Weight gain in hormone receptor-positive (HR+) early-stage breast cancer: is it menopausal status or something else?

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Abstract

Purpose This study investigates weight trajectories in pre- versus postmenopausal breast cancer (BC) survivors diagnosed with hormone receptor-positive tumors, with a specific focus on discerning menopausal status and type of endocrine treatment (ET) as risk factors for weight gain during ET.

Methods We conducted a retrospective review of electronic medical records. Descriptive statistics and Chi-squared and *t* tests were used to compare pre- and postmenopausal women. Chi-squared tests and ANOVA were used for within-group associations between patient characteristics and weight trajectories. Log-binomial regression models were used to estimate relative risk for weight gain.

Results The final sample was 32% premenopausal ($n = 140$) and 68% postmenopausal ($n = 298$). Relative risk (RR) for weight gain during ET was highest in women who were premenopausal (RR = 1.29, 1.03–1.52) and had Stage 3 BC (RR = 2.12, 1.59–2.82), mastectomy (RR = 1.49, 1.19–1.88), axillary node dissection (RR = 1.39, 1.11–1.73), and chemotherapy (RR = 1.80, 1.37–2.36). For each kg of weight gained between BC diagnosis and start of ET, and for each additional year of age, RR of gaining weight during ET decreased (RR = 0.98, 0.97–0.99, and RR = 0.99, 0.98–0.99, respectively). Menopausal status and type of ET were not significant predictors of weight gain. In multivariable analysis, only weight loss between BC diagnosis and start of ET was significant.

Conclusion The association of weight loss prior to ET and subsequent substantial weight gain during ET warrants further investigation.

Keywords Breast cancer · Hormone receptor positive · Weight gain · Endocrine treatment

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Introduction

Hormone receptor-positive (HR+) and Human Epidermal Growth Factor Receptor 2-negative (HER2−) tumors comprise about 70% of breast cancer (BC) subtypes diagnosed in women in the United States and are the most common subtype across all race/ethnicity groups [1–5]. The proportion of HR+/HER2− tumors is highest in non-Hispanic white women and lowest in African American women [6] and a higher proportion is seen in women diagnosed when they are postmenopausal and older compared to premenopausal and younger [7–9]. For both black and non-black women, being overweight or obese is associated with higher incidence of HR+/HER2− tumors [10].

Table 1 Comparison of pre- and postmenopausal study participant characteristics at breast cancer diagnosis ($N = 438$)

Variable	Premenopausal $N = 140$ (32%)	Postmenopausal $N = 298$ (68%)	p value
Age at BC diagnosis	44 (6.6)	65 (8.6)	<0.0001
	Range 26–55	Range 43–92	
Race: white	91 (66%)	226 (76%)	0.024
Married	79 (67%)	166 (64%)	0.558
Employed	89 (77%)	108 (44%)	<0.0001
Body mass index at BC diagnosis, mean (standard deviation/SD)	27 (5.8)	29 (6.7)	0.003
	Range 18–46	Range 19–59	
Body mass index			
Normal (18.5 to <25)	54 (40%)	94 (33%)	0.237
Obese (25 to <30)	39 (29%)	78 (28%)	
Obese I (30 to <35)	28 (21%)	59 (21%)	
Obese II (35 and above)	15 (11%)	52 (18%)	
BC Stage			
0	0%	5 (2%)	<0.0001
I	22 (16%)	127 (44%)	
II	69 (49%)	107 (37%)	
III	49 (35%)	51 (18%)	
BC Grade			
1	17 (13%)	77 (27%)	0.008
2	64 (50%)	122 (43%)	
3	46 (36%)	83 (29%)	
Tumor size, mean (SD)	3.9 (3.0)	2.4 (1.9)	<0.0001
	Range 0.40–20.0	Range 0.08–14.0	
Surgery			
Lumpectomy	48 (34%)	168 (57%)	<0.0001
Mastectomy	92 (66%)	127 (43%)	
Axillary surgery			
Axillary dissection	63 (46%)	90 (32%)	0.005
Sentinel biopsy	73 (54%)	190 (68%)	
Chemotherapy			
None	16 (11%)	152 (51%)	<0.0001
Neoadjuvant	89 (64%)	74 (25%)	
Adjuvant	35 (25%)	72 (24%)	
Chemotherapy			
No	16 (11%)	152 (51%)	<0.0001
Yes	124 (89%)	146 (49%)	
Radiation treatment	112 (80%)	201 (67%)	0.007
Endocrine treatment			
Tamoxifen only	110 (84%)	41 (14%)	<0.0001
Exemestane	0%	8 (3%)	
Anastrozole only	*7 (5%)	112 (38%)	
Letrozole only	*5 (4%)	57 (19%)	
Combination of aromatase inhibitors	1 (1%)	40 (13%)	
Combination of tamoxifen and aromatase inhibitor	8 (6%)	40 (13%)	

Some women were premenopausal at BC diagnosis but became postmenopausal prior to ET start

Note Percentages may not add exactly to 100% due to rounding

ET endocrine treatment, *BC* breast cancer

Most HR+/HER2− tumors are detected at an early, highly curable stage [11, 12], and adjuvant endocrine treatment (ET) is generally recommended for 5 years and potentially up to 10 years [13–16]. For women diagnosed when they are postmenopausal, adjuvant ET generally includes an aromatase inhibitor (AI) (anastrozole, letrozole, or exemestane), unless counter-indicated by bone health concerns [14, 17]. For women diagnosed when they are premenopausal, tamoxifen or AI plus ovarian suppression (OS) is recommended, unless counter-indicated by other side effect concerns [17, 18]. Women who transition from premenopausal to postmenopausal during BC treatment are often switched from tamoxifen to AI.

Weight gain post diagnosis is a common occurrence in breast cancer survivors [19–22], for reasons that include clinical, sociodemographic, and lifestyle factors [23–25]. In studies of HR+ breast cancer survivors conducted in the U.S. and other Western countries (comparable diet and sedentary behavior), some studies have identified ET as a risk factor for weight gain [26, 27] while others report no effect of ET [28–32], and still other studies report more gain with tamoxifen compared to AI [33], less gain [34] or no difference between tamoxifen and AI [35]. Similarly, some studies have reported greater weight gain in HR-positive BC survivors who were diagnosed when they were premenopausal or whose menopausal status changed during BC treatment [19, 33, 36, 37] or that there were no weight gain differences between pre- and postmenopausal BC survivors [24, 38]; either way, the finding was that menopausal status itself was a risk factor in weight trajectories. In an analysis of postmenopausal BC survivors, our research team found that a majority of women did not gain weight during the first two years of ET and that there were no weight trajectory differences by type of ET [39].

