RRs reported by Williams and Horm (1977) for lip/tongue, gum/mouth and pharynx separately by sex were internally pooled. RRs reported byWeikert *et al.* (2009), Merletti *et al.* (1989), Hayes *et al.* (1999), De Stefani *et al.* (1990) and Williams and Horm (1977) (for larynx and for oesophagus) for men and women separately were internally pooled. Victora *et al.* (1987) did not report RR or CIs while Williams and Horm (1977) did not report CIs, which we calculated using raw data.

CI: 1.35, 1.97) for rectal cancer comparing highest intake category to the lowest (Moskal *et al.*, 2007).

Generally, the strength of association based on our findings for these cancers did not differ markedly from what had been reported previously predominantly using intake around a point in time. Taken at face value, this finding raises an interesting issue for further investigation. However, we recognize that the result may be influenced by analytical procedures and by response biases. Thus the result of averaging intake over time into a single summary measure (e.g. grams/day or drinks/day) may have been a numeric value which did not differ much between lifetime and current intake. And retrospective recall of previous intake may have been influenced by the current level of drinking. It also needs to be noted that the pattern of intake, including binge drinking and the variation in intake from early adulthood to middle age, may be needed to capture a more complete measure of alcohol drinking during life. A direct comparison between lifetime and current intakes from identical studies and cancer risk was not undertaken, as only a very few studies had reported RRs for both current and lifetime intake.

The biological mechanisms whereby alcohol causes cancer are not clearly understood. Alcohol is thought to exert its action through reactive metabolites, oxidative stress followed by lipid peroxidation, epigenetic alterations due to a reduced methyl transfer, decreased retinoic acid concentrations and by interfering with oestrogen metabolism that may influence hormone levels and oestrogen receptors (World Cancer Research Fund/American Institute for Cancer Research, 2007; Seitz *et al.*, 2012). A direct carcinogenic effect of acetaldehyde on mucosal cells (World Cancer Research Fund/American Institute for Cancer Research, 2007; International Agency for Research on Cancer, 2010) and alcohol acting as a solvent to enable the penetration of other carcinogenic molecules (Schottenfeld and Fraumeni, 2006) has also been mentioned. Acetaldehyde also increases the rate of cellular proliferation in the rectal mucosa (Seitz and Simanowski, 1988). In addition, heterozygous carriers of variant allele ALDH2*2 (which encodes an inactive subunit of an enzyme that detoxifies acetaldehyde to acetate) are at a higher risk of developing alcohol-related aero-digestive tract cancers due to higher levels of acetaldehyde (Lewis and Smith, 2005; Matsuda *et al.*, 2006).

