

# Light alcohol drinking and cancer: a meta-analysis

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**Background:** There is convincing evidence that alcohol consumption increases the risk of cancer of the colorectum, breast, larynx, liver, esophagus, oral cavity and pharynx. Most of the data derive from studies that focused on the effect of moderate/high alcohol intakes, while little is known about light alcohol drinking (up to 1 drink/day).

**Patients and methods:** We evaluated the association between light drinking and cancer of the colorectum, breast, larynx, liver, esophagus, oral cavity and pharynx, through a meta-analytic approach. We searched epidemiological studies using PubMed, ISI Web of Science and EMBASE, published before December 2010.

**Results:** We included 222 articles comprising ~92 000 light drinkers and 60 000 non-drinkers with cancer. Light drinking was associated with the risk of oropharyngeal cancer [relative risk, RR = 1.17; 95% confidence interval (CI) 1.06–1.29], esophageal squamous cell carcinoma (SCC) (RR = 1.30; 95% CI 1.09–1.56) and female breast cancer (RR = 1.05; 95% CI 1.02–1.08). We estimated that ~5000 deaths from oropharyngeal cancer, 24 000 from esophageal SCC and 5000 from breast cancer were attributable to light drinking in 2004 worldwide. No association was found for colorectum, liver and larynx tumors.

**Conclusions:** Light drinking increases the risk of cancer of oral cavity and pharynx, esophagus and female breast.

**Key words:** alcohol, cancer, lifestyle, meta-analysis, public health, risk factor

## Introduction

The broad range of alcohol consumption patterns, from heavy to occasional hazardous drinking, creates significant public health and safety problems in nearly all countries. Globally, 6.2% and 1.1% of all male and female deaths are attributable to alcohol, and in 2004 over 2.2 million deaths were related to alcohol worldwide [1].

Regarding the association with cancer, 3.6% of all cancers (5.2% in men, 1.7% in women) are attributable to alcohol drinking [2]. There is convincing evidence that alcohol consumption increases the risk of cancer in the colorectum, female breast, larynx, liver, esophagus, oral cavity and pharynx [3] and a substantial increase in the risk of cancer with increasing doses of alcohol was observed for all those cancer sites [4]. Most of the evidence on the alcohol–cancer link derive from studies that focused on high and moderate intake

of alcohol, therefore a solid evidence of an association between low levels of alcohol intake and cancer is still lacking. From a public health point of view, it is of considerable interest to establish whether light drinking is associated with cancer, even if it implied only a modest risk increase. In fact, a risk increase of small magnitude affecting a large proportion of population could convert into major negative health impact [5, 6].

Therefore, to clarify this issue, we carried out a meta-analysis of published studies to evaluate the association between light drinking (defined as up to 1 drink/day) and cancer.

## Materials and methods

### Search rationale

We restricted the investigation on light drinking to those tumor sites for which there is evidence of an increased risk associated with alcohol consumption in general. For this purpose, we started from the indications drawn up by the International Agency for Research on Cancer [3], which listed all the tumor sites for which there is sufficient evidence for

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carcinogenicity (oral cavity and pharynx, larynx, esophagus, liver, colorectum and female breast). For the esophagus, we decided to restrict our analyses to esophageal squamous cell carcinoma (SCC), since the alcohol–cancer association was mostly appreciable in that histological subtype [7, 8].

### search strategy

We carried out a literature search in Medline, ISI Web of Science (Science Citation Index Expanded) and EMBASE for epidemiological studies published before December 2010. For the sake of completeness, we also reviewed references from all relevant studies, reviews and meta-analyses published on the alcohol–cancer association to identify additional studies. The key words used for the literature search are reported in supplementary material S1, available at *Annals of Oncology* online. We limited our search to studies published in English.

