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Review

Estrogen, alcohol and breast cancer risk ☆

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Abstract

Estrogen replacement has been used for many years to reverse the hypoestrogenic symptoms of menopause and prevent osteoporosis. Studies have found that estrogen replacement also decreases cardiovascular risk. In addition, social use of alcohol has been found to decrease cardiovascular risk. Therefore, both estrogen replacement therapy and alcohol use have been proposed to have cardiovascular benefits, and are often used in combination. Epidemiologic evidence indicates that estrogen replacement therapy after menopause increases breast cancer risk. Regular alcohol consumption is also associated with increase in risk. However, interactions between the two are poorly understood. In addition, if alcohol alters circulating estrogen levels in estrogen users, this may have implications in terms of altering the risks:benefit ratio of estrogen replacement in an undesirable direction. For example, there are data suggesting that the use of both alcohol and estrogen may increase breast cancer risk more than the use of either one alone. Data support both acute and chronic effects of alcohol in raising circulating estrogen levels in premenopausal women on no hormonal medications. In postmenopausal women studies focusing on acute effects of alcohol on estrogen metabolism indicate that alcohol has a much more pronounced effect in women using estrogen replacement than in those who do not. Studies evaluating chronic effects of alcohol ingestion on circulating estrogens in postmenopausal women are needed.

Keywords: Estrogen; Estradiol; Estrogen replacement therapy; Estrogen metabolism; Breast cancer; Alcohol

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1. Introduction

The incidence of breast cancer appears to be increasing, and the reason for this is unclear. Research efforts

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Table 1
Summary of breast cancer relative risks with alcohol ingestion (cc = case control study, n = number of cases)

Author	Grams EtOH/day or (drinks/day)	Relative risk (95% CI)
Smith-Warner [35], pooled cohort	10 g	1.09 (1.04–1.13)
	30 < 60	1.41 (1.18–1.69)
Royo-Bordonada [44], cc, (n = 315)	1.7	1.0 (0.60–1.67)
	6.0	1.01 (0.60–1.73)
	20	1.18 (0.69–2.03)
Longnecker [32], cc, (n = 6662)	12–18	1.39 (1.16–1.67)
	19–32	1.69 (1.36–2.10)
	33–45	2.30 (1.51–3.51)
	> 45 g	1.75 (1.16–2.64)
Friedenreich [31][a], cc, (n = 519)[b]	0 < 10	1.11 (0.71–1.71)
	10 < 20	1.37 (0.79–2.36)
	20 < 30	1.51 (0.80–2.86)
	> 30	1.86 (0.96–3.66)
Ferraroni [45], cc, (n = 214)[b]	0.1–5	1.1 (0.5–2.2)
	5–13	1.5 (0.8–2.8)
	13–24	1.2 (0.6–2.4)
	≥ 24	2.1 (1.1–3.9)
Sneyd [46], cc, (n = 891)[b]	< 14 drinks/wk	0.91 (0.51–1.6)
	≥ 14	1.8 (0.87–3.8)
Zaridze [47][b]	Any	3.39 (1.37–8.38)
Simon [48], cohort[b]	(≥2)	1.12 (0.25–5.01)
Howe [34], pooled cc[b]	≥ 40	1.69 (1.19–2.40)
Chu [49], cc, (n = 5382)[b]	1–3 drinks/wk	1.0 (0.8–1.2)
	4–7	0.9 (0.7–1.1)
	8–14	1.1 (0.9–1.3)
	15–21	1.0 (0.8–1.4)
Hiatt [50], cohort[b]	1–2 drinks/day	1.5 (1.0–2.3)
	3–5	1.5 (0.8–2.8)
	≥ 6	3.3 (1.2–9.3)
	≥ 22	1.2 (0.9–1.6)
Rohan [51], cc, (n = 451)	9.3	1.57 (0.99–2.51)
LaVecchia [52], cc, (n = 437)	(1–3 drinks/day)	1.24 (0.9–1.69)
	(> 3 drinks/day)	1.93 (1.17–3.17)
Nasca [53], cc, (n = 1617)[b]	15	1.37 (1.07–1.75)
Schatzkin [30], cohort[b]	0–1.2	1.4 (0.8–2.5)
	1.3–4.9	1.6 (0.9–3.1)
	≥ 5	2.0 (1.1–3.7)
Schatzkin [54], cohort[b]	0.1–1.4	0.7 (0.4–1.4)
	1.5–4.9	1.1 (0.7–1.8)
	≥ 5.0	0.8 (0.5–1.2)
Willett [55], cohort	5–14	1.3 (1.1–1.7)
	≥ 15	1.6 (1.3–2.0)
Harris [56], cc, (n = 1467)[b]	> 15	0.93
Harvey [57], cc, (n = 1524)[b]	≤ 1 (drink/day)	1.06 (0.9–1.3)
	> 1–2	1.31 (1.0–1.7)
	> 2	1.66 (1.2–2.4)
O'Connell [58], cc, (n = 276)	≥ 1 (drink/week)	1.45 (0.99–2.56)
Le [59], cc, (n = 500)[b]	≤ 80 g/wk	1.19 (NS)
	80–159	1.77 (P = 0.02)
Webster [60], cc, (n = 1226)[b]	Any	1.0 (0.8–1.2)

