

**ALCOHOL ASSOCIATION WITH BREAST CANCER: POSSIBLE
MECHANISMS
TABULATED DATA ON PLASMA AND URINARY SEX HORMONE LEVELS**

Introduction

This brief report is a summary and tabulation of data on the effects of alcohol on plasma and urinary sex hormone concentrations. It quantifies information already provided in the report “Alcohol Association with Breast Cancer: Possible Mechanisms” (CC/99/8). The data are presented in tabular form in Appendix 1.

Endogenous hormone levels

Most breast cancer has a hormonal aetiology (see Key and Pike, 1988), and any effects of alcohol on the endogenous hormonal milieu in women could provide a potential mechanism for carcinogenesis. Alcohol increases endogenous oestrogen levels in pre- and postmenopausal women (Reichman *et al.*, 1993; Ginsburg *et al.*, 1995), and elevated levels of oestrone sulphate, a long-term indicator of oestrogen levels, have been demonstrated in women who regularly consume alcohol (Hankinson *et al.*, 1995).

Several studies have examined the relationship between alcohol intake and serum oestrogens and other hormones. Such studies have generally been carried out in postmenopausal women. Women are also frequently exposed to exogenous oestrogens in the form of oral contraceptives (OCs) and hormone replacement therapy (HRT), and the effects of alcohol ingestion in these women are discussed in subsequent sections.

Premenopausal women

Four studies on the relationship between alcohol intake and serum sex hormone levels are described in Appendix 1. Three of the four studies demonstrated a positive relationship between alcohol consumption and serum oestradiol levels, while one found no relationship with plasma oestrogens, but a positive correlation with plasma androstenedione levels.

Reichman *et al.* (1993) undertook a controlled-diet study lasting for six consecutive menstrual cycles. Participants were randomly assigned to two groups and a crossover design was used. During the last three menstrual cycles, alcohol consumption of the two groups was reversed. In all, 34 premenopausal women, aged 21-40 years, with a history of regular menstrual cycles, consumed 30 g ethanol (approximately two average drinks) per day for three menstrual cycles and no alcohol for the other three.

Alcohol consumption was associated with statistically significant increases in plasma DHEA sulphate (DHEAS), oestrone, oestradiol and urinary oestradiol. No changes were found in the percentage of bioavailable oestradiol, but increased total oestradiol levels in the peri-ovulatory phase suggested elevated absolute amounts of bioavailable oestradiol.

Dorgan *et al.* (1994) undertook a cross-sectional study in 107 premenopausal women in the USA of alcohol intake and hormonal status. Oestrone, oestrone sulphate, oestradiol, androstenedione, DHEAS and sex hormone binding globulin (SHBG) were measured in plasma. After adjusting for age, weight and total energy intake, alcohol ingestion was found not to be associated with plasma oestrogens in the follicular, midcycle or luteal phases of the menstrual cycle, nor with the levels of SHBG or DHEAS in plasma averaged from the three phases of the cycle. However, alcohol was significantly positively associated with the average level of plasma androstenedione. The authors concluded that the increased risk of breast cancer related to alcohol ingestion did not appear to be mediated by increased plasma oestrogen levels in this population, but that the alcohol/breast cancer association could be mediated via androstenedione.

Alcohol is more often unpleasant and causes tissue damage more rapidly in women than in men. Eriksson and co-workers (1996) studied the effect of acetaldehyde, the first metabolite of alcohol, on plasma hormone levels in male and non-pregnant female volunteers, aged 19-33 years. A proportion of the female subjects were taking oral contraceptives. In the overall population of women, acetaldehyde correlated positively ($r = 0.406$, $P = 0.026$) with plasma oestradiol levels. Acetaldehyde levels did not correlate with any of the other hormones measured (progesterone, testosterone or cortisol). The authors admit that acetaldehyde estimations were not entirely reliable; nevertheless, all samples were subjected to the same assay procedures and should therefore be comparable. However, the authors state that the involvement of acetaldehyde, rather than the parent compound, ethanol, in the aetiology of breast cancer is still only a tentative possibility.

