Breast Cancer Research

RESEARCH Open Access

Effect of daily alcohol intake on sex hormone levels among postmenopausal breast cancer survivors on aromatase inhibitor therapy: a randomized controlled crossover pilot study

Elizabeth Mostofsky[1*], Julie E. Buring[1,2], Steven E. Come[3], Nadine M. Tung[4], Cancan Zhang[3] and Kenneth J. Mukamal[1,3]

Abstract

Background Alcohol intake is associated with a higher risk of estrogen receptor-positive (ER+) breast cancer (BC), presumably through its confirmed ability to increase sex hormone levels. Whether consuming alcohol within the recommended limit of one serving per day increases sex hormone levels among postmenopausal women taking aromatase inhibitors (AI) to inhibit estrogen production remains unknown. Therefore, we compared sex hormone levels following white wine to levels following white grape juice among ER + BC survivors taking AIs.

Methods In this 10-week randomized controlled two-period crossover trial conducted from September 2022 to July 2023 among 20 postmenopausal women on AIs, we examined within-person changes in sex hormone levels following 3 weeks of 5 ounces of white wine daily versus 3 weeks of 6 ounces of white grape juice daily, with each drinking period preceded by two-week washouts and drinking period sequence allocated by randomization.

Results All 20 participants completed the trial. Compared to daily grape juice, daily wine led to decreases in total estradiol (11.1%, 95%confidence interval[CI] -49.8%,57.2%), free estradiol index (0.7%, 95%CI -2%,0.7%), and free estradiol concentration (7.7%, 95%CI -48%, 63.9%) but increases in estrone (13.8%, 95%CI -9.5%,43.1%), dehydroepiandrosterone sulfate (DHEAS; 11.4%, 95%CI -3.3%,28.4%), and testosterone (12.6%, 95%CI -0.8%,27.7%) and decreased sex hormone-binding globulin (SHBG; -2.7%, 95%CI -21.9%,21.2%).

Conclusions Five ounces of white wine daily did not lead to statistically significant increases in estradiol, but it led to changes in other sex hormones suggesting higher BC risk. Whether this level of alcohol intake diminishes AI effectiveness warrants further investigation.

Trials Registration Clinicaltrials.gov NCT05423730 registered June 14, 2022.

Keywords Alcohol, Ethanol, Estrogen receptor-positive (ER+) breast cancer, Sex hormones, Aromatase inhibitors, Crossover trial, National Health and Nutrition Examination Surveys (NHANES)

*Correspondence:
Elizabeth Mostofsky
elm225@mail.harvard.edu

Full list of author information is available at the end of the article

Background

At least half of American women drink alcohol [1], and their alcohol intake has increased in recent years [2, 3]. Even when consumed within the recommended limits of up to one drink per day, it is associated with a dose-dependent risk of developing estrogen receptor-positive (ER+) breast cancer (BC), the most common cancer among women. Each 10 g (~1 drink) increase in daily alcohol intake is associated with a 10% higher rate of BC incidence [4–6]. Much of this risk seems attributable to the effect of alcohol on sex steroid hormones [7–9], as the alcohol-BC association is strongest for estrogen receptor-positive (ER+) subtypes [10–14]. This has been confirmed in randomized trials reporting that alcohol increases sex hormone levels among healthy women [15–18].

Women diagnosed with ER + BC routinely receive aromatase inhibitor (AI) therapy to block estrogen production, which dramatically minimizes BC recurrence [19–21]. Whether alcohol consumption increases sex steroid hormone levels in the setting of AI intake, thus potentially diminishing the benefit of AI therapy, is uncertain, particularly since the mechanisms underlying this effect are unknown. Despite potential risk, a cancer diagnosis is not associated with long-term changes in daily alcohol intake [22, 23] among more than 4 million women in the United States who are being treated or have completed treatment for BC [24, 25].

Therefore, as a first step in addressing this question, we conducted the Alcohol and Breast Cancer (ABC) Trial, a two-period controlled randomized crossover pilot study among postmenopausal women with ER + BC on AI therapy. We tested whether sex hormones and sex hormone binding globulin (SHBG) levels vary following three weeks of white wine consumption compared to levels following three weeks of white grape juice consumption.

Methods

Study population

We sent invitation letters to women taking AIs who received outpatient care at Beth Israel Deaconess Medical Center. Participants completed the study between September 2022 and July 2023. The inclusion criteria were ER + BC, female sex at birth, postmenopausal (either natural or induced), self-reported consumption of at least one alcoholic drink per week but not more than two servings per day, currently prescribed aromatase inhibitors, and liver function results below 1.5 times the upper limit of normal within 12 months of screening. The exclusion criteria were self-reported consumption of more than two drinks per day, a previous or current history of alcohol abuse (AUDIT [26] score ≥ 8), consumption of 4 or more drinks in one day within the last 6 months, currently undergoing cytotoxic chemotherapy or radiation planned in the next two months, any surgery planned in the next two months, alcohol flushing syndrome, current use of any pharmaceutical agent contraindicated with alcohol, including warfarin, dual antiplatelet therapy, and metronidazole, hemoglobin A1c > 8% or a fasting glucose result above 180 mg/dL within 6 months of screening, unable to speak or understand English, unable to understand and provide informed consent, or uncertain ability to complete the protocol, as judged by the study team. The study was approved by the Dana Farber/Harvard Cancer Center Institutional Review Board (DFHCC 21–698) and registered at Clinicaltrials.gov (NCT05423730) on June 14, 2022. All participants provided written informed consent. We followed the Consolidated Standards of Reporting Trials (CONSORT) reporting guidelines.

Sample size

A previous crossover trial of healthy postmenopausal women [16] reported that four weeks of 15 mg of alcohol per day led to a 7% increase (SD 42%) in estrone sulfate and an 8% increase (SD 13%) in DHEA-S. Therefore, we aimed to recruit 20 participants to achieve 80% power for a 28% increase in estrone sulfate and a 9% change in DHEA-S.