[a] Premenopausal women only.
[b] No ERT use data reported.

have focused on improved diagnosis and treatment rather than prevention. Women are increasingly health conscious and many use estrogen replacement therapy to decrease risks of heart disease and osteoporosis [1]. Alcohol ingestion may also have cardioprotective effects [2,3], and daily drinking has been suggested by some to decrease the incidence of coronary heart disease. Of concern are epidemiologic data indicating that daily alcohol consumption is associated with increased breast cancer risk (Table 1). Estrogen replacement therapy is also associated with increased breast cancer risk in the majority of large case control and cohort

Table 2
Selected papers: estrogen replacement therapy and relative risk of breast cancer (cc = case control study, n = number of cases)

Author	ERT long term	ERT ever	ERT current	ERT and alcohol
Colditz [5], cohort	0.7 (0.45–1.1)		1.36 (1.11–1.67)	1.56 (1.2–2.0)
Gapstur [4], cohort				1.88 (1.30–2.72)
Smith-Warner [35], pooled cohort				1.06 (0.98–1.16), (10 g EtOH/d only)
Bergkvist [43], cohort	1.7 (1.1–1.7)	1.1 (1.0–1.3)		
Wingo [61], cc[a], (n = 1369)	1.2 (0.6–2.3)	1.2 (0.9–1.6)		
Brinton [62], cc[a], (n = 1960)	1.28 (0.9–1.6)	1.03 (0.9–1.2)		
Sellers [39], cohort[a,b],	1.17 (0.9–1.51)		1.35 (0.72–2.53)	
Tavani A [63], cc[a], (n = 5984)	1.6 (1.1–2.3)	1.2 (1.0–1.4)		
Persson [64], cc[a], (n = 435)	2.1 (1.1–4.0)			

[a] Alcohol use not included in model as possible confounding variable.
[b] With family history of breast cancer.

studies (Table 2). There is also evidence suggesting that the combination of estrogen replacement and alcohol may increase breast cancer risk much more than either one alone [4,5]—that the risks may be additive. Possible biological mechanisms for this are as yet unknown. Animal data indicate that alcohol both promotes growth of mammary tumors, and causes estrogen-like biological effects in rats. Preliminary investigations in women indicate that alcohol may well impact estrogen metabolism in pre and postmenopausal women.

1.1. In vitro effects: estrogen and alcohol effects in vitro

Epidemiologic studies indicate that duration of estrogen exposure impacts breast cancer risk. In vitro estradiol treatment of estrogen receptor positive cancer cell lines leads to modulation of growth factors associated with tumor growth [6]. Women with breast cancer have been reported to have an increase in 16-α hydroxylase activity. It appears that the 16-α hydroxyestrogens resulting from 16-α hydroxylation of estradiol leads to proliferation of breast cancer cell lines [7]. Treatment of mouse mammary cell lines with 16-α-hydroxyestrone (in high concentration) causes a marked increase in DNA repair synthesis, proliferative activity, and rapid growth of colonies, suggesting that it may function as an initiator of preneoplastic transformation [8].

1.2. Animal studies: estrogen, alcohol and mammary cancer

Female rats fed drinking water containing 5% ethanol have increased uterine weights compared to controls, indicating that alcohol may increase endogenous estrogen production [9]. Alcohol may decrease the latency period before breast cancer growth. In rats bred to develop mammary tumors, those given 12% ethanol as compared to controls given water developed tumors at a median of 8 months as compared to 14.2 months in controls. The incidence of tumors in both groups was not significantly different [10]. It has been hypothesized that chronic ingestion by rats modulates the metabolic activation by pre-carcinogens to their reactive intermediates by redistribution of cytochrome P-450 isoenzymes [11].

