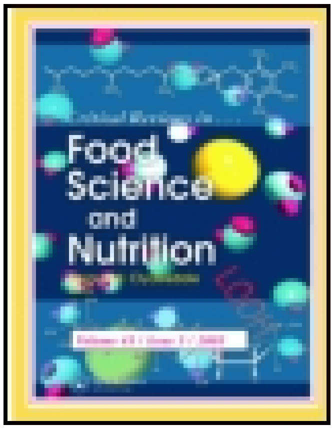


Critical Reviews in Food Science and Nutrition
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/bfsn20

# MEDITERRANEAN WAY OF DRINKING AND LONGEVITY.

Attilio Giacosa [a] [b] , Roberto Barale [c] , Luigi Bavaresco [d] , Milena Anna Faliva [e] , Vincenzo Gerbi [f] , Carlo La Vecchia [g] [h] , Eva Negri [g] , Annalisa Opizzi [e] , Simone Perna [e] , Mario Pezzotti [i] & Mariangela Rondanelli [e] [j]

[a] Department of Surgery , University of Genoa
[b] Department of Gastroenterology, Policlinico di Monza , Monza , Italy
[c] Department of Biology , University of Pisa , Italy
[d] CRA-Research Centre for Viticulture , Conegliano , Italy
[e] ASP (Azienda di Servizi alla Persona) of Pavia , Pavia , Italy
[f] Va. PRA, Microbiology and Food Technology Sector , University of Turin , Italy
[g] Mario Negri Institute for Pharmacological Research
[h] Department of Occupational Health , University of Milan , Milan , Italy
[i] Department of Biotechnology , University of Verona , Verona , Italy
[j] Department of Applied Health Science , University of Pavia , Pavia , Italy
Accepted author version posted online: 10 Sep 2014.

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Attilio Giacosa [1,2], Roberto Barale [3], Luigi Bavaresco [4], Milena Anna Faliva [5], Vincenzo Gerbi [6], Carlo La Vecchia [7,8], Eva Negri [7], Annalisa Opizzi [5], Simone Perna [5], Mario Pezzotti [9], Mariangela Rondanelli [5,10].

[1] Department of Surgery, University of Genoa, [2] Department of Gastroenterology, Policlinico di Monza, Monza, Italy;

[3] Department of Biology, University of Pisa, Italy;

[4] CRA-Research Centre for Viticulture, Conegliano, Italy;

[5] ASP (Azienda di Servizi alla Persona) of Pavia, Pavia, Italy,

[6] Va. PRA, Microbiology and Food Technology Sector, University of Turin, Italy;

[7] Mario Negri Institute for Pharmacological Research,

[8] Department of Occupational Health, University of Milan, Milan, Italy;

[9] Department of Biotechnology, University of Verona, Verona, Italy;

[10] Department of Applied Health Science, University of Pavia, Pavia, Italy;

Author author to whom all correspondence is to be sent:

Prof.ssa Mariangela Rondanelli, MD, PhD

Associate Professor, Department of Applied Health Sciences,

Section of Human Nutrition and Dietetics, Faculty of Medicine, University of Pavia

Azienda di Servizi alla Persona di Pavia, Servizio Endocrino Nutrizionale,

Istituto di Riabilitazione "Santa Margherita". Via Emilia 12, Pavia

tel.0039- 0382-381149, 3382559239; fax 0039-0382381218; mail:

mariangela.rondanelli@unipv.it



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ABSTRACT

The relation between alcohol consumption and mortality is a J-shaped curve in most of the many studies published on this topic. The Copenhagen Prospective Population Studies demonstrated in the year 2000 that wine intake may have a beneficial effect on all cause mortality that is additive to that of alcohol. Wine contains various poliphenolic substances which may be beneficial for health and in particular flavonols (such as myricetin and quercetin), catechin and epicatechin, proanthocyanidins, anthocyanins, various phenolic acids and the stilbene resveratrol. In particular, resveratrol seems to play a positive effect on longevity because it increases the expression level of Sirt1, besides its antioxidant , anti-inflammatory and anticarcinogenic properties. Moderate wine drinking is part of the Mediterranean diet, together with abundant and variable plant foods, high consumption of cereals, olive oil as the main (added) fat and a low intake of (red) meat. This healthy diet pattern involves a "Mediterranean way of drinking", that is a regular, moderate wine consumption mainly with food (up to two glasses a day for men and one glass for women). Moderate wine drinking increases longevity, reduces the risk of cardiovascular diseases and does not appreciably influence the overall risk of cancer.