In a study by Muti *et al.* (1998), alcohol intake was compared with serum oestradiol levels in 60 premenopausal women. Two blood samples were taken, 1 year apart. A significant association between alcohol intake and oestradiol levels was found when oestradiol was averaged across the two visits (Spearman's $r = 0.29$, $P < 0.05$). When intraindividual variability of oestradiol was controlled over time, women showing consistently high oestradiol levels at both visits were characterised by a significantly

higher alcohol intake (92.8 g/week) in comparison with those showing consistently low oestradiol levels at both visits (31.6 g/week). In addition, the prevalence of drinkers in the group with consistently high oestradiol was significantly higher than in the group with consistently low oestradiol. The authors concluded that alcohol intake seems to be associated with consistently higher oestradiol levels appear than in non-drinkers.

Postmenopausal women

A much larger number of studies on the effects of alcohol on hormone levels have been carried out in postmenopausal women. Three studies (Trichopoulos *et al.*, 1987, Cauley *et al.*, 1989, London *et al.*, 1991) found no association between plasma oestrogen levels and alcohol intake, but the majority found significant increases in plasma levels of oestrogens in women taking alcohol regularly, even after controlling for confounding factors.

Negative studies

In a study of 220 postmenopausal women aged 54-66 years, from Greece ($n = 99$) and the USA ($n = 121$), Trichopoulos *et al.* (1987) found no consistent association of urinary oestrogen levels (oestrone, oestradiol, oestriol or total oestrogens) with alcohol consumption.

A study by Cauley *et al.* (1989), carried out in 176 healthy postmenopausal women (mean age 58 years), examined several lifestyle factors in relation to serum sex hormone levels. They found that both oestrone and oestradiol levels tended to decline with increasing alcohol consumption, although this decline was not significant.

London *et al.* (1991), in a study of 325 healthy women in the USA aged 50-60 years who were at climacteric, investigated serum levels of oestrone, oestradiol, percent free oestradiol and SHBG in relation to alcohol and other dietary factors. Alcohol intake was not associated with concentrations of oestrogens in their study.

Positive studies

Gavaler and coworkers (1991) reported an international study of the relationship between alcohol intake and oestradiol levels in postmenopausal women. The major source of postmenopausal oestrogens is from the aromatisation of androgens, and alcohol has been reported to increase the rate of aromatisation. In a study of 128 postmenopausal women in the USA, a direct association was found between moderate alcohol consumption and serum oestradiol levels. Three comparable study populations were then recruited in Europe: 62 in Copenhagen, 34 in Lisbon and 20 in Madrid. No association was detected in the Madrid subjects, but in both the Copenhagen and Lisbon

study populations, not only were oestradiol levels increased in alcohol users compared to abstainers, they were also significantly correlated with the amount of alcohol consumed. It was concluded that the increase in oestradiol levels seen with moderate alcohol consumption is not an isolated finding. In a further analysis of the US cohort, Gaveler and Van Thiel (1992) found that among abstainers, serum oestradiol levels were 101 ± 12 pmol/l, compared with 163 ± 12 pmol/l in alcohol users, a 62% increase.

Using the same cohort of 128 US women, Gaveler and Love (1992), however, found that a relationship between alcohol intake and oestrogen levels could be demonstrated only when alcohol consumption based on the food record data was analysed; self-report data were found to be less reliable. The authors therefore advised that data based on self-reporting of alcohol consumption should be treated with caution.

Katsouyanni *et al.* (1991) determined levels of oestrone, oestradiol and oestriol in 88 postmenopausal women in relation to diet, including alcohol consumption. Alcohol intake was positively associated with urinary oestrogens (specifically oestrone and oestradiol), after controlling for energy intake, obesity and reproductive and biosocial variables.

Gaveler *et al.* (1993) were able to estimate the level of alcohol consumption associated with increases in oestrogen levels. In a comparison of alcohol-abstaining postmenopausal women with postmenopausal women with moderate alcohol intake, they showed that alcoholic beverage consumption in the range of 0.1-28 total weekly drinks produced detectable changes in oestradiol and testosterone levels.

Newcomb *et al.* (1995) examined the relationship between endogenous sex hormones and alcohol intake in a study of dietary and lifestyle factors. Oestrone, DHEAS, SHBG and free and total testosterone were measured in the serum of 253 postmenopausal women not using HRT. They found only a weak association with alcohol intake in these women. However, almost 50% of the women in this study were considered obese, and a positive association between adiposity and plasma oestrogen levels in postmenopausal women has been consistently reported (see Hankinson *et al.*, 1995, for discussion). This may have masked any effects of ethanol intake *per se*.

