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Endogenous Estradiol Is Not Associated with Poor Physical Health in Postmenopausal Breast Cancer Survivors

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Abstract

Background: Among postmenopausal breast cancer survivors, poor physical health has been associated with higher risks of breast cancer events. Obesity and physical inactivity are known risk factors for poor physical health, while circulating estrogen is an additional potential risk factor. We tested the hypothesis that the relationship between poor physical health and worse breast cancer outcomes is mediated by higher estrogen concentrations associated with body size and physical inactivity.

Methods: We used data from 1030 postmenopausal breast cancer survivors to examine the association between serum estradiol levels, body mass index (BMI), physical activity, and RAND-36-item Health Survey (SF-36) physical health.

Results: In univariate analysis, poor physical health was associated with higher estradiol levels, in addition to obesity and low physical activity. Higher estradiol levels were significantly associated with higher odds of poor physical health (odds ratio, OR, 1.20 [95% confidence interval 1.03–1.39]) in a multivariable model adjusting for age, cancer stage and treatment, alcohol use, and physical activity. However, the relationship between estradiol levels and poor physical health was no longer significant (OR 1.06 [0.91–1.24]) after adding BMI in the model. In multivariate analysis, only poor physical health resulted in higher risks of recurrence (hazard ratio 1.33 [95% CI 1.08–1.64]).

Conclusions: These findings indicate that estradiol is related to poor physical health, but is not an independent risk factor from body size or inactivity. While obesity and physical activity in survivorship are potential targets for improving physical health, other biological processes that impact physical health, e.g. inflammation, remain to be identified.

Introduction

IN THE UNITED STATES, there are an estimated 2.6 million breast cancer survivors who are at risk of secondary breast cancer outcomes and death.¹ Among breast cancer survivors, poor self-reported physical health was identified as a significant risk factor for additional breast cancer events and mortality in the Women's Healthy Eating and Living (WHEL) randomized trial, an observation recently confirmed in the After Breast Cancer Pooling Project.^{2,3} The mechanisms underlying the association between poor physical health and adverse breast cancer outcomes are not clear.

In the WHEL randomized trial, poor physical health was related to obesity and inactivity.^{2,4} The link between poor physical health, obesity and inactivity, and secondary breast

cancer outcomes may be mediated by circulating estradiol concentrations. Estrogen has been implicated in the pathogenesis of breast cancer^{5–7} as well as in disease progression⁸; the majority of tumors in this population express estrogen receptors.^{9,10} Minimizing estrogen exposure is a standard management strategy for the majority of patients who have estrogen responsive tumors.¹¹ In postmenopausal women, estrogen biosynthesis occurs at peripheral sites, particularly in adipose tissue where biosynthesis is mediated by aromatase enzymes.¹² Adipose production of estrone and estradiol, the principal estrogens in postmenopause, occurs as a result of aromatization of 19-carbon androgens primarily from adrenal glands, including androstenedione, DHEA and testosterone.¹³ With obesity, both androgen production and aromatase activity are increased.¹⁴ In the past ten years,

aromatase inhibitors have become standard adjuvant treatment for postmenopausal breast cancer survivors to control the peripheral production of estrogens.^{15,11} To date, the association between estradiol, the most potent circulating estrogen in postmenopausal women, and physical health has not been tested.

Among postmenopausal women, both larger body size¹⁶ and lower physical activity levels^{17,18} are known to be associated with higher circulating estrogen concentrations. Further, as those with larger body size are less likely to be physically active, the combination of these two lifestyle variables, as occurs in those with poor physical health, could be expected to be associated with even higher estradiol concentrations. The objective of this study was to test the hypothesis that poor physical health in breast cancer survivors may be explained by the higher estradiol concentrations associated with larger body size and lower physical activity levels.

Methods

Study population

Details of the WHEL trial have been published previously.¹⁹ WHEL participants were between ages 18 and 70 years at breast cancer diagnosis, had Stage I–III invasive disease, and completed primary therapy but were still within 1–4 years of diagnosis, with no evidence of recurrence. Menopausal hormone therapy was an exclusion criterion in the study. Participants were recruited between March 1995 and November 2000. Of 3088 participants, there were 2448 postmenopausal women.²⁰ Blood samples were drawn at the enrollment and year-1 clinic visits. The current analysis focused on the 1030 postmenopausal women who had serum estrogen levels measured at baseline to address other hypotheses.^{8,21} Among these women, 816 had estrogen levels also measured 1 year after baseline.

