# WINE, SPIRITS AND THE LUNG: GOOD, BAD OR INDIFFERENT?

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## ABSTRACT

The putative cardiovascular risks and benefits of the ingestion of wine and alcohol-containing spirits have been well publicized; however, less attention has been focused upon the health effects of wine and spirits consumption on the respiratory system. This paper will highlight epidemiologic, clinical and experimental data on the effects of wine and distilled spirits [and the chemical components thereof] on lung function, chronic obstructive pulmonary disease progression, lung cancer risk, risk of developing acute respiratory distress syndrome, high altitude pulmonary edema and wine [sulfite] associated asthma. Several studies have demonstrated a positive [beneficial] effect of light-to-moderate wine consumption on pulmonary function, while chronic ingestion of distilled spirits may have either no effect, or a negative effect. Studies in Scandinavia, Europe and South America have suggested a possible protective effect of wine ingestion against lung cancer, especially adenocarcinoma. Resveratrol [3,5,4′-trihydroxystilbene] a polyphenolic compound found in red wine, has anti-oxidant, anti-inflammatory and estrogen agonist effects and may be responsible for some of the health benefits of wine. The spectrum of potentially beneficial clinical effects of resveratrol and other wine-derived compounds is discussed.

## Introduction

Wine production, wine consumption and the health risks and benefits associated therewith provide the opportunity to explore a topic, which encompasses climatological and clinical considerations. The complexities of wine-grape cultivation and wine production are influenced tremendously by climate. As a result of the cultivation of the wine grape *Vitis vinifera*, mankind has the opportunity to benefit from these climatic influences through wine ingestion, which results in

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numerous physiologic effects, some of which may accrue clinical benefit. It is thus of interest to recognize that there is a critical interplay of climatological factors [sunshine, wind, rainfall] and local soil characteristics [including water retention] which affect viticulture [grape-growing for wine production] (1). These factors have a profound influence on the growth cycle of the grapes, and thus the quality and character of a wine, which is largely determined before the grapes are harvested. A winegrower selects the grape varieties best suited for the climate, manipulates the vines to maximize the sun exposure by positioning the canes for the best use of the available sunlight, and matches the crop to the ability of the vine to ripen the grapes (2). Although a number of the potentially clinically beneficial compounds occur within the grape or the grape skins, the post-harvesting processes of pressing, fermentation and barrel aging impart certain special characteristics to the unique beverage, perhaps the most important of which is the production of ethanol, to which some of the putative clinical benefit has also been attributed (3). The contention that some of the health benefits of wine are due, in part, to its ethanol also prompts an examination of the data on the effects of distilled spirits ingestion on the respiratory tract.

## Lung Function

Reduced pulmonary function has been associated with increased cardiovascular and all cause mortality. A number of studies suggest that this association is independent of smoking history, but obviously smoking may exacerbate the mortality risk via cardiovascular and pulmonary disease, as well as via cancer mortality. Exposure to oxidant substances may result in lung damage and reduced lung function. Substances providing an anti-oxidant effect could conceivably be associated with a beneficial effect on lung function, as has been suggested by a number of studies (4,5). Alcohol may have some beneficial effect on lung function, and in two recent reports the effect was stronger for white wine drinkers than for red wine drinkers. The effects of wine and spirits consumption were assessed among subjects selected from among 4,946 people aged between 35–79, living in Erie and Niagara counties in Western New York, who were randomly selected from New York State Department of Motor Vehicles and Health Care Finance Administration lists (5). Of these, 1,322 females and 1,215 males participated, but this number was again reduced due to exclusion criteria such as previous emphysema, asthma and pulmonary fibrosis or incomplete histories [diet, alcohol consumption, lost results etc.].

Data from 814 females and 741 males [with clinically normal lungs and complete histories] were included. Lifetime alcohol intake, as well as white and red wine intake, were correlated separately with pulmonary function. Study subjects were surveyed regarding lifestyle habits (including alcohol intake, socio-economic groups, diet, activity and smoking), measured (height, weight etc.) and subjected to pulmonary function testing. Forced expiratory volume in one second ($FEV_1$) and forced vital capacity (FVC) were measured, and using multiple linear regression analysis after adjustment for covariates [pack-years of smoking, weight, current smoking status, education, nutritional factors, $FEV_1$%, and eosinophil count], there was no significant correlation between total alcohol intake and lung function. A positive association of recent and lifetime wine intake was shown with $FEV_1$% and FVC%, but the association of lung function with red wine was weaker than the association for white wine. The authors (5) state: the "*residual confounding by healthy lifestyle factors might explain the difference*" between the level of effect of red and white wine. "Wine-only" consumption may be associated with "beneficial" life style factors including lower weight and body mass index, higher educational level, healthier diet and less smoking.

