CLINICAL REVIEWS

Medical Risks for Women Who Drink Alcohol

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OBJECTIVE: To summarize for clinicians recent epidemiologic evidence regarding medical risks of alcohol use for women.

METHODS: MEDLINE and PsychINFO, 1990 through 1996, were searched using key words "women" or "woman," and "alcohol." MEDLINE was also searched for other specific topics and authors from 1980 through 1996. Data were extracted and reviewed regarding levels of alcohol consumption associated with mortality, cardiovascular disease, alcohol-related liver disease, injury, osteoporosis, neurologic symptoms, psychiatric comorbidity, fetal alcohol syndrome, spontaneous abortion, infertility, menstrual symptoms, breast cancer, and gynecologic malignancies. Gender-specific data from cohort studies of general population or large clinical samples are primarily reviewed.

MAIN RESULTS: Women develop many alcohol-related medical problems at lower levels of consumption than men, probably reflecting women's lower total body water, gender differences in alcohol metabolism, and effects of alcohol on postmenopausal estrogen levels. Mortality and breast cancer are increased in women who report drinking more than two drinks daily. Higher levels of alcohol consumption by women are associated with increased menstrual symptoms, hypertension, and stroke. Women who drink heavily also appear to have increased infertility and spontaneous abortion. Adverse fetal effects occur after variable amounts of alcohol consumption, making any alcohol use during pregnancy potentially harmful.

CONCLUSIONS: In general, advising nonpregnant women who drink alcohol to have fewer than two drinks daily is strongly supported by the epidemiologic literature, although specific recommendations for a particular woman should depend on her medical history and risk factors.

KEY WORDS: alcohol consumption; alcoholism; women.
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Less than three quarters of women in the United States drink alcohol, and those who do drink consume fewer drinks and less absolute alcohol than men.¹ However, at similar levels of self-reported alcohol consumption, the risk of psychosocial problems or dependence is greater for women than men (for definitions, see Appendix A).²⁻⁶ Women also appear to develop alcohol abuse and dependence after fewer years of drinking than men.⁷ Although only 4% to 5% of women in the U.S. gen-

eral population meet criteria for past-year alcohol abuse or dependence,^{8,9} 9% of female primary care patients in some studies have reported recent heavy drinking or alcohol-related problems.^{10,11}

Many heavy drinkers decrease consumption following brief interventions that include explicit advice about safe drinking limits.¹²⁻¹⁴ In addition, offering feedback about specific risks or consequences of their drinking to patients who drink heavily can help motivate them to decrease alcohol consumption or seek treatment.^{15,16} Physicians report they would be more likely to advise patients about safe drinking practices if they were more confident of their knowledge about safe levels of alcohol consumption.¹⁷

Women who drink more than two drinks daily on average, or who frequently drink five or more drinks on one occasion, are at increased risk of alcohol dependence.⁶ The purpose of this review is to summarize and evaluate the literature on other health risks of alcohol use for women. First, several biological factors that may predispose women to alcohol-related medical problems are identified. Next, the epidemiologic literature comparing the health risks of alcohol use for women and men is evaluated. Finally, health risks of alcohol use that are unique to women are reviewed.

METHODS

Data Sources

Over 2,500 citations were initially identified by searching MEDLINE and PsychINFO from 1990 through 1995

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Dr. Bradley presented some of this review as part of a pre-course on women's health at the national meeting of the Society of General Internal Medicine, San Diego, Calif., 1995.

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using key words “women” or “woman,” and “alcohol,” limited to English and human subjects. This inclusive search strategy, using “alcohol” instead of “alcohol dependence” or “alcoholism,” was chosen in order to identify articles that included alcohol-related data even though they might not be focused primarily on alcohol use or alcohol-treatment populations. Other initial data sources included references from all reviewed articles as well as previous review articles about women and alcohol, or alcohol problems in general.^{18–28} MEDLINE searches for “women” or “woman” and “alcohol” were later repeated to identify citations published through December 1996.

Two authors (KAB and KB) both reviewed all titles and many abstracts of articles identified by our search to select articles relating to the following questions: Are the medical consequences of drinking different for women and men? Are there unique adverse medical consequences of drinking alcohol for women? How should women who currently drink alcohol be advised regarding “safe” levels of consumption?

