2024

Effect of light alcohol intake on depressive symptoms, pain and sleep among postmenopausal women on aromatase inhibitor therapy

BOSTON UNIVERSITY

ARAM V. CHOBANIAN & EDWARD AVEDISIAN SCHOOL OF MEDICINE

Thesis

EFFECT OF LIGHT ALCOHOL INTAKE ON DEPRESSIVE SYMPTOMS, PAIN AND SLEEP AMONG POSTMENOPAUSAL WOMEN ON AROMATASE INHIBITOR THERAPY

by

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B.S., Carnegie Mellon University, 2019

Submitted in partial fulfillment of the

requirements for the degree of

Master of Science

2024

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ACKNOWLEDGMENTS

I would like to thank Dr. Kenneth Mukamal and Dr. Elizabeth Mostofsky for their work on the clinical trial and their guidance and feedback during this writing process. I would also like to thank my advisors Dr. Vickery Trinkaus-Randall and Dr. Gwynneth Offner for their support through the MAMS program. Lastly, I would like to thank my parents for everything they do for me.

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ABSTRACT

Background: Little is known about the short-term effects of light alcohol intake on sleep, depressive symptoms, and pain among women on aromatase inhibitor therapy.

Objective: To examine changes in sleep quality, depressive symptoms, and pain following white wine compared to white grape juice among 20 postmenopausal women.

Methods: We conducted a 10-week randomized controlled two-period crossover trial from September 2022 to July 2023 among 20 postmenopausal women with estrogen receptor-positive breast cancer taking aromatase inhibitors to examine alcohol effects on sex hormones. We also measured sleep, pain, and depressive symptoms. We used mixed models to examine within-person changes in health characteristics 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 a

two-week washout period and sequence of drinking periods allocated by randomization.

Results: All 20 randomized women completed the trial. There were no statistically significant changes following wine compared to grape juice. There were no meaningful changes in sleep quality, a trend toward a slight increase in pain intensity, and a slight decrease in depressive symptoms during the wine period. These effects were not large enough to have clinically meaningful implications.

Conclusions: These data suggest that one serving of alcohol daily for three weeks did not have clinically meaningful effects on sleep quality, depressive symptoms, or pain intensity.

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LIST OF ABBREVIATIONS

ADH1C ..... Alcohol dehydrogenase 1C

AI ..... Aromatase inhibitor

AUDIT ..... Alcohol Use Disorders Identification Test

BC ..... Breast cancer

BIDMC ..... Beth Israel Deaconess Medical Center

BPM ..... Beats per minute

CESD-10 ..... Centre for Epidemiological Studies Depression Scale

CYP2E1 ..... Cytochrome P450 Family 2 Subfamily E Member 1

ER+ BC ..... Estrogen-receptor positive breast cancer

HER-2 ..... Human epidermal growth factor receptor 2

mmHg ..... Millimeters of mercury

Pain VAS ..... Pain Visual Analog Scale

PSQI ..... Pittsburgh Sleep Quality Index

REDCap ..... Research Electronic Data Capture

ROS ..... Reactive Oxygen Species

SHBG ..... Sex hormone binding globulin

SNP ..... Single nucleotide polymorphism

INTRODUCTION

Estrogen-Receptor Positive Breast Cancer and Current Therapies

There are currently more than four million women with a history of breast cancer in the United States[1] and it is the second most common cancer overall. Amongst women, breast cancer is the most commonly diagnosed cancer in both more and less developed regions worldwide. Age is a primary risk factor for breast cancer, such that risk increases with age. Although the incidence of breast cancer in women under 40 years old has recently been reported to increase, such that about 10% of new cases diagnosed are amongst women 45 years and younger.[2] Menstrual status of women also plays into the age-related risk of breast cancer, such that women with early menstruation or late menopause may have an increased risk of developing breast cancer. Approximately 10% of breast cancer in the Western world are due to a genetic predisposition. Breast cancers are categorized into several different subtypes that may be based on the histology, clinical symptoms and presentation, and its molecular components and markers. Approximately 80% of women with early-stage breast cancer (BC) have estrogen receptor-positive (ER+) BC[3] and more than 70% of breast cancers express the estrogen receptor alpha (ER).[4]

With different etiologies of breast cancer, there are also multiple types of therapies that may be used depending on various factors, such as tumor stage, age, and patient preference. Local treatments include mastectomy or breast radiotherapy. Primary prevention with surgery of BC for young women, such as bilateral mastectomy, which is generally is seen with women with BRCA1/2 mutations who may have an increased risk of breast cancer.[5] Systemic treatments of breast cancer include chemotherapy, HER-2 targeted therapies and endocrine therapies. Tumor stage and biological characteristics are also used as guiding factors in determining appropriate systemic treatment for both young and old women. Endocrine therapies are used for patients with estrogen receptor-positive (ER+) or progesterone receptor-positive (PR+) forms of breast cancer. These include treatments such as aromatase inhibitors or tamoxifen, a selective estrogen receptor modulator.[4] Both of these medications target the effects of estrogen on the estrogen receptors.

The pathology of ER+ BC is due to activation of the estrogen receptor (ER) and estrogen receptor beta (ERβ) when they interact with the ligand estrogen. This interaction of estrogen binding to its receptors promotes the development and proliferation of breast cancer through transcription of proto-oncogenes that contribute to the survival of cancerous breast tissue. Individuals with this

subtype of BC often receive endocrine therapy as treatment, and aromatase inhibitors (AIs), such as anastrozole, letrozole and exemestane, (Figure 1) are the first-line therapy for postmenopausal women with ER+ breast cancer.