In contrast, high alcohol consumption, predominantly of distilled spirits, has been associated with an independent negative effect on pulmonary function. Expiratory flow rates, residual volume-to-total lung capacity ratio [RV/TLC] and diffusing capacity [$D_LCO$] were determined in 44 former alcoholics [members of Alcoholics Anonymous] after 6 months to 32 years of abstinence (6). Of the study group, 32% were non-smokers, ex-smokers or cigar or pipe smokers. Airways obstruction, evidenced by abnormal expiratory flow rates was found in 64%, elevated RV/TLC in 39% and reduced $D_LCO$ capacity was present in 16%; 77% of the women in the study had obstructive airways disease. The high incidence of abnormal functional parameters could not be attributed to smoking or past pneumonias. When compared to data for actively drinking alcoholics, it was suggested that part of the obstructive airway disease component in the abstinent subjects was due to former heavy drinking; the reduction in $D_LCO$ that was highly prevalent among active alcoholics appeared to be reversible with sobriety.

Subsequently, 1,067 men were studied over a five-year period (7), with assessment of alcohol intake and pulmonary function testing at the onset and conclusion of the study period. Multiple regression analysis suggested that alcohol consumption did not significantly affect baseline or 5-year follow up levels of FVC or $FEV_1$, after control-

ling for age, height, smoking and education level. A larger 5-year study, conducted in Denmark, included 11,135 male and female subjects aged 20 to 90 years (8). The study sample focused on 32 women and 301 men with alcohol consumption ≥ 350 g/week, equivalent to the ingestion of ≥ 875 mL of 80 proof spirits; 78 of these subjects were non-smokers. Multiple regression analysis [controlled for smoking] revealed that heavy alcohol ingestion accelerated the loss of $FEV_1$ and FVC with time, and had an effect on $FEV_1$ comparable to smoking 15 g tobacco daily [a typical cigarette weighs 1 gram and contains about 65% tobacco].

Taken together, these studies suggest that low-to-moderate consumption of wine may have a beneficial effect on pulmonary function, while excess alcohol ingestion may have a detrimental effect on lung function, evidenced by airflow obstruction.

## Chronic Obstructive Pulmonary Disease

Beneficial effects of alcohol or wine ingestion on lung function in chronic obstructive pulmonary disease [COPD] have been suggested by a number of studies. The effects of fruit, vegetable, fish, alcohol and whole grain consumption were studied in relation to COPD symptoms and lung function in 13,651 Dutch men during the period 1994–1997 (9). Adjusting for age, gender, height, smoking, body mass index [BMI] and energy intake, fruit and whole grain intake showed beneficial associations with lung function ($P_{trend} < 0.001$), and in subjects who consumed 1 to 30 g/day alcohol [e.g., up to 250 mL of wine with an alcohol content of 12%], the $FEV_1$ was higher and COPD symptoms less prevalent than in non-drinkers. In 2998 subjects with favorable intake of fruits, grains and alcohol, the $FEV_1$ was 139 mL higher and COPD symptoms lower [odds ratio {O.R.} 0.44] than in subjects with unfavorable intakes of fruits, grains and alcohol [$P < 0.001$]. Data from 2,539 adults enrolled in an ongoing longitudinal study (10) of risk factors for airway obstruction were examined to determine the relationship between alcohol consumption and pulmonary function. FEV1/FVC% was utilized as a measure of airway obstruction and FVC% was used as a measure of restriction. After adjustment for confounding factors [e.g., cigarette smoking, low socioeconomic status, male sex and age], there was no association of alcohol consumption with obstructive or restrictive pulmonary disease.

Measures of smoking, alcohol use, body mass and diastolic blood pressure were determined annually in 5,887 cigarette smoking enrollees [3,702 men, 95% white] during the five year-duration of the multi-

center Lung Health Study clinical trial, sponsored by the Division of Lung Disease of the National Heart, Lung, and Blood Institute (11). After excluding heavy drinkers [> 8 drinks per occasion or > 25 drinks per week], a significant protective effect [reduced morbidity and mortality] of moderate drinking was found among the male subjects, but not in the women. Additionally, there was no apparent interaction between smoking status and drinks per week on morbidity and mortality.

