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WINE AND HEALTH RELATIONSHIPS. A QUESTION OF MODERATION?

RELAÇÃO ENTRE VINHO E SAÚDE. UMA QUESTÃO DE MODERAÇÃO?

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ABSTRACT

Evidences accumulated over the last thirty years suggest that light to moderate alcohol consumption, especially in the form of red wine, can have beneficial effects for health. Those benefits mostly refer to improvement in cardiovascular health, although relationships with a lower risk of other pathologies such as type 2 diabetes, dementia or cognitive decline in old age have also been established. Most evidences derive from observational studies or from *in vitro* or animal assays, whereas direct scientific data in human are scarce and incomplete. On the other hand, alcohol is a toxic product whose irresponsible and excessive consumption has well-established consequences for health and serious social implications. Furthermore, some adverse effects have been related with the moderate consumption of alcoholic beverages, including an increase in the incidence of different types of cancer. In this article, a revision about the current knowledge about alcohol and health relationships is made, paying particular attention to the case of red wine.

RESUMO

Observações acumuladas ao longo dos últimos trinta anos sugerem que um consumo de baixo a moderado de álcool, especialmente em forma de vinho tinto, pode ter efeitos benéficos para a saúde humana. As melhoras referem-se sobre tudo à saúde cardiovascular, mas também a outras patologias como a diabete de tipo 2, demências ou declínio cognitivo. As maiores evidencias derivam de estudos epidemiológicos ou foram obtidas em ensaios *in vitro* ou com animais, enquanto os dados científicos em pessoas são escassos e incompletos. Por outro lado, o álcool é uma substancia tóxica cujo consumo excessivo ou irresponsável tem graves consequências não só para a saúde mas também sociais. Aliás, o consumo moderado de bebidas alcoólicas foi também relacionado com alguns efeitos adversos incluindo um aumento na incidência de vários tipos de cancro. Em este artigo é feita uma revisão do estado dos conhecimentos sobre as relações entre o consumo de álcool e a saúde humana, com especial referência ao caso do vinho.

Key words: Red wine, alcohol, health, epidemiological studies, coronary heart disease, adverse effects

Palavras chave: Vinho tinto, álcool, saúde, estudos epidemiológicos, doença coronária, efeitos adversos

INTRODUCTION

It is beyond doubt that alcohol is harmful and that its irresponsible and excessive consumption has severe consequences for health and serious social implications. Alcohol is a well-known toxic substance related to more than 60 different disorders with short and long term consequences. It was estimated as responsible for about 195,000 deaths each year in the European Union, being the origin of 1 in 3 of road traffic accidents, 4 in 10 of murders, and 1 in 6 of suicides. The cost of treating this ill health in the EU was estimated in 2003 to be 17 billions €, together with more 5 billions € spent on treatment and prevention of harmful alcohol use and alcohol dependence. Especially worrying is alcohol abuse by adolescents and young adults, which is becoming a major health and social problem in European and other developed countries. Binge drinking1 in young people is associated with violence, antisocial and risky behaviours, accidents, suicide, reduced school and work performance and crime. Over 10% of youth female mortality and around 25% of youth male mortality in the EU are related to alcohol consumption (Anderson and Baumberg, 2006).

On the other hand, health benefits of moderate wine consumption have long been claimed and it is usual to quote Pasteur as a pioneer scientist supporting them (*"Le vin est le breuvage le plus sain et le plus hygiénique qui soit").* Especially over the last three decades evidences have been accumulated suggesting that light to moderate consumption of alcoholic drinks far to be harmful might likely be beneficial to some individuals. Those health benefits are mostly associated to wine and refer to improvement in cardiovascular health, although relationships with a lower risk of total mortality, type 2 diabetes, dementia or cognitive decline in old age have also been established. This has received the attention of the media, which have contributed to spread a message, sometimes confusing, contradictory or spurious, about putative health benefits of drinking.

In this review, an outline on the available knowledge on wine and health relationships is made. It is, however, pertinent to indicate that it is far from our intention to give arguments that might justify the consumption of wine (or any other alcoholic drink) in view to gain health benefits.

[1] **Binge drinking** is defined as the consumption within 2 hours of 4 or more drinks for women and 5 or more drinks for men (U.S. Department of Agriculture, 2010)