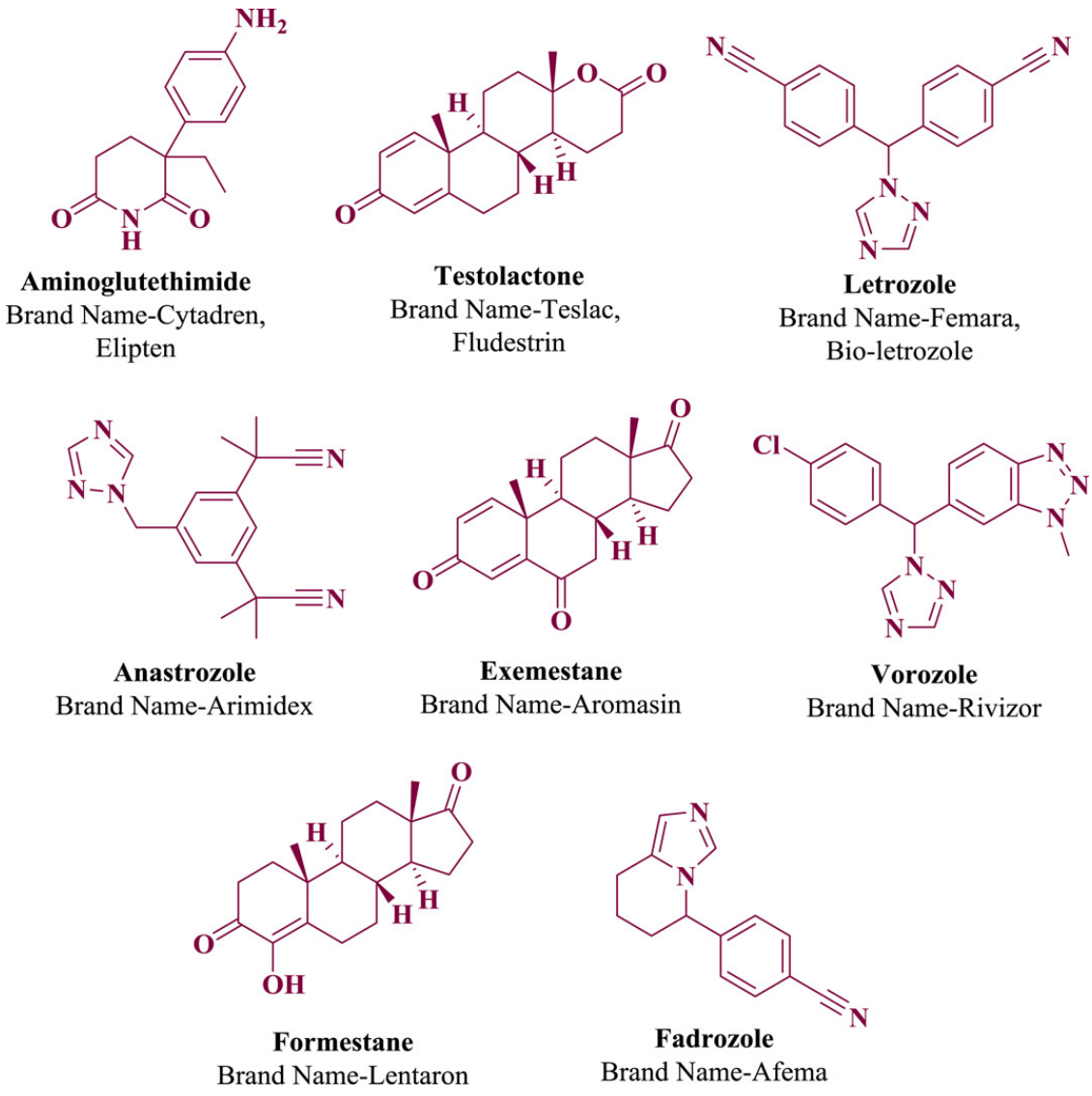


Figure 1. Chemical structures of clinically approved aromatase inhibitors[4]

Estrogen is a key hormone that is required for BC to grow and aromatase is an enzyme responsible for the conversion of androgens to estrogens, such as androstenedione to estrone and testosterone to estradiol.[6] AIs work to dramatically reduce estrogen levels by blocking the production of estrogen or by blocking the action of estrogen on its estrogen receptors through inhibiting the

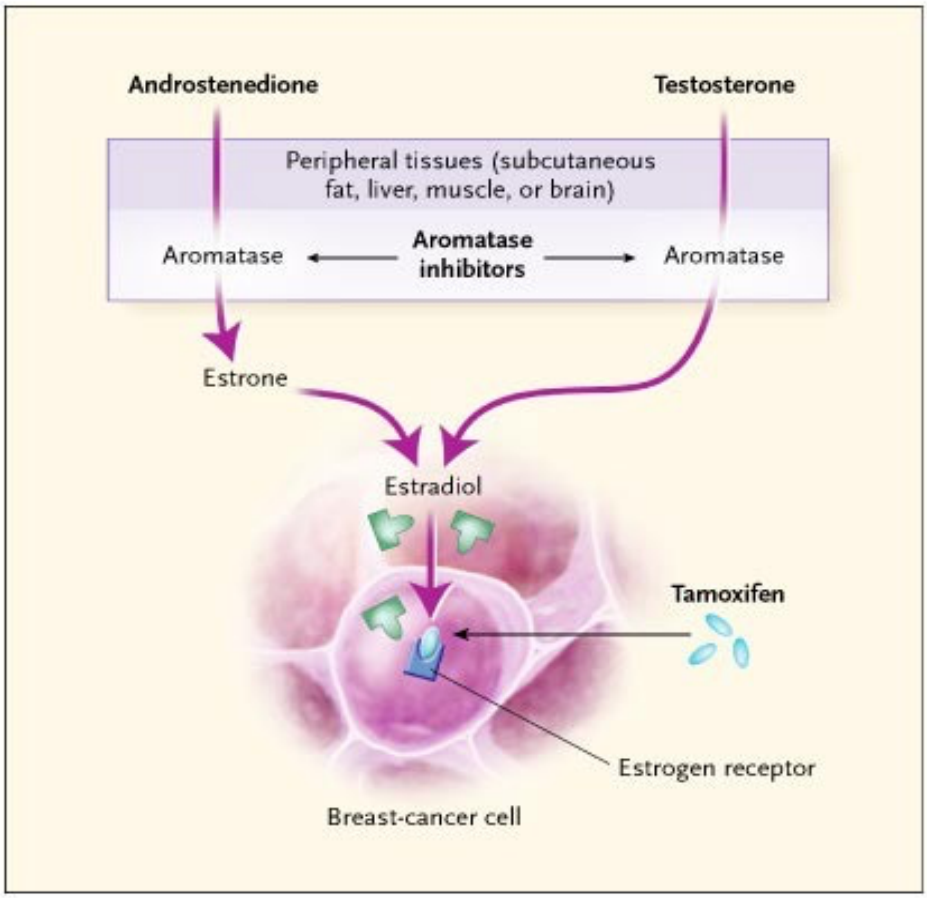


Figure 2. Mechanism of action of aromatase inhibitors [7]

aromatase enzyme, preventing the conversion of androgens to estrogen. (Figure 2) Less estrogen then leads to lowering the risk of BC recurrence.[7,8]

Aromatase is largely present in the ovaries and also present, at lower levels, in tissues such as subcutaneous fat, muscle and breast. AIs are thus particularly effective as treatment for postmenopausal women because the main source of estrogen for postmenopausal women is the conversion of androgens to estrogens by peripheral tissues in the body, as opposed to the production of estrogen in ovaries in premenopausal women.

Symptoms Associated with Aromatase Inhibitor Therapy

Although aromatase inhibitor therapy can benefit patients from the standpoint of a lower risk of recurrence of breast cancer, it is important to understand the other effects that may be seen with long-term AI use. Many women have reported the onset of symptoms of pain, sleep problems and mood issues with use of AIs. Use of AIs and the subsequent decrease of estrogen levels affects bone remodeling, particularly by increasing osteoclast activity and an overall loss of bone density. When compared to placebo, AI use caused statistically significant levels of bone loss and increase in fracture rates.[6] With

regard to musculoskeletal symptoms, nearly half of the women prescribed aromatase inhibitors report AI-related joint pain and stiffness.[9]

Estrogens have been shown to have some role in the regulation of sleep and at least 70% of women treated for various stages of breast cancer have reported problems with sleep disturbance. Aromatase inhibitors, which decrease said estrogen levels, thus may affect the quality of sleep amongst those who are prescribed AI treatment. Approximately 20% of women prescribed AIs report experiencing sleep problems and previous studies have also shown about a 20% increase in women with symptoms of insomnia after starting AI treatment.[10,11]

Approximately 32% of breast cancer patients experience depression[11,12] and age or cancer stage can be associated with depressive symptoms, where younger women and women with higher stage of breast cancer were associated with a higher risk of worse depressive symptoms. Some previous studies have shown an increased risk for worse depressive symptoms with AI therapy, while others have found no significant differences.

