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A pooled analysis of post-diagnosis lifestyle factors in association with late estrogen-receptor–positive breast cancer prognosis

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Cancer Epidemiology

Lifestyle factors have been well studied in relation to breast cancer prognosis overall; however, associations of lifestyle and late outcomes (>5 years after diagnosis) have been much less studied, and no studies have focused on estrogen receptor-positive (ER+) breast cancer survivors, who may have high risk of late recurrence and mortality. We utilized a large prospective pooling study to evaluate the associations of lifestyle factors with late recurrence and all-cause mortality among 6,295 5-year ER+ Stage I–III breast cancer survivors. Pooled and harmonized data were available on clinical factors and lifestyle factors (pre- to post-diagnosis weight change, body mass index (BMI) (kg/m^2), recreational physical activity, alcohol intake and smoking history), measured on average 2.1 years after diagnosis. Updated information for weight only was available. Study heterogeneity was evaluated by the Q-statistic. Multivariable Cox regression models were stratified by study. Adjusting for clinical factors and potential confounders, ≥10% weight gain and obesity (BMI, 30–34.99 and ≥35) were associated with increased risk of late recurrence (hazard ratios (95% confidence intervals): 1.24 (1.00–1.53), 1.40 (1.05–1.86) and 1.41 (1.02–1.93), respectively). Daily alcohol intake was associated with late recurrence, 1.28 (1.01–1.62). Physical activity was inversely associated with late all-cause mortality (0.81 (0.71–0.93) and 0.71 (0.61–0.82) for 4.9 to <17.4 and ≥17.4 metabolic equivalent-hr/week). A U-shaped association was observed for late all-cause mortality and BMI using updated weight (1.42 (1.15–1.74) and 1.40 (1.09–1.81), <21.5 and ≥35, respectively). Smoking was associated with increased risk of late outcomes. In this large prospective pooling project, modifiable lifestyle factors were associated with late outcomes among long-term ER+ breast cancer survivors.

In 2011, a meta-analysis of 20 clinical trials reported that even among women treated with tamoxifen for 5 years, there was considerable risk of recurrence in later years for women with estrogen receptor-positive (ER+) breast cancer.[1] Specifically, the probability of breast cancer recurrence was 25.9% at 10 years and 33.0% at 15 years. Studies have also shown that, compared to ER− breast cancer, women with ER+ breast cancer have a better prognosis in the first several years after diagnosis, but may have higher risk of recurrence in later years after diagnosis.[2–8] Despite this, risk factors for late outcomes are not yet established.

Key words: lifestyle factors, recurrence, mortality, breast cancer, prospective, cohort

Abbreviations: ABCPP: After Breast Cancer Pooling Project; BMI: body mass index; CI: confidence interval; ER: estrogen receptor; HR: hazard ratio; LACE: Life After Cancer Epidemiology Study; MET: metabolic equivalent; NHS: Nurses' Health Study; PR: progesterone receptor; WHEL: Women's Healthy Eating & Living Study

Additional Supporting Information may be found in the online version of this article.

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What's new?

Late recurrence is a major concern for women with ER+ breast cancer, which accounts for close to two-thirds of diagnosed breast cancers. The factors that predispose survivors to late recurrence, however, are not fully understood. This report describes a role for certain lifestyle factors. Using pooled data from prospective cohorts, the authors' show that post-diagnosis lifestyle factors, including alcohol intake, exercise, obesity and smoking, are associated with late breast cancer outcomes in estrogen receptor-positive breast cancer survivors. The modifiable nature of these factors could have implications for long-term survivorship care guidelines.

Modifiable lifestyle factors, such as body mass index (BMI), weight change and physical activity (PA), have been well-studied in relation to overall breast cancer prognosis.[9–13] Evidence is most consistent for an association of obesity at or around the time of diagnosis with poorer prognosis, and an association of PA with reduced risk of mortality in breast cancer survivors. Although the importance of lifestyle factors in overall breast cancer prognosis has been demonstrated in many studies, associations of lifestyle factors with late outcomes (>5 years after diagnosis) have been much less studied, especially in ER+ breast cancer survivors. Some studies have examined associations for tumor characteristics and molecular markers with late recurrence specifically in ER+ breast cancer[14–16]; however, no studies to date have investigated modifiable lifestyle factors.

Late breast cancer outcomes are a major concern in ER+ breast cancer, which accounts for close to two-thirds of all breast cancer diagnosed.[1,6,16] Therefore, it is of critical importance to understand potentially modifiable factors that may be uniquely associated with these late breast cancer outcomes among women with ER+ breast cancer. The After Breast Cancer Pooling Project (ABCPP) includes data from several long-term (>10 years), prospective cohorts of breast cancer survivors, providing the opportunity to evaluate the role of lifestyle factors after diagnosis in long-term breast cancer outcomes among a large sample of ER+ survivors. The purpose of this study was to evaluate the associations of post-diagnosis lifestyle factors that have been well-studied in association with breast cancer prognosis overall with late breast cancer outcomes among ER+ breast cancer survivors.