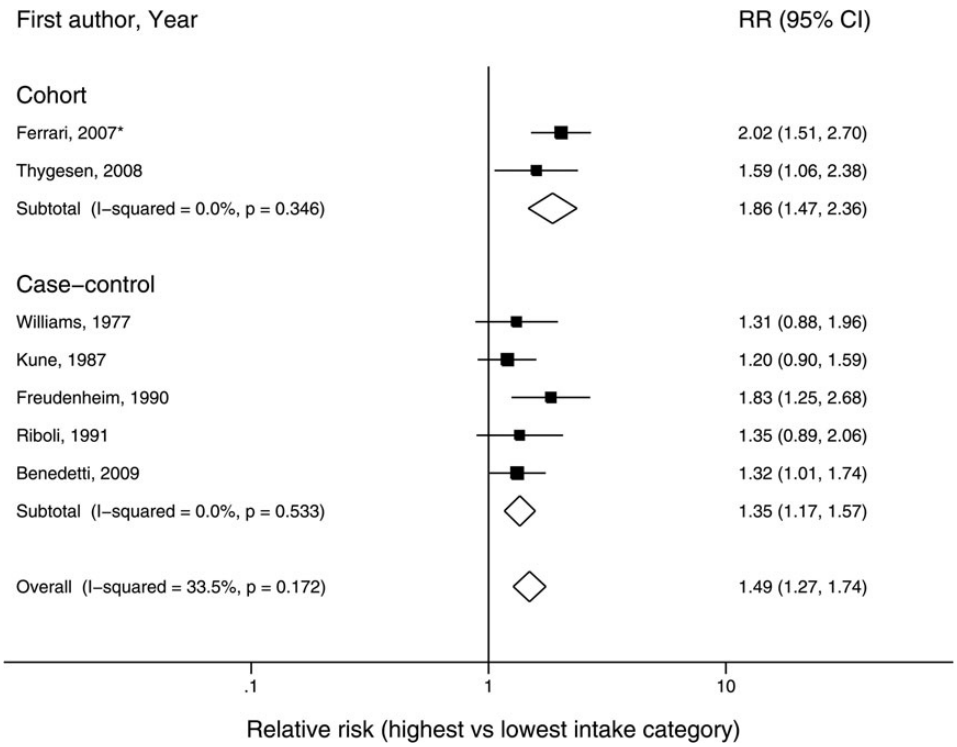

Fig. 5. Forest plot displaying meta-analysis of reported RRs for the association between alcohol consumption measured during lifetime/over time and colorectal cancer. Midpoint of box representing each study indicates RR, and area of box indicates weight given to the study (inverse of the sum of the individual sampling variance and the between-study variance); diamonds, pooled RR. RR, relative risk; CI, confidence interval. **RR and CIs recalculated for the highest category of alcohol intake making the lowest intake category the reference category. RRs reported by Benedetti *et al.* (2009) separately for colon and rectal cancer in men, by Freudenheim *et al.* (1990) for rectal cancer in men and women separately, and by Williams and Horm (1977), Kune *et al.* (1987) and Riboli *et al.* (1991) for colon and rectal cancer separately by sex were internally pooled.Williams and Horm (1977), Kune *et al.* (1987) and Riboli *et al.* (1991) did not report CIs, which we calculated using raw data.

These different mechanisms put forward vary in the extent to which they could have an effect in the relatively short term, or cumulatively over time, or in both time-spans. Brooks and Zakhari have described how for breast cancer alcohol could potentially play a role either as a cumulative carcinogen, or alternatively as a tumour promoter (Brooks and Zakhari, 2013). These mechanisms point to the relevance of drinking patterns respectively in the longer and in the shorter term. If the cumulative carcinogen theory is correct, then measuring intake from early adulthood onward is a more accurate measure of exposure than a measure of current intake. On the other hand, a pooled analysis of case-control studies has shown that higher daily intake for a shorter duration was associated with a higher risk of head and neck cancer than lower daily intake for a longer duration (Lubin *et al.*, 2009).

The main strength of this systematic review was that most studies included had a considerable time interval between measurements of exposure, thus allowing adequate time for participants' consumption to vary over time. The present analysis also had several potential limitations. First, a potential incompleteness of the literature search cannot be excluded considering that many studies, especially the earliest case-control studies, did not specifically mention that intake was measured over time. The inability to capture all relevant studies has been acknowledged as a limitation of electronic databases (Stroup *et al.*, 2000). We have minimized this effect by conducting a comprehensive electronic search, and complementing that with an elaborate secondary search of reference lists. Second, there was a degree of heterogeneity between studies. This was to be expected considering that alcoholic beverages are produced and marketed differently, contain varying strengths of ethanol and are offered in containers of different sizes, shapes and names (Stockwell and Chikritzhs, 2000). Third, a meta-analysis cannot address problems with confounding that could be inherent in the original studies. However, most authors had adjusted for key potential confounders, e.g. all studies on UADT cancer included some adjustment for smoking. Assessing the interaction between smoking and alcohol intake for UADT cancer was not undertaken in the present study. Pooled RRs were not presented separately for men and women for UADT and colorectal cancer considering the number of available studies. Finally, misclassification of alcohol intake is common in self-reported observational studies of alcohol consumption where bias usually arises from under-reporting of alcohol consumption (Dawson, 1998; White *et al.*, 2002). In cohort studies, this would generally lead to underestimates of associations, whereas the direction of bias in case-control studies is less predictable. Similarly, the alcohol intake could also have varied during follow-up in cohort studies leading to misclassification.

In conclusion, our findings reinforce an association between alcohol intake during lifetime and breast, UADT and colorectal cancer, but show that measuring lifetime intake may not substantially increase the strength of the associations between alcohol and cancers of the breast, UADT and colorectum.

FUNDING

The funding sources played no role in the design and conduct of the study; the collection, management, analysis and interpretation of the data; or the preparation, review and approval of the manuscript.

H.J. was the recipient of a postgraduate scholarship from the National Health and Medical Research Council (#1017346). R.R.'s position was funded by the Victorian Department of Health and the Foundation for Alcohol Research and Education.

CONFLICT OF INTEREST STATEMENT

None declared.

REFERENCES

Adami HO, Lund E, Bergstrom R, *et al.* (1988) Cigarette smoking, alcohol consumption and risk of breast cancer in young women. *Br J Cancer* **58**:832–7.

Baan R, Straif K, Grosse Y, *et al.* (2007) Carcinogenicity of alcoholic beverages. *Lancet Oncol* **8**:292–3.

