Light alcohol drinking and the risk of developing cancer, a systematic review.

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Abstract

Background: There is strong evidence that heavy alcohol consumption (>50g per day) is a risk factor for several disease, including cancer. However, the oncogenic role of light alcohol drinking (<12,5g per day) is still controversial. The purpose of this review is to assess whether the intake of a single daily dose of alcohol could determine an increased risk of malignancy onset.

Methods: A systemic PubMed research of meta-analysis studies, using the keywords “light alcohol drinking”, “light alcohol consumption” and “cancer”, was done. We established a period of 15 years, in order to select the most recent evidences; exclusively meta-analysis that specified levels of alcohol intake were included in the review. Studies focused on biochemical, molecular and genetic aspects, as well as duplicate articles were excluded.

Results: We included in this review 29 large meta-analysis; light alcohol drinking was not associated with an increased risk of occurrence of most cancers, with the exception of breast, prostate cancer and, with less evidence, melanoma. Furthermore, a protective role of alcohol assumption on the development of bladder, kidney ovarian cancer and Non Hodgkin Lymphoma (NHL), has been described.

Conclusions: We found that light alcohol drinking do not determine a higher risk for the insurgence of several malignancies, except for a light increase in the incidence of melanoma, breast cancer in women and prostate cancer in men.

Background

Alcohol consumption is recognised as a causal factor for several health problems and is actually the world third largest risk factor for disease and disability worldwide (1). It is strictly correlated with cardiovascular disease, cirrhosis of the liver, epilepsy, road accidents and several malignancies. In 2012 the International Agency for Research on Cancer (IARC) showed a strong relationship between alcohol consumption and carcinogenesis, estimating that 5.5% of all new cancer occurrences and 5.8% of all cancer deaths worldwide were related to alcohol drinking (2).

Alcohol consumption has been associated with cancers of oral cavity and pharynx, oesophagus, larynx, liver, stomach, pancreas, colon, rectum, breast and prostate (3-10). Based on this evidence alcohol is classified as Group 1 carcinogen by IARC (2). In 2015, European Code Against Cancer (ECAC) fourth edition on alcohol drinking and cancer recommends “If you drink alcohol of any type, limit your drinking. Not drinking is better for cancer prevention.” (11). While there is a strong correlation between heavy (>50g per day) and moderate alcohol drinking (>12,5g and <50g per day) and cancer, data regarding the carcinogenic role of light alcohol drinking (<12,5g per day) are still controversial (12). In this review we would like to clarify if even the assumption of a single daily dose of alcohol, like a glass of wine, could determinate an increase of the relative risk of malignancy onset.

Methods

A systematic literature review of meta-analysis was conducted in order to evaluate the association between light alcohol drinking and risk of cancer. We searched PubMed using keywords “light alcohol drinking,” “light alcohol intake,” “light alcohol consumption,” and “cancer,” using “meta-analysis”. We chose to establish a period of 15 years (from 2004 to 2019), in order to analyse the most recent evidences, which generated 29 studies (included in table 1). We used the following criteria for inclusion: meta-analysis studying the relationship between alcohol consumption and the risk of cancer published in English, focusing on the amount of alcohol intakes and evaluating the effects of low doses of alcohol. Publications only dealing with biochemical, molecular and genetic aspects, as well as duplicate articles were excluded.

Results

Alcohol consumption and the risk of cancer of non-Hodgkin lymphoma (NHL)

Two meta-analysis were identified evaluating the association between NHL and alcohol consumption (13,14). The first study found a 15% reduction of NHL risk in current alcohol drinkers compared with non-drinkers (relative risk RR 0,85, 95% CI 0,79-0,91), regardless of the amount of consumption [light: (RR 0,88, 95% CI 0,81-0,96); moderate: (RR 0,87, 95% CI 0,79-0,95); heavy: RR 0,84, 95% CI 0,70-1,00)], without finding significant differences across strata of sex, type of controls and the two main subtypes of NHL (i.e. T-cells versus B-cell lymphoma) (13). The second metanalysis reported a favourable role of alcohol drinking on NHL risk, both on ever and current drinkers (RR 0,89 95% CI 0,83-0,95). Interestingly, it was found a significant difference on the type of alcoholic beverage and on sex gender; only ever/current consumption of beer was associated with a reduced risk of NHL (RR 0,88 95% CI 0,81-0,95) compared to wine and liquor (respectively RR 0,96 95% CI 0,9-1,12; RR 0,9 95% CI 0,79-1,02), whereas the protective effect of alcohol drinking was demonstrated only in male subjects

(RR 0,88 95% CI 0,78-0,98) (14). Finally, regarding the histological subtype of NHL, an inverse correlation between alcohol intake and NHL was proved in diffuse large B-cell lymphoma and follicular lymphoma (13,14).

Alcohol consumption and the risk of cancer of oesophageal cancer (OSCC)

Islamini and colleagues conducted a meta-analysis of 40 case-control studies and 12 cohort studies, showing a link between light, moderate and high alcohol drinking and the risk of OSCC (RR: 1.31 CI 95% 1.10-1.57; RR: 2.27 CI 95% 1.89-2.72; RR: 4.89 CI 95% 3.84-6.23); however, the increased risk in light alcohol drinkers was limited to the Asian population (RR, 1.63; 95% CI, 1.20-2.22) (15). These associations were also evidenced among never-smokers (RR, 0.74 95% CI 0.47-1.16 for light, 1.54; 95% CI, 1.09-2.17 for moderate, and RR, 3.09; 95% CI, 1.75-5.46 for high intakes) (15). A second meta-analysis including 24 studies in 2012 reported no significant correlation between both oesophageal and gastric cardia adenocarcinoma risk and light (0.86; 95% CI 0.75–0.99), moderate (0.90 95% CI 0.73–1.10) and heavy (1.16; 95% CI 0.92–1.46) alcohol consumption (16).