### inclusion criteria

Articles were included in the meta-analysis only if they satisfied the following criteria:

- Case–control or cohort studies published as original articles (abstracts, letters, reviews and meta-analyses were excluded).
- Studies that reported findings expressed as odds ratio (OR), relative risk (RR) or hazard ratio (or reporting sufficient data to compute them) for light drinkers ( $\leq 12.5$  g ethanol;  $\leq 1$  drink) versus non-drinkers.
- Studies that reported standard errors or confidence intervals (CIs) of the risk estimates, or provided sufficient data to calculate them.

We excluded studies reporting on a specific type of alcoholic beverage only (e.g. beer only) because in those studies the non-drinkers of a specific beverage were possibly drinkers of other types of alcoholic beverages.

### data abstraction

The reports available for each cancer site were independently reviewed by one of the authors to determine the eligibility of each article for inclusion in the meta-analysis. Doubts or disagreement were resolved by consensus among all the investigators. When the results of the same study were published in more than one paper, only the most recent and/or complete article was included in the analysis.

For each included study, we extracted details on study design, outcome, country, gender, RR estimates and 95% CIs, adjustment variables, and, when available, the number of cases and controls (case–control studies) or number of events and subjects at risk/person-years (cohort studies) for light drinkers and non-drinkers. We also recorded whether the reference category of non-drinkers included occasional drinkers or not. Where possible, separate estimates were extracted for males and females.

Since different studies used different units of measurement to express alcohol consumption (grams, milliliters, ounces or drinks consumed every day, week, month or year) we used grams per day (g/day) as a standard measure of ethanol intake using the following equivalencies: 0.8 g/ml = 28 g/ounce = 12.5 g/drink. Moreover, since the included studies usually reported alcohol exposure in intervals, we decided to consider as light every interval whose midpoint was  $\leq 12.5$  g per day (or one drink per day) of alcohol. Also, some studies reported two or more adjusted risk estimates for light drinking (e.g. 6 g/day and 12 g/day). In that case, we combined them into a single estimate using the method for pooling non-independent estimates described by Hamling et al. [9]. This method uses the number of exposed to different levels of alcohol and non-exposed subjects and the associated reported risk estimates to derive a set of pseudo-numbers of

cases and controls/subjects at risk, by taking into account the correlation between the original estimates due to the common reference group. These pseudo-numbers can then be used to calculate a single pooled adjusted risk estimate and CI.

### statistical methods

Because cancer is a relatively rare outcome, we assumed that ORs, risk ratios and rate ratios were all comparable estimates of the RR [10]. Measures of association and the corresponding CIs were translated into log (RR)s and the corresponding variances.

We computed a pooled RR of site-specific cancer for light drinkers versus non-drinkers, using random-effects models. We used random-effects models to estimate pooled RRs in order to take into account the heterogeneity, albeit small, of the risk estimates. Each study log(RR) was weighted by the inverse of its variance. Weights were taken equal to the inverse of the reported within-study variance plus the between-study variance component  $\tau^2$ . The moment estimator of the between-study variance was used [11].

We evaluated the statistical heterogeneity among the studies using  $I^2$ , which is the proportion of total variation contributed by the between-study variance [12]. We examined the publication bias through the funnel plots and the Begg's rank correlation method [13].