Lifestyle assessments

At the enrollment clinic visit, height and weight were measured without shoes using a stadiometer and a medical balance or electronic scale by study personnel at the enrollment clinic visit and used to calculate body mass index (BMI, kg/m²), and standardized questionnaires were used to collect demographic, smoking history, and quality of life assessments. Alcohol intake was assessed by a set of four 24-hour dietary intake recalls. Cancer and treatment characteristics were abstracted from medical records and verified by a site oncologist. Ten percent of records were reviewed by the coordinating center oncologist for quality control purposes, with any discrepancies adjudicated by the study pathologist. Physical health was assessed using the RAND 36-item Health Survey (SF-36), which has four physical health subscales: general health perceptions, physical functioning, bodily pain, and role limitations due to physical health problems. These subscale scores were combined into a physical health summary score with a range of 0 to 100. Higher scores indicated better physical health. Physical activity was assessed using a 9-item measure of physical activity originally designed for the Women's Health Initiative²² and were validated in a subsample in this study.²³ Responses were converted to metabolic equivalent tasks (METs) in hours per week.²⁴

Estradiol assessment

Enrollment blood samples were assayed for estradiol concentrations in the Reproductive Endocrine Research Laboratory at the University of Southern California. Estradiol (total, bioavailable, and free) were selected over estrone and other endogenous estrogens because of high bioactivity and affinity for the estrogen receptor.¹³ Serum estradiol levels were measured by radioimmunoassay after organic solvent extraction and celite column chromatography to optimize sensitivity. The level of detection for estradiol was 4 pg/mL, and the intra-assay and inter-assay coefficients of variation ranged from 12% to 14% at low, medium, and high levels in quality-control samples. Levels below the sensitivity of the assay were assigned 3.0 pg/mL in analyses.

Statistical analysis

Demographic, cancer characteristics, physical health, and lifestyle variables were summarized by proportions and means (95% confidence interval [95% CI]), as appropriate. Estradiol levels were log-transformed to approximate a normal distribution. From our prior work^{2,25} and to provide clinical relevance, physical health scores were dichotomized into those below or above the 40th percentile of physical health scores (SF-36 score \leq 75.6), as this was the threshold associated with breast cancer outcomes. For physical activity, a cutoff of 10.0 MET-hours per week was selected, consistent with aerobic activity recommendations for this population from the American College for Sports Medicine.²⁴

Logistic regression models examined univariate associations with poor physical health for variables including estradiol, BMI, physical activity, and cancer and treatment characteristics. Multivariate analysis modeled the effect of serum estradiol on physical health, with adjustment for age at diagnosis, BMI, physical activity, and other potential confounders identified in the univariate models ($p < 0.1$). The association between change in physical health status and the change in serum estradiol levels from baseline to year 1 was tested using generalized estimating equation models for repeated measures. Finally, delayed entry Cox proportional hazards models (adjusted for time between diagnosis and study entry) examined associations with breast cancer recurrence for physical health and other predictors. Age, tamoxifen, and chemotherapy are known to impact estrogen levels in postmenopausal women and were included in multivariate models. Analysis was conducted in SAS version 9.3.

Results

Enrollment characteristics of the participants are depicted in Table 1. Of 1030 participants, 430 (42%) had SF-36 scores below the 40th percentile, consistent with our prior data. The mean age (SD) of participants was 53.5 (8.2) years, and the majority were white, never smokers, who consumed very little alcohol. Most women had been diagnosed with infiltrating ductal, estrogen receptor positive (ER+) Stage II disease. As expected, 62% of the population took endocrine therapy, namely tamoxifen, as enrollment occurred before aromatase inhibitors were in general use. In this postmenopausal population, estradiol levels were detectable in 90% of participants. The geometric mean estradiol level (SD, interquartile range) was 9.4 (2.5, 1.5–12.9) pg/mL. Just under one