Materials and Methods

After Breast Cancer Pooling Project

The ABCPP includes pooled data on 18,363 breast cancer survivors aged 20–83 years from four prospective cohorts recruited from the United States (US) sites and Shanghai, China, diagnosed with invasive breast cancer between 1976 and 2004.[17] Three cohorts recruited only breast cancer patients: the Shanghai Breast Cancer Survival Study,[18] the Life After Cancer Epidemiology (LACE) Study[19] and the Women's Healthy Eating & Living (WHEL) Study.[20] The WHEL study was an intervention trial (1995–2006) designed to test adoption of a diet high in vegetables, fruit and fiber and low in fat among breast cancer survivors. The findings were null, and therefore WHEL was treated as a cohort study.[21] The fourth cohort consists of breast cancer patients participating in the Nurses' Health Study (NHS).[22] WHEL and LACE only enrolled participants who had completed primary treatment. All participants provided informed consent. Institutional review board approval was obtained for each study and for the ABCPP. Pooled and harmonized data were available for post-diagnosis lifestyle factors, cancer treatment, tumor characteristics, sociodemographics and select major comorbidities.[17]

This study included breast cancer survivors from the US cohorts only, as the Shanghai Breast Cancer Survival Study cohort is the most recent cohort, and does not yet have enough long-term follow-up time for the evaluation of late outcomes (≥5 years after diagnosis). A detailed description of the study exclusions is shown in Figure 1. A total of 921 women were excluded from the recurrence analysis due to event/loss to follow-up prior to 5 years after diagnosis, resulting in 5,675 5-year disease-free survivors. A total of 599 women were excluded from the mortality analysis due to death/loss to follow-up prior to 5 years after diagnosis, resulting in 6,295 5-year ER+ survivors.

Post-diagnosis lifestyle factors

Lifestyle factors were initially assessed at a mean of 2 years post-diagnosis. If the first post-diagnosis survey was <1 year after diagnosis, the second post-diagnosis survey was used for measurement of lifestyle factors. Height and weight after diagnosis were measured in-person by study staff for WHEL and were self-reported in the NHS and LACE. Pre-diagnosis weight was self-reported after diagnosis for LACE and WHEL participants at cohort enrollment and on a pre-diagnosis mailed questionnaire for the NHS. Absolute weight change was calculated as weight at first post-diagnosis assessment minus pre-diagnosis weight (at about 1 year prior to diagnosis of breast cancer). We classified percent weight change pre- to post-diagnosis with the following categories based on our previous work: stable (within 5%), moderate loss (5–10%), large loss (≥10%), moderate gain (5–10%) and large gain (≥10%).[23,24]

Post-diagnosis BMI was calculated as weight in kilograms divided by height in meters squared and initially categorized using the World Health Organization classifications: underweight (<18.5 kg/m^2), normal weight (18.5–24.99 kg/m^2),

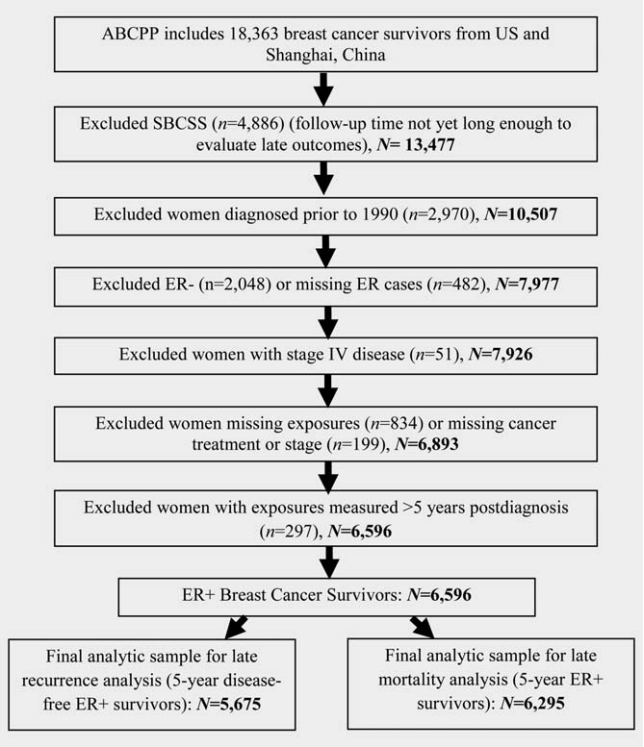

Figure 1. Study population: exclusions and final analytic sample.

overweight (25–29.99 kg/m^2) and obese ($\geq$30 kg/m^2). The sample size for <18.5 kg/m^2 was too small for stable estimates, and therefore we re-classified women in the lowest two BMI categories as follows:<21.5 and 21.5–24.99 kg/m^2. We further classified obese women as obese (BMI 30 to <34.99 kg/m^2) and severely obese (BMI $\geq$35 kg/m^2); sample sizes were too small to examine the morbidly obese (>40 kg/m^2) group.