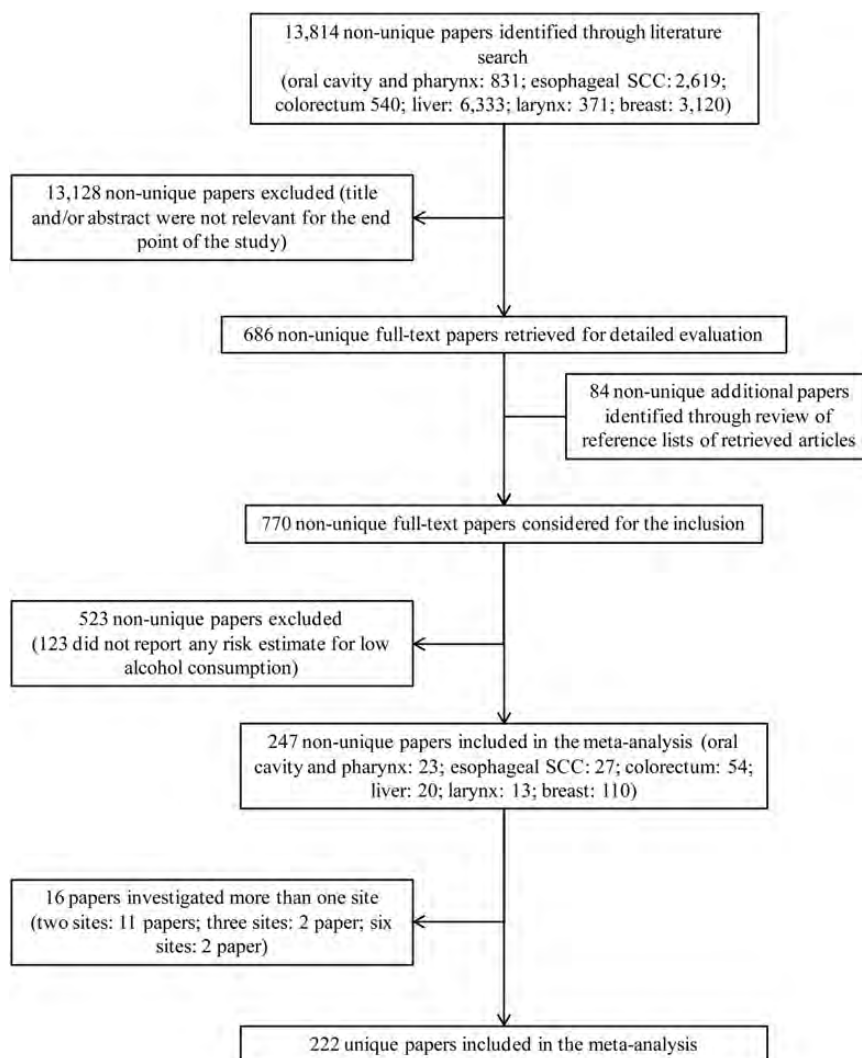
We carried out subgroup analyses and meta-regression models to investigate potential sources of between-study heterogeneity. We used a chi-square statistic to test for differences of summary estimates among the subgroups [10].

We estimated the proportion and number of cancer deaths attributable to light alcohol drinking and to alcohol drinking at any dose using the methods described in Gmel et al. [14]. For each cancer site and World Health Organization (WHO) subregion, we obtained the age-specific and dose-specific distribution of drinkers among adults for 2004 from the Global Burden of Disease project [15], along with number of deaths. For light drinking (up to 1 drink/day), we considered the pooled RRs estimated in the present meta-analysis. For drinking at any dose, we used the dose-specific RRs estimated in the meta-analysis of Bagnardi et al. [4]. The RRs were specific for sex, but not for age or WHO subregion.

We carried out all analyses using SAS software, version 9.1 (SAS Institute Inc., Cary, North Carolina). All *P* values were two-sided.

### results

Figure 1 shows the detailed paper selection strategy for the meta-analysis. We identified a total of 13 814 non-unique papers (some papers were counted more than once if they reported on more than one cancer site of interest). We screened titles and abstracts for eligibility and excluded 13 128 non-unique papers because they were not strictly related to the alcohol–cancer association. The remaining 686 articles were considered of interest, and the full text was retrieved for detailed evaluation. We also reviewed their references and identified 84 additional papers of possible interest, making a total of 770 non-unique papers. Subsequently, 523 papers were excluded because they did not satisfy the inclusion criteria. A total of 247 non-unique papers reporting site-specific risk estimates were included in the meta-analysis. Sixteen papers reported estimates for two or more cancer sites and accounted for a total of 25 risk estimates. Accordingly, 222 unique papers were considered. The complete reference list by cancer site is



**Figure 1.** Flowchart of selection of studies for inclusion in meta-analysis.

reported in supplementary material S2, available at *Annals of Oncology* online.

Table 1 summarizes the main characteristics of the included studies by specific cancer site.