Bagnardi V, Blangiardo M, La Vecchia C, *et al.* (2001) A meta-analysis of alcohol drinking and cancer risk. *Br J Cancer* **85**:1700–5.

Benedetti A, Parent ME, Siemiatycki J. (2009) Lifetime consumption of alcoholic beverages and risk of 13 types of cancer in men: results from a case-control study in Montreal. *Cancer Detect Prev* **32**:352–62.

Berstad P, Ma H, Bernstein L, *et al.* (2008) Alcohol intake and breast cancer risk among young women. *Breast Cancer Res Treat* **108**:113–20.

Brooks PJ, Zakhari S. (2013) Moderate alcohol consumption and breast cancer in women: from epidemiology to mechanisms and interventions. *Alcohol Clin Exp Res* **37**:23–30.

Castelletto R, Castellsague X, Munoz N, *et al.* (1994) Alcohol, tobacco, diet, mate drinking, and esophageal cancer in Argentina. *Cancer Epidemiol Biomarkers Prev* **3**:557–64.

Chandran U, Zirpoli G, Ciupak G, *et al.* (2013) Does alcohol increase breast cancer risk in African-American women? Findings from a case-control study. *Br J Cancer* **109**:1945–53.

Chen WY, Rosner B, Hankinson SE, *et al.* (2011) Moderate alcohol consumption during adult life, drinking patterns, and breast cancer risk. *JAMA* **306**:1884–90.

Cheng KK, Duffy SW, Day NE, *et al.* (1995) Stopping drinking and risk of oesophageal cancer. *BMJ* **310**:1094.

Cho E, Smith-Warner SA, Ritz J, *et al.* (2004) Alcohol intake and colorectal cancer: a pooled analysis of 8 cohort studies. *Ann Intern Med* **140**:603–13.

Colditz GA. (1993) Epidemiology of breast cancer. Findings from the nurses' health study. *Cancer* **71**:1480–9.

Dawson DA. (1998) Measuring alcohol consumption: limitations and prospects for improvement. *Addiction* **93**:965–8.

DerSimonian R, Laird N. (1986) Meta-analysis in clinical trials. *Control Clin Trials* **7**:177–88.

De Stefani E, Muñoz N, Estève J, *et al.* (1990) Mate drinking, alcohol, tobacco, diet, and esophageal cancer in Uruguay. *Cancer Res* **50**:426–31.

Egger M, Smith GD, Schneider M, *et al.* (1997) Bias in meta-analysis detected by a simple, graphical test. *BMJ* **315**:629–34.

Ellison RC, Zhang Y, McLennan CE, *et al.* (2001) Exploring the relation of alcohol consumption to risk of breast cancer. *Am J Epidemiol* **154**:740–7.

Fedirko V, Tramacere I, Bagnardi V, *et al.* (2011) Alcohol drinking and colorectal cancer risk: an overall and dose–response meta-analysis of published studies. *Ann Oncol* **22**:1958–72.

Ferrari P, Jenab M, Norat T, *et al.* (2007) Lifetime and baseline alcohol intake and risk of colon and rectal cancers in the European prospective investigation into cancer and nutrition (EPIC). *Int J Cancer* **121**:2065–72.

Franceschi S, Levi F, Dal Maso L, *et al.* (2000) Cessation of alcohol drinking and risk of cancer of the oral cavity and pharynx. *Int J Cancer* **85**:787–90.

Freudenheim JL, Graham S, Marshall JR, *et al.* (1990) Lifetime alcohol intake and risk of rectal cancer in western New York. *Nutr Cancer* **13**:101–9.

Freudenheim JL, Marshall JR, Graham S, *et al.* (1995) Lifetime alcohol consumption and risk of breast cancer. *Nutr Cancer* **23**:1–11.

Harrell FE Jr, Lee KL, Pollock BG. (1988) Regression models in clinical studies: determining relationships between predictors and response. *J Natl Cancer Inst* **80**:1198–202.

Hayes RB, Bravo-Otero E, Kleinman DV, *et al.* (1999) Tobacco and alcohol use and oral cancer in Puerto Rico. *Cancer Causes Control* **10**:27–33.

Herrinton LJ, Saftlas AF, Stanford JL, *et al.* (1993) Do alcohol intake and mammographic densities interact in regard to the risk of breast cancer? *Cancer* **71**:3029–35.

Higgins JPT, Green S. (2011) Cochrane handbook for systematic reviews of interventions version 5.1.0 [updated March 2011]. The Cochrane Collaboration. Available from www.cochrane-handbook.org.

Higgins JPT, Thompson SG. (2002) Quantifying heterogeneity in a meta-analysis. *Stat Med* **21**:1539–58.

