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# Weight Loss Patterns and Clinical Outcomes of GLP1 Receptor Agonists in Breast Cancer Survivors

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## ABSTRACT

The use of glucagon-like peptide-1 receptor agonists (GLP1-RA) for weight loss is increasing; implications in breast cancer survivors remain unclear. This retrospective cohort study evaluated treatment patterns, weight loss, and outcomes in breast cancer survivors receiving GLP1-RA at an academic institution. We evaluated patients with nonmetastatic [ductal carcinoma in situ (DCIS), stage 1–3] breast cancer who received GLP1-RA (2005–2024). Linear regression models estimated associations between weight change and clinical factors. After excluding DCIS, propensity score matching (1:2) was used to match patients who received GLP1-RA with patients who did not, based on confounding covariates. Kaplan–Meier estimates and log-rank tests compared disease-free survival (DFS) and overall survival (OS) between GLP1-RA users versus nonusers in the subgroup with invasive disease. We identified 1,022 patients; 79% had type 2 diabetes mellitus. The median weight and body mass index at GLP1-RA initiation were 86.8 kg (47.2–175 kg) and 33.5 kg/m$^2$ (18.9–61.8 kg/m$^2$). In semaglutide or tirzepatide users (442, 43.2%), the median weight change at 3, 6, and 12 months after GLP1-RA initiation was −1.9% (−13.2% to 14.9%), −3.1% (−20.2% to 19%), and −2.6% (−27.8% to 11.5%), respectively. Endocrine therapy and metformin use were associated with weight gain and loss, respectively; invasive disease stage was linked to greater weight loss. GLP1-RA was not associated with DFS, but OS significantly differed between GLP1-RA users ($n = 810$) and nonusers ($n = 1,620$; hazard ratio, 0.37; 95% confidence interval, 0.27–0.53; $P < 0.0001$). In conclusion, in this real-world study in breast cancer survivors, GLP1-RA was associated with modest weight loss and improved all-cause survival. Clinical trials are warranted to study GLP1-RA in this population.

Significance: This is the largest study describing real-world patterns of GLP1 receptor agonists in breast cancer survivors. Clinical trials should evaluate these agents for weight management as an adjunct to lifestyle interventions and the potential role in cancer control in breast cancer survivors.

## Introduction

The number of breast cancer survivors continues to increase with advances in early detection and treatment (1). Type 2 diabetes mellitus (DM2) in breast cancer survivors is associated with increased symptom burden, treatment complications, and greater mortality (2). Moreover, obesity in breast cancer survivors is prevalent and linked with adverse health sequelae, including a higher risk of comorbidities (e.g., cardiovascular disease and DM2) and compromised quality of life (e.g., fatigue, sexual dysfunction,

negative body image, lymphedema, and neuropathy; refs. 3, 4). Observational data support that obesity in breast cancer survivors is associated with increased recurrence risk and mortality, demonstrated across disease subtypes (hormone positive and negative) and independent of menopausal status (3–5). Weight gain following a breast cancer diagnosis is also common and a negative prognostic factor. Hence, targeting cardiometabolic risk and maintaining an ideal body weight is a key tenet of optimal health in breast cancer survivorship (6).

Glucagon-like peptide-1 receptor agonists (GLP1-RA) and dual GLP1-RA/glucose-dependent insulinotropic polypeptide receptor agonists (GIP-RA) are incretin-based drugs with favorable metabolic effects and are approved for DM2 and weight management in overweight/obesity (7–9). GLP1-RA and GIP-RA agents regulate postprandial glucose metabolism, promote satiety, and decrease gastric emptying. They have shown consistent benefit in glycemic control and reduction in energy intake, leading to significant weight loss (7–9). Their additional health benefits include reduced cardiovascular risk and improved all-cause mortality in certain populations, such as those with DM2 (9–12). The utilization of these agents is rapidly increasing, but their clinical implications in breast cancer survivors are not well understood. There have been few prior studies specifically in breast cancer

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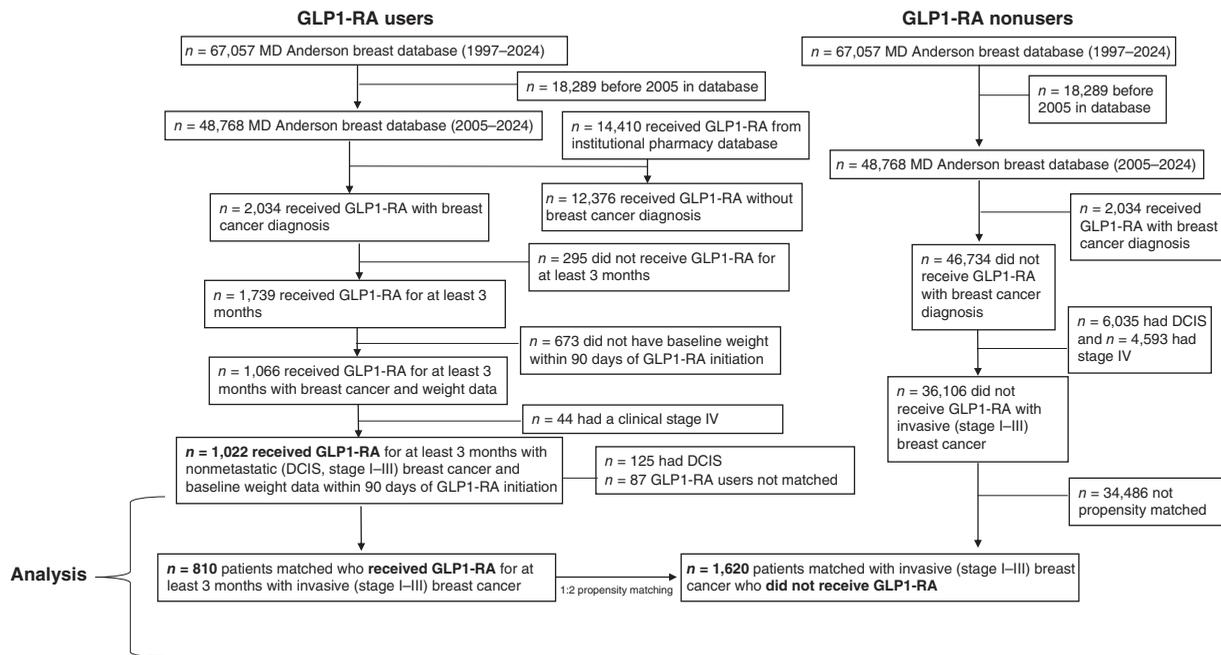
**FIGURE 1.** Patient selection flow chart.

