Postdiagnosis weight change is associated with poorer survival in breast cancer survivors: A prospective population-based patient cohort study

Audrey Y. Jung | Anika Hüsing | Sabine Behrens | Julia Krzykalla | Nadia Obi | Heiko Becher | Jenny Chang-Claude

Abstract
More women are surviving after breast cancer due to early detection and modern treatment strategies. Body weight also influences survival. We aimed to characterize associations between postdiagnosis weight change and prognosis in postmenopausal long-term breast cancer survivors. We used data from a prospective population-based patient cohort study (MARIE) conducted in two geographical regions of Germany. Breast cancer patients diagnosed 50 to 74 years of age with an incident invasive breast cancer or in situ tumor were recruited from 2002 to 2005 and followed up until June 2015. Baseline weight was ascertained at an in-person interview at recruitment and follow-up weight was ascertained by telephone interview in 2009. Delayed entry Cox proportional hazards regression was used to assess associations between relative weight change and all-cause mortality, breast cancer mortality, and recurrence-free survival. In total, 2216 patients were included. Compared to weight maintenance (within 5%), weight loss >10% increased risk of all-cause mortality (HR 2.50, 95% CI 1.61, 3.88), breast cancer mortality (HR 3.07, 95% CI 1.69, 5.60) and less so of recurrence-free survival (HR 1.43, 95% CI 0.87, 2.36). Large weight gain of >10% also increased all-cause mortality (HR 2.50, 95% CI 1.61, 3.88), breast cancer mortality (HR 3.07, 95% CI 1.69, 5.60) and less so of recurrence-free survival (HR 1.43, 95% CI 0.87, 2.36). Large weight gain of >10% also increased all-cause mortality (HR 1.64, 95% CI 1.02, 2.62) and breast cancer mortality (HR 2.25, 95% CI 1.25, 4.04). Weight maintenance for up to 5 years in long-term breast cancer survivors may help improve survival and prognosis. Post-diagnosis fluctuations in body weight of greater than 10% may lead to increased mortality. Survivors should be recommended to avoid large deviations in body weight from diagnosis onwards to maintain health and prolong life.

KEYWORDS
breast cancer, postmenopausal, survival, weight change

Abbreviations: BMI, body mass index; CCI, Charlson comorbidity index; CI, confidence interval; HR, hazard ratio; HR, hormone receptor; ICD, International Classification of Diseases; IQR, interquartile range; MARIE, Mammary Carcinoma Risk Factor Investigation; MET, metabolic equivalent of task.
1 | INTRODUCTION

Improvements in early detection, and personalized and targeted treatments have led to more women surviving after breast cancer.1,2 Modifiable factors such as body weight can also influence breast cancer prognosis.3 Results that include evidence from a large systematic review and meta-analysis point toward increasing risk of total mortality, breast cancer mortality and risk of developing a second primary breast cancer with obesity or excess body weight both before and after breast cancer diagnosis.3

Weight change is common during breast cancer. It may be a consequence of breast cancer or a combination of breast cancer and anticancer treatments such as surgery, chemo, radiation and/or hormonal therapies or combinations of these, which, while essential for improving survival, contribute considerably to therapy-associated side effects.4,6

There is accumulating evidence that weight gained in different periods during the breast cancer trajectory—during adulthood, from prediagnosis to postdiagnosis breast cancer, from pretreatment to posttreatment and during treatment—may impact adversely on total mortality, although there was large heterogeneity between studies in meta-analyses.3,7 Similar but weaker patterns of association between weight gain and breast cancer-specific mortality have also been observed, but there are fewer investigations between associations with recurrence.3,7 Although the bulk of weight change and prognosis research has focused on weight gain, results of a systematic review and meta-analysis conducted in six studies—without significant heterogeneity—revealed prediagnosis to postdiagnosis weight loss (highest vs lowest/stable) to be strongly associated with all-cause mortality.3 Collectively then, limited evidence suggests that weight maintenance may be optimal for health and survival following breast cancer. Sources of heterogeneity between studies can be mainly attributed to differences in study designs that affect timing and duration of weight measurements in relation to diagnosis and treatment. Indeed, time since diagnosis may influence the associations between weight change and survival.8

Risk of breast cancer and other chronic diseases increases with age. Therefore, at diagnosis and during survivorship, many breast cancer survivors have other chronic comorbid conditions that also affect survival.9,10 With this in mind, we aim to describe the associations between weight change after diagnosis and subsequent prognosis, including recurrence, in a population-based patient cohort of long-term breast cancer survivors in Germany. We further explore whether these associations differ by weight at recruitment, and number of comorbidities, and whether the rate at which weight changes also impacts survival. To the best of our knowledge, this is the first study to evaluate postdiagnosis weight change and prognosis within a European setting.

2 | MATERIALS AND METHODS

2.1 | Study population

We used data from the MARIE (Mammary Carcinoma Risk Factor Investigation) study,11 a prospective population-based patient cohort study that began as a case-control study conducted in two geographical regions of Germany—Rhine-Neckar-Karlsruhe and Hamburg. German-speaking breast cancer patients diagnosed between 50 and 74 years of age from January 1, 2001 to September 30, 2005 with an incident histologically confirmed invasive (according to 10th revision of the International Classification of Diseases (ICD-10-WHO; Stage I-IV) or in situ tumor (Stage 0; ICD-10-DO5) were recruited between 2002 and 2005. Potentially eligible subjects were identified based on frequent monitoring of hospital admissions, surgery schedules, and pathology records of 51 clinics serving these regions and through the Hamburg Cancer Registry. In 2009, patients were re-interviewed about weight and other exposures, and follow-up information about endpoints was ascertained in 2009 and 2015.12

The primary exposure of interest was weight change, so women who completed baseline and follow-up interviews (n = 2542) were included. After exclusion of patients who were premenopausal (n = 148), had metastases at diagnosis (n = 22), tumors other than breast cancer or nonmelanoma skin cancer before diagnosis (n = 138), missing baseline (n = 2) or follow-up weight (n = 16), there were 2216 patients available for analyses of all-cause and breast cancer-specific mortality (Figure 1). For recurrence-free survival, women who experienced a recurrence prior to the follow-up were additionally excluded leaving 2068 women for recurrence-free survival analyses.

