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Potential health benefits of moderate alcohol consumption: current perspectives in research

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The benefits of moderate amounts of alcohol for a better health and longer life expectancy compared with abstinence have been suggested by the findings of numerous studies. However, controversies have emerged regarding the influence of confounding factors and the systematic errors that might have been inadvertently disregarded in the early studies. This review includes a description of the findings of those research studies published in the last 5 years on the effects of moderate alcohol consumption on all-cause mortality, CVD and inflammation, the immune system, insulin sensitivity, non-alcoholic fatty liver disease (NAFLD) and cancer. Promising evidences exist from both animal studies and human clinical trials regarding intermediate endpoints of CHD and insulin sensitivity, such as HDL, adiponectin or fibrinogen. However, controversies and inconsistent findings exist regarding many of these diseases and related functions and biomarkers. Further research and human randomised-controlled trials with adequate standardisation of the study conditions are necessary in order to draw a comparison between studies, establish the causal effect of moderate alcohol intake on disease protection and reach consensus on the circumstances that allow the recommendation of moderate alcohol habitual intakes as a strategy for health maintenance.

Alcohol: Moderate consumption: Mortality: CVD: Insulin sensitivity

Moderate alcohol consumption, disease and mortality: relevant methodological issues in research studies

A substantial amount of observational studies have documented the complex relationship among alcohol consumption, health preservation and mortality. The U-shaped relationship between alcohol and death, which shows that moderate alcohol consumption is associated with lower mortality than complete abstinence or heavy alcohol use, was first described in 1923⁽¹⁾. Although many studies since then have repeatedly found that moderate drinkers have a survival advantage compared with abstainers and heavy drinkers, controversies have emerged regarding the importance of confounding factors and the validity of such results if these are taken into consideration. One thing seems clear from the beginning, and it is the fact that non-drinkers are different from alcohol consumers in several

characteristics. One might think of differences in socio-economic status (differences in social support, education and wealth) and health conditions (comorbidities, functional capacities, etc.), which are more favourable in moderate drinkers, as several studies have already shown^(1–4). Current drinkers are usually objectively found and/or tend to self-report to be in better health than never drinkers or ex-drinkers, the finding resulting probably from a ‘selection bias’^(5,6). Thus, some authors have spoken about the systematic error of not excluding from the abstainers category those people who decrease their alcohol consumption as they age and become ill⁽⁷⁾.

A recent study performed in 12 500 participants in the USA Health and Retirement Study showed that eliminating the confounding effect of traditional and non-traditional risk factors, such as those commented earlier, attenuated the protective effect (against all-cause

Abbreviations: CRP, C-reactive protein; FL, fatty liver; NAFLD, non-alcoholic fatty liver disease; RCT, randomised-controlled trial.

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mortality) of moderate drinking, but remained statistically significant (OR 0.72, 95% CI 0.57, 0.91)⁽⁴⁾. This study made a number of other corrections, trying to diminish additional error sources, and always the mortality OR of moderate drinkers was decreased in comparison with non-drinkers. One of the cautions in this study referred to the 'sick quitter' hypothesis first described by Fillmore *et al.*⁽⁷⁾, so that recent quitters were excluded from the primary results. Despite the encouraging results, there is still an argument to be made in opposition to the protective effect of moderate drinking (one drink per day) seen in this study. Adjusting the regression analysis for all risk factors, traditional (comorbidities, demographic, smoking and obesity) and non-traditional, led to a half attenuation of the alcohol–mortality relationship; this fact suggests that other factors not accounted for might explain the other half of the association.

Another study on moderate alcohol intake and risk of functional decline found that after adjusting for lifestyle-related variables the strength of the association between lower mobility disability and moderate alcohol consumption was substantially reduced⁽⁸⁾. Likely, the question of how important are confounding factors not controlled for in observational studies, could only be answered by randomised-controlled trials (RCT), which, despite being complicated because of logistical and ethical matters, seem to have come to be a priority⁽⁴⁾. However, after controlling for a variety of covariates, several recent publications still report that those who consume a moderate amount of alcohol have lower all-cause mortality and CHD mortality compared with non-drinkers^(9,10), which supports the argument that the relationship between moderate alcohol–CHD mortality and all-cause mortality is causal.