Key words: alcohol, longevity, Mediterranean diet, resveratrol, wine

INTRODUCTION

Alcohol has a number of negative effects on health (mainly liver cirrhosis, cancer and injuries); but, in moderate doses, alcohol shows beneficial effects. All cause mortality may be the best indicator to summarize the effects of alcohol on health, where the balance between negative and positive effects can be evaluated. A vast amount of studies have assessed the correlation between alcohol consumption and total mortality, and numerous reviews and meta-analyses have tried to summarize the results. In most studies the relation between alcohol consumption and mortality is a J-shaped curve which shows that moderate consumption of alcohol reduces mortality as compared to the absence of alcohol consumption (Doll, R., et al., 2005). The maximum protective effect is found at 20 g average of pure alcohol intake per day. The relative risk line equivalent to abstainers' risk (RR=1) is crossed at 72 g of average intake and there is a significant detrimental effect after 89 g average intake per day (Rehm, J., et al., 2003). Moreover, there is a pronounced gender effect showing that women have less protective effects at the same level of consumption, and an earlier upturn of the curve (Rehm, J., et al., 2003). These results refer to middle-age or later. Another relevant aspect concerns the effect of alcohol on the cognitive performance of elderly people. Among a large sample of german elderly individuals (75 years of age and older) without dementia at baseline, 50% consumed alcohol, in general less than 2 drinks per day (Weyerer, S., et al., 2011). After controlling for a number of potential confounders, current alcohol consumption was associated with a 29% decrease in overall dementia incidence and, respectively, a 42% decrease in Alzheimer dementia (Weyerer, S., et al., 2011), thus showing that mild to moderate consumption of alcohol influences positively the cognitive performance.

Wine is different from other alcoholic beverages, because it contains various polyphenolic substances which may be beneficial for health (Monagas, M., et al., 2005). The Copenhagen Prospective Population Studies demonstrated that wine intake may have a beneficial effect on all cause mortality that is additive to that of alcohol (Grønbaek, M., et al., 2000).



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An important problem when investigating alcoholic beverage effects is that beverage preferences in most cultures are linked with other variables such as socio-economic status and lifestyle variables. Alcohol consumption in Italy is different from that of Northern Europe, being mostly represented by wine, preferably consumed during meals and with regular daily intake instead of binge drinking.

A meta-analysis on drinking patterns published by Bagnardi et al. in 2008 suggests that binge and heavy irregular drinking modify the favourable effect of alcohol intake on the coronary heart disease (CHD) risk (Bagnardi, V., et al., 2008). However, this conclusion should be taken with caution because of the small number of studies considered. The Italian Rural Cohort of the Seven Countries Study evidenced that the relationship between life expectancy and alcohol consumption is confirmed to be non linear and wine (mostly red wine) represents the 97% of alcohol consumption in this Italian cohort (Farchi, G., et al., 2000). Men aged 45-64 years at entry, drinking about 5 drinks per day, have a longer life expectancy than occasional and heavy drinkers (Farchi, G., et al., 2000). The HALE Study (Healthy Aging: a Longitudinal Study in Europe) conducted in various European countries analyzed mortality in men and women aged between 70 and 90 years according to 4 factors considered to be beneficial, that is adhesion to mediterranean diet, moderate alcohol consumption, physical activity and not smoking (Knoops, K.T., et al., 2004). Compared to those with 0 or 1 factors, those who were positive for all 4 factors had an overall mortality reduced by 65% (Knoops, K.T., et al., 2004).

An optimal diet for the prevention of both CHD and cancer is likely to extensively overlap with the traditional Mediterranean diet (Trichopoulou, A., et al., 2004). It is not yet clear which components in the Mediterranean diet are more important for the promotion of healthy effects,



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but olive oil, plant foods and moderate wine consumption are likely candidates (Trichopoulou, A., et al., 2004).

MEDITERRANEAN WAY OF DRINKING

The Mediterranean diet is based on abundant and variable plant foods, high consumption of cereals, olive oil as the main (added) fat, low intake of (red) meat and moderate consumption of wine. From the point of view of the preventive mechanisms on CHD and cancer , the analysis of the typical Mediterranean diet shows various potential protective aspects, such as a balanced ratio of n-6/n-3 essential fatty acids (EFA), high amounts of fibre, antioxidants (especially polyphenols from olive oil and wine), vitamins E and C (Trichopoulou, A., et al., 2004).

