ESC
European Society
of Cardiology

Is drinking wine in moderation good for health or not?

Andrea Poli*

NFI—Nutrition Foundation of Italy, Milan, Italy

Drinking alcoholic beverages is associated with various health effects in the population. Generally speaking, the evidence from epidemiological studies suggest that moderate alcohol intake is associated with a reduction in the risk of cardiovascular events, such as myocardial infarction; the risk of cancer, on the other hand, tends to rise; whether an increase in the incidence of cancer is observed also in association with moderate consumption levels is yet not definitively ascertained. All these effects seem primarily to be associated with the amount of alcohol consumed; the role of the different alcoholic beverages, and of their minor components, in this regard is in fact not clearly defined. Due to the opposite direction of the association between alcohol consumption and cardiovascular and cancer events, the association with all-cause mortality is complex, and J-shaped, with a consumption window theoretically associated with a reduction in all-cause mortality, up to 25 g alcohol per day. However, this issue is the subject of intense scientific debate.

Introduction

The debate on the health effects of alcoholic beverages has gradually become more and more radical in recent years. A part of the scientific community, and almost all of the national and international institutions that deal with this topic, have in fact focused their attention on the effects of alcohol on the risk of cancer, concluding that any alcohol consumption is associated with an increased risk of these diseases and hence that only a *zero* consumption can be considered risk-free; the other part of the scientific community, on the opposite, thinks necessary to consider these well-known evidences in the context of the overall effects of alcohol on drinkers' health, taking into adequate account also the impact of moderate alcohol consumption on the risk of cardiovascular events and of all-cause mortality. This review will try to provide a balanced and integrated evaluation of these effects, also considering the information relating to the possible differences between the health effects of wine and of other alcoholic beverages.

As starting point, it should be remembered that in observational epidemiology alcohol consumption is generally expressed in *drinks*, a measurement unit corresponding to a 150 mL glass of wine, or to a 330 mL can of beer, or to a standard 40 mL dose of any super alcoholic beverage. Due to the different alcohol concentrations of these beverages, and the different volumes of their consumption unit, the standard drink in fact contains a relatively constant amount of alcohol, ranging between 10 and 13 grams.

Daily consumption levels up to two to three drinks for males (and therefore up to 25–40 g per day of alcohol) and up to one to two drinks for females (13–25 g per day) have been generally considered moderate; the very concept of 'moderate' consumption, once widely shared in the literature, has yet recently been rejected by some experts and institutions, who prefer to define it as low-risk consumption.

The published literature, on the other hand, shows that, especially if kept within two drinks a day for men and one for women, the so-called moderate intake is associated with a reduced coronary heart disease events risk, with a limited impact on the risk of cancer, and consequently with a favourable global effect on all-cause

*Corresponding author. Email: poli@nutrition-foundation.it

mortality, which can be considered the reference parameter to evaluate the effect of any intervention on the population health.

It is also interesting to underscore that, if consumed in moderation, alcohol is characterized by a specific metabolism, with the initial intervention of alcohol dehydrogenase (ADH) and subsequently of acetaldehyde dehydrogenase, which produce acetate as the final metabolite. Larger levels of intake activate an inducible metabolic mechanism known as metabolic microsomal oxidative system (MEOS) (hepatic microsomal oxidative system); its intervention generates free oxygen radicals and is therefore associated with an increase in oxidative stress.

It goes without saying that alcohol consumption beyond the limits of moderation, especially if maintained over time, is associated with a wide and well-known series of harmful effects on the human body, and that such levels of consumption must be actively advised against by doctors and health professionals.

Moderate alcohol intake and cardiovascular diseases risk

It has been known for decades that countries in which moderate consumption of wine is widespread the incidence of cardiovascular diseases is lower than that observed in countries with lower consumption.[1] This observation, initially obtained from ecological studies (comparisons between countries), has subsequently been confirmed by numerous epidemiological observations, which have fairly systematically detected a reduction in the risk of coronary events as consumption of wine/alcohol increases. The effect on coronary risk of alcohol intake is in fact not limited to moderate consumption and is also observed for daily intake over four to five drinks per day, which must be considered excessive. In a recent study, cardiovascular risk was progressively reduced in association with increasing alcohol consumption up to 48–60 g per day; at these levels of consumption the reduction was close to 50%.[2] In this study the possible effect of the preferential consumption of beer, liqueur, or wine was also evaluated, detecting no statistically significant differences in risk between drinkers preferring any of the three mentioned beverages.