The analysis included ~60 000 cancer cases in the reference category of non-drinkers and 92 000 in the light drinkers' category. These numbers are slightly underestimated, since for 16 studies the number of exposed and/or non-exposed cases was not reported.

One hundred and ten out of 222 included studies (50%) investigated the association between light drinking and breast cancer, accounting for >75% of the total cases. Fifty-four studies (24%) reported estimates for at least one of the upper aerodigestive sites (23 estimates for oral cavity and pharynx, 27 for esophageal SCC and 13 for larynx), 54 studies (24%) for colorectal cancer (30 estimates for the colorectum, 19 for colon and rectum separately, 4 for colon only and 1 for rectum only). Twenty studies reported estimates for liver cancer.

Overall, case-control was the most common study design (68% of studies); 46% of the included studies were from North America, 29% from Europe, 18% from Asia and 6% from other

regions or from more than one region; 22% of the studies did not present gender specific estimates; 46% of the reported estimates were adjusted for the main site-specific risk factors (for a list of considered site-specific risk factors, see supplementary material S3, available at *Annals of Oncology* online), while 15% of the estimates included occasional drinkers in the reference category.

Figure 2 shows the estimates for light drinkers versus non-drinkers reported in each single study, by site and year of publication. More than half the estimates (52%) derived from papers published since 2001. Heterogeneity between the study estimates was high ( $I^2 > 50\%$ ) for esophageal SCC, breast cancer and liver cancer, moderate or low for other sites.

Figure 3 shows the site-specific pooled RRs. Low alcohol intake was found to significantly increase the risk of esophageal SCC (RR = 1.30; 95% CI 1.09–1.56), oral cavity and pharynx cancer (RR = 1.17; 95% CI 1.06–1.29) and female breast cancer (RR = 1.05; 95% CI 1.02–1.08). No significant association was observed between light drinking and cancer of the colorectum (RR = 0.99, 95% CI 0.95–1.04), liver (RR = 1.03, 95% CI 0.90–1.17) and larynx (RR = 0.90, 95% CI 0.73–1.10).

**Table 1.** Characteristics of studies included in the meta-analysis

Cancer site	No. of studies (cases in reference category/cases in light drinking category) <sup>a</sup>	Study design		Outcome		Geographical area			Sex <sup>b</sup>		Adjusted estimates <sup>c</sup>	Occasional drinkers in reference category		
		Cohort	C-C	Incidence	Death	Eu.	North America	Asia	Other/mixed	M			W	M + W
Oral cavity and pharynx	23 (2783/2036)	3	20	21	2	5	12	6	0	11	7	9	19	5
Esophageal SCC	27 (1481/1841)	9	18	24	3	7	8	10	2	14	5	12	21	0
Colorectum	54 (11 574/12 013)	26	28	50	4	13	23	16	2	26	22	19	25	9
Liver	20 (2034/2592)	7	13	15	5	5	3	12	0	11	7	8	9	1
Larynx	13 (504/846)	3	10	12	1	4	6	3	0	8	3	4	7	4
Breast (female)	110 (41 995/72 902)	39	71	104	6	38	56	6	10	0	112	0	39	18
Total <sup>d</sup>	222 (60 371/92 230)	71	151	210	12	65	102	41	14	53	121	48	103	34

<sup>a</sup>Sixteen studies did not report the number of cases in the reference and/or low-dose category.  
<sup>b</sup>Studies that reported gender-specific estimates were counted twice (in both M and F columns).  
<sup>c</sup>The site-specific list of main confounders considered is reported in supplementary material Appendix S2, available at *Annals of Oncology* online.  
<sup>d</sup>Sixteen studies reported more than one site-specific estimate, therefore numbers in columns do not sum up to totals (with the exception of the number of cases in brackets).  
 C-C, Case-control; Eu., Europe; M, men; W, women; SCC, squamous cell carcinoma.

Stratified analyses conducted according to study design, geographical area and gender, revealed similar estimates across strata (Table 2). Of note, the effect of low intake of alcohol on the risk of esophageal SCC was statistically significant only in studies carried out in Asian populations (RR = 1.49, 95% CI 1.12–1.98).