Alcohol consumption and the risk of gastric cancer

A first meta-analysis showed no association between alcohol ingestion and gastric cancer for light and moderate alcohol assumption (RR: 0.95; 95% CI: 0.88–1.02; RR: 1.05; 95% CI: 0.98–1.13, respectively). Nevertheless, a significant increase in relative risk of development of gastric cancer in case of heavy consumption, was reported (RR: 1.13; 95% CI: 1.06–1.21). Interestingly, a lower risk of gastric cancer in women consuming low doses of alcohol, was found (RR: 0.74; 95% CI: 0.57–0.98. (17). A second meta-analysis by Rota and colleagues, reported an increase in the risk of developing gastric cancer in case of consumption of 4 to 6 drinks/day (RR: 1.26 95% CI, 1.08–1.48) and >6 drinks/day (RR: 1.48 95% CI 1.29–1.70), especially in never smoking subjects (RR 1.87, 95% CI 1.35–2.58). There was no significant correlation under that threshold (≤ 1 drink/day: RR 1.00 95% CI 0.86–1.16) (18).

Alcohol consumption and the risk of pancreatic cancer

Two studies were selected evaluating the role of alcohol intakes in the onset of pancreatic cancer (19,20). The first meta-analysis conducted by Wang and colleagues, concluded that only high level of consumption determined an increased risk of developing pancreatic cancer (RR, 1.15; 95 % CI: 1.06–1.25). The risk was higher in male gender (RR 1.18; 95 % CI: 1.00–1.39) and in case of liquor consumption (RR, 1.66; 95 % CI: 1.24–2.23) (19). A second study by Tramacere and colleagues, collecting 21 case control and 11 cohort studies, reported a 20% increase in the risk of pancreatic cancer among heavy alcohol drinkers (defined as 3 or more drinks/day), compared with non-or occasional drinkers, with a relative risk of 1.22 (95% CI, 1.12–1.34). Furthermore, no significant increase in cancer risk in case of drinking less than 3 drinks/day was found (RR: 0.92 95% CI, 0.86–0.97) (20).

Alcohol consumption and the risk of colon cancer

We selected four meta-analysis assessing the link between alcohol intakes and the overall risk of colorectal cancer (21-24). The first study, including 4687 cases of colorectal cancer, suggested an increased risk limited to alcohol intake of 30-45 g/day (RR: 1.21 CI 95% 1.04–1.42), and >45 g/day (RR: 1.51 CI 95% 1.25–1.83), but no significant correlation for consumption <30 g/day, and no significant differences among sex gender, type of alcohol beverage and tumor site (21). Fedirko and colleagues showed that drinkers of 12.6–49.9 g/day and more than ≥ 50 g/day of alcohol had respectively a 21% and 52% increased risk for colorectal cancer (RR: 1.21 95% CI 1.13–1.28 and 1.52 95% CI 1.27–1.81), whereas light alcohol consumption (≤ 12.5 g/day of ethanol) was not associated with an increased risk (RR: 1.00 95% CI 0.95–1.05). However, they found a slightly statistically significant 7% increase in the incidence of colorectal cancer risk for 10 g/day of alcohol intake at the dose-risk analysis; authors also highlighted an increase of overall risk in male moderate drinkers (RR = 1.24, 95% CI 1.13–1.37) and in Asiatic heavy drinkers (RR = 1.81, 95% CI 1.33–2.46) (22).

Another meta-analysis published by Mizoue and colleagues evidenced a strong correlation linking alcohol intakes and colon cancer in case of consumption of more than 23 g/day, while finding no correlation <23 g/day in men (RR: 1.22 CI 95% 0.92, 1.61), neither in women (RR: 0.93 CI 95% 0.70, 1.23) (23). Finally, the meta-analysis by Wang and colleagues, including 22 case-control and only 2 cohort studies, described a dose-response and a positive correlation in case of any amount of alcohol drinking, even in case of less than 12,5 g/day of ethanol (overall pooled RR: 1.07 95% CI, 1.02-1.13); however, by stratifying the results by study types, the increased risk was found only in case-control studies (RR= 1.08, CI 95% 1.02-1.14) and not in cohort studies (RR= 1.02, CI 95% 0.85-1.21) (24).

Alcohol consumption and the risk of brain tumours

One meta-analysis, including 13 case-control and 6 cohort studies, evidenced no association between alcohol and brain tumours (26). However, the authors reported a 20% increase in risk for spirit consumption (RR 1.20 95% CI 1.01-1.42; P 0.584).

Alcohol consumption and the risk of cutaneous melanoma (CM)

A first meta-analysis including 16 studies (14 case control and 2 cohort investigations), evidenced alcohol drinking as a risk factor for CM; the overall pooled RR was 1.20 (95% CI 1.06-1.37; $P=0.006$), similar between case-control (RR 1.20, 95%CI 1.01-1.44; $P=0.041$) and cohort studies (RR1.26, 95% CI 1.19-1.35; $P<0.001$) (26).

The pooled RR estimates for the correlation between light alcohol drinking and CM were 1.10 (95% CI 0.90-1.26) overall, 1.06 (95% CI 0.90-1.25) among case-control studies and 1.25 (95% CI 1.15-1.35) among cohort studies. For moderate-heavy alcohol drinking vs no drinking, the pooled RR were 1.18 (95%CI 1.01-1.40) overall, 1.13 (95% CI 0.9-1.41) among case-control studies and 1.29 (95%CI 1.17-1.43) among cohort studies. However, no significant association was found in the pooled RR from 10 studies adjusted for sun exposure (RR1.12, CI 95% 0.86-1.45). Another meta-analysis found a moderate association with melanoma risk (27). The summary relative risk (SRR) was 1.29 (95% CI 1.14-1.45 $I^2=13\%$) for those in the highest vs. lowest category of current alcohol intake and 1.96 (95% CI 1.02-3.76, $I^2=0$) for cumulative intake. Moreover, in the dose response analysis, the increase in risk associated with a 10 g increment in daily alcohol intake was 1.07 (95%CI 1.03-1.11, $I^2=50\%$).