Further MEDLINE searches were completed using specific key words and authors’ names relating to subtopics of each question. Regarding gender differences, subtopics examined included the relations between alcohol consumption and mortality, cardiovascular disease, injury, neurologic disease, and osteoporosis. The effects of alcohol consumption on physiology, including blood alcohol levels, first-pass metabolism, bone and lipid metabolism, and interactions between estrogen and alcohol, were also reviewed. With regard to potential consequences of drinking that are unique to women, the relations of alcohol consumption to breast, cervical, ovarian, and endometrial cancers, infertility, menstrual symptoms, and spontaneous abortions were reviewed. It was beyond the scope of this review to evaluate the extensive literature regarding fetal alcohol syndrome (FAS). However, because general internists are often the first medical care providers to counsel pregnant patients, data on FAS were summarized relying heavily on previous reviews and recent articles on the topic. Finally, references of all identified articles were reviewed for citations from before 1990 that appeared to include important primary data.

Study Selection and Data Extraction

Rules for study selection and data extraction varied depending on the available data on each subtopic. Study selection and data extraction were therefore integrated. Endnote software (End note Plus 2, 2.02 ed. Niles and Assoc., Berkeley, Calif. 1988–1995) was used to sort citations into bibliographies relating to subtopics of the three questions above, with many articles included on several bibliographies. Data relating to subtopics of each question were identified, extracted, and summarized by one of the five authors.

Studies of patients in alcohol treatment have suggested that women may be more susceptible than men to a

number of complications of heavy drinking,^{29,30} with a shortened time course between the onset of heavy drinking and development of alcohol-related problems.³¹ However, given gender-related biases in these populations,^{11,32} these findings cannot be generalized to other women. Therefore, for this review, data from the most generalizable studies relating to each subtopic were selected and reviewed. Preference was given to studies in the following order: population-based random samples of U.S. households, population-based studies from other countries or U.S. subpopulations (e.g., college students), population-based clinical samples (as from HMOs), and finally other clinical samples (e.g., visit-based sampling in emergency departments or clinics). Preference was also given to larger studies, and to those that allowed comparison of women and men. Data from recent meta-analyses were extracted when available. Gender differences observed consistently in treatment populations are reviewed only when no data were identified from other, more generalizable populations.

Limitations of the Literature

Epidemiologic studies of gender differences in susceptibility to alcohol-related problems have significant limitations. First, accurate measurement of alcohol consumption is challenging. As in all epidemiologic research, recall and social desirability biases cannot be avoided. Moreover, research suggests that heavy drinking is a greater stigma for U.S. women than for men,³³ which could lead to greater underreporting of alcohol consumption by women than by men. Also, heavy-drinking women drink less than heavy-drinking men.^{1,6,7,34} Therefore, even if women and men developed a certain complication of drinking at identical thresholds, the mean alcohol consumption reported by women with the complication would be lower than that reported by men who suffered from the same complication. These biases could lead to the mistaken conclusion that women develop medical complications at lower levels of alcohol consumption than men. Consequently, the conclusions of this review regarding levels of alcohol consumption associated with specific medical complications and differences in the vulnerabilities of men and women to alcohol-related complications are somewhat tentative.

Other important methodologic limitations of studies of alcohol use and health in women include biases in subject selection, confounding, and inadequate power. For instance, some case-control studies appear to have systematically excluded heavy drinkers from control groups. Important confounders such as smoking are not always evaluated or taken into account in analyses. Finally, women are much less likely than men to drink heavily, and heavy-drinking women are less likely to participate in surveys. Many studies therefore lack adequate numbers of subjects to draw conclusions about heavy-drinking women. Given the variability of the quality of the available data on different subtopics of this review, specific limitations are noted below as they pertain to each conclusion.

RESULTS

Biological Plausibility of Gender Differences

Higher Blood Alcohol Levels. Women achieve higher blood alcohol concentrations than men after consumption of equivalent doses of alcohol per body weight, making it biologically plausible that women are more susceptible to medical complications of drinking.³⁵ The difference in blood alcohol levels between women and men is partially explained by women's lower volume of distribution of alcohol owing to their lower total body water.³⁶ Young women also appear to have lower first-pass metabolism of alcohol than young men,³⁷⁻⁴² and many investigators conclude that this gender difference in young nonalcoholic subjects results primarily from lower gastric alcohol metabolism in women.^{37,38,43} However, gender differences in metabolism have not been consistently demonstrated, and the overall importance of gastric and hepatic first-pass metabolism of alcohol is still debated.^{35,44-52}