Building on the literature to date [40], the research question for our current study was the identification of differences between pre- and postmenopausal BC survivors that might provide further insights into reasons for similar or divergent weight trajectories during ET. We conducted a retrospective chart review of women diagnosed with early-stage BC, with a specific focus on the early years from diagnosis through the first two years of ET. We limited our review to these early years post diagnosis because women generally have frequent BC clinic visits to monitor ET adherence and side effects, and nursing staff commonly assess patient weight during these visits. If weight gain or weight loss is of concern to the patient or oncology provider, these visits provide an opportunity to monitor weight trajectories. The specific aims of our study were to (1) describe weight trajectories in premenopausal as compared postmenopausal women and (2) identify patient characteristics associated with weight gain *above* baseline weight at BC diagnosis, with particular attention to menopausal status and type of ET as potential risk factors.

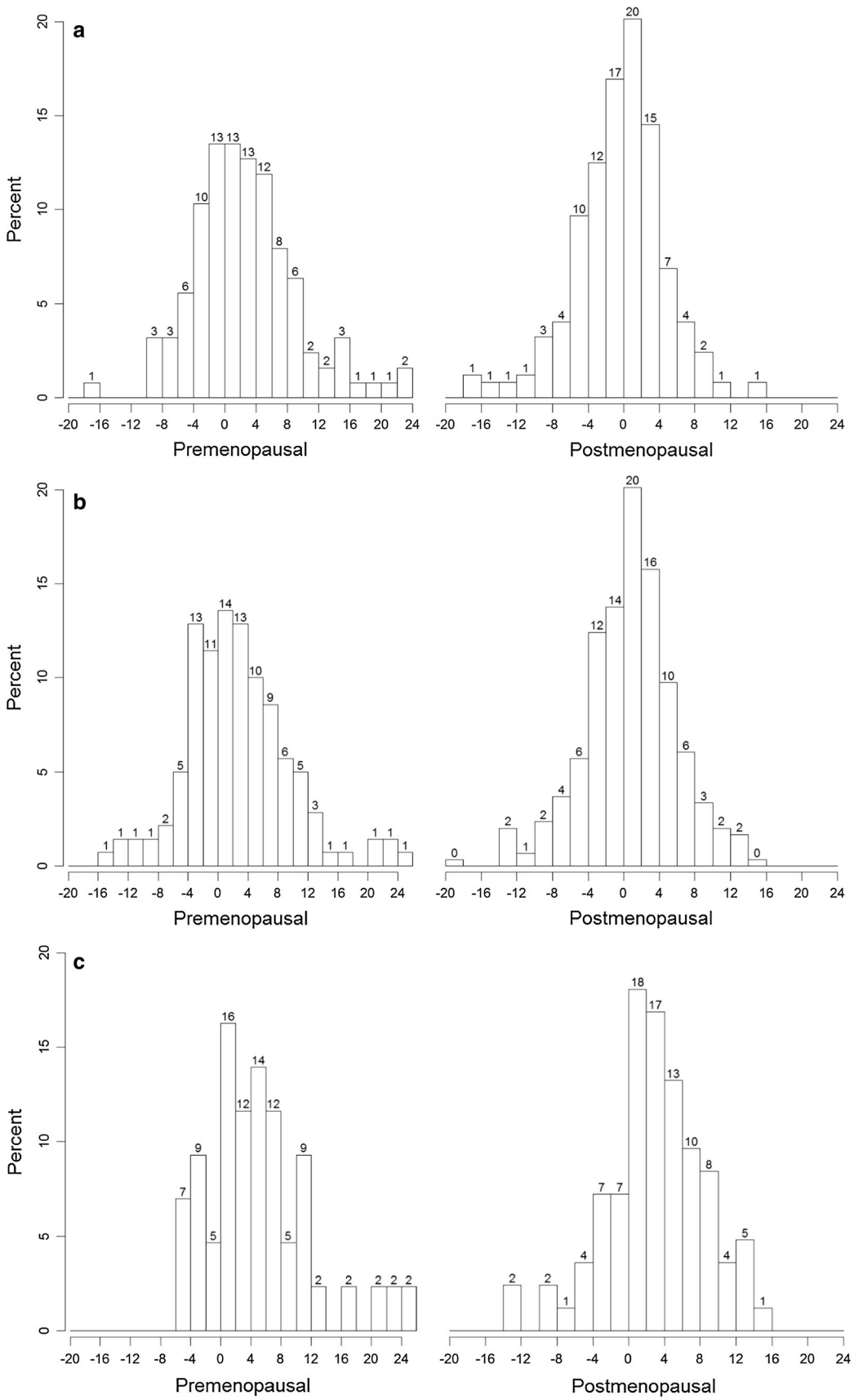
Methods

Data were gathered through a retrospective review of the electronic medical records (EMR) for women seen consecutively in BC clinics within a university-affiliated cancer hospital (71% of the sample) and from a list of participants in the Neoadjuvant Database at the University of North Carolina (UNC) Lineberger Comprehensive Cancer Center (29% of the sample). In the full sample of study participants, only 8% were diagnosed between 1992 and 2004, when BC chemotherapy was still largely anthracycline based [41]. An additional 21% were diagnosed between 2005 and 2009, and the majority (71%) were diagnosed between 2010 and 2014—all within the era of newer taxane-based chemotherapy regimens [41]. For inclusion in the study, women had to be diagnosed with Stage 0£3 HR-positive BC and on adjuvant ET for at least 2 years. Clinician notes were reviewed for evidence of ET adherence; women were excluded when notes revealed suboptimal ET adherence or discontinuation. Inclusion in the study also required weight data in the EMR—height and weight measures routinely assessed by nursing staff during clinic visits (not self-reported by patients)—from BC diagnosis through the first two years of ET.

Menopausal status was identified from clinician notes when the patient's treatment plan was determined and again at the initiation of ET. To ensure that weight trajectories were not influenced by disease progression [42], women whose BC had recurred or metastasized within the timeframe of our study were excluded. Women were also excluded from the study if there was evidence of non-cancer comorbidities or disabilities described in the clinician notes as poorly controlled or impairing mobility. Our concern was that these circumstances could affect a patient's ability to exercise and thereby have an independent effect on weight changes [43, 44]. Decisions regarding inclusion or exclusion of women from the study were discussed and determined by three authors (KAN, SSS, and JTL).

Measures

Participant characteristics selected for inclusion in the chart review were determined in advance of data extraction, based on the hypothesized potential association of each variable with weight trajectories. For weight and BMI calculations, time points of interest were (a) from baseline to end of 2 years of ET, (b) from baseline to start of ET, and (c) from start of ET until the end of 2 years of ET. For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◀**Fig. 1** **a** Net weight changes from BC diagnosis through 2 years of ET. **b** Net weight changes from start of ET through 2 years of ET. **c** Net weight changes from BC diagnosis through 2 years of ET, subset of women who lost the most weight between BC diagnosis and start of ET

each timeline, trajectories were categorized as (a) <2kg weight loss, (b) stable weight within 2 kg, and (c) >2 kg weight gain. Further details regarding our data extraction, study participants, variables, and methods for ensuring the best practice in retrospective chart review [45] have been published elsewhere [39]. The UNC Institutional Review Board approved this study.