Alcohol consumption was traditionally high in Mediterranean countries, particularly in France and Italy, but substantial declines have been observed over the last three decades. The pattern of alcohol drinking is peculiar in these countries, with regular (rather than binge) drinking, mainly at meals and with wine being the most common type of alcoholic beverage. Alcohol excess increases the risk of liver cirrhosis and cancer, mostly those of the upper digestive and respiratory tract. Incidence and mortality from these cancers were remarkably high in the 1970’s and 1980’s in some Mediterranean countries such as France, northern Italy and Spain. Total alcohol related deaths (liver disease, cancer and car accidents) were estimated in the 1990’s at approximately 25,000 per year in Italy (5% of all deaths), and over 50,000 (10% of all deaths) in France. Now these estimates are probably about 50% lower, due to the substantial (over 50%) fall in alcohol consumption (Arfè, A., et al., 2011).

In terms of risk assessment, high levels of alcohol consumption (i.e., more than four drinks per day) result in a substantial risk of cancer at several sites. At the same time, moderate alcohol




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consumption can have protective effects against Hodgkin lymphoma and certain types of heart disease, and in particular of ischemic heart disease (Tremacere, I., et al., 2012). Taking into account favorable and unfavorable effects of alcohol on health, a sensible individual advice should be given as for recommended limits to alcohol drinking: these limits should not exceed 30 g of ethanol per day (i.e. about to two drinks of beer, wine or spirits a day, meals included) for men and 15 g (one drink) for women (Giacosa, A., et al., 2012).

Red wine, which is typically consumed in Mediterranean countries, contains a complex mixture of potentially preventive bioactive compounds (predominantly phenolic) and in particular flavonols such as myricetin, kaempferol and the predominant quercetin, the flavan-3-ol monomers catechin and epicatechin, the oligomeric and polymeric flavan-3-ols or proanthocyanidins, various highly coloured anthocyanins, various phenolic acids (gallic acid, caftaric acid, caffeic acid, p-coumaric acid) and the stilbene resveratrol (Giacosa, A., et al., 2012). Recent advances in viticulture and oenology research allowed the increase of the phenolic compounds concentration in grapes and wines (Cagnasso, E., et al., 2008). Highly tannic red wines can contain up to 3 g of total polyphenols per litre and the amount of catechin and epicatechin derivatives, including oligomeric procyanidins, can even reach ~800 mg/L (200 mg in two glasses, that is 2.86 mg/kg for a man of 70 kg of body weight) (Landrault, N., et al., 2001) and the amount of resveratrol is ~5 mg/L of wine (1.25 mg in two glasses of wine, that is 18 μg/kg for a man of 70 kg of body weight) (Landrault, N., et al., 2001). Moderate red wine drinkers will consume polyphenols at levels well above the population average. Resveratrol inhibits proliferation of human cancer cell lines (Stervbo, U., et al., 2007; Aggarwal, B.B., et al., 2004; Baur, J.A., et al., 2006; Harikumar, K.B., et al., 2008) and similarly to curcumin and epigallocatechin gallate, it modulates the effects of deregulated cell cycle checkpoints (Meeran, S.M., et al., 2008). A Danish cohort study of 156 subjects with upper digestive tract cancers suggested that wine drinkers may be at a lower risk than drinkers who have a similar intake of beer or spirits (Grønbaek, M., et al., 1998). Other studies, however, showed inconsistent results (Boffetta, P., et al., 2006).

More recently, in a study of 380,000 Americans, a Mediterranean diet score defined from high intake of fruits, vegetables, nuts, grains, fish, low intake of dairy and meat and 5-25 grams/day of alcohol showed a reduction of mortality for cardiovascular disease (CVD), in both men and women, when highest versus lowest score tertiles were compared (Mitrou, P.N., et al., 2007). This study also confirmed that the Mediterranean food pattern is associated with decreased cancer mortality and with reduced all-cause mortality (Mitrou, P.N., et al., 2007).