EPIDEMIOLOGICAL AND INTERVENTION STUDIES

The starting-point in the study of wine and health relationships may be dated on the article published by St. Leger and co-workers in 'The Lancet' in 1979. Those authors analysing the data on mortality in 18 developed countries obtained from the World Health Statistics Annual for 1970 found a strong and specific negative association between ischemic heart-disease deaths and alcohol consumption, and in particular wine, which was independent of other factors such as smoking, dietary intake or gross national product. Werth (1980), a few months later, made similar observations using data from the United States that showed a negative correlation between death from acute myocardial infarction and wine consumption across all states. Soon after, Marmot *et al*. (1981) in a study with 1422 men also concluded that the rates of total and cardiovascular mortality were lower in moderate drinkers than in either abstainers or heavy drinkers (those whose reported alcohol intakes >34 g/day), and that that was largely independent of differences in smoking, blood pressure, plasma cholesterol and grade of employment. These authors were the first ones to refer to the existence of a U-shaped relationship between alcohol consumption and mortality, *i.e.*, existence of higher mortality rates in non-drinkers and heavy drinkers than in low to moderate alcohol consumers. Over the next years several prospective studies followed leading to similar conclusions and pointing to a reduced incidence of morbidity and mortality from coronary heart disease (CHD) among light to moderate alcohol consumers (*e.g.*, Klatsky *et al*., 1979; Korazevic *et al*., 1982; Gordon and Kannell, 1983; Marmot, 1984; Friedman and Kimball, 1986; Stampfer *et al*., 1988; Rimm *et al*., 1991). Nevertheless, the fact that most contributed to go round wine and health relationships to the public was the TV program "60 Minutes" from the CBS that in November 17, 1991 broadcasted a segment entitled "The French Paradox" (the episode can be watched on http://www.youtube.com/watch?v=njm1LkXP2sg). In that program Prof. Curtis Ellison from the Boston University School of Medicine (USA) and Prof. Serge Renaud from the University of Bordeaux (France) reported their observations on that French people showed lower incidence of CHD and mortality rates than people of other developed countries, despite having similar or higher intakes of saturated fats and other risk factors. Those scientists explained the paradox by the consumption of the Mediterranean diet, with an abundance of olive oil, fruits, vegetables and fish, and especially the regular intake of red wine, which was cited as the main protective factor. Those observations anticipated the results of a study that appeared half a year later in the journal The Lancet (Renaud and de Lorgeril, 1992), in which mortality rates from CHD obtained from the MONICA project (**MONI**toring of Trends and Determinants in **CA**rdiovascular Disease, http://www.ktl.fi/monica/), the world's largest study on heart disease conducted by the World Health Organization (WHO), were analysed and related with different risk factors for CHD. The authors concluded that wine and dairy fat consumption were the only dietary factors that correlated significantly, in a negative and positive way, respectively, with CHD mortality, suggesting that the intake of wine could counteract the untoward effects of saturated fats. Based on other studies, Renaud and de Lorgeril (1992) proposed that the inhibition of platelet reactivity might be an explanation for the protection offered by wine (alcohol) against CHD. The "French paradox" soon became popular. By February 1992, a Gallup poll showed that 58 percent of Americans were aware of research linking moderate drinking to lower rates of heart disease, and the sales of red wine in the U.S. increased by 44 percent (Abramson, 2008).

The Renaud and de Lorgeril's study received, however, serious criticisms from different scientists. A main one was that it compared mortality rates with fat intake in the same years (late 1980's) without taking into account that CHD takes years to develop; therefore, mortality rates should have been related to past levels of serum cholesterol and fat consumption rather than to current ones (Law and Wald, 1999). It seems that for decades up to 1970's the consumption of animal fat and levels of serum cholesterol were lower in France than in other countries (*e.g.*, about 21% of total energy consumption *vs* 31%, and 5.7 *vs* 6.3 mmol/L, respectively, compared to the UK); only between 1970 and 1980 did French values increase to those in Britain. Further, there must be a time lag between the increase in serum cholesterol concentration and the full effect of the resulting increase in coronary artery atheroma and risk of death from ischemic heart disease. Using earlier data of serum cholesterol and fat consumption, Law and Wald (1999) found that mortality from heart disease across countries, including France, correlated strongly with levels of animal fat consumption and serum cholesterol in the past (30 years ago). In other words, based on past levels, mortality data for France were not discrepant and fitted in with the trend of other countries with similar cholesterol and fat intake. This was called the 'time-lag hypothesis'.

Similarly, systematic errors might also exist in other observational studies about the protective effects of moderate drinking, as uncontrolled, unknown and/or unavoidable confounding factors may not have been taken into account leading to misinterpretation, as reviewed by Emberson and Bennett (2006) or Fillmore *et al*. (2007). For example, most of studies use mortality data but not incidence of disease; therefore, no actual estimation of association of alcohol consumption with overall cardiovascular disease can be made. On the other hand, associations between alcohol intake and mortality are usually established for total alcohol consumption without taking into account drinking patterns (*e.g.*, drinking

during or outside meals, binge drinking) that would also have an influence on the risks (Marmot, 2001). Furthermore, studies normally rely on self-reported alcohol consumption, raising doubts about the ability of respondents to accurately recall their own alcohol intakes; additionally very few individuals maintain one single drinking pattern throughout life (Chikritzhs *et al*., 2009). Another common indicated limitation is that in the group of non-drinking people, ex-drinkers who have given up alcohol because of cardiovascular-related illness (Klatsky *et al*., 1990a) and/or aged people that abstain from alcohol as they become ill or increase the use of medication (Shaper *et al*., 1988) are included. This would artifactually raise the coronary risk in non-drinkers group. Indeed, there is a need for CHD mortality studies that use lifelong abstinence as the reference point for estimating CHD protection (Stockwell *et al*., 2007). Misclassification in the group of non-drinkers has led some authors to consider them not adequate for use as a baseline in examining the effects of alcohol on morbidity or mortality, and proposed occasional/light drinkers who have never been heavier drinkers as more suitable (Sharper *et al*., 1988).

