This review focuses on selected aspects of the relation between alcohol consumption and cancer risk. Heavy alcohol consumption (i.e., ≥4 drinks/day) is significantly associated with an increased risk of about 5-fold for oral and pharyngeal cancer and esophageal squamous cell carcinoma, 2.5-fold for laryngeal cancer, 50% for colorectal and breast cancers, and 30% for pancreatic cancer. These estimates are based on a large number of epidemiological studies and are generally consistent across strata of several covariates. The evidence suggests that at low doses of alcohol consumption (i.e., ≤1 drink/day) the risk is also increased by about 20% for oral and pharyngeal cancer and 30% for esophageal squamous cell carcinoma. Thus, for these sites there is little evidence of a threshold effect. While consumption of fewer than 3 alcoholic drinks/wk is not associated with an increased risk of breast cancer, an intake of 3 to 6 drinks/wk might already yield a (small) increase in risk. On the other hand, intakes up to 1 drink/day are not associated to the risk of laryngeal, colorectal, and pancreatic cancer. The positive association between alcohol consumption and the risk of head and neck cancers is independent from tobacco exposure.

INTRODUCTION

This article reviews the association between alcohol consumption and cancer risk for those sites for which sufficient or limited evidence for carcinogenicity is available (1,2), i.e., cancers of the upper digestive and respiratory tract (oral and pharyngeal cancer, esophageal squamous cell carcinoma, and laryngeal cancer), colorectum, pancreas, and breast. In particular, we focus on aspects related to amount of consumption (high and low doses, dose-risk relation) and on the interaction with tobacco for head and neck cancer.

This review does not consider adenocarcinoma of the esophagus because this neoplasm is not associated with alcohol drinking (3,4). A positive association between alcohol and liver cancer is established (1). Liver cancer is highly prevalent in China, and it has been estimated to account for almost two-thirds of all alcohol-related neoplasms in that country (5). However, liver cancer is not analyzed here because of problems in the interpretation of results from epidemiological, mainly case-control, studies. In fact, most alcohol-related liver cancers follow cirrhosis, which leads to a reduction of alcohol drinking, and thus to a substantial underestimation of the real association (6). Quantification of risks and of any threshold level for alcohol and liver cancer therefore remain open to discussion. Alcohol drinking may be inversely associated with kidney cancer and non-Hodgkin’s lymphoma (2). These issues are, however, not considered here.

HEAVY ALCOHOL DRINKING

Fig. 1 shows the main results from meta-analyses of studies on selected digestive tract cancers and larynx (7–11), and a collaborative reanalysis of breast cancer studies (12), on the relation with heavy alcohol consumption (i.e., ≥45 g/day for
FIG. 1. Heavy alcohol drinking and the risk of selected cancers. Estimates for alcohol consumption of 4 or more drinks/day vs. non/occasional drinkers, except for pancreatic (i.e., ≥3 drinks/day vs. non/occasional drinkers) and breast (i.e., ≥45 g/day vs. nondrinkers) cancers.

breast, ≥3 drinks/day for pancreatic cancer, and ≥4 drinks/day for other cancer sites). A brief description of the main studies and results for each cancer site of interest is provided below.

Alcohol consumption, together with tobacco smoking, is the major recognized risk factor for upper digestive and respiratory tract cancers (13). These neoplasms show the strongest associations with heavy alcohol consumption. In a meta-analysis of studies on oral and pharyngeal cancers (9), 29 case-control and 2 cohort studies provided information on heavy alcohol drinking. The summary relative risk (RR) for consumption of 4 or more drinks/day vs. non/occasional alcohol drinkers was 5.24 [95% confidence interval (CI) = 4.36–6.30]. The results were consistent across study design and were not materially changed after sensitivity analyses that showed no influence of 5 studies not adjusted for main risk factors, including tobacco. A companion meta-analysis (14) examining heavy alcohol consumption in relation to subsites reported higher RRs for pharyngeal (RR = 6.62; 95% CI = 4.72–9.29, based on 17 studies) than for oral (RR = 4.64; 95% CI = 3.78–5.70, 17 studies) cancers. Furthermore, the summary RRs were 4.11 (95% CI = 2.46–6.87) for tongue (5 studies), 7.76 (95% CI = 4.77–12.62) for oropharyngeal (4 studies), and 9.03 (95% CI = 4.46–18.27) for hypopharyngeal (4 studies) cancers.