Little evidence for publication bias was detected for colorectal cancer ( $P = 0.059$ ). The funnel plot showed that low alcohol consumption had a large positive effect in small studies (supplementary material S4, available at *Annals of Oncology* online). There was no evidence for publication bias for other cancer sites.

The effect of the quality of the reported estimates on the pooled RRs was evaluated in a sensitivity analysis that included only estimates adjusted for the main risk factors or estimates not considering occasional drinkers in the reference category of non-drinkers. As shown in supplementary material S5, available at *Annals of Oncology* online, the results did not change appreciably from those of the overall analysis.

Table 3 shows the attributable fraction and the worldwide number of deaths due to light alcohol drinking and to alcohol drinking in general, by site and sex, in 2004. We limited this analysis to oral cavity and pharynx, esophageal SCC and breast cancer.

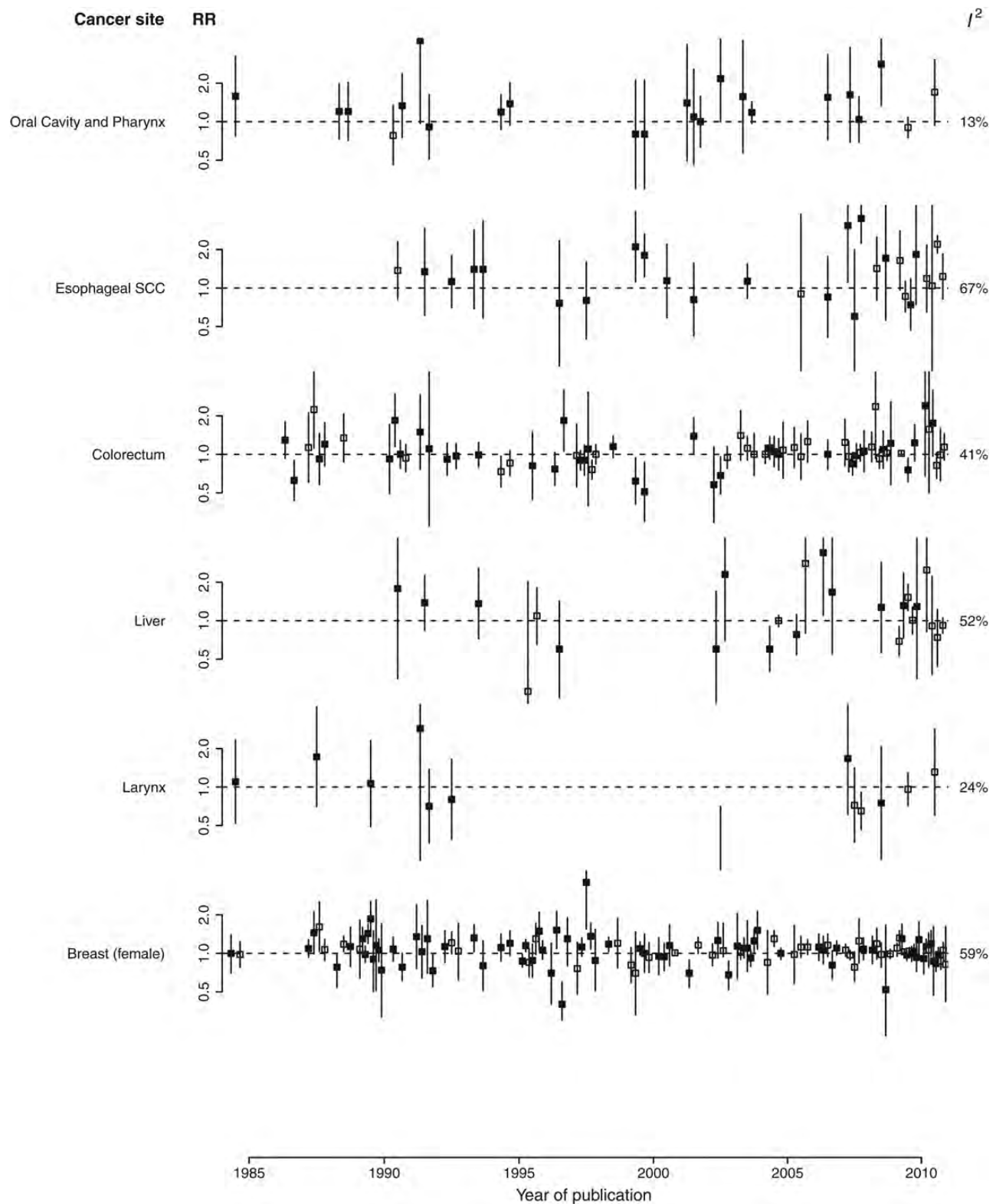
Attributable fraction due to light drinking ranged from 0.95 for breast cancer in women to 4.87 for esophageal SCC in men. We estimated that 3521 male deaths and 1359 female deaths from oropharyngeal cancer were attributable to light drinking. The same figures were 16 116 and 7728 for esophageal SCC. We estimated that 4909 female deaths from breast cancer were attributable to light drinking.