The observed risk reduction also extends to secondary prevention of cardiovascular disease, as shown by the recent follow-up data from the Alpha-Omega study cohort, which confirm that moderate drinkers with a previous myocardial infarction experience both a lower frequency of coronary recurrences over time and a lower all-cause mortality compared to non-drinkers.[3]

It is interesting to underline that the studies that have observed these effects have been mainly performed in the Western world (Europe, United States),[4] while in the Eastern world such effects are not evident. Such difference could be attributed to the fact that in Asia a large part of the population is not equipped with an efficient enzymatic mechanism for alcohol removal, being deficient of the acetaldehyde dehydrogenase activity, and therefore accumulates toxic acetaldehyde even after drinking low amount of alcohol.

The associated between alcohol intake and stroke risk is less clear: ischaemic events are usually reduced, but the risk of haemorrhagic ones is increased. The overall correlation between alcohol intake and stroke, then, takes a J shape: with a global incidence of events reduced among moderate consumers compared to abstainers, but significantly increased among excessive consumers. The relationship between alcohol consumption and the risk of sudden death or heart failure is similar, and also J-shaped. Among cardiovascular diseases, only atrial fibrillation tends to increase significantly, in a dose-related manner, with the increase in alcohol consumption.[5]

Since all this information is derived from observational epidemiology studies, it is of course not possible to establish whether the observed relationships are causal in nature or not. From a mechanistic point of view, however, it is important to note that moderate alcohol consumption is associated with modifications of biochemical parameters known to have an anti-atherosclerotic effect, which could plausibly explain the protective effect observed. For example, the levels of HDL cholesterol are increased in drinkers (although today this increase is generally considered less or not relevant), while the plasma levels of two markers of inflammation, the C reactive protein and interleukin interleukin-6, are reduced.[6] Insulin sensitivity is also generally improved, as well as the risk of developing type 2 diabetes, which certainly contributes to the risk of coronary events.

The observations relating to a possible different effect of wine, compared to other alcoholic beverages, on cardiovascular risk are rather uneven. In fact, most authors agree on the greater importance of the alcohol content of the drinks considered, compared to their minor components, often provided with antioxidant and anti-inflammatory action (as resveratrol). The actual concentration of these compounds, in wine, even if red, is indeed low; moreover, their bioavailability is often poor. However, some data suggest that wine consumption, especially if incorporated in a Mediterranean-type diet, is associated with better cardiovascular performance than that of other alcoholic beverages. It is possible that this different effect may reflect the small compositional differences, which concern the presence of the aforementioned compounds: however, it is also possible that it is rather the most widespread way of consuming wine (at meals, in divided doses, distributed evenly throughout the day and the week) which better captures the favourable aspects related to alcohol consumption. It would not be a direct effect of wine, in other words, but rather of its prevailing mode of consumption, to explain the larger protective effects sometimes observed in epidemiological studies, especially in the Mediterranean world, in association to (red) wine intake.

Alcohol and cancer

Alcohol is classified by the International Agency for the Research on Cancer as a carcinogen for humans. It needs to be underscored, on the other hand, that the quality of

the scientific evidence supporting the effect of alcohol on the risk of cancer is similar to that supporting the protective effect of alcohol on coronary risk: it is in fact essentially based on observational epidemiology studies, which do not allow to establish causal links.

With these limitations, the association between alcohol consumption and cancer risk is well documented for tumors of some specific sites (especially the upper digestive and respiratory tracts, but also the colon-rectum and the female breast). The published studies generally concern non-moderate consumption of alcohol (over 2–3 drinks per day for men, and 1–2 for women); some authors, however, consider this association to be without a 'threshold effect', and therefore to be extended to moderate consumption (within the limits described above).