populations, albeit with small sample sizes (13–15). This retrospective cohort study evaluated real-world patterns of GLP1-RA utilization in patients with breast cancer. We also explored the impact of these drugs on weight change, evaluating clinical factors associated with weight loss efficacy. Moreover, we investigated the relationship of GLP1-RA with breast cancer recurrence risk and mortality [disease-free survival (DFS) and overall survival (OS)].

## Materials and Methods

This retrospective cohort study was approved by The University of Texas MD Anderson Cancer Center (MDACC) institutional review board and followed Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.

### Population

We identified patients diagnosed with nonmetastatic breast cancer between January 2005 (the first year in which GLP1-RAs were approved for DM2) through January 2024 who were 18 years or older, had body weight data available (before and after GLP1-RA initiation), and received GLP1-RA for at least 3 months (Fig. 1). The MDACC pharmacy database serves as a complementary data source for medication exposure and captures detailed records of systemic anticancer and noncancer therapies dispensed. Medication records were comprehensive, incorporating drug names with doses and route of administration, reconciled appointment-based medication lists, prescriptions through patient-reported medication histories and admission/discharge summaries, documented home medications, and prescriptions dispensed within and outside MDACC (retail medications). GLP1-RA agents included exenatide, liraglutide, semaglutide, dulaglutide, lixisenatide, albiglutide, and the dual GLP1/GIP-RA tirzepatide.

Individuals identified from the pharmacy database without a breast cancer diagnosis were excluded. The resulting cohort of patients with breast cancer was then evaluated in the MDACC Breast Medical Oncology Management System (BCMS) database. This is a well-annotated prospectively gathered database of patients with breast cancer at the academic institution. Clinical data such as demographics, clinicopathologic features, and breast cancer treatment history were obtained from the electronic medical records (EMR) at MDACC, with linkage to the institutional Tumor Cancer Registry, which queries the Social Security Death Index and Texas Bureau of Vital Statistics and external databases for prescription and outcome verification.

### GLP1-RA data collection

The start date and duration of GLP1-RA treatment were determined from the medication list in the EMR, updated at each patient visit. The start date was defined as the earliest pharmacy dispensing date (first visit) for each patient. The 3-month treatment duration was defined as continuous medication supply for at least 90 days. Individuals who used more than one GLP1-RA for longer than 3 months (indicative of a switch) were classified according to the first GLP1-RA used.

### Clinical data collection

Nonmetastatic breast cancer diagnosis was defined as a diagnosis of ductal carcinoma in situ (DCIS) or stage I to III invasive breast cancer. Clinical staging was defined by the American Joint Committee on Cancer guidelines at diagnosis. The collected demographic and clinical data encompassed age, sex, menopausal status, DM2 (defined as a DM2 diagnosis and/or prior receipt of insulin), metformin and insulin use, body weight, body mass index (BMI), race/ethnicity, cancer stage, breast cancer subtype, (neo)adjuvant treatments, pathologic data, use of endocrine therapy (tamoxifen or aromatase inhibitors), and disease status at the time of last contact or death. The

body weight and height values used were those obtained and recorded in the EMR by clinic staff at each routine oncology clinic visit.

For weight change analysis, baseline body weight was defined as weight within 90 days before and on the date closest to GLP1-RA initiation. Body weight was also collected at three time points after GLP1-RA initiation to evaluate relative change over time: 3 months (90 ± 45 days), 6 months (180 ± 45 days), and 12 months (360 ± 60 days). DFS was defined as the time from breast cancer diagnosis to disease recurrence or death due to breast cancer. OS was defined as the time from breast cancer diagnosis to death from any cause; patients alive at the time of analysis or lost to follow-up were censored at the last contact date.

## Statistical analysis

Continuous variables were summarized by mean, median, SD, range, and quartiles. Categorical variables were summarized using frequency tables. Weight change was summarized using box plots for patients who specifically received the agents semaglutide or tirzepatide (dual GLP1-RA/GIP-RA agonist); these GLP1-RAs, which are approved in the United States for weight loss, are now the most commonly used and most effective agents for this indication in contemporary practice. Statistical tests were performed using two-sided tests with 5% type I error rate. Univariate and multivariate linear regression models were used to assess the association of weight change with clinical factors (DM2, metformin use, endocrine therapy use, duration of GLP1-RA, menopausal status, and breast cancer stage) in GLP1-RA recipients with DCIS and invasive breast cancer. Estimates by regression coefficients (β) were provided.