Another question that deserves attention is the effect of ethnicity as a factor leading to differences in the effects of moderate alcohol consumption in observational studies. A review of recent studies performed in Chinese cohorts with results adjusted by age, socio-economic status and lifestyle and/or type of home, shows that the same survival advantage and the same protection against CVD or cognitive decline is found from moderate alcohol use and occasional use in this population^(5,11). Since occasional use is not believed to possibly exert any physiological effect, the result seems to point towards factors different from alcohol, such as a confounding effect by a general moderation in lifestyle driving the association between alcohol and health benefits, instead of being a causal effect. On the other hand, according to a study by Sun *et al.*⁽⁵⁾ the benefit would be restricted, at best, to old and unhealthy people. There are, however, genetic differences driven by race and also different ways of life and environmental factors that might lead to different results in western and eastern populations.

Gender-dependent differences appear very frequently in studies on alcohol and its effects on health and disease. The differences between men and women who are moderate alcohol users have been described for multiple outcomes, such as oxidative stress status⁽¹²⁾, brain grey matter decrease (seen only in males)^(13,14) and cognitive performance and decline (benefits seen only in females)⁽¹⁵⁾. In addition to the need to differentiate what dose and pattern of consumption is

an average moderate intake in women *v.* men, the intrinsic hormonal and physiological characteristics of both sexes must be considered for a reliable investigation of the possible mechanisms of alcohol influence on health maintenance and disease prevention.

A topic of relevance in the current state of investigations on moderate alcohol intake in human subjects is the effect of low-to-moderate intakes of alcohol during pregnancy in neonatal status of the foetus. Some reviews have failed to find a demonstrable negative effect on variables such as miscarriage, gestation length, birth weight or small for gestational age outcomes⁽¹⁶⁾. The authors, however, are aware that the studies have methodological weaknesses. Moreover, the interest in the prenatal exposure to toxic substances derives from their possible health implications according to the 'foetal programming' hypothesis⁽¹⁷⁾. However, these reviews advise that some retrospective studies and small prospective studies cannot account for all confounding factors associated with substance use in pregnant mothers and suggest that novel approaches and innovative methods are preferable⁽¹⁷⁾. Individual susceptibility and genotype–exposure interactions have been addressed in a number of studies in animals⁽¹⁸⁾. A very recent study on 1258 pregnant women found, in contrast with previous results, that when controlling for a series of confounding factors, moderate drinking was related to lower birth weight ($P < 0.01$) and also with neonatal asphyxia at trend level ($P = 0.06$)⁽¹⁹⁾.

Moderate alcohol consumption, inflammation and CVD

The beneficial effects of moderate alcohol consumption on the cardiovascular system have been extensively discussed in the literature⁽²⁰⁾. Several epidemiological studies have demonstrated an association between moderate intake of alcohol and reduced CVD risk, including CHD and ischaemic stroke^(21,22). These cardioprotective effects are not only observed in healthy individuals but also in patients who suffered from myocardial infarction, stroke or hypertensive risk^(23–25).

Epidemiological, clinical and experimental studies have indicated that inflammatory mechanisms are involved in the pathogenesis of CVD mainly in atherosclerosis^(26,27). The initial event of atherosclerosis is the endothelial dysfunction, which is characterised by an imbalance between vasodilation and vasoconstriction, caused in part by the increased expression of adhesion molecules, pro-inflammatory cytokines, pro-thrombotic factors and oxidative stress (reviewed by Sitia *et al.*⁽²⁸⁾). Some inflammatory markers, such as C-reactive protein (CRP), are used to monitor the disease process and cardiovascular risk⁽²⁹⁾.

Moderate alcohol consumption could decrease the risk of CVD through various mechanisms: increase of HDL, apoA1 and adiponectin levels, reduction of LDL concentration, blood pressure, coronary blood flow, platelet aggregation, fibrinogen levels and others (reviewed by Klatsky⁽²⁰⁾ and Brien *et al.*⁽²²⁾). Recent studies have demonstrated that moderate alcohol consumption can lead to an improvement of inflammation and this effect could explain the protective action of alcohol consumption on