The existence of different behavioural or dietary habits among drinkers and non-drinkers that might affect CHD risk have also been indicated by some authors as another possible confounding factor. Naimi *et al*. (2005) reported that 27 of 30 factors associated to cardiovascular risk that they assessed were significantly more prevalent among non-drinkers than in light to moderate drinkers, which might contribute to enhance the difference in cardiovascular disease between both groups. On the other side, heart-unhealthy behaviours are also common among heavy drinkers than in moderate consumers, contributing to increase their mortality rates. It has been, however, noted that coronary atherosclerosis and myocardial infarction are less frequent in alcoholics, who also show a lower degree of coronary narrowing in autopsy studies (Moore and Pearson, 1986). This "coronary-protective effect" of heavy drinking would obscure rather than exaggerate any coronary protection (Jackson *et al*., 2005). Confounders might, therefore, act in both directions which obliges to be cautious when interpreting the results from epidemiological studies.

Despite these and other possible bias, when confounding factors are specifically adjusted for in the analyses, they usually do not result in a great reduction or elimination of benefits found for low to moderate alcohol intake on CHD risk (Fagrell *et al*., 1999; Naimi *et al*., 2005; Hansel *et al*., 2010). Further, although confounded, large prospective observational trials still show remarkably consistent data, pointing to the reduced incidence of morbidity and mortality from CHD among those who consume alcohol in moderation (De Lange, 2007). This has been illustrated in different meta-analyses that have confirmed the existence of a statistically significant inverse association between moderate alcohol consumption and cardiovascular disease, especially CHD (Maclure, 1993; Cleophas, 1999; Rimm *et al*., 1999; Corrao *et al*., 1999, 2000, 2004; di Castelnuovo *et al*., 2002, 2006; Reynolds *et al*., 2003). However, opposite to cardiovascular disease, no benefits of alcohol consumption have been found for non-vascular causes of death like different cancers (see below), liver cirrhosis or chronic pancreatitis, for which significant increased risks with alcohol intake were observed (Corrao *et al*., 2004).

Most studies describe the relationship between alcohol intake and the risk of CHD as a J-shaped curve with a minimum situated at a level of consumption between 10 and 30 g/day (equivalent to 1 to 3 standard alcoholic drinks per day[2]) depending on the study, at which the reduction in the CHD risk is estimated to be around 20 to 30%. Protective cardiovascular effects might extend up to 70 g/day, above which the risk increases greatly (Corrao *et al*., 2004). Similar associations have been established for all cause mortality, although in this case the risk of death was reported to be progressively greater for levels of alcohol consumption of above about 3 units a day (Curtis Ellison, 1990; Doll *et al*., 1994).

Beneficial effects of moderate alcohol intake[3] have also been observed on different cardiovascular risks biomarkers (blood lipids, haemostatic factors, homocysteine) (Gaziano *et al*., 1993; Rimm *et al*., 1999; Burger *et al*., 2004) and type 2 diabetes (Carlsson *et al*., 2005; Koppes *et al*., 2005, 2006; Djousse *et al*., 2007). Evidence of a beneficial threshold effect of moderate alcohol intake on ischemic and hemorrhagic strokes was also found by Corrao *et al*. (2004). As for hypertension, another important cardiovascular risk determinant, a significant increase in blood pressure for alcohol consumption above 2 drinks/day is concluded in most studies, but the effect of light alcohol intakes is unclear (see below).

Some studies have found that elderly moderate drinkers showed lower risks of coronary heart disease (Mukamal *et al*., 2006) and cardiovascular mortality (Perissinotto *et al*., 2010), and that they tended to have lower levels of systemic inflammatory markers and insulin resistance, and higher levels of HDL cholesterol, which might counteract the effect of cardiovascular risk factors like higher blood pressure, leading to a net benefit on health (Pontes-Ferreira *et al*., 2008; Perissinotto *et al*., 2010). Light to moderate alcohol consumption was also shown to be associated with a lower risk of type 2 diabetes in large population-based cohort studies among elderly men and women aged more than 65 years (Djousse *et al*.,

[2] A **standard drink unit** would correspond to the volume of an alcoholic beverage that contributes 10 to 15 g of alcohol depending on the country, e.g., approximately 100-150 mL of wine; 300-350 mL of, or 30-40 mL of a spirituous drink.

[3] **Moderate alcohol consumption** is defined by the U.S. Department of Agriculture (2010) as up to 1 drink per day for women and up to 2 drinks per day for men.

2007). A recent meta-analysis has also found evidence that small amounts of alcohol could be protective against incident dementia and Alzheimer's disease in the elderly (Peters *et al*., 2008).