This position is controversial. A recent Italian meta-analysis, for example, concludes instead that no clear relationship can be found between moderate alcohol intake and cancer risk; more in detail, a positive association is observed between moderate consumption and the risk of melanoma, breast cancer among women and prostate cancer among men, but a negative (and therefore theoretically protective) association can be found with the risk of some lymphomas, bladder and kidney cancer. The final overall effect seems to be null.[7]

A direct effect of a moderate alcohol intake on cancer risk is also questioned by the results of a US study, coordinated by one of the most authoritative epidemiological research groups.[8] An increased risk of cancer associated with moderate alcohol consumption, in male subjects, is observed in this study only among smokers, but is not detected among non-smokers. It is possible that alcohol requires the additional effect of substances with documented carcinogenic action (certainly present in cigarette smoke) or that unidentified confounding factors (and for which the necessary statistical adjustment has not therefore been made) explain the association found in the presence, but not in the absence, of cigarette smoke: but a direct positive effect of a low alcohol intake on the cancer risk seems unlikely based on these data.

The most complex aspect of the relationship between alcohol and cancer is probably that concerning female breast cancer. It is known that this effect can be observed for very low levels of consumption (around 2–3 drinks per week); it is generally estimated that 4% of the tumors observed in this anatomical site are attributable to alcohol. Relatively recent data, however, show that this effect is not homogeneously distributed in the population, but reflects some behavioural, lifestyle, or genetic individual characteristics. In a US study, for example, it was observed that among women with no family history of breast cancer, and with a dietary folate intake greater than 400 mg per day, alcohol consumption levels up to one drink per day were not associated with any effect on the risk of this type of cancer. On the other hand, the increase in risk was marked among women with low intakes of dietary folate and with a clearly positive family history for breast cancer.[9]

Alcohol and all-cause mortality

The majority of published cohort studies observe a curvilinear association between alcohol intake and all-cause mortality. The shape of this association (usually referred to as the 'J-curve') suggests that moderate consumers face a risk of mortality from any cause that is lower than that of abstainers, but also of consumers of larger amounts. The minimum mortality is usually observed for daily consumption levels of one drink for women and one to two for men; at intakes around three to four drinks in men, and two to three in women, mortality from all causes is similar to that of abstainers.[10]

A meta-analysis by Italian authors, published 15 years ago, and referring to more than 1 million subjects followed over time, was among the first to shows the shape of the relationship.[11] The authors concluded that 'Low levels of alcohol intake (1–2 drinks per day for women and 2–4 drinks per day for men) are inversely associated with total mortality in both men and women. Our findings, while confirming the hazards of excess drinking, indicate potential windows of alcohol intake that may confer a net beneficial effect of moderate drinking, at least in terms of survival'. In a much more recent study, conducted in an older population (over 56 years at enrolment), followed for over 15 years, all-cause mortality was lowest among moderate or occasional users, and highest in the group of excessive consumers, among those who had always been abstainers or among those who had stopped consuming alcohol.[12]

Since the large majority of total deaths observed in a population is due to cardiovascular diseases or cancer, the shape of the alcohol intake vs. the all-cause mortality curve suggests that among moderate drinkers the effect of the negative (and therefore favourable) association with the risk of cardiovascular disease prevails on the positive (and therefore unfavourable) association with the risk of cancer.

It should be noted that the veracity of the J-shaped correlation between alcohol consumption and all-cause mortality is questioned by several groups of researchers. It is generally argued that among abstainers many subjects stopped indeed drinking due to the alcohol-associated diseases they had developed over time. It would be the presence of these diseases, and not the abstention from alcohol consumption, to explain the excess mortality that is usually observed among abstainers compared to moderate consumers. All the most recent papers on the topic, on the other hand, differentiate ex drinkers from lifelong abstainers: this potential error source is consequently neutralized. One of the most cited papers supporting this argument (the so-called 'sick quitter' issue), published in the Lancet, differentiated indeed very carefully, in the studied cohorts, ex-drinkers from long-time abstainers, noting among the latter a significant excess of fatal diseases compared to moderate consumers.[13] Interestingly, the authors decided to show in their paper a correlation between alcohol and mortality from any cause in which abstainers had been deliberately hidden. Only in the additional figures, data are presented in their completeness, and the classical J-shaped correlation curve reappears.

Conclusions

The health effects of alcohol consumption are articulated and different when the associations with cardiovascular diseases or cancer is considered. Within the limits of the so-called moderate consumption, the association with a reduced cardiovascular risk seems to prevail over the increase in neoplastic risk, with the consequence that all-cause mortality is reduced as compared to abstainers, according to the previously described J-shaped conformation.[14]

It is currently not possible to decide with certainty whether the consumption of the different alcoholic beverages and in particular that of wine, has specific health effects, different from those of the other alcohol beverages. In the literature studies that support, or instead deny, this hypothesis can be found.

