Vascular Function of Breast Cancer Survivors on Aromatase Inhibitors Over Time

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ABSTRACT

Background: Aromatase inhibitors (AIs) have been an effective method of reducing breast cancer mortality in estrogen receptor positive (ER+) breast cancer patients. However, AIs have been associated with risk factors of cardiovascular disease (CVD), such as hyperlipidemia and hypertension. The impact of AIs on body composition and overall cardiovascular risk continue to be unclear.

Methods: 18 postmenopausal women (9 on AIs, 9 healthy controls) had physical measurements, blood samples, and DEXA scans of body fat composition collected at baseline, 4 weeks, 12 weeks, and 52 weeks.

Results: At baseline, the AI group had higher median weight (78.1 kg vs 63.9 kg) and insulin level (10 units vs 5 units), suggesting that they may start at a higher risk for CVD than the controls. The median of changes from baseline to 52 weeks of the AI group and control group were measured for total cholesterol (3 mg/dL vs 3.5 mg/dL, p=0.54), LDL (-10 mg/dL vs -2.5 mg/dL, p=0.92), HDL (1 mg/dL vs 8.5 mg/dL, p=0.31), blood pressure (systolic -3 mmHg vs -10 mmHg, p=0.037; diastolic -1 mmHg vs -6.5 mmHg, p=0.47), lean body mass (0.46 kg vs 0.034 kg, p=0.37), total fat mass (-0.10 kg vs 0.27 kg, p=1), and percent body fat (0.7% vs -0.3%, p=0.32).

Conclusion: These results suggest the use of AIs for ER+ breast cancer treatment may adversely increase the risk for CVD.

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INTRODUCTION

Breast cancer is one of the most common cancer and leading causes of cancer death among women in the United States. It was estimated that in 2013, approximately 232,340 new cases of invasive breast cancer will be diagnosed and 39,620 deaths due to breast cancer will occur among US women.

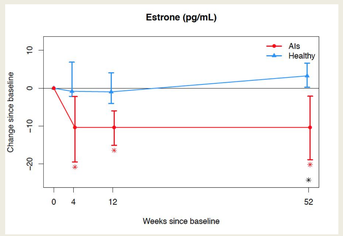
AIs have been an effective method of reducing breast cancer mortality in estrogen receptor positive (ER+) breast cancer patients. The AI works by blocking the activity of the aromatase enzyme, which is responsible for the synthesis of estrogen. The prevention of estrogen synthesis will thus inhibit tumor growth.

However, there has been suggestions in literature about AI usage and related musculoskeletal pain, as well as risk factors of cardiovascular disease (i.e.: hyperlipidemia and hypertension). The association between AIs and risk factors for cardiovascular disease (CVD) need to be further explored.

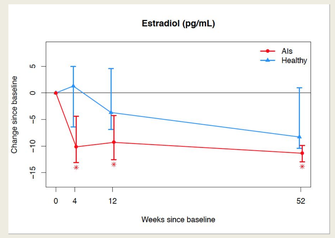
This poster presents the results of a prospective, observational pilot study on CV risk factors in females with breast cancer on AIs as compared to healthy controls.

METHODS AND MATERIALS

This study recruited 18 postmenopausal (55 to 85 years of age) women. Nine of the women were prescribed an AI treatment, and the other nine women were the healthy, age-matched controls. The inclusion criteria for the AI treatment group was women diagnosed with nonmetastatic, ER+ breast cancer, undergone lumpectomy (but not chemotherapy), and were currently prescribed to an AI. Exclusion criteria for both groups included tobacco users (defined as any tobacco use for the last three years), steroid users, or those diagnosed with a clinically significant thyroid abnormality. Participants in the study had physical measurements, blood samples, and DEXA body scans collected at baseline (before AI and radiation therapy), 4 weeks, 12 weeks, and 52 weeks. IRB approval and informed consent was obtained. The data collected was analyzed using the Wilcoxon-Rank Sum test.



Graph 1. Changes in Estrone Levels Over Time



Graph 2. Changes in Estradiol Levels Over Time

RESULTS

- At baseline, the AI group had higher median weight, initial insulin level, initial glucose level, BMI measurement, Insulin-like Growth Factor 1 (IGF-1) count, total cholesterol, low density lipoprotein (LDL) and very low density lipoprotein (VLDL) count, triglyceride count, testosterone levels, and total percent fat than the healthy control group
- At baseline, the AI group had a lower age, high density lipoprotein (HDL) count, estradiol levels, and globulin concentrations than the healthy control group
- In the changes in the physical data from baseline to 52 weeks, the only variables with a p-value <0.05 were the VLDL count, triglyceride count, and estrone levels
- The variables above are also outlined in tables 1 & 2

Table 1. Baseline Data in AI Group and Healthy Control Group

[1] The summary shown is median (1st quantile, 3rd quantile)
[2] One woman on AI is missing initial insulin measurements