Alcohol consumption and the risk of lung cancer

A study by Bagnardi and colleagues showed no association between lung cancer and alcohol drinking in never smokers (RR 1.21 95% CI: 0.95-1.55) (28). Moreover, at the dose-response analysis, RR for an increase in alcohol intake of 10 g/day was 1.01 (95% CI: 0.92-1.10) (28).

A second meta-analysis based on 10 studies, demonstrated a decrease in risk of lung cancer for light alcohol drinking (RR 0.91 95%CI: 0.90-0.94 $I^2=0$) (29).

Alcohol consumption and the risk of laryngeal cancer

Regarding the correlation between alcohol consumption and the risk of laryngeal cancer, Islamini and colleagues showed a 2-fold increase in risk of laryngeal cancer for drinkers vs non-drinkers (RR 1.90 95% CI: 1.59-2.28 $p < 0.001$) (30). While light alcohol drinking was not linked with the risk of developing laryngeal cancer (RR0.88 95% CI: 0.71-1.08), moderate alcohol drinking (RR 1.47, 95% CI: 1.25-1.72) and heavy alcohol drinking (RR 2.62, 95% CI: 2.13-3.23) determined respectively a 1.5 and 2.5-fold increase compared to non-/occasional drinking (30).

Alcohol consumption and the risk of oral and pharyngeal cancer

A meta-analysis of Bagnardi and colleagues showed an increased risk of developing oral and pharyngeal cancer with a RR of 1.13 (95% CI, 1.00-1.26) for light, RR 1.83 (95% CI, 1.62-2.07) for moderate and RR 5.13 (95% CI, 4.31-6.10) for heavy alcohol drinking (12). However, for light alcohol consumption, no increase in tumorigenic risk was found in cohort studies (RR 0.86 95% CI, 0.60-1.23). Moreover, light alcohol intake determined an increase in the risk only in the Asian population (RR 1.33 95% CI, 1.06-1.68), in contrast with European (RR 0.95, 95% CI 0.80-1.12) and North American population (RR 1.09 95%CI, 0.92-1.29).

Alcohol consumption and the risk of breast cancer

A first meta-analysis evidenced a higher risk of breast cancer with increasing consumption of alcoholic beverages; in comparison with non-drinkers, women that assume 12 g/day of alcohol had a relative risk of 1.10 (95% CI: 1.06-1.14). Moreover, no significant difference was found regarding the state of menopause or the type of drink consumed (31). Suzuki et colleagues evidenced a positive relationship between alcohol drinking and development of breast cancer. Authors reported that consumption of more than 10g of ethanol per day determined a 12% increase in the occurrence of oestrogen receptor positive breast cancer and 7% increase for oestrogen receptor negative tumours (32).

Alcohol consumption and the risk of ovarian cancer

A first meta-analysis by Kelemen and colleagues, evidenced that alcohol intake was not associated with risk of ovarian carcinoma (consumption of >3 drinks per day compared to none: OR=0.92, 95% CI=0.76-1.10, P trend=0.27) (33).

Another meta-analysis showed no effects of alcohol consumption on the incidence of ovarian cancer in drinkers vs non-drinkers (RR 1.03 95% CI 0.96-1.10). Furthermore, low (RR 1.02 95% CI 0.94-1.11), moderate (RR 1.08, 95% CI 0.92-1.27) and heavy alcohol consumption (RR 0.99, 95% CI 0.88-1.12) showed no significant effects on the risk of this neoplasm. Finally, authors also noticed a protective effect of low doses of alcohol on ovarian cancer incidence when the participants were from outside US (34).

Alcohol consumption and the risk of prostatic cancer

A recent meta-analysis by Rota and colleagues reported an association between alcohol consumption and prostate cancer (35).

Interestingly, the authors noticed an overall RR of 1.06 (95% CI, 1.01–1.10) for any alcohol drinking compared with non/occasional drinking. Furthermore, the dose–risk analysis showed borderline statistically significant RRs of 1.05 (95% CI, 1.02–1.09) for light alcohol drinking (≤ 1 drink/ day) and 1.06 (95% CI, 1.01–1.11) for moderate drinking (>1 to <4 drinks/day). Finally, they found a non-significant association at high levels of alcohol drinking (≥ 4 drinks/day), with a pooled RR of 1.08 (95% CI, 0.97–1.20) (35).

Another meta-analysis reported a statistically significant dose-response relationship between alcohol consumption and risk of prostate cancer starting with <25 g ethanol / day (RR 1.08, 95% CI 1.04-1.11) (36). Medium (25– <45 g/day), high (45– <65 g / day) and higher volume drinkers ($65+$ g / day) had a significantly enhanced risk [RR 1.07 (95% CI 1.02-1.12), 1.14 (95% CI 1.08-1.22) and 1.18 (95% CI 1.10-1.27) respectively]. The increase in incidence observed for low-volume drinkers was relatively small in the aggregate analysis (8%), but was 23% in studies without erroneous classification errors (for example, the common practice of considering drinkers like abstainers).

Alcohol consumption and the risk of bladder cancer

A large meta-analysis by Mao and colleagues, including 19 studies (both case-control studies and cohort studies) reported no significant association between alcohol drinking and bladder cancer (OR = 1.00, 95% CI 0.89–1.10) (37). The authors also found a negative relation between beer and wine consumption and the probability of bladder cancer.

Another more recent meta-analysis confirmed the findings from meta-analysis of Mao and colleagues (38). The pooled RRs for <3 drinks per day, were 1.00 (95% CI 0.92–1.09), specifically 1.07 (95% CI 0.85–1.36) among cohort and 0.99 (95% CI 0.89–1.09) among case–control studies. All the data on heavy drinkers were from case–control studies (RR = 1.02, 95% CI 0.78–1.33). Results were consistent in several subgroup analyses, including those of studies adjusted for smoking (38).