A meta-analysis of heavy alcohol consumption and squamous cell carcinoma of the esophagus included 39 studies providing data on high levels of consumption (30 case-control, 9 cohort studies) (7). It reported a RR of 4.89 (95% CI = 3.84–6.23) for heavy, i.e., ≥4 drinks/day, as compared to non/occasional drinkers. The RR was slightly higher for case-control (odds ratio [OR] = 5.39; 95% CI = 4.13–7.04) than for prospective studies (RR = 3.35; 95% CI = 2.06–5.46). This can be attributed to recall and selection bias in case-control studies or to changes in drinking over time for cohort studies. When studies not adjusted at least for age, sex, and tobacco smoking were excluded, the RR increased to 5.54 (95% CI = 3.92–7.82).

Another meta-analysis investigated the association between alcohol consumption and laryngeal cancer (8). Forty studies were included, 33 of which (32 case-control, 1 cohort study) reported risk estimates for heavy alcohol consumption—again defined as 4 or more drinks/day. The summary RR was 2.62 (95% CI = 2.13–3.23) for heavy vs. non/occasional drinkers. When the analyses were conducted among subgroups of studies, i.e., those with population-based controls, or with non-drinkers only as reference category, or adjusted for tobacco and other main confounding factors, the results were similar and robust.

In 2007, the International Agency for Research on Cancer (IARC) concluded that there was sufficient evidence for colorectal cancer to be added to the list of malignancies causally
related to alcohol (1). A meta-analysis of studies published until May 2010, including 27 cohort and 34 case-control studies, reported summary results on alcohol consumption and risk of colorectal cancer (11). Seven cohort and 12 case-control studies included data on heavy consumption. Compared to non/occasional alcohol drinkers, consumption of 4 or more drinks/day yielded a 52% increased risk (95% CI = 27–81%) of colorectal cancer. The corresponding RRs were 1.43 (95% CI = 1.23–1.67) for colon and 1.59 (95% CI = 1.18–2.15) for rectal cancers. There was no heterogeneity of the estimates across strata of several covariates, including sex, study design, source of controls, quality score of the study, adjustment for relevant factors and year of publication, whereas the association was strongest in studies from Asian countries (RR = 1.81; 95% CI = 1.33–2.46) and weakest in those from European countries (RR = 1.16; 95% CI = 0.95–1.43).

The IARC working group also indicated that there was limited evidence supporting a relation between alcohol consumption and pancreatic cancer (2). A meta-analysis (10) estimated a RR of 1.22 (95% CI = 1.12–1.34) for heavy alcohol drinkers (defined as 3 or more drinks/day) as compared to non/occasional drinkers. This estimate was based on data from 8 case-control and 5 cohort studies. The RR was almost unchanged (RR = 1.23; 95% CI = 1.12–1.35) when the analyses included only studies adjusted for tobacco smoking. Consistent with this finding, a recently published analysis from the PanScan Consortium nested case-control study (15), including 1,530 cases and 1,530 controls, reported an OR of 1.38 (95% CI = 0.86–2.23) for consumption of 60 or more g/day of alcohol vs. low consumption (i.e., >0 to <5 g/day), after adjustment for smoking status and other risk factors for pancreatic cancer. The findings of the Pancreatic Cancer Case-Control Consortium (Panc4), a pooled analysis based on 5,585 cases and 11,827 controls from 10 case-control studies, gave a RR of 1.5 (95% CI = 1.2–1.8) for ≥6 drinks/day, reaching 1.6 (95% CI = 1.2–2.2) for subjects drinking ≥9 drinks/day (16). Thus, the available data provide support for a positive association between heavy alcohol drinking and risk of pancreatic cancer.

Over 100 epidemiological studies investigated the relationship between female breast cancer and alcohol consumption, and a positive association is now established (1). In a collaborative reanalysis of 53 epidemiological studies (12), including 58,515 women with breast cancer and 95,067 controls, the RRs were 1.32 (95% CI = 1.19–1.45) for consumption of 35–44 g/day and 1.46 (95% CI = 1.33–1.61) for consumption of ≥45 g/day of alcohol compared to nondrinkers. Results were adjusted for smoking and were similar across subgroups of never- and ever-smokers. Further, the Million Women Study (3), conducted in the UK on a cohort of around 1,300,000 middle-aged women, including 28,380 breast cancer cases, found a RR of 1.29 (95% CI = 1.23–1.35) for the highest level of consumption considered, i.e., ≥21 g/day, after adjustment for several covariates, including smoking.