A 23-year prospective study (12) of 12,000 male British physicians [aged 48 to 78 years] was undertaken in 1978, with entry questionnaires [including questions on drinking and smoking] completed at the onset and again in 1989–91. The mean alcohol consumption per drinker was 2 to 3 drink "units" per day. Vascular disease and respiratory disease accounted for more than half of the 7000 deaths observed in this elderly population during the study period, but the deaths were *significantly lower in frequency* among the current drinkers, compared to the non drinkers, and overall mortality was significantly lower [relative risk {RR} 0.81, 95% confidence interval {95% C.I.} 0.76–0.87, P = 0.001]. In this study, to prevent possible analysis bias, the non-drinkers included the ex-drinkers, some of whom may have ceased alcohol consumption for cause. The 239 ex-drinkers were considered with the 6271 "current" drinkers, and compared to the 750 non-drinkers [per both survey questionnaires]. Respiratory disease mortality was *significantly lower* in the drinkers vs. non-drinkers [RR 0.69, 95% C.I. 0.52–0.92, P = 0.01], ischemic heart disease mortality [RR 0.72, 95% C.I. 0.58–0.88, P = 0.002] and all-cause mortality [RR 0.88, 95% C.I. 0.79–0.98, P = 0.02] were all lower in the drinkers than in the non-drinkers. An apparent protective effect of alcohol against fatal respiratory disease is supported by these data.

## Proposed Mechanisms: Lung Protective Effects of Wine & Spirits

The presence of anti-inflammatory polyphenols [e.g., resveratrol] in wine may account for the observation of beneficial effects (9,10,11) on pulmonary function and the decline in the rate of progression of airway obstruction in COPD, observed in subjects with moderate wine ingestion (9). Support for potential anti-inflammatory effects of a red wine extract was provided by a study (13) of the effects of resveratrol [3,5,4′-trihydroxystilbene] on the release of inflammatory mediators from alveolar macrophages obtained from the bronchoalveolar lavage [BAL] of 15 COPD patients [$FEV_1$ < 70% predicted and $FEV_1$/FVC% <

70 were the inclusion criteria]. Actual mean pulmonary function data for the COPD subjects: $FEV_1$ %predicted = 54% [$P < 0.001$ for the difference from healthy smokers], and $FEV_1$/FVC ratio = 0.53 [$P < 0.001$ for the difference from healthy smokers]. The 15 control smokers without airway obstruction had mean $FEV_1$ %predicted = 93% and mean $FEV_1$/FVC ratio = 0.84. All study subjects were current smokers, with > 20 pack-year smoking history; the COPD subjects continued taking their $beta_2$-agonist, corticosteroid and anticholinergic inhalational medications. Fiberoptic bronchoscopy and BAL were performed, and alveolar macrophages were isolated and enriched by adherence, followed by 24 hours of cell culture, and an additional 24-hour period of culture under experimental conditions. To reproduce the smokers' intra-alveolar milieu, the macrophages were stimulated during the second 24 hour incubation period with either interleukin-1$\beta$ [IL-1$\beta$] or cigarette smoke medium [CSM]. IL-1$\beta$ was used because it is found in increased levels in the BAL of smokers, and CSM is prepared by bubbling the smoke from 2 cigarettes through 20 mL culture medium, and then it is standardized and diluted [importantly, CSM has been shown to be non-cytotoxic]. Resveratrol and either IL-1$\beta$ or CSM were added together at time zero of the second 24-hour incubation period. The effect of resveratrol on basal and stimulated cytokine release from the cultured alveolar macrophages was determined. Basal release of IL-8 [a macrophage chemotactic factor] was inhibited by resveratrol by 94% in the macrophages from healthy smokers and by 88% in the macrophages from the COPD patients. Resveratrol inhibited basal release of granulocyte-macrophage colony stimulating factor [GM-CSF] by 79% in the macrophages from smokers and by 76% in the macrophages from the COPD subjects. IL-1$\beta$ stimulated release of IL-8 and GM-CSF was inhibited by resveratrol to below basal levels in both the smokers' macrophages and the COPD macrophages. CSM stimulated IL-8 release was reduced by resveratrol 61% in the smoker's macrophages and 51% in the COPD macrophages; GM-CSF release was reduced 49% by resveratrol for both groups.