Self-reported information on recreational PA was available for all cohorts, and was converted into metabolic equivalents (METs)[25] in MET-hr/week for all activities combined. The PA assessments used in each cohort were previously evaluated for reproducibility and validity.[26–28] PA was classified based on tertiles (0 to <4.9, 4.9–17.4 and $\geq$17.4) and as meeting (yes or no) the US 2008 recommendations ($\geq$10 MET-hr/week, equivalent to about 2.5 hrs of moderate intensity activity per week),[29] as results were similar regardless of classification only those for the tertile categorization are shown for multivariable models.

Post-diagnosis alcohol intake was assessed in each cohort *via* food frequency questionnaires.[30] Alcohol intake was classified using cutpoints: <0.36 g/day (non-drinkers), 0.36–6 g/day, >6 to <12 g/day, $\geq$12 g/day (6 g is equivalent to about one-half of an alcoholic beverage), and these cutpoints were used previously in our research.[30] Smoking status was assessed at the first post-diagnosis survey, including information on current smoking and past smoking habits. Pack-years were calculated using the number of years smoked and number of cigarettes smoked. Smoking status at about 2 years post-diagnosis was categorized as never, former (<20 pack-years, $\geq$20 pack-years)[31] and current (sample size was not large enough to examine pack-years of exposure among current smokers). Updated weight information was available for all cohorts at a second post-diagnosis time point (weight was the only lifestyle factor with updated information available). The updated weight was used to create updated post-diagnosis BMI and weight change (pre-diagnosis to the second post-diagnosis weight) variables, using the same classifications as earlier.

Clinical characteristics and additional covariates

Data on treatment included chemotherapy (yes, no), radiotherapy (yes, no), mastectomy (yes, no) and hormonal therapy (yes, no). Most women received tamoxifen, as the majority of cases were diagnosed before aromatase inhibitors were widely available. Tumor characteristics included ER status, progesterone receptor (PR) status and AJCC 6th edition stage (I, II, III, IV). Age at diagnosis, race/ethnicity, education and family history of breast cancer were available for all cohorts. Menopausal status at diagnosis (or pre-diagnosis measurement closest to diagnosis for NHS) was classified as premenopausal, postmenopausal and unclear/unknown.

Outcome ascertainment

Detailed methods on outcome and follow-up have been previously published for the ABCPP[17] and each cohort (WHEL,[20] LACE[19] and NHS[32]). Briefly, during active follow-up, each cohort followed participants to ascertain breast cancer outcomes (recurrence, metastasis, new primary breast cancer (except NHS), overall mortality and cause-specific mortality). For the WHEL study, outcomes were obtained *via* semi-annual telephone contact and clinic visits through the end of the trial (June 2006), with all reported events confirmed by medical records review.[21] Active follow-up for over half the cohort continued until June 2010 with subsequent follow-up for mortality outcomes only *via* linkage to death registries. For the LACE study, outcomes were ascertained on a semi-annual basis *via* mailed surveys until 5 years post-diagnosis and yearly thereafter, and medical records were obtained to verify any reported breast cancer outcomes.[19] For the NHS, recurrences were collected *via* questionnaires to breast cancer patients (if a woman died of breast cancer without self-report of a recurrence, the date of recurrence was assigned as 1 year prior to death). For all cohorts, mortality information was obtained *via* periodic linkages to the Social Security Index and the National Death Index, and for LACE, periodic linkages were also made to Kaiser Permanente Northern California electronic data sources, whereas for NHS deaths were also reported through next of kin and the post office. Cause of death information was obtained from the National Death Index, state death certificates and/or medical records.

Statistical analysis

Outcomes for this analysis included late (≥5 years) disease-free survival (hereafter referred to as recurrence for brevity) with an event defined as recurrence, metastasis, new breast primary or breast cancer death, whichever occurred first; and late (≥5 years) all-cause mortality. Follow-up time started at 5 years post-diagnosis,[33] and the recurrence analysis included 5-year disease-free survivors and the mortality analysis included 5-year survivors, regardless of whether they had a recurrence.[34] The exit date was date of death (or recurrence for the recurrence analysis) or date of last contact (*i.e.*, date of last follow-up survey or last registry linkage, whichever was most recent).

Initially, study-specific adjusted hazard ratios (HRs) and their corresponding 95% confidence intervals (CIs) were derived from Cox regression models. The Q-statistic was used to test for heterogeneity in risk estimates across studies.[35] If heterogeneity was observed, we conducted a random-effects meta-analysis, with study-specific HRs using inverse-variance weights in random-effects models.[36] If heterogeneity was not observed, we conducted a pooled analysis using combined data with HRs and 95% CIs from Cox regression models stratified by study (*i.e.*, study was included in the STRATA statement).[36] The Q-statistic was statistically significant for four models for only a specific category of the exposure, including (*i*) late recurrence and post-diagnosis BMI 25–29.99 kg/m^2 ($p = 0.026$), (*ii*) late mortality and weight loss ≥ 10% ($p = 0.036$), (*iii*) late mortality and post-diagnosis BMI 30–34.99 kg/m^2 ($p = 0.016$) and (*iv*) late mortality and alcohol intake of 6 to <12 g/day ($p = 0.0095$). To be consistent, all results for these associations were from a random effects meta-analysis,[36] all other results shown are from the individually pooled analysis, and we provide a footnote to indicate if the results displayed in the Tables are from the random effects meta-analysis (see Refs. 17 and 36 for additional details on the analytic approach).