Statistical considerations

Descriptive statistics are reported and Chi-squared and t tests were used to compare premenopausal and postmenopausal study participants. Within each group, associations between patient characteristics and weight changes during ET (>2 kg weight loss, stable weight, and >2 kg weight gain) were evaluated using Chi-squared tests and ANOVA. For the full sample, univariable log-binomial regression models were used to estimate the relative risk of >2 kg weight gain as compared to stable weight/>2 kg weight loss. A multivariable log-binomial regression model was fit to evaluate the difference in risk based on menopausal status, controlling for variables identified as significant in univariable analysis. All analyses were conducted using SAS Version 9.3 (Cary NC).

Results

Baseline study participant characteristics

Table 1 presents an overview of study participant characteristics at BC diagnosis. Our final sample included 438 BC survivors, of which 32% were premenopausal (mean age 44) and 68% were postmenopausal (mean age 65) ($p < 0.0001$) at BC diagnosis and p values underscore significant differences between the two groups. The premenopausal sample includes more non-white women ($p = 0.024$) and women who were employed at BC diagnosis ($p < 0.0001$). Postmenopausal survivors had higher mean BMI at diagnosis ($p = 0.003$). The proportion of women who were overweight (BMI 25 to <30) or obese (BMI 30 or higher) at diagnosis was similar between premenopausal (61%) and postmenopausal women (67%) ($p = 0.237$). None of the women in our sample were underweight at BC diagnosis (BMI < 18.5). On average, premenopausal BC survivors had higher stage ($p < 0.0001$), higher grade ($p = 0.008$), larger tumor size ($p < 0.0001$), and more progesterone receptor (PR)-positive ($p = 0.021$) tumors. They also had a higher proportion of mastectomies ($p < 0.0001$), axillary node dissection surgery ($p = 0.005$), neoadjuvant chemotherapy ($p < 0.0001$), and radiation treatment ($p = 0.007$). A higher proportion of postmenopausal women received no chemotherapy (p < .0001).

Unadjusted univariable analysis: weight change within the first two years of endocrine treatment

Figure 1a illustrates overall weight changes for the entire study period, from BC diagnosis (baseline) through 2 years of ET. Thirty-eight percent of premenopausal women had a net weight gain of 4 kg or more above their weight at BC diagnosis compared to 15% of postmenopausal women.

Table 2 (Fig. 1b) presents the findings regarding unadjusted univariable associations between participant characteristics and three weight categories at 2 years of ET, stratified by menopausal status. Most women in our sample had stable weight or lost weight during ET; however, 49% of premenopausal and 38% of postmenopausal women gained >2 kg ($p = 0.07$). In postmenopausal women, higher weight and BMI at BC diagnosis were associated with >2 kg weight loss during ET ($p = 0.0002$ and $p = 0.001$, respectively). Postmenopausal women who were obese II at BC diagnosis were most likely to lose >2 kg during ET, while women who were overweight or obese I at diagnosis tended to gain >2 kg during ET ($p = 0.008$). In sub-analysis, we found no significant differences in weight trajectories during ET between women who remained premenopausal throughout the study period (77%) and those who became postmenopausal (23%) ($p = 0.43$) within the study period.

For both pre- and postmenopausal women, patient characteristics significantly associated with >2 kg weight gain during ET were higher tumor stage, larger tumor size, and receipt of neoadjuvant chemotherapy. In premenopausal women, younger age was associated with weight loss during ET ($p = 0.035$), while younger age in postmenopausal women was associated with weight gain ($p = 0.028$). In postmenopausal women only, >2 kg weight gain was associated with having a mastectomy ($p = 0.034$) and axillary dissection surgery ($p < 0.001$). In both pre- and postmenopausal women, there were no significant differences in weight trajectories by type of ET. In a sub-analysis of all study participants on tamoxifen, 47% of premenopausal and 34% of postmenopausal women gained >2 kg during ET ($p = 0.068$).

In both pre- and postmenopausal women, substantial weight loss between BC diagnosis and start of ET was associated with >2 kg weight gain during two years of ET

Table 2 Weight change categories within 2 years of endocrine treatment in premenopausal and postmenopausal women diagnosed with breast cancer (separate *p* values)—unadjusted univariable analysis

Variable	>2 kg weight loss during ET	Stable weight during ET	>2 kg weight gain during ET	*p* value*
Menopausal Status, *N* and %				
Premenopausal ($N = 140$)	35 (25%)	36 (26%)	69 (49%)	0.071**
Postmenopausal ($N = 298$)	81 (27%)	103 (35%)	114 (38%)	
Weight at start of ET (kg), mean (SD)				
Premenopausal	77.7 (14.2)	71.3 (14.3)	71.9 (15.8)	0.125
	Range 51.7–103.2	Range 50.3–103.1	Range 46.8–117.8	
Postmenopausal	84.0 (21.3)	73.3 (17.0)	75.2 (15.4)	0.0001
	Range 46.8–149.0	Range 42.7–124.5	Range 42.3–120.9	
BMI at BC diagnosis, mean (SD)				
Premenopausal	27.5 (5.7)	26.1 (5.1)	27.8 (6.2)	0.366
	Range 19.1–41.6	Range 18.6–37.9	Range 18.9–45.9	
Postmenopausal	31.6 (7.6)	27.5 (6.0)	29.4 (6.1)	0.0002
	Range 20.9–58.6	Range 18.6–47.2	Range 19.3–45.7	
BMI category at BC diagnosis				
Premenopausal				
Normal (18.5 to <25)	12 (22%)	17 (32%)	25 (46%)	0.829
Overweight (25 to <30)	8 (21%)	9 (23%)	22 (56%)	
Obese I (30 to <35)	9 (32%)	6 (21%)	13 (46%)	
Obese II (35+)	4 (27%)	3 (20%)	8 (53%)	
Postmenopausal				
Normal (18.5 to < 25)	20 (21%)	41 (44%)	33 (35%)	0.008
Overweight (25 to < 30)	22 (28%)	23 (30%)	33 (42%)	
Obese I (30 to < 35)	12 (20%)	23 (39%)	24 (41%)	
Obese II (35 +)	24 (46%)	9 (17%)	19 (37%)	
Weight change: BC diagnosis to ET start (kg), mean (SD)				
Premenopausal	2.8 (5.2)	0.23 (4.9)	-2.0 (4.6)	<0.0001
	Range −6.5 to 17.4	Range −17.4 to 7.1	Range −13.8 to 9.9	
Postmenopausal	0.12 (3.0)	−0.57 (3.1)	−2.9 (4.9)	<0.0001
	Range −7.2 to 9.4	Range −15.7 to 13.2	Range −19.9 to 6.5	
Years from BC diagnosis to start of ET, mean (SD)				
Premenopausal	0.6 (.3)	0.6 (.2)	0.6 (.2)	0.333
	Range −0.05 to 1.4	Range .11–1.05	Range 0.04 to 1.1	
Postmenopausal	0.41 (0.4)	0.44 (0.3)	0.49 (0.3)	0.199
	Range −0.22 to 3.25	Range 0–1.557	Range −0.85 to 1.16	
Age at BC diagnosis, mean (SD)				
Premenopausal	42 (6.7)	46 (5.9)	44 (6.6)	0.035
	Range 30–52	Range 30–55	Range 26–55	
Postmenopausal	65 (9.4)	66 (8.8)	63 (7.6)	0.028
	Range 43–86	Range 50–92	Range 45–84	
Race				
Premenopausal				
Non-white	11 (23%)	11 (23%)	26 (54%)	0.741
White	24 (26%)	24 (26%)	43 (48%)	
Postmenopausal				
Non-white	23 (32%)	26 (36%)	23 (32%)	0.397
White	58 (26%)	77 (34%)	91 (40%)	
Married at BC diagnosis				
Premenopausal	24 (30%)	20 (25%)	35 (45%)	0.858

