Do Hormones Link Alcohol With Breast Cancer?

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In the first study to examine the long-term effects of ethanol on hormone levels in non-alcoholic, premenopausal women, Reichman et al. (*1*) found that consumption of 30 g of alcohol daily (about two drinks) increased levels of the following hormones (percent increase): plasma dehydroepiandrosterone sulfate (7%) in the follicular phase of the menstrual cycle (days 5-7); plasma estrone (21%), estradiol (28%), and urinary estradiol (32%) in the peri-ovulatory phase (days 12-15); and urinary estrone, estradiol, and estriol (all 15% or more) in the luteal phase (days 21-23).

The findings of this well-designed study conducted by Reichman and co-workers (*1*) are consistent with the results of short-term experiments in non-alcoholic, premenopausal women (*2-4*). In those experiments, luteinizing hormone increased serum estradiol levels when no alcohol was consumed. When alcohol was consumed in a single intoxicating dose of 45-50 g (about four drinks), luteinizing hormone induced much greater increases in serum estradiol levels (160%-800% greater). In the normal menstrual cycle, luteinizing hormone levels peak 1 day prior to ovulation. Thus, like the findings in the short-term studies, the data from the study by Reichman and colleagues, which showed that alcohol increased plasma estradiol levels only during the peri-ovulatory period, suggest that this increase occurs when luteinizing hormone is present. Short-term experimental results suggest that alcohol does not affect the level of luteinizing hormone (*2,3*); whether the study by Reichman et al. confirms this conclusion is unclear because the luteinizing hormone results were not presented. The short-term results are also consistent with the hypothesis that alcohol augments follicle-stimulating hormone induction of increased estradiol levels. However, Reichman and co-workers' finding of a peri-ovulatory plasma estrogen increase and the much higher levels of peri-ovulatory luteinizing hormone compared with peri-ovulatory follicle-stimulating hormone more strongly supports the importance of an alcohol–luteinizing hormone interaction.

Mendelson et al. (*2*) have proposed an explanation for the ethanol-induced rise in estradiol in short-term experiments: The increase occurs because alcohol elevates the ratio of reduced nicotinamide-adenine dinucleotide to oxidized nicotinamide-adenine dinucleotide (NAD^+) in hepatocytes, and therefore, less estradiol is converted to estrone by an NAD^+ dependent reaction. The net result is an increase in estradiol levels.

While this theory is supported by biochemical evidence, does it account for all the observations now at hand? The NAD^+ depletion theory, if operative within several hours after alcohol is completely metabolized, predicts an increase in the ratio of plasma estradiol to estrone. In the study by Reichman et al. (*1*), the ratio remained essentially unchanged, and plasma estradiol and estrone levels both increased. In addition, the NAD^+ depletion theory does not explain why plasma estrogens increased only during the peri-ovulatory phase of the cycle. In other investigations (*5-8*), a large single dose (45-65 g) of alcohol given in the follicular or luteal phase (when luteinizing hormone levels are low) increased estradiol in just two (*5,7*) of the four studies, whereas alcohol given with luteinizing hormone increased estradiol in three of three studies (*2-4*). As noted above, the results obtained by Reichman et al. also suggest an alcohol–luteinizing hormone interaction. Thus, an as yet unidentified mechanism consistent with what may be an alcohol–luteinizing hormone interaction might better account for the observations than the NAD^+ depletion theory.

The consumption of alcoholic beverages among younger women has been associated with increased risk of both premenopausal and postmenopausal breast cancer, although the results are inconsistent (*9*). Alcohol consumption among postmenopausal women, however, may be more strongly related to risk than consumption earlier in life (*10*).

In non-alcoholic, postmenopausal women, alcohol consumption has been associated with altered estrogen metabolism in two cross-sectional studies. Gavaler and Van Thiel (*11*) found that the serum estradiol concentration in drinkers (mean intake, 9 g/day) was 60% greater than in abstainers ($P<.05$). Katsouyanni et al. (*12*) found that one alcoholic drink daily was associated with a 20% increase in urinary estrone and a 16% increase in urinary estradiol ($P<.05$ for both). However, in one additional cross-sectional study (*13*) in postmenopausal women, alcohol consumption was not associated with increased estrogen levels. London et al. (*14*) examined the association of plasma estrogen levels with alcohol intake in a cross-sectional study of peri-menopausal women and found no relationship. Thus, in non-alcoholic postmenopausal women, results regarding alcohol consumption and estrogen levels are mixed. Moreover, if alcohol influences estrogen levels in postmenopausal women, the mechanism may differ from that in premenopausal women.

If one assumes that alcohol consumption has an effect on hormone levels in women, does this assumption establish a mechanism by which alcohol might increase risk of breast cancer? Exposure to endogenous estrogens probably is the key causal factor in breast cancer (*15,16*), yet the evidence relating blood and urine estrogen levels to risk is not entirely consistent. For example, in premenopausal women, plasma estradiol levels in breast cancer patients compared with control subjects showed a statistically significant excess in just two of 13 studies [reviewed in (*16*); see also (*17,18*)].

*See "Notes" section following "References."

An effect of estrogen in these studies, if any, would have been attenuated because frequently just one blood sample from each subject was used to characterize premenopausal exposure—an insufficient number of samples for accurate measurement. In postmenopausal women, a role of estrogens is more strongly supported. In particular, greater risk of breast cancer in postmenopausal women with an increased proportion of free plasma estradiol has been found by virtually all investigators (*16*). Also, elevated serum dehydroepiandrosterone or dehydroepiandrosterone sulfate has been implicated as a risk factor for breast cancer in several recent studies (*19,20*), although the evidence is inconsistent (*21*). The relationship of hormone levels to risk of breast cancer should become clearer as data become available from large prospective studies with careful measurement of hormone levels.

A dose–response relationship between alcohol and hormone levels is plausible. Alcohol is distributed throughout the aqueous phase of the body; i.e., its volume of distribution is total body water (*22*). Total body water is related to both height and weight. Given the variation in height (SD = 6.6 cm) and weight (SD = 12.5 kg) among subjects in the study by Reichman et al. (*1*), the dose of alcohol the subjects received in grams per day per liter of total body water, which may be more physiologically relevant, must have varied. However, these doses were probably too similar to define a dose–response curve, especially with only 34 subjects. The generalizability of Reichman et al.'s findings to the majority of drinking women is not known. Less than 3% of American women drink 30 g of alcohol daily (*23*). Further, women who abstain in the peri-ovulatory phase of the cycle may not have an increase in estradiol.

As epidemiologic data on alcohol and breast cancer accumulate, the evidence for a subtle dose–response relationship appears to be getting stronger (*9*). Yet the relationship is, on average, so modest (*24*) that whether alcohol consumption causes breast cancer will be difficult to determine with epidemiologic data of the type now available. Until innovative uses of the epidemiologic approach allow a definitive assessment of the issue (if ever), major advances in thinking about causality are likely to be based on mechanistic evidence, such as that provided by Reichman et al. (*1*).

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Notes

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