Resveratrol and quercetin [another plant-derived polyphenol] have been shown to inhibit inflammatory mediator release by airway epithelial cells (14), reducing IL-8 and GM-CSF release from cultured primary airway [A549] cells. Resveratrol has been demonstrated to possess estrogen receptor agonist activity, which has been offered as the explanation for the observed cardiovascular protective benefits of wine by mechanisms that include defense against ischemia-reperfusion injury, promotion of vasorelaxation, protection and maintenance of intact endothelium, anti-atherosclerotic properties, inhibition of

low-density lipoprotein oxidation, suppression of platelet aggregation, and estrogen-like actions (15). However, the observed inhibitory effect of resveratrol on airway epithelial cell release of inflammatory mediators was due to mechanisms other than estrogen agonist activity, since the estrogen receptor antagonist tamoxifen did not alter resveratrol induced inhibition (14). Resveratrol and quercetin inhibited nuclear factor-κB [NF-κB], activator protein-1 and cAMP response element binding protein-dependent transcription more effectively than dexamethasone. Resveratrol inhibited cytokine-stimulated inducible nitric oxide synthase expression and nitrite production in the A549 cells, and also inhibited GM-CSF release, IL-8 release and cyclooxygenase expression in these cells.

These observations suggest a potent non-steroidal anti-inflammatory effect of the red wine extract resveratrol on both alveolar macrophages [exposed to cytokine stimulation and CSM] and primary pulmonary airway epithelial cells.

In a rodent model (15) of lipopolysaccharide [LPS, a component of endotoxin]-induced airway inflammation, resveratrol reduced lung tissue neutrophilia, pro-inflammatory cytokines and prostanoids. This reduction was not attributable to an impact on NF-κB activation, suggesting yet another anti-inflammatory mechanism. These laboratory observations (13,14,16) may explain, in part, the benefits described in clinical studies of lung function and COPD progression (9,10,11,12).

### Acute Respiratory Distress Syndrome [ARDS]

Chronic alcohol abuse has been associated with an increased incidence of ARDS (17,18). In a prospective study, 351 medical and surgical intensive care unit [ICU] patients (17) with an "at-risk" diagnosis were observed for the development of ARDS. The incidence of ARDS was significantly higher in patients with chronic alcohol abuse than in those without it: 43% vs. 22%, $P < 0.001$; RR 1.98, 95% C.I. 1.29–5.12. Of the patients who did develop ARDS, the in-hospital mortality rate was higher [$P = 0.03$] for those with a history of chronic alcohol abuse than for the others.

A multi-center prospective epidemiologic study (18) was conducted in 4 university hospital ICUs, enrolling 220 patients in septic shock. The incidence of ARDS in patients with a history of chronic alcohol abuse was 70% [46 of 66] compared to 31% [47 of 154] in individuals without chronic alcohol abuse [$P < 0.001$]. The investigators concluded that chronic alcohol abuse is an independent risk factor for ARDS and

demonstrated that it increases the severity of non-pulmonary organ dysfunction. In contrast, a 15-year cohort study (19) in a San Francisco area managed care setting *did not* demonstrate an association between alcohol consumption [not specifically focused on *chronic alcohol abuse*] and ARDS risk. Among 121,012 health plan subscribers studied over a median of 9.9 years, only 56 cases of ARDS developed. ARDS was independently related to increasing age and to cigarette smoking, but not to alcohol consumption.

Interestingly, resveratrol has been shown to ameliorate the ARDS-like microcirculatory disorder of the lung observed in a rat model of lung injury accompanying severe acute pancreatitis (20). Pancreatitis was induced by injecting 4% sodium taurocholate, 1 mL/kg through the pancreatic ducts of rats. Resveratrol was given at 0.1 mg/kg intraperitoneally. Compared to the pulmonary findings in the severe acute pancreatitis group of rats that did not receive resveratrol, the treated rats demonstrated decreased leukocyte endothelial interaction, reduced blood viscosity, and reduced edema and infiltration of leukocytes in the lungs (20).

Polymorphonuclear [PMN] leukocyte aggregation and the formation of mixed-cell conjugates between PMNs and thrombin stimulated platelets was inhibited by trans-resveratrol (21). In addition, transresveratrol markedly inhibited the release of reactive oxygen species from formyl methionyl leucyl phenylalanine [fMLP] stimulated PMNs, and prevented the release of leukocyte derived degradative enzymes [elastase and beta-glucuronidase] (21).

These *in-vitro* studies (20,21) suggest that the red wine extract, resveratrol, may play an important inhibitory role on leukocyte aggregation and mediator release [an important pathogenetic mechanism in ARDS], and may thus ameliorate lung injury in ARDS.