For survival analysis, patients with DCIS were removed given their generally different disease trajectory and cancer outcomes compared with those with invasive disease. This left patients with stage I to III breast cancer and GLP1-RA nonusers. The GLP1-RA nonuser patients were identified and extracted from the MDACC BCMS database and included with those with stage I to III invasive breast cancer from 2005 to 2024 who did not receive any prior GLP1-RA (Fig. 1). Propensity score matching was used to match patients who received GLP1-RA with patients who did not (1:2 ratio, respectively) based on baseline clinical characteristics of BMI at breast cancer diagnosis (mean ± SD, kg/m²), DM2 (yes or no), age at breast cancer diagnosis (mean ± SD, years), cancer stage (I, II, or III), and breast cancer subtype [hormone receptor (HR) positive or HR negative]. Kaplan–Meier estimates and log-rank tests compared DFS and OS between treatment groups. Hazard ratios were estimated using Cox proportional hazards models. To address potential immortal time bias, we conducted landmark analyses at 6, 12, 24, 36, and 60 months after diagnosis (Supplementary Fig. S2), restricting the analysis to patients who survived and remained under observation at each respective time point. For each landmark, we recalculated OS starting from the landmark date and compared outcomes between the GLP-1RA users and GLP1-RA nonusers using Kaplan–Meier analysis and log-rank tests. All statistical analyses were performed using SAS version 9.4.

## Results

### Patient characteristics

Of a total of 48,768 patients with breast cancer in the database from years 2005 to 2024, the cohort of GLP1-RA recipients for at least 3 months with weight data available and with DCIS or stage I to III invasive breast cancer

**TABLE 1.** Baseline clinical characteristics of patients with breast cancer who received GLP1-RA.

| Patients (n = 1,022) | n (%) |
| --- | --- |
| Sex | |
| Female | 1,015 (99.3%) |
| Male | 7 (0.7%) |
| Age | |
| Mean ± SD, years | 54.07 ± 10.46 |
| ≤50 years | 380 (37.2%) |
| >50 years | 642 (62.8%) |
| Menopausal status | |
| Postmenopausal | 581 (56.8%) |
| Premenopausal | 441 (43.2%) |
| Race/ethnicity | |
| Non-Hispanic Black | 181 (17.7%) |
| Non-Hispanic White | 629 (61.5%) |
| Hispanic/Latino | 150 (14.7%) |
| Other | 62 (6.1%) |
| GLP1-RA type | |
| Semaglutide | 383 (37.5%) |
| Tirzepatide | 59 (5.8%) |
| Lixisenatide | 5 (0.5%) |
| Albiglutide | 9 (0.9%) |
| Dulaglutide | 310 (30.3%) |
| Exenatide | 43 (4.2%) |
| Liraglutide | 213 (20.8%) |
| DM2 | 816 (79.8%) |
| Metformin use | 653 (63.9%) |
| Insulin use | 487 (47.7%) |
| Breast cancer subtype | |
| HR+/HER2+ | 80 (7.8%) |
| HR+/HER2− | 624 (61.1%) |
| HR−/HER2+ | 50 (4.9%) |
| TNBC | 142 (13.9%) |
| DCIS | 125 (12.2%) |
| Unknown | 1 (0.1%) |
| Cancer stage | |
| DCIS | 125 (12.2%) |
| I | 376 (36.8%) |
| II | 370 (36.2%) |
| III | 144 (14.1%) |
| Receipt of chemotherapy | 546 (53.4%) |
| Endocrine therapy use | 673 (65.9%) |
| Tamoxifen | 416 (40.7%) |
| Aromatase inhibitor | 257 (25.1%) |

included 1,022 patients (Fig. 1; Table 1). The median follow-up time from breast cancer diagnosis was 4.7 years (range, 0–30.9 years). Patients were 99.3% female (n = 1,015) and predominantly over the age of 50 years (642, 62.8%); most patients (n = 581, 56.9%) were postmenopausal. There were 816 (79.8%) with DM2. A total of 653 (63.9%) received metformin and 487 (47.7%) received insulin.
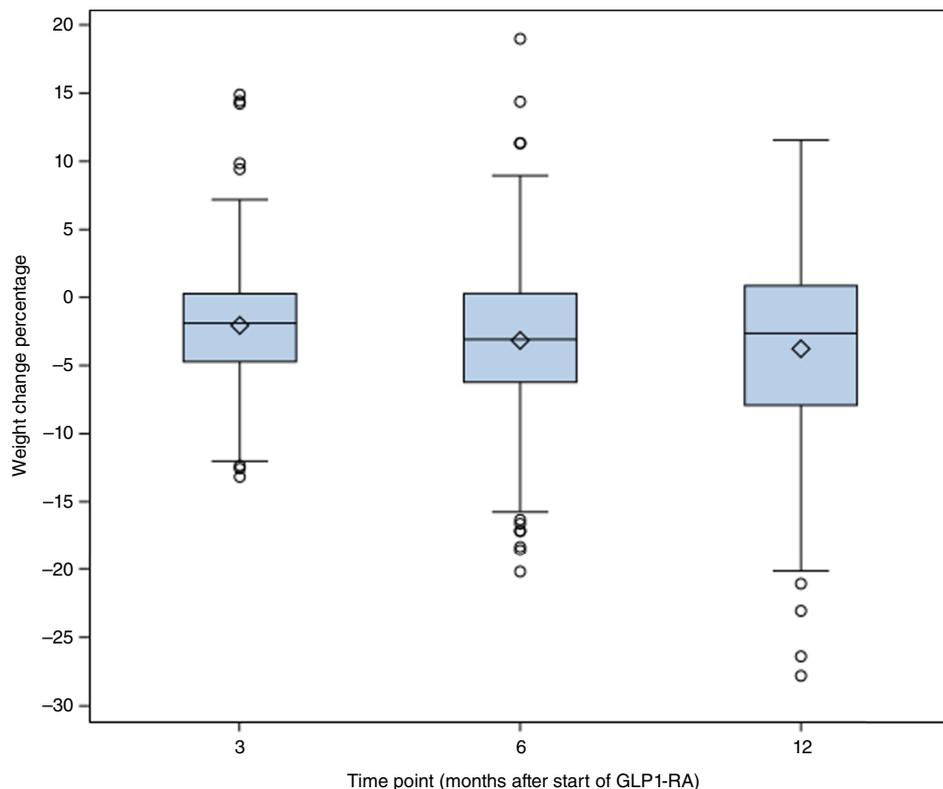
**FIGURE 2.** Box plot of weight change percentage at 3, 6, and 12 months in patients with DCIS and invasive breast cancer who received semaglutide or tirzepatide ($n = 442$, 43.2%). Shown are medians, IQRs, and ranges.