Covariates selected *a priori* included clinical characteristics and known breast cancer prognostic factors (age at diagnosis, stage, PR status, race/ethnicity, mastectomy, chemotherapy, radiotherapy, hormonal therapy and menopausal status), and select major comorbidities available for all cohorts (diabetes, hypertension). Weight change models were adjusted for pre-diagnosis BMI. Multivariable models were also adjusted for the lifestyle factors of interest (when these variables were not the main exposures being modeled). Time between exposure measurement and start of follow-up was included as a covariate.

For comparison, we also evaluated associations for each lifestyle factor and early recurrence and all-cause mortality (event within 5 years after diagnosis) (Supporting Information Table S1). It is important to note that (*i*) women survived on average 2 years before they were enrolled in the cohorts and (*ii*) lifestyle factors were measured on average 2 years after diagnosis and up to 4 years after diagnosis; therefore, investigations of post-diagnosis lifestyle in association with early events are limited in this analysis, in particular as survivors are ER+ breast cancer survivors, who have better survival in the first 5 years after diagnosis, which further reduces the number of early events.

Tests for linear trend were calculated using the Wald test. The proportional hazards assumption was evaluated by testing the statistical significance of interaction terms for each covariate and survival time for all models. All analyses were performed using SAS (version 9.4; SAS Institute, Cary, NC). Tests of statistical significance were two-sided, and $p < 0.05$ were considered statistically significant.

Results

Table 1 displays the number of events, follow-up time, clinical characteristics and post-diagnosis lifestyle data by cohort and combined for women diagnosed with ER+ breast cancer. About 49% of deaths were due to breast cancer, 17% were due to other cancers, 13% were due to CVD and 21% were due to other causes. Disease-free survival was 92.7% at 5 years and 84.9% at 10 years. Overall survival was 96.7% at 5 years and 86.6% at 10 years.

Table 2 displays results for the associations of lifestyle factors and late recurrence. Table 3 displays results for the associations of lifestyle factors and all-cause mortality. A nonsignificant inverse association between ≥10% pre- to post-diagnosis weight loss and late recurrence was observed (HR: 0.67; 95% CI: 0.42–1.05). Pre- to post-diagnosis weight gain ≥10% was associated with increased risk of late breast cancer recurrence (HR: 1.24, 95%: 1.00–1.53). Weight loss and weight gain were not significantly associated with late all-cause mortality.

High BMI at about 2 years after diagnosis was associated with increased risk of late recurrence (HR: 1.40, 95% CI: 1.05–1.86) and (HR: 1.41, 95% CI: 1.02–1.93) for BMI 30–34.99 and ≥35 kg/m^2, respectively). While there was an overall pattern of a U-shaped association for higher BMI and late all-cause mortality, results were not statistically significant. Higher BMI was associated with increased risk of breast cancer-specific mortality, HRs (95% CIs): 1.33 (1.07–1.66), 1.18 (0.90–1.54) and 1.43 (1.04–1.97) for 25–29.9, 30–34.99 and ≥35 kg/m^2, respectively (reference = 21.5–24.99 kg/m^2). Updated information on weight only was available for all cohorts (mean of 4.6 years after diagnosis, with some measurements up to 9.9 years after diagnosis). The association for high post-diagnosis BMI and increased risk of late recurrence was again observed, with evidence for a stronger association using the updated weight. For mortality, we observed a significant U-shaped association, with increased risk for both low BMI (<21.5 kg/m^2) and high BMI (≥35 kg/m^2).

Post-diagnosis recreational PA was not associated with late recurrence. Higher levels of post-diagnosis recreational PA were strongly inversely associated with late all-cause mortality (HR: 0.81, 95% CI: 0.71–0.93 and HR: 0.71, 95% CI: 0.61–0.82 for 4.9 to <17.4 and ≥17.4 MET-hr/week, respectively, $p_{trend} < 0.0001$). Post-diagnosis alcohol intake ≥1 drink/day was associated with increased risk of late recurrence (HR: 1.28, 95% CI: 1.01–1.62); however, a consistent

Table 1. Follow-up time, events, clinical characteristics and lifestyle factors for ER+ breast cancer survivors by cohort and combined ($N = 6,596$)