2. Effects of alcohol on circulating estrogen levels in premenopausal women

Mendelson et al. found that acute ingestion of a vodka based punch (0.7 g/kg ethanol) raised circulating estradiol levels by 55–66% in women in the follicular phase of the menstrual cycle [12]. When the same dose of alcohol was given in the luteal phase or when blood samples were integrated and analyzed only every 20 min [13,14], no significant change was reported. It was unclear whether this effect was mediated by gonadotropins, since no clear effect of alcohol on gonadotropin secretion has been identified.

A study of 107 premenopausal women found no association between random circulating estrogens (estradiol, estrone, estrone sulfate) and the amount of alcohol drinking reported [15]. An elegant study by Reichman et al. took this one step further and evaluated the effects of chronic alcohol drinking in a controlled study. Thirty premenopausal women were randomized to receive either a 30 g alcohol (approximately equal to 2 drinks) or placebo beverage nightly at home for 3 months and then crossed over to the other treatment arm. Blood and urine samples were measured during the last month of each treatment arm. After the chronic alcohol consumption, midcycle estradiol levels increased by 27.5%, plasma estrone by 21% and urinary estradiol increased by 31.9% as compared to after placebo drink ingestion months [16]. In the luteal phase urinary estradiol, estrone and estriol were also higher (by 21.6, 15.2 and 29.1%, respect-

ively). All these differences were statistically significant. Interestingly, plasma DHEAS was higher in the follicular phase of the menstrual cycle, but estrogens were not.

3. Alcohol effects on estrogen levels in postmenopausal women

In ERT users acute alcohol consumption causes rapid and pronounced changes in circulating estradiol. In a study of 12 women using transdermal estradiol there was an acute increase in circulating estradiol levels with the area under the curve 40% higher than after placebo drink ingestion (Fig. 1) [17]. In addition, there was an associated slight decline in estrone levels. The time course of the estradiol changes was remarkably similar to Mendelson's study in premenopausal women. In another study twelve subjects were studied after alcohol and placebo drink ingestion and the transdermal patch removed in order to evaluate half-life of estradiol. The half-life of estradiol was significantly longer after alcohol than after placebo ingestion (378 vs 245 min), indicating that metabolic clearance was diminished (Table 3) [18].

The effect of acute alcohol ingestion on postmenopausal women using oral estrogen has also been evaluated. There was a dramatic increase in circulating estradiol levels within 10 min after drinking began in women using oral estradiol therapy (1 mg/day). Estradiol levels peaked 50 min after drinking began, and blood alcohol peaked 60 min after the start of drinking. The increase in estradiol levels was greater than 300% above baseline, and remained significantly elevated over the 6 h study (Fig. 2) [19]. Estradiol levels did not increase after placebo drink ingestion in this study or in those using transdermal estradiol. All of these studies are limited by the fact that the alcohol drink was given rapidly (over 15–20 min) in a fasting state. The mechanism behind these changes is unclear. Increased absorption from the skin due to the vasodilation with alcohol intake [20] could increase estradiol delivery with transdermal use and increased intestinal absorption after oral estradiol use [21] are possible mechanisms, but do not explain the decrease in estrone levels seen after oral estradiol use. In addition, a similar effect occurs in premenopausal women [12], indicating that altered estrogen metabolism is probably also occurring. In addition there are data supporting the hypothesis that acute alcohol ingestion alters metabolism of various compounds due to alterations in hepatic redox potential [22].

Table 3
Half-life (T 1/2) and area under the curve (AUC) data for the 8 study subjects

Subject No.	T1/2, min	AUC
1	144	18,786
2	124	14,515
3	107	14,965
4	156	19,030
5	221	23,785
6	165	22,159
7	157	23,087
8	217	19,070

Alcohol does not appear to have marked acute effects on circulating estradiol or estrone levels in normal weight postmenopausal women who do not use ERT [19]. However, here are data indicating that basal estradiol levels are increased in postmenopausal women who drink alcohol as compared to abstainers: Gavaler et al. obtained blood samples from 164 postmenopausal women and found that estradiol levels were significantly higher in women who consumed alcohol (average 4.8 drinks/week) than in those who did not (100.8 vs 162.6 pmol/l). This study suggests that chronic alcohol intake leads to chronic changes in circulating estradiol levels [23].