## Lung Cancer

A number of studies have examined the epidemiologic relationship between alcohol ingestion and lung cancer risk, and laboratory investigations have explored potential mechanisms for the observation of reduced lung cancer incidence in wine drinkers (22,23,24,25,26,27,28, 29,30). Interestingly, significant ingestion of "hard liquor" [distilled spirits] has been associated with increased lung cancer risk (22,23,26), and heavy beer ingestion was associated with increased lung cancer risk in one study (23) but did not show an increased risk in a subsequent study (26). Methodologic differences among the studies may account for variation in the observed associations between drinking,

type of alcoholic beverage consumed, and increments or decrements in lung cancer risk.

A lung cancer case-control study conducted in Los Angeles County between 1991 and 1994 enrolled 261 incident cases of lung cancer and 615 population controls (22). Recent and past type-specific alcohol consumption, smoking history, dietary habits and other lung cancer risk factors were examined by the investigators. An association with increased lung cancer risk [RR 1.87, 95% C.I. 1.02–3.42] was noted for recent hard liquor consumption [$\geq$ 1.5 ounces hard liquor daily] vs. infrequent liquor drinking [0 to 3 drinks per month]. Small inverse associations were noted for beer or wine, though the 95% C.I.'s were wide. The authors noted that there might be an increased risk of lung cancer with moderate consumption of hard liquor, but suggested further studies to elucidate the possible relationship (23).

A 28-year [1964–1992] Danish study (23) enrolled 28,160 men and women and provided the opportunity to examine lung cancer risk in relation to type-specific alcohol ingestion. After adjustment for age, smoking and education, a low to moderate alcohol consumption [1 to 20 drinks per week] was not associated with increased lung cancer risk in men. Increased risk was noted in men who consumed 21 to 41 drinks per week [for *total drinks*, RR 1.23, 95% C.I. 0.88–1.74; for distilled spirits, RR 1.21, 95% C.I. 0.97–1.50; and for beer RR 1.09, 95% C.I. 0.83–1.43] and in those consuming $>$ 41 drinks per week the risk of lung cancer was even higher [for *total drinks*, RR 1.57, 95% C.I. 1.06–2.33; for distilled spirits, RR 1.46, 95% C.I. 0.99–2.14; and for beer RR 1.36, 95% C.I. 1.02–1.82]. After excluding abstainers, a positive "preventive" benefit of wine ingestion was noted, with those consuming 1 to 13 glasses of wine per week having a relative risk of 0.78 [95% C.I. 0.63–0.97], and for $>$ 13 glasses of wine per week, RR 0.44 [95% C.I. 0.22–0.86], as compared to non-drinkers of wine. In women, the ability to detect associations with high intake and type of beverage was reduced because of a limited range of alcohol intake (23).

Among 27,111 male smokers followed for an average of 7.7 years in the Finnish Alpha Tocopherol Beta Carotene [ATBC] Cancer Prevention Study (24), there were 1059 incident lung cancer cases. Non-drinkers [11% of the population] were at increased lung cancer risk compared to the drinkers [RR 1.2, 95% C.I. 1.02–1.4]. Among drinkers only, there was no association between lung cancer and total or type specific [beer, wine, spirits] ethanol consumption. For men in the highest quartile of alcohol intake, there was a slight increase in lung cancer risk for light smokers [$<$ 1 pack/day] and a reduced risk among the heaviest smokers [$>$ 30 cigarettes/day].

A case control study conducted in Uruguay (26) suggested that wine drinking had a protective effect against adenocarcinoma of the lung. Review of 160 cases of lung adenocarcinoma and 520 hospitalized control subjects revealed that consumption of hard liquor was associated with a 40% increase in risk, whereas wine drinking displayed a marginally significant reduction in risk with an odds ratio of 0.4, 95% C.I. 0.2–1.1. Beer drinking was not associated with adenocarcinoma of the lung (26).

A hospital-based case control study (29) of 319 subjects in Spain [132 lung cancer cases, 187 control patients] suggested a slight association of lung cancer risk with white wine consumption [odds ratio 1.2 for each daily glass], but interestingly, red wine consumption had an odds ratio of 0.43 [95% C.I. 0.19–0.96] for each daily glass of red wine consumed. There was no apparent association of lung cancer with the consumption of beer or distilled spirits.