Holmberg L, Baron JA, Byers T, *et al.* (1995) Alcohol intake and breast cancer risk: effect of exposure from 15 years of age. *Cancer Epidemiol Biomarkers Prev* **4**:843–7.

International Agency for Research on Cancer (2010) *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans*, vol. **96**. Lyon, France: International Agency for Research on Cancer.

Jackson D, White IR, Thompson SG. (2010) Extending DerSimonian and Laird's methodology to perform multivariate random effects meta-analyses. *Stat Med* **29**:1282–97.

Jayasekara H, MacInnis RJ, Hodge AM, *et al.* (2015) Lifetime alcohol consumption and upper aero-digestive tract cancer risk in the Melbourne Collaborative Cohort Study. *Cancer Causes Control* **26**:297–301.

Johnstone BM, Leino EV, Ager CR, *et al.* (1996) Determinants of life-course variation in the frequency of alcohol consumption: meta-analysis of studies from the collaborative alcohol-related longitudinal project. *J Stud Alcohol* **57**:494–506.

Katsouyanni K, Trichopoulou A, Stuver S, *et al.* (1994) Ethanol and breast cancer—an association that may be both confounded and causal. *Int J Cancer* **58**:356–61.

Kune S, Kune GA, Watson LF. (1987) Case-control study of alcoholic beverages as etiological factors: the Melbourne Colorectal Cancer Study. *Nutr Cancer* **9**:43–56.

Launoy G, Milan CH, Faivre J, *et al.* (1997) Alcohol, tobacco and oesophageal cancer: effects of the duration of consumption, mean intake and current and former consumption. *Br J Cancer* **75**:1389–96.

Lenz SK, Goldberg MS, Labreche F, *et al.* (2002) Association between alcohol consumption and postmenopausal breast cancer: results of a case--control study in Montreal, Quebec, Canada. *Cancer Causes Control* **13**:701–10.

Lewis SJ, Smith GD. (2005) Alcohol, ALDH2, and esophageal cancer: a meta-analysis which illustrates the potentials and limitations of a Mendelian randomization approach. *Cancer Epidemiol Biomarkers Prev* **14**:1967–71.

Lieberman DA, Prindiville S, Weiss DG, *et al.* (2003) Risk factors for advanced colonic neoplasia and hyperplastic polyps in asymptomatic individuals. *JAMA* **290**:2959–67.

Liu Y, Colditz GA, Rosner B, *et al.* (2013) Alcohol intake between menarche and first pregnancy: a prospective study of breast cancer risk. *J Natl Cancer Inst* **105**:1571–8.

Longnecker MP, Newcomb PA, Mittendorf R, *et al.* (1995a) Risk of breast cancer in relation to lifetime alcohol consumption. *J Natl Cancer Inst* **87**:923–9.

Longnecker MP, Paganini-Hill A, Ross RK. (1995b) Lifetime alcohol consumption and breast cancer risk among postmenopausal women in Los Angeles. *Cancer Epidemiol Biomarkers Prev* **4**:721–5.

Lopez-Abente G, Pollan M, Monge V, *et al.* (1992) Tobacco smoking, alcohol consumption, and laryngeal cancer in Madrid. *Cancer Detect Prev* **16**:265–71.

Lubin JH, Purdue M, Kelsey K, *et al.* (2009) Total exposure and exposure rate effects for alcohol and smoking and risk of head and neck cancer: a pooled analysis of case-control studies. *Am J Epidemiol* **170**:937–47.

Männistö S, Virtanen M, Kataja V, *et al.* (2000) Lifetime alcohol consumption and breast cancer: a case-control study in Finland. *Public Health Nutr* **3**:11–8.

Matsuda T, Yabushita H, Kanaly RA, *et al.* (2006) Increased DNA damage in ALDH2-deficient alcoholics. *Chem Res Toxicol* **19**:1374–8.

Merletti F, Boffetta P, Ciccone G, *et al.* (1989) Role of tobacco and alcoholic beverages in the etiology of cancer of the oral cavity/oropharynx in Torino, Italy. *Cancer Res* **49**:4919–24.

Moskal A, Norat T, Ferrari P, *et al*. (2007) Alcohol intake and colorectal cancer risk: a dose–response meta-analysis of published cohort studies. *Int J Cancer* **120**:664–71.

Orsini N, Bellocco R, Greenland S. (2006) Generalized least squares for trend estimation of summarized dose–response data. *Stata J* **6**:40–57.