Hankinson et al. evaluated estrogen levels in stored plasma from 217 postmenopausal women in the Nurses' Health Study. After adjustment for possible confounders estrone sulfate levels were positively as-

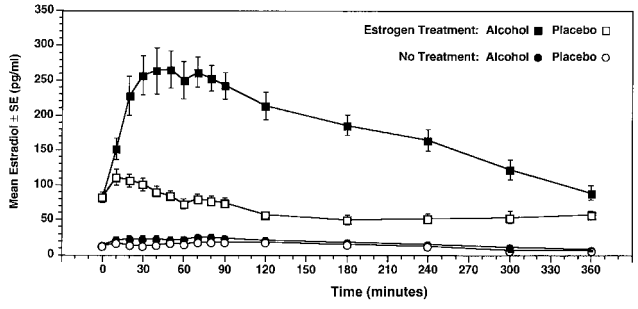

Fig. 1. Plasma alcohol levels after placebo and alcohol drink ingestion in estrogen users and non-users.

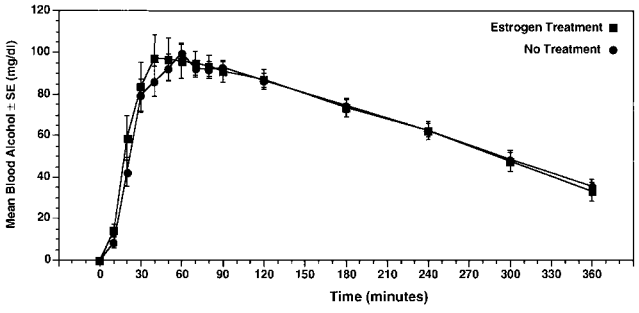

Fig. 2. Estadiol levels after placebo and alcohol drink ingestion in estrogen users and non-users.

sociated with alcohol consumption ($r = 0.17$, $P = 0.02$) Mean estrone sulfate levels were 159 pg/ml in abstainers and 211 pg/ml in 20 women who consumed 30 g alcohol per day. Even after these women were excluded from analysis, however, estrone sulfate remained positively correlated with alcohol intake. Interestingly, total and free estradiol, estrone and estrone sulfate levels were all independently positively correlated with body mass index. Weight gain of > 20 kg after age 18 increases postmenopausal breast cancer risk in women who do not use postmenopausal ERT (RR 1.99, CI 1.43–2.76) [24]. Given the previous findings, this may well due to higher circulating estrogen levels in obese women. Obese ERT users have higher estrogen levels, perhaps masking BMI as an independent risk predictor. In addition, women with higher bone density, perhaps a marker for integrated estrogen exposure, have higher breast cancer risk than women with low bone density [25]. These data support the epidemiologic findings that obesity (perhaps due to elevated circulating estrogens) and alcohol ingestion increase breast cancer risk. In addition, the increase in estrone sulfate, the estradiol metabolite in highest concentration in the circulation, would be the expected result from repetitive acute perturbations in estradiol and /or estrone metabolism. As noted previously, when alcohol was acutely administered to postmenopausal women using no estrogen replacement, the small increases in estradiol seen after alcohol ingestion did not reach statistical significance [19]. Changes in estrone sulfate would be difficult to measure acutely since it is present in very high concentrations and has a half-life of over 5 h.

Older studies are contradictory. Plasma estradiol [26] and urinary estrogens [27] have been associated with alcohol use in some studies, but not related to estrone [28] or estradiol [29] in others. The lack of consistency may be related to the alcohol doses used, frequency of blood sampling, and assays used.

4. Breast cancer, estrogen and alcohol

There is still debate currently about whether breast cancer risk is increased by regular alcohol ingestion. Unfortunately, well done case control and cohort studies use a variety of somewhat arbitrary cutoffs used in assessing levels or 'doses' when assessing amounts of alcohol consumed. This can make it difficult to know what amount of alcohol consumption actually does increase risk, and whether any particular type of alcohol is more problematic. At this point these questions have not been fully answered. As few as three alcohol drinks per week (5 g/day) have been associated with a relative risk of breast cancer of 2.0 [30]. However, the majority of studies have found that only higher levels of consumption are significant, and one large cohort study that found a significant dose dependent risk in premenopausal but not postmenopausal breast cancer (Table 1) [31]. A very large case control study found a significant dose response effect between the amount of alcohol consumed and breast cancer risk, but found that only alcohol consumption after the age of 30 was an important risk determinant [32]. It is also possible that breast cancer mortality might be higher in women drinking more than one drink daily [33]. There does appear to be a dose response effect, with the relative risk increasing with the average amount of alcohol consumed. The weight of the evidence suggests that daily ingestion of two or more alcohol drinks daily, i.e. 6 oz glass of wine = 1 can of beer = 1 oz of spirits increases the relative risk of breast cancer. There is a trend suggesting that lower doses may have an effect, however in many studies (especially the smaller case control studies) confidence levels overlap 1 (Table 1). Methodological problems are common, including the lack of reporting information about other breast cancer risk factors such as estrogen replacement therapy [34] (Table 1). A recent pooled analysis of fix large cohort studies had enormous statistical power to answer this question. The authors found a significant dose response effect with one or more drinks per day increasing breast cancer risk by 9%, and 2–5 drinks/ day (30–60 g/day or more) increasing it by 41% (Table 1) [35].