**LIGHT ALCOHOL DRINKING**

Quantification of the association between low doses of alcohol consumption and cancers known to be alcohol-related is particularly important, as it is still unclear whether there is any threshold in intake below which no effect of alcohol drinking on cancer is evident. The same meta-analyses described above of upper digestive and respiratory tract, colorectal and pancreatic cancers also provided results for low doses of alcohol consumption, defined as 1 or fewer drink/day, while summary data on light drinking and breast cancer risk were extracted from the collaborative reanalysis of 53 epidemiological studies of breast cancer and from the Million Women Study (Fig. 2).

For oral and pharyngeal cancer, 2 meta-analyses provided evidence that an increased risk is present also at low doses of consumption (9,14). The overall RR of oral and pharyngeal cancer, based on 19 case-control and 1 cohort study, was 1.21 (95% CI = 1.10–1.33) for 1 or fewer drink/day vs. non/occasional drinkers (9). The corresponding estimates were 1.17 (95% CI = 1.01–1.35, based on 9 studies) for oral cavity and 1.23 (95% CI = 0.87–1.73, based on 5 studies) for pharyngeal cancers (14). The sensitivity analyses provided no evidence for a substantial influence of studies reporting estimates unadjusted for smoking.

A meta-analysis of esophageal squamous cell carcinoma reported an association with low doses of alcohol similar to that of oral and pharyngeal cancer (7). The summary RRs for light drinking were 1.31 (95% CI = 1.10–1.57) for the overall analysis, based on 26 studies, and 1.35 (95% CI = 0.92–1.98) for cohort studies alone (8 studies). When the analysis was stratified by geographical area, the association was stronger in Asia (RR = 1.63; 95% CI = 1.20–2.22) than in other regions of the world (RR = 1.17; 95% CI = 0.99–1.39), suggesting a potential effect modification by genetic susceptibility (17). No increase in risk with consumption of low doses of alcohol was observed in never-smokers (RR = 0.74; 95% CI = 0.47–1.16), but the estimate was based on 5 studies only.

In contrast, laryngeal cancer was not associated with alcohol consumption up to 1 drink/day (8). The summary RR for light drinking, based on 10 case-control and 2 prospective studies, was 0.88 (95% CI = 0.71–1.08). Results were materially unchanged in several subgroup analyses, including those of studies adjusted for smoking.

Almost 50 studies provided information on low doses of alcohol and colorectal cancer risk (11). No overall association was reported with colorectal (RR = 1.00; 95% CI = 0.95–1.05), colon (RR = 0.96; 95% CI, 0.90–1.02), nor rectal (RR = 1.06; 95% CI, 0.98–1.14) cancers. Results were consistent across strata of sex, geographical area, and various other covariates.

The meta-analysis on alcohol and pancreatic cancer considered moderate alcohol consumption, defined as fewer than 3 drinks/day, and found strong evidence for a lack of any positive association at low to moderate intakes (10). Seventeen case-control and 7 cohort studies were included, and the summary RR was 0.92 (95% CI = 0.86–0.97). The estimates were
FIG. 2. Light alcohol drinking and the risk of selected cancers. Estimates for alcohol consumption of 1 or fewer drink/day vs. non/occasional drinkers, except for breast cancer. *Estimate for alcohol consumption of 14 or less g/day vs. nondrinkers, calculated from Ref. 12. #Estimate for alcohol consumption of 6 or fewer drinks/week vs. nondrinkers, calculated from Ref. 3.

almost the same when case-control and prospective studies were considered separately. When we repeated the analyses comparing consumption of 1 or fewer drink/day to non/occasional drinkers, the RR was 0.91 (95% CI = 0.86–0.98). Likewise, in the Panc4 study, the OR for light drinkers was 0.91 (95% CI = 0.71–1.17) (16). Likewise, in the PanScan study (15), the pooled OR was, if anything, higher in nondrinkers (OR = 1.19; 95% CI = 0.97–1.48) compared to drinkers of less than 5 g/day of alcohol, and there was no clear association up to consumption of <30 g/day.