	Women on AIs[1] (n = 9)	Healthy Controls[1] (n = 9)
Baseline Age (years)	62 (60, 65)	67 (67, 74)
Weight (kg)	78.1 (73.9, 81.0)	63.9 (63.2, 70.9)
BMI (kg/m^2)	29.8 (28.6, 31.9)	24.4 (22.8, 31.1)
Insulin-like Growth Factor 1 (ng/mL)	99 (72, 153)	94 (79, 138)
Total Cholesterol (mg/dL)	195 (189, 203)	188 (174, 202)
LDL (mg/dL)	127 (121, 137)	123 (96, 128)
VLDL (mg/dL)	21 (17, 30)	16 (15, 17)
HDL (mg/dL)	52 (42, 59)	62 (57, 69)
Triglycerides (mg/dL)	105 (84, 148)	82 (77, 83)
Estradiol (pg/mL)	48.4 (43.4, 58.4)	50.6 (33.5, 63.1)
Testosterone (ng/mL)	1.07 (0.477, 1.44)	0.406 (0.272, 0.824)
Globulin (nmol/L)	70.3 (45.7, 85.4)	97.7 (73.4, 126)
Initial Glucose (mmol/L)	94 (91, 96)	93 (91, 95)
Initial Insulin[2] (units)	10 (4, 25)	5 (4, 7)
Total Fat (kg)	33.2 (28.4, 37.4)	19.5 (19.0, 28.4)
Total Lean (kg)	43.5 (40.4, 46.8)	42.0 (41.3, 44.8)
Total Percent Fat	40.3 (39.6, 44.3)	34.6 (29.4, 39.7)

Table 2. Changes in Data from Baseline to Week 52 in AI Group and Healthy Control Group

[1] The summary shown is median (1st quantile, 3rd quantile)
[2] Two women on AIs are missing IGF-1 measurements at the week 52 visit

	Women on AIs[1] (n = 9)	Healthy Controls[1] (n = 8)	p-value
Weight (kg)	1.2 (0.40, 2.2)	0.15 (-0.65, 0.57)	0.20
BMI (kg/m^2)	0.53 (0.26, 0.84)	0.22 (-0.20, 0.38)	0.24
Insulin-like Growth Factor 1[2] (ng/mL)	10 (-1, 34)	-16 (-28, 24)	0.32
Total Cholesterol (mg/dL)	3 (-4, 25)	3.5 (-12, 12)	0.54
LDL (mg/dL)	-10 (-21, 8)	-2.5 (-14, 3.8)	0.92
VLDL (mg/dL)	**6 (3, 7)**	**-3 (-6, 0.25)**	**0.010**
HDL (mg/dL)	1 (-2, 10)	8.5 (0.75, 12)	0.31
Triglycerides (mg/dL)	**30 (17, 33)**	**-16 (-29, 1)**	**0.0045**
Estrone (pg/mL)	**-10 (-19, -2.1)**	**3.3 (0.29, 6.6)**	**0.0093**
Estradiol (pg/mL)	-11 (-13, -9.9)	-8.3 (-10, 0.98)	0.17
Testosterone (ng/mL)	0.048 (-0.083, 0.22)	0.036 (0.015, 0.18)	0.96
Globulin (nmol/L)	-4.3 (-7.4, 2.3)	7.5 (-9.8, 14)	0.74
Total Fat (kg)	0.46 (0.043, 1.5)	0.034 (-1.0, 0.82)	0.37
Total Lean (kg)	-0.10 (-1.5, 1.2)	0.27 (-0.34, 0.61)	1
Total Percent Fat	0.7 (-0.5, 1.9)	-0.3 (-1.7, 0.8)	0.32

DISCUSSION

- Higher median weight, BMI measurement, Insulin-like Growth Factor 1 (IGF-1) count, total cholesterol, triglyceride count, and total percent fat, all are contributing risk factors to CVD. At baseline, these variables were present at higher concentrations in the AI treatment group than in the healthy control, suggesting that the AI treatment group may already be at a higher risk for CVD prior to AI usage.
- Initial insulin levels were present at higher concentrations in the AI group than the control group. But one healthy control did not have data for that variable-- which could have skewed the data. However, initial glucose levels were also present at higher concentrations in the AI group than the control group, albeit not by much. High levels of glucose and insulin are precursors to diabetes, and diabetes increases risk for CVD.
- LDL and VLDL are considered to be the “bad” cholesterols, because high concentrations will increase CVD risk. At baseline, the AI group had higher concentrations of LDL and VLDL than the healthy control, suggesting that the AI group may already be at a higher risk for CVD prior to AI usage.
- Globulin binds to testosterone to degrade it, thus lower globulin concentrations indicates higher levels of free testosterone. Higher testosterone levels have been associated with a higher risk for CVD.
- The AI group overall were younger than the healthy controls. Despite being younger, the data suggests that they have a higher CV risk than the controls. These risks will continue to increase with age.
- The control group had higher HDL count and estradiol levels. HDL is the “good” cholesterol, associated with a lower CVD risk. Estradiol and estrone are derivatives of the hormone estrogen, which has also been associated with a lower CVD risk.
- “Significant” data in table 2 (p-value <0.05) suggests that the contrast of risk for CVD between the AI group and control group increased during the study.
- One of the limitations of this study was the small sample size.

CONCLUSIONS

These results suggest the use of AIs for ER+ breast cancer treatment may increase triglyceride count, increase VDL count, and decrease estrone levels. Because of the associations mentioned in the discussion, these changes may adversely increase the risk for CVD.

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