Since the effects of alcohol intake are to some extent different from person to person, or from country to country, consumption recommendations addressed to the entire population, which do not take these differences into account, are likely inaccurate; 'tailor-made' indications, based on the clinical, genetic, metabolic, socioeconomic situation of individuals, would be preferable.

The widely shared consensus that no one should start drinking alcoholic beverages for health reasons should in any case not be forgotten.[15]

Funding

References

1. St Leger AS, Cochrane AL, Moore F. Factors associated with cardiac mortality in developed countries with particular reference to the consumption of wine. *Lancet* 1979;**8124**:1017–1020.
2. Song RJ, Nguyen XT, Quaden R, VA Million Veteran Program *et al*. Alcohol consumption and risk of coronary artery disease (from the million veteran program). *Am J Cardiol* 2018;**121**:1162–1168.
3. Cruijsen E, de Ruiter AJ, Küpers LK, Busstra MC, Geleijnse JM. Alcohol intake and long-term mortality risk after myocardial infarction in the alpha omega cohort. *Am J Clin Nutr* 2022;**115**:633–642.
4. Leong DP, Smyth A, Teo KK, INTERHEART Investigators *et al*. Patterns of alcohol consumption and myocardial infarction risk: observations from 52 countries in the INTERHEART case-control study. *Circulation* 2014;**130**:390–398.
5. Conen D. Alcohol consumption and incident cardiovascular disease: not just one unifying hypothesis. *Eur Heart J* 2015;**36**:897–898.
6. Bell S, Mehta G, Moore K, Britton A. Ten-year alcohol consumption typologies and trajectories of C-reactive protein, interleukin-6 and interleukin-1 receptor antagonist over the following 12 years: a prospective cohort study. *J Intern Med* 2017;**281**:75–85.
7. Caprio GG, Picascia D, Dallio M *et al*. Light alcohol drinking and the risk of cancer development: A controversial relationship. *Rev Recent Clin Trials* 2020;**15**:164–177.
8. Cao Y, Willett WC, Rimm EB, Stampfer MJ, Giovannucci EL. Light to moderate intake of alcohol, drinking patterns, and risk of cancer: results from two prospective US cohort studies. *BMJ* 2015;**351**:h4238.
9. Kim HJ, Jung S, Eliassen AH, Chen WY, Willett WC, Cho E. Alcohol consumption and breast cancer risk in younger women according to family history of breast cancer and folate intake. *Am J Epidemiol* 2017;**186**:524–531.
10. Costanzo S, de Gaetano G, Di Castelnuovo A, Djoussé L, Poli A, van Velden DP. Moderate alcohol consumption and lower total mortality risk: justified doubts or established facts? *Nutr Metab Cardiovasc Dis* 2019;**29**:1003–1008.
11. Di Castelnuovo A, Costanzo S, Bagnardi V, Donati MB, Iacoviello L, de Gaetano G. Alcohol dosing and total mortality in men and women: an updated meta-analysis of 34 prospective studies. *Arch Intern Med* 2006;**166**:2437–2445.
12. Keyes KM, Calvo E, Ornstein KA *et al*. Alcohol consumption in later life and mortality in the United States: results from 9 waves of the health and retirement study. *Alcohol Clin Exp Res* 2019;**43**:1734–1736.
13. Wood AM, Kaptoge S, Butterworth AS, Emerging Risk Factors Collaboration/EPIC-CVD/UK Biobank Alcohol Study Group *et al*. Risk thresholds for alcohol consumption: combined analysis of individual-participant data for 599 912 current drinkers in 83 prospective studies. *Lancet* 2018;**391**:1513–1523.
14. Bell S, Daskalopoulou M, Rapsomaniki E *et al*. Association between clinically recorded alcohol consumption and initial presentation of 12 cardiovascular diseases: population-based cohort study using linked health records. *BMJ* 2017;**356**:j909.
15. Poli A, Marangoni F, Avogaro A *et al*. Moderate alcohol use and health: a consensus document. *Nutr Metab Cardiovasc Dis* 2013;**23**:487–504.