These symptoms of increased musculoskeletal pain and stiffness, sleep problems and depression can all lead to more severe pain, fatigue, and diminished quality of life.[13]

Association between Alcohol and Breast Cancer

At least half of American women drink alcohol[14] and their alcohol intake has increased in recent years.[15] Even when consumed within recommended limits of up to one drink per day, it is associated with a dose-dependent risk of developing female breast cancer (BC), the most common cancer among women. Each 10 g (~1 drink) increase in daily alcohol intake is associated with an approximately 10% higher risk of BC incidence and the risk is about 11% for postmenopausal women.[16,17]

There is consistent evidence of heightened breast cancer risk with even moderate alcohol intake, but it remains unclear if certain women have higher susceptibility to the harmful effects of alcohol intake. Over 100 single nucleotide polymorphisms (SNPs) for BC risk have been discovered in genome-wide association studies, but the known risk alleles explain only 16% of BC heritability. Several studies have explored whether there are SNPs that modify the association between alcohol intake and breast cancer incidence, with some focusing on genes that impact alcohol metabolism and other studies selecting a small group of genes that may be related to a variety of established BC risk factors. In most studies, there was no statistically significant evidence of a

particular SNP that modifies the impact of alcohol intake on BC risk after adjustment for multiple tests.

The process of the biochemical metabolism of ethanol generates metabolites that may disturb normal cell function or even lead to cellular death. The role of enzyme CYP2E1 in alcohol metabolism is convert ethanol to acetaldehyde and then to acetic acid.[17] CYP2E1 from the liver mitochondria has been shown to be effective in the production of reactive oxygen species (ROS) that can contribute to cellular damage. Additionally, the ADH1C gene has been linked to having a critical role in breast cancer risk amongst premenopausal women. One study showed that a person homozygous for the ADH1C*1 allele was at a higher risk for breast cancer compared to those who were heterozygous. Premenopausal women who were homozygous for the ADH1C*1 allele and also consumed large amounts of alcohol were had an even great risk for breast cancer compared to those who only consumed a moderate amount of alcohol.

Previous studies have also shown that individuals who metabolize alcohol quickly are at a higher risk for breast cancer due to alcohol consumption, in comparison to individuals who metabolize alcohol more slowly. Although evidence from prior studies has linked alcohol consumption to breast cancer, the

actual mechanism by which alcohol promotes carcinogenesis is still unclear. (Figure 3)

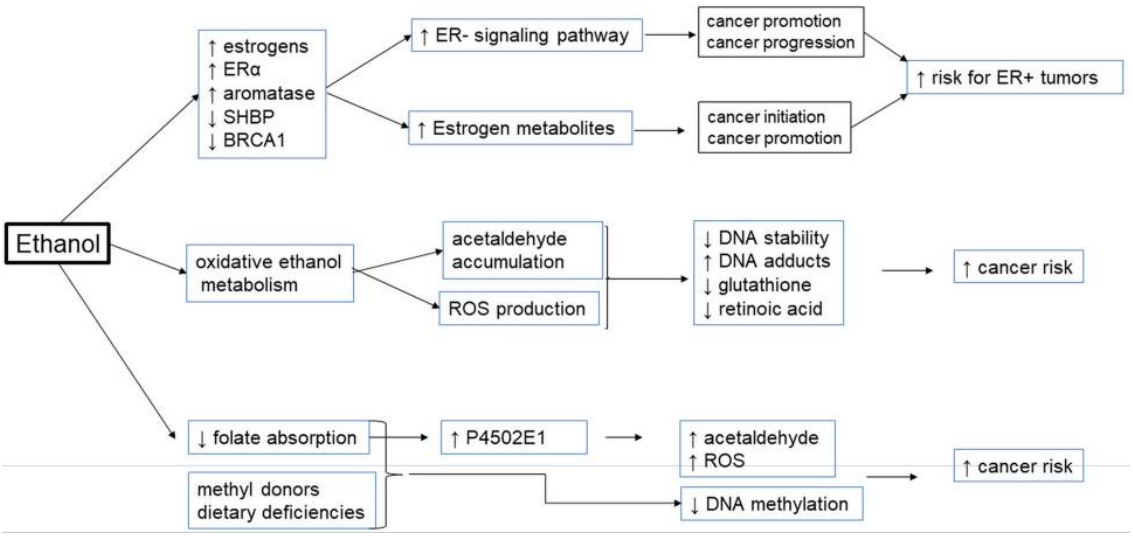


Figure 3. Main hypothesized mechanisms of alcohol carcinogenicity[15]

The recommendation to limit alcohol intake to up to one drink per day is the same for healthy women and for breast cancer survivors. These recommendations do not mandate abstinence. It is important to better understand the relationship between alcohol intake and risk of breast cancer.

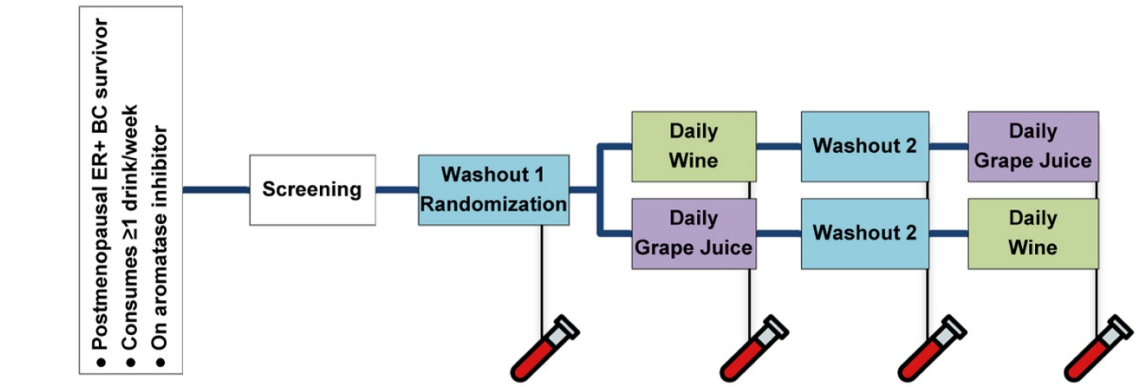
Among adults with no cancer, prior studies suggest that alcohol may lead to immediate decrements in objective markers of sleep quality,[18–21] but habitual intake may improve self-reported sleep quality.[22,23] Some studies also have found

an association between alcohol consumption and short sleep duration.[24] A few studies reported that alcohol transiently improves mood[25,26] but other studies report no acute changes in affect following alcohol intake.[27] There have been discrepant findings on the relationship between alcohol and acute pain sensitivity.[28,29]

Aromatase Inhibitor Therapy and Alcohol use

Half of all women with BC report some alcohol intake following their BC diagnosis.[30] However, there is limited information on the role of alcohol on health symptoms among women on AI therapy. This study was conducted as part of a trial aimed at examining the effects of alcohol on sex steroid hormones to understand the mechanisms linking alcohol with BC risk and explore whether there may be factors that heighten the risk of BC associated with alcohol intake. Estrogen receptor positive (ER+) BC survivors are routinely prescribed AI therapy to lower their estrogen levels, and alcohol use is associated with symptoms of pain, depression, and sleep problems. The potential effects of alcohol consumption among the large population of women on AI therapy warrants attention.

