A 42-Year-Old Man Considering Whether to Drink Alcohol for His Health

Kenneth J. Mukamal

JAMA. 2010;303(20):2065-2073 (doi:10.1001/jama.2010.550)

http://jama.ama-assn.org/cgi/content/full/303/20/2065

A 42-Year-Old Man Considering Whether to Drink Alcohol for His Health

Kenneth J. Mukamal, MD, MPH, Discussant

Alcohol consumption is widespread and, in excess, a leading cause of morbidity and mortality worldwide. At the same time, a consistent body of observational evidence has found that individuals who consume alcohol within recommended limits have a lower risk of coronary heart disease than do abstainers. These observations have led many to consider small amounts of alcohol as a cardioprotective strategy. Mr Q, a 42-year-old man who has consistently sought ways to preserve his health, is at a crossroads in his discussions with his physicians about the health effects of his regular, limited alcohol intake. The discussion reviews the epidemiology of drinking in the United States, the established effects of moderate alcohol intake on key pathophysiological biomarkers and pathways, the strengths and limitations of observational evidence linking alcohol intake to lower risk of coronary heart disease, other chronic diseases linked to moderate alcohol intake, and a framework in which Mr Q can discuss the potential risks and benefits of alcohol consumption with his physicians.

JAMA. 2010;303(20):2065-2073 www.jama.com

DR SHIP: Mr Q is a 42-year-old man who works as a health care consultant. He lives in the greater Boston area and has preferred provider organization insurance.

Mr Q drank socially in college and found he didn't have much tolerance for alcohol. About 10 years ago, he read some popular literature about the potential benefits of drinking red wine for cardiovascular health. Soon afterward, he found out that his cholesterol level was high and began a regimen of drinking 3 to 4 oz of red wine nightly. He occasionally substitutes or adds a martini.

His comfort with drinking alcohol for his health was stable until about 4 months ago, when he saw a consultant for an unrelated medical issue. That physician queried him about his alcohol intake and suggested that regular use might be associated with long-term damaging effects. Mr Q now wonders whether the benefits outweigh the risks.

In addition to red wine, Mr Q regularly drinks yerba maté tea and eats dark chocolate in small amounts, both for their antioxidant benefits. He exercises about 4 days a week, does not smoke, and is attentive to his diet, watching his calorie intake and weight carefully.

His medical history is significant for childhood obesity. He lost a significant amount of weight with diet and exercise and subsequently underwent abdominoplasty in 2000 for removal of redundant skin. He has had bilateral inguinal hernia repairs. He had a positive skin test result for tuberculosis in 1992 and took isoniazid at that time. He has recurrent temporomandibular joint pain. He has no family history of premature cardiovascular disease or alcoholism.

His medications include finasteride, 1 mg/d, for hair loss and zolpidem, 5 mg nightly, as needed for insomnia. He takes a multivitamin daily. He has no allergies to any medications.

On examination, his blood pressure was 124/68 mm Hg, pulse was 69/min and regular, and weight was 199 lb (90 kg). He was 73 in (185 cm) tall and his body mass index was 26.3. The remainder of his examination was unremarkable in detail.

His laboratory results revealed a total cholesterol level of 217 mg/dL (5.62 mmol/L), triglyceride level of 121 mg/dL (1.37 mmol/L), high-density lipoprotein cholesterol level of 48 mg/dL (1.24 mmol/L), low-density lipoprotein cholesterol level of 145 mg/dL (3.76 mmol/L), and a ratio of 4.5. These measurements have been largely stable for the past 8 years. Other laboratory test results, including complete blood count, electrolytes, renal function, and thyrotropin, were all normal.

CME available online at www.jamaarchivescme.com and questions on p 2090.

MR Q: HIS VIEW

About 10 or 15 years ago, there seemed to be a lot of literature coming out on the benefits of drinking alcohol, specifically red wine. I read some of the research on alcohol and found other resources that talked about the benefits of other kinds of beverages—green tea, grape juice, red wine, etc. Also, right around this time, my primary care doctor noticed that my cholesterol level was starting to eke up a little bit.

This conference took place at the Medicine Grand Rounds at Beth Israel Deaconess Medical Center, Boston, Massachusetts, on January 15, 2009.
Author Affiliation: Dr Mukamal is Associate Professor of Medicine, Harvard Medical School, and Associate Physician, Division of General Medicine and Primary Care, Beth Israel Deaconess Medical Center, Boston, Massachusetts.
Corresponding Author: Kenneth J. Mukamal, MD, MPH, Beth Israel Deaconess Medical Center, 1309 Beacon St, Second Floor, Brookline, MA 02446 (kmukamal@bidmc.harvard.edu).
Clinical Crossroads at Beth Israel Deaconess Medical Center is produced and edited by Risa B. Burns, MD, series editor; Tom Delbanco, MD, Howard Libman, MD, Eileen E. Reynolds, MD, Amy N. Ship, MD, and Anjala V. Tess, MD.
Clinical Crossroads Section Editor: Margaret A. Winker, MD, Deputy Editor.

Table 1. Estimated Caloric and Ethanol Content per Serving for Various Alcoholic Beverages[3]

	Beer	Light Beer	Wine	Spirits
Serving size, oz	12	12	5	1.5
Energy, kcal	150	100	120-125	100
Ethanol, g	14	11	15	14-15

As a result of my cholesterol, my doctor said, "Well, why don't you enjoy a little bit more red wine?" And I said, "Why don't I? Sounds good to me! I like red wine!" And so, since that time, I've really been going out of my way to drink more red wine—maybe 3 or 4 oz an evening.

Then, about a month ago, I saw a specialist for a follow-up appointment. During the regular health history, the doctor asked me, "Do you drink alcohol?" I said, "Yes," and explained that I have about 3 or 4 oz of wine about 5 nights a week. She gave me the feedback that I might want to rethink that. She cited a particular study—and I really think it was only 1 study—where some of the findings suggested that alcohol may accelerate the rate of brain size shrinkage as you age. Though I certainly enjoy alcohol, I've been drinking it for medicinal reasons. Now, suddenly, I have to rethink my decision—maybe this isn't the right thing to do.

I already use a different kind of antioxidant drink, yerba maté, which is basically a South American equivalent to coffee but a lot better for you than coffee. I think it has some of the benefits of green tea. I also make a point of having 2 dark chocolate squares a day, but only 2, because I watch my weight very carefully as well. Sometimes the alcohol presents a problem because when I'm drinking it, despite the moderate amount I'm drinking, I notice that I tend to eat more. Because maintaining my weight is of great concern to me, I sometimes think that I should find an alternative to red wine.

I would like to know more about the "shrinking brain" study. I would also like to know a bit more about the vetting process that goes on between scientific literature and the information that actually makes it into a conversation with a patient. I was a little surprised and thrown off by the way 1 small piece of preliminary evidence—the "shrinking brain" study—could suddenly change a decision I had contracted with my primary care physician 10 years ago.

AT THE CROSSROADS: QUESTIONS FOR DR MUKAMAL

What is known about the benefits and harms of moderate alcohol intake? Do they vary by type and frequency of alcohol intake or by sex? Are there end points (eg, cholesterol values) that should be monitored? Should any laboratory measures be monitored? What medications or diseases would argue against drinking therapeutically? What should patients understand when interpreting medical studies related to alcohol? What do you recommend for Mr Q?