In the study of Hankinson *et al.* (1995), involving a cohort of 217 postmenopausal participants in the Nurses' Health Study (61.5 ± 5.0 years of age, mean \pm SD), alcohol consumption was positively associated with plasma oestrone sulphate concentrations ($r = 0.17$, $P = 0.02$), after controlling for age, height, smoking status and BMI. There appeared to be a direct relationship between the amount of alcohol

consumed per day and oestrone sulphate levels in plasma. No association was found between alcohol consumption and plasma levels of oestradiol, oestrone or prolactin. The authors concluded that the association of alcohol consumption with subsequent breast cancer risk could be mediated, at least in part, through an effect on postmenopausal plasma oestrogen levels, but that further studies would be necessary to elucidate the physiological basis for this association.

Nagata *et al.* (1997), in a study of the association of alcohol consumption with serum hormone concentrations in 61 postmenopausal Japanese women (60.5 ± 6.3 years of age, mean \pm SD), found that serum oestradiol levels showed a strong positive correlation with alcohol consumption after controlling for age ($P = 0.01$), the significance of which increased after also controlling for height and BMI ($P = 0.001$). There was also a trend for increasing serum DHEAS levels with alcohol consumption ($P = 0.01$) (see Table). There was no effect on progesterone levels, and a slight but non-significant decrease in SHBG levels. The authors concluded that, since DHEAS is an intermediate in the synthesis of oestrogens, alcohol could affect the risk of breast cancer through effects on either or both oestradiol and DHEAS.

Madigan *et al.* (1998) have related serum hormone and SHBG levels to various lifestyle factors, including alcohol intake, in 125 postmenopausal women in the USA. Oestrogens were associated positively, while SHBG was associated negatively with alcohol intake. However, these findings were significant only for plasma oestrone levels (see Appendix 1).

Prolactin

Elevated circulating prolactin levels have been suggested to be associated with breast cancer (Ginsburg *et al.*, 1995). Hankinson *et al.* (1995) found no effect of alcohol consumption on plasma prolactin levels and in postmenopausal women.

Ginsburg *et al.* (1995) reported two randomised, crossover studies to examine the effects of ethanol on prolactin levels in menopausal women using transdermal oestradiol for hormonal replacement. In study 1, transdermal oestradiol patches (0.15 mg) were administered to seven menopausal women (59.3 ± 1.7 years) on the day before ethanol administration. Prolactin levels were measured for up to 6.3 hours after alcohol intake. Serum prolactin levels were significantly higher after ethanol ingestion than after ingestion of an isocaloric carbohydrate drink ($P < 0.03$). In study 2 ($n = 8$, 58.6 ± 1.9 years), the transdermal oestradiol patches were removed after completion of ethanol or carbohydrate ingestion. Serum prolactin was again greater after ethanol ingestion than

after carbohydrate ingestion ($P < 0.001$). The authors concluded that in these women, therefore, acute alcohol ingestion was associated with an increase in serum prolactin.

Oral contraceptives

Only one study (Eriksson *et al.*, 1996) has been found where the relationship between alcohol intake and serum sex hormone levels was specifically reported in women on OCs. No overall correlations were found between acetaldehyde concentrations and those of ethinyloestradiol or other sex hormones. However, when OC users were divided into those in the use and non-use phases of the menstrual cycle, differences emerged, with significant levels appearing only during the use phase. Oestradiol and ethinyloestradiol levels were 73 ± 94 and <100 pM (OC-) and 13 ± 33 and 457 ± 319 pM (OC+), respectively.

Hormone replacement therapy

Ginsburg *et al.* (1996) sought to determine if moderate alcohol drinking increased circulating oestradiol levels in 12 postmenopausal women on HRT (54.5 ± 4.0 years of age). This group was compared with 12 postmenopausal women who were not using HRT (61.7 ± 6.4 years). Each group drank 0.7 g/kg alcohol or an isocaloric placebo on consecutive days. Alcohol ingestion led to a three-fold increase in circulating oestradiol in women on HRT, but did not change oestradiol levels significantly in control women, who were not on HRT. Blood alcohol levels did not differ significantly in women who used HRT and those who did not (21 mmol/l in both groups). The authors concluded that acute alcohol ingestion could lead to significant and sustained elevations in circulating oestradiol to levels 300% higher than those achieved in clinical use of HRT.