There have been no studies to examine whether alcohol intake hampers the effectiveness of AI therapy or whether alcohol intake affects psychosocial domains amongst BC survivors on AI therapy. Therefore, we conducted a pilot crossover trial (Figure 4) to examine the effect of wine versus grape juice on sleep, depressive symptoms, and pain among twenty postmenopausal women on AI therapy.



Visit #	1	2	3	4	5
Week	0	1	2-4	5	6-8

Figure 4. Timeline of pilot crossover trial

SPECIFIC AIMS

Previous research has been conducted regarding the use of aromatase inhibitors as treatment for women with ER+ breast cancer. Additionally, many previous studies have linked alcohol use with symptoms of pain, sleep problems and depression. Women with a history of ER+ breast cancer will often be prescribed long term use of AI's, due to the decreased risk of recurrence. However, previous literature has not examined many of the effects of alcohol use amongst women who have been prescribed long term use of AI.

The goal of this study is to examine changes in sleep quality, depressive symptoms and pain following consumption of white wine compared to consumption of white grape juice amongst 20 postmenopausal women with a history of ER+ breast cancer and on AI treatment. We predict that consumption of white wine may worsen sleep, depressive symptoms and pain, as use of alcohol has a similar effect in individuals without cancer or history of cancer.

METHODS

Study Population

We sent invitation letters and made phone calls to reach out 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 diagnosis of 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 one serving per day, currently prescribed aromatase inhibitors, and liver function results that were below 1.5 times the upper limit of "normal" range 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 (defined as an AUDIT[31] score greater than or equal to 8), consumption of 4 or more drinks in one day within the last 6 months, currently undergoing cytotoxic chemotherapy or radiation planned within the next two months, any surgery planned within 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 greater than 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 of participant 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). All participants provided written informed consent.

Study Design

We conducted a two-period randomized controlled crossover design. In this design, participants are compared to themselves at different time points, with the sequence of the two treatment arms (wine or grape juice) assigned by randomization (Figure 5).

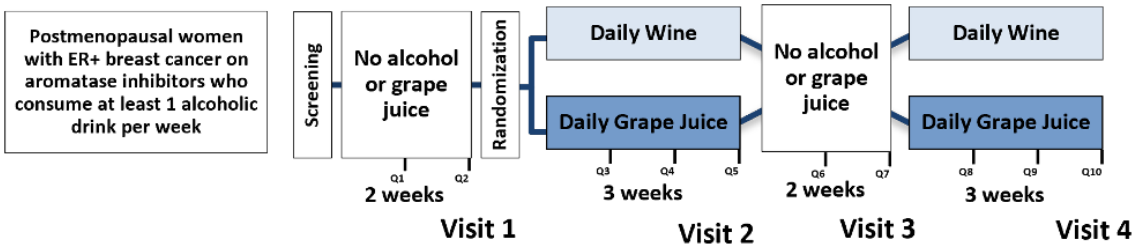


Figure 5. Crossover study design of pilot trial with four visits and 10 questionnaires

To prevent a potential carryover effect of the drink consumed in the first treatment period affecting hormone levels in the second treatment period, participants underwent "washout periods" where they refrained from drinking any alcohol or grape juice for two weeks before starting each treatment arm. After obtaining written informed consent and confirming eligibility, participants began an initial two-week washout period.

We then randomized the treatment sequence on a 1:1 basis using a computer-generated allocation schedule and participants were either assigned to an intervention schedule of wine followed by grape juice or grape juice followed by wine. There was no blinding of the alcoholic beverages, meaning that all participants knew when they had been randomized to drink the white wine or the grape juice during the study. We asked participants to drink alcohol 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 consumption other than advised by the protocol and to otherwise follow their usual diet and lifestyle habits throughout the 10-week study.

For this study, we compared measures of self-reported sleep quality, depressive symptoms, and pain following three weeks of one serving (defined as 5 oz or approximately 14 g) of white wine per day to levels of those same

measures following three weeks of a calorically equivalent serving (6 ounces) of white grape juice per day.

Clinic Visits

Participants completed four study clinic visits, one following each washout and drinking period. (Table 1) The BIDMC Clinical Research Center obtained the blood samples and measured vital signs and body mass index. In postmenopausal women, the major source of peripheral estrogen production is from subcutaneous fat. Thus, estrogen levels and aromatase activity are correlated with body mass index. Part of the blood sample obtained 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 (either alcohol or grape juice) needed for the following three weeks of "drinking" periods. 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, average pain (visual analog scale ranging from 1 to 100), the short version of the Centre for Epidemiological Studies Depression Scale (CESD-10)[32] with scores ranging from 0 to 30, and a visual analog scale to rate their average pain intensity over the prior week (range 0 to 100). (Table 1)

In the surveys following each of the drinking periods, the participants also completed the Pittsburgh Sleep Quality Index (PSQI)[33] to rate their sleep quality over the prior month. The questionnaire includes 19 questions with responses ranging from 0, meaning no difficulty, to 3, meaning severe difficulty, and yields scores for seven domains of sleep quality: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication, and daytime dysfunction. The sum of scores for these seven components yields one global score (range 0 to 21), with a lower sum score indicating better sleep quality.

We collected and managed all screening, clinical, visit, and questionnaire data using a research electronic data capture (REDCap)[34] system, a secure, web-based application designed to support data capture for research studies.

Table 1. Data Matrix of Measures Obtained through Clinical Assessments and Questionnaires over 10-week Study period

		Screening	Washout 1	Washout 1	Visit 1	Drinking Period	Drinking Period	Drinking Period	Visit 2	Washout 2	Washout 2	Visit 3	Drinking Period	Drinking Period	Drinking Period	Visit 4	# Assessments
	Study Day	0	1-7	8-14	15	15-21	22-28	29-35	36	36-42	43-49	50	51-57	58-64	65-71	72	
	Window Allowance (Days)		±4	±4	±4	±4	±4	±4	±4	±4	±4	±4	±4	±4	±4	±4	
	Type of Visit	Clinic	Phone	Phone	Clinic	Phone	Phone	Phone	Clinic	Phone	Phone	Clinic	Phone	Phone	Phone	Clinic	
Admin, Body Measurements, and Vitals																	
	Consent, , contact information	X															1
	Eligibility: e.g. Alcohol use Disorders Identification Test (AUDIT) and hepatic panel, if none in the past 12 months*	X															1
	Randomization				X												1
	Verification of consent and documentation				X				X			X				X	4
	Height				X												1
	Weight, waist circumference				X				X			X				X	4
	Vital signs- blood pressure, heart rate				X				X			X				X	4
	Distribute drink				X							X					2
	Measure leftover drink								X							X	2
	Pay participant, reimburse parking				X				X			X				X	4
Blood Draw																	
	Hepatic panel	*			X				X			X				X	4
	Complete blood count with differential				X				X			X				X	4
	Basic metabolic panel (fasting)				X												1
	Lipid panel								X							X	2
	Dehydroepiandrosterone sulfate (DHEAS)				X				X			X				X	4
	Sex hormone binding globulin (SHBG)				X				X			X				X	4
	Estradiol				X				X			X				X	4
	Testosterone				X				X			X				X	4
Weekly Call																	
	Health events		X	X		X	X	X		X	X		X	X	X		10
	Other health changes		X	X		X	X	X		X	X		X	X	X		10
Weekly REDCap Questionnaires																	
	Timeline follow-back (or daily REDCap text)		X	X		X	X	X		X	X		X	X	X		10
	Pittsburgh Sleep Quality Index (PSQI)							X							X		2
	Depressive Symptoms (CES-D-6)		X	X		X	X	X		X	X		X	X	X		10
	Overall pain (visual analog scale)		X	X		X	X	X		X	X		X	X	X		10
	Open text-any questions, concerns, comments		X	X		X	X	X		X	X		X	X	X		10

Adherence

We assessed adherence in three ways. We called participants each week and conducted a timeline follow-back assessment[35] of alcohol and grape juice intake since the prior call. In addition, we measured the amount of unused wine and grape juice at the end of each drinking period. Finally, we measured participant HDL levels, which are typically positively correlated with recent alcohol consumption.