Alcohol intake and risk of renal cell carcinoma (RCC)

A first meta-analysis observed an inverse association between alcohol intake and risk of RCC, when comparing the highest versus the lowest alcohol consumption categories, with a statistically significant 30% reduction in incidence of RCC (RR 0.70, 95% CI 0.60-0.81) (39). Remarkably, alcohol consumption of 12 g ethanol per day was correlated with a 5% reduction in the risk of RCC (OR 0.67, 95% CI 0.62-0.73).

Another meta-analysis confirmed an inverse relationship between alcohol intake and risk of RCC (RR 0.73, 95% CI 0.67-0.79) (40). Interestingly, the inverse association was stronger for cohort studies (RR 0.71, 95% CI 0.63-0.78) than for case-control studies (RR 0.76, 95% CI 0.68-0.85) (40). However, the authors highlighted that consumption up to 15 g per day of ethanol, could lead to a decrease in the risk of RCC, but additional consumption does not confer further benefits in the prevention of RCC.

Finally, a third meta-analysis, reported a negative link between alcohol consumption and risk of RCC, significant for both light (<12 , 49 g/day) and moderate (12.5-49.9 g/day), but not for heavy drinking (≥ 50 g/day) [RR: 0.90 (95% CI: 0.84–0.97), 0.79 (95% CI: 0.71–0.88) and 0.98 (95% CI 0.58-1.39), respectively) (41).

Discussion

Collectively the current analysis evidences that light alcohol drinking does not increase the risk of developing most of cancer, with the exception of breast cancer, prostate cancer and, with less evidence, melanoma. Furthermore, a protective effect of alcohol assumption on the occurrence of bladder, kidney, cancer and NHL, has been described. The role of light alcohol drinking as a causal factor for the insurgence of malignancies is still debated (11). A meta-analysis by Bagnardi and colleagues, showed an increased risk of oral cavity, pharynx, oesophagus and female breast cancer even for light alcohol drinking (42). However, as already supported by Myung in his letter to Annals of Oncology, this assumption was principally derived by the analysis of case-control studies, which are more susceptible to recall, or selection bias compared to cohort studies (43). Furthermore, Myung stated that a significant statistical increase in risk of cancers for light alcohol drinkers was confirmed exclusively in breast cancer, while it does not reach a significance for the other tumors (43).

Recently, Griswold and colleagues published a large systemic meta-analysis of the correlation between alcohol consumption and global disease burden; the authors concluded: “the level of consumption that minimizes health loss is zero” (44). However, the study had several limitations and does not take in account key issues, like environmental factors, genetic differences among the various ethnic groups included in the analysis, together with possible underestimation bias.

Surely, even though mechanisms underlying alcohol-related carcinogenesis are not completely elucidated, different studies showed that chronic alcohol consumption, especially for high doses, could cause the onset of cancers (45-47).

The mechanisms of alcohol on tumorigenesis include the production of acetaldehyde (derived from ethanol metabolism), oxidative stress, effects on metabolism, endocrine and immunity system, together with the influence of genetic polymorphisms regulating the absorption and the metabolic pathway of this substance (45-47). A multitude of genes contribute to the correct metabolism of alcohol, like those for

ADH, ADLH, CYP2E1, and methylene-tetrahydrofolate reductase (MTHFR). The presence of some polymorphisms in these genes could reduce the elimination of acetaldehyde and favour the development of malignancies. In fact, carriers of *ALDH2*1/*2* or *ALDH2*2/*2* genotypes of the *ALDH2* gene, compared to *ALDH2*1/*1*, exhibit a reduced enzymatic activity, leading to an increased accumulation of acetaldehyde (48).

This polymorphism is predominant in the Asian population and could be responsible of the higher risk of upper digestive cancers in moderate and heavy drinkers in that area (49). However, some bias could influence these results. Regarding this point, a recent study of Cao and colleagues, demonstrated that alcohol intakes ≥ 30 g/day were strongly associated with risk of total cancer only among male ever smokers, while for women, even an alcohol consumption of 5-14.9 g/day could increase that risk, but this result was found to be mainly driven by breast cancer (50).

Alcohol is also responsible for changes in hormonal balance and metabolism (51). In this respect, we observed a link between breast cancer and light alcohol drinking; these results are consistent with literature evidence. Chen and colleagues carried out a large prospective cohort study concluding that even a consumption as low as 5.0-9.9 gm/day could determine an increased breast cancer risk, independently from the type of beverages (52).

The association between alcohol drinking and breast cancer can be explained by the increase of circulating oestrogens (caused by a decrease in aromatase activity). Moreover, recent studies *in vitro* and *in vivo* suggest that alcohol could promote cancer growth through epigenetic regulation of gene expression in the breast tissue, beside enhancing its progression by stimulating epithelial-mesenchymal transition (53).

We also found a correlation between light alcohol drinking and increased risk of prostatic adenocarcinoma, in agreement with a recent study (54). The biological mechanisms by which ethanol intake could increase the risk of prostate cancer are not completely understood. Acetaldehyde could have a genotoxic effect, promote induction of microsomal cytochrome P450 2E1 (CYP2E1), increase oxidative stress, augment oestrogen concentration, act as a solvent for tobacco carcinogens, determine changes in metabolism of folates and DNA repair (54).

New evidences suggest a possible link between alcohol and an increased risk of CM. In fact, acetaldehyde could act as a photosensitizing agent causing an enhanced susceptibility to UV-mediated cell damage (26, 27).