Table 2 continued

Variable	>2 kg weight loss during ET	Stable weight during ET	>2 kg weight gain during ET	*p* value*
Postmenopausal	41 (25%)	54 (33%)	71 (43%)	0.067
Employed at BC diagnosis				
Premenopausal	19 (21%)	28 (32%)	42 (47%)	0.129
Postmenopausal	30 (28%)	36 (33%)	42 (39%)	0.932
BC Stage				
Premenopausal				
0	0%	0%	0%	0.003
1	10 (46%)	5 (23%)	7 (32%)	
2	17 (25%)	24 (35%)	28 (41%)	
3	8 (16%)	7 (14%)	34 (69%)	
Postmenopausal				
0	3 (60%)	1 (20%)	1 (20%)	0.002
1	46 (36%)	43 (34%)	38 (30%)	
2	26 (24%)	37 (35%)	44 (41%)	
3	5 (10%)	16 (31%)	30 (59%)	
BC Grade				
Premenopausal				
1	3 (18%)	5 (29%)	9 (53%)	0.880
2	15 (23%)	18 (28%)	31 (49%)	
3	13 (28%)	10 (22%)	23 (50%)	
Postmenopausal				
1	27 (35%)	24 (31%)	26 (34%)	0.277
2	35 (29%)	41 (34%)	46 (38%)	
3	16 (19%)	32 (39%)	35 (42%)	
Tumor size, mean (SD)				
Premenopausal	3.3 (2.4)	3.1 (2.4)	4.7 (3.4)	0.016
	Range 0.40–9.0	Range 0.40–13.0	Range 0.40–20.0	
Postmenopausal	1.9 (1.4)	2.4 (2.0)	2.8 (1.9)	0.003
	Range 0.08–8.0)	Range 0.10–14)	Range 0.12–11)	
Breast surgery				
Premenopausal				
Lumpectomy	14 (29%)	16 (33%)	18 (38%)	0.122
Mastectomy	21 (23%)	20 (22%)	51 (55%)	
Premenopausal				
Lumpectomy	54 (32%)	60 (36%)	54 (32%)	0.034
Mastectomy	27 (21%)	42 (33%)	58 (46%)	
Axillary surgery				
Premenopausal				
Axillary dissection	16 (25%)	17 (27%)	30 (48%)	0.981
Sentinel biopsy	18 (25%)	19 (26%)	36 (49%)	
Premenopausal				
Axillary dissection	10 (11%)	31 (34%)	49 (54%)	<0.0001
Sentinel biopsy	65 (34%)	63 (33%)	62 (33%)	
Chemotherapy				
Premenopausal				
No chemotherapy	4 (25%)	6 (38%)	6 (38%)	0.019
Adjuvant chemo.	14 (40%)	11 (31%)	10 (29%)	
Neoadjuvant chemo.	17 (19%)	19 (21%)	53 (60%)	

Table 2 continued

Variable	>2 kg weight loss during ET	Stable weight during ET	>2 kg weight gain during ET	*p* value*
Postmenopausal				
No chemotherapy	54 (36%)	57 (38%)	41 (27%)	<0.0001
Adjuvant chemo.	21 (29%)	23 (32%)	28 (39%)	
Neoadjuvant chemo.	6 (8%)	23 (31%)	45 (61%)	
Chemotherapy				
Premenopausal				
No	4 (25%)	6 (38%)	6 (38%)	0.476
Yes	31 (25%)	30 (24%)	63 (51%)	
Postmenopausal				
No	54 (36%)	57 (38%)	41 (27%)	<0.0001
Yes	27 (19%)	46 (32%)	73 (50%)	
Radiation				
Premenopausal				
No	8 (29%)	6 (21%)	14 (50%)	0.806
Yes	27 (24%)	30 (27%)	55 (49%)	
Postmenopausal				
No	30 (31%)	35 (36%)	32 (33%)	0.391
Yes	51 (25%)	68 (34%)	82 (41%)	
Type of ET				
Premenopausal				
Tamoxifen	31 (28%)	27 (25%)	52 (47%)	0.601
Exemestane only	0%	0%	0%	
Anastrozole only[a]	1 (14%)	3 (43%)	3 (43%)	
Letrozole only[a]	2 (40%)	2 (40%)	1 (20%)	
Combination of AIs	0%	1 (100%)	0%	
Tamoxifen plus AI	1 (13%)	3 (38%)	4 (50%)	
Postmenopausal				
Tamoxifen	9 (22%)	18 (44%)	14 (34%)	0.143
Exemestane only	3 (38%)	0%	5 (63%)	
Anastrozole only	36 (32%)	36 (32%)	40 (36%)	
Letrozole only	10 (18%)	21 (37%)	26 (46%)	
Combination of AIs	9 (23%)	12 (30%)	19 (48%)	
Tamoxifen plus AI	14 (35%)	16 (40%)	10 (25%)	

Note Percentages may not add exactly to 100% due to rounding

BMI body mass index, *BC* breast cancer, *ET* endocrine treatment, *kg* kilogram

**p* values are within group (stratification by menopausal status) unless otherwise indicated

***p* value compares pre- with postmenopausal women

[a]Some women were premenopausal at BC diagnosis but became postmenopausal prior to ET start

($p < 0.0001$). To explore this finding, we conducted a sub-analysis and found that women who lost >2 kg prior to ET, compared to the remainder of the sample, were less likely to be white ($p = 0.016$), had higher BMI at diagnosis ($p < 0.0001$), longer time period from BC diagnosis to ET start ($p < 0.0001$), higher BC stage ($p = 0.002$), more likely to receive mastectomy ($p = 0.006$) and axillary surgery ($p = 0.003$), and more likely to receive chemotherapy in general ($p < 0.0001$) and neoadjuvant chemotherapy specifically ($p < 0.0001$). In this sub-analysis, 50% of premenopausal and 41% of postmenopausal women had 4 kg or more net gain above their baseline weight at BC diagnosis (Fig. 1c).