Study design

We conducted a two-period randomized controlled crossover design. In this design, participants are compared to themselves at different times, with the sequence of the two treatment arms assigned by randomization (Fig. 1). To prevent a potential carryover effect of the drink in the first period affecting hormone levels in the

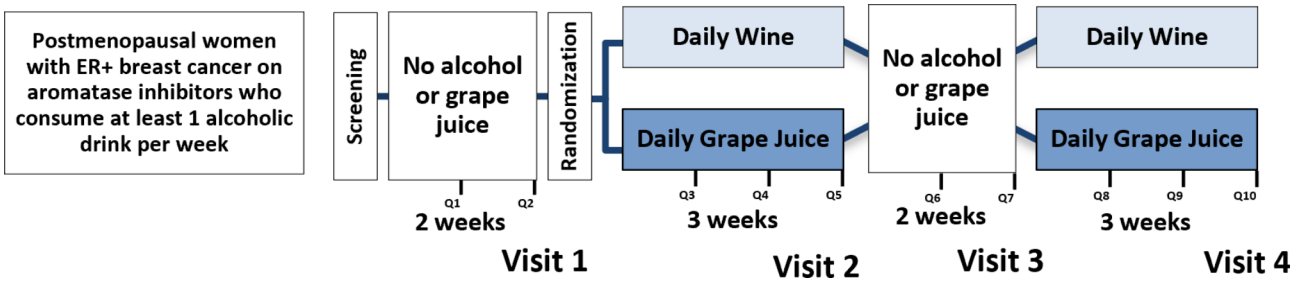

Fig. 1 Alcohol and breast cancer (ABC) crossover trial study design

second treatment period, participants refrained from drinking any alcohol or grape juice for two weeks before starting each treatment arm (washout periods). After obtaining written informed consent and confirming eligibility, participants began a two-week washout period. We randomized participants on a 1:1 basis to consume one serving (5 oz ≈ 14 g) of a commercial white wine daily for three weeks, followed by three weeks of a calorically equivalent serving (6 ounces) of a commercial white grape juice per day, or the converse. The sequence was randomly assigned using a computer-generated allocation schedule. Laboratory technicians, but not participants or clinical staff, were blinded to treatment assignment. We asked participants to drink the wine in the evening and the grape juice could be consumed at any time of day. We instructed participants to refrain from all alcohol and grape juice other than advised by the protocol and to otherwise follow their usual diet and lifestyle habits throughout the 10-week study.

Clinic visits

Participants completed four study visits, one following each washout and drinking period. The BIDMC Clinical Research Center obtained the blood samples and measured vital signs and body mass index. Part of the blood sample was immediately sent to the laboratory to assess safety measures. The remaining sample was frozen for measurement of sex hormones and SHBG once all participants completed the study. At the study visits following washout periods, we gave participants the drinks needed for the following three weeks. At the study visits following drinking periods, participants returned unused drinks, and we measured the remaining amount as an indicator of adherence to the study protocol.

Weekly assessments

A member of the study team called participants once per week to assess alcohol adherence and ask about any health concerns. Participants completed a secure weekly online questionnaire to report the number of AI pills taken that week, the short version of the Centre for Epidemiological Studies Depression Scale (CES-D 10) [27], and a visual analog scale to rate their average pain intensity over the prior week. In the surveys following the drinking periods, participants also completed the Pittsburgh Sleep Quality Index (PSQI) [28] to rate their sleep quality over the prior month. We collected and managed all screening, clinical, visit, and questionnaire data using a research electronic data capture (REDCap) [29] system, a secure, web-based application designed to support data capture for research studies.

Adherence

We assessed adherence in three ways. We called participants each week and conducted a timeline follow-back assessment [30] of alcohol and grape juice intake since the prior call. In addition, we measured unused wine and grape juice at the end of each drinking period. Finally, we measured HDL cholesterol levels that are typically positively correlated with recent alcohol consumption.

Sex steroid hormones

Following each drinking and washout period, we obtained blood samples to measure sex hormone levels including estradiol, testosterone, dehydroepiandrosterone sulfate (DHEA-S), and sex hormone-binding globulin (SHBG). Since total estradiol includes both protein-bound and unbound estradiol, we calculated free estradiol index (FEI) as total estradiol divided by SHBG. We estimated the bioavailable free estradiol concentrations using Mazer and colleagues' mathematical model accounting for estradiol's binding to SHBG and albumin [31]. The Brigham Research Assay Core Laboratory measured sex hormones and SHBG levels using liquid chromatography with tandem mass spectrometry (LC-MS/MS) certified by the HoSt Program [32]. These assays have a lower level of detection than standard approaches, which is critical when studying postmenopausal women who already have low sex hormone levels, particularly those on AIs that further suppress hormone levels. For the estradiol and estrone assays, the lower limit of quantitation was 0.5 pg/mL (linear range, 1-500 pg/mL); the intraassay coefficient of variation was less than 5%, and the inter-assay coefficient of variation was less than 12%. For the estradiol assay, the mean bias for quality control specimens provided by the Centers for Disease Control and Prevention (CDC) Hormone Standardization (HoSt) Program [33] was 0.81 pg/mL for estradiol concentrations lower than or equal to 20 mg/mL and 1.9% for specimens with estradiol concentrations higher than 20 pg/mL. The imprecision was 4.6% in HoSt Program quality control pools with concentrations ranging from 2.6 to 24.2 pg/mL, 3.8% in the concentration range of 27.7 to 39.3 pg/mL, and 3.7% in the concentration range of 39.4 to 230.0 pg/mL[34]

Statistical analysis

In descriptive analyses, we calculated counts and percentages for categorical data and medians and interquartile ranges for continuous data. For inferential analyses, we calculated the natural log of hormone and SHBG concentrations to normalize the distributions, and we exponentiated results so that treatment effects could be interpreted as relative changes. We used mixed models to examine estimates and 95% confidence intervals (CIs) of within-person changes in sex hormone and SHBG

levels by comparing responses after wine vs. grape juice, adjusted for each period's baseline levels. We included fixed terms for treatment, period, and sequence and a random effect with unstructured covariance for autocorrelation among each participant's repeated measures [35].