2.2 | Assessment of weight and other exposures

At baseline interview (median 3.9 months after diagnosis), self-reported current body weight in kg and height in cm were recalled in an in-person interview. In 2009 (median 5.8 years after diagnosis), self-reported current height and body weight were ascertained at the follow-up telephone interview. Clinical and pathological characteristics were obtained from hospital and pathology records. Information on lifestyle, socioeconomic and demographic, comorbidities and other pertinent protective and risk factors were collected from baseline and follow-up interviews.
2.3 | Outcome assessment

Participant vital status was determined through population registries of the study regions up until the end of June 2015, and all deaths were verified by death certificates. Self-reported recurrences of the primary breast cancer, second cancers and metastatic events were identified during 2009 and 2015 telephone interviews with patients and verified by clinical records or with treating physicians. For patients who died, medical records were checked or treating physicians were contacted. Primary outcomes were all-cause mortality (death from any cause) and breast cancer-specific mortality (death from breast cancer). Recurrence-free survival (including ipsilateral/local/regional invasive recurrence, distant recurrence and metastases occurring after primary diagnosis, death)\(^\text{13}\) was a secondary outcome. Participants without events of interest were censored at date of last contact or June 30, 2015, whichever came first.

2.4 | Statistical analysis

Relative weight change was calculated using \(\text{[(follow-up weight} - \text{baseline weight})/\text{baseline weight}] \times 100\). To assess weight change, five categories were created: weight stable (weight change within 5% from baseline to follow-up), moderate gain/loss (weight gain/loss of \(\geq 5\%\) to \(\leq 10\%\)), large gain/loss (weight gain/loss of \(>10\%\)), respectively.\(^\text{7}\) These categories were selected for comparisons with other studies\(^\text{7}\) and considered to be clinically meaningful.\(^\text{14}\)

To estimate hazard ratios (HRs) and corresponding 95% confidence intervals (CIs) for associations between weight change with all-cause mortality, breast cancer mortality and recurrence-free survival, delayed-entry Cox proportional hazards regression models from follow-up interview until event of interest/censoring were constructed. Time-to-event started from date of diagnosis, and time-at-risk started from the date of follow-up interview. Weight stable women served as reference. The proportional hazards assumption was examined using a weighted least-squares line fitted to the plots of scaled Schoenfeld residuals.\(^\text{15}\) No indication for violation of the proportional hazards assumption was found. Follow-up time was calculated using reverse Kaplan-Meier.\(^\text{16}\)

Subgroup analyses were defined a priori, and effect modification was tested applying the likelihood ratio test to a model with the interaction term of the main exposure and potential modifier and a model without the interaction term. For this purpose, five weight change categories were collapsed into three (weight stable (weight change within 5%), weight loss (weight change \(\geq 5\%\)), and weight gain (weight change \(\geq 5\%\))). Associations between weight change and outcomes by baseline BMI (18.5 to <25.0 kg/m\(^2\)/\(\geq 25\) kg/m\(^2\)), and comorbidities using the Charlson Comorbidity Index (CCI 0-1/\(\geq 2\)) were evaluated. The CCI was built from 17 conditions\(^\text{17,18}\) and adapted. The CCI at follow-up was used, as new comorbidities may have been acquired after baseline.

The rate of weight change (% weight change per 1 year) was also assessed to facilitate comparisons between our results and those of other studies, where there was large variation in the duration or window in which weight was gained or lost.\(^\text{3,7}\) To calculate rate of weight change, percent weight change was divided by time between baseline and follow-up in years. Five categories for rate of weight change were constructed: weight maintenance (within 0.5% per year), slow weight gain/loss (\(\geq 0.5\%\) to \(\leq 1.0\%\) per year) and fast gain/loss (\(>1.0\%\) per year). Relative weight change was also modeled continuously using absolute values in all women and also allowing for different slopes in those who gained or lost \(\geq 5\%\) body weight. A model was fit using an