## discussion

Quantitative estimates of the association between alcohol and cancer are mainly based on the effect of moderate to high intake, while little is known about light drinking. Our meta-analysis provided sufficient evidence that alcohol, even at low intakes, significantly increases the risk of oropharyngeal cancer, esophageal SCC and breast cancer. Albeit small in absolute terms, the estimated effects might be important at the population level because of the high prevalence of light drinkers. We estimated that in 2004, ~24 000 deaths from esophageal SCC, 5000 deaths from oropharyngeal cancer and 5000 deaths from breast cancer were attributable to light drinking worldwide.

The risk of cancer for alcohol drinkers may be modulated by genetic factors, such as variants in genes for alcohol metabolism, folate and methionine metabolism and DNA repair [16, 17].

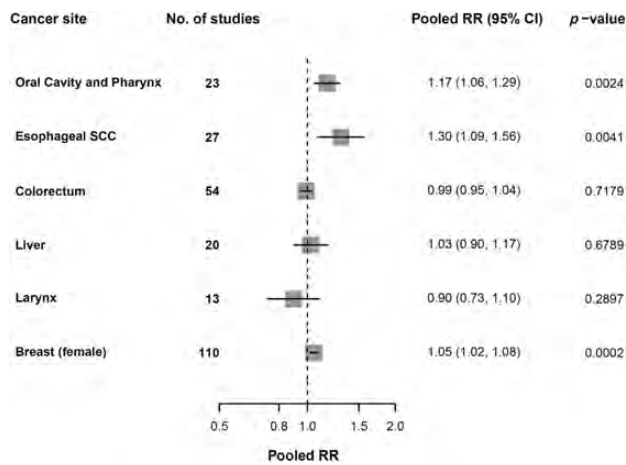
Acetaldehyde, a toxic metabolite of alcohol that damages DNA, is considered a major cause of the observed carcinogenic effect on the upper aerodigestive tract. Ingested ethanol is oxidized by the enzymes alcohol dehydrogenase (ADH), cytochrome P-450 2E1 (CYP2E1) and catalase to form acetaldehyde, which is subsequently oxidized by aldehyde dehydrogenase 2 (ALDH2) to produce acetate, not toxic to the body. Polymorphisms of the genes that encode enzymes for ethanol metabolism affect the ethanol/acetaldehyde oxidizing



**Figure 2.** Study-specific relative risk (RR) estimates for low alcohol intake, by site and year of publication. Empty square: cohort study; full square: case-control study.  $I^2$  proportion of total variation contributed by between-study variance. Gender-specific estimates from the same study were reported separately.

capacity, and are responsible for the limited action of the enzyme that converts acetaldehyde to acetate [18]. As a confirmation to this, the risk of cancers of the upper

aerodigestive tract associated with alcohol is highest in East Asia, where 28%–45% of the population has a variation of the gene ALDH2 [19, 20].