We assigned one-half the detection limit for estradiol values below the limit of detection; no other hormones fell below this limit. We also examined the frequency of estradiol ≥ 0.5 pg/mL and estrone ≥ 1.3 pg/mL previously shown to predict BC recurrence [36]. As sensitivity analyses, we (1) constructed Tobit models to model estradiol levels below the limit of detection; (2) parameterized models using within-person changes in hormones between the beginning and end of each drinking period; (3) excluded data for one participant with particularly high estradiol levels (likely to be nonadherent with AI therapy); and (4) excluded data for eight samples (not participants) that were hemolyzed. We performed mixed models using SAS (version 9.4; SAS Institute Inc., Cary, NC, USA). All hypothesis tests were two-tailed.

Given the small sample size of this pilot study, we conducted a preliminary analysis of the association between any current alcohol intake and estradiol levels using cross-sectional data from the 2013–2014 and 2015–2016 National Health and Nutrition Examination Surveys (NHANES). We restricted to women 50 years or older and conducted weighted linear regression comparing current drinkers to past or never drinkers, adjusted for age 50–70 versus > 70 years old (R version 4.2.2). We constructed models for women on AI therapy and women not on AI therapy and compared these associations with a test for interaction. All hypothesis tests were two-tailed.

Results

All 20 women who were randomized completed the study (Fig. 2). The baseline characteristics of the 20 postmenopausal women on AI therapy are summarized in Table 1. Participants had a median age of 61 years and a median body mass index of 24.7 kg/m^2. One-fifth of the participants were Black. Participants reported that they typically consumed alcohol on 2 to 3 days per week, and consistent with eligibility criteria, they typically consumed one drink on days that they had alcoholic beverages. There were no serious adverse events during the study.

Based on self-reported intake and measurements of leftover drinks, there were no major deviations in protocol adherence. Although alcohol intake is typically associated with higher HDL cholesterol levels, levels were similar following the wine period (median 68, IQR 56.0–80.0) and the grape juice period (median 67.5, IQR 54.5–75.5), which may be due to the high HDL cholesterol levels at baseline or the low level of alcohol intake for only three weeks.

Almost half of estradiol and estrone levels surpassed thresholds potentially indicative of BC recurrence risk, regardless of drink phase. The sex hormones and SHBG levels were not highly correlated (Table 2). Therefore, we conducted separate models to assess the independent effects of wine on each hormone. The percentage changes in log-transformed hormone levels are presented in Fig. 3. Compared to daily grape juice, daily wine led to an 11.1% decrease (95% confidence interval [CI] -49.8–57.2%) in total estradiol, a 0.7% decrease (95%CI -2–0.7%) in free estradiol index, and a 7.7% (95%CI -48%, 63.9%) decrease in free estradiol concentration. However, it led to increases in estrone (13.8%, 95%CI -9.5–43%), DHEAS (11.4%, 95%CI -3.3–28.4%), and testosterone (12.6%, 95%CI -0.8–27.7%) and decreased SHBG (-2.7%, 95%CI -21.9–21.2%). Results were similar in sensitivity analyses.

In confirmatory analyses of the cross-sectional NHANES data, we observed the expected positive association between current alcohol intake and estradiol levels among 2,849 women not taking AIs. In contrast, current alcohol intake was not associated with a meaningful change in estradiol levels among the 21 women taking AI's, with a difference between these associations that almost reached statistical significance ($p = 0.06$).

Discussion

In this pilot randomized controlled crossover trial among women taking AIs, alcohol exhibited no clear statistically significant effect on sex hormone levels, but we observed a suggestion of increased levels of estrone, DHEAS, and testosterone and slightly decreased SHBG.

We observed no clear effect of alcohol on estradiol levels either in this trial or in complementary observational analyses of NHANES. However, given the suggestion of higher levels of other sex hormones, our results overall suggest caution in the consumption of alcohol in the growing population of BC survivors using AIs.

There is strong evidence that alcohol alters sex steroid hormones among premenopausal [37] and postmenopausal [7, 8, 38] women. Several short-term feeding trials have shown that daily alcohol intake as low as one serving per day for a few weeks increased sex hormones, particularly DHEAS [15–17]. A few studies reported that acute increases in hormones in the hours after alcohol intake may only occur in the presence of a transdermal patch [39] or hormone replacement therapy [18]. Conversely, there is preliminary evidence that hormone suppressants attenuate the unfavorable effect of alcohol on sex hormones. In a cross-sectional study of 490 postmenopausal BC survivors [40], alcohol intake and sex hormone levels were strongly associated despite the relatively low