The most common breast cancer subtype was HR positive/HER2 negative (624, 61.1%), followed by triple-negative breast cancer (TNBC; $n = 142$, 13.9%), DCIS ($n = 125$, 12.2%), HR positive/HER2 positive ($n = 80$, 7.8%), and HR negative/HER2 positive ($n = 50$, 4.9%). Clinical cancer stage distribution showed 36.8% ($n = 376$) stage I, 36.2% stage II ($n = 370$), 14.1% ($n = 144$) stage III, and 12.2% ($n = 125$) with DCIS. More than half ($n = 546$, 53.4%) received chemotherapy. Moreover, 65.9% ($n = 673$) received endocrine therapy. Specifically, 416 patients (40.7%) received tamoxifen and 257 ($n = 25.2$%) received aromatase inhibitors. Of those who received endocrine therapy, 38 (5.6%) received it overlapping (±90 days) with GLP1-RA.

## GLP1-RA characteristics

Of 1,022 patients, 989 (96.8%) received GLP-RA exclusively after breast cancer (no prescription prior to breast cancer diagnosis). The GLP1-RA types were semaglutide ($n = 383$, 37.5%), dulaglutide ($n = 310$, 30.3%), liraglutide ($n = 213$, 20.8%), tirzepatide ($n = 59$, 5.8%), exenatide (43, 4.2%), and lixisenatide and albiglutide in less than 1% each. GLP1-RA was started after definitive breast cancer therapy (chemotherapy, surgery, and radiation) in 83% ($n = 848$); the median time from breast cancer diagnosis to GLP1-RA initiation in these patients was 4.7 (range, 0–34) years. The median duration of GLP1-RA use was 1.2 (range, 0.3–8.1) years.

## Baseline weight and weight loss

In all 1,022 patients who received GLP1-RA, the median BMI at breast cancer diagnosis was 33.3 kg/m$^2$ (range, 20.2–56 kg/m$^2$). Baseline median weight and median BMI at GLP1-RA initiation (within 90 days prior) were 86.8 kg (range, 47.2–175 kg) and 33.5 kg/m$^2$ (range, 18.9–61.8 kg/m$^2$), respectively. In patients who specifically received semaglutide or tirzepatide ($n = 442$, 43.2%), weight data were available in 22.2%, 23.4%, and 18.2% at 3, 6, and 12 months, respectively. The median weight change (range) at 3, 6, and 12 months in these patients was −1.9% (−13.2% to 14.9%), −3.1% (−20.2% to 19%), and −2.6% (−27.8% to 11.5%) from baseline weight, respectively (Fig. 2). In a subgroup of patients who did not have DM2 ($n = 206$), the median weight change (range) at 3, 6, and 12 months was −1.3% (−13.2% to 9.9%), −2.3% (−18.6% to 19%), and −2.3% (−27.8% to 11.5%), respectively. In a subgroup of patients who were premenopausal ($n = 441$), the median weight change (range) at 3, 6, and 12 months was −2.9% (−13.2% to 14.9), −3.3% (−18.6% to 19.9), and −3.5% (−26.4% to 11.5%), respectively. In a subgroup of patients who were postmenopausal ($n = 581$), the median weight change (range) at 3, 6, and 12 months was −1.8% (−12.6% to 14.4%), −2.9% (−20.2% to 11.3%), and −2.4% (−27.8% to 11.6%), respectively.

In an exploratory analysis of patients who received semaglutide or tirzepatide, we also evaluated the 6- and 12-month median weight change in the subgroup of patients who received the GLP1-RA prescription for at least 6 ($n = 175$) and 12 ($n = 133$) months, respectively, as well as predictors of weight change in these subgroups (Supplementary Tables S1 and S2).