Table 3 Combined pre- and postmenopausal patients' (full sample) relative risk for greater than 2 kg weight gain within 2 years of endocrine treatment; unadjusted univariate analysis

Variable	Relative Risk (95% CI)	Univariate p value
Menopausal status (postmenopausal is referent)		
Premenopausal ($N = 298$)	1.29 (1.03,1.52)	0.025
BMI at BC diagnosis (Normal weight is referent)		
Overweight	1.20 (0.91,1.58)	0.200
Obese I	1.09 (0.79,1.49)	0.612
Obese II	1.03 (0.72, 1.46)	0.887
Weight change between BC diagnosis and start of ET (1-kg increments)	0.98 (0.97,0.99)	<0.0001
Weight at start of ET (1-kg increments)	0.99 (0.99,1.00)	0.087
Age at BC diagnosis (1-year increments)	0.99 (0.98, 0.99)	0.001
Race (non-white is referent)		
White	1.04 (0.81,1.33)	0.787
Marital status (not married is referent)		
Married	1.28 (0.97,1.69)	0.083
Employment status (not employed is referent)		
Currently employed	1.05 (0.82,1.35)	0.681
BC stage (Stage 1 is referent)		
Stage 0	0.66 (0.11, 3.89)	0.648
Stage 2	1.35 (1.00, 1.83)	0.049
Stage 3	2.12 (1.59, 2.82)	<0.0001
BC grade (Grade 1 is referent)		
Grade 2	1.11 (0.81, 1.52)	0.507
Grade 3	1.21 (0.87, 1.67)	0.255
Breast surgery (lumpectomy is referent)		
Mastectomy	1.49 (1.19,1.88)	0.0007
Lymph surgery (sentinel is referent)		
Axillary	1.39 (1.11,1.73)	0.004
Chemotherapy (no chemotherapy is referent)		
Adjuvant	1.27 (0.89,1.81)	0.184
Neoadjuvant	2.15 (1.64,2.82)	<0.0001
Chemotherapy (no chemotherapy is referent)		
Yes	1.80 (1.37, 2.36)	<0.0001
Radiation (no is referent)		
Yes	1.19 (0.92,1.55)	0.194
Endocrine treatment drug (tamoxifen is referent)		
Anastrozole	0.83 (0.61,1.12)	0.213
Exemestane	1.43 (0.81,2.52)	0.216
Letrozole	1.00 (0.71,1.39)	0.983
Combination of AIs	1.06 (0.73,1.54)	0.760
Tamoxifen plus AI	0.67 (0.41,1.07)	0.096

Relative Risk for >2 kg weight gain during ET

Relative risks (RR) for >2 kg weight gain during ET (versus stable weight and >2 kg weight loss) were calculated for the full sample of pre- and postmenopausal women combined. In unadjusted univariate analysis (Table 3), women who were premenopausal had increased risk of weight gain (RR = 1.29, 1.03–1.52). For each kg of weight gained between BC diagnosis and start of ET, and for each additional year of age, the relative risk of gaining weight during ET *decreased* (RR = 0.98, 0.97–0.99, and RR = 0.99, 0.98–0.99, respectively). Patients with Stage 3

Table 4 Relative risk for greater than 2 kg weight gain within 2 years of endocrine treatment; multivariate analysis

Variable	Relative Risk (95% CI)	Multivariate p value
Menopausal status (postmenopausal is referent)		
Premenopausal	0.97 (0.83, 1.13)	0.687
Weight change between BC diagnosis and start of ET (1-kg increments)	0.98 (0.98, 0.99)	<0.0001
Age at BC diagnosis (1-year increments)	1.00 (0.99, 1.00)	0.279
BC stage	1.07 (0.97, 1.17)	0.163
Breast surgery (lumpectomy is referent)		
Mastectomy	1.04 (0.92, 1.17)	0.526
Lymph surgery (sentinel is referent)		
Axillary	0.99 (0.88, 1.12)	0.885
Chemotherapy (no chemotherapy is referent)		
Yes	1.02 (0.87, 1.20)	0.795

Limited to variables that were significant in unadjusted univariate analysis

cancer had significantly increased risk for weight gain compared to those with Stage 0 cancer (RR = 2.12, 1.59–2.82). Patients who had a mastectomy (RR = 1.49, 1.19–1.88), those who had axillary node dissection (RR = 1.39, 1.11–1.73), and those who had chemotherapy (RR = 1.80, 1.37–2.36) all had increased risk of weight gain. There were no significant differences in relative risk for weight gain by type of ET.

In multivariable analysis (Table 4), adjusting for age at diagnosis, weight change from diagnosis to start of ET, BC stage, BC surgery, lymph node surgery, and chemotherapy yes/no, the previously noted difference by menopausal status did not persist ($p = 0.69$). The only variable that remained independently predictive of weight gain during ET was weight loss from diagnosis to start of ET ($p < 0.0001$).

Discussion and conclusions

This study builds on our prior research describing weight trajectories during ET [39], with the current study aiming to provide further insights into menopausal status as a potential risk factor for weight gain in BC survivorship. Our data show considerable weight fluctuations during three time points of interest: (1) from BC diagnosis through 2 years of ET, (2) from BC diagnosis through the start of ET, and (3) from the start of ET through 2 years of ET. Our finding that 38% of premenopausal women and 15% of postmenopausal women experienced a net weight gain of 4 kg or more *above* their baseline weight at BC diagnosis by the end of 2 years of ET illustrates the importance of this investigation.

As in the general population of women diagnosed with BC, the premenopausal women in our sample had on average higher BC severity (stage, grade, tumor size) and more extensive treatment (higher proportion of mastectomies, axillary node dissection, neoadjuvant chemotherapy, and radiation treatment). This finding reflects the larger literature regarding higher risk for more advanced disease in younger as compared to older breast cancer patients [46, 47]. In unadjusted univariate analysis, relative risks for weight gain were highest in premenopausal and younger women but also in all women (pre- and postmenopausal) with higher BC stage and having a mastectomy, axillary surgery, and neoadjuvant chemotherapy, and experiencing the most weight loss between BC diagnosis and start of ET. We did not assess whether any specific type of ET was associated with weight gain. In multivariable analysis, however, the only variable that remained independently significant was substantial weight loss prior to start of ET.

This finding warranted further investigation through a sub-analysis of women who lost the most weight between BC diagnosis and start of ET. We found that a substantial proportion (58–63%) of women in this subsample regained their baseline weight but then gained well beyond that baseline. Again, we noted a pattern of higher BC severity and more extensive treatment in this subgroup of women. To understand this dynamic, future research should prospectively follow women from BC diagnosis through 2 years of ET and include longitudinal data on eating habits, physical activity, and patient-reported outcomes such as stress, anxiety, fatigue, and social support. Future research should also aim to clarify why these women are at the greatest risk for substantial weight gain during ET.