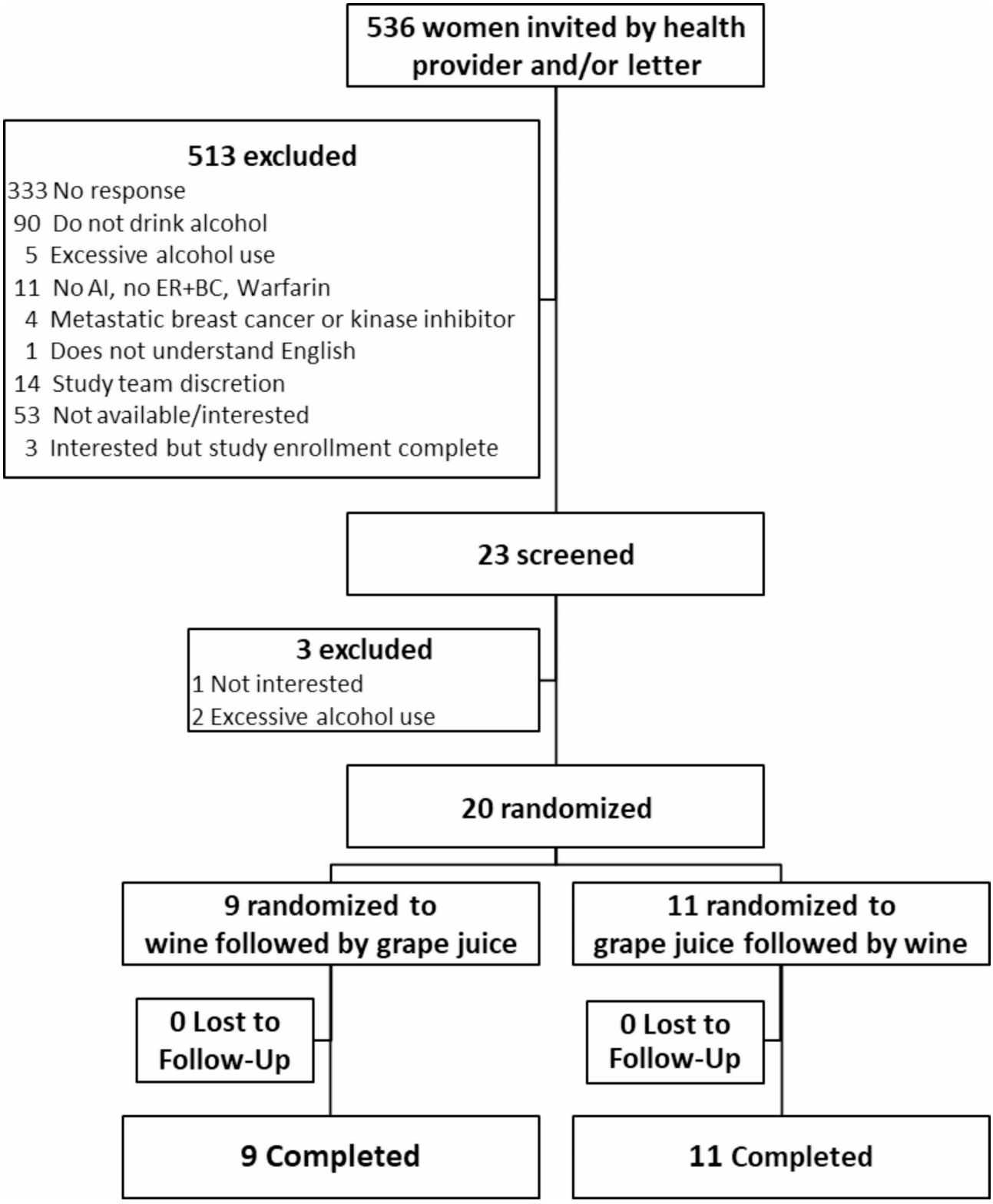

Fig. 2 Consort diagram of recruitment and participation in the alcohol and breast cancer (ABC) crossover trial

Table 1 Baseline characteristics for alcohol and breast Cancer trial participants, *n* (%) or median[IQR]

Age, years	61.0 [50.0, 70.0]
Race	
Black or African American	4 (20.0%)
White	16 (80.0%)
Hispanic	
Hispanic or Latino	3 (15.0%)
Not Hispanic or Latino	17 (85.0%)
Body Mass Index, kg/m^2	24.7 [23.5, 28.5]
Heart Rate	64.5 [60.0, 71.0]
Systolic Blood Pressure	124.5 [111.5, 137.3]
Diastolic Blood Pressure	76.8 [69.0, 82.5]
Alanine Transaminase (ALT), U/L	13.5 [11.0, 18.5]
Aspartate Aminotransferase (AST), U/L	16.0 [15.0, 20.0]
Estimated Glomerular Filtration Rate (eGFR), mL/min/1.73m^2	83.5 [70.0, 87.5)
Aromatase Inhibitor	
Anastrozole	13 (65.0%)
Exemestane	2 (10.0%)
Letrozole	5 (25.0%)
Aromatase Inhibitor Use (years)	3.1 [1.8, 5.1]
Alcohol Use Disorders Identification Test (AUDIT) Score	3.0 [2.0, 3.0]
# Days Per Week that Drink Alcohol	2.3 [1.0, 3.0]
# Servings of Alcohol Per Drink Day	1.0 [1.0, 1.0]
Estradiol, pg/mL	0.8 [0.3, 1.4)
Free Estradiol Index	0.012 [0.005, 0.048]
Free estradiol concentration, pg/mL	0.014 [0.005, 0.026]
Estrone pg/mL	0.9 [0.7, 2.1]
DHEA-S ug/dL	57.5 [35.9, 101.8]
Testosterone ng/dL	15.3 [11.7, 25.2]
SHBG nmol/L	56.8 [29.7, 92.1]

range of alcohol intake in study participants. Tamoxifen use, an estrogen blocker, blunted the association between alcohol intake and DHEAS, and among participants with ER + tumors, there was no association between alcohol intake and SHBG.

Several observational studies have reported a dose-response association between alcohol intake and BC incidence [4–6]. For instance, a pooled analysis of six cohort studies [4] reported that each additional 10 g/day of alcohol (about 0.75-1 drink) was associated with a 1.09-fold (95%CI 1.04–1.13) higher rate of BC. The association between alcohol and BC is more pronounced among those using postmenopausal hormone therapy [10–14, 41–44], particularly for ER + BC [10–14].

Our trial and our preliminary analysis of NHANES data both suggest that alcohol intake may not increase estradiol levels in the presence of AI therapy, which is specifically intended to reduce estradiol levels. Prior trials on alcohol and sex hormones among postmenopausal women not taking AIs have not been definitive [15–18], but large observational studies among such women strongly suggest positive associations [7–9]. Our findings on alcohol and sex hormones other than estradiol among women on AI therapy are consistent with these prior studies of women not taking AIs. In contrast, we found that in postmenopausal women taking AIs, alcohol did not increase estradiol, free estradiol index, or free estradiol concentration. The basis for the disparity between the effects of alcohol on estradiol as opposed to other sex hormones appears to suggest that aromatase inhibition may blunt the effect of alcohol specifically on estradiol alone.