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**FIGURE 1** Flow chart of inclusion and exclusion criteria for participants of the MARIE study for analyses relating to changes in weight and all-cause mortality, breast cancer mortality and recurrence-free survival.
| Characteristic                                      | Overall n = 2216 | Relative weight change | Large loss (>10%) n = 111 (5.0) | Moderate loss (≥5% to ≤10%) n = 234 (10.6) | Weight stable (within 5%) n = 1421 (64.1) | Moderate gain (≥5% to ≤10%) n = 304 (13.7) | Large gain (>10%) n = 146 (6.6) |
|---------------------------------------------------|-----------------|------------------------|----------------------------------|-------------------------------------------|----------------------------------------|-------------------------------------|------------------------------|
| Age at diagnosis, years, median (IQR)             | 62.9 (58.5-66.5) |                        | 64.2 (60.8-67.7)                 | 63.4 (59.6-67.3)                          | 63.0 (58.6-66.7)                      | 61.8 (57.6-65.0)                    | 61.6 (57.4-66.1)               |
| Time between diagnosis and recruitment, months, median (IQR) | 3.9 (0.4-12.6)   |                        | 3.4 (0.4-16.5)                  | 5.5 (0.5-16.9)                            | 4.6 (0.4-13.3)                       | 2.3 (0.4-8.1)                      | 2.1 (0.4-9.6)                 |
| Absolute weight change, kg, median (IQR)          | 0.0 (−2.0-3.0)   | −10.0 (−12.0−[−8.0])   | −5.0 (−6.0−[−4.0])              | 0.0 (−1.0-2.0)                           | 5.0 (4.0-6.0)                        | 10.0 (8.0-12.0)                    |                             |
| Baseline height, m, median (IQR)                  | 1.65 (1.60-1.69) |                        | 1.65 (1.60-1.68)                | 1.64 (1.60-1.68)                          | 1.65 (1.60-1.69)                     | 1.65 (1.60-1.69)                    |                             |
| Baseline BMI, kg/m², median (IQR)                 | 25.2 (22.9-28.1) |                        | 27.5 (25.1-30.5)                | 25.8 (23.5-29.0)                          | 24.9 (22.8-27.7)                     | 25.3 (22.7-28.3)                    | 24.5 (21.8-27.5)               |
| Follow-up BMI, kg/m², median (IQR)                | 25.3 (22.9-28.3) |                        | 23.7 (21.6-26.2)                | 24.2 (22.1-27.2)                          | 25.0 (22.8-27.7)                     | 27.0 (24.3-30.5)                    | 28.2 (24.8-31.6)               |
| Follow-up waist-hip ratio, median (IQR)           | 0.87 (0.83-0.90) |                        | 0.85 (0.82-0.90)                | 0.87 (0.83-0.89)                          | 0.87 (0.83-0.90)                     | 0.87 (0.83-0.91)                    | 0.88 (0.83-0.92)               |
| Follow-up leisure time physical activity, MET-hrs/week, median (IQR) | 40.0 (22.6-66.0) |                        | 30.9 (15.4-52.2)                | 38.2 (22.7-59.2)                          | 40.0 (23.8-67.9)                     | 38.8 (24.0-64.5)                    | 36.0 (20.0-62.0)               |
| Follow-up alcohol intake, g/day, median (IQR)     | 5.1 (1.9-13.6)   |                        | 3.6 (1.2-12.5)                  | 3.9 (1.4-12.4)                            | 5.4 (2.0-13.4)                       | 5.4 (2.2-16.8)                      | 4.3 (1.6-14.3)                 |
| Follow-up smoking status, n (%)                   |                 |                        |                                |                                           |                                       |                                     |                             |
| Never                                             | 1198 (54.1)      |                        | 53 (47.7)                       | 123 (52.6)                                | 791 (55.7)                           | 166 (54.6)                         | 65 (44.5)                     |
| Former                                            | 811 (36.6)       |                        | 42 (37.8)                       | 83 (35.5)                                 | 498 (35.0)                           | 123 (40.5)                         | 65 (44.5)                     |
| Current                                           | 207 (9.3)        |                        | 16 (14.4)                       | 28 (12.0)                                 | 132 (9.3)                            | 15 (4.9)                           | 16 (11.0)                     |
| Education, n (%)                                   |                 |                        |                                |                                           |                                       |                                     |                             |
| Low                                               | 1243 (56.1)      |                        | 71 (64.0)                       | 139 (59.4)                                | 768 (54.0)                           | 177 (58.2)                         | 88 (60.3)                     |
| Medium                                            | 625 (28.2)       |                        | 28 (25.2)                       | 65 (27.8)                                 | 406 (28.6)                           | 81 (26.6)                          | 45 (30.8)                     |
| High                                              | 348 (15.7)       |                        | 12 (10.8)                       | 30 (12.8)                                 | 247 (17.4)                           | 46 (15.1)                          | 13 (8.9)                      |
| Follow-up self-perceived health, n (%)            |                 |                        |                                |                                           |                                       |                                     |                             |
| Excellent/very good                               | 444 (20.0)       |                        | 13 (11.7)                       | 37 (15.8)                                 | 315 (22.2)                           | 55 (18.1)                          | 24 (16.5)                     |
| Good                                              | 1134 (51.2)      |                        | 44 (39.6)                       | 120 (51.3)                                | 726 (51.1)                           | 172 (56.6)                         | 72 (49.3)                     |
| Not good/bad                                      | 635 (28.6)       |                        | 54 (48.6)                       | 77 (32.8)                                 | 379 (26.7)                           | 76 (25.0)                          | 49 (33.6)                     |
| Ever menopausal hormone therapy, n (%)            | 1083 (48.9)      |                        | 56 (50.5)                       | 115 (49.1)                                | 684 (48.1)                           | 153 (50.3)                         | 75 (51.4)                     |
| Mode of tumor detection                           |                 |                        |                                |                                           |                                       |                                     |                             |
| Self-detected by palpation / secretion / pain     | 1095 (49.4)      |                        | 65 (58.6)                       | 103 (44.0)                                | 706 (49.7)                           | 144 (47.4)                         | 77 (52.7)                     |
| Routine examination / mammography / ultrasound     | 1115 (50.3)      |                        | 45 (40.5)                       | 129 (55.1)                                | 714 (50.2)                           | 158 (52.0)                         | 69 (47.3)                     |
| Type of surgery, n (%)                            |                 |                        |                                |                                           |                                       |                                     |                             |
| Mastectomy                                        | 57 (2.6)         |                        | 4 (3.6)                         | 6 (2.6)                                   | 40 (2.8)                             | 6 (2.0)                            | 1 (0.7)                       |
| Mastectomy + axilla                               | 520 (23.5)       |                        | 30 (27.0)                       | 61 (26.1)                                 | 312 (22.0)                           | 78 (25.7)                          | 39 (26.7)                     |
| Breast-conserving therapy                         | 190 (8.6)        |                        | 6 (5.4)                         | 17 (7.3)                                  | 130 (9.1)                            | 25 (8.2)                           | 12 (8.2)                      |
interaction term between weight change as a continuous variable and a dummy for ≥5% weight gained or lost.

In addition, associations between baseline weight (per 5 kg increase) as well as associations between follow-up weight (per 5 kg increase) and the three endpoints were investigated separately. Associations between follow-up weight and cancer outcomes were stratified by baseline BMI (normal/overweight and obese).

All models included the prognostic factors tumor size, nodal status, tumor grade, hormone receptor (HR) status, as well as mode of tumor detection and were stratified by study center and age at diagnosis in 5-year categories to allow for variation in baseline hazard.