TABLE 1. BASELINE CHARACTERISTICS OF THE STUDY POPULATION AND UNIVARIATE ASSOCIATIONS WITH POORER PHYSICAL HEALTH

Participant characteristic	N=1030	OR [95% CI]
Age at diagnosis, mean±SD	53.5±8.2	1.0 [0.99–1.0]
Years between diagnosis and study entry, mean±SD	2.1±1.0	0.8 [0.7–0.9]
Ethnicity, n (%)		
White	886 (86.0)	Ref
Black	29 (2.8)	1.8 [0.8–3.7]
Hispanic	49 (4.8)	1.5 [0.8–2.7]
Asian	34 (3.3)	0.9 [0.4–1.8]
Other	32 (3.1)	0.9 [0.4–1.8]
BMI (kg/m ²), mean±SD	28.0±6.3	
Normal weight(<25)	385 (37.3)	Ref
Overweight (25–29.99)	333 (32.3)	1.4 [1.1–2.0]
Obese (>30)	312 (30.3)	3.0 [2.2–4.1]
Smoking (pack-years), n (%)		
Never	556 (54.0)	Ref
<20	316 (30.8)	1.1 [0.8–1.4]
>20	152 (14.8)	1.3 [0.9–1.9]
Alcohol consumption (>1 grams/day), n (%)	412 (40.1)	0.6 [0.5–0.8]
Tumor type, n (%)		
Infiltrating ductal	836 (81.2)	Ref
Infiltrating ductal and lobular invasive	58 (5.6)	0.8 [0.5–1.4]
Infiltrating lobular	97 (9.4)	1.2 [0.8–1.9]
Other	39 (3.8)	1.4 [0.7–2.6]
ER+, n (%)	750 (74.0)	1.0 [0.7–1.3]
PR+, n (%)	649 (64.5)	1.1 [0.9–1.5]
Breast cancer stage, n (%)		
I	295 (28.6)	Ref
II	479 (46.5)	1.3 [0.9–1.7]
III	256 (24.9)	1.6 [1.2–2.3]
Breast cancer subtype, n (%)		
Luminal (ER+ or PR+)	784 (76.1)	Ref
Her2 enriched (Her2+, ER–)	54 (5.2)	0.8 [0.5–1.4]
Triple negative (ER–, Pr– and Her2–)	116 (11.3)	0.9 [0.6–1.3]
Unspecified Receptors	76 (7.4)	1.2 [0.8–2.0]
Chemotherapy, n (%)	741 (72.0)	1.3 [1.0–1.7]
Tamoxifen use (current), n (%)	643 (61.6)	0.8 [0.6–1.1]
Physical activity (MET-hours/week) n(%)		
≤10	531 (51.6)	Ref
≥10	499 (48.5)	0.5 [0.4–0.6]
Estradiol level pg/mL, geometric mean±SD	9.4±2.5	1.2 [1.0–1.3]
Bioavailable estradiol level pg/mL, geometric mean±SD	4.7±3.2	1.1 [1.0–1.2]
Free estradiol level pg/mL, geometric mean±SD	0.2±3.7	1.1 [1.0–1.2]

ER, estrogen receptor; Her2, human epidermal growth factor receptor 2; MET, metabolic equivalent tasks; OR, odds ratio; CI, confidence interval; PR, progesterone receptor; SD, standard deviation.

third of women had a BMI greater than 30. Forty-eight percent of women self-reported physical activity greater than 10 MET-hours per week.

In univariate analysis, poorer physical health was significantly associated with higher estradiol levels at baseline (Table 1). Poor physical health was also significantly associated with increased body size, low physical activity, low alcohol consumption, chemotherapy exposure, and higher stage at diagnosis.

Higher estradiol levels were associated with younger age ($p < 0.001$), higher BMI ($p < 0.001$), and lower physical activity ($p = 0.007$). Women who consumed more than 1 gram of alcohol per day tended to have lower estradiol levels ($p = 0.07$).

Estradiol levels were not associated with current tamoxifen use ($p = 0.17$), chemotherapy, cancer stage or smoking (data not shown).

Multivariate analyses modeled the association between poorer physical health and estradiol (Table 2). In Model 1, higher estradiol levels were significantly associated with higher odds of poor physical health (odds ratio, OR, 1.20 [95% CI, 1.03–1.39]) after adjusting for age, time since diagnosis, tamoxifen use, prior chemotherapy, alcohol use, cancer stage, and physical activity. In Model 2, the relationship between estradiol levels and poorer physical health was no longer significant (OR 1.06 [0.91–1.24]) after adjusting further for BMI.

TABLE 2. MULTIVARIATE ANALYSIS OF ASSOCIATION BETWEEN PARTICIPANT CHARACTERISTICS AND PHYSICAL HEALTH (BASELINE)

	Model 1 adjusted OR [95% CI]	Model 2 adjusted OR [95% CI]
Log-transformed estradiol	1.16 [1.01–1.35]	1.03 [0.88–1.20]
Age at diagnosis < 50 (Reference)		
50–59	1.00 [0.73–1.37]	0.88 [0.64–1.22]
60–69	1.37 [0.93–2.00]	1.17 [0.79–1.73]
70–74	1.97 [0.35–11.01]	2.22 [0.40–12.31]
Cancer stage (Reference I)		
II	1.24 [0.89–1.73]	1.24 [0.87–1.75]
III	1.67 [1.11–2.50]	1.64 [1.08–2.44]
Tamoxifen (current use vs. no use)	0.80 [0.61–1.05]	0.86 [0.65–1.13]
Chemotherapy (prior chemotherapy vs. none)	1.20 [0.84–1.72]	1.01 [0.69–1.46]
Years diagnosis to study entry	0.79 [0.69–0.90]	0.76 [0.67–0.87]
Alcohol consumption (> 1g/day vs. < 1g/day)	0.63 [0.49–0.83]	0.70 [0.53–0.92]
Physical activity	0.51 [0.39–0.67]	0.59 [0.45–0.77]
BMI (Reference <25) Overweight	–	1.38 [1.00–1.90]
Obese	–	2.59 [1.83–3.67]