5. Postmenopausal estrogen replacement therapy and breast cancer

How well has estrogen been linked to breast cancer risk? The fact that men rarely develop breast cancer has led to the assumption that estrogen exposure contributes to risk. Early menarche and late menopause, both of which are independent risk factors for breast cancer, increase lifetime estrogen exposure.

Adipose tissue directly adjacent to breast cancers has been found to display increased estrogen biosynthesis [36]. In vitro data show that estrogen modulates growth factor production by breast cancer cell lines, and may itself cause proliferation [6]. These data have been used to explain the finding that in about half of premenopausal breast cancers estrogen receptors are negative. There are data suggesting that free estradiol levels may be higher in postmenopausal women with breast cancer than in controls but studies are small and uncontrolled for many confounders [37].

Interestingly, despite the fact that large studies have found that estrogen replacement after menopause is associated with modest increases in breast cancer risk, this has not been generally acknowledged by the medical community. The most convincing data come from

the large cohort studies, however relative risk estimates vary greatly when one looks at case control studies, some of which are very small and poorly done (Table 2). Meta-analyses can be helpful to sum findings. The meta-analysis by Steinberg shows a RR of 1.3 (1.2–1.6) after 15 years of use, with a significant increase in risk seen after 5 years of use [38]. The relative risk was 3.4 (2.0–6.0) for estrogen users with a family history of breast cancer. A recent study found that life expectancy was increased in all estrogen users except those with relatives with a family history of breast cancer [39]. However others have not confirmed this. It is important to emphasize the fact that unfortunately many studies take few potential confounders into consideration in multivariate analyses, possibly accounting for the widely discrepant findings between studies. It is unclear whether the Women's Health Initiative which is randomizing postmenopausal women to estrogen or placebo will have the power to answer this question definitively.

6. Postmenopausal estrogen replacement, alcohol and breast cancer risk

What of the combination of estrogen use and alcohol ingestion? There are two studies suggesting that the use of both may increase breast cancer risk more than either alone [4,5]. Unfortunately, as previously noted many studies evaluating the effect of alcohol on breast cancer risk do not take postmenopausal estrogen use into account, and by the same token studies focusing on estrogen's impact on relative risk do not account for alcohol use (Table 2) [40]. An interesting question arising from the apparent increase in estrogen levels caused by acute and perhaps chronic estrogen levels in women using ERT is whether the level of circulating estrogens reached has an effect. In other words, if estrogen levels are repeatedly elevated in ERT users who use alcohol, is the higher 'dose' of estrogen that results harmful in terms of causing breast cancer. In a recent editorial, Zumoff proposed that estrogen levels modulate breast cancer risk in individuals with particular genotypes, or dietary or exposure history, accounting for the discrepant findings in the literature, as well as the biological interactions documented with concurrent estrogen and alcohol use [41]. The question of whether ERT in women with a family history of breast cancer increases breast cancer risk more than in women without a family history is still unanswered also. Studies still have contradictory findings, with some showing no increased risk in ERT users with a family history (mother, sister or daughter) as compared to never users of ERT [39].

This question cannot be fully answered at this time. The Nurses' Health Study, the study with the largest cohort of postmenopausal women followed to date still has insufficient power to answer this question because the vast majority of women using ERT use 0.625 mg of conjugated equine estrogens (Premarin). In addition, there are insufficient data to answer the question of whether non-oral routes of ERT confer the same relative risk of breast cancer as do conjugated estrogens, or whether other oral forms confer the same or different risk. There is more to this puzzle than circulating estrogen levels alone. For example, smokers who use ERT have lower circulating estrogen levels than do non-smokers, but do not have lower risks of breast cancer [42]. Whether components or metabolites of nicotine or other components of cigarette smoke may have other carcinogenic effects in the breast is unknown. In fact, interactions between hormones, and other medications with each other or with other commonly encountered substances in the environment and diet have not been well studied. The question of whether estrogen–progestin replacement therapy increases breast cancer risk more (or less) than does estrogen alone is still unanswered as there is little consensus among studies [43]. As we look more deeply into the epidemiology of breast cancer additional associations are found that require basic science research to elucidate possible mechanisms, and ultimately to confirm or refute causality.

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