the cardiovascular system⁽³⁰⁾. Interventional studies on the effects of alcohol consumption on biological markers of coronary disease risk have been reviewed⁽²²⁾. They concluded that the moderate consumption of alcohol can be protective for CHD since the studies showed increased levels of HDL and adiponectin and decreased levels of fibrinogen. Moderate beer consumption for 1 month causes favourable changes on the blood lipid profile⁽³¹⁾. Raum *et al.*⁽³²⁾ performed repeated measures of CRP in seventy-two middle-aged adults during 12 months and observed that the lowest levels of CRP were found in moderate alcohol consumers (<16 g/d). Similar results were obtained in another study⁽³⁰⁾ where 636 healthy individuals were analysed and moderate alcohol consumption (20–70 g/d) was negatively correlated with CRP levels. In addition, daily alcohol consumption was found to have an apparent U-shaped association with fibrinogen levels. Moreover, fibrinogen levels of alcohol consumers were lower than levels of abstainers in patients who had suffered venous thrombosis⁽³³⁾. In 26 399 women from the Women's Health Study, the main two factors mediating the decreased CVD risk associated with moderate amounts of alcohol were lipids and glycated Hb levels; however, inflammatory and haemostatic factors including intercellular adhesion molecule-1, fibrinogen and CRP, explained 5% of the risk reduction⁽¹⁰⁾. Imhof *et al.*⁽³⁴⁾ conducted a study to investigate whether the moderate consumption of alcoholic (ethanol, beer or red wine) and non-alcoholic beverages (de-alcoholised beer or red wine and water) could affect the monocyte migration, an important step in atherogenesis. They showed that the intake of ethanol or de-alcoholised red wine (20–30 g ethanol/d) reduced monocyte migration induced by macrophage chemoattractant protein-1 or N-formyl-methionyl-leucyl-phenylalanine, but the consumption of all tested beverages did not change the macrophage chemoattractant protein-1 receptor expression. The authors suggested that this inhibition of monocyte migration could represent one mechanism mediating the reduction of cardiovascular risk by alcoholic beverages. The population-based Northern Manhattan Study showed that the brachial artery flow-mediated dilation was better in moderate alcohol consumers than non-drinkers⁽³⁵⁾. A study conducted by Hamed *et al.*⁽³⁶⁾ described that the consumption of 250 ml red wine during twenty-one consecutive days improved the vascular endothelial function, increasing the migration and proliferation of endothelial progenitor cells. Moderate alcohol consumers had higher plasma levels of nitrite and nitrate than teetotalers with a more favourable lipid profile. NO in plasma has been involved in the cardioprotective effect but was considered to have a biphasic role and a dose-dependent effect regarding the findings of even highest NO levels and higher lipid-related cardiovascular risk in heavy drinkers⁽³⁷⁾. The moderate intake of red wine (100 ml daily for 3 weeks) enhanced circulating endothelial progenitor cell and plasma levels of NO in healthy subjects while beer (250 ml) and vodka (30 ml) consumption did not produce any effect⁽³⁸⁾. A study with an experimental model of atherosclerosis (induced by infusion of angiotensin II in apoE-deficient mice) showed that mice treated with a low dose of ethanol for 28 d exhibited less dilation and fewer atheromatous lesions than mice treated with a high dose⁽³⁹⁾.

Authors discuss that the circulating levels of stromal cell-derived growth factor-1 could be involved, since the treatment with low-dose ethanol increased these levels.

Although moderate alcohol consumption has a protective action on the cardiovascular system and related diseases, some of the effects seem to be exclusive for wine intake. Wine has other components besides ethanol, such as resveratrol and hydroxytyrosol, which have important antioxidative and anti-inflammatory effects⁽⁴⁰⁾. Several studies have shown that some beneficial actions of moderate wine consumption on the cardiovascular system are not observed with other alcoholic beverages^(38,41).

Moderate alcohol consumption and the immune system

The interplay between alcohol and the immune function is dependent upon several factors, including the amount, frequency and duration of the alcohol administration⁽⁴²⁾. Abuse of ethanol has been associated with an increased incidence and severity of infections in human beings and experimental animals, which has been attributed to induced immunosuppression^(43–45). But while the effect of excessive alcohol consumption has been extensively studied, little is known about the consequences of moderate alcohol consumption on the immune system.