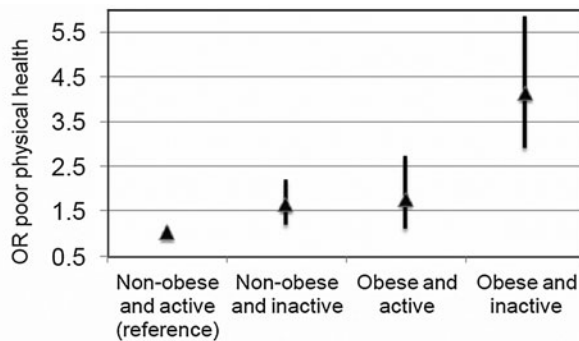
BMI, body mass index.

In the fully adjusted model, overweight or obese, low physical activity, older age, shorter time since diagnosis, higher stage cancer, and low alcohol consumption were independently associated with poor physical health, while estradiol was not. The odds of poor physical health was 4.1-fold higher in participants who were both obese and inactive compared to the reference group of active, non-obese women, and this was significantly higher than the odds of poor physical health with either obesity (OR 1.74 [1.10–2.73]) or inactivity (OR 1.61 [1.18–2.19]) alone (Fig. 1). In examining estradiol across these four groups, estradiol levels were significantly higher in obese than non-obese women but did not vary by physical activity status, supportive of estradiol as a marker of increased body size. The geometric mean (SD) estradiol level in non-obese women was 8.0 (2.5) pg/mL compared with 13.6 (2.0) pg/mL in obese women ($p < 0.001$). Among obese women, the geometric mean (SD) estradiol level was 14.2 (2.0) pg/mL in those with low physical activity compared to 12.4 (2.2) pg/mL in those with physical activity at recommended levels ($p = 0.12$). Mean estradiol levels did

not differ by physical activity status in women who were non-obese [8.1 (2.4) pg/mL vs. 8.0 (2.6) pg/mL]. There were no significant interactions between body size and physical activity and their association with physical health (data not shown).

Repeated measures analysis was performed to test the association between changes in physical health and changes in estradiol between baseline and year 1 of follow-up. Confirming the baseline analysis, there was a statistically significant association between poor physical health and higher estradiol levels in a model adjusting for age, time since diagnosis, stage, tamoxifen, chemotherapy, alcohol consumption, and physical activity ($p = 0.02$). However, once BMI was added to this model, the relationship between change in estradiol and change in physical health was no longer significant ($p = 0.46$).

Finally, in analyzing the association with breast cancer recurrence in this cohort, poor physical health was significantly associated with the hazards of developing recurrence in a Cox regression model adjusting for cancer stage and grade, time between diagnosis and study entry, chemotherapy, tamoxifen, age, alcohol intake, and smoking history (hazard ratio



Estradiol, Geometric mean (SD)

	N=401	N=317	N=98	N=214
Estradiol, Geometric mean (SD)	8.0 (2.6)	8.1 (2.4)	12.4 (2.2)*	14.2 (2.0)*

* $p < 0.001$ compared to reference

FIG. 1. Adjusted odds ratios (OR) of poor physical health by body mass index and physical activity categories.

TABLE 3. COX PROPORTIONAL HAZARDS MODELS FOR TIME TO BREAST CANCER RECURRENCE

	Model 1 ¹ adjusted HR (95% CI)	Model 2 ² adjusted OR (95% CI)
Poor physical health	1.33 (1.08–1.64)	1.35 (1.09–1.67)
Overweight		0.93 (0.72–1.20)
Obese		1.0 (0.74–1.15)
Low physical activity		0.87 (0.70–1.08)

¹Model 1 is adjusted for cancer stage and grade, chemotherapy, tamoxifen, age, alcohol intake, and time between diagnosis and study entry.

²Model 2 is fully adjusted for overweight/obesity, low physical activity, in addition to cancer stage and grade, chemotherapy, tamoxifen, age, alcohol intake, and time between diagnosis and study entry.