One of the problems to definitely conclude about safe or healthy levels of alcohol intake is that the associations between alcohol consumption and health mostly rely on observational studies and indirect evidences as those obtained in *in vitro* and animal assays, but hardly randomised interventional studies exist to actually prove cause and effect. Such trials have notable difficulties for their implementation, due, on the one hand, to ethical concerns, as alcohol is a potentially hazardous substance with severe side-effects, danger of addiction and misuse, and, on the other hand, to the obvious limitations to make these assays blinded, as consuming alcohol does not go unnoticed (De Lange, 2007). Nevertheless, randomised intervention trials have been carried out by Estruch and coworkers (Estruch *et al*., 2004, 2011; Sacanella *et al*., 2007) who observed that consumption of 30 g/ethanol/day, as either red wine or gin, for four weeks by healthy people may exert significant beneficial effects on the cardiovascular system. They found that this level of alcohol intake resulted in an increase in the HDL-cholesterol levels and an improved antioxidant (*e.g.*, decreases in LDL oxidation, MDA concentrations or SOD activity) and anti-inflammatory status (*e.g.*, decrease in plasma fibrinogen and IL-1α levels) of the individuals. Clinical intervention trials previously performed in healthy volunteers by Nigdikar *et al*. (1998) also concluded that moderate consumption of red wine for two weeks improved the plasmatic levels of antioxidant markers. Although these results provide biological plausibility to the epidemiological observations about beneficial cardiovascular effects of moderate drinking, the own authors advise that they must be taken with caution due to the increased risk of even low alcohol consumption in other pathologies and especially breast cancer in women.

IS WINE HEALTHIER THAN OTHER ALCOHOLIC DRINKS?

The question whether the type of beverage matters in the cardiovascular protective effects of moderate alcohol intake has been long object of discussion. Many observational studies have just focused on overall alcohol consumption without considering the type of drink. There are, however, a number of studies where the effects of different types of alcoholic beverages have been assessed. In those cases, whereas some authors conclude that all forms of alcohol may be equally beneficial (Rimm *et al*., 1996; Cleophas, 1999), others conclude that higher benefits are provided by wine, and particularly red wine (Grønbaek *et al*., 1995, 2000; Truelsen *et al*., 1998). Some studies also suggest that beer could offer similar or slightly lower cardiovascular protection than wine but higher than liquors (Grønbaek *et al*., 2000; Di Castelnuovo *et al*., 2002). Nevertheless, when considering non-vascular causes of death only wine might offer some protection (Grønbaek *et al*., 2000). Similarly, light to moderate wine consumption but not beer or spirits has been significantly associated with a lower risk of dementia (Truelsen *et al*, 2002; Pinder and Sandler, 2004; Pinder, 2009), although this association is not concluded from all studies, some of which do not find significant differences of the type of beverage on the protective effects of alcohol on different types of dementia or cognitive decline (Letenneur, 2004, Stampfer *et al*., 2005; Peters *et al*., 2008).

The possibility of red wine producing greater benefits than other alcoholic drinks has also been supported by the results obtained in clinical intervention trials. Thus, Estruch *et al*. (2004, 2011) showed that, for the same amounts of alcohol intake, better antioxidant and anti-inflammatory status was provided by red wine than by gin, suggesting that components other than alcohol are contributing for extra benefits of red wine. Similarly, Sacanella *et al*. (2007) in a randomized cross-over study in women observed that low-dose intake of red wine showed superior anti-inflammatory effects in women than white wine, which was explained by the higher contents of polyphenols in the first one. Further, Hampton *et al*. (2010) found that similar responses on endothelial-dependent dilatation of blood vessels were produced by red grape juice with and without alcohol, which was interpreted as an evidence of a beneficial effect of non-alcoholic components on vascular function. Indeed, red wine contain significant amounts phenolic compounds and namely flavonoids that have been shown in numerous *in vitro* and animal studies to possess a number of health-promoting biological activities (see, *e.g.*, recent reviews by Leopoldini *et al*., 2011, and Wang *et al*., 2011).

It is recognised that ethanol itself may exert positive effects on the cardiovascular system by increasing high-density lipoprotein cholesterol as well as preventing platelet aggregation and enhancing fibrinolysis, which favourably affects thrombolytic processes (Covas *et al*., 2010). However, it is also known that ethanol metabolism produces reactive oxygen species (ROS) that may oxidize lipids, proteins and DNA, and reduce the levels of glutathione, the major cellular protection against oxidative stress. Alcohol consumption also shows a direct relationship with the plasma concentration of oxidized low density lipoproteins (LDL). Phenolic compounds could counteract, at least in part, oxidative stress and oxidative damage induced by the alcohol, which might explain the differential effects of red wine on vascular health when compared with other alcoholic drinks (Covas *et al*., 2010). The inhibition of LDL oxidation by grape phenolics oxidation has also been proposed by Wollin y Jones (2001) to be involved in the protective effects of red wine consumption on cardiovascular disease. Other vascular effects reported for wine polyphenols are the enhancement in

endothelium-dependent relaxation and expression of iNOS and cyclooxygenase-2 within the arterial wall (Diebolt *et al*., 2001), and their ability to increase eNOS expression and subsequent endothelial NO release in a dose-dependent manner, which would antagonize the development of endothelial dysfunction and atherosclerosis (Leikert *et al*., 2002). The suppression of the production of endothelin-1 (ET-1), a potent vasoconstrictor, has also been linked to the cardiovascular benefits of wine polyphenols (Corder *et al*., 2001).