Postmenopausal Estrogen Levels. Postmenopausal women who drink alcohol may have increased serum estrogen levels, further increasing the plausibility of gender differences in the medical risks of drinking.⁵³⁻⁵⁵ Acute increases in estrogen levels, up to threefold higher than baseline, have been observed after alcohol ingestion among postmenopausal women taking estrogen replacement.⁵⁶ This acute effect was not observed in postmenopausal women not taking estrogen replacement.⁵⁶ However, some studies of non-estrogen-using postmenopausal women have observed increased estrogen levels in drinkers compared with abstainers, suggesting that chronic alcohol use may also be associated with increased estrogen levels.^{53,55} For these reasons, increased estrogen levels associated with alcohol use may contribute to some of the observed relationship between alcohol and health in older women.

Medical Risks of Drinking for Women Compared with Men

All-Cause Mortality. Women have elevated mortality at lower levels of alcohol consumption than men. A meta-analysis of cohort studies evaluating the relationship between alcohol consumption and death from all causes found that the relative risk (RR) of death increased significantly in women consuming 2.0 to 2.9 standard drinks in a usual day (RR 1.13; 95% confidence interval [CI] 1.10, 1.16), while the RR of death for men did not increase significantly until usual daily consumption reached 4 standard drinks (RR 1.06; 95% CI 1.03, 1.10).⁵⁷ Among Kaiser Permanente patients, women—but not men—who reported drinking 3 to 5 drinks a day had higher age-adjusted mortality than lifelong nondrinkers (adjusted RR 1.4; 95% CI 1.1, 1.8).⁵⁸ The increased mortality associated with heavy alcohol consumption by women is largely due to noncardiovascular causes. Relative risks of death

from cirrhosis,^{58,59} cancer,⁵⁹ and injury⁵⁹ are increased for women who drink more than 2 to 3 drinks a day.

Cardiovascular Mortality. Although not apparent in smaller studies,⁶⁰ large cohort studies have found a J- or U-shaped relation between alcohol consumption and mortality among women, similar to that observed in men.^{58,59,61,62} The mortality benefits of low-level drinking may be limited to postmenopausal women and possibly to those with preexisting cardiovascular disease.^{62,63} Like men, women appear to experience a U-shaped relation between alcohol consumption and fatal (and nonfatal) coronary artery disease, with low-level consumption (usually less than 2 drinks daily) associated with decreased risk.^{58,64-70} The Nurses Health Study,⁶⁵ a Kaiser Permanente cohort study,⁷¹ a Swedish cohort study,⁷² and a meta-analysis,⁵⁷ all suggest that low-level alcohol consumption decreases the risk of ischemic stroke and stroke mortality among women.

The benefits of low levels of alcohol consumption on cardiovascular mortality have been demonstrated in women aged 35 years and over,⁵⁷ and may be limited to women with at least one cardiovascular risk factor.^{59,73} The cardiovascular benefits of alcohol consumption for women appear to be associated with both habitual and recent alcohol consumption.⁷⁴ Mechanisms by which low-level alcohol consumption decreases the risk of cardiovascular disease most likely include chronic alterations in lipids and lipoproteins, as well as more acute antithrombotic effects.^{67,75-77} Studies have consistently demonstrated a positive association between alcohol intake and levels of the cardioprotective high-density lipoproteins (HDLs) in women.^{75,78,79} Furthermore, this effect appears to be dose dependent.⁷⁹ One small study of alcohol-dependent women also showed that abstinence consistently decreased total HDL levels and raised levels of atherogenic lipoprotein (a) particles.⁸⁰

Despite the benefits of low-level consumption, heavy alcohol use may be linked to premature cardiovascular death in young women. A case-control study found a higher rate of previously diagnosed alcoholism among women with sudden death than among age-matched women from the general population (RR 12.0; 95% CI 3.4, 41.9) or age-matched women with new myocardial infarctions (RR 4.8; 95% CI 1.3, 18.2).⁸¹ Another retrospective study also suggested that young, heavy-drinking women might have higher-than-expected premature cardiovascular mortality.⁸² An association between sudden death and heavy drinking has been observed in case-control studies of men,⁸³ and is probably confounded by factors such as other substance abuse. However, several alcohol-related mechanisms have been suggested, including an arrhythmogenic effect of high blood alcohol concentrations and conduction abnormalities due to subclinical alcohol-related cardiomyopathy.^{84,85} Rates of cardiomyopathy (and myopathy) are higher among women and men in alcohol treatment than in the general population.^{29,86,87}