1.33 [95% CI 1.08–1.64]) (Model 1, Table 3). The addition of overweight/obesity and low physical activity did not change the magnitude or significance of the associations between physical health and recurrence (Model 2, Table 3).

Discussion

In postmenopausal breast cancer survivors, poor physical health is an important risk factor for cancer recurrence and mortality. In this report, women who were in poor physical health had higher circulating estradiol concentrations. However, our multivariate analysis suggests that the higher circulating estradiol concentrations among those in poor physical health probably came from obesity in this population. These findings indicate that estradiol may be in the pathway of developing poor physical health, but it is not an independent risk factor from body size. Additionally, these data show that poor physical health, not obesity or physical inactivity, resulted in higher risks for cancer recurrence. Therefore, there are likely additional mechanisms through which poor physical health confers higher risks for adverse outcomes.

Health-related quality of life has been shown to predict clinical outcomes. In particular, poor physical health has been associated with cancer prognosis.^{2,25,26} First demonstrated in the WHEL trial, this observation has been confirmed in the Nurses Health Study (JP Pierce, personal communication). As assessed by the SF-36, physical health is comprised of general health perceptions, bodily pain, physical functioning, and role limitations. In the WHEL cohort, physical functioning and role limitations subscales, as well as both baseline and change in physical health scores over the first year were, associated with shorter time to additional breast cancer events. Mechanistically, estradiol does not appear to explain the risk for poor physical health independent of obesity, suggesting additional mechanisms that impact physical health. Thus, future studies are needed to examine other candidate pathways, such as inflammation, that contribute to poor physical health.

Importantly, the combined effect of both obesity and low physical activity resulted in significantly higher odds of poor physical health than either risk alone. This finding suggests the possibility that interventions to improve physical health via targeting both risk factors may achieve a synergistic effect.

The data also showed that some alcohol consumption was positively associated with physical health. Data on the link between alcohol consumption and additional breast cancer events and mortality are not consistent.²⁷ In our prior analysis of WHEL data, alcohol intake was associated with favorable prognostic indicators such as lower cancer stage and grade, no chemotherapy, better educated, and more physically active.²⁷ These factors along with modest alcohol intake may contribute to better physical health.

In this study, we sampled 1030 WHEL Study participants with estradiol levels measured to test other hypotheses. Compared to postmenopausal participants in whom estradiol was not measured ($n=1418$), there are no differences in age, years between diagnosis and study entry, race/ethnicity, tumor type, alcohol consumption, or physical activity. Significant differences in recurrence rate (34.7% versus 1.9%), chemotherapy (72% vs 67%), tamoxifen (61.6% versus 66.4%), cancer Stage (28.6% Stage I versus 44.1% Stage I) were observed, a result of estradiol measurements from a case-control

substudy on recurrence).⁸ BMI was slightly higher in the participants included (28.0 versus 27.2), and current smoking was slightly lower (4% versus 5%). We conducted further sensitivity analyses to examine the effects of the sampling design on results. We used inverse probability weighting²⁸ to account for missing data on the estradiol measures. The weights were estimated using a logistic regression model to estimate the probability of being sampled for the estradiol study. The R package *survey* was used. The results from the weighted analysis were generally concordant with the unweighted models in Table 2: the odds ratio with 95% CI for log-estradiol in the weighted models were 1.27 [1.07,1.51] in Model 1 and 1.13 [0.94,1.37] in Model 2.

The strengths of this paper include sample size and use of validated and standardized questionnaires to assess quality of life measures. In addition, measurement of low postmenopausal estrogen levels was performed in a highly regarded research endocrinology laboratory with expertise in reliable and specific measurements of sex steroids. However, other biological processes—including inflammation as measured by markers such as C-reactive protein—were not assayed for this report, but are the topic of a future study. Our study enrolled participants who received endocrine therapy prior to widespread use of aromatase inhibitors. As aromatase inhibitors (AIs) lead to decreases in the already low postmenopausal estrogen levels, it is possible that the association between estrogen and poor physical health may not be observed among more recent cohorts of breast cancer survivors. However, this needs to be tested, as we and others have demonstrated variability in estradiol levels in postmenopausal breast cancer survivors on AIs.²⁹ A small proportion of participants had elevated estradiol levels.

In summary, elevated estradiol is not a mechanism independent of obesity for poor physical health—an important risk factor for breast cancer prognosis—in postmenopausal breast cancer patients. While obesity and physical activity in survivorship are two potential targets for improving physical health, other biological processes that impact physical health (e.g., inflammation) remain to be identified.

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Disclosure Statement

No competing financial interests exist.

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