## Predictors of weight change

The 3-month percentage change in weight was significantly associated with metformin use in both univariate ($P = 0.011$) and multivariate ($P = 0.007$) regression analysis (Table 2). Specifically, in multivariate analysis, patients who received metformin experienced 1.9% greater weight loss on average at

**TABLE 2.** Univariate and multivariate regression analysis of predictors of weight change from baseline at 3, 6, and 12 months.

| Variable | Category | Estimate (β) | P value |
|---|---|---|---|
| Univariate regression analysis at 3 months | | | |
| Stage | Invasive disease vs. DCIS | −1.22 | 0.251 |
| Endocrine therapy | Yes vs. No | −0.68 | 0.272 |
| GLP1-RA use duration (year) | | −0.02 | 0.944 |
| DM2 | Yes vs. No | −0.18 | 0.790 |
| Metformin use | Yes vs. No | −1.57 | **0.011** |
| Menopausal status | Post vs. Pre | 0.30 | 0.634 |
| Multivariate regression analysis at 3 months | | | |
| Stage | Invasive disease vs. DCIS | −1.29 | 0.236 |
| Endocrine therapy | Yes vs. No | −0.60 | 0.338 |
| GLP1-RA use duration (year) | | 0.17 | 0.590 |
| DM2 | Yes vs. No | 0.65 | 0.406 |
| Metformin use | Yes vs. No | −1.88 | **0.007** |
| Menopausal status | Post vs. Pre | 0.30 | 0.645 |
| Univariate regression analysis at 6 months | | | |
| Stage | Invasive disease vs. DCIS | 0.72 | 0.619 |
| Endocrine therapy | Yes vs. No | −0.28 | 0.734 |
| GLP1-RA use duration | | −0.05 | 0.896 |
| DM2 | Yes vs. No | −0.42 | 0.632 |
| Metformin use | Yes vs. No | −0.21 | 0.796 |
| Menopausal status | Post vs. Pre | −0.13 | 0.875 |
| Multivariate regression analysis at 6 months | | | |
| Stage | Invasive disease vs. DCIS | 0.73 | 0.613 |
| Endocrine therapy | Yes vs. No | −0.24 | 0.780 |
| GLP1-RA use duration (year) | | 0.005 | 0.990 |
| DM2 | Yes vs. No | −0.21 | 0.840 |
| Metformin use | Yes vs. No | −0.11 | 0.908 |
| Menopausal status | Post vs. Pre | −0.01 | 0.991 |
| Univariate regression analysis at 12 months | | | |
| Stage | Invasive disease vs. DCIS | −4.02 | **0.015** |
| Endocrine therapy | Yes vs. No | 2.36 | **0.035** |
| GLP1-RA use duration (year) | | 0.426 | 0.454 |
| DM2 | Yes vs. No | −0.68 | 0.573 |
| Metformin use | Yes vs. No | 1.60 | 0.138 |
| Menopausal status | Post vs. Pre | 0.58 | 0.593 |
| Multivariate regression analysis at 12 months | | | |
| Stage | Invasive disease vs. DCIS | −4.31 | **0.010** |
| Endocrine therapy | Yes vs. No | 1.93 | 0.088 |
| GLP1-RA use duration (year) | | 0.33 | 0.568 |
| DM2 | Yes vs. No | −2.11 | 0.115 |
| Metformin use | Yes vs. No | 1.76 | 0.136 |
| Menopausal status | Post vs. Pre | 0.97 | 0.384 |

*P* values that are bolded were statistically significant.

3 months compared with those who did not receive metformin. However, there was no significant association between weight change at 3 months and DM2, endocrine therapy use, duration of GLP1-RA, menopausal status, or breast cancer stage in univariate or multivariate analysis. There was no significant association observed between weight change at 6 months and any clinical factors in both univariate and multivariate analysis.

Weight change at 12 months was significantly associated with endocrine therapy in univariate analysis, in which tamoxifen or aromatase inhibitor use was associated with weight gain ($P = 0.035$). Patients who received endocrine therapy experienced, on average, a 2.4% greater weight gain at 12 months compared with those who did not. However, in multivariate analysis, endocrine therapy was no longer significantly associated with weight change ($P = 0.088$). Similarly, weight change at 12 months was significantly associated with stage, such that those with invasive breast cancer lost more weight than those with DCIS in both univariate ($P = 0.015$) and multivariate ($P = 0.010$) analysis. Specifically, in multivariate analysis, patients with invasive breast cancer experienced 4.3% greater weight loss at 12 months compared with those with DCIS. There was no significant association between weight change at 12 months and other clinical factors (univariate or multivariate analysis).

## Survival outcome analysis

For the propensity-matched survival analysis of patients with invasive breast cancer, 810 patients receiving GLP1-RA were matched with 1,620 patients who did not receive GLP1-RA (Table 3). Although the raw means for BMI and diabetes status (DM2) seem to be different in Table 3, we assessed covariate balance using standardized mean differences (SMD), a more appropriate metric for balance in matched data (16). All covariates had SMDs <0.1 after matching, including BMI (SMD = 0.10) and DM2 (SMD = −0.01), indicating good balance. We have included a Love plot (Supplementary Fig. S1) to visually display covariate balance before and after propensity matching.