Cardiovascular Disease. There are no consistent differences between women and men with regard to the relation between alcohol consumption and hypertension,⁸⁸⁻⁹⁵ ischemic heart disease,^{58,64,65,67,96} or stroke.^{57,65,69-71}

Hypertension. Although men may be slightly more susceptible to the hypertensive effects of alcohol than women,⁹⁷ blood pressures increase in both men and women who consume more than 3 to 4 alcoholic drinks daily.^{89,95,98,99} Several large cohort studies have suggested that the risk of hypertension is increased in women who drink as few as 2 drinks a day,^{91,97,100,101} with recent intake being more important than average intake.^{90,102} The association between alcohol consumption and hypertension might be strongest in older, postmenopausal women,^{92,99} particularly those not taking estrogens.¹⁰³

Stroke. A meta-analysis⁵⁷ and a Finnish case-control study^{104,105} suggest that more than 4 drinks daily on average increases the risk of stroke. Other Finnish studies have also suggested that acute intoxication might be associated with ischemic stroke in women, especially young women.^{106,107} An increased risk of subarachnoid hemorrhage was observed among women who drank more than 1.2 drinks per day in the Nurses Health Study,⁶⁵ and trends toward increased hemorrhagic stroke have been observed in other cohort studies of women.^{71,108} An evaluation of U.S. mortality data for 1987 suggested that women experienced greater alcohol-related cardiovascular mortality than men, largely due to cerebrovascular disease.¹⁰⁹ Studies showing no increased risk of stroke in women who drink heavily had relatively small numbers of women,¹¹⁰ or did not evaluate levels of alcohol use above 4 drinks per day.^{111,112}

Alcohol-Related Liver Disease. Several prospective population-based cohort studies have suggested that women are more likely to develop and die from alcohol-related liver disease than men drinking at comparable levels. In a recent Danish cohort study with 12 years of follow-up, the risk of alcohol-related liver disease and alcohol-induced cirrhosis increased beginning at weekly consumption of 7 drinks in women and 14 drinks in men.¹¹³ With consumption of 28 to 40 drinks a week, the RR of cirrhosis for women was 17.0 (95% CI 6.8, 40.8), compared with 7.0 (95% CI 3.8, 12.8) for men.¹¹³ Among Kaiser Permanente patients followed for up to 11 years, women who drank 3 to 5 drinks per day on average had an RR of death due to cirrhosis of 7.7 compared with women who drank less than 1 drink a day ($p < .001$), whereas the comparable RR for men was 4.9 ($p < .01$).⁵⁸ Many case-control studies and case series of patients with liver disease or alcohol dependence have also suggested increased sensitivity of women to the deleterious effects of alcohol on the liver.^{30, 114-120}

Postmenopausal women with cirrhosis have elevated estrogen and decreased testosterone levels that appear to correlate with the severity of liver disease.¹²¹ One case-control study suggested that reproductive hormone levels

may have prognostic value for women with end-stage alcohol-related liver disease. Among women awaiting transplant for alcohol-induced cirrhosis, those who died had higher estrogen levels, higher estradiol-to-testosterone ratios, and lower levels of luteinizing hormone, than those who survived.¹²² If future studies corroborate these findings, laboratory tests for reproductive hormone levels may offer women with end-stage liver disease helpful prognostic information.

Injury. The amount of alcohol consumed per occasion increases the risk of fatal injury among men and women, probably in a dose-dependent manner.¹²³ In the 1971 National Health and Nutrition Examination Survey (NHANES), U.S. women who reported that they usually had 5 or more drinks when they drank alcohol had a significantly increased risk of death due to injury.¹²³ Similar findings have been observed in the Kaiser Permanente population and the Nurses Health Study.^{58,59}