Wine phenolics are a variable mixture of flavonoid (mainly anthocyanins and flavan-3-ols) and non-flavonoid compounds (e.g., phenolic acid derivatives and estilbenes), extracted from the grape during winemaking. Since white wines are not usually submitted to maceration with grape solids, they contain much lower amounts of phenolic compounds than red wines. Among wine phenolics, two particular types of compounds have been especially associated to the putative healthy effects: procyanidins (*i.e.*, oligo- and polymeric flavan-3-ols, also called condensed tannins) and the estilbene resveratrol. Procyanidins have been proposed by Corder *et al*. (2006) as the vasoactive components in red wines, as they are responsible for the suppression of ET-1 synthesis, a key factor in the development of vascular disease and atherosclerosis. Indeed, procyanidins possess a range of biological activities demonstrated in *in vitro* and animal assays (Santos-Buelga and Scalbert, 2000; Rasmussen *et al*., 2005), and they have been related to the cardiovascular and cancer protective effects associated to the consumption of plant-derived foods, being red wine one of the richest dietary sources of these compounds. Resveratrol (3,5,4'-trihydroxystilbene) is another important biologically active phenolic compound for which a variety of biological activities has been demonstrated in *in vitro* and animal studies, and attributed for potential multiple health benefits, ranging from chemoprevention to cardiovascular protection (Baur and Sinclair, 2006; Das *et al*., 2010). In assays in model organisms, including *Saccharomyces cerevisiae, Caenorhabditis elegans, Drosophila melanogaster*, fish and mice, it has been observed that resveratrol is able to extend lifespan by mimicking the effects of caloric restriction through a mechanism that involves the activation of Sir2 proteins (sirtuins). These latter are a family of NAD^+-dependent deacetylases and mono-ADP-ribosyltransferases implicated in important regulation processes, such as glucose and insulin production, fat metabolism, regulation of p53 tumour suppressor, and cell survival (Howitz *et al*., 2003; Valenzano *et al*., 2006; Baur *et al*., 2006). This protein family is highly conserved in superior animals, which has led to speculation that sirtuins might also mediate effects of caloric restriction in mammals, increasing longevity and improving health, which would confer resveratrol a high therapeutic potential (Baur and Sinclair, 2006). Nevertheless, it seems unlikely that these effects can be produced with the levels of resveratrol contained in wine that are quite low. In a rough estimation, an intake of 375 mL/day (around 3 standard alcohol units) of a red wine containing a (optimistic) concentration of 5 mg resveratrol/L would contribute ~27 μg/kg of body weight in a person of 70 Kg, a dose around 800-fold lower than the one assayed in mice (22,4 mg/kg/day). On the other hand, it should be indicated that not all authors are equally optimistic, but rather critical, with regard to the healthy effects of resveratrol as related with its activity on sirtuins and caloric restriction mimesis (Garber and Arbor, 2008).

Further information about vascular effects of wine polyphenols can be obtained in the reviews recently published by Dell'Agli *et al*. (2004), Covas *et al*. (2010) or Rodrigo *et al*. (2011). Nevertheless, polyphenols may not be the only reason to explain the possible greater health benefits of wine consumption compared to other alcoholic drinks. In fact, the existence of causal relationship between moderate wine consumption and cardiovascular benefits, as due to alcohol or polyphenol content, has been questioned by some authors that suggest that socio-economical and contextual factors could be equally or more important in explaining this association. For instance, adherence to the Mediterranean diet, one of whose characteristics is the regular intake of moderate amounts of red wine, was already given by Renaud and de Lorgeril (1992) as an explanation for the French Paradox. The Mediterranean diet has been consistently associated with reduced markers of vascular inflammation, improved endothelial function and lower rates of cardiovascular mortality in several epidemiologic and intervention studies (see, *e.g.*, Chrysohoou *et al*., 2004; Esposito *et al*., 2004; Knoops *et al*., 2004, 2006; Estruch *et al*., 2006). The virtues of the Mediterranean diet have been recently acknowledged by the UNESCO that has added it to its World Heritage List in November 2010 as an intangible cultural heritage.