In our study, we found out that light drinking could be a protective factor for renal cell carcinoma, bladder cancer and, with less evidence, for LNH. Concerning the two genitourinary malignancies, the protective role of alcohol could be explained by the presence of other compounds in alcoholic beverages (xanthohumol and resveratrole), by enhancing insulin sensitivity and/or to its diuretic effect, responsible for a higher frequency of bladder emptying and a consequent lower exposure of the carcinogens to the bladder epithelium (56-59). Less clear is the decrease of incidence of NHL in light drinkers; it could be related, according to Psaltopoulou and colleagues, to a reduced activation of mammalian target of rapamycin (mTOR) complex, capable of inducing autophagy in cell lines of NHL; other possible mechanisms includes immune-modulating effect of ethanol, the antioxidant effect, improved insulin sensitivity (58-60).

Conclusions

In conclusion, the current study highlights how the intake of low alcohol doses does not correlate with an increase in the incidence of different types of cancer, with the exception of breast cancer in women, and prostate cancer in men. On the other hand, alcohol drinking could even have a protective effect, as in the case of kidney cancer, bladder cancer, and the NHL.

Although new evidence suggests that abstention from alcoholic beverages is the only way to prevent various diseases, the correlation with tumorigenesis for low doses of alcohol drinking (like the daily consumption of a glass wine), is still unclear and has to be confirmed by modern large cohort studies.

Abbreviations

NHL: Non Hodgkin Lymphoma; IARC: International Agency for Research on Cancer; ECAC: European Code Against Cancer; RR: Relative Risk; OSCC: Oesophageal cancer; CM: cutaneous melanoma; RCC: renal cell carcinoma; MTHFR: methylene-tetrahydrofolate reductase;

Declarations

Ethics approval and consent to participate

Not Applicable.

Consent for publication

Not Applicable.

Competing interests

The authors have no conflict of interest to declare.

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Contributions

GC, DP, DC, CL and FC have made significant contribution to the conception of the study. MD, PPV, AGG, FA, EFG, VDF, VF AND EM were involved in data analysis. GC, DP, DC and CL have drafted the manuscript and substantially revised it. All authors read and approved the final manuscript.

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r, Year	Inclusion Period	N. of articles	Quantity of alcohol	Risk analysis, relative risk (RR) (95% CI)				
r, Year	InclusionPeriod	N. of articles	Quantity of alcohol	Consumption results (dose/day)	Response-dose (g/day)	Type of beverage	Sex	Geographic region
colorectal malignancies								
Acere I 2012	1992-2010	29	1 drink: 12.5 g of ethanol. Light drinkers: ≤1/day; moderate drinkers: >1 to <4/day; heavy drinkers: ≥4/day	Drinkers vs non-drinkers: RRs 0.85 (0.79-0.91). ≤1 drink: RRs 0.88 (0.81-0.96); >1-<4 drinks: RRs 0.87 (0.79-0.95); ≥4 drinks: RRs 0.84 (0.70-1.00)	<10 g/day: RRs 0.91 (0.87-0.94); 10-25 g/day: RRs 0.85 (0.80-0.90); 25-50 g/day: RRs 0.80 (0.74-0.87); 50-75 g/day: RRs 0.80 (0.70-0.91); 75-100 g/day: RRs 0.81 (0.66-1.00)		Male: RRs 0.83 (0.75-0.92); Female: RRs 0.86 (0.76-0.98)	Asia: RRs 0.69 (0.57-0.84) Non asia: RRs 0.88 (0.82-0.93)
Popoulou I. 2018	Until August 2016	53	1 drink: 12.5 g of ethanol. Light drinkers: ≤12.5 g/day; moderate drinkers: >12.5 to 50 g/day; heavy drinkers: ≥50g/day	Drinkers vs non-drinkers: RRs 0.89 (0.83-0.95). ≤1 drink: RRs 0.93 (0.87-1.00) >1-<4 drinks: RRs 0.85 (0.80-0.90) ≥ 4 drinks: RR=0.73 (0.60-0.89)		Beer: RRs 0.88 (0.81-0.95) Wine: RRs 0.96 (0.90-1.12) Liquor: RRs 0.90 (0.79-1.02)	Male: RRs 0.88, (0.78-0.98) Female: RRs 0.94, (0.83-1.07)	
esophageal cancer								
Al-Fet 2012	1961-2010	53	1 drink: 12.5 g of ethanol. Light drinkers: ≤1 drink/day; Moderate drinkers: >1 to < 4 drinks/day Heavy drinkers: ≥ 4 drinks/day	≤1 drink: RRs 1.31 (1.10-1.57) >1-<4 drinks: RRs 2.27 (1.89-2.72) ≥ 4 drinks: RRs 4.89 (3.84-6.23)				≤1 drink/day Asia: RRs 1.63 (1.20-2.22) Non Asia: RRs 1.17 (0.99-1.39) >1 to < 4 drinks/day Asia: RRs 2.17 (1.58-2.96) Non Asia: RRs 2.34 (1.9-2.88). ≥ 4 drinks/day Asia: RRs 4.02 (2.76-5.83) Non Asia: RRs 5.73 (4.41-7.44)
Acere I 2012	1989-2010	24	1 drink: 12.5 g of ethanol. Light drinkers: ≤1 drink/day; Moderate drinkers: >1 to < 4 drinks/day Heavy drinkers: ≥ 4 drinks/day	Drinkers vs nondrinkers Esophageal carcinoma: RRs 0.87 (0.74-1.01) Gastric cardia adenocarcinoma: RRs 0.89 (0.76-1.03) ≤1 drink/day: RRs 0.86 (0.75-0.99)	No increase in risk up to 70 g/day		Male: RRs 1.02 (0.69-1.49) Female: RRs 0.86 (0.68-1.07)	