Alcohol consumption is also associated with increased nonfatal injury in women and men, with a dose-response relation.¹²⁴ Several cohort studies have found that alcohol consumption specifically increases the risk of fractures in middle-aged and elderly women.¹²⁵⁻¹²⁷ Women in the Nurses Health Study who were 34 to 59 years old and consumed over about 2 drinks daily had an RR of hip fracture of 1.38 (95% CI 1.09, 1.74) during 6 years of follow-up.¹²⁵ Cross-sectional studies have found a similar association between alcohol and injury in women. Women who seek emergency care for injuries are significantly more likely than comparable, noninjured women to have positive breath alcohol tests (3%-3.4% vs 6%-7.1%) and to report having 5 or more drinks on one occasion at least monthly (15.5% vs 23.3%).^{128,129} Although some studies have observed no association between alcohol consumption and injury, these have generally evaluated the risk associated with any alcohol use, the frequency of alcohol use, or mean daily consumption, not quantity consumed per occasion.¹³⁰⁻¹³² In addition, several reports suggesting no relation between alcohol consumption and injury in women have classified daily drinking of up to 4 drinks on one occasion as "low" consumption, potentially resulting in classification bias.^{133,134}

Although men have higher rates of alcohol-related injuries than women, this reflects the higher prevalence of heavy drinking among men. In fact, the risk of injury may be elevated at lower levels of alcohol consumption for women than for men. Among Kaiser Permanente enrollees, the adjusted RR of unnatural death (e.g., due to a motor vehicle accident, suicide, or homicide) was 11.5 for women drinking 6 or more drinks a day (95% CI 3.7, 36), compared with 2.1 for men reporting an equivalent amount (95% CI 1.0, 4.5).¹³⁵ A study of college students suggested that women are at significantly increased risk of injury when they drink 4 or more drinks per occasion, whereas similar risks were seen in male students who drank 5 or more drinks per occasion.^{4,136} Studies of national,

primary care, and emergency care populations that found no gender difference in the relation between alcohol consumption and injuries may have included too few heavy drinkers to measure such a difference.^{124,128,129,137,138}

Osteoporosis and Bone Metabolism. Whereas men who drink heavily have increased osteoporosis,¹³⁹⁻¹⁴¹ alcohol use among postmenopausal women may decrease the risk of osteoporosis. A recent European study found that women over 65 years old who drank alcohol at least 5 days a week had a decreased risk of vertebral deformity.¹⁴² Several other epidemiologic studies have also suggested that heavy alcohol consumption may be associated with increased bone mineral density in postmenopausal women.¹⁴³⁻¹⁴⁶ In the Framingham study, postmenopausal women who drank more than about 14 drinks per week had significantly increased bone mineral density.¹⁴³ Despite limitations in this study (women who drank more alcohol also tended to be taking hormone replacement therapy, and the method for measuring bone mineral density was not described), other studies have also observed increased bone density in women who drink.¹⁴⁴⁻¹⁴⁶

The findings of *decreased* vertebral deformity and *increased* bone density in postmenopausal women who drink contrasts with small studies suggesting that premenopausal alcohol-dependent women may be more likely to develop osteoporosis.^{125,147} A study of 19 noncirrhotic alcohol-dependent women with normal menstrual cycles who drank more than 15.5 drinks a day on average, found that serum markers of bone formation were significantly lower in these women than in age- and weight-matched control women.¹⁴⁷ Bone mineral density and serum markers of bone degradation, however, did not differ between alcohol-dependent women and control women. With abstinence, one measure of bone formation (serum osteocalcin) normalized, while another (depressed levels of vitamin D metabolites) remained unchanged. These results suggest that decreased bone formation and abnormal vitamin D metabolism may predispose alcohol-dependent premenopausal women to osteoporosis.

Neurologic Effects of Alcohol. Women may experience greater sedation than men with equivalent blood alcohol levels.⁴⁴ An increased sensitivity to the sedative effects of alcohol could contribute to the increased risk of traffic violations and accidents among women (but not men) who report drinking more than 5 drinks on occasion, or who drink and drive.¹⁴⁸ Studies of chronic neurologic deficits in patients treated for alcoholism have found women and men to have similar rates of neuropsychologic impairment,¹⁴⁹⁻¹⁵² brain shrinkage,¹⁵³⁻¹⁵⁵ and peripheral neuropathy.^{29,30} Given the shorter duration of heavy drinking and lower lifetime consumption among women in alcohol treatment, these studies might reflect greater susceptibility of women to the toxic effects of alcohol or its metabolites on the nervous system.¹⁵⁶ However, there is no consistent dose-response relation between specific

cognitive deficits and alcohol consumption, and confounding factors such as affective disorders and antisocial behavior could explain at least some of the neuropsychologic deficits observed in alcoholic populations.¹⁵⁷