One review on this topic by Romeo *et al.*⁽⁴⁶⁾ published in 2007 refers to the scarce number of studies reporting effects on immunity with moderate alcohol consumption to that date. Two of them report a decreased incidence of common cold in human subjects^(47,48), and others describe anti-inflammatory effects such as those on adhesion properties of monocytes⁽⁴⁹⁾, fibrinogen⁽⁵⁰⁾ and inflammatory cytokine production^(50–52) and the transcription factor NF- κ B⁽⁵²⁾. Another study by Romeo *et al.*^(53,54) reports an enhancement in a wide spectrum of immune variables, from leucocyte counts (only in women), to cytokine production and Ig concentrations.

The effect on adhesion molecules has been documented in a number of studies recently. Modest amounts of alcohol intake (150 ml red wine/d) in an RCT decreased vascular cell adhesion molecule-1 levels only in females⁽⁵⁵⁾. Both cava (sparkling wine from Catalonia region) and gin decreased adhesion molecules in a cross-over study with 30 g ethanol during 28 d periods⁽⁵⁶⁾. Both alcoholic beverages decreased significantly vascular cell adhesion molecule-1, P-selectin and E-Selectin and the expression of Sialyl-Lewis(x) (SLe(x)), while intercellular adhesion molecule-1 was only decreased after cava intake (all $P < 0.05$). The effect of cava was also significant for the expression of both, lymphocyte function-associated antigen-1 and very late activation antigen-4. Polyphenols in cava might explain the superior anti-inflammatory findings.

Regarding these previous studies, it is necessary to consider that although wine and beer are a source of alcohol, they also contain other components such as carbohydrates, soluble fibre, minerals and vitamins, as well as polyphenols^(57–59) that also influence the immune system. Several studies have reported on the potential health and immune system benefits of xanthohumol, principal prenylated flavonoid found in beer, and resveratrol,

a polyphenolic phyto-alexin present in the red wine. Xanthohumol has important immunosuppressive effects on T-cell proliferation, development of IL-2 activated killer cells, cytotoxic T-lymphocytes and production of Th1 cytokines (IL-2, interferon- γ and TNF α) and exhibits antioxidant and anti-inflammatory activity⁽⁶⁰⁾. Resveratrol and its derivatives have been shown to have a wide spectrum of biological activity including anti-tumour^(61,62), antioxidant⁽⁶³⁾ and also anti-inflammatory effects⁽⁶⁴⁾. This compound may interfere with immune activation and cytokine cascades, suppressing interferon- γ -mediated biochemical pathways⁽⁶⁵⁾, which could be of a great relevance to interrupt development and progression of some diseases related to the immune system. Therefore, further studies focused on moderate alcohol consumption from both fermented and distilled drinks are necessary to elucidate their effects on the immune system.

On the other hand, little is known about the effect of discontinuous moderate consumption of ethanol on immunity. A recent study⁽⁶⁶⁾ compared the effect of the discontinuous feeding (3 d/week) of a liquid diet containing a moderate amount of ethanol with that of a continuous ethanol administration or a control diet on the immune system in rats. A significant ($P < 0.001$) decrease of splenic cells' response to concanavalin A, and of lymph node and splenic cells' response to lipopolysaccharide was found in rats under the discontinuous ethanol regime, when compared with control- or ethanol-chronic rats. Under discontinuous ethanol feeding, mean values of lymph node and splenic CD8(+) and CD4(+)-CD8(+) cells decreased, whereas those of lymph node and splenic T-cells, and splenic B-cells augmented. In rats chronically fed with ethanol, splenic mean levels of CD8(+) and CD4(+)-CD8(+) cells increased. Mean plasma prolactin levels increased by 3.6- and 8.5-fold in rats chronically or discontinuously fed with alcohol, respectively. These results suggest that the discontinuous drinking of a moderate amount of ethanol can be more harmful for the immune system than a continuous ethanol intake. Due to the scarcity of data in the literature about this subject, further studies would be necessary, especially considering that a significant proportion of adolescents and youth tend to consume alcohol in a discontinuous pattern at weekends.

Various metabolic effects of moderate alcohol consumption

Insulin sensitivity

The relationship between alcohol consumption and insulin resistance shows a U-shaped curve: insulin resistance is minimal in individuals with regular mild-to-moderate alcohol consumption and increases in both heavy drinkers and subjects without any alcohol consumption. Improved insulin sensitivity seems to explain the fact that moderate alcohol consumption is associated with a decreased risk of type 2 diabetes in numerous research studies^(67–69). Positive associations between alcohol consumption and insulin sensitivity are consistently reported in cross-sectional studies^(70–71), but RCT^(72–75) as well as studies in patients with diabetes mellitus⁽⁷⁶⁾ report contradictory results.