The exact mechanisms by which alcohol affects sex hormones and BC risk remain unclear. Among women not using AIs, alcohol has been hypothesized to promote the aromatization of androgens to estrogen [45] and slow the clearance of estradiol, thereby increasing exposure to

Table 2 Spearman correlations and *p*-values for sex hormones and SHBG, alcohol and breast Cancer trial

	Estradiol, pg/mL	Free Estradiol Index	Free Estradiol Concentration	Estrone pg/mL	DHEA-S ug/dL	Testosterone ng/dL	SHBG nmol/L
Estradiol, pg/mL	1	0.82	0.91	0.47	-0.06	0.15	-0.23
		$p<0.0001$	$p<0.0001$	$p<0.0001$	$p=0.6$	$p=0.2$	$p=0.04$
Free Estradiol Index		1	0.98	0.33	0.18	0.04	-0.70
			$p<0.0001$	$p=0.002$	$p=0.1$	$p=0.7$	$p<0.0001$
Free Estradiol Concentration			1	0.39	0.10	0.08	-0.57
				$p=0.0003$	$p=0.4$	$p=0.5$	$p<0.0001$
Estrone pg/mL				1	0.03	0.30	-0.09
					$p=0.8$	$p=0.006$	$p=0.4$
DHEA-S ug/dL					1	0.02	-0.41
						$p=0.9$	$p=0.0001$
Testosterone ng/dL						1	-0.01
							$p=0.9$
SHBG nmol/L							1

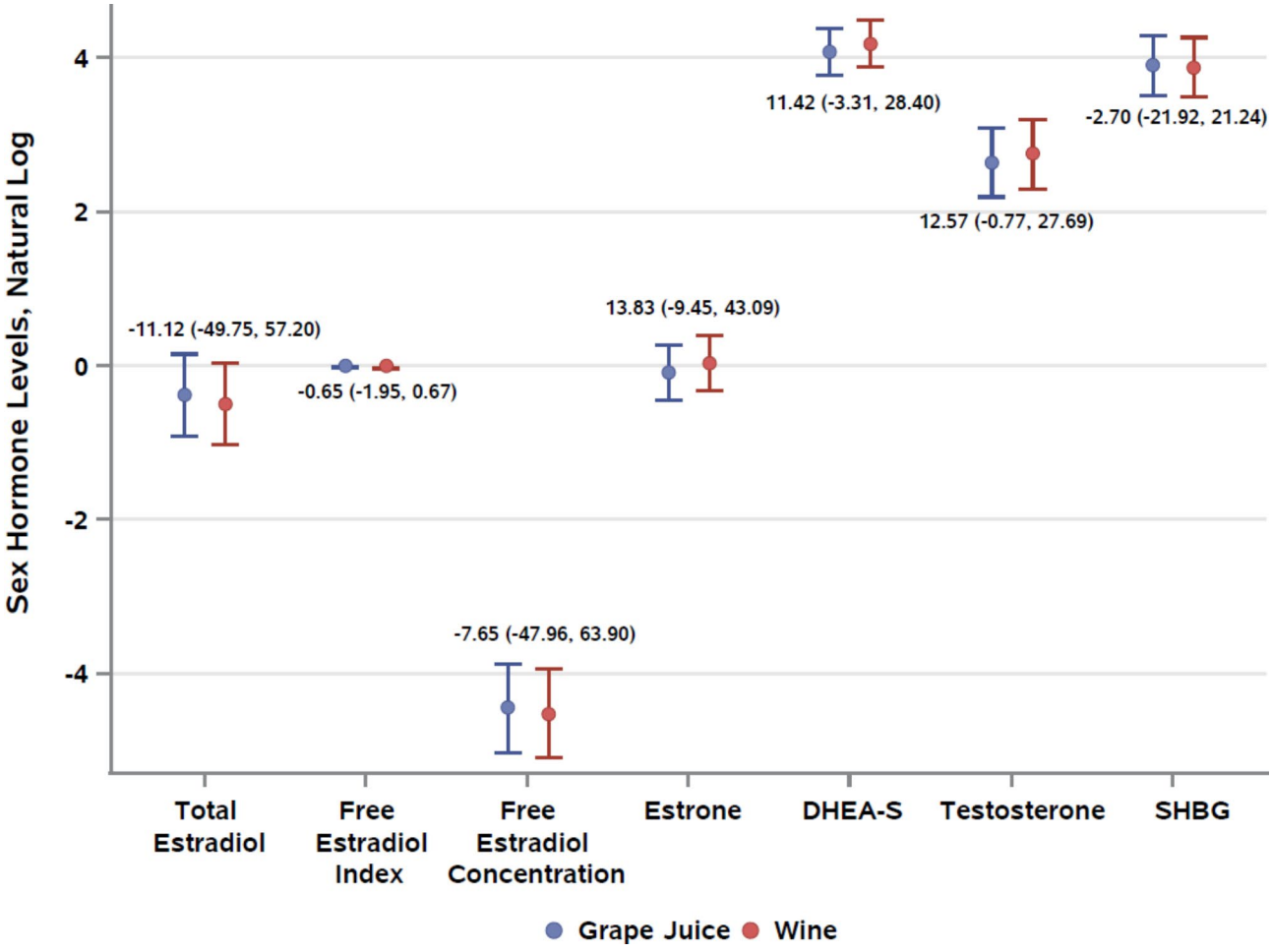

Fig. 3 Within-person log-transformed hormone concentrations and percentage changes in sex hormones following 3 weeks of white wine compared to following 3 weeks of white grape juice

Circles and vertical lines indicate the least squared means and 95% confidence intervals for each hormone by drink phase. Estimates represent the percentage change (and 95% confidence interval) in log-transformed hormone levels for wine compared to grape juice

Estimates of relative change are from linear mixed models, including participant as a random effect and interaction terms for drink and sequence to adjust for period-specific baseline values (Kenward approach)

sex hormones and increasing BC risk [46]. There is also some evidence that estrogen may induce hormone-receptor-mediated cell proliferation and genetic alterations that cause BC [47]. Studies showing the effect of alcohol is modified by hormone therapy and estrogen blockers are concordant with a study of cell cultures showing that alcohol diminishes the molecular actions of tamoxifen on BC cells [48, 49]. Since maintaining low hormone levels predicts BC recurrence [36], it is critical to assess the safety of alcohol intake on BC risk for women on AI therapy.