DFS did not significantly differ between GLP1-RA users and nonusers (Fig. 3), with a median of 27.5 [95% confidence interval (CI), 21.92–not reached and range, 0–30.7] years in the GLP1-RA group versus 32 (95% CI, 25.49–not reached and range, 0–38) years in the GLP1-RA nonuser group (hazard ratio, 0.95; 95% CI, 0.79–1.14; $P = 0.567$). However, OS was significantly improved in the GLP1-RA group (Fig. 3), with median survival not reached (range, 0–30.7) in the GLP1-RA group versus 29.5 (95% CI, 24.63–36.84 and range, 0–38) years in the GLP1-RA nonuser group (hazard ratio, 0.37; 95% CI, 0.27–0.53; $P < 0.0001$). Our results also consistently demonstrated significantly improved OS in the GLP-1RA group across all landmark points, with log-rank *P* values < 0.001 at 6, 12, 24, 36, and 60 months (Supplementary Fig. S2).

## Discussion

To our knowledge, this the largest study to date describing GLP1-RA use in patients with breast cancer. In this population, we shed light on real-world patterns of weight loss and clinical outcomes (recurrence risk and survival) associated with these widely used pharmaceuticals approved for DM2 and weight loss. A sample of more than 1,000 patients with breast cancer who received any GLP1-RA within a single institution highlights the uptake of these drugs in a modern cohort of adult cancer survivors. Moreover, although the majority (79.8%, $n = 816$) had a DM2 diagnosis, 20.2% ($n = 206$) notably did not. This latter group presumably received GLP1-RA for weight loss, representing the largest report of breast cancer survivors who received this class of drugs for a weight management indication alone.

We observed successful weight loss at 3, 6, and 12 months from GLP1-RA in both those with and without DM2 who received semaglutide or tirzepatide,

**TABLE 3.** Baseline clinical characteristics of GLP1-RA user and nonuser cohorts in propensity matching analysis[a].

| Patients | Patients prescribed GLP1-RA (N = 810) | Patients not prescribed GLP1-RA (N = 1,620) |
| --- | --- | --- |
| BMI[a] (mean ± SD, kg/m$^2$) | 34.21 ± 6.84 | 31.41 ± 6.80 |
| Sex | | |
|   Female | 805 (99.4%) | 1,602 (98.9%) |
|   Male | 5 (0.6%) | 18 (1.1%) |
| Age[a] (mean ± SD, years) | 54.24 ± 10.52 | 56.04 ± 11.65 |
| Menopausal Status | | |
|   Postmenopausal | 469 (57.9%) | 1,323 (81.7%) |
|   Premenopausal | 341 (42.1%) | 297 (18.3%) |
| Race/ethnicity | | |
|   Non-Hispanic Black | 143 (17.7%) | 273 (16.9%) |
|   Non-Hispanic White | 506 (62.5%) | 1,049 (64.8%) |
|   Hispanic/Latino | 124 (15.3%) | 0 |
|   Other | 37 (4.6%) | 267 (16.5%) |
|   Unknown | NA | 31 (1.9%) |
| DM2[a] | 642 (79.3%) | 1,059 (65.4%) |
| Metformin use | 517 (63.8%) | 731 (45.1%) |
| Insulin use | 394 (48.6%) | 562 (34.7%) |
| Breast cancer subtype[a] | | |
|   HR+ | 645 (79.6%) | 443 (27.3%) |
|   HR− | 165 (20.4%) | 1,177 (72.7%) |
| Cancer stage[a] | | |
|   I | 343 (42.4%) | 620 (38.3%) |
|   II | 338 (41.7%) | 697 (43%) |
|   III | 129 (15.9%) | 303 (18.7%) |
| Receipt of chemotherapy | 490 (60.5%) | 1,056 (65.2%) |
| Endocrine therapy use | 557 (68.8%) | 1,028 (63.4%) |
|   Tamoxifen | 193 (23.8%) | 355 (21.9%) |
|   Aromatase inhibitor | 364 (44.9%) | 673 (41.5%) |

[a]Matching factors included BMI at breast cancer diagnosis, DM2 diagnosis, age, breast cancer stage, and breast cancer subtype.