Psychiatric Comorbidity. Although data linking alcohol consumption per se with psychiatric diseases were not identified, there are data suggesting that women who develop alcohol dependence have increased psychiatric comorbidity. The five-community Epidemiologic Catchment Area survey found that both women and men with alcohol abuse and dependence had increased rates of other substance abuse, antisocial personality disorder, phobic disorder, major depression, panic disorder, and somatization compared with the general population. However, 65% of alcohol-abusing or alcohol-dependent women had a second psychiatric diagnosis, compared with 44% of men.¹⁵⁸ Similarly, in a Canadian general population survey, among women who were identified as problem drinkers (2.1% of all women), 42% and 15% had positive screening tests for anxiety and depression, respectively, in contrast to 11% and 5% of male problem drinkers ($p < .001$).¹⁵⁹ Studies of alcohol treatment populations have also demonstrated greater depression¹⁶⁰⁻¹⁶⁶ and anxiety^{161,163,164,167-169} among women than men. However, depression and anxiety do not appear to be caused by problem drinking in women. In the Epidemiologic Catchment Area study, among women and men with both depression and alcohol dependence, 66% of women reported that depression preceded problem drinking, while 78% of men reported that alcohol abuse or dependence preceded depression.¹⁵⁸

Alcohol-Related Consequences Unique to Women

Fetal Alcohol Syndrome. The prevalence of FAS is highest among children born to Native Americans (0.3% of live births), followed by African Americans (0.06%), whites (0.009%), and Hispanics (0.008%), with the lowest rate among Asian Americans (0.003%), although detection bias may contribute to these differences.¹⁷⁰ Subtler developmental defects related to maternal alcohol consumption are probably more common. No single threshold level of alcohol consumption has been associated with the development of FAS, apparently owing to differences in fetal vulnerability to the toxic effects of alcohol. Alcohol consumption during the first trimester has been associated with low birth weight, decreased birth length and head circumference, minor physical anomalies, and fetal alcohol effects that do not meet diagnostic criteria for FAS,¹⁷¹ while consumption during the second and third trimesters has been associated with developmental delay at birth¹⁷² and in early childhood.^{173,174} Adverse psychosocial, behavioral, physical, and intellectual consequences of prenatal alcohol exposure continue into adulthood.¹⁷⁵ Although extremely low-level alcohol consumption (i.e.,

1 drink every 10 days, or less) might be safe during pregnancy,¹⁷⁶ women should be advised to abstain before conception and during pregnancy because of the variability in fetal vulnerability to alcohol.^{27,177}

Infertility. Very heavy drinking was associated with previous infertility in a survey of U.S. women.¹⁷⁸ The highest rate of reported infertility (30%) was among women who drank 6 or more drinks at least five times a week.¹⁷⁸ Two case-control studies have also found alcohol consumption to be associated with infertility,^{179,180} while one that evaluated relatively low levels of consumption found no association.¹⁸¹

The possible link between alcohol consumption and infertility is most likely multifactorial and may be bidirectional.^{179,180,182} Heavy alcohol consumption has been associated with causes of infertility that include tubal disease,^{180,183,184} ovulatory dysfunction,^{179,185,186} and endometriosis.¹⁸² A prospective study found that problem drinkers who reported infertility at follow-up were more likely to also report continued heavy drinking, compared with baseline problem drinkers who did not report infertility at follow-up.¹⁸⁷

Spontaneous Abortion. Rates of spontaneous abortion and stillbirth, often due to placental abruption, are increased among women who drink more than 2 drinks daily according to prospective cohort studies,^{188–191} a retrospective cohort study,¹⁹² and a case-control study.¹⁹³ This association has also been suggested by retrospective surveys of women from the U.S. general population¹⁷⁸ and obstetric populations,^{192,194} although these studies do not adequately control for the increased gravidity observed among heavy-drinking women. Studies that have failed to demonstrate a relation between heavy alcohol consumption and spontaneous abortion may have been limited by retrospective designs, insufficient power,^{195–200} or use of inadequate measures of alcohol consumption.¹⁹⁴ Alcohol-related risks of spontaneous abortion may also vary depending on ethnicity and on beverage type.¹⁸⁹