As a pilot trial with limited statistical power, more research is needed before translating these findings for clinical guidance on alcohol intake among women using AIs to determine whether alcohol.

affects patient response to modern endocrine therapy. Our study provides actionable preliminary estimates of effect sizes and variability that can be used for power calculations in future confirmatory trials.

The current recommendation for all women, regardless of BC status [50] is that if women drink, alcoholic beverages they should limit their intake to one drink per day on days when alcohol is consumed [51]. Despite potential alcohol-related risks, a cancer diagnosis is not associated with long-term changes in daily alcohol intake [22, 23]. Approximately 51% [52] to 58% [53] of BC patients are drinkers, with 16.7% reporting alcohol intake of >2 drinks per day and 37.3% consuming more than four drinks on one occasion [54]. Therefore, it is important to assess the role of alcohol in BC treatment and recurrence. Maintaining low hormone levels predicts BC recurrence [36]. Therefore, it is critical to assess the potential synergistic effect of alcohol and AI therapy on BC risk.

We conducted a pilot crossover trial with only 20 participants and short intervention and washout periods. Although we maximized statistical efficiency by using a within-person comparison and the length of our drinking and washout periods were similar to prior trials on alcohol and sex hormones [16], our results require confirmation in larger studies. We did not have sufficient power to examine a potential differential effect across AI types but previous studies have shown they have similar efficacy [20]. It is also possible that higher doses of alcohol would have led to larger increases in hormone levels that would raise concern. Nonetheless, we aimed to assess the effects of drinking at a dose that lies within current limits for women. The lower dose that we used, and its limited duration, may be responsible for the lack of clear effect of alcohol on HDL cholesterol in this trial, especially because other assessment methods suggested reasonable adherence to the assigned interventions. We chose to use wine rather than pure ethanol because we have learned from prior experience that the poor taste of pure ethanol severely impairs recruitment and adherence [55]. Some [4, 6, 56] but not all [42, 57, 58] studies have reported that the association between alcohol and BC is similar for wine, beer, and spirits. We chose to use white wine since red wine is a rich source of polyphenols and may have AI properties [59] and the hops and barm in beer may be estrogenic [60]. In addition, most women with BC who drink alcoholic beverages prefer wine [52], so it improved the likelihood of high adherence.

Conclusions

In this randomized controlled crossover trial, one serving of white wine per day exhibited a suggestion of higher levels of estrone, DHEAS, and testosterone, but not estradiol. Additional studies are warranted to follow up on these exploratory findings.

Abbreviations

ER+	Estrogen receptor-positive
BC	Breast cancer
AI	Aromatase inhibitor
CI	Confidence interval

Acknowledgements

The authors thank the study participants, the Beth Israel Deaconess Medical Center Insight Core, Jinni Yoon, the Data Safety Monitoring Board, Kristin Fleischman-Rose, and Katrina Hanscom.

Author contributions

EM, JEB, and KJM designed the study and SEC and NMT provided feedback on the study design and implementation; EM conducted the trial analyses; CZ conducted the NHANES analyses; EM, JEB, SEC, NMT, and KJM interpreted the data and provided feedback on the manuscript. All authors read and approved the manuscript.

Funding

This study is funded by Grant #K01AA027831 from the National Institute on Alcohol Abuse and Alcoholism (NIAAA). This work was conducted with support from Harvard Catalyst | The Harvard Clinical and Translational Science Center (National Center for Advancing Translational Sciences, National Institutes of Health Award UL 1TR002541) and financial contributions from Harvard University and its affiliated academic healthcare centers. The content is solely the responsibility of the authors and does not necessarily represent the official views of Harvard Catalyst, Harvard University and its affiliated academic healthcare centers, or the National Institutes of Health.

Data availability

A de-identified dataset for this study is available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

The study was approved by the Dana Farber/Harvard Cancer Center Institutional Review Board (DFHCC 21–698) and registered at Clinicaltrials.gov (NCT05423730). All participants provided written informed consent.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

Author details

[1]Department of Epidemiology (EM, JEB) and Nutrition (KJM), Harvard T.H. Chan School of Public Health, 677 Huntington Ave, Kresge 505-B, Boston, MA 02115, USA
[2]Division of Preventive Medicine, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA
[3]Department of Medicine (SEC, NMT, CZ, KJM), Beth Israel Deaconess Medical Center, Harvard Medical, School, Boston, MA, USA
[4]Cancer Risk and Prevention Program and Breast Medical Oncology, Beth Israel Deaconess Medical Center, Harvard Medical, School, Boston, MA, USA

Received: 1 March 2024 / Accepted: 29 November 2024
Published online: 09 January 2025