A Czech case control study (30) of dietary habits in smoking and non-smoking women included 435 confirmed cases of lung cancer and 1710 control subjects. Smoking was associated with an odds ratio of 7.03 for the development of lung cancer, compared to an odds ratio of 1.0 for non-smokers. Among smoking women, daily or weekly wine consumption had an odds ratio of 0.60, 95% C.I. 0.37–0.98; monthly wine consumption was associated an odds ratio of 0.60, 95% C.I. 0.39–0.94. An apparent protective effect of wine ingestion against the development of lung cancer is once again suggested.

When considering potential mechanisms for these observations, it is most likely that resveratrol [perhaps with other polyphenols derived from wine] is responsible for the apparent protective effect of wine [red wine in particular] against lung cancer (25,27,28). The expression of genes involved in the metabolism of polycyclic aromatic hydrocarbons [cigarette smoke constituents] in the human bronchial epithelial cell line BEP2D was studied (25), after exposure of the cells to benzo{a}pyrene or 2,3,7,8-tetrachlorodibenzo-p-dioxin in the presence or absence of resveratrol. Resveratrol inhibited the constitutive and induced expression of cytochrome P450 1A1 and 1B1 genes in a dose-dependent manner. The altered gene expression was associated with a reduced overall level of benzo{a}pyrene metabolism, resulting in altered formation of its metabolites in BEP2D cells, thus exerting lung cancer chemopreventive activity (25). Resveratrol treatment of human lung carcinoma A549 cells (27) results in a concentration-dependent induction of S phase arrest in cell cycle progression. This effect is apparently mediated through the inhibition of phosphorylation of the pRB retinoblastoma protein, accompanied by induction of the cyclin-

dependent kinase inhibitor p21WAF1/CIP. Resveratrol treatment also induced apoptosis of A549 cells, which correlated with activation of caspase-3. These observations suggest that resveratrol has potential as a human lung cancer preventive agent (27). Resveratrol exerts anti-cancer effects through cell cycle arrest, and the inhibition of transcription factors such as NF-$\kappa$B, and potentiates the apoptotic effects of cytokines, chemotherapeutic agents and gamma-irradiation (28).

## High Altitude Pulmonary Edema

High altitude pulmonary edema [HAPE] is a major concern to climbers, and is a cause of significant morbidity and occasional mortalities. The decrease in barometric pressure that occurs with ascent to altitude during a climb leads to alveolar hypoxia [at 5000 meters the reduction in barometric pressure results in an inspired partial pressure of oxygen $< 50\%$ of that at sea level], and this is followed by an increase in pulmonary vascular tone (31), attributable to increased endothelin-1 [ET-1] production [ET-1 is a potent pulmonary artery vasoconstrictor] and increased generation of reactive oxygen species [superoxide anion, $O_2$-]. Many mountain climbers drink a glass of red wine at medium altitudes to feel better (31), despite the known potential risk of decreased acclimatization to altitude (32). The theoretical "benefit" of the glass of red wine prior to or during the ascent may be related to the inhibition of ET-1 synthesis by red wine polyphenols, especially resveratrol. With respect to the concern regarding reduced ventilatory adaptation to altitude, the ingestion of 50 g of ethanol has been shown to inhibit the initial stages of adequate ventilatory adaptation to mild hypoxia at moderate altitude [3000 meters]: one hour after ingestion of 50 g of ethanol, there was a median decrease in $PaO_2$ of 4 mmHg and a median increase in $PaCO_2$ of 3 mmHg in 10 healthy climbers, compared to the blood gas parameters in those receiving placebo instead of ethanol. These findings however, are not incompatible with the purported benefit (31) of one glass [100 mL] of standard dry red wine [12% alcohol], which provides only 12 grams of ethanol, or one-quarter of the dose studied (32). The "low-dose" ethanol in the glass of red wine may not inhibit ventilatory adaptation, but may inhibit increased ET-1 synthesis and superoxide anion [$O_2$-] generation in response to altitude hypoxia.