				>1 to < 4 drinks/day: RRs 0.90 (0.73-1.10) ≥ 4 drinks/day: RRs 1.16 (0.92-1.46)				
ccancer								
et al.	1984-2015	22		Drinkers vs. non drinkers: RRs 1.03 (0.99-1.08). Light drinkers: RRs 0.95 (0.88-1.02). Moderate drinkers: RRs 1.05 (0.98-1.13). Heavy drinkers: RRs: 1.13 (1.06-1.21)	No increased risk up to 60 g/day		Light drinkers Male: RRs 0.96 (0.90-1.03) Female: RRs 0.74 (0.57-0.98) Heavy drinkers Male: RRs 1.13 (1.06-1.22) Female: RRs 1.33 (0.79-2.24)	Heavy drinkers Non Asia: RRs 1.20 (1.03- 1.41) Asia: RRs 1.12 (1.04-1.20)
M et al.	1989-2015	23	1 drink = 12 g of ethanol categorized across studies as: ≤1 drink/day; >1 to 4 drinks/day; >4 to 6 drinks/day; >6 to 8 drinks/day; >8 drinks/day	Drinkers vs no drinkers: RRs 1.10 (0.99-1.21) ≤1: drink RRs 1.00 (0.86-1.16) >1-4 drinks: RRs 1.11 (1.01-1.23) >4-6 drinks: RRs 1.26 (1.08-1.48) >6 drinks: RRs 1.48 (1.29-1.70) >6-8 drinks: RRs 1.46 (1.18-1.80); >8 drinks: RRs 1.50 (1.26-1.78)	6 g/day: RRs 1.02 (1.01-1.03) 30 g/day: RRs 1.11 (1.05-1.17) 60 g/day: RRs 1.24 (1.11-1.38) 84 g/day: RRs 1.34 (1.15-1.57) 100 g/day: RRs 1.42 (1.15-1.57)	Wine >0 to 1 drink/day: RRs 1.03 (0.80- 1.31) >1 to 3 drinks/day: RRs 1.22 (1.02- 1.45) >3 drinks/day: RRs 1.44 (0.98- 2.11) Beer >0 to 1 drink/day: RRs 1.33 (0.97- 1.83) >1 drink/day: RRs 1.27 (0.89- 1.82) Spirit >0 to 1 drink/day: RRs 0.94 (0.70- 1.27) >1 drink/day: RRs 1.66 (1.23- 2.22)		
eatric cancer								
YT et		19	1 drink: 12 g of ethanol Light drinkers: 0-12 g/day Moderate drinkers; 12- 24 g/day Heavy drinkers: ≥24 g/day	1 drink: RRs 0.97 (0.89- 1.05); 1-2 drinks: RRs 0.98 (0.93-1.03) Total alcohol intake: RRs 1.02 (0.95-1.08) ≥2: RRs 1.15 (1.06-1.25)	No linear relationship up to 55 g/day	Liquor ≥24 g/day: RRs 1.43 (1.17-1.74)	≥24 g/day Male: RRs 1.18 (1.00-1.39) Female: RRs 1.07 (0.96-1.19)	
acere I	1983-2009	32	1 drink: 12.5 g of ethanol.	<3 drinks: RRs 0.92 (0.86-0.97)	25 g/day: RRs 1.03		≥5 drinks/day Male: RRs 1.17	

			Moderate drinkers: <3 drinks/day Heavy drinkers: ≥3 drinks/day	≥3 drinks: RRs 1.22 (1.12-1.34)	(0.99-1.07) 50 g/day: RRs 1.10 (1.02-1.20) 75 g/day: RRs 1.19 (1.06-1.35) 100 g/day: RRs 1.30 (1.08-1.55) 125 g/day: RRs 1.40 (1.06-1.85)		(0.99-1.38) Female: RRs 0.79 (0.43-1.44) ≥7 drinks/dayMale: 1.27 (1.03-1.56) Female: RRs 0.78 (0.40-1.51)	
cancer								
et al.	1980-1998	8	1 drink: 12.8 g of ethanol.	30-<45 g/day: RR=1.21 (1.04-1.42) ≥45 g/day: RR=1.51 (1.25-1.83)	>0 -<5 g/day: RRs 0.94 (0.86-1.03); 5 - <15 g/day: RRs 0.97 (0.88-1.06) 15 - <30 g/day: RRs 1.01 (0.86-1.18) 30 - <45 g/day: RRs 1.16 (0.99-1.36) >45 g/day: RRs 1.41 (1.16-1.72)			
co V et	1979-2007	61 studies	1 drink = 12.5 g of ethanol. Light drinkers: ≤1 drink/day (≤12.5 g/day of ethanol) Moderate drinkers: 2-3 drinks/day (12.6-49.9 g/day of ethanol) Heavy drinkers: ≥4 drinks/day (≥50 g/day of ethanol).	Drinkers vs non drinkers: RRs 1.12 (1.06-1.19) ≤1 drink: RRs 1.00 (0.95-1.05) 2-3 drinks: RRs 1.21 (1.13-1.28) ≥4 drinks: RRs 1.52 (1.27-1.81)	10: RRs 1.07 (1.04-1.10) 25: RRs 1.18 (1.12-1.25) 50: RRs 1.38 (1.28-1.50) 100: RRs 1.82 (1.41-2.35)		Any drinker Male: RRs 1.25 (1.13-1.39) Female: RRs 1 (0.94-1.07) p=0.001. 2-3 drinks/day Male: RRs 1.24 (1.13-1.3) Female: RRs 1.08 (1.03-1.1) p=0.02	
e T et	1988 to 2004	5	nondrinkers (never and ex-drinkers), occasional drinkers (<once/week), and regular drinkers (≥once/week: for men, 0.1-22.9 g/day, 23-45.9 g/day, 46-68.9 g/day, 69-91.9 g/day, or ≥92 g/day; for women,	increased risk of colorectal cancer in a dose-response manner in men RRs: for 23-45.9 g/day, 46-68.9 g/day, 69-91.9 g/day, and ≥92 g/day (compared with nondrinking) were 1.42 (1.21, 1.66), 1.95 (1.53, 2.49), 2.15 (1.74, 2.64), and 2.96 (2.27, 3.86), respectively			Colorectal cancer: 0.1-4.9 g/day, 5-14.9 g/day, 15-29.9 g/day, 30-44.9 g/day, and ≥45 g/day were 1.11 (0.74, 1.67), 1.10 (0.86, 1.42), 1.35 (1.10, 1.66), 1.61 (1.32, 1.95), and 2.09 (1.65, 2.64). Women: 0.1-22.9 g/day; ≥23 g/day 0.93 (0.7-	