DR MUKAMAL: Mr Q, a 42-year-old executive concerned with preserving his good health, presents with a deceptively simple question: should he drink alcohol? The simplicity of the question belies a complex answer. Although alcohol has long been part of both mammalian and human diets and social and religious activities,[1] it has been ranked the third most important preventable cause of death in the United States.[2]

Ethanol in Alcoholic Beverages

Ethanol, a 2-carbon alcohol and intoxicant, is the dominant bioactive compound in all commercially produced alcoholic beverages. Servings of beer, wine, and spirits have similar quantities of ethanol (TABLE 1); thus, guidelines limit daily intake regardless of source (BOX). Notably, flavored alcoholic beverages, which attract underage drinkers,[5] may contain twice the caloric content.

Given differences in first-pass metabolism, volume of distribution, and overall body size between men and women,[6] women experience toxic effects of alcohol at approximately half the daily dose of alcohol of men, a finding reflected in sex-specific limits that guidelines endorse.

How Alcohol Is Consumed in the United States

Rates of drinking vary predictably across the life span. In the United States, the percentage of the adult population drinking alcohol in a given month peaks at approximately 70% among adults aged 21 to 25 years and declines steadily with older age to a minimum of approximately 40% among adults aged 65 years or older.[7] However, among 21- to 25-year-old drinkers, fully two-thirds report binge drinking (≥5 drinks on an occasion) within the last month, a proportion that declines to approximately 25% among 55- to 59-year-olds. Not until age 35 to 39 years (ie, Mr Q's age) do more drinkers deny binge drinking than endorse it. Given the widespread prevalence of binge drinking, its strong explanatory power for alcohol use disorders,[8] and ready integration with more common quantity-frequency questions,[9] all drinkers should be specifically questioned about their usual frequency and quantity of drinking and occasional episodes of heavier drinking and counseling tailored accordingly.

Health Consequences of Alcohol

Short-term Experimental Studies. Evidence regarding the health effects of alcohol consumption within recommended limits comes from 2 complementary sources, feeding studies that manipulate alcohol consumption experimentally and much larger observational studies that do not. Although the former have generally been limited to several weeks of active alcohol consumption, they clearly show that even moderate drinking directly affects several important biomarkers and, by extension, key physiological pathways central to the most common chronic diseases that men like Mr Q face.

Mr Q and his physician specifically view alcohol as potentially cardioprotective, a view espoused by some physicians for at least a century.[10] In cataloging the effects of alcohol from experimental trials (TABLE 2), those tied to coronary heart disease (CHD) figure prominently and include effects on lipids, inflammation, coagulation, and glucose metabolism.

High-density lipoprotein cholesterol (HDL-C; to convert to mmol/L, multiply by 0.0259) is the biomarker most consistently and strongly affected by alcohol consumption. Short-term trials clearly demonstrate that alcohol intake increases HDL-C in a dose-dependent manner.[11] Comparing the effect seen in meta-analyses of these trials (4 mg/dL with a 30-g/d intake) with other agents that affect HDL-C levels,[26] alcohol is likely the most potent available agent for increasing HDL-C; it is more strongly correlated with HDL-C than are smoking or exercise.[27]

The relationship of alcohol and triglycerides is more complex. An increase in triglycerides of 6.6 mg/dL (to convert to mmol/L, multiply by 0.0113) with 2 drinks per day has been estimated among men,[11] but trials in women have found that alcohol may reduce triglycerides at moderate doses.[18,28] In general, alcohol does not markedly influence low-density lipoprotein cholesterol.

In trials, alcohol consumption consistently decreases levels of fibrinogen,[11,14,15] an acute-phase reactant and clotting factor. Whether this decrease influences thrombosis directly is uncertain, although ethanol prolongs bleeding time.[29]

Feeding studies also demonstrate that alcohol increases circulating levels of adiponectin,[18,19] an abundant adipokine that improves insulin sensitivity and whose levels are associated with a lower risk of diabetes.[30] In concert, regular alcohol administration appears to improve insulin sensitivity[18,28,31]; it also acutely decreases gluconeogenesis and postprandial circulating glucose levels.[32]

A final class of potential mediators is the sex steroid hormones. Feeding trials have shown inconsistent effects on testosterone and estradiol but have consistently found that alcohol intake increases circulating levels of estrone and dehydroepiandrosterone sulfates.[21-23]

Longer-term Parallel-Design Trials. Short-term feeding studies cannot necessarily be generalized to long-term alcohol intake, which spans decades. Two randomized trials have used somewhat longer durations of drinking.

Shai and colleagues[33] randomly assigned 109 abstaining patients with diabetes in Israel to receive 13 g of red or white wine daily or a nonalcoholic diet beer control, of whom 91 completed the 3-month trial. Mean fasting glucose levels (to convert to mmol/L, multiply by 0.0555), the primary outcome measure, decreased by 21.6 mg/dL (from 139.6 [SD, 41] to 118.0 [SD, 32.5] mg/dL) among those assigned to alcohol but increased by 1.9 mg/dL among those assigned to the control beverage ($P = .02$), supporting results of shorter-term studies on insulin sensitivity. While other significant changes within groups were observed, none was significantly different between groups.

Marfella and colleagues[34] performed a randomized trial of advice to drink 4 oz of red wine daily vs advice to drink no alcohol among 131 patients with diabetes in Italy who had been recently hospitalized for acute myocardial infarction; no beverage was distributed. At 12 months, of the 115 who completed the trial, those assigned to red wine had significantly lower levels of fasting insulin (–1.8 μIU/mL; to convert to pmol/L, multiply by 6.945), interleukin 18 (–34 pg/mL), and insulin resistance (–0.3 HOMA-IR) and significantly higher HDL-C (+34 mg/dL), consistent with short-term trials. Surprisingly, those in the red wine group experienced improved myocardial performance (ejection fraction, +4% [$P<.05$]; myocardial performance index, 0.2 [$P<.02$]; left ventricular mass, –9 g/m^2 [$P<.05$]), although the rate of recurrent clinical events was not reported, and the observed effects may be due to ethanol, other constituents of red wine, or both.

How do the findings from clinical trials affect Mr Q? He reports regular drinking with no evidence of misuse, suggesting that continued intake is unlikely to lead to abuse. His triglyceride level is normal. His current HDL-C level is at the national average for white men[35]; values that precede his regular alcohol use would be useful to establish whether he has had the expected increase in HDL-C.

Box. National Institute of Alcohol Abuse and Alcoholism Guidelines for Safe Drinking[4]

Up to 2 drinks per drinking day for men younger than 65 years

Up to 1 drink per drinking day for nonpregnant women and older adults

No alcohol for

- Women who are pregnant or trying to become pregnant
- Persons with medical conditions that can be made worse by drinking
- Persons who plan to engage in activities that require alertness and skill (such as driving a car)
- Persons taking certain over-the-counter or prescription medications
- Persons recovering from alcoholism
- Persons younger than 21 years

The individual medical conditions and medications that may contraindicate alcohol are not specified. The safety of alcohol in such settings may vary by age, sex, number and dose of medications, and severity of medical conditions.

Observational Evidence on Alcohol

Recognizing Limitations. Before considering the large number of observational studies of alcohol consumption and chronic disease, it is important for patients and physicians to recognize their limitations and strengths. Two particularly important limitations are the difficulty in identifying an appropriate reference group to which drinkers can be compared and the possibility of incompletely controlled confounding by differences between drinkers and abstainers.

