

The Serge Renaud Memorial Lecture – “The J-shaped curve: The good, the bad, & the ugly”

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It is a great honor and privilege to present the first Serge Renaud Memorial Lecture. Serge probably contributed more than any other individual to our understanding of the “J-shaped curve” that describes the association between wine and alcohol intake and cardiovascular disease (CVD). Starting medical training in his native France, he moved to Canada in 1951 where he noted high rates of CVD, which he blamed largely on diet: no fruits, few vegetables, high saturated fat, and no wine. His key early research on platelet function [1, 2] was instrumental in expanding an important new field, evaluating thrombosis as a key factor in the development of CVD.

Professor Renaud spent decades evaluating many components of diet and CVD, early identifying the importance of the omega-3 fatty acid alpha-linolenic acid (ALA) in the diet of Cretan subjects in the Seven Countries Study. This led to the Lyon Diet Heart Study, which showed a dramatic reduction in morbidity and mortality among subjects with a myocardial infarction who were assigned a high-ALA diet [3, 4].

After extensive research, Professor Renaud showed that the regular, moderate consumption of wine was one important explanation for the “French Paradox,” the relatively low risk of coronary heart disease in the French despite relatively high levels of risk factors [2]. Until his death in 2012, just before he reached his 85th birthday, he was a great advocate of moderate wine consumption as part of a healthy lifestyle.

Further research on wine and CVD since the seminal work of Serge Renaud: Since the early work of

Renaud, there have been literally thousands of scientific studies supporting the role that the moderate consumption of wine or alcohol, versus no alcohol intake, has in reducing the risk of CVD. The evidence has been based on data from hundreds of thousands of subjects in epidemiologic studies, on clinical trials, and on a huge amount of basic scientific research. An important paper published in 2011 by Brien et al. [5] described the large number of mechanisms by which moderate alcohol intake prevents coronary heart disease. These investigators summarized the data from human intervention studies; they found that alcohol favorably affects lipid biomarkers (especially an increase in HDL-cholesterol), inflammatory markers (including CRP and tumor necrosis factor alpha levels), hemostatic factors (affecting fibrinogen, t-PA, and many other clotting factors), endothelial function, and adipocyte hormones.

There is considerable scientific evidence that the polyphenols and other substances in wine (other than alcohol) provide additional protection against cardiovascular disease. Early work by Booyse and his coworkers reported the separate effects on genes related to fibrinolysis from both alcohol and from certain polyphenols present in wine [6, 7]. A recent trial in high-risk humans by Chiva-Blanch et al. [8] found a beneficial effect of the non-alcoholic fraction of red wine (mainly polyphenols) on insulin resistance, thus greater protective effects on cardiovascular disease from red wine than from other alcoholic beverages.

Rodrigo et al. [9] carried out an extensive review of studies related to anti-oxidant capacities of wine. These authors reported that the overall protective effect of polyphenols is due to their large array of biological

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actions, such as free radical-scavenging, metal chelation, enzyme modulation, cell signaling pathways modulation and gene expression effects, among others. Wine possesses a variety of polyphenols, with resveratrol its most outstanding representative, due to its pleiotropic biological properties. The presence of ethanol in wine aids to polyphenol absorption, thereby contributing to their bioavailability.

Given the large number of mechanisms by which alcohol and wine polyphenols relate to lower risk factors for CVD, it is no surprise that prospective epidemiologic studies have consistently shown that moderate drinkers are at lower risk for both morbidity and mortality from such diseases. An excellent summary of 84 well-done epidemiologic studies by Ronksley et al. [10] synthesized results from longitudinal cohort studies comparing alcohol drinkers with non-drinkers for the outcomes of overall mortality and mortality from cardiovascular disease, incident coronary heart disease (CHD), mortality from CHD, incident stroke, and mortality from stroke. These authors concluded that light to moderate alcohol consumption is associated with a 29% reduced risk of incident CHD, 25% lower risk of CHD mortality, 25% lower risk of CVD mortality, and 13% lower risk of all-cause mortality. Further, these authors conclude that current scientific data satisfy Hill criteria indicating causality, indicating that alcohol intake is the *cause* of the lower risk of cardiovascular disease among moderate drinkers.

Thus, the early work of Serge Renaud showing beneficial effects of alcohol and wine on cardiovascular disease risk factors has been confirmed through recent decades by a plethora of animal experiments and clinical trials in humans. Further, his description of a “J-shaped curve” for wine/alcohol and CVD has been confirmed among essentially all prospective studies: there is no question that moderate drinkers, especially those who regularly consume wine, have lower risk of all types of ischemic CVD than do abstainers. In most, but not all studies, heavier drinking is associated with an increase in risk of certain cardiovascular diseases, above that of abstainers.

Effects of alcohol consumption on other diseases: Studies now indicate also that the risks of diabetes, osteoporosis, and dementia are similarly lower among moderate drinkers than among abstainers, and increasingly, biologic mechanisms have been identified for such effects. Most recent studies confirm earlier research showing that, in comparison with abstainers,

moderate drinkers have a 30% lower risk of developing *diabetes mellitus*. In a recent population-based study from Norway, [11] the results support most previous work showing a rather large (approximately 30% or more) reduction in the risk of Type II diabetes mellitus to be associated with moderate drinking. In this study, the strongest protective effect related to the consumption of wine, rather than beer or spirits. Several clinical trials in humans have provided experimental data that support the epidemiologic evidence of a protective effect of wine/alcohol against diabetes [12, 13].