Another reason suggested to explain the differential effects of wine in relation to other alcoholic drinks is the pattern of consumption. Irregular (binge) drinking, which is related with higher mortality rates than steady drinking, seems more frequent among beer and spirits drinkers than in wine consumers, although this may differ among countries (Grønbaek, 2003; Rehm *et al*., 2003; Grønbaek *et al*., 2004). Furthermore, wine tends to be more drunk with meals than other alcoholic drinks, which could have metabolic advantages; for instance, this might contribute to reduce the post-prandial oxidative stress produced after a meal, due to the antioxidant properties of wine polyphenols (Covas *et al*., 2010). Consumption of grape juice with or without alcohol with a meal has been shown to improve vascular function by increasing the endothelial-dependent dilatation in the post-prandial state, supporting the role of non-alcoholic wine components on vascular function (Hampton

et al., 2010). Beer, that also contains polyphenols although in lower levels than red wine, has also been reported to have protective effects on cardiovascular risk in countries where it is consumed regularly with meals (*e.g.*, southern Germany or Czech Republic) in a way similar to wine in Mediterranean countries (Keil *et al*., 1997; Bobak *et al*., 2000).

A tendency of moderate wine drinkers to have healthier dietary habits and lifestyle behaviours, and better health status than consumers of other alcoholic beverages has also been pointed out by some authors as a further explanation for the apparent superior effects of wine consumption. Ruidavets *et al*. (2005), in a study carried out in three areas of France, concluded that healthier behaviours were more often observed in wine drinkers than in consumers of other alcoholic beverages, raising the question of if the lower cardiovascular incidence and mortality associated to moderate wine consumption were rather a surrogate of the influence of other healthy behaviours on the coronary risk. A tendency towards a higher socioeconomical status and educational level and healthier habits in moderate wine consumers was also found in countries where consumption of wine is not as traditional as in Mediterranean regions. Klatsky *et al*. (1990b), in a study on a Californian population about preferences of alcoholic drink, found that persons who prefer wine tended to be young or middle women, temperate, non-smokers, better educated, and with a moderate alcohol intake, whereas people who prefer beer were likely to be young men with a higher alcohol intake. In another study about health determinants with data obtained between 1995 and 2002 from more than 15,000 individuals that participated in the National Longitudinal Study of Adolescent Health in the USA, Paschall *et al*. (2005) found that wine drinkers generally had more formal education, better dietary and exercise habits, and more favourable health status indicators than other drinkers and non-drinkers. A larger proportion of wine drinkers were light-moderate consumers compared to beer or liquor drinkers, and they were also less likely to report smoking or problem drinking than beer or liquor drinkers. According to those authors, these findings in young people would help to explain the association between light-moderate wine consumption and morbidity, and mortality risk in later adulthood. Mortensen *et al*. (2001), in a cross-sectional study of characteristics associated with beverage choice in a Danish cohort, observed that wine drinking was significantly associated with higher intelligence quotient (IQ), higher parental educational level and higher socioeconomic status, whereas beer drinking was significantly associated with lower scores on the same variables. They concluded that wine drinking was a general indicator of optimal social, cognitive and personality development in Denmark also associated with better health, which might explain the apparent health benefits of wine. In another study in the same country about supermarket food choices, Johansen *et al*. (2005) showed that people that bought wine, in general also bought other food products considered 'healthy' such as olives, fruit and vegetables, poultry, cooking oil, and low fat cheese, milk and meat than beer buyers. However, those who purchased beer were more likely to also purchase ready-to-cook dishes, sugar, cold cuts, chips, pork, butter or margarine, sausages, lamb and soft drinks than wine buyers. These authors also indicated that, in addition to better dietary habits, wine drinkers in Denmark tend to have a higher socioeconomic status and better psychological functioning than beer consumers, suggesting that some of the health benefits associated with drinking wine may be related to these social variables. In general, it seems that moderate wine (and alcohol) consumption might represent a marker of higher social level and superior health status with subsequent lower CV risk, as also concluded from a study of Hansel *et al*. (2010) in a French cohort. These authors also found that wine choice increased with age, whereas those of beer and appetizers decreased, and that low to moderate drinkers displayed better health status than never drinkers.

Finally, in addition to the social environment and social conditions of alcohol drinkers, genetic differences that predispose to alcohol consumption or abstinence and which are associated with differing health outcomes should also play a key role in explaining the effects of alcohol in health. Indeed, as pointed out by Anstey and Cherbuin (2010), the interpretation of the varying research findings in relation to the health benefits of wine and other alcoholic drinks is difficult as not only the biological effects of the beverage consumed are measured but rather the combined effect of behaviour and biology.

ADVERSE EFFECTS OF MODERATE ALCOHOL DRINKING

The recognition of the benefits of light to moderate alcohol intake should not overlook the problems associated to drinking. In addition to the well-established detrimental effects of heavy drinking and alcohol dependence, some adverse effects have also been described as related with the moderate consumption of alcoholic beverages.

In women the level of alcohol consumption has been consistently related with an increase in the risk of breast cancer (Garfinketl *et al*., 1988; Longnecker, 1994; Smith-Warner *et al*., 1998; Curtis-Ellison *et al*., 2001). It has been estimated that, compared with non-drinkers, women reporting approximately one alcoholic drink per day may have a 10 percent higher breast risk (Curtis-Ellison *et al*., 2001), and that two daily drinks increase the risk by 1.4 (Longnecker *et al.*, 1988).