	WHEL ($N = 2,118$)	LACE ($N = 1,543$)	NHS ($N = 2,935$)	All ($N = 6,596$)
Median follow-up time for mortality (SD), years since diagnosis	13.6 (3.0)	12.6 (2.9)	10.5 (4.1)	12.0 (3.8)
Median follow-up time for recurrence (SD), years since diagnosis	10.9 (3.5)	11.9 (3.6)	9.6 (4.4)	10.6 (4.0)
Total deaths, *n*	374	387	666	1,427
Recurrence[1], *n*	377	319	613	1,309
Year of diagnosis, range	1991–2000	1996–2000	1990–2004	1990–2004
Age at diagnosis (years), mean (SD)	52.2 (8.7)	59.4 (10.5)	64.6 (7.5)	59.4 (10.2)
Chemotherapy, *n* (%)	1,332 (62.9)	763 (49.5)	951 (32.4)	3,046 (46.2)
Radiotherapy, *n* (%)	1,320 (62.3)	958 (62.1)	1,785 (60.8)	4,063 (61.6)
Mastectomy, *n* (%)	1,080 (51.0)	776 (50.3)	1,347 (45.9)	3,203 (48.6)
Hormonal therapy, *n* (%)	1,766 (83.4)	1,433 (92.9)	2,490 (84.8)	5,689 (86.3)
TNM stage, *n* (%)				
I	871 (41.1)	761 (49.3)	1,876 (63.9)	3,508 (53.2)
II	922 (43.5)	619 (40.1)	813 (27.7)	2,354 (35.7)
III	325 (15.3)	163 (10.6)	246 (8.4)	734 (11.1)
PR+, *n* (%)	1,768 (84.2)	1,268 (82.2)	2,296 (80.0)	5,332 (81.9)
Postmenopausal, *n* (%)	1,052 (49.7)	1,047 (67.9)	2,709 (92.3)	4,808 (72.9)
Years between diagnosis and measurement of post-diagnosis lifestyle factors, mean (range)	2.2 (1.0–4.0)	2.1 (1.0–3.7)	2.1 (1.0–4.9)[2]	2.1 (1.0–4.9)
Years between diagnosis and first post-diagnosis weight measurement, mean (SD)	2.2 (0.83)	2.1 (0.60)	2.1 (0.70)	2.1 (0.72)
Years between diagnosis and second post-diagnosis weight measurement, mean (SD)	3.7 (0.99)	7.0 (9.4)	4.1 (0.87)	4.6 (1.6)
Pre- to post-diagnosis weight change, *n* (%)				
Stable (±5%)	910 (43.5)	730 (47.9)	1,760 (60.8)	3,400 (52.2)
Weight loss of 5–10%	172 (8.2)	153 (10.0)	317 (10.9)	642 (9.9)
Weight loss of ≥10%	94 (4.5)	106 (7.0)	174 (6.0)	374 (5.7)
Weight gain of 5–10%	370 (17.7)	254 (16.7)	435 (15.0)	1,059 (16.3)
Weight gain of ≥10%	546 (26.1)	282 (18.5)	211 (7.3)	1,039 (16.0)
BMI at 2 years post-diagnosis (kg/m^2), *n* (%)				
<21.5	264 (12.5)	187 (12.1)	376 (12.8)	827 (12.5)
21.5–24.99	637 (30.1)	420 (27.2)	901 (30.7)	1,958 (29.7)
25–29.99	672 (31.7)	531 (34.4)	1,002 (34.1)	2,205 (33.4)
30–34.99	331 (15.6)	249 (16.1)	456 (15.5)	1,036 (15.7)
≥35	214 (10.1)	156 (10.1)	200 (6.8)	570 (8.6)

Table 1. Follow-up time, events, clinical characteristics and lifestyle factors for ER+ breast cancer survivors by cohort and combined ($N = 6,596$) (Continued)

	WHEL ($N = 2,118$)	LACE ($N = 1,543$)	NHS ($N = 2,935$)	All ($N = 6,596$)
Post-diagnosis recreational physical activity, *n* (%)				
MET-hr/week				
<4.9	634 (29.9)	573 (37.1)	960 (32.7)	2,167 (32.9)
4.9 to <17.4	743 (35.1)	475 (30.8)	968 (33.0)	2,186 (33.1)
≥17.4	741 (35.0)	495 (32.1)	1,007 (34.3)	2,243 (34.0)
Alcohol consumption (g/day), *n* (%)				
Non-drinker	751 (35.5)	714 (47.7)	1,140 (41.8)	2,605 (41.1)
0.36 to <6	717 (33.9)	387 (25.9)	838 (30.7)	1,942 (30.6)
6 to <12	263 (12.4)	144 (9.6)	296 (10.8)	703 (11.1)
≥12	386 (18.2)	252 (16.8)	456 (16.7)	1,094 (17.2)
Smoking status, *n* (%)				
Never	1,115 (52.9)	817 (53.7)	1,222 (42.1)	3,154 (48.3)
Former <20 pack-years	653 (31.0)	381 (25.1)	803 (27.7)	1,837 (28.1)
Former ≥20 pack-years	245 (11.6)	212 (13.9)	633 (21.8)	1,090 (16.7)
Current	95 (4.5)	111 (7.3)	244 (8.4)	450 (6.9)