References

1. Tan CH, Denny CH, Cheal NE, Sniezek JE, Kanny D. Alcohol use and binge drinking among women of childbearing age - United States, 2011–2013. MMWR Morb Mortal Wkly Rep. 2015;64(37):1042–6.
2. Dwyer-Lindgren L, Flaxman AD, Ng M, Hansen GM, Murray CJ, Mokdad AH. Drinking patterns in US counties from 2002 to 2012. Am J Public Health. 2015;105(6):1120–7.
3. Grant BF, Chou SP, Saha TD, et al. Prevalence of 12-Month Alcohol Use, High-Risk drinking, and DSM-IV Alcohol Use Disorder in the United States, 2001–2002 to 2012–2013: results from the national epidemiologic survey on Alcohol and related conditions. JAMA Psychiatry. 2017;74(9):911–23.
4. Smith-Warner SA, Spiegelman D, Yaun SS, et al. Alcohol and breast cancer in women: a pooled analysis of cohort studies. JAMA. 1998;279(7):535–40.
5. Romieu I, Scoccianti C, Chajes V, et al. Alcohol intake and breast cancer in the European prospective investigation into cancer and nutrition. Int J Cancer. 2015;137(8):1921–30.
6. Jung S, Wang M, Anderson K, et al. Alcohol consumption and breast cancer risk by estrogen receptor status: in a pooled analysis of 20 studies. Int J Epidemiol. 2016;45(3):916–28.
7. Key TJ, Appleby PN, Reeves GK, et al. Circulating sex hormones and breast cancer risk factors in postmenopausal women: reanalysis of 13 studies. Br J Cancer. 2011;105(5):709–22.
8. Assi N, Rinaldi S, Viallon V, et al. Mediation analysis of the alcohol-postmenopausal breast cancer relationship by sex hormones in the EPIC cohort. Int J Cancer. 2020;146(3):759–68.
9. Tin Tin S, Smith-Byrne K, Ferrari P, et al. Alcohol intake and endogenous sex hormones in women: Meta-analysis of cohort studies and mendelian randomization. Cancer. 2024;130(19):3375–86.
10. Hvidtfeldt UA, Tjønneland A, Keiding N, et al. Risk of breast cancer in relation to combined effects of hormone therapy, body mass index, and alcohol use, by hormone-receptor status. Epidemiology. 2015;26(3):353–61.