the agents most clinically utilized for weight management. However, the median weight change of only −3.1% at 6 months and −2.6% at 12 months was lower than expected, particularly when considering the magnitude observed in the general adult population, in which approximately 10% to 15% weight loss is expected at a similar time point from these agents (17, 18). Our findings of only modest weight loss are consistent with three other single-institution retrospective studies in patients with breast cancer. In one abstract of patients with HR-positive breast cancer who received endocrine therapy, at 12 months after GLP1-RA initiation, a mean weight change of −4.34% (95% CI, −7.7% to −1%) was observed with semaglutide and −2.31% (95% CI, −11.45% to 20.5%) with tirzepatide (13). In another study of 75 patients with breast cancer (85% with stage I–III disease and 83% with an HR-positive subtype), the median weight change at 12 months after GLP1-RA initiation was −4.2 kg (95% CI, −2.1 to −6.2 kg), or approximately 5%, and there was no association between covariates (baseline BMI,
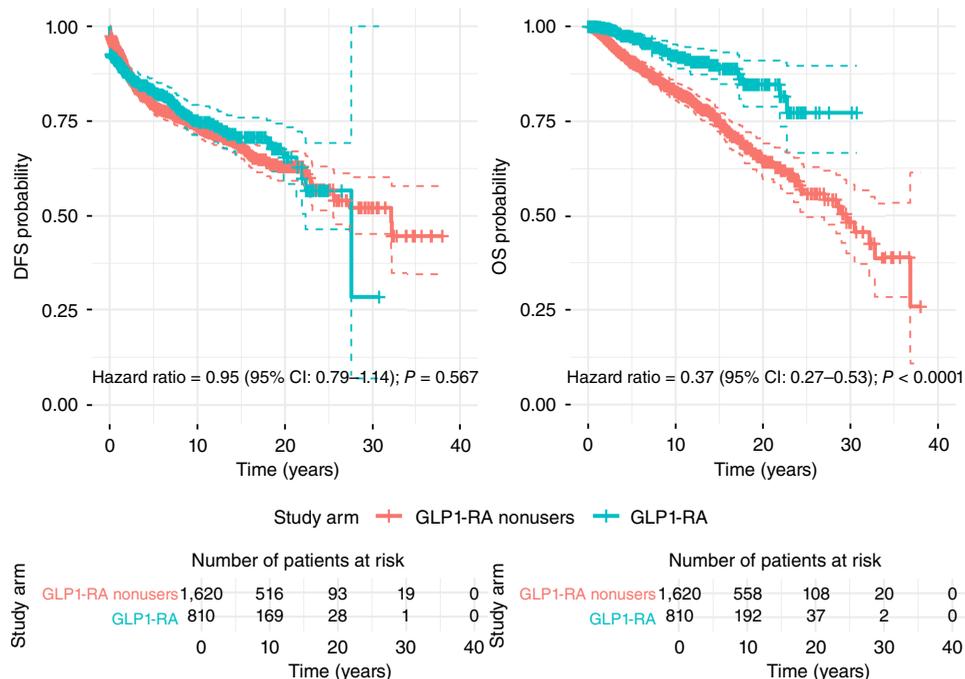
concurrent endocrine therapy, duration of GLP1-RA, and DM2 diagnosis) and weight change (19). Similarly, in an abstract by Fischbach and colleagues (15) of 70 patients with stage I to III invasive breast cancer treated with semaglutide or tirzepatide, the mean weight loss was 3 kg (95% CI, 2.1–3.9 kg), and the mean maximal weight loss was 8.9 kg (95% CI, 6.7–11 kg) over the GLP1-RA duration. In summary, although direct comparisons between studies are not feasible, the signal of attenuated weight loss effect observed among multiple separate breast cancer cohorts is perplexing and warrants further investigation.

One potential explanation for reduced weight loss compared with a non–breast cancer population and existing clinical trial data may be due to variations in drug dosing, schedule, and treatment adherence. Additionally, this may relate to endocrine therapy given that antiestrogen treatments in women with HR-positive breast cancer are linked to weight gain (20, 21). Approximately two thirds of our study population received endocrine therapy, and we found that its use was significantly associated with decreased weight loss efficacy at 12 months. Patients who received prior endocrine therapy contradictorily experienced, on average, weight gain despite receipt of GLP1-RA. However, in multivariate regression, controlling for other factors, the use of endocrine therapy no longer significantly affected relative weight change. Emerging evidence suggests synergy between the estrogen and GLP1 receptor, and future studies should explore the body composition effect from concurrent GLP1-RA and endocrine therapy use (22). Given the small sample of those in our dataset receiving both GLP1-RA and endocrine therapy at overlapping time points (n = 38), this analysis was not feasible. Moreover, the clinical implications when GLP1-RA is administered with other classes of anticancer therapies are not well elucidated. This is particularly relevant in patients undergoing treatment with agents contributing to metabolic dysfunction (e.g., chemotherapy, PI3K/AKT/mTOR inhibitors, and immune checkpoint inhibitor therapy; refs. 14, 23, 24).

With regard to the relationship of other clinical factors and weight loss, metformin use was associated with modestly increased weight loss with GLP1-RA at 3 months but not at 6 or 12 months. Metformin is associated with favorable metabolic effects, including modest weight loss in some individuals (25). Moreover, cancer stage was significantly associated with weight loss at 12 months as those with invasive breast cancer experienced more weight loss with GLP1-RA compared with patients with DCIS. This result could be related to the differential uptake of endocrine therapy in DCIS versus invasive disease; however, further study is warranted to better understand this association.

After propensity matching using multiple prognostic factors, we did not identify a DFS benefit with GLP1-RA compared with those who did not receive the GLP1-RA. These findings are similar to those of another study that evaluated breast cancer outcomes when GLP1-RA was administered after a breast cancer diagnosis that did not find a difference in locoregional or distant breast cancer recurrence in those who received semaglutide or tirzepatide compared with those who did not (15). Our findings are also consistent with existing epidemiologic data in cancer prevention research (26, 27). Namely, a study utilizing the national TriNetX platform to review more than 1.6 million patients with DM2 who received GLP1-RA evaluated the incident risk of developing multiple cancers (26). Compared with insulin, GLP1-RA use was associated with a decreased risk of developing 10 obesity-related malignancies (26); however, GLP1-RA use was not associated with

**FIGURE 3.** Kaplan–Meier estimates of DFS and OS in patients with invasive breast cancer who received and did not receive GLP1-RA.