Table excludes missing, where applicable.
[1]Includes first breast cancer event (recurrence, metastasis, new breast primary or death due to breast cancer).
[2]For NHS, this date is for BMI measurement, as the dates vary by lifestyle factor (exercise, mean: 2.4 (range: 1.0–4.99); alcohol, mean: 3.0 (range: 1.0–4.99), smoking, mean: 2.0 (range: 1.0–3.7)).

trend for increasing intake was not observed. Post-diagnosis alcohol intake was not significantly associated with late all-cause mortality. Compared with never smokers, positive associations were observed for former smokers of ≥20 pack-years and current smokers and risk of late recurrence (HR: 1.32, 95% CI: 1.05–1.66 and HR: 1.30, 95% CI: 0.94–1.81, respectively). Strong positive associations were also observed for former smokers of ≥20 pack-years and current smokers with late all-cause mortality. Formers smokers of ≥20 pack-years and current smokers also had increased risk of breast cancer-specific mortality, HRs (95% CIs): 1.27 (1.01–1.61) and 1.75 (1.30–2.35), respectively.

Discussion

In this prospective, pooled analysis of over 6,200 ER+ breast cancer survivors who had survived on average 2 years at study entry, we found that large post-diagnosis weight gain, obesity and daily alcohol consumption (≥1 drink/day) were associated with increased risk of late recurrence (≥5 years after diagnosis). PA was inversely associated with late all-cause mortality, but not late recurrence. Current and heavy former smoking was associated with increased risk of late recurrence and all-cause mortality. To our knowledge, our study is the first to specifically focus on the evaluation of post-diagnosis lifestyle factors and late outcomes in long-term ER+ breast cancer survivors, a group that is continuing to increase and has been shown to have a higher risk of late outcomes. Our findings demonstrate that lifestyle factors after diagnosis may have a long-term impact on breast cancer outcomes among 5-year survivors. These results support the critical need for the incorporation of lifestyle recommendations and modifications into long-term survivorship care plans,[23,37] in particular promotion of regular exercise participation, avoidance of large weight gain, careful consideration of the risks and benefits of moderate alcohol consumption and smoking cessation.

Although some studies have evaluated tumor/molecular markers in association with late outcomes in ER+ breast cancer survivors[14–16] or among all 5-year breast cancer survivors,[34,38] none of these studies have evaluated lifestyle factors. We did identify one study of pre-diagnosis BMI and breast cancer survival that investigated associations by time since diagnosis among all breast cancer subtypes using registry-linked data from Denmark.[39] That study reported that the association of pre-diagnosis obesity and risk of distant metastasis varied by time since diagnosis, with stronger associations observed in the later time period (5–10 years after diagnosis). Although our study differs from the Denmark study in that we evaluated post-diagnosis BMI, have follow-up beyond 10 years and focused on ER+ breast cancer, our findings of increased risk of late recurrence for high post-diagnosis BMI are supported by this earlier study.

We also found that BMI at both 2.1 and 4.6 years after diagnosis (on average) were associated with increased risk of recurrence. However, for all-cause mortality, results were inconsistent by time point of post-diagnosis weight. Specifically, BMI

Table 2. Hazard ratios[1] for post-diagnosis lifestyle factors in association with late recurrence (≥5 years) among ER+ breast cancer survivors ($N = 5{,}675$)[2]

	Events	Cohort	HR	95% CI
Pre- to post-diagnosis weight change				
Loss of 5–10%	44	547	0.77	0.56–1.07
Loss of ≥10%	20	313	0.67	0.42–1.05
Stable	282	2,898	1.00	reference
Gain of 5–10%	109	927	1.05	0.84–1.31
Gain of ≥10%	138	919	1.24	1.00–1.53
BMI at 2 years post-diagnosis (kg/m^2)[3]				
<21.5	68	704	1.17	0.87–1.57
21.5–24.99	138	1,712	1.00	reference
25–29.99	230	1,892	1.49	0.98–2.25
30–34.99	107	876	1.40	1.05–1.86
≥35	61	491	1.41	1.02–1.93
p_{trend}				0.007
Post-diagnosis BMI using second available weight measurement (kg/m^2)[4]				
<21.5	61	653	1.36	0.99–1.86
21.5–24.99	110	1,558	1.00	Reference
25–29.99	194	1,750	1.59	1.25–2.01
30–34.99	94	821	1.62	1.22–2.15
≥35	51	421	1.65	1.16–2.32
p_{trend}				0.0003
Post-diagnosis recreational physical activity (MET-hr/week)				
0 to <4.9	218	1,856	1.00	Reference
4.9 to <17.4	200	1,876	0.93	0.76–1.13
≥17.4	186	1,943	0.89	0.73–1.09
p_{trend}				0.27
Post-diagnosis alcohol consumption (g/day)				
Non-drinker (0 to <0.36)	233	2,267	1.00	reference
0.36–6	186	1,668	1.09	0.89–1.32
<6 to <12	61	608	1.06	0.79–1.42
≥12 (≥1 drink/day)	113	973	1.28	1.01–1.62
p_{trend}				0.06
Smoking status at first post-diagnosis survey				
Never	284	2,773	1.00	reference
Former <20 pack-years	164	1,603	1.04	0.86–1.27
Former ≥20 pack-years	106	894	1.32	1.05–1.66
Current	43	353	1.30	0.94–1.81