11. Suzuki R, Ye W, Rylander-Rudqvist T, Saji S, Colditz GA, Wolk A. Alcohol and postmenopausal breast cancer risk defined by estrogen and progesterone receptor status: a prospective cohort study. J Natl Cancer Inst. 2005;97(21):1601–8.
12. Suzuki R, Orsini N, Mignone L, Saji S, Wolk A. Alcohol intake and risk of breast cancer defined by estrogen and progesterone receptor status–a meta-analysis of epidemiological studies. Int J Cancer. 2008;122(8):1832–41.
13. Zhang SM, Lee IM, Manson JE, Cook NR, Willett WC, Buring JE. Alcohol consumption and breast cancer risk in the women's Health Study. Am J Epidemiol. 2007;165(6):667–76.
14. Horn-Ross PL, Canchola AJ, Bernstein L, et al. Alcohol consumption and breast cancer risk among postmenopausal women following the cessation of hormone therapy use: the California teachers Study. Cancer Epidemiol Biomarkers Prev. 2012;21(11):2006–13.
15. 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):780–5.
16. 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;3:11.
17. Dorgan JF, Baer DJ, Albert PS, et al. Serum hormones and the alcohol-breast cancer association in postmenopausal women. J Natl Cancer Inst. 2001;93(9):710–5.
18. Ginsburg ES, Mello NK, Mendelson JH, et al. Effects of alcohol ingestion on estrogens in postmenopausal women. JAMA. 1996;276(21):1747–51.
19. Dowsett M, Donaldson K, Tsuboi M, Wong J, Yates R. Effects of the aromatase inhibitor anastrozole on serum oestrogens in Japanese and caucasian women. Cancer Chemother Pharmacol. 2000;46(1):35–9.
20. Kümler I, Knoop AS, Jessing CA, Ejlertsen B, Nielsen DL. Review of hormone-based treatments in postmenopausal patients with advanced breast cancer focusing on aromatase inhibitors and fulvestrant. ESMO Open. 2016;1(4):e000062.
21. Smith IE, Dowsett M. Aromatase inhibitors in breast cancer. N Engl J Med. 2003;348(24):2431–42.
22. Williams K, Steptoe A, Wardle J. Is a cancer diagnosis a trigger for health behaviour change? Findings from a prospective, population-based study. Br J Cancer. 2013;108(11):2407–12.
23. Sprague BL, Trentham-Dietz A, Nichols HB, Hampton JM, Newcomb PA. Change in lifestyle behaviors and medication use after a diagnosis of ductal carcinoma in situ. Breast Cancer Res Treat. 2010;124(2):487–95.
24. Miller KD, Nogueira L, Mariotto AB, et al. Cancer treatment and survivorship statistics, 2019. CA Cancer J Clin. 2019;69(5):363–85.
25. American Cancer Society. Cancer Facts & Fig. 2023. Atlanta: American Cancer Society;2023.
26. Reinert DF, Allen JP. The alcohol use disorders identification test: an update of research findings. Alcohol Clin Exp Res. 2007;31(2):185–99.
27. Andresen EM, Malmgren JA, Carter WB, Patrick DL. Screening for depression in well older adults: evaluation of a short form of the CES-D (center for epidemiologic studies Depression Scale). Am J Prev Med. 1994;10(2):77–84.
28. Buysse DJ, Reynolds CF 3rd, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. Psychiatry Res. 1989;28(2):193–213.
29. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)--a metadata-driven methodology and workflow process for providing translational research informatics support. J Biomed Inf. 2009;42(2):377–81.
30. Sobell LC, Brown J, Leo GI, Sobell MB. The reliability of the Alcohol Timeline Followback when administered by telephone and by computer. Drug Alcohol Depend. 1996;42(1):49–54.
31. Mazer NA. A novel spreadsheet method for calculating the free serum concentrations of testosterone, dihydrotestosterone, estradiol, estrone and cortisol: with illustrative examples from male and female populations. Steroids. 2009;74(6):512–9.
32. Jasuja GK, Travison TG, Davda M, et al. Age trends in estradiol and estrone levels measured using liquid chromatography tandem mass spectrometry in community-dwelling men of the Framingham Heart Study. J Gerontol Biol Sci Med Sci. 2013;68(6):733–40.
33. Centers for Disease Control and Prevention (CDC). Hormone Standardization (HoSt) Program. HoSt Estradiol Certified Procedures. https://www.cdc.gov/labstandards/csp/pdf/hs/CDC_Certified_Estradiol_Assays-508.pdf. Published 09/2023. Accessed October 23, 2023.
34. Mitchell CM, Larson JC, Crandall CJ, et al. Association of Vaginal Estradiol Tablet with Serum Estrogen Levels in women who are Postmenopausal: secondary analysis of a Randomized Clinical Trial. JAMA Netw Open. 2022;5(11):e2241743.
35. Kenward MG, Roger JH. The use of baseline covariates in crossover studies. Biostatistics. 2010;11(1):1–17.
36. Ingle JN, Cairns J, Suman VJ, et al. Anastrozole has an Association between Degree of Estrogen Suppression and outcomes in early breast Cancer and is a Ligand for estrogen receptor α. Clin Cancer Res. 2020;26(12):2986–96.
37. Key TJ, Appleby PN, Reeves GK, et al. Sex hormones and risk of breast cancer in premenopausal women: a collaborative reanalysis of individual participant data from seven prospective studies. Lancet Oncol. 2013;14(10):1009–19.
38. Tin Tin S, Key TJ, Reeves GK. Alcohol intake and endogenous hormones in pre- and Postmenopausal women: findings from the UK Biobank. Cancer Epidemiol Biomarkers Prev. 2021;30(12):2294–301.
39. Ginsburg ES, Walsh BW, Gao X, Gleason RE, Feltmate C, Barbieri RL. The effect of acute ethanol ingestion on estrogen levels in postmenopausal women using transdermal estradiol. J Soc Gynecol Investig. 1995;2(1):26–9.
40. Wayne S, Neuhouser ML, Ulrich CM, et al. Association between alcohol intake and serum sex hormones and peptides differs by tamoxifen use in breast cancer survivors. Cancer Epidemiol Biomarkers Prev. 2008;17(11):3224–32.
41. Colditz GA, Stampfer MJ, Willett WC, Hennekens CH, Rosner B, Speizer FE. Prospective study of estrogen replacement therapy and risk of breast cancer in postmenopausal women. JAMA. 1990;264(20):2648–53.
42. Gapstur SM, Potter JD, Sellers TA, Folsom AR. Increased risk of breast cancer with alcohol consumption in postmenopausal women. Am J Epidemiol. 1992;136(10):1221–31.
43. Chen WY, Colditz GA, Rosner B, et al. Use of postmenopausal hormones, alcohol, and risk for invasive breast cancer. Ann Intern Med. 2002;137(10):798–804.
44. Nielsen NR, Grønbaek M. Interactions between intakes of alcohol and postmenopausal hormones on risk of breast cancer. Int J Cancer. 2008;122(5):1109–13.
45. Purohit V. Can alcohol promote aromatization of androgens to estrogens? A review. Alcohol. 2000;22(3):123–7.
46. Ginsburg ES, Walsh BW, Shea BF, Gao X, Gleason RE, Barbieri RL. The effects of ethanol on the clearance of estradiol in postmenopausal women. Fertil Steril. 1995;63(6):1227–30.
47. Starek-Świechowicz B, Budziszewska B, Starek A. Alcohol and breast cancer. Pharmacol Rep. 2023;75(1):69–84.
48. Zhong Q, Shi G, Zhang Q, Lu L, Levy D, Zhong S. Tamoxifen represses alcohol-induced transcription of RNA polymerase III-dependent genes in breast cancer cells. Oncotarget. 2014;5(23):12410–7.
49. Candelaria NR, Weldon R, Muthusamy S, et al. Alcohol regulates genes that are associated with response to endocrine therapy and attenuates the actions of tamoxifen in breast cancer cells. PLoS ONE. 2015;10(12):e0145061.
50. Runowicz CD, Leach CR, Henry NL, et al. American Cancer Society/American Society of clinical oncology breast Cancer Survivorship Care Guideline. J Clin Oncol. 2016;34(6):611–35.
51. U.S. Department of Agriculture and U.S. Department of Health and Human Services. Dietary Guidelines for Americans, 2020–2025. 9th Edition. December 2020. Available at DietaryGuidelines.gov. Accessed January, 2024.
52. Kwan ML, Kushi LH, Weltzien E, et al. Alcohol consumption and breast cancer recurrence and survival among women with early-stage breast cancer: the life after cancer epidemiology study. J Clin Oncol. 2010;28(29):4410–6.
53. Kwan ML, Chen WY, Flatt SW, et al. Postdiagnosis alcohol consumption and breast cancer prognosis in the after breast cancer pooling project. Cancer Epidemiol Biomarkers Prev. 2013;22(1):32–41.
54. Bell RJ, Lijovic M, Fradkin P, Schwarz M, Davis SR. Changes in patterns of use of cigarettes and alcohol in women after a first diagnosis of invasive breast cancer: a cohort study of women from Victoria, Australia. Support Care Cancer. 2012;20(4):783–9.
55. Mukamal KJ, Na B, Mu L, Mantzoros CS, Manning WJ, Mittleman MA. Lessons and challenges from a 6-Month Randomized Pilot study of daily ethanol consumption: Research Methodology and Study Design. Curr Dev Nutr. 2017;1(7):e000505.
56. Allen NE, Beral V, Casabonne D, et al. Moderate alcohol intake and cancer incidence in women. J Natl Cancer Inst. 2009;101(5):296–305.
57. Harvey EB, Schairer C, Brinton LA, Hoover RN, Fraumeni JF. Jr. Alcohol consumption and breast cancer. J Natl Cancer Inst. 1987;78(4):657–61.

58. Willett WC, Stampfer MJ, Colditz GA, Rosner BA, Hennekens CH, Speizer FE. Moderate alcohol consumption and the risk of breast cancer. N Engl J Med. 1987;316(19):1174–80.
59. Shufelt C, Merz CN, Yang Y, et al. Red versus white wine as a nutritional aromatase inhibitor in premenopausal women: a pilot study. J Womens Health. 2012;21(3):281–4.
60. Lapcík O, Hill M, Hampl R, Wähälä K, Adlercreutz H. Identification of isoflavonoids in beer. Steroids. 1998;63(1):14–20.

Publisher's note