Evidence of the ability of polyphenols [made from Cabernet Sauvignon {red wine}] to inhibit ET-1 synthesis in cultured bovine aortic endothelial cells [BAECs] was provided in a study designed to determine whether this property is unique to red wine (33). Ethanol-free

extracts were prepared from 23 red wines, four white wines, one rosé wine and one red-grape juice. The extracts were tested on BAECs to determine the concentration of each wine that would cause a 50% reduction in basal ET-1 synthesis [the $IC_{50}$]. For the red wines, the degree of inhibition of ET-1 synthesis was correlated with the total polyphenol content of the wine; the mean $IC_{50}$ was 5.0 ± 0.4 $\mu$L/mL. Red grape juice was far less potent than red wine [$IC_{50}$ = 35 $\mu$L/mL], and there was no effect of white or rose wine on ET-1 synthesis. Thus very small amounts of ethanol free red wine extract can suppress ET-1 synthesis (33), perhaps explaining the preference of some mountain climbers (31) for that "glass of red wine" that makes them "feel better."

**Sulfite in Wines: Relation to Asthma**

The sulfite family of food additives has been implicated in the pathogenesis of wine-induced asthma, however, there may be other mechanisms involved (34,35,36).

Eighteen patients with a history of red-wine induced asthma were studied (34), with incremental dosing of 3 different types of red wine up to a total dose of 385 mL, or until sequential measurement of peak expiratory flow rate [PEFR] revealed a reduction ≥ 15%. Wines contained one of three combinations of sulfur dioxide [$SO_2$] and amines: low $SO_2$/high amine, both high and high $SO_2$/low amine. Nine of 18 subjects demonstrated a fall in PEFR, in all cases after a wine with high $SO_2$. This 1986 study (34) suggested that $SO_2$ was the most important factor in red wine-induced asthma.

In a 1999 study (35), the potential sensitivity of asthmatics to non-sulfite components of wine, red and white low-sulfite wines and wine-placebo drinks was assessed, and $FEV_1$, forced expiratory flow, mid-expiratory phase and PEFR of subjects were determined before a beverage challenge and at 5, 10, 15, 30 and 60 minutes after challenge. Only one of 16 adults with a strong history of wine-induced asthma exhibited a positive reaction [> 15% fall in $FEV_1$] after a negative response to placebo. Only two of 10 subjects challenged with a high sulfite wine demonstrated a marked and rapid fall in $FEV_1$. While reactivity to low-sulfite wine occurred in a very small number of subjects, there were only 2 clear-cut reactions to the high sulfite wine in this study, indicating that wine induced asthma is a complex phenomenon. Further support for the complexity of the relationship between wine containing sulfites and asthma is derived from a study (36) in which subjects [with a strong history of wine-induced asthma] underwent single dose challenge, and then those demonstrating sen-

sitivity to the single challenge were re-challenged in a cumulative fashion on a subsequent day, utilizing wines with increasing concentrations of sulfites. Only a small number of wine-sensitive asthmatic subjects responded to a single dose challenged with sulfited wine under laboratory conditions. Cumulative sulfite dose challenges did not detect an increased sensitivity to sulfite in wine-sensitive asthmatics. This suggests that the role of sulfites and/or wine in triggering asthma may either be overestimated or other factors or wine components may play a role in wine-sensitive asthmatic subjects (36).

## Discussion

There is a general awareness of the potential benefits of wine and spirits ingestion for "vascular health." Many studies have suggested that wine, and particularly red wine, confers cardiovascular protective benefits, and this literature has recently been reviewed (3,37). Alcoholic beverages, consumed in moderation [and inclusive of distilled spirits] have been significantly associated with decreases in ischemic cardiac and cerebrovascular events and in the associated mortality (38,39).

In this paper, data regarding the benefits and risks of wine and spirits consumption for respiratory system "health" have been presented. Widely varied methodological approaches have been utilized in the clinical studies which evaluated the effects of wine and spirits consumption on various aspects of "lung health." Thus some degree of caution must be applied when attempting to make recommendations based on the data presented in the studies cited in this paper.

Excessive intake of *distilled spirits* has been shown to have a detrimental effect on pulmonary function (6,7,8) independent of the role of smoking; indeed, heavy alcohol ingestion (8) accelerated the loss of $FEV_1$ and FVC with time, and had an effect on $FEV_1$ comparable to smoking 15 g tobacco daily [a typical cigarette weighs 1 gram and contains about 65% tobacco]. A study (4,5) of pulmonary function in individuals without significant lung disease found no significant correlation between total alcohol intake and lung function, but did reveal a positive association of recent and lifetime wine intake with $FEV_1$% and FVC%, but the association of lung function with red wine was weaker than the association for white wine. Several studies (9,11,12) have demonstrated a "mitigating effect" of low to moderate wine consumption on the decrement in lung function associated with COPD. Anti-inflammatory effects of wine polyphenols [resveratrol and others] that have been demonstrated in *in vitro* studies (13,14) provide possible explanations for the wine-related benefits observed in the clinical studies (4,5,9,11,12).