In the collaborative reanalysis on breast cancer (12), compared to women who drank no alcohol, the RRs were 1.01 (P > 0.05) for women reporting alcohol consumption <5 g/day and 1.03 (P > 0.05) for those consuming 5–14 g/day. The Million Women Study (3) found RRs of 1.00 (P > 0.05) for ≤2 drinks/week (i.e., <3 g/day) of alcohol and 1.08 (P < 0.05) for 3–6 drinks/wk (i.e., around 4 to 8 g/day), compared to non-drinkers. Exclusive consumption of wine showed a similar risk pattern. Thus, results for breast cancer are not totally consistent but indicate a small increase in risk even for light drinking, in the order of 1 drink/day.

DOSE-RISK

Fig. 3 shows the best-fitting dose-response relationships, extracted from the meta-analyses, between alcohol consumption and the risk of oral and pharyngeal cancer, esophageal squamous cell carcinoma, and laryngeal, colorectal, and pancreatic cancers. These were calculated using random-effects meta-regression models in a nonlinear dose-response relationship framework, providing the best-fitting 2-term fractional-polynomial model (18–19). The fact that some of the studies included in the meta-analyses were not adjusted for smoking might affect the dose-response curves. However, as reported above and since the 2 factors were largely independent (20), exclusion from the meta-analyses of studies that did not adjust for smoking did not change substantially the risk estimates. Below, we also discuss the major findings from the meta-analyses as well as from the largest investigations of breast cancer.

The dose-response analysis of alcohol consumption and oral and pharyngeal cancer showed increased risk estimates even at low doses of consumption, as the pooled RR estimate was 1.29 for 10 g/day of alcohol. The estimated RRs increased with alcohol intake following a quadratic relation and were thus
3.24 for 50 g/day, 8.61 for 100 g/day, and 13.01 for 125 g/day (9).

The random-effects, model-based, pooled estimates of RR of esophageal squamous cell carcinoma were 2.81, 5.11, and 11.00 for consumptions of 25, 50, and 100 g/day of alcohol, respectively (19). Thus, there is further indication on the relation between alcohol intake and esophageal squamous cell carcinoma. In terms of risk assessment, it is evident that high levels of alcohol consumption (i.e., more than 100 g/day, equivalent to more than 8 drinks/day) resulted in a substantial risk of esophageal squamous cell carcinoma as compared to nondrinkers.

For laryngeal cancer, the RRs estimated by the meta-regression model, at selected amounts of alcohol consumption, were 1.20 for 12.5 g/day, 1.45 for 25 g/day, 2.04 for 50 g/day, and 3.77 for 100 g/day (8). These estimates are consistent with the results reported above for high levels of consumption. On the other hand, the model-based estimates reported a significant 20% increase in risk of laryngeal cancer for light drinkers, while the meta-analysis of data on low doses conducted in the same investigation found no association with laryngeal cancer risk.

Compared to nondrinkers, the model-based estimates of the RRs of colorectal cancer were 1.18 for 25 g/day, 1.38 for 50 g/day, and 1.82 for 100 g/day of alcohol (11). Though the estimates were considerably lower than those reported for upper digestive and respiratory tract cancers, the meta-regression models provided additional quantification of the positive dose-risk relation between alcohol and colorectal cancer. As for laryngeal cancer, results from model-based analysis showed a significantly increased risk of colorectal cancer even for light drinkers (+7% for 10 g/day of alcohol), in contrast with the meta-analysis of low doses from the same report.

The differences observed for both laryngeal and colorectal cancers between the results of the meta-analyses and the model-based analyses at light drinking levels can be explained by the limitations of modeling. In fact, the RR estimates for low doses of alcohol consumption from dose-risk analyses may be influenced by the function used and affected by observations in high dose categories (18).

For pancreatic cancer, the pooled estimates of the RRs were 1.03 for 25 g/day, 1.10 for 50 g/day, 1.19 for 75 g/day, and 1.30 for 100 g/day of alcohol compared to nondrinkers (10). Thus, the dose-risk analysis reported no apparent effect of moderate alcohol drinking on pancreatic cancer risk, while a significant increase in risk was observed for consumption of 40 or more g/day of alcohol.