Moreover, the only study in which a direct measure of insulin-mediated glucose uptake (the euglycaemic, hyperinsulinaemic clamp) indicated that moderate alcohol consumption significantly improved insulin sensitivity (43%; $P = 0.02$) was performed in patients with type 2 diabetes⁽⁷⁷⁾. Kim *et al.*⁽⁷⁸⁾ trying to reconcile prior conflicting findings conducted a study on a group of twenty subjects who were in the upper tertile of insulin resistance for individuals with normal glucose tolerance. They performed the steady-state insulin suppression test before and after consuming 30 g alcohol for 8 weeks. At best, there was a trend towards enhanced insulin sensitivity in the total group of approximately 8%, with a significant improvement of a modest degree in men (approximately 11%; $P = 0.04$).

Despite insulin sensitivity itself not improving significantly, several molecules involved in energy and macronutrient metabolism such as adiponectin, ghrelin and the acylation stimulating protein seem to respond to moderate alcohol consumption in line with the hypothesised improvement of insulin sensitivity⁽⁷⁹⁾. Moderate alcohol consumption increased adiponectin and ghrelin, while it decreased acylation-stimulating protein concentrations in a group of healthy lean and overweight men. The orexigenic peptide ghrelin has been recently shown to be required for alcohol-induced reward, inducing moderate alcohol consumption in mice⁽⁸⁰⁾.

Adiponectin

Different RCT with moderate alcohol consumption in the form of wine, beer or whisky confirmed an increase in serum adiponectin levels in young men, pre-menopausal, normal-weight women and middle-aged men and women^(68,75,79,81,82). Sierksma *et al.*⁽⁶⁸⁾ suggested that an increase in adiponectin could precede changes in insulin sensitivity with moderate alcohol consumption. Adiponectin is thought to improve insulin sensitivity by increasing glucose uptake and fatty acid oxidation in muscle tissue⁽⁸³⁾.

A study conducted in middle-aged men with abdominal overweight consuming moderate amounts of alcohol (red wine) during 4 weeks, showed moderately increased plasma adiponectin concentration, whereas fat distribution, serum resistin and insulin sensitivity index were unaffected⁽⁷⁵⁾. Changes in adiponectin were not associated with changes in body weight, fat distribution or insulin sensitivity index, suggesting that other mechanisms mediate the effect of moderate alcohol consumption on adiponectin concentrations. Plasma adiponectin concentration increased by 10% after 28 d of moderate consumption of red wine compared with de-alcoholised red wine. This increase in adiponectin is consistent with the 11% increase observed by Sierksma *et al.*⁽⁶⁸⁾ and two observational studies^(84,85). Lately, another cross-over study in lean and overweight young men consuming three cans of beer daily, confirmed an increase in adiponectin with no change in the insulin sensitivity index. However, this time a positive association was observed between both variables. According to the authors of this study, adiponectin may predict changes of insulin sensitivity, but interventions longer than 3–4 weeks

may be needed to detect changes of insulin sensitivity with moderate alcohol consumption⁽⁷⁹⁾. On the contrary, Sierksma *et al.*⁽⁶⁸⁾ found in his cross-over study that adiponectin increased more in the insulin-sensitive subgroup than in the insulin-resistant one, despite only the last subgroup showing a borderline significant increase ($P = 0.11$) in insulin sensitivity.

In 2009, Imhof *et al.*⁽⁸²⁾ conducted a study with a total of seventy-two healthy individuals (22–56 years) enrolled in a cross-over RCT. After washout, two interventions for 3 weeks followed, with another 3 weeks-wash-out between periods. The subjects were randomly allocated to consumption of ethanol (concentration 12.5%), beer (5.6%) or red wine (12.5%) equivalent to 30 g ethanol/d for men and 20 g/d for women or the same de-alcoholised beverages or water. Among women, adiponectin significantly increased after consuming red wine (29.8%, $P < 0.05$) and increased among men after ethanol solution (17.4%, $P < 0.05$) and beer (16.1%, $P < 0.05$). De-alcoholised beverages had no substantial effect on adiponectin concentrations. In conclusion, the authors confirmed that moderate amounts of ethanol-containing beverages increase serum adiponectin concentrations, but sex-specific effects might depend on the type of beverage consumed.