Menstrual Symptoms. Women who drink heavily may have painful, heavy, or irregular menses more often than other women. A survey of U.S. women found that among women who drank 6 or more drinks a day at least weekly, 80% reported heavy menstrual flow and painful menstruation, compared with 59% of other women ($p < .001$).¹⁷⁸ Women who drank 6 or more drinks five or more times a week reported irregular or interrupted menses more often than other women.¹⁷⁸ Women seeking care for premenstrual syndrome also have higher rates of heavy drinking^{201–203} and alcohol abuse and dependence,^{204,205} compared with other women seeking gynecologic care^{201,202,204} or comparable women in the general population.^{203,205} Substantial evidence in animals, and some based on humans, suggests

that chronic heavy alcohol consumption disrupts the hypothalamic-pituitary-ovarian axis.²⁰⁶

Breast Cancer. More than 50 case-control studies, 20 cohort studies, and seven meta-analyses have documented a relation between alcohol consumption and breast cancer,^{207–213} and such an association is biologically plausible.^{214–216} A recent study of pooled data from six prospective cohort studies demonstrated a linear dose-response relation between levels of alcohol consumption below about 5 drinks a day and increased breast cancer. Specifically, women consuming more than about 2 drinks a day had a 31% to 41% increased risk of developing invasive breast cancer.⁵⁵ In another study, Longnecker evaluated data from 10 cohort and 28 case-control studies that met rigorous methodologic criteria. A random effects model revealed a dose-response relation, with RRs of developing breast cancer for those consuming 1, 2, and 3 drinks per day of 1.11 (95% CI 1.07, 1.16), 1.24 (95% CI 1.15, 1.34), and 1.38 (95% CI 1.23, 1.55), respectively.²⁰⁷ Although it has been suggested that the risk of breast cancer in women who use alcohol may be limited to women who have ever taken postmenopausal estrogens,^{216,217} the large study of pooled data mentioned above found no interaction.⁵⁵

Gynecologic Malignancies. Although several studies have suggested that heavy drinking might increase a woman's risk of uterine or ovarian cancers,^{218–220} the data are insufficient to support this conclusion. A cohort study of more than 3,000 Danish women in treatment for alcohol abuse followed for a mean of 9.4 years found no increased risk of endometrial or ovarian cancer, compared with the entire female Danish population.²²¹ A similar Swedish study also found no association.²²² In addition, a population-based cohort study²²³ and a number of case-control studies^{224–228} have found no significant adverse association between relatively low-level alcohol consumption and endometrial cancer^{224,226–228} or ovarian cancer.^{225,227,229,230} One study noted a *decreased* rate of ovarian cancer in heavy drinkers,²²⁵ and several have suggested a decreased risk of endometrial cancer with moderate alcohol consumption.^{226,231} Case-control studies suggesting an increased risk of endometrial and ovarian cancers in women who drink heavily were performed by one group of researchers, and heavy drinkers may have been systematically underrepresented in their control groups.^{218–220}

In addition, there is inadequate evidence to indicate an independent association between alcohol use and cervical cancer. The Danish cohort study mentioned above observed an increased risk of cervical cancer in women treated for alcohol-related problems (RR 2.0; 95% CI 1.2, 3.0) compared with the general Danish population.²²¹ A similar Swedish retrospective cohort study also found an association between cervical, vaginal, and vulvar cancers in women registered with temperance boards.²²² However, both these studies, and another smaller one reporting a

Table 1. Summary of Medical Risks of Drinking Alcohol for Women Compared with Men

Outcome	Alcohol Consumption Associated with Increased Risk for Women	Increased Risk for Women vs Men?*
Mortality	≥2 drinks/day (average)	Yes
Hypertension	>3 drinks/day (average); possibly ≥2 drinks/day (average)	No
Stroke	>4 drinks/day (average); possible association with acute intoxication	No
Alcohol-related liver disease	≥7 drinks/week (average)	Yes

*With equivalent self-reported consumption.

similar association,²³² were unable to control for known risk factors for cervical cancer or rates of Pap screening. Therefore, the observed increased risk of cervical cancer may be due not to alcohol use, but to known confounders such as cigarette smoking or sexually transmitted diseases, or decreased preventive screening among the women treated for alcohol problems.²³³ A large U.S. case-control study observed no association between low-level alcohol consumption and cervical cancer, controlling for age and race.²²⁷ Although alcohol abuse has been associated with a worse prognosis in women with cervical cancer, multivariate analyses suggest that only age less than 50, advanced cancer stage, or use of heroin or cocaine are independently associated with a poor prognosis.²³⁴

DISCUSSION

This review is limited by publication bias because data that show no relation between women's health and alcohol use are less likely to have been published or identified. Epidemiologic studies of gender differences in the relation between alcohol use and medical conditions have several other limitations as outlined above. Nonetheless, biological plausibility, and the consistency of many findings in countries with different drinking norms, support differences in the risks associated with alcohol consumption for men and women (Tables 1 and 2).