### TABLE 1 (Continued)

| Characteristic | Overall | Large loss (>10%) | Moderate loss (5% to ≤10%) | Weight stable (within 5%) | Moderate gain (≥5% to ≤10%) | Large gain (>10%) |
|----------------|---------|------------------|--------------------------|-------------------------|---------------------------|-----------------|
|                | n = 2216 | n = 111 (5.0)    | n = 234 (10.6)           | n = 1421 (64.1)         | n = 304 (13.7)            | n = 146 (6.6)   |
| Breast-conserving therapy + axilla | 1446 (65.3) | 71 (64.0) | 149 (63.7) | 937 (66.0) | 195 (64.1) | 94 (64.4) |
| Tumor size, n (%) | | | | | | |
| <2 cm | 1259 (56.8) | 61 (55.0) | 149 (63.7) | 808 (56.9) | 164 (53.9) | 77 (52.7) |
| 2-5 cm | 679 (30.6) | 37 (33.3) | 60 (25.6) | 432 (30.4) | 97 (31.9) | 53 (36.3) |
| >5 cm / growth into chest wall | 79 (3.6) | 7 (6.3) | 10 (4.3) | 45 (3.2) | 13 (4.3) | 4 (2.7) |
| Neoadjuvant chemotherapy-treated carcinoma | 69 (3.1) | 2 (1.8) | 4 (1.7) | 45 (3.2) | 14 (4.6) | 4 (2.7) |
| In situ | 127 (5.7) | 3 (2.7) | 10 (4.3) | 90 (6.3) | 16 (5.3) | 8 (5.5) |
| Nodal status, n (%) | | | | | | |
| 0 | 1436 (64.8) | 72 (64.9) | 150 (64.1) | 934 (65.7) | 188 (61.8) | 92 (63.0) |
| 1-3 | 436 (19.7) | 25 (22.5) | 56 (23.9) | 265 (18.6) | 56 (18.4) | 4 (2.7) |
| >3 | 148 (6.7) | 9 (8.1) | 14 (6.0) | 87 (6.1) | 30 (9.9) | 8 (5.5) |
| Tumor grade, n (%) | | | | | | |
| Low/moderate | 1531 (69.1) | 76 (68.5) | 169 (72.2) | 976 (68.7) | 203 (66.8) | 107 (73.3) |
| High | 480 (21.7) | 27 (24.3) | 51 (21.8) | 305 (21.5) | 70 (23.0) | 27 (18.5) |
| Hormone receptor status, n (%) | | | | | | |
| ER+PR+ | 1439 (65.0) | 73 (65.8) | 166 (70.9) | 902 (63.5) | 198 (65.1) | 100 (68.5) |
| ER+PR−/ER−PR+ | 322 (14.5) | 25 (22.5) | 30 (12.8) | 209 (14.7) | 36 (11.8) | 22 (15.1) |
| ER− PR− | 259 (11.7) | 8 (7.2) | 24 (10.3) | 175 (12.3) | 40 (13.2) | 12 (8.2) |
| Her2 status, n (%) | | | | | | |
| Her2 positive | 365 (16.5) | 19 (17.1) | 40 (17.1) | 212 (14.9) | 62 (20.4) | 32 (21.9) |
| Her2 negative | 1549 (69.9) | 78 (70.3) | 170 (72.6) | 1006 (70.8) | 199 (65.5) | 96 (65.8) |
| Chemotherapy, n (%) | 1010 (45.6) | 58 (52.3) | 109 (46.6) | 623 (43.8) | 157 (51.6) | 63 (43.2) |
| Radiation therapy, n (%) | 1772 (80.0) | 86 (77.5) | 189 (80.8) | 1141 (80.3) | 245 (80.6) | 111 (76.0) |
| Tamoxifen/aromatase inhibitor use, n (%) | 1792 (80.9) | 100 (90.1) | 198 (84.6) | 1128 (79.4) | 239 (78.6) | 127 (87.0) |
| Follow-up Charlson Comorbidity Index, n (%) | | | | | | |
| 0 | 1161 (52.4) | 48 (43.2) | 106 (45.3) | 791 (55.7) | 154 (50.7) | 62 (42.5) |
| 1 | 663 (29.9) | 32 (28.8) | 72 (30.8) | 418 (29.4) | 87 (28.6) | 54 (37.0) |
| ≥2 | 386 (17.4) | 30 (27.0) | 54 (23.1) | 209 (14.7) | 63 (20.7) | 30 (20.5) |

*aFor patients with nonzero alcohol use (56.0%). Percentages of patients with nonzero alcohol use are 56.9% for maintenance, 53.8% for moderate increase, 56.9% large increase, 54.9% for moderate decrease and 52.2% for large decrease.

*bApplies also to nodal status, tumor grade, hormone receptor status and Her2 status.
**TABLE 2**  Hazard ratios and corresponding 95% confidence intervals for the association between weight change and survival

| Weight change from baseline to follow-up | All-cause mortality HR (95% CI) | Breast cancer-specific mortality HR (95% CI) | Recurrence-free survival HR (95% CI) |
|-----------------------------------------|---------------------------------|---------------------------------------------|--------------------------------------|
| Events/follow-up time (years)          | 129/5.48                        | 239/5.51                                    |                                      |

Large gain (>10%)  21/5.50  1.64 (1.02, 2.62)  15/5.48  2.24 (1.25, 4.02)  18/5.51  1.22 (0.74, 2.01)

Moderate gain (≥5% to ≤10%)  26/5.51  0.77 (0.50, 1.20)  17/5.49  0.81 (0.46, 1.42)  22/5.51  0.73 (0.46, 1.15)

Maintenance (within 5%)  127/5.50  1.00 (Ref.)  67/5.48  1.00 (Ref.)  147/5.51  1.00 (Ref.)

Moderate loss (≥5% to ≤10%)  32/5.50  1.42 (0.95, 2.13)  13/5.46  1.16 (0.62, 2.16)  33/5.51  1.28 (0.86, 1.89)

Large loss (>10%)  28/5.50  2.49 (1.61, 3.88)  17/5.45  3.09 (1.70, 5.62)  19/5.52  1.43 (0.86, 2.35)

Note: Adjusted for BMI at baseline, tumor size, nodal status, grade, mode of detection, HR status, time between baseline and follow-up 1, recurrences between diagnosis and follow-up 1 and stratified by study center and age at diagnosis in 5-year age categories.