Non-alcoholic fatty liver disease

The effect of alcohol consumption on the liver is controversial. Excessive alcohol consumption and obesity are known to lead to accumulation of fat in hepatic tissue and to induce changes in serum liver-derived enzymes. However, moderate alcohol consumption effects are not so clear. A protection against the development of hypertransaminasaemia among male subjects without other liver conditions has been found associated with light-to-moderate alcohol consumption⁽⁸⁶⁾.

Non-alcoholic fatty liver disease (NAFLD) is a common cause of elevated liver enzymes and chronic liver disease in Western countries. The NAFLD is characterised by hepatic steatosis in the absence of significant alcohol use or other known liver disease⁽⁸⁷⁾. The term NAFLD comprises a spectrum of diseases which range from fat accumulation in hepatocytes with no associated inflammation or fibrosis (simple steatosis) or steatosis with inflammation to non-alcoholic steatohepatitis that includes macrovesicular steatosis, lobular inflammation, ballooning degeneration of hepatocytes and zone 3 pericellular fibrosis⁽⁸⁸⁾.

Results from a study including 5599 Japanese asymptomatic male subjects indicated that the prevalence of fatty liver (FL) was significantly and independently decreased by light and moderate alcohol consumption ($P = 0.044$ and 0.008 , respectively)⁽⁸⁹⁾. In another study, also in Japanese population, the major risk factors for FL in Japanese men were factors related to adiposity, while consistent alcohol consumption (> 21 d/month) was inversely associated with the prevalence of FL⁽⁹⁰⁾. Also in the severely obese, moderate alcohol consumption seems to reduce the risk of NAFLD, possibly by reducing insulin resistance^(91–92).

Conversely, Alatalo *et al.*⁽⁹³⁾ showed that increased BMI and moderate drinking have additive effect on enzymes reflecting hepatocellular health in the Nordic population. In

their study of 2164 healthy adults, glutamyltransferase seems to be most sensitive to ethanol intake, while alanine aminotransferase seems to be the predominant responder to increasing BMI.

Regarding the relationship of altered liver enzymes with the risk of type 2 diabetes in the context of varying habitual alcohol intakes, a prospective study showed that glutamyltransferase, alanine aminotransferase and daily alcohol consumption were independently associated with the risk of type 2 diabetes⁽⁹⁴⁾. Moderate daily alcohol consumption (16.4–42.6 g ethanol/d) decreased the risk of type 2 diabetes, and higher levels of glutamyltransferase and alanine aminotransferase increased the risk. At every level of glutamyltransferase, moderate, but also heavy, alcohol drinkers (≥ 42.7 g ethanol/d) had a lower risk of type 2 diabetes than non-drinkers. However, the authors do not mention the possible confounding effect of recent quitters among the non-drinkers.

A pre-existing condition of hepatic damage seems to change the response to moderate amounts of alcohol. Hézode *et al.*⁽⁹⁵⁾ found a relationship between the level of alcohol intake and the degree of steatosis in chronic hepatitis C patients, but an interesting finding was the relationship between histological lesions and steatosis. They suggested that steatosis might play a role explaining the aggravation of histological lesions associated with even moderate alcohol intake in hepatitis C patients. Both heavy (more than 50 g/d in women and 60 g/d in men) and moderate (21–50 g/d in women and 31–50 g/d in men) alcohol intake showed a deleterious effect in this setting. Similarly, with a pre-existing non-alcoholic steatohepatitis condition, a recent study with rats demonstrated that a moderate consumption of alcohol can lead to more hepatic inflammation and cell death⁽⁹⁶⁾.

Whether the amount of alcohol consumption (light to moderate), the frequency or both are responsible for the beneficial effect on NAFLD development is unknown, and little is known also about the association between alcohol consumption and FL in women alone. Recently, Moriya *et al.*⁽⁹⁷⁾ confirmed that the drinking frequency was inversely correlated to the prevalence of ultrasonographically determined FL and alanine aminotransferase elevation in men, whereas light and infrequent alcohol consumption was associated with a low risk of FL in women.