			0.1-22.9 g/day or ≥23 g/day				1.23); 1.57 (1.11-2.21) respectively	
Y et	1991-2013	24	1 drink = 12.5 g of ethanol Light drinkers: ≤1 drink/day (≤12.5 g/day of ethanol) Moderate drinkers: 2-3 drinks/day (12.6-49.9 g/day of ethanol) Heavy drinkers: ≥4 drinks/day (≥50 g/day of ethanol).	Drinkers vs. non drinkers: RRs 1.13 (95% CI, 1.09-1.17) ≤1 drink: RRs 1.07 (95% CI, 1.02-1.13) >1- 3 drinks: RRs 1.23 (1.15-1.32)			Male: RRs 1.11, (1.00-1.23) Female: RRs 1.03, (0.95-1.10)	Asia: RRs 1.19 (1.11-1.27) Europe: RRs 1.22 (1.10-1.34) US: RRs 1.10, (1.05-1.15)

cancer								
ne C. 2013		20	1 drink: 12.5 g of ethanol. Moderate drinkers: <25 g of ethanol/day Heavy drinkers: ≥25 g of ethanol/day	Drinkers versus non-drinkers: RRs 0.97 (0.82-1.15) Moderate drinkers: RRs 1.01 (0.81-1.25) Heavy drinkers: RR 1.35 (0.85-2.15)		Wine: RRs 1.01 (0.70-1.48) Beer: RRs 0.96 (0.82-1.12) Spirits: RRs 1.20 (1.01-1.42)	Brain cancer drinkers vs non-drinkers Male: RRs 1.65 (1.27-2.13) Female: RRs 0.84 (0.63-1.12)	America: RRs 0.74 (0.63-0.89) Europe: RRs 1.05 (0.94-1.16) Asia/Australia: RRs 1.16 (0.87-1.63)

ous melanoma								
ni S et 14	1986-2009	16	1 drink: 12.5 g of ethanol. Light drinkers: ≤1 drink, or ≤12,5 g of ethanol/day Moderate to heavy drinkers: >1 drink, or >12,5 g of ethanol/day	Drinkers vs no/occasional drinkers: RRs 1.20 (1.06-1.37) ≤1 drink: RRs 1.10 (0.96-1.26) >1drinks: RRs 1.18 (1.01-1.40)	12 g/day: RRs 1.11 (1.01-1.23) 25 g/day: RRs 1.25 (1.01-1.53) 50 g/day: RRs 1.55 (1.02-2.35)		Male: RRs 1.47 (0.94-2.29); Women: RRs 1.26, (1.19-1.35)	Australia: RRs 1.20 (0.87-1.66) Europe: RRs 1.04 (0.79-1.37) America: RRs 1.41 (1.21-1.66)
ni S et 18	1986-2016	20	1 drink = 12 g of ethanol	Highest vs. lowest category of actual alcohol intake: RRs 1.29 (1.14-1.45)	For an increase of 10g/day: RRs 1.07 (1.03-1.11)	Wine: RRs 1.22 (0.95-1.57) Beer: RRs 1.03 (0.81-1.29) Liquor: RRs 1.08 (0.91-1.28)		

cancer								
irdi V 2011	1988-2010	10	1 drink: 12.5 g of ethanol	Never smokers Drinkers vs non drinkers: RRs 1.21 (0.95-1.55)	For an increase of 10g/day up to 75 g/day: RRs 1.01 (0.92-1.10)			
TJ et al.								

x cancer								

1 F et 10	1956-2009	40	1 drink = 12.5 g. Light drinkers: ≤12.5 g ethanol = ≤1 drink/day Moderate drinkers: >12.5 to <50 g ethanol = >1 to <4 drinks/day Heavy drinkers: ≥50 g ethanol = ≥4 drinks/day	Drinkers vs no/occasional drinkers: RRs 1.84 (1.50-2.26) ≤1 drink: RRs 0.88 (0.70-1.12) >1-4: RRs 1.50 (1.23-1.83); ≥4: RRs 2.46 (1.88-3.22)	12.5 g/day: RRs 1.20 (1.15-1.25) 25 g/day: RRs 1.45 (1.33-1.57) 37.5 g/day: RRs 1.72 (1.52-1.90) 50 g/day: RRs 2.04 (1.76-2.36) 100 g/day: RRs 3.77 (2.93-4.86)			
larynx and pharynx cancer								
1 RC et 11	1966-1999	42	Based on the categories reported in the original paper	6 g/day: RRs 4.9% (1.03-1.07); 12 g/day: RRs 10% increased risk (1.06-1.14); 24 g/day: RRs 21% increased risk (1.13-1.30)		Beer: RRs 0.96 (0.91-1.02) Spirits: RRs 1.01 (0.93-1.09)		US: RRs 1 Outside US: RRs 1.05 (0.99-1.12)
1 R. et 17	1970-2007	20	1 drink=10 g	Highest vs lowest category of alcohol intake: ER+ tumors: RRs 1.27 (1.17-1.38); ER- tumors: RRs 1.14 (1.03-1.26); ER+ PR+ tumors: RRs 1.22(1.11-1.34); ER+PR- tumors: RRs 1.28 (1.07-1.53)	For an increase in alcohol intake of 10 g/day up to 40 g/day ER+ tumors: RRs 12% (8%-15%); ER- tumors: RRs 7% (0%-14%); ER+PR+ tumors: RRs 11% (7%-14%); ER+PR- tumors: RRs 15% (2%-30%)			
stomach cancer								
1 en LE 2013	1989-2009	12	1 drink of alcohol from any source = 10 g; 1 drink of beer = 12.2 g; 1 drink of wine = 10.5 g 1 drink of liquor = 9.5 g. Alcohol intake categories were derived in increments of one standard drink	Drinkers vs non drinkers of alcohol from any source 1 drink: RRs 0.94 (0.85-1.03); 1-2 drinks: RRs 0.97 (0.85-1.11); 2-3 drinks: RRs 0.91 (0.74-1.11); ≥3 drinks: RRs 0.92 (0.76-1.10)		Beer Up to 1 drink/day: RRs 0.92 (0.83-1.02); ≥ 1 drink/day: RRs 1.09 (0.86-1.37). Wine Up to 1 drink/day: RRs 0.94 (0.85-1.04);		