## RESVERATROL AND LONGEVITY

Most of the advantage correlated to moderate wine consumption, appears correlated to the biological responses to resveratrol and other polyphenols preferably found in red wine, including flavonols, monomeric and polymeric flavan-3-ols, highly coloured anthocyanins, as well as phenolic acids. Phenolic changes associated with winemaking begin with selective extraction of grape constituents into the must during crushing, maceration, pressing and continues during wine aging. These phenomena are influenced by reactant concentrations, temperature, pH, EtOH, $SO_2$ and by the technological processes.

The phenolic compounds are responsible for color of red grapes and wines, oxidative browning of white wines and contribute to taste and astringency and for the antioxidant action in human body. Resveratrol in particular appears of relevant importance because it prevents or delays the onset of chronic diseases such as diabetes, inflammation, Alzheimer's disease and cardiovascular disease; moreover, resveratrol induces neuroprotection and inhibits proliferation of human cancer cell lines and favours the increase of longevity (table 1) (Stervbo, U., et al., 2007; Aggarwal, B.B., et al., 2004; Baur, J.A., et al., 2006; Harikumar, K.B., et al., 2008; Smoliga, J.M., et al., 2011; Fernández, A.F., et al., 2011). The breadth of the therapeutic potential of resveratrol is shown by the extension of the lifespan and improved motor function in mice fed a high-calorie diet as shown by Baur et al (Baur, J.A., et al., 2006). This study indicates new approaches for treating obesity-related diseases and the diseases of ageing and shows that resveratrol produces changes associated with longer lifespan, including increased insulin sensitivity, reduced insulin-like growth factor-1 (IGF-I) levels, increased AMP-activated protein kinase (AMPK), increased peroxisome proliferator-activated receptor- gamma coactivator 1alpha (PGC-1alpha) activity, increased mitochondrial number and improved motor function (Baur, J.A., et al., 2006).

Resveratrol is usually considered as an antioxidant, primarily by increasing nitric oxid bioavailability, but resveratrol can also exhibit pro-oxidant properties in the presence of transition metal ions such as copper, leading to oxidative breakage of cellular DNA (de la Lastra, C.A., et al., 2007). This pro-oxidant action could be the common mechanism for anticancer and chemopreventive properties of plant polyphenols. Resveratrol at lower doses (5 mg/kg) activates survival signals by up-regulating the antiapoptotic and redox proteins Akt and Bcl-2, while an higher dose of 25 mg/kg potentiates a death signal by down-regulating redox proteins and up-regulating proapoptotic proteins (Mukherjee, S., et al., 2010) thus inducing hormetic dose responses (Calabrese, E.J., et al., 2010).

Many of the same compounds, including resveratrol, curcumin and epigallocatechin gallate, modulate the effects of deregulated cell cycle checkpoints, and this could contribute to the prevention of cancer (Meeran, S.M., et al., 2008).

Also wine catechins and proanthocyanidins appear of relevant importance due to their ability to improve endothelial function, vascular tone and platelet reactivity *in vivo*. A recent study of Park et al showed that resveratrol ameliorates aging-related metabolic phenotypes (Park, S.J., et al., 2012). According to these authors, the metabolic effects of resveratrol result from competitive inhibition of cAMP-degrading phosphodiesterases, leading to elevated cAMP levels. The resulting activation of Epac1, a cAMP effector protein, increases intracellular Ca2+ levels and activates the CamKKb-AMPK pathway via phospholipaseC and the ryanodine receptor Ca2+-release channel. As a consequence, resveratrol increases NAD+ and the activity of Sirt1, which appears to be tightly related to the increase of longevity (Park, S.J., et al., 2012).



## RESVERATROL AS SIRTUIN ACTIVATOR

Sirtuins 1-7 (SIRT1-7) belong to the third class of deacetylase enzymes, which are dependent on NAD(+) for activity. Sirtuins activity is linked to gene repression, metabolic control, apoptosis and cell survival, DNA repair, development, inflammation, neuroprotection, and healthy aging (Villalba, J.M., et al., 2012).

Resveratrol activates SIRT1 mimicking the positive effect of calorie restriction and might help in the treatment or prevention of obesity and in preventing the aging-related decline in heart function and neuronal loss. As resveratrol has low bioavailability and interacts with multiple molecular targets, the development of new molecules with better bioavailability and targeting sirtuin at lower concentrations is a promising field. Human trials with a formulation of resveratrol with improved bioavailability and with a synthetic SIRT1 activator are in progress (Alcaín, F.J., et al., 2009).