Conclusions

The tabulated data suggest that ingestion of alcohol is in general associated with an increase in sex hormone levels, particularly oestradiol and oestrone sulphate. This seems to hold even when data are corrected for BMI, obesity being recognised as a confounding factor in this analysis (Hankinson *et al.*, 1995; Nagata *et al.*, 1997). However, out of 13 studies looking at the effect of alcohol on oestradiol levels, only eight report a significant increase, one of which was in women on HRT only. Two report no association, and three report a non-significant trend. While these results are intriguing and should be examined further, they do not yet confirm a causal association between alcohol ingestion and increased serum sex hormone levels.

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APPENDIX 1

ALCOHOL AND BREAST CANCER: MECHANISMS

Alcohol effects on **plasma** hormone concentrations

Premenopausal women

Author	DHEAS	Oestrone	Oestradiol	SHBG	Androstenedione
Reichman <i>et al.</i> (1993)	7% increase $p < 0.05$	21% increase $p < 0.01$	27% increase $p < 0.01$	4% decrease	
Dorgan <i>et al.</i> (1994)	No association	No association	No association		27% increase (CI 5.6-53.5)
Eriksson <i>et al.</i> (1996) (acetaldehyde)			Positive association $r = 0.4, p = 0.026$		
Muti <i>et al.</i> (1998)			18% increase $p < 0.05$		

Postmenopausal women

Author	DHEAS	Oestrone	Oestrone sulphate	Oestradiol	SHBG	Prolactin	Testosterone	Androstenedione
Cauley <i>et al.</i> (1989)		Decrease ($F = 1.39, p = 0.24$)		Decrease ($F = 3.59, p = 0.06$)			No change ($F = 0.64, p = 0.42$)	No change ($F = 1.67, p = 0.28$)
Gavaler <i>et al.</i> (1991) USA Madrid Copenhagen Lisbon				Positive association No association Positive association Positive association (all reported as significant)				

Author	DHEAS	Oestrone	Oestrone sulphate	Oestradiol	SHBG	Prolactin	Testosterone	Androstenedione
London (1991) (n = 325)		No association		No association				
Gavaler and Love (1992) (n = 128)				62% increase ($p < 0.01$, 2-tailed)				
Gavaler and Van Thiel (1992) (same cohort as above)				62% increase ($r < 0.255$)			15% decrease ($r < 0.175$)	
Gavaler <i>et al.</i> (1993) (same cohort as above)				61% increase			15% decrease	
Ginsburg <i>et al.</i> (1995)						Increase $p < 0.03$		
Hankinson <i>et al.</i> (1995)		No association	33% increase with ≥ 2 drinks per day $r = 0.17$, $p = 0.05$	No association		No association		
Newcomb <i>et al.</i> (1995)	Pearson correlation coefficient 0.077	Pearson correlation coefficient 0.018			Pearson correlation coefficient -0.059		Pearson correlation coefficient 0.022	
Ginsburg <i>et al.</i> (1996)		Decrease in women on HRT $p < 0.05$		228% increase ONLY in women on HRT $p < 0.001$				
Nagata <i>et al.</i> (1997)	65% increase $p < 0.01$ for trend			110% increase $p < 0.01$ for trend	17% decrease $p = 0.25$ for trend			
Madigan <i>et al.</i> (1998)		33% increase $p = 0.02$	42% increase $p = 0.37$	18% increase $p = 0.17$	15% decrease $p = 0.45$			23% increase $p = 0.39$

Alcohol effects on urinary hormone concentrations

Premenopausal women

Author	DHEAS	Oestriol	Oestrone	Oestradiol	Androstenedione
Reichman <i>et al.</i> (1993)		29% increase $p < 0.03$	15% increase $p < 0.05$	32% increase $p < 0.009$ (peri-ovulatory phase) 22% increase $p < 0.02$ (luteal phase)	

Postmenopausal women

Author	DHEAS	Oestriol	Oestrone	Oestradiol	Androstenedione
Trichopoulos <i>et al.</i> (1987)		-7% decrease (CI -20, +8)	0% increase (CI -11, +13)	-2% decrease (CI -14, +11)	
Katsouyanni <i>et al.</i> (1991) (n = 88)		15% (95% CI -5, +40)	20% increase (95% CI 4, 38)	16% increase (95% CI 2, 31)	