Recent data have also supported scientific evidence of a lower risk of *osteoporosis* among moderate drinkers than among abstainers. Investigators in Finland related alcohol consumption to changes over three years in bone mineral density (BMD), the underlying factor associated with osteoporosis, among 300 women. The results support much earlier research indicating that regular, moderate drinking is associated with higher levels of BMD (i.e., lower risk of osteoporotic fractures) than is abstinence [14].

Studies have also shown that moderate drinkers, especially of wine, are less likely to demonstrate *obesity* than non-drinkers; heavier drinkers tend to have greater body weight. A recent extensive review of research on this topic from Spain [15] concluded that “As positive associations between alcohol and weight gain were mainly found in studies with data on higher levels of drinking, it is possible that an effect on weight gain or abdominal adiposity may only be experienced by heavy drinkers.” A second conclusion of these authors was that “The type of alcoholic beverage might play an important role in modifying the effect of alcohol consumption on weight gain,” with more favorable effects generally seen among consumers of wine. Hiramane et al. [16] found that regular moderate drinking was associated not only with less obesity but with a lower risk of fatty liver disease.

Another of the most common, and most-feared, “diseases of ageing” is Alzheimer’s disease and other types of dementia. A key paper by Neafsey and Collins [17] reviewed 74 studies, based on a total of more than 250,000 subjects, that provided risk estimates for dementia according to varying levels of alcohol consumption; this allowed the investigators to include them in a comprehensive meta-analysis. Overall, in their meta-analysis, the average risk ratio for cognitive decline or dementia associated with moderate drinking of alcohol was 0.77 (95% CI, 0.73, 0.80), with

nondrinkers as the reference group. They state that this estimate is close to the estimates of reduction in the risk of cognitive dysfunction (RR of 0.73 and 0.74) seen in other recent selective meta-analyses. The present study found that both light and moderate drinking provided a similar benefit, but heavy drinking was associated with non-significantly higher cognitive risk for dementia and cognitive impairment.

There is a complex relation between alcohol and *cancer*. Heavy drinkers, especially alcohol-dependent persons, are at increased risk of most of the upper aerodigestive cancers, such as cancer of the mouth, tongue, pharynx, larynx, and esophagus. An increase in such cancers is seen especially (almost exclusively) among heavy drinkers who are also heavy smokers. These types of cancer are not a feature of light-to-moderate drinking.

However, women who consume even small amounts of alcohol appear to have a slight increase in their risk of *breast cancer*. Most studies have shown that women who report an average intake of only about 1 typical drink/day show an increase in risk; in our analyses, the increase was generally in the range of 7 to 10%, in comparison with non-drinkers [18]. The increase in risk is greater for heavier drinkers. However, recent analyses have shown that among women with breast cancer, their subsequent risk of total mortality is lower among moderate drinkers (including those drinking before as well as after the diagnosis of cancer) than it is among non-drinkers [19]. This may relate primarily to a lower risk of dying from much more common cardiovascular diseases than from breast cancer.

A recent study based on 40,000 California teachers [20] indicated that the effects on breast cancer risk of moderate drinking appear to relate especially to previous or concurrent use of hormone replacement therapy (HRT) among drinkers. For women who never used HRT, there was an increase in the risk of breast cancer only among those who consumed more than 20 grams of alcohol per day (about 1 ½ to 2 drinks). The authors of this study conclude: “Our findings confirm that concurrent exposure to HRT and alcohol has a substantial adverse impact on breast cancer risk. However, after HRT cessation, this risk is reduced.” These findings support many other reports that the effects on breast cancer risk associated with alcohol intake are much higher among women who use HRT, drink heavily or in binges, or have lower levels of folate.

The effects of alcohol consumption on *total mortality* have been consistent in epidemiologic studies over

many decades. Moderate drinkers tend to have lower risk of all-cause mortality than non-drinkers. On the other hand, heavy drinkers tend to have a greater risk of dying.

The good, the bad, and the ugly: From extensive research over many years, including data from epidemiologic observational studies, clinical trials, animal experiments, and biochemical studies, it is quite clear that light-to-moderate drinking, without binge drinking or consuming in certain circumstances (e.g., before driving), is almost always associated with “good” results. There are clearly many “bad” and “ugly” aspects of alcohol consumption; these are almost exclusively related to binge drinking or heavy drinking. While some continue to argue that even “moderate” drinking leads to many adverse effects, generally these investigators are basing their results on people who *average* a certain number of drinks/week, without taking into consideration the pattern of drinking. As shown by Rehm et al. [21] the increased number of deaths attributed to “moderate” drinking (especially those in the young from violence, accidents, etc.) tend to be eliminated when binge drinkers are not included in the “moderate” drinking category.

Drinking to excess can surely lead to “bad” and “ugly” outcomes, both for society and for the health of the drinker. On the other hand, people who consume alcohol in a regular and moderate fashion, especially those who also have other moderate lifestyle behaviors (not smoking, avoiding obesity, eating a healthy diet, getting physical exercise) can expect only “good” outcomes. Indeed, as suggested many decades ago by Serge Renaud, for most people the regular, moderate consumption of an alcoholic beverage, especially wine, can be considered as an important component of a “healthy lifestyle.”

A tribute to Serge Renaud: Professor Fulvio Ursini of the University of Padova expressed so well the love and respect many of us had for our late colleague, Serge Renaud:

“We are all in debt to Serge for the lesson he gave to our scientific community:

curiosity as the sole reason to investigate,
diligence in observing the facts,
unbiased stringency in interpreting results, and definitely not least,
the *modesty* that only a great man can have.

We shall keep him in our memory as an example and a mentor of the meaning of being a scientist.”

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