Higher risks of colorectal cancer with alcohol consumption were concluded in a meta-analysis performed by Longnecker *et al*. (1990). Another

meta-analysis conducted by Bagnardi *et al*. (2001) characterized the associations between alcohol consumption and oesophageal cancer as strong, and of cancers of the stomach, colon, rectum and liver as moderate. Benedetti *et al*. (2009), in large-population case-control study in Canada on the incidence of 13 types of cancer, concluded that moderate and high alcohol intake levels over the lifetime may increase the risk of cancer at 6 sites (oesophagus, stomach, colon, liver, pancreas, lung and prostate), with odds ratios ranging from 1.6 for lung cancer to a high of 7.9 for cancer of the liver. The risk increased as total drink-years increased. Unclear relationships were found between alcohol consumption and kidney cancer, and no evidences with respect to an alcohol effect were observed for cancers of the testes, penis or gall bladder. Interestingly, for most sites, it was beer and to a lesser extent spirits consumption that drove the excess risks. Smoking may also have an influence on the risk of cancer among moderate drinkers. In the Iowa Women's Health Study, Ebbert *et al*. (2005) observed that consuming at least 1 drink per day was positively associated with cancer incidence among former and current smokers, while there were weak, non-significant inverse associations with cancer mortality and incidence for never smokers.

Contradictory observations have been made for prostate and lung cancers. In the meta-analysis conducted by Bagnardi *et al*. (2001) the association of both types of cancer with alcohol consumption was characterized as weak, whereas in the study of Benedetti *et al*. (2009) an increase in their relative risks was reported even for moderate alcohol intakes. Increased risks of lung cancer (as well as of mouth, throat and liver cancers) among drinkers were reported by Pelucchi *et al*. (2008). However, Ruano-Ravina *et al*. (2004), in a hospital based case-control study conducted on 319 Spanish men (132 lung cancer patients and 187 controls), concluded that the consumption of red wine was associated with a slight but statistically significant reduction in the development of lung cancer. However, those authors observed a very slight but significant positive association between the risk of lung cancer and white wine consumption. Regarding prostate cancer, Sutcliffe *et al*. (2007), in large cohort study among American male professionals, observed a reduced risk of prostate cancer in men who consumed <4 glasses of red wine/week included the sub-groups who reported unchanged alcohol consumption in the prior 10 years and those <65 years of age, whereas null or slight increased risk was found for men who consumed greater than this amount. As a global conclusion, those authors indicated that red wine consumption was unlikely to contribute appreciably to the aetiology of prostate cancer.

The International Agency for Research on Cancer (IARC, 1988) classified alcohol as a Group 1 carcinogen, being considered to be causally associated with the development of cancers of the oral cavity, pharynx, larynx, oesophagus, and liver, and suggested to be positively associated with rectal and breast cancer.

Hypertension is another health issue for which unclear conclusions have been obtained concerning its association with alcohol consumption. In general, most authors agree that the intake of above 2 drinks/day is positively related with a significant increase in blood pressure. However, whereas some authors found that the risk of hypertension is positively related to alcohol intake consumption at all levels of consumption (Marmot *et al*., 1994; Corrao *et al*., 2004), others observed a threshold below which alcohol would not be deleterious for the hypertension risk. Sesso *et al*. (2008) analysing the results of two prospective studies (the Women's Health Study and the Physicians' Health Study) concluded that alcohol consumptions up to 1 drink/day may be related to a decreased risk of hypertension, at least in beer and wine drinkers, although differential effects existed in men and women; thus, levels of consumption >1 drink per day increased the risk of hypertension in men, whereas in women the hypertension risk decreased up to 4 drinks per day. More recently, Halanych *et al*. (2010), analysing the results of a 20-year longitudinal study on coronary artery disease risk factors in American young adults (the CARDIA Study), also found discrepant results for men and women, as light to moderate alcohol consumption was associated with lower risk of hypertension in European-American women, whereas African Americans and men in general had an increased risk of hypertension. Different results were also observed among white and black American men by Fuchs *et al*. (2001), who did not find that light to moderate alcohol amounts increase substantially the risk of hypertension among white men, whilst they were associated with an increased risk of hypertension in black men. On the other hand, a reduction in alcohol consumption in fairly heavy drinkers (>3 g/day) has been shown to lead to a significant decreased in mean systolic and diastolic blood pressures in a dose-response relationship (Xin *et al*., 2001).

Another point of concern is the possible association between alcohol consumption and obesity. Alcoholic beverages are energy dense (alcohol provides 7 Kcal/g) and are probably not substituting food but rather added to the total daily energy intake. Furthermore, alcohol might also act as an appetite stimulant. Both aspects could increase the risk of developing obesity and, subsequently, of associated diseases such as type 2 diabetes, stroke or coronary heart disease. Nonetheless, whereas total amount alcohol intake was positively associated to obesity, frequent consumption of small amounts of alcohol has been inversely associated with waist and hip circumferences and body mass index, both in men and women, which given the relationship between abdominal fat and cardiovascular risks might contribute to explain the protective cardiovascular effects (Tolstrup *et al*., 2005, 2008). Appetite-stimulant properties of alcohol might be useful in cancer patients to help increasing

energy intake. Although there are no studies demonstrating that alcohol simulates appetite in ill cancer patients or that it prevents weight loss, drinking an alcoholic beverage may provide a more relaxed and convivial atmosphere, which may increase food intake (Gandy, 2010).