The problem of reference category has commonly been framed in terms of individuals who give up alcohol consumption after previously drinking. Because an individual's health status informs such a decision, comparing current with former drinkers can be biased. Whether occasional

drinkers or long-term abstainers are the appropriate reference category remains controversial.[36,37] In a meta-analysis of alcohol and mortality, inclusion of studies with former or occasional drinkers in the reference group led to stronger estimates of lower risk among moderate drinkers, but a clinically and statistically significant inverse relation remained even after exclusion of such studies.[38]

A second problem is accounting for the many ways that drinkers and nondrinkers differ in observational studies. Even after adjustment for age, sex, race, and education, my coauthors and I have found that drinkers are less likely to be in poor or fair health, obese, of low income, or physically inactive.[39] However, drinkers are also more likely to be smokers and, among smokers, to smoke heavily, extremely strong risk factors for CHD and mortality. Thus, it is overly simplistic to suggest that alcohol consumption is completely intertwined with healthy lifestyle, for perhaps its strongest association is with tobacco.

One attractive way to address confounding is to evaluate different alcoholic beverages. For example, wine is associated with several features of a healthy diet.[40] Johansen and colleagues,[41] in an analysis of 3.5 million supermarket transactions in Denmark, showed that purchases of wine tended to cluster with purchases of olives, oil, and veal, while beer tended to be purchased with chips and soft drinks. As a result, studies of wine may well be confounded by a healthy diet, but studies of beer may be confounded by unfavorable diet choices. It may also be possible to reduce confounding by studying differences in risk of CHD from variation in genes related to alcohol metabolism, as these variants are randomly distributed even when alcohol intake is not and could help to individualize drinking recommendations.[42,43]

Coronary Heart Disease. The relationship of alcohol consumption with CHD has been investigated in studies worldwide dating back at least 25 years.[44] These studies have consistently suggested inverse associations of alcohol consumption with risk of CHD, with an apparent plateau in risk reduction of some 20% to 30% at about 1 drink per day (or approximately 1% lower absolute 10-year risk for a 50-year-old man at average risk).[45,46] The CHD risk associated with heavier drinking is less clear and has been identified as lower than, similar to, or higher than abstainers in various studies.[45-47] As expected, the level of drinking associated with lowest risk tends to be lower for women than for men; in a meta-analysis of 28 high-quality cohort studies, the magnitudes of lower risk were similar for both sexes, but the lowest risk occurred at 10 g/d among women and 25 g/d among men.[46]

The apparent inverse association of moderate alcohol intake with ischemic stroke risk occurs at a lower dose and with a lower magnitude of risk reduction than does the corresponding association with CHD risk.[48] For example, Kaiser Permanente investigators have reported a U-shaped association between alcohol intake and risk of ischemic stroke, with the lowest relative risk of 0.8 among those who consumed alcohol less than daily but a direct inverse association between alcohol use and risk of CHD, with relative risks of 0.6 to 0.7 among consumers of 3 or more drinks per day.[49,50]

Particularly in men, the frequency of alcohol consumption appears to be most strongly associated with lower risk of CHD. In a population-based study of Danish men, there was a graded inverse relation of drinking frequency with risk of CHD independent of the overall amount of alcohol consumed.[51] Studies of male health care professionals show similar results, with approximately 35% lower risk among men consuming alcohol 3 to 4 or 5 to 7 days per week.[52] This also appears to be true in women,[53] although data are less consistent.[51,54] From these findings, it would appear that intake 1 to 2 days per week may be weakly associated with lower risk, but intake 3 to 4 days per week clearly is, and there may be

Table 2. Biochemical Effects of Light to Moderate Alcohol Consumption in Short-term Feeding Studies and Expected Interrelationships With Chronic Diseases Associated With Alcohol Intake

Biomarker	Pathway(s)	Short-term Effect of Light to Moderate Alcohol Intake	Expected Effect on Chronic Diseases Related to Alcohol in Population Studies	Additional Notes
High-density lipoprotein cholesterol	Reverse cholesterol transport	Increase of 4 mg/dL[11]	Lower risk of coronary heart disease	The mechanism is not well characterized but relates to ethanol itself.[12] It is strongest for those with the lowest baseline levels.[11] In populations, the dose response is linear until approximately 60 g/d in men and 35 g/d in women.[13]
Triglycerides	Lipoprotein transport	Increase of approximately 5-7 mg/dL[11]	Higher risk of coronary heart disease	Association is strongest for beer, which has more carbohydrates. It appears sex-specific and may reduce levels in women.
Fibrinogen	Inflammation/ coagulation	Decrease of approximately 10-20 mg/dL[11,14,15]	Lower risk of coronary heart disease	May represent anti-inflammatory effect, as alcohol also decreases other inflammatory markers.[15,16] Dose response is seen in populations.[17]
Adiponectin	Insulin sensitivity	Increase of approximately 0.5-1 mg/L[18,19]	Lower risk of diabetes	Alcohol preferentially increases the most active high-molecular-weight form. It is also higher in population studies.[20]
Estrone/ dehydroepi-androsterone sulfate	Endogenous sex steroid hormones	Increase of 5% to 20%[21-23]	Higher risk of breast cancer, greater bone density	This association is also seen in epidemiological and genetic studies.[24,25]

little decrement in risk associated with intake more frequent than 3 to 4 days per week.

Given Mr Q's admirable lifestyle choices, it is tempting to speculate that alcohol intake would provide little incremental benefit. However, we have found that the pattern and relative magnitude of lower risk associated with alcohol consumption are similar among men with varying intensities of healthy lifestyle,[55] as have others studying alcohol and physical activity.[56] This may reflect the lesser effect that other lifestyle factors have on HDL-C levels.

Mr Q primarily drinks red wine, presumably for resveratrol and its other nonalcoholic constituents. However, the concentrations of such constituents even in red wine are much lower than the concentration of ethanol and, given their limited bioavailability, are unlikely to have substantial physiological effects at the modest doses consumed by most Americans.[57]

Epidemiological evidence generally supports the view that alcoholic beverages are nearly equivalent in their associations with CHD. Although reviews of this topic have differed,[58,59] studies of wine intake are most susceptible to confounding, likely explaining any differences between beverages. In fact, we found red wine to be associated with lower risk to a lesser degree than white wine, beer, or spirits.[52] Of note, red wine was also least correlated with drinking frequency, supporting drinking frequency as the primary component of the inverse association of alcohol intake with CHD.

A final question is whether adopting moderate alcohol intake in middle age has the same benefit as does drinking moderately throughout adulthood. Drinking habits are reasonably stable,[60] so most moderate drinkers in cohort studies have consumed alcohol for some duration. **TABLE 3** summarizes cohort studies that have identified individuals who increased their alcohol consumption during the period of follow-up.[52,61-65] These studies have consistently found a lower risk of CHD of approximately 30% among those who take up regular alcohol use, although most have not been powered for this degree of risk reduction.

Other Important Outcomes of Moderate Drinking. Even moderate drinking clearly influences a number of other conditions beyond CHD. The evidence for potential harms of moderate drinking on other conditions comes from the same sources—small feeding studies and large cohort studies—that the evidence on CHD does. As such, physicians should carefully recognize the suggestive but imperfect data supporting all of these associations.