**TABLE 3**  Associations between postdiagnosis weight change and prognosis stratified by recruitment BMI, and comorbidities

| Baseline BMI categories (WHO classification)a | All-cause mortality | Breast cancer-specific mortality | Recurrence-free survival |
|---------------------------------------------|---------------------|---------------------------------|--------------------------|
| Events/follow-up time (years)               | Normal (n = 1033)   | Events/follow-up time (years)   | Overweight/obese (n = 1144) |
| Weight gain (≥5%)                           | 17/5.50             | 1.11 (0.62, 1.99)               | 28/5.51 0.94 (0.60, 1.48)  |
| Maintenance (within 5%)                     | 48/5.50             | 1.00 (Ref.)                     | 78/5.50 1.00 (Ref.)        |
| Weight loss (≥5%)                           | 18/5.50             | 2.33 (1.30, 4.16)               | 42/5.50 1.70 (0.97, 2.96)  |

| Events/follow-up time (years)               | None to mild (0-1)  | Events/follow-up time (years)   | Severe (≥2) (n = 383)      |
|---------------------------------------------|---------------------|---------------------------------|---------------------------|
| Weight gain (≥5%)                           | 32/5.50             | 1.08 (0.71, 1.62)               | 15/5.51 0.97 (0.47, 1.99)  |
| Maintenance (within 5%)                     | 102/5.50            | 1.00 (Ref.)                     | 25/5.51 1.00 (Ref.)        |
| Weight loss (≥5%)                           | 37/5.50             | 1.48 (1.00, 2.20)               | 22/5.51 2.80 (1.46, 5.34)  |

| Charlon Comorbidity Indexb                  | Events/follow-up time (years) | Events/follow-up time (years)   | Severe (≥2) (n = 383)      |
|---------------------------------------------|---------------------------------|---------------------------------|---------------------------|
| Weight gain (≥5%)                           | 23/5.49 1.45 (0.87, 2.42)      | 9/5.48 1.39 (0.45, 4.26)        |
| Maintenance (within 5%)                     | 57/5.48 1.00 (Ref.)           | 10/5.47 1.00 (Ref.)            |
| Weight loss (≥5%)                           | 22/5.47 1.63 (0.95, 2.79)     | 7/5.40 2.56 (0.74, 8.90)        |
| Recurrence-free survival (n = 1700)         |                                 | (n = 349)                       |
| Weight gain (≥5%)                           | 30/5.51 0.91 (0.60, 1.36)      | 10/5.52 0.77 (0.35, 1.68)       |
| Maintenance (within 5%)                     | 117/5.51 1.00 (Ref.)          | 30/5.52 1.00 (Ref.)            |
| Weight loss (≥5%)                           | 31/5.51 1.08 (0.71, 1.62)     | 21/5.53 2.57 (1.33, 4.95)       |

Note: Adjusted for BMI at baseline, tumor size, nodal status, grade, mode of detection, HR status, time between baseline and follow-up, recurrences between diagnosis and follow-up and stratified by study center and age at diagnosis in 5-year age categories.

Note: Adjusted for tumor size, nodal status, grade, mode of detection, HR status, time between baseline and follow-up 1, recurrences between diagnosis and follow-up 1 and stratified by study center and age at diagnosis in 5-year age categories.

Note: Adjusted for BMI at baseline, tumor size, nodal status, grade, mode of detection, HR status, time between baseline and follow-up, recurrences between diagnosis and follow-up and stratified by study center and age at diagnosis in 5-year age categories.
The weight change model was additionally adjusted for BMI at baseline, time between baseline and follow-up and occurrence of recurrence between diagnosis and follow-up (this covariate was not included when recurrence-free survival was the outcome). Associations between both baseline and follow-up weight and cancer outcomes were further adjusted for baseline height, menopausal hormone therapy at diagnosis and chemotherapy. Potential confounding variables (ie, physical activity, waist-hip ratio, type of surgery, radiation therapy, tamoxifen/aromatase inhibitor therapy, comorbidities [CCI], smoking, alcohol, education, HER2 status, self-perceived health) were determined a priori. Examining whether risk estimates changed by at least 10% when excluding one covariate at a time using backward elimination yielded no changes in risk estimates, so no potential confounding factors were included in the final models. Categories for all variables can be seen in Table 1.

In sensitivity analyses, all analyses were repeated for all three outcomes, excluding (1) women who developed a recurrence (ipsilateral, local/regional, distant and metastatic recurrence or second tumor) by the first follow-up interview (n = 117), and (2) women with in situ tumors (n = 127).

For all analyses, complete-case analysis was performed, as the proportion of missing was less than 5% for all variables. All tests of statistical significance were two-sided and significance level was set to 0.05. Analyses were conducted using the SAS statistical software package (version 9.4).

### 3 | RESULTS

Median age at breast cancer diagnosis for the 2216 postmenopausal survivors included was 62.9 years. By June 30, 2015, a median follow-up time of 5.5 years after the re-interview in 2009, 235 (10.6%) women died, 130 (5.9%) of which were from breast cancer, and 363 (16.4%) women developed a recurrence (n = 117 of which occurred between the initial diagnosis and 2009 follow-up interview). Median (IQR) BMI at baseline and follow-up was 25.2 (22.9-28.1) and 25.2 (22.9-28.3) kg/m², respectively.

Compared to weight stable women, women who lost >10% body weight were at increased risk for all-cause mortality (HR [95% CI]: 2.49 (1.61, 3.88)), breast cancer-specific mortality (HR [95% CI]: 3.09 (1.70, 5.62)), and possibly poorer recurrence-free survival (HR [95% CI]: 1.43 (0.86, 2.35); Table 2). Weight gain >10% also increased risk of all-cause mortality (HR [95% CI]: 1.64 (1.02, 2.62) and breast cancer-specific mortality (HR [95% CI]: 2.24 (1.25, 4.02)), and possibly suggestive of poorer recurrence-free survival (HR [95% CI]: 1.22 (0.74, 2.01)). Neither moderate gain nor moderate loss was associated with any outcome.

In subgroup analysis stratified by baseline BMI, weight loss was again associated with increased all-cause mortality in women with normal baseline BMI (HR [95% CI]: 2.33 (1.30, 4.16)) and women who were overweight/obese (HR [95% CI]: 1.70 (1.15, 2.53)) compared to weight stable women (Table 3). Associations tended to be stronger for those with normal baseline BMI than those who were overweight. Associations between ≥5% weight gain and all-cause mortality as well as recurrence-free survival were comparable in normal and overweight/obese women, while there could be suggestions for a differential association with breast cancer-specific mortality based on direction of HRs (for normal-weight women 1.76 (0.84, 3.69) and for overweight/obese women 0.88 (0.48, 1.59)). Stratified by the CCI, associations were found in those with severe comorbidities (≥2), whereby weight loss compared to weight maintenance increased all-cause mortality (HR [95% CI]: 2.80 (1.46, 5.34)) and recurrence-free survival (HR [95% CI]: 2.57 (1.33, 4.95); Table 3). Weight gain and loss were associated with nonsignificant increased risk of breast cancer-specific mortality irrespective of number of comorbidities.