To the extent that there is clinician interest in monitoring significant weight gain during ET, our study suggests focusing on both pre- and postmenopausal women who are overweight or obese at BC diagnosis as well as women whose more severe tumor type will require more extensive treatment. In our sample, 28% of both premenopausal and postmenopausal women were overweight at BC diagnosis, and an additional 33% of premenopausal and 39% of postmenopausal women were obese. Higher BMI is a common finding among women diagnosed with BC, and obesity is a known risk factor for BC in postmenopausal women [48–50]. In early-stage BC, high BMI has also been associated with larger tumor size [51, 52] and more advanced disease [53, 54].

Weight gain after BC diagnosis is a further concern because women who are overweight or obese at BC diagnosis may be at increased risk for obesity-related diseases, complications and mortality, such as cardiovascular disease, diabetes, and other obesity-related cancers [10]. Furthermore, post-diagnosis weight gain may impact their quality of life in survivorship. Weight gain can intensify menopausal symptoms such as hot flashes [55, 56] and clustering with other menopausal symptoms [57], raise concerns about body appearance [58], reduce physical function [59], precipitate poor sleep quality, increase fatigue [60], and increase fear of recurrence [61]. For women on AI, there is the added concern that weight gain during ET will exacerbate the common AI side effect of joint pain, stiffness, or achiness (arthralgia) [62] and reduce their engagement in physical activity [63].

Specifically with regard to women diagnosed with early-stage HR + tumors in U.S. or western countries, higher BMI at diagnosis or post-diagnosis weight gain has also been associated with worse prognosis and survival, although the evidence in this regard is mixed. For example, in a recent study comparing BC recurrence and survival by PAM50 subtype, class II/III obesity at BC diagnosis doubled the risk of BC mortality in women with Luminal A tumors; every 5-unit increase in BMI increased the risk for BC mortality by 31% and the risk for BC recurrence by 24% [64]. And, in a study of early-stage ER + BC survivors, obesity at diagnosis was associated with reduced disease-free survival and increased risk for second primary cancer [65]. Other studies have similarly found increased risk of BC recurrence and increased BC death [66–69]. With regard to weight gain after BC diagnosis, in a study largely of women with Luminal A tumors (71%), BMI gain >5.7% was associated with higher rates of BC recurrence [70]. Another study of ER + breast cancer survivors identified a 24% increased risk of late recurrence in women who experienced >10% post-diagnosis weight gain [71]. Other studies have similarly found higher rates of BC recurrence and/or BC mortality with weight gain after diagnosis [72, 73]. For all of the reasons, high BMI at diagnosis and weight gain after diagnosis should be of concern in both pre- and postmenopausal women diagnosed with HR+ breast cancer.

As a retrospective review of medical records, our analysis was limited to variables collected and recorded in the clinical setting. It is a strength of our study that our findings are immediately applicable to clinical practice, as all of the data used in our analysis are collected during routine clinic visits. The variables analyzed in our study were used for the same purposes as their clinical intent (BC diagnosis and treatment), without ascribing new or alternative meaning to the clinical data. Our weight measures were independently assessed by nursing personnel using standardized procedures, and clinician notes from a single study site/institution were consistent in quality and depth of detail. A further strength of our study is that the sample consists primarily of women diagnosed in the taxane era of chemotherapy—a still largely understudied period regarding potential weight gain associations with chemotherapy [25].

A limitation of using data from medical records is that these records did not contain consistent information on patient behavior that could affect weight trajectories during ET, specifically dietary habits and physical activity. These are modifiable behaviors that could be included in discussions with patients whose BMI at diagnosis or risk factors for subsequent weight gain (tumor severity and associated treatment) would warrant attention to healthy weight. Weight trajectories can also be influenced by depression, anxiety, fatigue, pain, and other symptoms, and availability of consistent information on these variables in the medical records would have enabled a more comprehensive exploration of factors associated with differing weight trajectories.

Our study shows that BC survivors can both lose and gain weight from BC diagnosis through the first two years of ET. During a busy clinic visit, it is important to identify patients at the highest risk for clinically significant weight changes and to offer referrals to a nutritionist or other weight management program. Words of support and encouragement from the oncology provider may help BC survivors manage their weight with exercise and healthy eating habits [74–76]. Healthy eating and regular exercise are safe and feasible "self-management" activities both during treatment and throughout survivorship that can have great benefits for function and quality of life and potentially also for prognosis and survival in early-stage BC survivors.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent This study did not entail direct contact with humans and therefore did not entail obtaining informed consent.