A further aspect to notice is that average moderate consumptions of alcohol may hide risky drinking behaviours such as irregular binge drinking, that is associated with an increased risk of traumas and accidents, violence, suicides or antisocial behaviour and higher mortality rates in general (Rehm *et al*., 2001, 2003; Nordqvist *et al*., 2006). A pattern of irregular heavy drinking is associated with pathophysiological mechanisms that increase the risk of sudden cardiac death, hypertension, atrial or ventricular fibrillation, and cardiomyopathy, even if the average consumption is comparable to moderate consumption (De Lange, 2007).

For some groups of people there is not a level of alcohol consumption that can be considered free of risks. Thus, in younger people clear positive relationships between alcohol consumption and total mortality have been found at all levels of consumption (Anderson and Baumberg, 2006; Emberson and Bennett, 2006). Adolescent alcohol use is also associated with an increased risk for development of chronic alcohol use disorders in adulthood. Further, an association between adolescent alcohol exposure and altered decision making during adulthood has been demonstrated in studies with rats (Nasrallah *et al*., 2009). Heavy drinking during pregnancy is known to produce the foetal alcohol syndrome leading to abnormalities and mental retard. However, there are also some evidences that prenatal exposure to light to moderate levels of alcohol could affect the foetal development and result in decreased body weight, neurodevelopmental deficits and long-term effects on growth of children (Olson *et al*., 1997; Larroque *et al*., 1998; Day *et al*., 1999). Since there is no sufficient information about the level of alcohol intake that is completely safe during pregnancy, its consumption must be avoided by pregnant women, as well as during the period of breastfeeding.

Similarly, despite the observations made by some authors (*e.g.*, Mukamal *et al*., 2006; Djousse *et al*., 2007; Peters *et al*., 2008; Pontes-Ferreira *et al*., 2008; Perissinotto *et al*., 2010) on the possible protective effects of light alcohol consumption on the risks of type 2 diabetes, dementia and cardiovascular disease in elder persons, particular caution must also be taken in relation with alcohol intake in these people, as they are progressively more sensitive and vulnerable to the adverse effects of alcohol. On the one hand, there is a decrease in lean body mass and water proportion in the organism, which modify alcohol metabolization and distribution. On the other hand, nutritional and health conditions differ from those in young and middle-age people, and other undesirable outcomes such an increase in the risk of falls or adverse interactions with medication may occur. For that reason, the American Geriatrics Society and the National Institute on Alcohol Abuse and Alcoholism recommend that older adults who have no contraindications to alcohol use limit their intake to no more than one drink per day (Mukamal *et al*., 2006).

Finally, alcohol should be avoided by individuals at risk of addiction, people with reduced activity of the enzyme alcohol dehydrogenase (*e.g.*, some ethnic groups like Aboriginal Australians, Native Americans and some East Asians) and/or other types of alcohol intolerance (*e.g.*, migraines, flushes), and persons with certain specific medical conditions (*e.g.*, liver disease, hypertriglyceridemia, pancreatitis) or taking medication that can interact with alcohol, as well as by individuals that have to drive, operate machinery or develop activities that require attention, skill or coordination (U.S. Department of Agriculture, 2010).

CONCLUDING REMARKS

Evidences accumulated over the last 30 years suggest that light to moderate alcohol consumption, especially in the form of red wine, can have beneficial effects for health, particularly by decreasing the risk of cardiovascular disease. However, most of these evidences have been obtained in observational studies or from *in vitro* or animal assays, whereas direct scientific data in human are scarce and incomplete. On the other hand, it is well known that alcohol is a toxic product whose irresponsible and/or excessive consumption has serious consequences for health. Furthermore, the effects of the alcohol in the organism are complex and variable depending on individuals, and for some health issues an increasing risk seems to exist from minimum alcohol intakes. This makes difficult, if not impossible, to make accurate recommendations about safe levels, not to say about potential 'healthy' levels, of alcohol consumption. Based on the epidemiological observations about alcohol and (cardiovascular) mortality relationships, most national and international agencies recommend not to exceed an amount of 3 units alcohol/day (*i.e.*, <30-40 g alcohol/day) and even reduce this level to 1-2 units/day in the case of women (International Center for Alcohol Policies, http://www.icap.org/PolicyIssues/DrinkingGuidelines). In our opinion, with the level of available knowledge, it is not possible to go further in the recommendations about alcohol consumption, as releasing any message that might induce people to drink in the hope of gaining health benefits could likely be more harmful than beneficial. Wine should be regarded as a fruitive food, whose moderate and responsible consumption in the context of an adequate diet can constitute another element of a healthy lifestyle, but never a product to be consumed by its intended pharmacological properties.

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