Although the association with CHD has been the most widely studied, very similar evidence links moderate alcohol consumption with a lower risk of diabetes of roughly the same magnitude.[66] This corresponds well with findings from trials on adiponectin reviewed herein.

Whether alcohol intake within recommended limits causes chronic liver disease remains controversial.[67,68] However, even alcohol intake within recommended limits may raise the risks of cirrhosis and hepatocellular carcinoma among individuals with chronic hepatitis B or C.[69,70]

The cancer most clearly associated with moderate drinking is breast cancer in women, with a roughly linear dose-response relationship throughout the range of drinking,[71,72] corresponding to an approximate 1% increase in the relative risk for each 1 g/d of alcohol (or approximately 0.1% increase in overall 5-year risk for a 50-year-old woman at average risk consuming 10 g/d). Although data are inconsistent,[73] risk appears particularly increased for estrogen receptor–positive tumors,[74] providing at least 1 mechanistic link via increased sex steroid hormone levels. Malignancies of the upper aerodigestive tract, including the oral cavity, larynx, and esophagus, are also increased in moderate drinkers, with relative risks of approximately 1.4 to 1.7 with intake of 2 drinks per day.[75]

Three of the most common cancers among middle-aged nonsmoking men are lung, colorectal, and prostate. Large pooled cohort studies suggest increased relative risks for lung cancer of 1.2 and for colorectal cancer of 1.2 to 1.4 only at levels of intake above recommended limits and at which uncontrolled confounding by smoking is likely.[76,77] Prostate cancer is unrelated to alcohol intake in similar cohort studies.[78]

Some malignancies may actually be less common among moderate drinkers. For example, a 15% to 30% lower risk of lymphoma has been observed in several studies, consistent with an anti-inflammatory effect of alcohol.[72,79]

Among the most complex effects of limited alcohol use is its relationship to complications of trauma. Blood alcohol concentrations well below standard legal limits impair driving and other concentration-intensive tasks,[80] and risk of injury to self and others may increase with average intake of even 1 drink daily.[81] However, moderate alcohol intake has been consistently associated with greater bone mineral density,[82] likely related to its effects on sex steroids. Consequently, the association of alcohol use with fractures and injuries is age- and dose-dependent. Among younger and middle-aged adults worldwide, injuries and accidents are the single greatest source of morbidity related to drinking.[83] Among older adults, fractures related to osteoporosis are related to alcohol intake with a J-shaped curve, reflecting competing effects of higher bone density even with light drinking but a greater number of falls with heavier drinking.[82,84]

Great concern exists about concurrent use of alcohol and medications.[85] Mr Q currently takes finasteride and zolpidem. Finasteride reduces alcohol intake in mice[86] but is unlikely to interact meaningfully with alcohol. Zolpidem and alcohol produce additive levels of sedation that could interfere with activities occurring after the time of dosing and could produce excessive morning sedation, but risk is unlikely if zolpidem dosing occurs just before bed and 1 or 2 drinks are taken with dinner.

Finally, the relationship of alcohol consumption and mortality has been reviewed at length.[38] Overall, the relationship appears curvilinear, with lowest risk among light drinkers, but it varies based on age, sex, and comorbidity. In the largest prospective study,[87] among men aged 35 to 59 years who were free of cardiovascular disease, diabetes, or hyper-

tension, like Mr Q, rates of death per 100 000 person-years were 329 among abstainers, 300 among consumers of less than 1 drink daily, and 305 for consumers of 1 drink daily. The corresponding death rates among those with cardiovascular disease, diabetes, or hypertension were roughly 2-fold higher, so any mortality benefit among middle-aged, healthy men related to alcohol appears modest and unlikely to require daily drinking.

Putting Alcohol Into Context

Many have argued that alcohol could never be approved and used pharmacologically.[88] Indeed, alcohol consumption clearly has the potential to be addictive and toxic. Nonetheless, it has beneficial effects on HDL-C, a surrogate marker like many others that suffices for US Food and Drug Administration (FDA) approval and is further supported by observational data. Addictive potential alone is not a contraindication to FDA approval; hydrocodone-acetaminophen is the most commonly dispensed drug in the United States by a considerable margin.[89] Furthermore, the cited risks of alcohol are chiefly related to alcohol overuse, a risk that could be extended to virtually all approved drugs.

Alcohol is also a macronutrient, not a pharmaceutical. It replaces or supplements foods and drinks in the diet, not lifestyle features or medications. For patients whose lifestyle bears improvement in other ways, such as smoking or lack of exercise, clinicians should use the limited time available for counseling to improve those factors, as their potential benefits are larger and more diverse. In Mr Q's case, however, his decision to drink alcohol has not precluded his attention to exercise, weight, smoking, and diet, and he well illustrates the type of individual with whom a frank discussion of the risks and benefits of alcohol is appropriate.

It is also important to put the evidence relating alcohol and CHD into context. The examples of vitamin E and postmenopausal estrogen are commonly cited as proof that interventions without randomized trial evidence should not be incorporated into clinical practice.[90] However, observational studies usually yield qualitatively correct conclusions,[91] and alcohol is not uniformly associated with potentially confounding healthy lifestyle features as are estrogen and vitamin E.[39] Consider another dietary example in *trans* unsaturated fatty acids, for which feeding trials[92] and cohort studies,[93] but no randomized trials on outcomes, have led to their complete ban in localities across the world; the evidence relating moderate drinking to lower risk of CHD is reasonably considered as compelling. Thus, until randomized trials of alcohol on clinical end points are conducted, if ever, clinicians are faced with difficult decisions as to recommendations for individual patients.

RECOMMENDATIONS FOR MR Q

Some general conclusions are appropriate. First, clinicians have imperfect information for a complete cost-benefit assessment of alcohol, particularly regarding misuse among those who start drinking; hence, this must still be estimated for patients individually. Because younger adults are most apt to misuse alcohol, and because the risk is least certain among lifetime abstainers, middle-aged and older individuals with an established history of safe drinking are the

Table 3. Prospective Studies of Increased Alcohol Consumption During Follow-up and Subsequent Risk of Cardiovascular Disease

Study	No.[a]	Years Between Assessments	Alcohol Intake		Outcome	Follow-up, y	RR (95% CI)[b]	Covariates
			Baseline	Follow-up				
Copenhagen City Heart Study[61]	653	5	<1 drink/wk	1-6 drinks/wk	CHD mortality	12	0.71 (0.44-1.14)	Age, sex, smoking, education, BMI
Physicians' Health Study[62]	1919 Men	7	≤1 drink/wk	>1-6 drinks/wk	CVD	6.7	0.70 (0.49-0.99)	Age, trial group, smoking, parental history of MI, physical activity, BMI, hypertension, diabetes
Atherosclerosis Risk in Communities Study[63]	442	4	0	M: 1-14 F: 1-7 drinks/wk	CVD	4	0.62 (0.40-0.95)	Age, sex, race, smoking, education, physical activity, BMI, aspirin use, hypertension/diabetes/ hypercholesterolemia
MONICA/KORA[64]	74 Men	3	0	>0	CHD	10	0.32 (0.09-1.18)	Age, smoking, education, physical activity, marital status, BMI, cholesterol, hypertension
Health Professionals Follow-up Study[52]	1532 Men	4	<7.5 g/d	≥7.5 g/d	MI	8	0.82 (0.58-1.16)	Age, smoking, parental history of MI, physical activity, BMI, aspirin use, hypertension, diabetes, hypercholesterolemia, intakes of fiber, energy, folate, saturated fat, trans fat, and vitamin E
British Regional Heart Study[65]	305 Men	5	≤2 drinks/ mo	>1 drink/wk	CHD	16.8	0.70 (0.48-1.03)	Age, smoking, social class, employment status, physical activity, BMI, history of stroke, diabetes, any medication, health status