[1]Adjusted for age at diagnosis, TNM stage, PR status, chemotherapy, radiotherapy, surgery, hormonal therapy, race/ethnicity, menopausal status, comorbidity (diabetes, hypertension), other studied lifestyle factors (as appropriate) and time between exposure measurement and 5-year post diagnosis date, stratified by study. Models for weight change also adjusted for pre-diagnosis BMI.
[2]Table is limited to women who were 5-year disease-free survivors and not missing date of recurrence. In addition, specific models excluded the following: 80 women missing pre-diagnosis BMI (for weight change models), 245 women missing alcohol intake (alcohol models) and 64 women missing pack-years information (smoking models).
[3]Q-statistic was statistically significant for one exposure category for one model (post-diagnosis BMI 25–29.99 kg/m^2 ($p = 0.026$)); all results for this model were from random effects models.[1]
[4]Using second post-diagnosis weight instead of first post-diagnosis weight, assessed at on average 4.6 years after diagnosis. Model excludes women with second weight measured after recurrence ($n = 31$). Excludes an additional 441 women missing second measurement of BMI.

Table 3. Hazard ratios[1] for post-diagnosis lifestyle factors in association with late all-cause mortality (≥5 years) among ER+ breast cancer survivors ($N = 6,259$)[2]

	Events	Cohort	HR	95% CI
Pre- to post-diagnosis weight change[3]				
Loss of 5–10%	129	595	1.16	0.95–1.41
Loss of ≥10%	69	348	1.17	0.53–2.59
Stable	599	3,217	1.00	reference
Gain of 5–10%	199	1,021	1.08	0.85–1.36
Gain of ≥10%	187	1,001	1.06	0.82–1.38
BMI at 2 years post-diagnosis (kg/m^2)[3]				
<21.5	151	784	1.19	0.98–1.45
21.5–24.99	314	1,877	1.00	reference
25–29.9	400	2,093	1.05	0.81–1.37
30–34.99	211	970	1.12	0.78–1.63
≥35	133	535	1.37	0.93–2.01
p_{trend}				0.19
Post-diagnosis BMI using second available weight measurement (kg/m^2)[4]				
<21.5	144	716	1.42	1.15–1.74
21.5–24.99	244	1,702	1.00	reference
25–29.9	320	1,927	1.06	0.90–1.26
30–34.99	162	891	1.11	0.91–1.36
≥35	92	445	1.40	1.09–1.81
p_{trend}				0.013
Post-diagnosis recreational physical activity (MET-hr/week)				
0 to <4.9	503	2,027	1.00	reference
4.9 to <17.4	382	2,076	0.81	0.71–0.93
≥17.4	324	2,156	0.71	0.61–0.82
p_{trend}			<0.0001	
Post-diagnosis alcohol consumption (g/day)[3]				
Non-drinker	529	2,491	1.00	reference
0.36–6	328	1,864	0.94	0.81–1.08
<6 to <12	121	676	1.00	0.64–1.57
≥12	185	1,055	0.93	0.75–1.17
p_{trend}				0.29
Smoking status at first post-diagnosis survey				
Never	513	3,045	1.00	reference
Former <20 pack-years	268	1,751	0.94	0.81–1.09
Former ≥20 pack-years	266	996	1.46	1.25–1.70
Current	144	408	2.20	1.82–2.66

[1]Adjusted for age at diagnosis, TNM stage, PR status, chemotherapy, radiotherapy, surgery, hormonal therapy, race/ethnicity, menopausal status, comorbidity (diabetes, hypertension), studied lifestyle factors (as appropriate) and time between exposure measurement and 5-year post diagnosis date, stratified by study. Models for weight change also adjusted for pre-diagnosis BMI.
[2]Table limited to 5-year survivors. In addition, specific models excluded the following: 82 missing pre-diagnosis BMI (for weight change models), 252 missing alcohol intake (for alcohol models), 65 missing pack-year information (smoking models).
[3]The Q-statistic was statistically significant for one exposure category for three models (weight loss ≥ 10%, $p = 0.036$, post-diagnosis BMI 30–34.99 kg/m^2, $p = 0.016$, alcohol intake of 6 to <12 g/day, $p = 0.0095$); therefore, the results were from a random effects meta-analysis for these models.[1]
[4]Using second post-diagnosis weight instead of first post-diagnosis weight, assessed at on average 4.6 years after diagnosis. Model excludes women with second weight measured after recurrence ($n = 31$). Excludes an additional 547 women missing second measurement of BMI.