When we evaluated the rate of weight change-survival associations, compared to weight maintenance, fast weight loss (>1.0% body weight per year) was associated with an increased risk of all-cause

### TABLE 4  Weight change and prognosis associations: rate of weight change (weight change per 1 year), and weight change as a continuous variable

| Weight change per percent increase | Total relative weight change (median [IQR]) | Events/follow-up time (years) | All-cause mortality HR (95%CI) | Events/follow-up time (years) | Breast cancer-specific mortality HR (95%CI) | Events/follow-up time (years) | Recurrence-free survival HR (95%CI) |
|-----------------------------------|------------------------------------------|-------------------------------|-------------------------------|-------------------------------|-----------------------------------------------|-------------------------------|-----------------------------------|
| Weight change per 1 year          | 234/5.50                                 | 129/5.48                      | 239/5.51                      | 234/5.50                      | 129/5.48                                      | 239/5.51                      | 234/5.50                          |
| Fast weight gain (>1.0%)          | 8.08 (6.58, 11.67)                       | 49/5.50                       | 1.23 (0.84, 1.79)             | 34/5.49                       | 1.54 (0.93, 2.55)                             | 41/5.51                       | 0.95 (0.65, 1.39)                  |
| Slow weight gain (≥0.5–1.0%)      | 3.51 (2.99, 4.48)                        | 27/5.51                       | 1.04 (0.66, 1.64)             | 17/5.49                       | 1.38 (0.75, 2.52)                             | 32/5.52                       | 0.88 (0.58, 1.35)                  |
| Maintenance (within 0.5%)         | 0.00 (−1.27, 1.41)                       | 70/5.50                       | 1.00 (Ref.)                   | 34/5.48                       | 1.00 (Ref.)                                   | 86/5.51                       | 1.00 (Ref.)                       |
| Slow weight loss (≥0.5–1.0%)      | −8.33 (−11.25, −6.25)                    | 56/5.50                       | 1.83 (1.27, 2.63)             | 28/5.46                       | 1.82 (1.07, 3.10)                             | 53/5.52                       | 1.32 (0.93, 1.89)                  |

Note: Adjusted for BMI at baseline, tumor status, nodal status, grade, mode of detection, HR status, recurrences between diagnosis and follow-up and stratified by study center and age at diagnosis in 5-year age categories.
increased all-cause mortality (HR (95% CI): 1.05 (1.03, 1.08)) and weight since baseline, per percent weight change was associated with recurrence-free survival. In women who had lost ≥5% weight since baseline, per percent weight change was associated with increased all-cause mortality (HR (95% CI): 1.05 (1.03, 1.08)) and breast cancer-specific mortality (HR (95% CI): 1.06 (1.03, 1.10)). In women who had gained ≥5% in weight since baseline, per percent weight increase was also associated with breast cancer-specific mortality (HR (95% CI): 1.04 (1.02, 1.07); Table 4).

Higher baseline weight was associated with increasing all-cause mortality (per 5 kg HR 1.04 [95% CI 1.01, 1.07]) and possibly recurrence-free survival (per 5 kg HR 1.03 [95% CI 1.00, 1.06]) but not breast cancer-specific mortality (per 5 kg HR 1.05 [95% CI 0.98, 1.13]). There was no evidence for associations between follow-up weight and subsequent prognosis according to baseline BMI (data not shown).

To better understand how various therapies may affect baseline weight, we compared baseline weight and BMI in the whole population against different subsets of the study population: in women who never/before or during baseline/after baseline received aromatase inhibitor therapy, tamoxifen, either aromatase or tamoxifen, chemotherapy, radiation therapy, mastectomy and breast-conserving therapy. We did not find meaningful differences in weight or BMI at recruitment between any of these subsets (data not shown).

4 | DISCUSSION

Postdiagnosis weight change in relation to prognosis was evaluated in 2216 postmenopausal long-term breast cancer survivors in Germany. Weight loss >10% of body weight was associated with poorer prognosis compared to weight maintenance. The increased mortality associated with weight loss was independent of baseline BMI, and more pronounced in those with severe comorbidities, who were more likely to be negatively impacted by weight loss. Per percent increments of postdiagnosis weight from baseline to the follow-up was likewise associated with poorer subsequent prognosis. That we see stronger associations and a dose-response relationship with weight loss could indicate that “reserves” are necessary for health and to possibly withstand metabolic challenges from breast cancer and its sequelae. In further support that “reserves” may be necessary after breast cancer, we found evidence of a possible nonlinear dose-response relationships between weight gain and survival. Moderate weight gain was associated with nonsignificant decreased risk for all three endpoints rather than increased risk.

Several proposed biological mechanisms may underpin the associations between weight gain and survival. Obesity creates an expanded, metabolically active adipose tissue as well as systemic obesity-associated alterations that involve increased insulin and insulin-like growth factors, elevated circulating estradiol and production of proinflammatory cytokines and decreased sex hormone-binding globulin, all of which influences breast mammary tumor cells as well as the breast tumor microenvironment to encourage breast tumor progression (reviewed in References 20 and 21). Neither intentional nor unintentional weight loss, which could potentially increase or decrease mortality, were collected in our study and may bias our results, although our results do demonstrate poorer survival with weight loss independent of baseline weight, and associations were not modified by self-perceived health (data not shown). Consequently, additional mechanisms linking energy balance and imbalance following breast cancer may be involved.