References

1. Kohler BA, Sherman RL, Howlader N et al (2015) Annual report to the Nation on the status of cancer, 1975–2011, featuring incidence of breast cancer subtypes by race/ethnicity, poverty, and state. J Natl Cancer Inst 107(6):djv048
2. Clarke CA, Keegan TH, Yang J et al (2012) Age-specific incidence of breast cancer subtypes: understanding the black-white crossover. J Natl Cancer Inst 104(14):1094–1101
3. DeSantis CE, Fedewa SA, Goding Sauer A, Kramer JL, Smith RA, Jemal A (2016) Breast cancer statistics, 2015: convergence of incidence rates between black and white women. CA Cancer J Clin 66(1):31–42
4. Howlader N, Altekruse SF, Li CI et al (2014) US incidence of breast cancer subtypes defined by joint hormone receptor and HER2 status. J Natl Cancer Inst. doi:10.1093/jnci/dju055
5. Yang XR, Chang-Claude J, Goode EL et al (2011) Associations of breast cancer risk factors with tumor subtypes: a pooled analysis from the breast cancer association consortium studies. J Natl Cancer Inst 103(3):250–263
6. Chen L, Li CI (2015) Racial disparities in breast cancer diagnosis and treatment by hormone receptor and HER2 status. Cancer Epidemiol Biomark Prevent 24(11):1666–1672
7. Clark GM, Osborne CK, McGuire WL (1984) Correlations between estrogen receptor, progesterone receptor, and patient characteristics in human breast cancer. J Clin Oncol 2:1102–1109
8. Benz CC (2008) Impact of aging on the biology of aging. Crit Rev Oncol Hematol 66(1):65–74
9. Parise CA, Caggiano V (2014) Breast cancer survival defined by the ER/PR/HER2 subtypes and a surrogate classification according to tumor grade and immunohistochemical biomarkers. J Cancer Epidemiol 2014:469251
10. Gershuni V, Li YR, Williams AD et al (2017) Breast cancer subtype distribution is different in normal weight, overweight, and obese women. Breast Cancer Res Treat 163(2):375–381
11. Dunnwald LK, Rossing MA, Li CI (2007) Hormone receptor status, tumor characteristics, and prognosis: a prospective cohort of breast cancer patients. Breast Cancer Res 9(1):R6
12. Eppenberger-Castori S, Moore DH Jr, Thor AD et al (2002) Age-associated biomarker profiles of human breast cancer. Int J Biochem Cell Biol 34(11):1318–1330
13. Schiavon G, Smith IE (2014) Status of adjuvant endocrine therapy for breast cancer. Breast Cancer Res 16(2):206
14. Taylor WC, Muss HB (2010) Recent advances: adjuvant therapy for older women with breast cancer. Cancer J 16(4):289–293
15. Dowsett M, Cuzick J, Ingle J et al (2010) Meta-analysis of breast cancer outcomes in adjuvant trials of aromatase inhibitors versus tamoxifen. J Clin Oncol 28(3):509–518
16. Goss PE, Ingle JN, Pritchard KI et al (2016) Extending aromatase-inhibitor adjuvant therapy to 10 years. N Engl J Med 375:209–219
17. Burstein HJ, Temin S, Anderson H et al (2014) Adjuvant endocrine therapy for women with hormone receptor-positive breast cancer: american society of clinical oncology clinical practice guideline focused update. J Clin Oncol 32(21):255–2269
18. Burstein HJ, Lacchetti C, Anderson H et al (2016) Adjuvant endocrine therapy for women with hormone receptor-positive breast cancer: American society of clinical oncology clinical practice guideline update on ovarian suppression. J Clin Oncol 34(14):1689–1701
19. Goodwin PJ, Ennis M, Pritchard KI, McCready D, Koo J et al (1999) Adjuvant treatment and onset of menopause predict weight gain after breast cancer diagnosis. J Clin Oncol 17(1):120–129
20. Rock CL, Flatt SW, Newman V, Caan BJ, Haan MN et al (1999) Factors associated with weight gain in women after diagnosis of breast cancer. Women's healthy eating and living study group. J Am Diet Assoc 99:1212–1221
21. Demark-Wahnefried W, Rimer BK, Winer EP (1997) Weight gain in women diagnosed with breast cancer. J Am Diet Asso 97(5):519–526, 529; quiz 527–518
22. Saquib N, Flatt SW, Natarajan L, Thomson CA, Bardwell WA et al (2007) Weight gain and recovery of pre-cancer weight after breast cancer treatments: evidence from the women's healthy eating and living (WHEL) study. Breast Cancer Res Treat 105(2):177–186
23. Kim SH, Cho YU, Kim SJ (2013) Weight gain and its correlates among breast cancer survivors. Asian Nurs Res 7(4):161–167
24. Irwin ML, McTiernan A, Baumgartner RN, Bernstein L, Gilliland FD, Ballard-Barbash R (2005) Changes in body fat and weight after a breast cancer diagnosis: influence of demographic, prognostic, and lifestyle factors. J Clin Oncol 23(4):774–782
25. van den Berg MM, Winkels RM, de Kruif JT et al (2017) Weight change during chemotherapy in breast cancer patients: a meta-analysis. BMC Cancer 17(1):259
26. Mortimer J, Behrendt CE (2013) Severe menopausal symptoms are widespread among survivors of breast cancer treatment regardless of time since diagnosis. J Palliat Med 16(9):1130–1134
27. Sadim M, Xu Y, Selig K et al (2017) Clinical and genetic predictors of weight gain in patients diagnosed with breast cancer. Cancer 109:872
28. Gross AL, May BJ, Axilbund JE, Armstrong DK, Roden RB, Visvanathan K (2015) Weight change in breast cancer survivors compared to cancer-free women: a prospective study in women at familial risk of breast cancer. Cancer Epidemiol Biomark Prevent 24(8):1262–1269
29. Heideman WH, Russell NS, Gundy C, Rookus MA, Voskuil DW (2009) The frequency, magnitude and timing of post-diagnosis body weight gain in Dutch breast cancer survivors. Eur J Cancer 45:119–126
30. Makari-Judson G, Judson CH, Mertens WC (2007) Longitudinal patterns of weight gain after breast cancer diagnosis: observations beyond the first year. Breast 13(3):258–265