Abbreviations: BMI, body mass index; CHD, coronary heart disease; CI, confidence interval; CVD, cardiovascular disease; MI, myocardial infarction; RR, relative risk.
[a] No. indicates number of individuals reporting increased alcohol consumption during follow-up.
[b] Adjusted relative risk compared with individuals who remained in the lower drinking category at follow-up.

only group in whom this risk is apt to be reliably low. Second, drinkers are disproportionately likely to smoke, and these 2 exposures must be addressed simultaneously. Third, its extraordinary prevalence mandates that clinicians reliably assess for problem drinking, especially binge drinking. Fourth, given time constraints, clinicians would be best served to maximize interventions that may prevent multiple diseases first (eg, smoking, diet, overweight, physical activity), although these interventions have, like alcohol, not been extensively subjected to randomized trials. Fifth, alcohol is unlikely to benefit premenopausal women who have low cardiovascular disease risk but moderate breast cancer risk. Sixth, randomized trials suggest that those with low levels of HDL-C and, perhaps, diabetes are most likely to have a favorable (if still unknown) cost-benefit balance for moderate drinking. Seventh, there are as yet no clear advantages to red wine, although it was used in the only published medium-term randomized trial of advice regarding alcohol.[34] Eighth, and perhaps most importantly, individualized discussions between patients and clinicians with whom they share strong and lasting relationships must form the basis for these complex and personal decisions.

How do these conclusions apply to Mr Q? He has a longstanding and concerned internist and no contraindication to drinking, and he currently drinks alcohol safely. He practices a healthy lifestyle with no additional striking opportunities to reduce his cardiovascular risk. However, his estimated risk of cardiovascular disease in the next 10 years, derived from individuals like Mr Q,[94] is only 2%. Assuming his HDL-C were to decline from 48 mg/dL to 40 mg/dL if he were to abstain, his cardiovascular disease risk would increase to 3%.[94] Drinking alcohol is also unlikely to alter his risk of total mortality markedly, given his good health. Thus, the best evidence to date suggests that his regular alcohol intake will increase his HDL-C and lower his risk of myocardial infarction, but the absolute benefit is modest, and there is unlikely to be meaningful benefit at levels beyond 1 drink every 1 to 2 days. If, given the totality of this information, he views alcohol intake as a desirable part of his lifestyle, he will have made a reasoned decision.

QUESTIONS AND DISCUSSION

QUESTION: I wonder about the neurocognitive effects of alcohol, independent of cardiovascular effects. Heavy drinkers can clearly have cerebellar degeneration, peripheral neuropathy, and other effects on the nervous system. How does that look for lighter drinking?

DR MUKAMAL: That was Mr Q's question as well. There are clear effects of alcohol on the brain, and Mr Q references one of those effects—the relationship of alcohol to brain shrinkage or atrophy. The Framingham Offspring Study reported that alcohol intake was cross-sectionally associated with lower brain volume.[95] Our cross-sectional data are similar from 3500 older adults who had routine brain magnetic resonance imaging in the Cardiovascular Health Study,[96] as are data from the Atherosclerosis Risk in Communities study,[97] all of which suggest that greater levels of alcohol consumption are associated with larger ventricular and sulcal sizes, features perceived radiographically as brain atrophy.

Interestingly, when these same types of scans have been conducted among individuals with alcoholism, their brains also appear atrophied. However, when those individuals abstain from alcohol and the scans are repeated, much of the atrophy seems to resolve.[98] This suggests that not all of what we label atrophy reflects irreversible cell death.

However, atrophy is only half of the story. In addition, 2 other important pathological findings in adult brains are white matter lesions, which are strongly associated with dementia and mortality in prospective studies,[99,100] and subclinical infarctions. In the Cardiovascular Health Study, in which alcohol intake was clearly associated with brain atrophy, it also had a U-shaped relation to white matter lesions, with the lowest risk among light drinkers, and a roughly dose-dependent inverse relation to subclinical infarctions.[96]

So, it is true that alcohol does affect brain structure, but it appears to reflect a mix of what we might call structural or atrophic effects and vascular effects. Data from the Cardiovascular Health Study suggest that the net balance may be positive, but only at low levels of drinking.

QUESTION: Would your recommendation for drinking change if Mr Q was Mrs Q and had the same cardiac risk factors and a more tangible risk of breast cancer?

DR MUKAMAL: It would depend on Mrs Q's age and other characteristics. A woman with the same set of Framingham risk score components as Mr Q would have an estimated risk of less than 1%, with little possibility of absolute benefit, whereas her breast cancer risk would still be tangible.[72] Because the benefit of alcohol on HDL-C tends to be greatest among persons with lower baseline levels,[11] the typically high HDL-C levels among premenopausal women would appear to make any clinical benefit limited at best. As such, it is difficult to envision any scenario in which premenopausal women would, on average, profit from drinking.

That being said, with increasingly aged and obese populations, in whom chronic risk factors like insulin resistance become more prevalent, it may be reasonable to reconsider that balance. Thus, Mrs Q might have a very different risk-benefit ratio at age 62 years than she did at Mr Q's age of 42 years. In fact, the evidence that alcohol reduces insulin resistance is strongest precisely among postmenopausal women.[18,28]

QUESTION: Cross-nationally, the French drink much more heavily than we do. Yet the French paradox is that their cardiovascular mortality is lower than ours. To what degree do you attribute their lower cardiovascular mortality to drinking French wine regularly?

DR MUKAMAL: These sorts of observations stirred much interest in this topic in the 1970s. When countries around the world are ranked by their alcohol consumption and their cardiovascular mortality, the higher their alcohol intake, the lower their rates of cardiovascular disease.[101] It is difficult

to know with certainty how much of their lower cardiovascular risk is attributable to drinking alcohol, but it is easy to speculate that regular, limited alcohol intake may have been at least part of the explanation for those observations.

To extend your question slightly, however, one interesting observation comes from parallel case-control studies in France and Northern Ireland.[102] In France, wine consumption was inversely associated with lower risk. In Northern Ireland, nonwine intake (which exceeds wine intake there) was strongly associated with lower risk. Thus, it is less the specific beverage than the frequency of consumption that appears to drive coronary risk.

Financial Disclosures: Dr Mukamal reports that he has received grants from the National Institute on Alcohol Abuse and Alcoholism and the American Heart Association.
Additional Contributions: We thank the patient for sharing his story and providing permission to publish it.