With reference to breast cancer, in the collaborative reanalysis of data from 53 epidemiological studies (12), the RR of breast cancer increased by 7.1% (95% CI = 5.5–8.7%) for each additional 10 g/day of alcohol intake. In the Million Women Study (3), the same increase of 10 g/day of consumption was associated to a 12% (95% CI = 9–14%) increased risk of breast cancer. Further, the trend in risk was highly significant \( P < 0.001 \). There is, therefore, consistent evidence for a positive dose-risk relation between alcohol drinking and breast cancer.
THE COMBINED EFFECT OF TOBACCO AND ALCOHOL IN HEAD AND NECK CANCER

Tobacco and alcohol use, the two major recognized risk factors for head and neck cancer, are often correlated. The confounding and modifying effect of tobacco on the relation between alcohol drinking and head and neck cancer risk has been extensively investigated (20–22). There is evidence of a combined effect of alcohol and tobacco use on the risk of these neoplasms, compatible with a multiplicative—or even a supra-multiplicative for oral cavity and pharynx—effect on cancer risk (20). Alcohol drinking is, however, positively associated with these neoplasms independently from smoking.

![Graph A: Interaction between alcohol drinking and cigarette smoking](image1)

![Graph B: OR for ever versus never cigarette smoking in never alcohol drinkers](image2)

**FIG. 4.** The modifying effect of tobacco on the relation between alcohol drinking and head and neck cancers. A: Interaction. B: Exclusive smoking/drinking.

Figures taken from Refs. 24 and 23, respectively.
Hereby, we report the major findings from the International Head and Neck Cancer Epidemiology (INHANCE) consortium pooled analysis, including over 10,000 cases of oral, pharyngeal, and laryngeal cancer and over 15,000 controls with detailed information on tobacco and alcohol use from 15 European and American case-control studies (23,24).

Fig. 4A shows the alcohol–tobacco interaction observed in the INHANCE study (24). The risk increased with both an increase in tobacco, in the absence of alcohol, and in alcohol use, in the absence of tobacco consumption. Furthermore, a supramultiplicative synergistic effect of the combined exposure was found, because ORs were 4.2 for never-drinkers who smoked ≥20 cigarettes/day, 1.9 for never-smokers who drank ≥3 drinks/day, and 14.2 for heavy drinkers and smokers (>20 cigarettes/day and ≥3 drinks/day), compared to never-smokers and never-drinkers. When head and neck cancers were considered separately, a significant interaction was found for oral and pharyngeal but not for laryngeal cancer.

Fig. 4B, taken from another report of the INHANCE study (23), shows the ORs for ever vs. never cigarette smoking in never-drinkers (left panel) and for drinking ≥3 drinks/day vs. never-drinkers in never users of tobacco (right panel). An effect of both smoking in the absence of drinking (OR = 2.13) and of (heavy) drinking in the absence of tobacco use (OR = 2.04) was found. Among never-users of tobacco, the association with heavy alcohol consumption appeared to be limited to cancers of the oropharynx/hypopharynx and larynx in this large pooled analysis.

DISCUSSION

Heavy alcohol consumption, defined as 4 or more drinks/day, is significantly associated with an increased risk of about fivefold for oral and pharyngeal cancer and esophageal squamous cell carcinoma, 2.5-fold for laryngeal cancer, 50% for colorectal and breast cancers, and 30% for pancreatic cancer. On the other hand, light drinking, defined as up to 1 drink/day, leads to an increased risk of 20% to 30% of oral and pharyngeal cancer and of esophageal squamous cell carcinoma, though these estimates remain open to discussion due to possible underreporting. No meaningful association emerged with the risk of laryngeal, colorectal, and pancreatic cancers. An increased risk of breast cancer is already present at intakes of 3 to 6 drinks/wk. A positive association between alcohol and liver cancer is established, but no reliable quantification of the risks is possible. Alcohol consumption increases the risk of head and neck cancers also in absence of tobacco. However, exposure to both habits has a combined effect, compatible with a greater than multiplicative increase, in oral and pharyngeal cancer risk.

In terms of attributable fraction of cancers that would be eliminated by restricting alcohol consumption, in 2002 about 390,000 (3.6%) cancers and 230,000 (3.5%) cancer deaths were attributed to alcohol drinking worldwide (25). These included over 5% of cancers and cancer deaths in men and about 1.5% of cancers and cancer deaths in women. Restriction of alcohol drinking to the limits indicated by the European Code Against Cancer (26) (i.e., 20 g/day for men and 10 g/day for women) would avoid about 90% of alcohol-attributable cancers and cancer deaths in men and over 50% of cancers in women, i.e., about 330/390,000 cancer cases and about 200/230,000 cancer deaths. Avoidance, or moderation of alcohol consumption to 2 drinks/day in men and 1 drink/day in women, is therefore a global public health priority.

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