Chronic excessive alcohol intake (17,18) is a risk factor for ARDS; however, a large cohort study (19) in a large managed care setting did not detect an association of ARDS with alcohol consumption. Managed care plan enrollees may have a healthier life style, and the proximity of the study population {San Francisco} to the Napa and Sonoma wine growing regions may have been associated with a more frequent choice of wine as the "alcoholic beverage of choice." Although there are no clinical studies which demonstrate a "protective or preventive role" of wine consumption for ARDS, experimental data from a rat model of severe acute pancreatitis (20) with associated ARDS-like lung injury suggested that the red wine extract resveratrol decreased leukocyte endothelial interaction, reduced blood viscosity, and reduced edema and infiltration of leukocytes in the lungs. Another *in vitro* study (21) demonstrated trans-resveratrol related inhibition of leukocyte aggregation and diminution of release of reactive oxygen species and leukocyte derived degradative enzymes from fMLP stimulated PMNs.

Observed reductions in lung cancer risk associated with wine consumption (23,26,29,30) may be related to the presence of resveratrol [and other polyphenols]. Potential mechanisms for the resveratrol "anti-cancer" effect include alteration in the metabolism of known lung carcinogens such as the polycyclic aromatic hydrocarbons [cigarette smoke constituents] (25), concentration-dependent induction by resveratrol of S phase arrest in cell cycle progression and induction of apoptosis of human lung carcinoma A549 cells (27,28).

Another possible beneficial effect of red wine is that it may help to ameliorate/prevent symptoms of high altitude pulmonary edema (31) by inhibition of release of the potent vasoconstrictor, endothelin-1 (33).

Wine-induced asthma (34,35) is a troublesome and potentially serious problem for patients with a history of the problem. Sulfites in wine are generally considered to be causative, although the role of sulfites and/or wine in triggering asthma may either be overestimated or other factors or wine components may play a role in wine-sensitive asthmatic subjects (36).

Taken together, these multiple studies suggest that consumption of moderate amounts of wine could play a role in promoting "lung health." The obvious caveats are to avoid excessive ingestion of alcohol, particularly distilled spirits, and to avoid sulfite-containing wines in individuals with wine induced asthma.

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## DISCUSSION

**Mackowiak,** Baltimore: That was terrific Steve, particularly so because it resonated with me, and I would suspect, a lot of people here. I love wine. And I'm embarrassed to say, probably the only things I love more than wine are my wife and daughters. But whenever I hear these presentations, I'm reminded of a Roman playwright's quote that "one readily believes what one earnestly hopes for". And I can't help but suspect that publication bias has favored these results. I would just be interested in your thoughts on that.

**Kamholz,** Manhasset: I think that is very, very important. Phil already has my manuscript and there is a pretty big disclaimer in the discussion about how one uses this information. If you do a PUBMED search looking for health benefits of wine or alcohol consumption, there are almost 30,000 "hits" on PUBMED. And one can go through the literature and clearly select papers that support what you would like them to support. My interest in this goes back forty years to when I was the night and weekend manager of a wine shop. Having been in that business prior to medical school, it's been a life-long interest. I think that there are substantial, well-designed, prospective, epidemiologic studies that suggest some clinical benefit from modest consumption. They're very hard to discount. Then if you look at some of the data that come from the countries where both wine and olive oil are constituents of the so called "Mediterranean diet," again there seem to be some health benefits. So yes, I'm not writing prescriptions for wine in my office at this point, but I just thought this would be an interesting topic for the organization to ponder.

**Bray,** Houston: My question is very similar. But I'll try and target the broader question: does wine make you healthy, or do healthy people drink wine? So are there clinical trials where people are randomized to wine and placebo?

**Kamholz:** No, but we could start one. No, the Schunemann study from Buffalo clearly suggested that the choice of wine as the alcoholic beverage to consume is related to educational level, accompanied by increased levels of exercise, and to diets that include whole fruits and whole grains. And it may be the entire lifestyle that is beneficial rather than just the wine itself. Although, when one looks at some of the constituents of wine, clearly the *in vitro* effects of those in a variety of systems seem to be beneficial.

**Bray:** True. That was true for hormone therapy also, which is why I'm asking.

**Kamholz:** We can all avoid the cocktail hour this evening.

**Bray:** Well I just figured this group would not be part of the placebo group.