STATISTICAL ANALYSIS

We calculated counts and percentages for categorical data and medians and interquartile ranges for continuous data. We used mixed models to examine estimates and 95% confidence intervals (CI)s of within-person changes in sleep quality, depressive symptoms, and pain 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.[36] We performed analyses using SAS (version 9.4; SAS Institute Inc., Cary, NC, USA). All hypothesis tests were two-tailed.

RESULTS

536 women, who receive outpatient care at Beth Israel Deaconess Medical Center, were invited to participate in the study. 386 women were either not available or not interested in participating or did not respond to our invitation letter or call. 151 women were assessed for eligibility for participation and 131 of those women met some form of exclusion criteria. All 20 women who met inclusion criteria and were randomized completed the study (Figure 6). 9 of the 20 women were randomized to a drinking period of wine followed by a drinking period of grape juice and 11 of the 20 women were randomized to a drinking period of grape juice followed by wine.

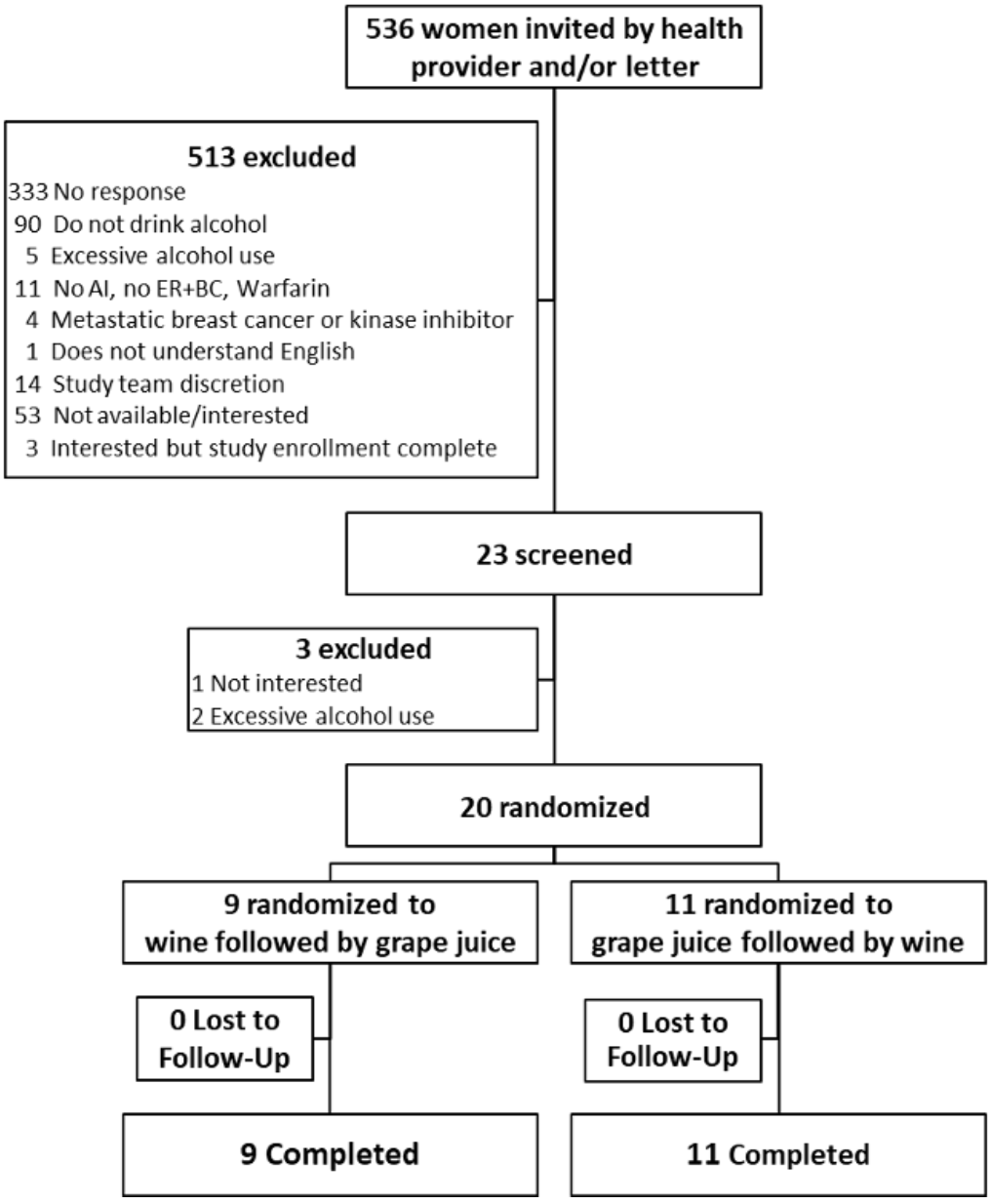


Figure 6. Consort diagram of recruitment and participation of 20 women in a pilot crossover trial

The baseline characteristics of the 20 participants of this study, who are postmenopausal women on AI therapy, are summarized in Table 2. The median age of all participants was 61 years, with an interquartile range of 50 years to 70 years. Twenty percent of the participants were Black or African American and fifteen percent identified as Hispanic or Latino. The median body mass index of 24.7 kg/m^2. Vital signs obtained from the BIDMC Clinical Research Center showed that the median heart rate measured amongst participants during baseline clinic visit was 64.5 BPM, the median systolic blood pressure was 124.5 mmHg and the median diastolic blood pressure was 76.8 mmHg. At the start of the study, participants had been taking aromatase inhibitors for about 2 to 5 years, with 65 percent of the participants taking anastrozole. The participants reported that they typically consumed alcohol 2 to 3 days out of the week, and consistent with eligibility criteria, they typically consumed one drink (one serving) on days that they consumed alcoholic beverages. There were no serious adverse events that occurred during the course of the study.