REFERENCES

1. Dudley R. Ethanol, fruit ripening, and the historical origins of human alcoholism in primate frugivory. *Integr Comp Biol*. 2004;44(4):315-323.
2. Mokdad AH, Marks JS, Stroup DF, Gerberding JL. Actual causes of death in the United States, 2000. *JAMA*. 2004;291(10):1238-1245.
3. US Department of Agriculture. National Nutrient Database for Standard Reference. http://www.nal.usda.gov/fnic/foodcomp/search/. Accessed April 30, 2010.
4. National Institute of Alcohol Abuse and Alcoholism. FAQ for the general public. http://www.niaaa.nih.gov/FAQs/General-English/default.htm. Accessed April 30, 2010.
5. Mosher JF, Johnsson D. Flavored alcoholic beverages: an international marketing campaign that targets youth. *J Public Health Policy*. 2005;26(3):326-342.
6. Baraona E, Abittan CS, Dohmen K, et al. Gender differences in pharmacokinetics of alcohol. *Alcohol Clin Exp Res*. 2001;25(4):502-507.
7. Substance Abuse and Mental Health Services Administration. *Results From the 2006 National Survey on Drug Use and Health: National Findings.* Vol 7. Rockville, MD: Dept of Health and Human Services; 2007.
8. Saha TD, Chou SP, Grant BF. Toward an alcohol use disorder continuum using item response theory: results from the National Epidemiologic Survey on Alcohol and Related Conditions. *Psychol Med*. 2006;36(7):931-941.
9. Frank D, DeBenedetti AF, Volk RJ, Williams EC, Kivlahan DR, Bradley KA. Effectiveness of the AUDIT-C as a screening test for alcohol misuse in 3 race/ethnic groups. *J Gen Intern Med*. 2008;23(6):781-787.
10. Leary T. Therapeutic value of alcohol, with special consideration of relations of alcohol to cholesterol, and thus to diabetes, to arteriosclerosis, and to gallstones. *N Engl J Med*. 1931;205:231-242.
11. Rimm EB, Williams P, Fosher K, Criqui M, Stampfer MJ. Moderate alcohol intake and lower risk of coronary heart disease: meta-analysis of effects on lipids and haemostatic factors. *BMJ*. 1999;319(7224):1523-1528.
12. van der Gaag MS, van Tol A, Vermunt SH, Scheek LM, Schaafsma G, Hendriks HF. Alcohol consumption stimulates early steps in reverse cholesterol transport. *J Lipid Res*. 2001;42(12):2077-2083.
13. Johansen D, Andersen PK, Jensen MK, Schnohr P, Gronbaek M; Copenhagen City Heart Study. Nonlinear relation between alcohol intake and high-density lipoprotein cholesterol level: results from the Copenhagen City Heart Study. *Alcohol Clin Exp Res*. 2003;27(8):1305-1309.
14. Hansen AS, Marckmann P, Dragsted LO, Finne Nielsen IL, Nielsen SE, Gronbaek M. Effect of red wine and red grape extract on blood lipids, haemostatic factors, and other risk factors for cardiovascular disease. *Eur J Clin Nutr*. 2005;59(3):449-455.
15. Estruch R, Sacanella E, Badia E, et al. Different effects of red wine and gin consumption on inflammatory biomarkers of atherosclerosis: a prospective randomized crossover trial. *Atherosclerosis*. 2004;175(1):117-123.
16. Sierksma A, van der Gaag MS, Kluft C, Hendriks HF. Moderate alcohol consumption reduces plasma C-reactive protein and fibrinogen levels; a randomized, diet-controlled intervention study. *Eur J Clin Nutr*. 2002;56(11):1130-1136.
17. Mukamal KJ, Jadhav PP, D'Agostino RB, et al. Alcohol consumption and hemostatic factors: analysis of the Framingham Offspring cohort. *Circulation*. 2001;104(12):1367-1373.
18. Joosten MM, Beulens JW, Kersten S, Hendriks HF. Moderate alcohol consumption increases insulin sensitivity and ADIPOQ expression in postmenopausal women: a randomised, crossover trial. *Diabetologia*. 2008;51(8):1375-1381.
19. Beulens JW, de Zoete EC, Kok FJ, Schaafsma G, Hendriks HF. Effect of moderate alcohol consumption on adipokines and insulin sensitivity in lean and overweight men: a diet intervention study. *Eur J Clin Nutr*. 2008;62(9):1098-1105.
20. Beulens JW, Rimm EB, Hu FB, Hendriks HF, Mukamal KJ. Alcohol consumption, mediating biomarkers and risk of type 2 diabetes among middle-aged women. *Diabetes Care*. 2008;31(10):2050-2055.
21. Mahabir S, Baer DJ, Johnson LL, et al. The effects of moderate alcohol supplementation on estrone sulfate and DHEAS in postmenopausal women in a controlled feeding study. *Nutr J*. 2004;3(1):11.
22. Reichman ME, Judd JT, Longcope C, et al. Effects of alcohol consumption on plasma and urinary hormone concentrations in premenopausal women. *J Natl Cancer Inst*. 1993;85(9):722-727.
23. Sierksma A, Sarkola T, Eriksson CJ, van der Gaag MS, Grobbee DE, Hendriks HF. Effect of moderate alcohol consumption on plasma dehydroepiandrosterone sulfate, testosterone, and estradiol levels in middle-aged men and postmenopausal women: a diet-controlled intervention study. *Alcohol Clin Exp Res*. 2004;28(5):780-785.
24. Hankinson SE, Willett WC, Manson JE, et al. Alcohol, height, and adiposity in relation to estrogen and prolactin levels in postmenopausal women. *J Natl Cancer Inst*. 1995;87(17):1297-1302.
25. Hines LM, Hankinson SE, Smith-Warner SA, et al. A prospective study of the effect of alcohol consumption and *ADH3* genotype on plasma steroid hormone levels and breast cancer risk. *Cancer Epidemiol Biomarkers Prev*. 2000;9(10):1099-1105.
26. Briel M, Ferreira-Gonzalez I, You JJ, et al. Association between change in high density lipoprotein cholesterol and cardiovascular disease morbidity and mortality: systematic review and meta-regression analysis. *BMJ*. 2009;338:b92.
27. Ellison RC, Myers RH, Zhang Y, et al. Effects of similarities in lifestyle habits on familial aggregation of high density lipoprotein and low density lipoprotein cholesterol: the NHLBI Family Heart Study. *Am J Epidemiol*. 1999;150(9):910-918.
28. Davies MJ, Baer DJ, Judd JT, Brown ED, Campbell WS, Taylor PR. Effects of moderate alcohol intake on fasting insulin and glucose concentrations and insulin sensitivity in postmenopausal women: a randomized controlled trial. *JAMA*. 2002;287(19):2559-2562.
29. Elmér O, Goransson G, Zoucas E. Impairment of primary hemostasis and platelet function after alcohol ingestion in man. *Haemostasis*. 1984;14(2):223-228.
30. Heidemann C, Sun Q, van Dam RM, et al. Total and high-molecular-weight adiponectin and resistin in relation to the risk for type 2 diabetes in women. *Ann Intern Med*. 2008;149(5):307-316.
31. Sierksma A, Patel H, Ouchi N, et al. Effect of moderate alcohol consumption on adiponectin, tumor necrosis factor-α, and insulin sensitivity. *Diabetes Care*. 2004;27(1):184-189.
32. Brand-Miller JC, Fatema K, Middlemiss C, et al. Effect of alcoholic beverages on postprandial glycemia and insulinemia in lean, young, healthy adults. *Am J Clin Nutr*. 2007;85(6):1545-1551.
33. Shai I, Wainstein J, Harman-Boehm I, et al. Glycemic effects of moderate alcohol intake among patients with type 2 diabetes: a multi-center, randomized clinical intervention trial. *Diabetes Care*. 2007;30(12):3011-3016.
34. Marfella R, Cacciapuoti F, Siniscalchi M, et al. Effect of moderate red wine intake on cardiac prognosis after recent acute myocardial infarction of subjects with type 2 diabetes mellitus. *Diabet Med*. 2006;23(9):974-981.
35. Lloyd-Jones D, Adams R, Carnethon M, et al; American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics—2009 update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. *Circulation*. 2009;119(3):e21-e181.
36. Fillmore KM, Kerr WC, Stockwell T, Chikritzhs T, Bostrom A. Moderate alcohol use and reduced mortality risk: systematic error in prospective studies. *Addict Res Theory*. 2006;14(2):101-132.
37. Shaper AG, Wannamethee SG. The J-shaped curve and changes in drinking habit. *Novartis Found Symp*. 1998;216:173-188.
38. Di Castelnuovo A, Costanzo S, Bagnardi V, Donati MB, Iacoviello L, de Gaetano G. Alcohol dosing and total mortality in men and women: an updated meta-analysis of 34 prospective studies. *Arch Intern Med*. 2006;166(22):2437-2445.
39. Mukamal KJ, Ding EL, Djousse L. Alcohol consumption, physical activity, and chronic disease risk factors: a population-based cross-sectional survey. *BMC Public Health*. 2006;6:118.
40. Tjønneland A, Gronbaek M, Stripp C, Overvad K. Wine intake and diet in a random sample of 48 763 Danish men and women. *Am J Clin Nutr*. 1999;69(1):49-54.
41. Johansen D, Friis K, Skovenborg E, Gronbaek M. Food buying habits of people who buy wine or beer: cross sectional study. *BMJ*. 2006;332(7540):519-522.
42. Davey Smith G, Ebrahim S. "Mendelian randomization": can genetic epidemiology contribute to understanding environmental determinants of disease? *Int J Epidemiol*. 2003;32(1):1-22.
43. Hines LM, Stampfer MJ, Ma J, et al. Genetic variation in alcohol dehydrogenase and the beneficial effect of moderate alcohol consumption on myocardial infarction. *N Engl J Med*. 2001;344(8):549-555.
44. Klatsky AL, Friedman GD, Siegelaub AB. Alcohol consumption before myocardial infarction: results from the Kaiser-Permanente epidemiologic study of myocardial infarction. *Ann Intern Med*. 1974;81(3):294-301.