Orsini N, Li R, Wolk A, *et al*. (2012) Meta-analysis for linear and nonlinear dose–response relations: examples, an evaluation of approximations, and software. *Am J Epidemiol* **175**:66–73.

Riboli E, Cornee J, Macquart-Moulin G, *et al*. (1991) Cancer and polyps of the colorectum and lifetime consumption of beer and other alcoholic beverages. *Am J Epidemiol* **134**:157–66.

Rolon PA, Castellsague X, Benz M, *et al*. (1995) Hot and cold mate drinking and esophageal cancer in Paraguay. *Cancer Epidemiol Biomarkers Prev* **4**:595–605.

Russell M, Peirce RS, Vana JE, *et al*. (1998) Relations among alcohol consumption measures derived from the Cognitive Lifetime Drinking History. *Drug Alcohol Rev* **17**:377–87.

Schottenfeld D, Fraumeni JF. (2006) *Cancer Epidemiology and Prevention*. 3rd ed. Oxford, New York: Oxford University Press.

Seitz HK, Simanowski UA. (1988) Alcohol and carcinogenesis. *Annu Rev Nutr* **8**:99–119.

Seitz HK, Pelucchi C, Bagnardi V, *et al*. (2012) Epidemiology and pathophysiology of alcohol and breast cancer: update 2012. *Alcohol Alcohol* **47**:204–12.

Skog O, Rossow I. (2006) Flux and stability: individual fluctuations, regression towards the mean and collective changes in alcohol consumption. *Addiction* **101**:959–70.

Smith-Warner SA, Spiegelman D, Yaun S, *et al*. (1998) Alcohol and breast cancer in women: a pooled analysis of cohort studies. *JAMA* **279**:535–40.

Stockwell T, Chikritzhs T. (2000) *International Guide for Monitoring Alcohol Consumption and Related Harm*. Geneva, Switzerland: Department of Mental Health and Substance Dependence, Noncommunicable Diseases and Mental Health Cluster, World Health Organization.

Stroup DF, Berlin JA, Morton SC, *et al*. (2000) Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. *JAMA* **283**:2008–12.

Swanson CA, Coates RJ, Malone KE, *et al*. (1997) Alcohol consumption and breast cancer risk among women under age 45 years. *Epidemiology* **8**:231–7.

Terry MB, Zhang FF, Kabat G, *et al*. (2006) Lifetime alcohol intake and breast cancer risk. *Ann Epidemiol* **16**:230–40.

Thygesen LC, Keiding N, Johansen C, *et al*. (2007) Changes in alcohol intake and risk of upper digestive tract cancer. *Acta Oncologica* **46**:1085–9.

Thygesen LC, Wu K, Gronbaek M, *et al*. (2008) Alcohol intake and colorectal cancer: a comparison of approaches for including repeated measures of alcohol consumption. *Epidemiology* **19**:258–64.

Tjonneland A, Christensen J, Thomsen BL, *et al*. (2004) Lifetime alcohol consumption and postmenopausal breast cancer rate in Denmark: a prospective cohort study. *J Nutr* **134**:173–8.

Victora CG, Muñoz N, Day NE, *et al*. (1987) Hot beverages and oesophageal cancer in southern brazil: a case-control study. *Int J Cancer* **39**:710–6.

Weaver AM, McCann SE, Nie J, *et al*. (2013) Alcohol intake over the life course and breast cancer survival in Western New York exposures and breast cancer (WEB) study: quantity and intensity of intake. *Breast Cancer Res Treat* **139**:245–53.

Weikert C, Dietrich T, Boeing H, *et al*. (2009) Lifetime and baseline alcohol intake and risk of cancer of the upper aero-digestive tract in the European Prospective Investigation into Cancer and Nutrition (EPIC) study. *Int J Cancer* **125**:406–12.

White IR, Altmann DR, Nanchahal K. (2002) Alcohol consumption and mortality: modelling risks for men and women at different ages. *BMJ* **325**:191.

Williams RR, Horm JW. (1977) Association of cancer sites with tobacco and alcohol consumption and socioeconomic status of patients: interview study from the third National Cancer Survey. *J Natl Cancer Inst* **58**:525–47.

World Cancer Research Fund / American Institute for Cancer Research (2007) *Food, Nutrition, Physical Activity, and the Prevention of Cancer: A Global Perspective*. Washington: AICR.

Young TB. (1989) A case control study of breast cancer and alcohol consumption habits. *Cancer* **64**:552–8.

Zheng TZ, Boyle P, Hu HF, *et al*. (1990) Tobacco smoking, alcohol consumption, and risk of oral cancer: a case-control study in Beijing, People's Republic of China. *Cancer Causes Control* **1**:173–9.