## CONCLUSIONS

Mediterranean diet involves a “Mediterranean way of drinking”, that is a regular, moderate wine consumption mainly with food (up to two glasses a day for men and one glass for women). This drinking pattern increases longevity, reduces the risk of cardiovascular disease and does not appreciably influence the overall risk of cancer.

## Conflict of Interests

None of the authors of this paper have any financial interest that has influenced the results or interpretation of this paper.

## Acknowledgments

The work of Carlo La Vecchia and Eva Negri was supported by the Associazione Italiana per la Ricerca sul Cancro (AIRC).



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List of abbreviations: ADP: adenosine 5'diphosphate; Akt: protein kinase A; COX: cyclooxygenase; ET: endothelin; IL: interleukin; GLUT: glucose transporter; LPS: lipopolysaccharide; NAD: nicotinammide-adenine dinucleotide; NADPH: nicotinammide-adenine dinucleotide phosphate; MAPK: mitogen activated protein kinase; NO nitrose monoxidum; NOS: Nitrous Oxide Systems; PG: prostaglandin; SIRT: sirtuin; TNF: tumor necrosis factor;




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Table 1. Biochemical and molecular effects of resveratrol and their potential benefits in disease prevention.

| Disease prevention | Healthy effects | Biochemical and molecular mechanisms of action | References |
|---|---|---|---|
| Cardiovascular protection | Antioxidant activity | - Inhibition of NADPH and of ADP-$Fe^{+}$-lipid peroxidation<br>- Ability to activate the Sirtuin class of $NAD^{+}$ histone deacetylases<br>- Upregulation of the expression of the Nrf2 target genes NAD(P)H:quinine oxidoreductase 1 | Miura, T., et al., 2000<br>Chen, C.J., et al., 2009<br>Yu, W., et al., 2012 |
| | Anti-inflammatory activity | - Inhibition of the TNF-α induced vascular permeability changes<br>- Inhibition of LPS-induced TNF-α and IL-6 production with the downregulation of relative genes expression in macrophages<br>- Suppression of the synthesis of PGe2 by inhibiting COX-2 enzyme activity | Fulgenzi, A., et al., 2001<br>Kang, L., et al., 2010<br>Subbaramaiah, K., et al., 1998 |
| | Inhibition of platelet aggregation | - Inhibition arachidonic acid induced platelet aggregation<br>- Inhibition of surface P-selectin-positive platelets<br>- Enhancement of the inhibitory activity of PGs on platelet aggregation | Crescente, M., et al., 2009<br>Yang, Y.M., et al., 2008<br>Wu, C.C., et al., 2007 |
| | Improvement of endothelial function | - Attenuation of basal and ET-1-evoked protein tyrosine phosphorylation<br>- Inhibition of strain-induced ET-1 gene expression<br>- Inhibition of angiotensin II induced cell proliferation<br>- Prevention of degeneration of NO | El-Mowafi, A.M., et al., 1999<br>Liu, J.C., et al., 2003<br>Chao, H.H., et al., 2005<br>Cavallaro, A., et al., 2003 |
| Cancer | -Inhibition of initiation, promotion and progression of various cancers | - Induction of cell cycle arrest<br>- Induction of apoptosis and cell cycle arrest<br>- DNA strand breaks<br>- Anti-invasive activity | Liu, B.Q., et al., 2010<br>Kweon, S.H., et al., 2010<br>Bai, Y., et al., 2010<br>Papoutsis, A.J., et al., 2010<br>Weng, T.T., et al., 2010 |
| Type II diabetes | Anti-hyperglycemic effect | - Improvement of hepatic glycogen content<br>- Improvement of hyperglycemia mediated oxidative stress<br>- Enhanceing of GLUT-4 translocation through MAPK/Akt/eNOS signalling pathway | Palsamy, P., et al., 2009<br>Palsamy, P., et al., 2010<br>Penumathsa, S.V., et al., 2008 |
| Neurological conditions | -Prevention of Alzheimer disease | - Reduction of levels od secreted and intracellular amyloid.beta peptides | Marambaud, P., et al., 2005 |





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| | -Protection against axotomy neuronal degeneration<br>-Prevention of Parkinson's disease | - Enhancement of SIRT2 mediated tubulin deacetylation<br><br>- Neuroprotective effect related to the reduced inflammatory reaction | Suzuki, K., et al., 2007<br><br>Jin, F., et al., 2008 |





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