Moderate alcohol consumption and cancer risk

Alcohol consumption has been associated with a variety of different forms of cancer in man for several centuries. The evidence linking alcohol drinking to cancer risk has been reviewed in different occasions, some of them recently^(98–100).

Many epidemiological studies have investigated the relationship between high alcohol intake and risk of cancer; however, there are very few intervention studies relating the risk of cancer associated with moderate intakes, with the exception of breast cancer⁽¹⁰¹⁾.

Several case-control studies derived from measurements of alcohol intake in women suggest that both, moderate and excessive alcohol intake, may contribute to the risk of

breast cancer⁽¹⁰²⁾. Results from the Nurses' Health Study (1980) in the United States, initially based on 89 538 US nurses aged between 34 and 59 years, with no history of cancer, showed that, among the low-to-moderate drinkers (5–14 g alcohol daily; three to nine drinks per week), the age-adjusted relative risk of breast cancer was 1.3 *v.* non-drinkers⁽¹⁰²⁾. Consumption of 15 g alcohol or more per day was associated with a relative risk of 1.6. Significant associations were observed for beer and liquor when considered separately. Similarly, The National Institutes of Health–AARP Diet and Health Study (1995–2003), including 184 418 post-menopausal women aged 50–71 years, reported that, during an average of 7 years of follow-up, even a moderate amount of alcohol (>10 g/d) significantly increased breast cancer risk. And definitely, in a comparison of >35 *v.* 0 g/d alcohol, the multivariate relative risks were 1.35 for total breast cancer, 1.46 for ductal tumours, and 1.52 for lobular tumours⁽¹⁰³⁾.

The mechanism by which alcohol contributes to breast tumour initiation or progression is yet to be definitively established. There appear to be multiple mechanisms by which alcohol may contribute to breast malignancies or may modulate the behaviour of mammary epithelial and tumour cells *in vivo* and *in vitro*. Mill *et al.*⁽¹⁰⁴⁾ postulate three mechanisms by which alcohol may contribute to breast tumour genesis, progression or aggressiveness. A common feature of these mechanisms is the increase in epidermal growth factor receptor tyrosine kinase signalling⁽¹⁰⁴⁾.

On the other hand, results from some other studies suggest that alcohol may reduce the risk of some cancers such as rectal cancer⁽¹⁰⁵⁾ and renal cell carcinoma⁽¹⁰⁶⁾. In the population-based case–control North Carolina Colon Cancer Study, moderate alcohol intake was inversely associated with distal colorectal cancer. The OR for moderate alcohol consumption (≤ 14 g/d) was 0.66, whereas the OR for >14 g/d was 0.93 *v.* no alcohol intake. Moderate beer and wine intakes were also inversely associated with this cancer⁽¹⁰⁵⁾.

Conclusions

In the literature there are a substantial amount of RCT with moderate alcohol consumption, at least in regular and occasional alcohol drinkers. Although receiving ethical permission for such trials with abstainers might seem difficult, some have already been published, for instance, among type 2 diabetic subjects⁽¹⁰⁷⁾. Several RCT and their meta-analysis⁽²²⁾ have shown that intermediate end-points related to CVD and/or insulin sensitivity, such as HDL, adiponectin and fibrinogen improve with moderate alcohol consumption, which are indirect evidence of a causal protective effect of alcohol. The logistical problems of performing sufficiently powerful studies, with a large number of healthy people recruited to be on the randomised-controlled intervention for time enough to assess the effect of moderate alcohol on variables such as cognitive decline, functional decline or all-cause mortality, seem more restraining than the ethical issues.

In summary, most aspects of health and illness reviewed here are still insufficiently studied in relation with the advantage of moderate alcohol. Controversy and inconsistent findings appear on the effects of moderate alcohol on insulin sensitivity as derived from RCT, the number of studies regarding immune modulation is scarce, lack of positive effects have been reported in most cancer studies and the effect on the liver is controversial. As a conclusion, it seems to be too soon to recommend moderate consumption of ethanol as a strategy to promote better health. Finally, important methodological issues should be considered in future studies. In this sense, it seems important to define and standardise what a moderate dose for each sex is, taking into account age range, pattern of drinking, health status and lifestyle (*i.e.* only household elderly or institutionalised, not both), so that comparisons can be made between studies.

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