31. Vagenas D, DiSipio T, Battistutta D et al (2015) Weight and weight change following breast cancer: evidence from a prospective, population-based, breast cancer cohort study. BMC Cancer 15(1):28
32. Sestak I, Harvie M, Howell A, Forbes JF, Dowsett M, Cuzick J (2012) Weight change associated with anastrozole and tamoxifen treatment in postmenopausal women with or at high risk of developing breast cancer. Breast Cancer Res Treat 134(2):727–734
33. Sedjo RL, Byers T, Ganz PA et al (2014) Weight gain prior to entry into a weight-loss intervention study among overweight and obese breast cancer survivors. J Cancer Surviv 8(3):410–418
34. Francini G, Petrioli R, Montagnani A et al (2006) Exemestane after tamoxifen as adjuvant hormonal therapy in postmenopausal women with breast cancer: effects on body composition and lipids. Br J Cancer 95(2):153–158
35. Aiello Bowles EJ, Boudreau DM, Chubak J et al (2012) Patient-reported discontinuation of endocrine therapy and related adverse effects among women with early-stage breast cancer. J Oncol Prac. 8(6):49–57
36. Malinovszky KM, Cameron D, Douglas S et al (2004) Breast cancer patients' experiences on endocrine therapy: monitoring with a checklist for patients on endocrine therapy (C-PET). Breast 13(5):363–368
37. Hoskin PJ, Ashley S, Yarnold JR (1992) Weight gain after primary surgery for breast cancer–effect of tamoxifen. Breast Cancer Res Treat 22(2):129–132
38. Han HS, Lee KW, Kim JH et al (2009) Weight changes after adjuvant treatment in Korean women with early breast cancer. Breast Cancer Res Treat 114(1):147–153
39. Nyrop KA, Deal AM, Lee JT et al (2017) Weight changes in postmenopausal breast cancer survivors over 2 years of endocrine therapy: a retrospective chart review. Breast Cancer Res Treat 162:375–388
40. Nyrop KA, Williams GR, Muss HB, Shachar SS (2016) Weight gain during adjuvant endocrine treatment for early-stage breast cancer: what is the evidence? Breast Cancer Res Treat 158(2):203–217
41. Giordano SH, Lin YL, Kuo YF, Hortobagyi GN, Goodwin JS (2012) Decline in the use of anthracyclines for breast cancer. J Clin Oncol 30(18):2232–2239
42. Kritchevsky SB, Wilcosky TC, Morris DL, Truong KN, Tyroler HA (1991) Changes in plasma lipid and lipoprotein cholesterol and weight prior to the diagnosis of cancer. Can Res 51(12):3198–3203
43. McTiernan A, Sorensen B, Irwin ML et al (2007) Exercise effect on weight and body fat in men and women. Obesity 15(6):1496–1512
44. Myers CA, Slack T, Martin CK, Broyles ST, Heymsfield SB (2016) Change in obesity prevalence across the United States is influenced by recreational and healthcare contexts, food environments, and hispanic populations. PLoS ONE 11(2):e0148394
45. Vassar M, Holzmann M (2013) The retrospective chart review: important methodological considerations. J Educ Eval Health Prof 10:12
46. Lee MK, Varzi LA, Chung DU et al (2015) The effect of young age in hormone receptor positive breast cancer. Biomed Res Int 2015:325715
47. Chollet-Hinton L, Anders CK, Tse CK et al (2016) Breast cancer biologic and etiologic heterogeneity by young age and menopausal status in the Carolina breast cancer study: a case-control study. Breast Cancer Res 18(1):79
48. Coughlin SS, Smith SA (2015) The insulin-like growth factor axis, adipokines, physical activity, and obesity in relation to breast cancer incidence and recurrence. Cancer Clin Oncol 4(2):24–31
49. Keum N, Greenwood DC, Lee DH et al (2015) Adult weight gain and adiposity-related cancers: a dose-response meta-analysis of prospective observational studies. J Natl Cancer Inst 107(2):djv088
50. Cheraghi Z, Poorolajal J, Hashem T, Esmailnasab N, Doosti Irani A (2012) Effect of body mass index on breast cancer during premenopausal and postmenopausal periods: a meta-analysis. PLoS ONE 7(12):e51446
51. Biglia N, Peano E, Sgandurra P et al (2013) Body mass index (BMI) and breast cancer: impact on tumor histopathologic features, cancer subtypes and recurrence rate in pre and postmenopausal women. Gynecol Endocrinol 29(3):263–267
52. Loi S, Milne RL, Friedlander ML et al (2005) Obesity and outcomes in premenopausal and postmenopausal breast cancer. Cancer Epidemiol Biomark Prevent 14(7):1686–1691
53. Ewertz M, Jensen MB, Gunnarsdottir KA et al (2011) Effect of obesity on prognosis after early-stage breast cancer. J Clin Oncol 29(1):25–31
54. Litton JK, Gonzalez-Angulo AM, Warneke CL et al (2008) Relationship between obesity and pathologic response to neoadjuvant chemotherapy among women with operable breast cancer. J Clin Oncol 26(25):4072–4077
55. Caan BJ, Emond JA, Su HI et al (2012) Effect of postdiagnosis weight change on hot flash status among early-stage breast cancer survivors. J Clin Oncol 30(13):1492–1497
56. Su H, Sammel MD, Springer E, Freeman EW, DeMichele A, Mao JJ (2010) Weight gain is associated with increased risk of hot flashes in breast cancer survivors on aromatase inhibitors. Breast Cancer Res Treat 124(1):205–211
57. Glaus A, Boehme C, Thurlimann B et al (2006) Fatigue and menopausal symptoms in women with breast cancer undergoing hormonal cancer treatment. Ann Oncol 17(5):801–806
58. Alfano CM, McGregor BA, Kuniyuki A et al (2006) Psychometric properties of a tool for measuring hormone-related symptoms in breast cancer survivors. Psychooncology. 15(11):985–1000
59. Young A, Weltzien E, Kwan M, Castillo A, Caan B, Kroenke CH (2014) Pre- to post-diagnosis weight change and associations with physical functional limitations in breast cancer survivors. J Cancer Surviv 8(4):539–547
60. Imayama I, Alfano CM, Neuhouser ML et al (2013) Weight, inflammation, cancer-related symptoms and health related quality of life among breast cancer survivors. Breast Cancer Res Treat 140(1):159–176
61. Befort CA, Austin H, Klemp JR (2011) Weight control needs and experiences among rural breast cancer survivors. Psychooncology. 20(10):1069–1075
62. Sestak I, Cuzick J, Sapunar F et al (2008) Risk factors for joint symptoms in patients enrolled in the ATAC trial: a retrospective, exploratory analysis. Lancet Oncol. 9(9):866–872
63. Brown JC, Mao JJ, Stricker C, Hwang WT, Tan KS, Schmitz KH (2013) Aromatase inhibitor associated musculoskeletal symptoms are associated with reduced physical activity among breast cancer survivors. The Breast J. 20(1):22–28
64. Cespedes Feliciano EM, Kwan ML, Kushi LH et al (2017) Body mass index, PAM50 subtype, recurrence and survival among patients with nonmetastatic breast cancer. Cancer 123:2535–2542
65. Dignam JJ, Wieand K, Johnson KA et al (2006) Effects of obesity and race on prognosis in lymph node-negative, estrogen receptor-negative breast cancer. Breast Cancer Res Treat 97(3):245–254
66. Kamineni A, Anderson ML, White E et al (2013) Body mass index, tumor characteristics, and prognosis following diagnosis of early-stage breast cancer in a mammographically screened population. Cancer Causes Control 24(2):305–312
67. Minicozzi P, Berrino F, Sebastiani F et al (2013) High fasting blood glucose and obesity significantly and independently

increase risk of breast cancer death in hormone receptor-positive disease. Eur J Cancer 49(18):3881–3888
68. Petrelli JM, Calle EE, Rodriguez C, Thun MJ (2002) Body mass index, height, and postmenopausal breast cancer mortality in a prospective cohort of US women. Cancer Causes Control 13(4):325–332
69. Sparano JA, Wang M, Zhao F et al (2012) Obesity at diagnosis is associated with inferior outcomes in hormone receptor-positive operable breast cancer. Cancer 118(23):5937–5946
70. Fedele P, Orlando L, Schiavone P et al (2014) BMI variation increases recurrence risk in women with early-stage breast cancer. Future Oncol. 10(15):2459–2468
71. Nechuta S, Chen WY, Cai H et al (2016) A pooled analysis of post-diagnosis lifestyle factors in association with late estrogen-receptor-positive breast cancer prognosis. Int J Cancer 138(9):2088–2097
72. Kroenke CH, Chen WY, Rosner B, Holmes MD (2005) Weight, weight gain, and survival after breast cancer diagnosis. J Clin Oncol 23(7):1370–1378
73. Nichols HB, Trentham-Dietz A, Egan KM, Titus-Ernstoff L (2009) Holmes MD, al. e. Body mass index before and after breast cancer diagnosis: associations with all-cause, breast cancer, and cardiovascular disease mortality. Cancer Epidemiol Biomarkers Prev 18(5):1403–1409
74. Wolin KY, Schwartz AL, Matthews CE, Courneya KS, Schmitz KH (2012) Implementing the exercise guidelines for cancer survivors. J Support Oncol. 10(5):171–177
75. Santa Mina D, Alibhai SM, Matthew AG et al (2012) Exercise in clinical cancer care: a call to action and program development description. Curr Oncol. 19(3):e136–e144
76. Ruiz-Casado A, Lucia A (2014) The time has come for oncologists to recommend physical activity to cancer survivors. Arch Exerc Health Dis. 4(1):214–215