						1-2 drinks/day: RRs 1.00 (0.83- 1.20); ≥2 drinks/day: RRs 0.83 (0.68- 1.01). Liquor Up to 1 drink/day: RRs 0.97 (0.88- 1.08); ≥ 1 drink/day: RRs 1.03 (0.85-1.26)		
ong Y. 2015	1997-2012	13	Low alcohol intake: ≤15 g ethanol/day Moderate alcohol intake: 15-30 g ethanol/day Heavy alcohol intake: ≥30 g ethanol/day	Drinkers vs no/occasional drinkers: RRs 1.03 (0.96-1.10); Low alcohol intake: RRs 1.02 (0.94-1.11); Moderate alcohol intake: RRs 1.18 (0.98-1.42); Heavy alcohol intake: RRs 1.13 (0.90-1.41)				Low alcohol intake US: RRs 1.01 (0.92-1.12); Other: RRs: 0.96 (0.92- 1.00)

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et al.	1971-2010	72	1 drink = 12.5 g of ethanol Light drinkers: ≤12.5 g ethanol = ≤ 1drink/day Moderate drinkers: >12.5 to <50 g ethanol = >1 to <4 drinks/day Heavy drinkers: ≥50 g ethanol = ≥4 drinks/day	Drinkers vs no/occasional drinkers: RRs 1.06 (1.01-1.10); Light drinkers: RRs 1.05 (1.02-1.08); Moderate drinkers: RRs 1.06 (1.01-1.11); Heavy drinkers: RRs 1.08 (0.97-1.20)	10 g/day: RRs 1.02 (1.00- 1.04); 25 g/day: RRs 1.05 (1.01- 1.09); 50 g/day: RRs 1.09 (1.02- 1.16); 100g/day: RRs 1.12 (0.97-1.30)			
et al,	1990-2014	27	1 drink = 8 g/drink for the UK; 10 g/drink for Australia, Austria, France, Greece, Hungary, Ireland, Netherlands, New Zealand, Poland, Spain, Sweden; 11 g/drink for Finland; 12 g/drink for Denmark,	Drinkers vs no drinkers: RRs 1.08 (1.04-1.12); Up to 1 drink/week: RRs 1.02 (0.86-1.21); ≤2 drinks/day: RRs 1.09 (1.03-1.16); 2-4 drinks/day: RRs 1.03 (0.93-1.14); 2-6 drinks/day: RRs 1.13 (0.98-1.30); ≥6 drinks/day: RRs 1.15 (1.01-1.13)				

			Germany, Italy, South Africa and Switzerland; 13.45 g/drink for Canada; 14 g/drink for US; 12.5 g/drink for China, 19.75 g/drink for Japan and 12 g/drink for other countries. No/occasional drinkers; current occasional drinkers, <1.30 g/day = ≤1 drink/week; low volume drinkers: 1.30-24 g ethanol = ≤2 drinks/day; medium volume: 25-44 g ethanol = 2-4 drinks/day; high volume drinkers: 25-64g ethanol = 2-6 drinks/day; higher volume drinkers: ≥65g ethanol = ≥6 drinks/day						
cancer									
J G et al 2010	1980-2010	24	1 drink= 12 g	Highest vs lowest: RRs 0.7 (0.6-0.81)	for an increase of 12 g alcohol intake up to 70 g/day: RRs 5% (3%-7%) decrease				
DY et al 2012	1974-2010	24	1 drink = 15 g	Highest vs lowest: RRs 0.73 (0.67-0.79)					
McRae et al 2012	1966-2010	20	1 drink = 12.5 g Ever drinkers: ≥0.01 g/day Light drinkers: 0.01-12.49 g/day; Moderate drinkers: 12.5-49.9 g/day; Heavy drinkers: ≥50 g/day.	Drinkers vs no drinkers: RRs 0.85 (0.80-0.92); Light drinkers: RRs 0.90 (0.84-0.97); Moderate drinkers: RRs 0.79 (0.71-0.88); Heavy drinkers: RRs 0.89 (0.58-1.39)	12 g/day: RRs 0.84 (0.79-0.90); 32 g/day RRs 0.68 (0.59-0.78); 50 g/day: RRs 0.60 (0.50-0.73); 100 g/day: RRs 0.61				

					(0.39-0.95)			
er cancer								
et al,	1980-2009	19	1 drink = 12 g	Drinkers vs no drinkers: RRs 1.00 (0.89-1.10)		Beer: RRs 0.86 (0.76-0.96); Wine: RRs 0.85 (0.71-1.00); Spirits: RRs 1.01 (0.87-1.15)		
chi C 2011	1983-2009	19	1 drink = 12.5 g Moderate drinkers: <37.5 g of ethanol = <3 drinks/day; Heavy drinkers: ≥37.5 g of ethanol = ≥3 drinks/day	<3: RRs 1.00 (0.92-1.09) ≥3: RRs 1.02 (0.78-1.33)		<3 drinks/day Male: RRs 1.09 (0.98-1.22) Female: 0.91 (0.76-1.09) ≥3 drinks/day Male: RRs 1.52 (0.99-2.23); Female: RRs 0.81 (0.38-1.72)		

Table 1: characteristics of the study included in the review.