To date, three systematic reviews7,22 and two meta-analyses3,7 have examined weight change and prognosis after breast cancer. One of these evaluated weight gain and found that only those who gained >10% were at increased risk of all-cause mortality,7 in line with our results. There was no association with modest weight gain, and when stratified by baseline BMI, there were no differences in all-cause mortality. In the second systematic review and meta-analysis, weight gained and weight lost at different time points were explored. Adult weight gain (highest vs lowest/stable), and weight gain before and 12 months or more after diagnosis/treatment (highest vs lowest/stable) was associated with about 30% to 50% increased risk of all-cause mortality. Only weight gained before and 12 months or more after diagnosis/treatment (highest vs lowest/stable) was associated with breast cancer-specific mortality (1.59 [1.05, 2.41]). Weight loss was also examined in the second systematic review and meta-analysis with overall relative risks of 2.33 (95% CI 1.42, 3.83) and 1.86 (95% CI 0.43, 7.89) for all-cause mortality and breast cancer-specific mortality, respectively, with significant heterogeneity between studies.3 In the third systematic review, greater weight loss was associated with higher all-cause mortality with HRs ranging from 1.40 to 4.75.22

Definitions and categories for weight change are different across studies with studies using various categorizations for absolute weight change,23,24 relative weight change8,25 and BMI change,26 which may partially drive inconsistencies in results between studies. Different time points where weight change is measured relative to diagnosis and treatment may also partially explain observed differences in results between studies. Indeed, associations of weight change on all-cause mortality have been reported to be more pronounced during the first 2 years after diagnosis (>5% gain HR (95% CI) 5.87 (0.89, 47.8)) than more than 2 years after diagnosis (HR (95%CI) 1.49 (0.85, 2.57)).3 This could be due to a greater immediate consequence of the breast cancer itself and its sequelae or a result of the rate of weight change, as the rate for a given amount of weight change will be higher within 2 years than over a longer period of time. Along with these lines, our results indicate that gaining and losing weight quickly (faster than >1.0% body weight per year) may be associated with poorer outcomes than slow weight change. We suppose that a higher rate implies faster weight change (and a lower rate implies slower weight change).
Furthermore, large weight losses of >10% were associated with poorer recurrence-free survival, which was similar to results from one study. These results were not supported by another study that assessed BMI change stratified by smoking status, which may possibly account for the heterogeneous findings. Recurrence rather than recurrence-free survival was the endpoint of interest in these two studies. Results from a meta-analysis of three studies did not indicate an association between weight gain and recurrence. Similarly, we observed no association between weight gain and recurrence-free survival. An additional challenge of summarizing associations with recurrence is inconsistent definitions of recurrence: we have used those defined by Hudis. Of all studies identified in the systematic literature reviews and included in the meta-analyses on postdiagnosis weight change and prognosis, none were European. Yet we are aware of three studies from Europe, two of which assessed weight gain during adulthood and total and breast cancer-specific mortality and one that examined weight change during chemotherapy and total mortality and disease-free survival. We are not aware of any studies from Europe evaluating weight loss in breast cancer survivors. Weight is a result of myriad components involving environmental factors along the life course (eg, physical activity, smoking, nutrition) and genetics. Given that lifestyles in Europe—and Germany specifically—are distinct and not like those in the United States and Asia, studies investigating these associations in European countries are essential to further delineate these complex relationships between weight and prognosis.

A limitation of our study is that weight directly before surgery was not collected. Because weight can be affected by external influences at any point along with the course of treatment and afterward, baseline weight may not represent true weight before, at, or immediately after diagnosis. Another limitation is use of self-reported exposure information. Those who have low BMI may overestimate true BMI and those who have high BMI may tend to underestimate true BMI; older respondents may also underestimate BMI. In this analysis, however, relationships between weight change and cancer endpoints were evaluated, so systematic underestimation or overestimation of weight at both time points in the same direction may be less likely to bias results than if evaluating weight alone. Weight underestimation and overestimation by overweight and underweight women, respectively, to normal weight would also dilute observed associations, thus true associations could likely be stronger. Also, though comorbidities used to generate the CCI were self-reported and unverified, use of patient questionnaires to ascertain comorbidities has been shown to be reliable. Reverse causation is possible if women loss or gain weight because they are sicker than those who are weight stable. Although tumor size, nodal status and grade were similar between weight change groups, women severely impacted by comorbidities were apparently more likely to have poorer prognosis from weight loss than women who had no or mild comorbidities.

Study strengths include longitudinal follow-up data from breast cancer survivors over more than 10 years. Most studies on weight gain or loss have examined weight change before (as prediagnosis or usual weight) and 12 months or more after diagnosis or treatment with time between measurements a median 1.5 years, during which time patients may still be undergoing treatment or may still be experiencing the effects of treatment. Duration between the two weight measurements in our study was median 5.1 years, so weight change due to acute effects of different treatment regimens could possibly have been circumvented. Weight at follow-up may better indicate long-term weight, when acute sequelae of breast cancer or behavioral changes related to initial diagnosis or treatment may have abated or plateaued. Information on numerous important potential confounding factors were collected and tested in our comparison models. In the current analysis, we only included women for whom we had both weight measures—at baseline (between 2002 and 2005) and follow-up (2009)—so these women may reflect a healthier subset of women, as they survived at least 5 years after the initial breast cancer. To the best of our knowledge, this is the largest analysis to elucidate associations between postdiagnosis weight change and prognosis in a European population. Specifically, our results further contribute to the literature by demonstrating evidence for the first time in our study sample that weight loss, particularly weight that is lost quickly, may be associated with higher risk of recurrence in breast cancer survivors.

5 | CONCLUSIONS

In conclusion, our results are the first within a European setting to underline the importance of weight maintenance for up to 5 years after diagnosis in long-term breast cancer survivors for the benefit of survival and prognosis after diagnosis. Survivors should strive to avoid large changes in weight, especially in a short period of time, from diagnosis onwards to maintain health and prolong life.

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CONFLICT OF INTEREST

Authors declare that they have no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data can be made available upon reasonable request to the principal investigator(s) (J. C.-C. and H. B.).

ETHICS STATEMENT

The study was approved by the ethics committees of the University of Heidelberg, the State of Rhineland-Palatinate and the Hamburg Medical Council, and was conducted in accordance with the
Declaration of Helsinki. All study participants provided informed written consent.

ORCID
Audrey Y. Jung  https://orcid.org/0000-0003-0875-6673

REFERENCES

1. Berry DA, Cronin KA, Plevritis SK, et al. Effect of screening and adjuvant therapy on mortality from breast cancer. N Engl J Med. 2005;353:1784-1792.

2. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018;68:394-424.

3. World Cancer Research Fund International/American Institute for Cancer Research Continuous Update Project Expert Report 2018. Diet, nutrition, physical activity, and breast cancer survivors. Available at dietandcancerreport.org.

4. De Ruyscher D, Niedermann G, Burnet NG, Siva S, Lee AWM, Hegi-Johnson F. Radiotherapy toxicity. Nat Rev Dis Primers. 2019;5:13.

5. Nurgali K, Jago RT, Abalo R. Editorial: adverse effects of Cancer chemotherapy: anything new to improve tolerance and reduce Sequelae? Front Pharmacol. 2018;9:245.

6. Colleoni M, Giobbie-Hurder A. Benefits and adverse effects of endocrine therapy. Ann Oncol. 2010;21(Suppl 7):vi107-vi111.

7. Playdon MC, Bracken MB, Sanft TB, Ligibel JA, Harrigan M, Irwin ML. Weight gain after breast cancer diagnosis and all-cause mortality: systematic review and meta-analysis. J Natl Cancer Inst. 2015;107:djv275.

8. Bradshaw PT, Ibrahim JG, Stevens J, et al. Postdiagnosis change in bodyweight and survival after breast cancer diagnosis. Epidemiology. 2012;23:320-327.

9. Obi N, Gornyk D, Heinz J, et al. Determinants of newly diagnosed comorbidities among breast cancer survivors. J Cancer Surviv. 2014;8:384-393.

10. Patnaik JL, Byers T, Diguiseppi C, Denberg TD, Dabelea D. The influence of comorbidities on overall survival among older women diagnosed with breast cancer. J Natl Cancer Inst. 2011;103:1101-1111.

11. Flesch-Janys D, Slinger T, Mutschelknauss E, et al. Risk of different histological types of postmenopausal breast cancer by type and regimen of menopausal hormone therapy. Int J Cancer. 2008;123:933-941.

12. Jung AY, Behrens S, Schmidt M, et al. Pre- to postdiagnosis leisure-time physical activity and prognosis in postmenopausal breast cancer survivors. Breast Cancer Res. 2019;21:117.

13. Hudis CA, Barlow WE, Costantino JP, et al. Proposal for standardized definitions for efficacy end points in adjuvant breast cancer trials: the STEEP system. J Clin Oncol. 2007;25:2127-2132.

14. Rock CL, Doyle C, Demark-Wahnefried W, et al. Nutrition and physical activity guidelines for cancer survivors. CA Cancer J Clin. 2012;62:243-274.

15. Grambsch PM, Therneau TM. Proportional hazards tests and diagnostics based on weighted residuals. Biometrika. 1994;81:515-526.

16. Schepler M, Smith TL. A note on quantifying follow-up in studies of failure time. Control Clin Trials. 1996;17:343-346.

17. Quan H, Sundararajan V, Halfon P, et al. Coding algorithms for defining comorbidities in ICD-9-CM and ICD-10 administrative data. Med Care. 2005;43:1130-1139.

18. Sundararajan V, Henderson T, Perry C, Muggivan A, Quan H, Ghali WA. New ICD-10 version of the Charlson comorbidity index predicted in-hospital mortality. J Clin Epidemiol. 2004;57:1288-1294.

19. Maldonado G, Greenland S. Simulation study of confounder-selection strategies. Am J Epidemiol. 1993;138:923-936.

20. Roberts DL, Dive C, Renehan AG. Biological mechanisms linking obesity and cancer risk: new perspectives. Ann Rev Med. 2010;61:301-316.

21. Ando S, Gelsomino L, Panza S, Giordano C, Bonofiglio D, Barone I, Catalano S. Obesity, lepition and breast cancer: epidemiological evidence and proposed mechanisms. Cancers. 2019;11:62. Available from: http://doi.org/10.3390/cancers11010062

22. Jackson SE, Heinrich M, Beeken RJ, Wardle J. Weight loss and mortality in overweight and obese cancer survivors: a systematic review. PLoS One. 2017;12:e0169173.

23. Chen X, Lu W, Zheng W, et al. Obesity and weight change in relation to breast cancer survival. Breast Cancer Res Treat. 2010;122:823-833.

24. Nichols HB, Trentham-Dietz A, Egan KM, et al. Body mass index before and after breast cancer diagnosis: associations with all-cause, breast cancer, and cardiovascular disease mortality. Cancer Epidemiol Biomarkers Prev. 2009;18:1403-1409.

25. Abrahamson PE, Gammon MD, Lund MJ, et al. General and abdominal obesity and survival among young women with breast cancer. Cancer Epidemiol Biomarkers Prev. 2006;15:1871-1877.

26. Kroenke CH, Chen WY, Rosner B, Holmes MD. Weight, weight gain, and survival after breast cancer diagnosis. J Clin Oncol. 2005;23:1370-1378.

27. Caan BJ, Kwan ML, Hartzell G, et al. Pre-diagnosis body mass index, post-diagnosis weight change, and prognosis among women with early stage breast cancer. Cancer Causes Control. 2008;19:1319-1328.

28. Dal Maso L, Zucchotto A, Talamini R, et al. Prospective analysis of case-control studies on environmental f, health study g. effect of obesity and other lifestyle factors on mortality in women with breast cancer. Int J Cancer. 2008;123:2188-2194.

29. Ewertz M, Gillanders S, Meyer L, Zedeler K. Survival of breast cancer patients in relation to factors which affect the risk of developing breast cancer. Int J Cancer. 1991;49:526-530.

30. Thivat E, Therondel S, Lapirot O, et al. Weight change during chemotherapy changes the prognosis in non metastatic breast cancer for the worse. BMC Cancer. 2010;10:648.

31. Stommel M, Schoenborn CA. Accuracy and usefulness of BMI measures based on self-reported weight and height: findings from the NHANES & NHS 2001-2006. BMC Public Health. 2009;9:421.

32. Spencer EA, Appleby PN, Davey GK, Key TJ. Validity of self-reported height and weight in 4808 EPIC-Oxford participants. Public Health Nutr. 2002;5:561-565.