Table 2. Baseline characteristics for of 20 postmenopausal female trial participants, n (%) or median [IQR]

Age, years	61.0 [50, 70]
Black or African American	4 (20%)
Hispanic	
Hispanic or Latino	3 (15%)
Not Hispanic or Latino	17 (85%)
Body Mass Index, kg/m^2	24.7 [23.5, 28.5]
Heart Rate	64.5 [60, 71]
Systolic Blood Pressure	124.5 [111.5, 137.3]
Diastolic Blood Pressure	76.8 [69, 82.5]
Alanine Transaminase (ALT), U/L	13.5 [11, 18.5]
Aspartate Aminotransferase (AST), U/L	16 [15, 20]
Estimated Glomerular Filtration Rate (eGFR), mL/min/1.73m^2	83.5 [70, 87.5)
Aromatase Inhibitor	
Anastrozole	13 (65%)
Exemestane	2 (10%)
Letrozole	5 (25%)
Aromatase Inhibitor Use (years)	3.1 [1.8, 5.1]
Alcohol Use Disorders Identification Test (AUDIT) Score	3.0 [2, 3]
# Days Per Week that Drink Alcohol	2.3 [1.0, 3]
# Servings of Alcohol Per Drink Day	1 [1, 1]

Participants were asked to assess their depressive symptoms and pain intensity throughout the first drinking period in Surveys 3, 4, 5 and throughout the second drinking period in Surveys 8, 9, 10. Surveys were also conducted following each of the respective drinking periods in Surveys 5 and 10. The Center

for Epidemiologic Studies Depression Scale (CESD-10) was used to assess depressive symptoms. Scores on the scale range from 0 to 30, with a higher score reflecting a higher level of depressive symptoms. During both of the 3-week drinking periods, those drinking wine rated their depressive symptoms as 1.3, while those drinking grape juice rated their symptoms as 1.62, showing a nearly negligible difference between the two groups. (Table 4) After the two drinking periods, rating of depressive symptoms on the CESD-10 were slightly lower following wine consumption compared to grape juice consumption, with scores of 3.28 versus 2.41, respectively. (Table 3)

Pain was assessed using a pain visual analog scale (VAS), where participants rated their average pain intensity on a scale of 0 to 100. During both drinking periods, participants rated their pain intensity to be marginally higher with wine consumption with a pain rating of 15.77 as compared to grape juice consumption with a pain rating of 12.78. After the drinking periods, the rating of pain intensity was slightly lower compared to ratings during the drinking periods. Again, there is a marginal difference between wine and grape juice, with a higher rating of pain of 13.97 after wine consumption than a rating of 11.68 after grape juice.

Table 3. Measure of Depressive Symptoms and Pain following First and Second Drinking Periods

			Surveys 5 and 10				
Measure	**Exposure**	**Drink**	**Estimate**	**Lower**	**Upper**	**95% CI**	**Probability**
CESD-10	Depressive Symptoms (Range 0 to 30)	Grape Juice	3.2775	1.6588	4.8962		
CESD-10	Depressive Symptoms (Range 0 to 30)	Wine	2.4129	0.7959	4.0299	-0.86 (-1.73, 0)	0.0507
Pain VAS	Pain (Range 0 to 100)	Grape Juice	11.6841	3.0641	20.3041		
Pain VAS	Pain (Range 0 to 100)	Wine	13.9716	5.3586	22.5846	2.29 (-0.54, 5.12)	0.1069

Table 4. Measure of Depressive Symptoms and Pain during First and Second Drinking Periods

			Surveys 3,4,5 and 8,9,10				
Measure	**Exposure**	**Drink**	**Estimate**	**Lower**	**Upper**	**95% CI**	**Probability**
CESD-10	Depressive Symptoms (Range 0 to 30)	Grape Juice	1.6232	0.8176	2.4287		
CESD-10	Depressive Symptoms (Range 0 to 30)	Wine	1.2974	0.5173	2.0774	-0.33 (-0.87, 0.22)	0.2271
Pain VAS	Pain (Range 0 to 100)	Grape Juice	12.775	9.6444	15.9055		
Pain VAS	Pain (Range 0 to 100)	Wine	15.7694	12.7817	18.757	2.99 (-1.17, 7.16)	0.1489

We did not observe clinically meaningful or statistically significant changes in sleep, depressive symptoms, or pain between drinking grape juice versus drinking wine. There was a slight trend toward lower scores for depressive symptoms following wine consumption period compared to grape juice consumption period, but with a decrement of 0.86 (95% CI: converse -1.73 to 0) points on a CESD-10 score ranging from 0 to 30. With this scale, the decrease observed in depressive symptoms score is close to negligible. Conversely, we

observed a slight trend toward higher pain scores following wine consumption compared to grape juice consumption with a 2.29 (95% CI: -0.54 to 5.12) increase in a visual analog scale ranging from 0 to 100. Once again, on this scale, the increase in pain scores observed with wine consumption is close to negligible (Figure 7).

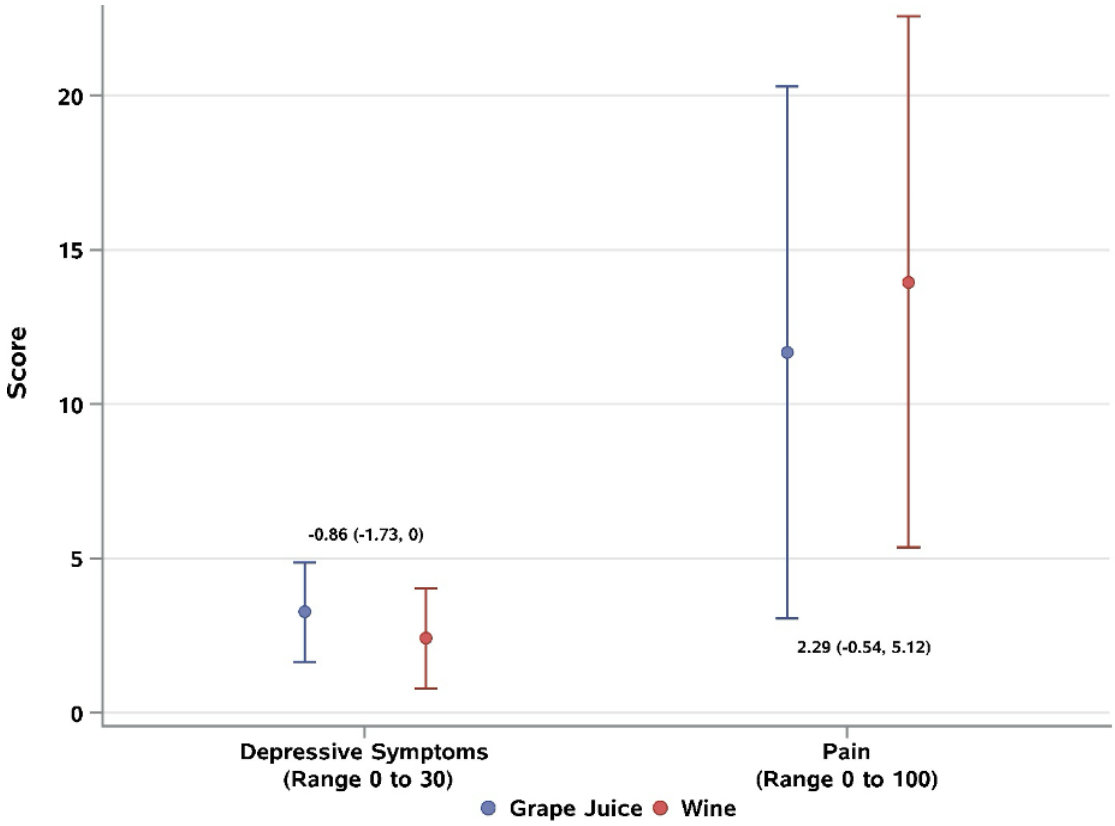


Figure 7. Within-person changes in depressive symptoms and pain

In this figure, we see a graphical presentation of within-person changes in depressive symptoms (from the Center for Epidemiologic Studies Depression Scale-10) and pain (from a visual analog scale) following white wine compared to following white grape juice among 20 postmenopausal women on aromatase inhibitor therapy. Vertical lines indicate least squared means and 95% confidence intervals for each domain by drink phase. The difference (and 95% confidence interval) in least squared means between wine compared to grape juice are included.