45. Maclure M. Demonstration of deductive meta-analysis: ethanol intake and risk of myocardial infarction. *Epidemiol Rev*. 1993;15(2):328-351.
46. Corrao G, Rubbiati L, Bagnardi V, Zambon A, Poikolainen K. Alcohol and coronary heart disease: a meta-analysis. *Addiction*. 2000;95(10):1505-1523.
47. Cleophas TJ. Wine, beer and spirits and the risk of myocardial infarction: a systematic review. *Biomed Pharmacother*. 1999;53(9):417-423.
48. Reynolds K, Lewis B, Nolen JD, et al. Alcohol consumption and risk of stroke: a meta-analysis. *JAMA*. 2003;289(5):579-588.
49. Klatsky AL, Armstrong MA, Friedman GD. Red wine, white wine, liquor, beer, and risk for coronary artery disease hospitalization. *Am J Cardiol*. 1997;80 (4):416-420.
50. Klatsky AL, Armstrong MA, Friedman GD, Sidney S. Alcohol drinking and risk of hospitalization for ischemic stroke. *Am J Cardiol*. 2001;88(6):703-706.
51. Tolstrup J, Jensen MK, Tjonneland A, Overvad K, Mukamal KJ, Gronbaek M. Prospective study of alcohol drinking patterns and coronary heart disease in women and men. *BMJ*. 2006;332(7552):1244-1248.
52. Mukamal KJ, Conigrave KM, Mittleman MA, et al. Roles of drinking pattern and type of alcohol consumed in coronary heart disease in men. *N Engl J Med*. 2003;348(2):109-118.
53. Mukamal KJ, Jensen MK, Gronbaek M, et al. Drinking frequency, mediating biomarkers, and risk of myocardial infarction in women and men. *Circulation*. 2005; 112(10):1406-1413.
54. Dorn JM, Hovey K, Williams BA, et al. Alcohol drinking pattern and non-fatal myocardial infarction in women. *Addiction*. 2007;102(5):730-739.
55. Mukamal KJ, Chiuve SE, Rimm EB. Alcohol consumption and risk for coronary heart disease in men with healthy lifestyles. *Arch Intern Med*. 2006;166 (19):2145-2150.
56. Pedersen JØ, Heitmann BL, Schnohr P, Gronbaek M. The combined influence of leisure-time physical activity and weekly alcohol intake on fatal ischaemic heart disease and all-cause mortality. *Eur Heart J*. 2008;29(2):204-212.
57. Goldberg DM, Yan J, Soleas GJ. Absorption of three wine-related polyphenols in three different matrices by healthy subjects. *Clin Biochem*. 2003;36 (1):79-87.
58. Rimm EB, Klatsky A, Grobbee D, Stampfer MJ. Review of moderate alcohol consumption and reduced risk of coronary heart disease: is the effect due to beer, wine, or spirits? *BMJ*. 1996;312(7033):731-736.
59. Di Castelnuovo A, Rotondo S, Iacoviello L, Donati MB, De Gaetano G. Meta-analysis of wine and beer consumption in relation to vascular risk. *Circulation*. 2002; 105(24):2836-2844.
60. Gruenewald PJ, Johnson FW. The stability and reliability of self-reported drinking measures. *J Stud Alcohol*. 2006;67(5):738-745.
61. Grønbaek M, Johansen D, Becker U, et al. Changes in alcohol intake and mortality: a longitudinal population-based study. *Epidemiology*. 2004;15(2):222-228.
62. Sesso HD, Stampfer MJ, Rosner B, Hennekens CH, Manson JE, Gaziano JM. Seven-year changes in alcohol consumption and subsequent risk of cardiovascular disease in men. *Arch Intern Med*. 2000;160(17):2605-2612.
63. King DE, Mainous AG III, Geesey ME. Adopting moderate alcohol consumption in middle age: subsequent cardiovascular events. *Am J Med*. 2008;121 (3):201-206.
64. Wellmann J, Heidrich J, Berger K, Doring A, Heuschmann PU, Keil U. Changes in alcohol intake and risk of coronary heart disease and all-cause mortality in the MONICA/KORA-Augsburg cohort 1987-97. *Eur J Cardiovasc Prev Rehabil*. 2004; 11(1):48-55.
65. Wannamethee SG, Shaper AG. Taking up regular drinking in middle age: effect on major coronary heart disease events and mortality. *Heart*. 2002;87(1):32-36.
66. Koppes LL, Dekker JM, Hendriks HF, Bouter LM, Heine RJ. Moderate alcohol consumption lowers the risk of type 2 diabetes: a meta-analysis of prospective observational studies. *Diabetes Care*. 2005;28(3):719-725.
67. Corrao G, Arico S, Lepore R, et al. Amount and duration of alcohol intake as risk factors of symptomatic liver cirrhosis: a case-control study. *J Clin Epidemiol*. 1993;46(7):601-607.
68. Corrao G, Bagnardi V, Zambon A, Torchio P. Meta-analysis of alcohol intake in relation to risk of liver cirrhosis. *Alcohol Alcohol*. 1998;33(4):381-392.
69. Poynard T, Bedossa P, Opolon P. Natural history of liver fibrosis progression in patients with chronic hepatitis C: the OBSVIRC, METAVIR, CLINIVIR, and DOSVIRC groups. *Lancet*. 1997;349(9055):825-832.
70. Hassan MM, Hwang LY, Hatten CJ, et al. Risk factors for hepatocellular carcinoma: synergism of alcohol with viral hepatitis and diabetes mellitus. *Hepatology*. 2002;36(5):1206-1213.
71. Smith-Warner SA, Spiegelman D, Yaun S-S, et al. Alcohol and breast cancer in women: a pooled analysis of cohort studies. *JAMA*. 1998;279(7):535-540.
72. Allen NE, Beral V, Casabonne D, et al; Million Women Study Collaborators. Moderate alcohol intake and cancer incidence in women. *J Natl Cancer Inst*. 2009; 101(5):296-305.
73. Colditz GA, Rosner BA, Chen WY, Holmes MD, Hankinson SE. Risk factors for breast cancer according to estrogen and progesterone receptor status. *J Natl Cancer Inst*. 2004;96(3):218-228.