at 2 years post-diagnosis was not associated with all-cause mortality, whereas a statistically significant U-shaped association was found for BMI at 4.6 years post-diagnosis and all-cause mortality with increased risk observed for low BMI <21.5 kg/m^2 and high BMI >35 kg/m^2. It could be that the measure of BMI closer to when the event occurs has a larger impact on overall survival, or that obesity at this later time point represents women who have been obese long term after diagnosis. The association of low BMI and increased risk of mortality may be due to underlying illness leading to unintentional weight loss. However, we did not collect information on type of weight loss and could not evaluate the reason for weight loss as a potential explanatory mechanism.[23,40]

Findings for weight change and breast cancer outcomes have been inconsistent across studies.[10,24,40,41] To our knowledge, no studies have specifically evaluated weight change and late outcomes. In our study, we found that pre- to post-diagnosis weight gain increased risk of late recurrence, but was not associated with late all-cause mortality. Although not established, potential biological pathways that may explain the association between high adiposity and recurrence/metastasis include insulin, steroid hormone, adipokine and inflammatory pathways, which may promote breast cancer cell proliferation and tumor growth.[42] Similar associations were seen when we evaluated weight gain using the second post-diagnosis weight measurement, measured on average 4.6 years after diagnosis (HRs (95% CIs) for large weight gain $\geq$10% were 1.52 (1.21–1.91) and 1.18 (0.98–1.42) for late recurrence and all-cause mortality, respectively). In contrast, weight loss using the second post-diagnosis weight measurement was associated with a statistically significant increased risk of all-cause mortality (HR (95% CI) for large weight loss $\geq$10%: 1.53 (1.23–1.90)). As noted earlier, we did not have information on whether weight loss was intentional. As discussed in detail by Caan *et al.*[23] there are several mechanism that may explain an association between weight loss and increased risk of mortality, including loss of lean body mass and interactions with comorbidity status and pre-diagnosis weight, and these must be carefully considered when providing recommendations regarding weight loss among breast cancer survivors.[23]

Higher levels of post-diagnosis recreational PA were inversely associated with late all-cause mortality, with a dose–response pattern observed. PA before and after diagnosis has been consistently associated with reduced risk of total and breast cancer-specific mortality.[10,43–46] However, to our knowledge, no studies have examined the association of post-diagnosis PA and late breast cancer outcomes overall or particularly for ER+ breast cancer survivors. Exercise has many known potential health benefits for breast cancer survivors, including reduced risk of comorbidities, improved quality of life, reduced fatigue and enhanced immune function.[47] Our results add to the literature regarding the benefits of PA in breast cancer survivors and specifically support that post-diagnosis recreational PA may reduce risk of late all-cause mortality among ER+ breast cancer survivors.

Alcohol intake was not associated with recurrence or total mortality overall in a previous report in the ABCPP among all breast cancer subtypes.[30] This previous report did not consider late breast cancer outcomes. In this study of late outcomes among ER+ breast cancer survivors, no clear association was found for alcohol and late all-cause mortality; however, alcohol intake of at least one drink per day (compared with non-drinkers) was associated with increased risk of late recurrence. One limitation of this analysis is that we did not have more than one measure of alcohol intake after diagnosis, and future studies with multiple measures of alcohol intake after diagnosis are needed.

The main strengths of our study included the large sample size, long-term follow-up beyond 10 years for breast cancer outcomes and detailed information on post-diagnosis modifiable lifestyle-related factors and tumor characteristics. Limitations should also be considered. One limitation was that we only had binary yes/no cancer treatment information; therefore, we could not evaluate the impact of therapy adherence, in particular for long-term adjuvant hormonal therapy, on the observed associations. Another limitation was that we could only evaluate those lifestyle factors that were harmonized across cohorts in this secondary data analysis. Further, although we had pre-diagnosis information on BMI, we did not have pre-diagnosis information on alcohol or PA for all breast cancer survivors, and could not investigate change from pre-to-post diagnosis for these factors on long-term outcomes. Another limitation was that we only had information for the majority of lifestyle factors at one time point after diagnosis. Although we did have updated weight available, the timing of measurement after diagnosis varied greatly by study, and future studies with post-diagnosis measures of lifestyle factors at multiple uniform time-points are needed. Finally, although weight and height were measured in-person in WHEL, weight and height were self-reported in other cohorts, potentially contributing to measurement error, as under-reporting of weight has been observed in some studies for overweight and obese women.[48] However, self-reported weight has been shown to be accurate based on comparison of self-reported and technician-measured weight in the NHS.[22]

In summary, we found that modifiable lifestyle factors were important predictors of late recurrence and mortality among long-term ER+ breast cancer survivors. These results set the stage for future research in this area, particularly in cohorts with long-term follow-up $>$10 years after diagnosis and multiple post-diagnosis lifestyle assessments, including measurements $\geq$5 years post-diagnosis.

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