To assess sleep quality following alcohol consumption, the Pittsburgh Sleep Quality Index (PSQI) was used to evaluate aspects of sleep such as sleep quality, sleep disturbances and sleep latency. Each of the component scores that assess a different aspect of sleep are scored on a scale of 0 to 3 and all of the component scores are summed together into a PSQI total, ranging on a scale of 0 to 21. Higher scores on the PSQI scale indicate higher levels of sleep disturbance. Following the drinking periods, overall sleep quality with wine consumption was slightly better than grape juice consumption, with a total PSQI score of 5.95 versus 6.44, respectively. No meaningful differences in sleep latency were observed between wine and grape juice consumption. There was a negligible difference in score, with a 1.79 rating of latency after drinking wine for 3 weeks compared to a 1.84 rating of latency after drinking grape juice. Total duration of sleep time (in hours) also did not have any meaningful difference between wine and grape juice. Following wine consumption, participants slept an average of 7.01 hours versus 6.97 hours following grape juice consumption. Following the period of wine drinking, sleep efficiency was marginally higher at 88.94% compared to a sleep efficiency of 85.56% following grape juice drinking.

Table 5. Measure of Sleep Quality following First and Second Drinking Periods

			Surveys 5 and 10				
Measure	**Exposure**	**Drink**	**Estimate**	**Lower**	**Upper**	**95% CI**	**Probability**
PSQI	PSQI Total (Range 0 to 21)	Grape Juice	6.4442	4.6014	8.2869		
PSQI	PSQI Total (Range 0 to 21)	Wine	5.9460	4.0935	7.7985	-0.5 (-1.83, 0.84)	0.4438
PSQI	Sleep Quality (Range 0 to 3)	Grape Juice	0.5193	0.2049	0.8336		
PSQI	Sleep Quality (Range 0 to 3)	Wine	0.3353	0.01861	0.6519	-0.18 (-0.49, 0.12)	0.2227
PSQI	Sleep Latency (Range 0 to 3)	Grape Juice	1.8350	0.9161	2.7539		
PSQI	Sleep Latency (Range 0 to 3)	Wine	1.7999	0.8836	2.7162	-0.04 (-0.39, 0.32)	0.8373
PSQI	Sleep Disturbances (Range 0 to 3)	Grape Juice	1.2592	1.0197	1.4987		
PSQI	Sleep Disturbances (Range 0 to 3)	Wine	1.2481	1.0063	1.4899	-0.01 (-0.3, 0.28)	0.9364
PSQI	Sleep Duration (Hours)	Grape Juice	6.9676	6.5244	7.4108		
PSQI	Sleep Duration (Hours)	Wine	7.0104	6.5460	7.4749	0.04 (-0.53, 0.61)	0.8761

PSQI	Sleep Efficiency (%)	Grape Juice	85.5614	77.9624	93.1603		
PSQI	Sleep Efficiency (%)	Wine	88.9362	81.3785	96.4939	3.37 (-7.24, 13.99)	0.5127

There were no meaningful changes in sleep quality with wine versus grape juice. There was a small but negligible decrease in the overall PSQI score for sleep problems, suggestive of small improvements in sleep quality (-0.42, 95%CI -1.6 to 0.77) .There were no meaningful changes between grape juice versus wine consumption in any of the seven components of sleep quality (Figure 8).

The median HDL levels were almost identical following grape juice (67.5 mg/dL) and wine (68 mg/dL). There were no major concerns of nonadherence based on self-reported intake and measurements of leftover drinks.

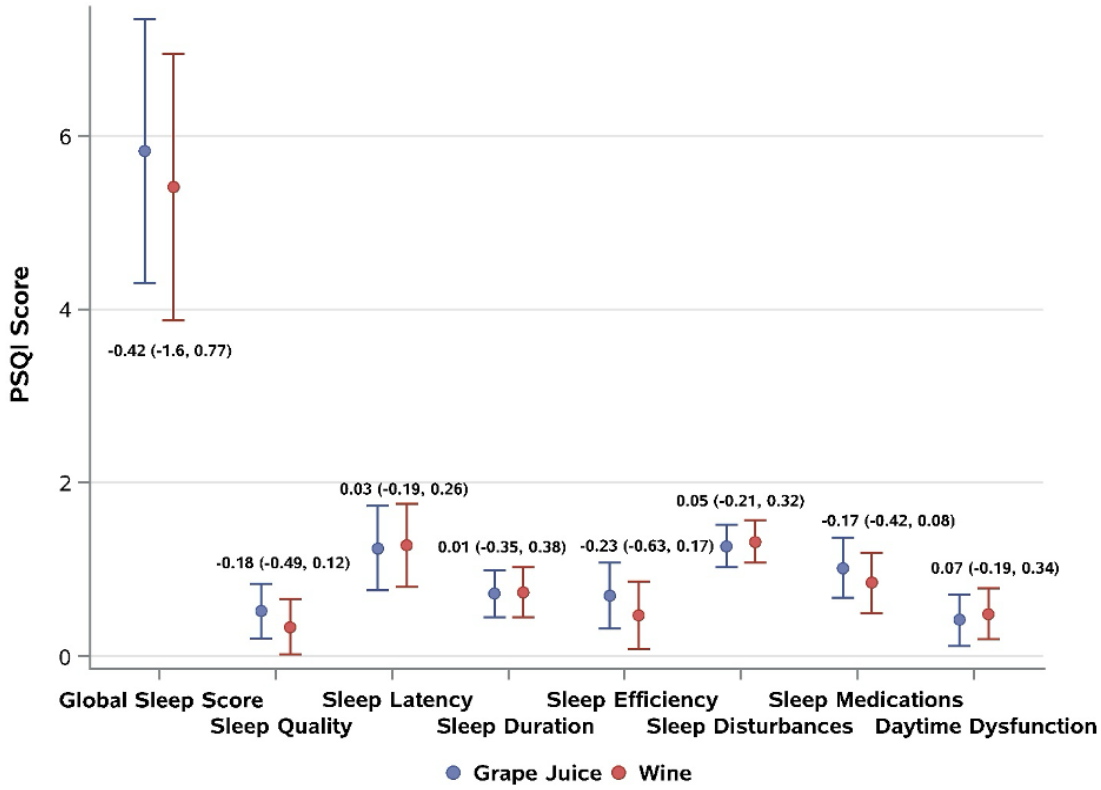


Figure 8. Within-person changes in overall sleep quality and sleep domains from the Pittsburgh Sleep Quality Index

This figure shows a graphical represention of within-person changes in overall sleep quality and sleep domains from the Pittsburgh Sleep Quality Index following white wine compared to following white grape juice among 20 postmenopausal women on aromatase inhibitor therapy. Vertical lines indicate least squared means and 95% confidence intervals for each sleep domain by drink phase. The difference (and 95% confidence interval) in least squared means between wine compared to grape juice are included.