**Figure 3.** Pooled relative risk (RR) estimates by cancer site.

The association between light alcohol drinking and the risk of oropharyngeal cancer was consistent across studies. On the other hand, estimates for esophageal SCC were heterogeneous by the geographical region; the risk for Asia was the highest and the only statistically significant risk (RR 1.49 (95% CI 1.12–1.98)). This can be explained by the fact that Asian populations have a higher prevalence of polymorphisms of the genes encoding enzymes for ethanol metabolism [19] than other populations.

This meta-analysis suggests that light drinking is not associated with the risk of laryngeal cancer (RR = 0.90, (95% CI 0.73, 1.10)). The estimates were homogenous among studies. The results from a recent pooled analysis of 15 case-control studies on the risk associated with alcohol drinking among never-smokers were similar to our findings: the RR estimate for less than one drink versus non-drinking was 0.92 (0.50–1.69) [21].

While excessive alcohol intake is a consistent risk factor for colorectal neoplasia [22], we did not find a significant increase of risk of colorectal cancer due to low doses of alcohol. The association did not differ by colon and rectal subsites (data not shown), consistently with previous pooled analysis [23, 24].

These findings suggest that, even at low doses, alcohol increases the risk of cancer in those sites where there is direct contact with alcohol. This observation can be related to the local formation of acetaldehyde in the saliva via microbial ADHs [25]. Since metabolism of acetaldehyde to acetate by oral bacterial is limited, salivary acetaldehyde comes into direct contact with the mucosa of the upper digestive tract, resulting in mucosal hyperproliferation [25, 26]. As a consequence of high acetaldehyde concentrations in hyper-regenerative environment, the generation of DNA adducts may be facilitated in these tissues [27]. Moreover, hyperproliferation itself increases susceptibility to other inhaled or ingested carcinogens [6]. As an example, a synergic effect involving alcohol and tobacco smoking was shown in the upper aerodigestive tract [28, 29].

There was a moderate but significant association with breast cancer, based on the results of more than 100 studies. Women drink less than men [30], and therefore, low and moderate intakes are usually investigated more frequently and more in

**Table 2.** Comparison of pooled relative risks between main population and study characteristics

Cancer site	Study design		P*	Geographical area <sup>a</sup>			P*	Sex		P*
	Cohort RR (95% CI)	Case-control RR (95% CI)		Europe RR (95% CI)	North America RR (95% CI)	Asia RR (95% CI)		Men RR (95% CI)	Women RR (95% CI)	
Oral cavity and pharynx	1.01 (0.70, 1.45)	1.22 (1.11, 1.35)	0.312	1.44 (0.87, 2.37)	1.15 (1.01, 1.30)	1.34 (1.06, 1.68)	0.395	1.20 (1.06, 1.36)	1.09 (0.89, 1.34)	0.436
Esophageal SCC	1.34 (0.96, 1.87)	1.28 (1.04, 1.59)	0.840	1.05 (0.79, 1.38)	1.21 (0.96, 1.54)	1.49 (1.12, 1.98)	0.212	1.46 (1.19, 1.80)	1.28 (0.84, 1.96)	0.585
Colorectum	1.00 (0.95, 1.05)	0.98 (0.91, 1.06)	0.801	1.01 (0.95, 1.07)	0.97 (0.91, 1.04)	1.03 (0.90, 1.19)	0.603	1.05 (0.95, 1.16)	0.93 (0.87, 0.99)	0.052
Liver	1.00 (0.85, 1.18)	1.10 (0.86, 1.41)	0.543	1.10 (0.77, 1.58)	0.92 (0.56, 1.51)	1.02 (0.89, 1.17)	0.835	0.99 (0.89, 1.10)	1.00 (0.64, 1.57)	0.954
Larynx	0.96 (0.71, 1.30)	0.83 (0.63, 1.09)	0.487	0.84 (0.43, 1.62)	0.89 (0.66, 1.20)	0.91 (0.60, 1.37)	0.978	0.89 (0.67, 1.16)	0.93 (0.71, 1.22)	0.802
Breast (female)	1.05 (1.02, 1.09)	1.05 (1.01, 1.10)	0.955	1.05 (0.99, 1.12)	1.06 (1.02, 1.09)	1.01 (0.89, 1.14)	0.756	–	1.05 (1.02, 1.08)	–

<sup>a</sup>Studies conducted in other/mixed geographical areas were not considered in the heterogeneity analysis.