74. Lew JQ, Freedman ND, Leitzmann MF, et al. Alcohol and risk of breast cancer by histologic type and hormone receptor status in postmenopausal women: the NIH-AARP Diet and Health Study. *Am J Epidemiol*. 2009;170(3):308-317.
75. Bagnardi V, Blangiardo M, La Vecchia C, Corrao G. A meta-analysis of alcohol drinking and cancer risk. *Br J Cancer*. 2001;85(11):1700-1705.
76. Freudenheim JL, Ritz J, Smith-Warner SA, et al. Alcohol consumption and risk of lung cancer: a pooled analysis of cohort studies. *Am J Clin Nutr*. 2005;82 (3):657-667.
77. Cho E, Smith-Warner SA, Ritz J, et al. Alcohol intake and colorectal cancer: a pooled analysis of 8 cohort studies. *Ann Intern Med*. 2004;140(8):603-613.
78. Rohrmann S, Linseisen J, Key TJ, et al. Alcohol consumption and the risk for prostate cancer in the European Prospective Investigation Into Cancer and Nutrition. *Cancer Epidemiol Biomarkers Prev*. 2008;17(5):1282-1287.
79. Lim U, Morton LM, Subar AF, et al. Alcohol, smoking, and body size in relation to incident Hodgkin's and non-Hodgkin's lymphoma risk. *Am J Epidemiol*. 2007;166(6):697-708.
80. Council on Scientific Affairs. Alcohol and the driver. *JAMA*. 1986;255(4): 522-527.
81. Cherpitel CJ, Tam T, Midanik L, Caetano R, Greenfield T. Alcohol and nonfatal injury in the US general population: a risk function analysis. *Accid Anal Prev*. 1995;27(5):651-661.
82. Berg KM, Kunins HV, Jackson JL, et al. Association between alcohol consumption and both osteoporotic fracture and bone density. *Am J Med*. 2008;121 (5):406-418.
83. Rehm J, Room R, Monteiro M, et al. Alcohol as a risk factor for global burden of disease. *Eur Addict Res*. 2003;9(4):157-164.
84. Mukamal KJ, Robbins JA, Cauley JA, Kern LM, Siscovick DS. Alcohol consumption, bone density, and hip fracture among older adults: the Cardiovascular Health Study. *Osteoporos Int*. 2007;18(5):593-602.
85. Weathermon R, Crabb DW. Alcohol and medication interactions. *Alcohol Res Health*. 1999;23(1):40-54.
86. Ford MM, Yoneyama N, Strong MN, Fretwell A, Tanchuck M, Finn DA. Inhibition of 5α-reduced steroid biosynthesis impedes acquisition of ethanol drinking in male C57BL/6J mice. *Alcohol Clin Exp Res*. 2008;32(8):1408-1416.
87. Thun MJ, Peto R, Lopez AD, et al. Alcohol consumption and mortality among middle-aged and elderly US adults. *N Engl J Med*. 1997;337(24):1705-1714.
88. Goldberg IJ. To drink or not to drink? *N Engl J Med*. 2003;348(2):163-164.
89. 2007 Top Products by US Dispensed Prescriptions. 2009. http://www.imshealth.com/deployedfiles/imshealth/Global/Content/Document/Top-LineIndustrydata/2007TopProductsbyRXs.pdf. Accessed January 28, 2009.
90. Lauer MS, Sorlie P. Alcohol, cardiovascular disease, and cancer: treat with caution. *J Natl Cancer Inst*. 2009;101(5):282-283.
91. Concato J, Shah N, Horwitz RI. Randomized, controlled trials, observational studies, and the hierarchy of research designs. *N Engl J Med*. 2000;342(25): 1887-1892.
92. Mensink RP, Zock PL, Kester AD, Katan MB. Effects of dietary fatty acids and carbohydrates on the ratio of serum total to HDL cholesterol and on serum lipids and apolipoproteins: a meta-analysis of 60 controlled trials. *Am J Clin Nutr*. 2003; 77(5):1146-1155.
93. Mozaffarian D, Katan MB, Ascherio A, Stampfer MJ, Willett WC. Trans fatty acids and cardiovascular disease. *N Engl J Med*. 2006;354(15):1601-1613.
94. Wilson PW, D'Agostino RB, Levy D, Belanger AM, Silbershatz H, Kannel WB. Prediction of coronary heart disease using risk factor categories. *Circulation*. 1998; 97(18):1837-1847.
95. Paul CA, Au R, Fredman L, et al. Association of alcohol consumption with brain volume in the Framingham study. *Arch Neurol*. 2008;65(10):1363-1367.
96. Mukamal KJ, Longstreth WT Jr, Mittleman MA, Crum RM, Siscovick DS. Alcohol consumption and subclinical findings on magnetic resonance imaging of the brain in older adults: the Cardiovascular Health Study. *Stroke*. 2001;32(9): 1939-1946.
97. Ding J, Eigenbrodt ML, Mosley TH Jr, et al. Alcohol intake and cerebral abnormalities on magnetic resonance imaging in a community-based population of middle-aged adults: the Atherosclerosis Risk in Communities (ARIC) study. *Stroke*. 2004;35(1):16-21.
98. Pfefferbaum A, Sullivan EV, Mathalon DH, Shear PK, Rosenbloom MJ, Lim KO. Longitudinal changes in magnetic resonance imaging brain volumes in abstinent and relapsed alcoholics. *Alcohol Clin Exp Res*. 1995;19(5):1177-1191.
99. Kuller LH, Lopez OL, Newman A, et al. Risk factors for dementia in the cardiovascular health cognition study. *Neuroepidemiology*. 2003;22(1):13-22.
100. Kuller LH, Arnold AM, Longstreth WT Jr, et al. White matter grade and ventricular volume on brain MRI as markers of longevity in the cardiovascular health study. *Neurobiol Aging*. 2007;28(9):1307-1315.
101. LaPorte RE, Cresanta JL, Kuller LH. The relationship of alcohol consumption to atherosclerotic heart disease. *Prev Med*. 1980;9(1):22-40.
102. Marques-Vidal P, Ducimetiere P, Evans A, Cambou JP, Arveiler D. Alcohol consumption and myocardial infarction: a case-control study in France and Northern Ireland. *Am J Epidemiol*. 1996;143(11):1089-1093.