DISCUSSION

Alcohol Consumption on Sleep, Pain and Depressive Symptoms in women on Aromatase Inhibitor Therapy

In this pilot randomized controlled crossover trial with women taking aromatase inhibitors, there were no clinically meaningful changes in sleep, depressive symptoms, or pain following one serving of white wine daily compared to scores following one serving of grape juice daily.

While this is the first study to examine the effects of alcohol on sleep, depressive symptoms, and pain among women on AI therapy, there have a been a few studies of alcohol effects on these symptoms in other populations. The effect of alcohol on sleep characteristics is complex; on the one hand, its sedative effects may suggest that it would improve sleep. On the other hand, it disrupts circadian rhythm and increases breathing-related sleep events, which can diminish sleep quality.[37]

In a crossover trial of 31 participants who completed two overnight laboratory visits with polysomnographic sleep recording, alcohol led to decreased total sleep time, sleep efficiency, and altered sleep architecture.[18–20] In a 7-day in-home study, 785 participants in the Jackson Heart Sleep Ancillary Study completed a nightly questionnaire and reported whether they consumed “any

alcoholic drinks in the 4 hours before bedtime (beer, wine, hard liquor)". Sleep characteristics were measured with wrist actigraphy. Compared to a night without alcohol use before 4 hours of bedtime, a night with evening use of alcohol had an average 0.98% (95% CI: −1.67% to −0.29%) lower sleep efficiency score, but did not have statistically significant differences in wake after sleep onset or sleep duration, even after controlling for age, BMI, educational attainment, having work/school the next day, and mental health symptomatology.[21] Conversely, randomized trials that assessed the effects of habitual alcohol intake reported that 150 mL of wine per day increased self-reported sleep quality. In a 3-month trial of 109 people with type 2 diabetes, participants in the alcohol group reported an improvement in the ability to fall asleep.[22] In a two-year study of 224 participants with type 2 diabetes, sleep quality improved among those randomized to wine compared to those randomized to water.[23] Recent studies suggest that even low levels of alcohol intake are associated with sleep disturbances.[38] From our study, we used the PSQI, a self-report measure, to assess sleep quality. Amongst our participants, we observed a small, negligible decrease in sleep score, suggesting slight improvement in sleep quality. However, no significant changes were found in regard to sleep quality between consumption of wine versus grape juice.

Regarding the effects of alcohol on mood, a crossover trial randomized 28 women to four conditions; they received 3 glasses of sparkling white wine (30 g alcohol) or alcohol-free sparkling white wine while having dinner in a room with either a pleasant or unpleasant created ambiance. Moderate alcohol consumption increased happiness scores in the unpleasant, but not in the pleasant ambiance. Alcohol consumption increased happiness and stimulation feelings within 1 hour and increased sedative feelings and sleepiness for 2.5 hours.[25] A small, randomized trial reported that alcohol transiently decreases negative affect among women,[26] but other studies report no acute changes in affect following alcohol intake.[27] Using the CESD-10 scale to evaluate for mood via reporting of depressive symptoms, we found that there were slightly lower scores for depressive symptoms following wine consumption, suggesting an improvement to mood with alcohol consumptions, but again the changes observed were not significant.

There are a few discrepant findings on the acute effect of alcohol on pain sensitivity. A meta-analysis of 18 experiments reported that alcohol intake may reduce pain sensitivity at higher levels of intake.[28] However, another review concluded that moderate alcohol intake reduced pain whereas excessive drinking led to greater pain sensitivity.[29] Using a pain visual analog scale for

participants to rate pain intensity, our study found a slight trend towards higher pain ratings following wine consumption. This, however, was a nearly negligible difference and cannot provide a clinically meaningful association between alcohol consumption and pain for women on AI therapy.

Strengths and Limitations of Study Design

Strengths of our study design are the crossover design and placebo control that we used. By having each participant consume both grape juice and wine at different time points, it allowed for us to use each participant as a control for themselves. Using a within-person comparison allowed us to maximize statistical efficiency. Additionally, we used two different visual analog scales to have participants assess both average pain and pain intensity, which gave us multiple measurements for rating pain. With only 20 participants and a study design with a short intervention period and washout periods, it allowed for us to monitor adherence to the intervention more easily and may have contributed to the high compliance amongst participants. We also chose to use wine rather than pure ethanol because we have learned from prior experience that the poor taste severely impairs recruitment and adherence.[39] Additionally, most women with

breast cancer who drink alcoholic beverages prefer wine, so that improved the likelihood of high adherence.

The limitations of our study were the small sample size of only 20 participants, and that there were no objective measures we used for alcohol adherence, sleep quality or pain. As a pilot study with only 20 women, this may have affected the statistical significance we were able to achieve in our results. We did not have sufficient power to examine a potential differential effect across aromatase inhibitor types, but previous studies have shown they have similar efficacy. However, through this study we were able to learn about the potential for conducting a larger study to explore within-person changes in symptoms following alcohol intake, and the results of our study would require confirmation through larger scale studies.

Alcohol adherence was assessed with self-report from participant calls, measurement of leftover wine at the end of the drinking period and HDL levels that are usually positively correlated with alcohol consumption. It is possible that higher doses of alcohol would have led to larger changes in scores. We chose to use white wine since red wine is a rich source of polyphenols and may have some AI properties. Nonetheless, we aimed to assess the effects of drinking

within the current recommendation for current drinkers to limit their intake to one serving per day.

Pain was assessed using visual analog scales with a self-report measure of pain levels and no objective measurement was used. However, we used multiple measurements that assessed for pain and participants were assessed each week, allowing us to collect more information about a participant's pain symptoms. Sleep quality was assessed using the Pittsburgh Sleep Quality Index (PSQI) where participants rate their own sleep quality, and thus also was not an objective measurement. In addition, we only used one measurement to assess sleep quality and the PSQI was only conducted after each of the two drinking periods. Obtaining an objective measurement of sleep would likely not be feasible for this scale of study and the PSQI is already able to provide us with ratings of different elements of sleep quality, such as subjective sleep quality, sleep duration and sleep disturbances.

Implications for Public Health and Future Research

As a pilot trial with limited statistical precision, more research is needed before translating these findings for clinical guidance on alcohol intake among women using AIs. The current recommendation for all women is that if women

drink, alcoholic beverages they should limit their intake to one drink per day on days when alcohol is consumed.[40] Our study largely suggests that there are not significant changes seen within these psychosocial domains. Women on AI therapy may want to continue adhering to current recommendations of limiting alcohol intake, but they may be reassured that wine consumption likely will not have a severe negative impact on factors such as sleep, pain or mood.

With our sample of 20 women, we saw some borderline statistical significance in our results regarding changes in sleep, pain and mood. Thus, it could be useful for further studies in larger clinical trials to assess these effects with a larger sample of participants and more measurements of each of these symptoms. With more participants, it could potentially confirm the magnitude of the effects of alcohol consumption on these psychosocial domains.

Future studies may want to further explore symptoms of sleep, pain and mood using different questionnaires and scales to obtain more measurements and may want to consider using more frequent assessments or a longer intervention period in order to collect more values. Our study only assessed these three elements of sleep, pain and mood, but a larger study may also consider including measures to look at other psychosocial factors such as stress, cognitive function and memory.

Conclusions

In conclusion, in this randomized controlled crossover trial, one serving of alcohol daily for three weeks did not have clinically meaningful effects on sleep quality, depressive symptoms, or pain intensity. Additional studies would be warranted to follow up on these exploratory findings.

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