\*Chi-square testing homogeneity of pooled estimates among strata.

RR, relative risk; CI, confidence interval, SCC, squamous cell carcinoma.

**Table 3.** Attributable fraction and number of deaths due to low alcohol intake and alcohol intake at any dose worldwide, 2004

Cancer site	Sex	Low alcohol intake		Alcohol Intake (any dose)	
		AF	Number of deaths	AF	Number of deaths
Oral cavity and pharynx	Men	1.5	3521	33.5	80 155
	Women	1.4	1359	10.4	9985
Esophageal SCC	Men	4.9	16 116	27.7	91 538
	Women	4.4	7728	11.2	19 835
Breast	Women	0.9	4909	8.4	43 188

AF, attributable fraction; SCC, squamous cell carcinoma.

detail in women than in men [31]. The mechanism responsible for this association may involve increased estrogen and androgen levels [32, 33] or increased levels of plasma insulin-like growth factors produced by the liver following consumption of alcohol [34].

Alcohol intake has been recognized as a cause of several liver diseases, including cirrhosis and cancer [35]. However, no significant association was observed between light drinking and cancer of the liver (RR = 1.03, 95% CI 0.90–1.17). Given the association between heavy alcoholic beverage consumption and liver cancer, our results suggest the existence of a threshold dose below which the effect of alcohol is negligible.

Our study has several limitations. The first one is that the heterogeneity across studies reporting on esophageal, breast and liver cancer was high. Therefore, even if we used random-effects models to take heterogeneity into account, our pooled estimates should be interpreted with caution. We tried to overcome this problem by calculating pooled estimates in more homogeneous subsets of studies (subgroup analysis) and by additionally reporting pooled RRs of adjusted estimates only. A second limitation is that we could not investigate the role of different drinking patterns in modifying the effect of the total amount of alcohol consumed. In fact, the great majority of studies on the alcohol–cancer association reported information on the total amount of alcohol consumed during a period that includes both drinking and non-drinking days. A third issue is the possible interaction effect between alcohol consumption and tobacco smoking on the development of cancer. A simple yet effective way to clarify whether alcohol is an independent risk factor for cancer is to stratify the investigation by smoking status, but only a small number of studies reported the effect of light drinking in different smoking strata. A fourth limitation is the possible existence of publication bias. Anyway, the focus of many included studies was not only alcohol, so that in those studies data on alcohol were published even in the absence of significant findings. Also, the funnel plots and Begg's test did not reveal any evidence for publication bias for any cancer site. Finally, an under-reporting of alcohol consumption in drinkers may partly explain the association with light alcohol drinking. In fact, alcohol consumption might be systematically under-reported by both cases and controls (non-differential under-reporting). This would lead to an overestimation of the RR for low doses. However, studies investigating reproducibility and validity of self-reported alcohol drinking in various populations found generally satisfactory correlation coefficients [36–41]. Another problem regarding misclassification is the

possible inclusion of former drinkers in the non-drinkers category. Subjects with cancer symptoms or signs might tend to stop drinking more frequently than controls, thus diluting the risk of cancer among current drinkers. We could not address this issue because the majority of the studies did not report separate estimates between former drinkers and lifelong never drinkers.

In conclusion, alcohol increases the risk of cancer of the oral cavity and pharynx, SCC of the esophagus and breast even at low doses. Given the high proportion of light drinkers in the population and the high prevalence of these tumors, especially of breast cancer [42], even small increases in cancer risk are of great public health relevance.

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## disclosure

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