The extensive literature regarding nonmedical risks associated with heavy drinking is not included in this review. Heavy daily alcohol use and episodic heavy drinking are both associated with a number of important behavioral and psychosocial consequences. Among U.S. women in a national survey who drank 2 or more drinks daily on average, 45% reported driving while intoxicated, 34% re-

ported starting fights with their partners, and 36% reported blackouts, in the past year.²³⁵ Women who drink 4 or more drinks on any single occasion have also been shown to be at increased risk of psychosocial problems.^{3,4,136}

This review has also focused almost exclusively on adverse health effects of drinking alcohol for women, and does not thoroughly review the growing literature relating to potential beneficial health effects of low-level alcohol consumption. In addition to potential cardiovascular and skeletal benefits of alcohol use noted, low-level alcohol consumption has been associated with improved functional status²³⁶ and cognitive performance²³⁷ in postmenopausal women. Nevertheless, there are insufficient data to suggest that women who do not currently drink should be advised to start drinking alcohol.

Clinical Implications

Guidelines have recommended lower limits of alcohol use for women than for men.^{3,27,238} The above review of the literature supports guidelines recommending that women who drink should have no more than 1 or 2 drinks daily. It seems prudent, therefore, to advise all women who drink alcohol to have fewer than 2 standard-sized drinks daily, on average. Because women develop higher blood alcohol levels than men after a given amount of alcohol consumption, they should also be counseled about the risks associated with intoxication and advised not to exceed 3 drinks on an occasion. Women who are or may become pregnant should be advised to abstain, as should women with alcohol dependence.

Beyond these general guidelines, alcohol-related advice for a particular woman will depend on her medical history and risk factors. For instance, a woman with cardiovascular risk factors could be advised of the relation between hypertension and heavy drinking, whereas a woman with liver disease could be warned about the increased susceptibility of women to alcohol-related liver damage even at low levels of alcohol use. Women with breast cancer or concern about breast cancer could be educated about the increased risk associated with drinking alcohol. In such ways, offering female patients specific feedback linking their health concerns and alcohol use may help motivate those who drink excessively to reduce alcohol consumption or abstain.

Table 2. Medical Risks of Drinking Unique to Women

Outcome	Alcohol Consumption Associated with Significantly Increased Risk
Infertility	≥6 drinks/day, at least 5 times weekly
Spontaneous abortion	>2 drinks/day (average)
Menstrual symptoms	≥6 drinks/day, at least weekly
Breast cancer	≥2 drinks (approx.)/day (average)

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APPENDIX A

Definitions Used in this Review

Heavy drinking: Drinking patterns that have been associated with increased risk. In general, more than 2 standard drinks daily on average, or 4 or more drinks on any single occasion, are associated with increased risk among women.^{3,6,113,136} However, studies have defined heavy drinking differently; specific definitions used in studies are included in the text and tables.

Alcohol dependence: Patterns of alcohol use reflecting lack of control over or preoccupation with drinking, often with tolerance and symptoms of withdrawal. The term "alcohol abuse and/or dependence" describes conditions that meet specific diagnostic criteria such as those put forth by the American Psychiatric Association Diagnostic and Statistical Manual of Mental Disorders.²³⁹

Alcohol problems, drinking problems, and problem drinking: The entire spectrum from mild alcohol-related problems to severe alcohol dependence.

One drink: A standard U.S. drink is equivalent to about 0.5 fluid U.S. oz, 12 g, and 15 mL of absolute alcohol, or a 12-oz beer, 4-5 oz of wine, or a shot of hard liquor. Standard drink sizes used in other English-speaking countries are equivalent to the following standard U.S. drinks: 0.68 for the United Kingdom, 0.857 for Australia, and 1.153 for Canada.²⁴⁰ Unless otherwise specified, a drink refers to a standard U.S. drink.

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