Hazard ratio = 0.95 (95% CI: 0.79–1.14); P = 0.567

Hazard ratio = 0.37 (95% CI: 0.27–0.53); P < 0.0001

Study arm — GLP1-RA nonusers — GLP1-RA

Number of patients at risk

| Study arm | 0 | 10 | 20 | 30 | 40 |
|---|---|---|---|---|---|
| GLP1-RA nonusers | 1,620 | 516 | 93 | 19 | 0 |
| GLP1-RA | 810 | 169 | 28 | 1 | 0 |

Number of patients at risk

| Study arm | 0 | 10 | 20 | 30 | 40 |
|---|---|---|---|---|---|
| GLP1-RA nonusers | 1,620 | 558 | 108 | 20 | 0 |
| GLP1-RA | 810 | 192 | 37 | 2 | 0 |

reduced risk of postmenopausal breast cancer (26). Similarly, in a meta-analysis of more than 50 randomized clinical trials (women aged 45–70 years and 7.5-year follow-up), there was no significant difference in breast cancer in patients who received GLP1-RA compared with placebo or other antidiabetic agents (28). Another population-based cohort study (nearly 45,000 women 40 years and older and mean follow-up of 3.5 years) also showed no difference in the risk of breast cancer development with the use of GLP1-RA compared with other antidiabetic drugs (29).

These observational data in the pre– and post–breast cancer diagnosis setting suggesting no impact on breast cancer outcomes conflict with preclinical findings in which GLP1-RA has favorable antineoplastic effects (bioRxiv 2024.01.20.576484; refs. 30, 31). In one study of a murine model with obesity-driven endometrial cancer, tirzepatide inhibited both body weight and tumor growth through direct effects on immune and metabolic pathways of the tumor (31). This included modulation in genes (e.g., downregulation of ErbB signaling pathway and increase in B-cell receptor signaling) and mediation of glycolysis/fatty acid metabolism (31). In another study with a TNBC mouse model of diet-induced obesity, tirzepatide resulted in sustained weight loss and suppressed mammary tumor growth (bioRxiv 2024.01.20.576484). Notably, chronic caloric restriction promoted even greater weight loss and tumor suppression (bioRxiv 2024.01.20.576484). Clinical trials and prospective studies are crucial to shed light on potential anticancer effects of GLP1-RA and whether such findings could be related to a direct anti-proliferative biologic impact versus a more indirect effect (i.e., related to favorable metabolic regulation as a result of caloric restriction and weight loss). Moreover, the optimal timing to introduce these pharmaceuticals in the context of the cancer care continuum is unanswered.

The improved all-cause mortality in GLP1-RA users despite no observed difference in breast cancer outcomes is intriguing. These findings remained consistent after landmark analyses at several time points after breast cancer diagnoses, reinforcing the robustness of our results and indicating that the survival benefit observed is unlikely to be solely driven by immortal time bias. This survival benefit could potentially be explained by the established benefits of GLP1-RA for health outcomes. Beyond their known efficacy for glycemic control and weight loss, GLP1-RA can mitigate risk related to broad pleiotropic effects on multiple organ systems in adult populations. Examples include reduced cardiovascular disease risk and renal protective effects. Emerging data now extend to benefits in other comorbid conditions, such as substance use/addiction and steatotic liver disease (9–12, 32). Moreover, the association of GLP1-RA with improved OS in patients with DM2 is well established (33, 34).

This retrospective cohort study has limitations. A single-center study could limit generalizability of the results and future investigation should encompass diverse breast cancer populations across representative geographic and sociodemographic groups. Although we adjusted for multiple prespecified factors, there remains the possibility of residual confounding. While we matched multiple prognostic factors in the outcome analysis, we could not account for all differences (e.g., socioeconomic status), which could have inadvertently affected results, and there is also the potential for selection bias affecting survival results. This is important given that socioeconomic status may contribute to disparities in access to these therapies, owing to their high cost, and may likewise affect breast cancer survival. Moreover, a median follow-up time of 4.7 years is relatively short, considering the natural history of breast cancer. Additionally, because of limitations in prescription data within the database, we were unable to delineate the precise drug exposure with each GLP1-RA to account for certain factors related to dosing and schedule (e.g., medication adherence and treatment interruptions), which could have affected weight loss data and the outcome assessment. GLP1-RA exposure was defined based on EMR-documented prescriptions and pharmacy dispensing dates, and

continued use was inferred from prescription refills and absence of documented noncompliance in follow-up clinic visits. Although this approach captures prescribing and likely patient use, it does not allow direct confirmation of adherence. Misclassification of GLP1-RA use is a potential limitation as some exposures may not have been captured in the electronic health record. However, most GLP1-RA use in this cohort occurred before the widespread off-label or nonprescription use for weight management became common, reducing the likelihood of significant under-ascertainment. Still, unmeasured use (e.g., via compounding pharmacies) may have occurred and could bias the observed associations. Future studies should entail more granular data in this regard and also separate DM2 versus non-DM2 diagnoses because of differences in drug prescriptions between these indications.

## Conclusions

In a cohort of more than 1,000 breast cancer survivors, GLP1-RA use was associated with modest weight loss; however, endocrine therapy could have decreased this impact. Metformin use and cancer stage may also affect weight loss. An improvement in all-cause survival was observed but not a significant difference in breast cancer recurrence risk. Clinical trials are needed to investigate the role of these agents for weight loss as an adjunct to lifestyle interventions in patients with breast cancer with obesity, including those with and without DM2. Further exploration of their long-term safety and potential anticancer biological effects, particularly in the context of breast cancer risk reduction and cancer control, is also warranted.

## Data Availability

The data that support the findings of this study are not publicly available because of patient privacy concerns; however, they are available upon reasonable request from the corresponding author.

## Authors' Disclosures

No disclosures were reported.

## Authors' Contributions

**J.S. Sukumar:** Conceptualization, resources, data curation, supervision, funding acquisition, validation, investigation, visualization, methodology, writing–original draft, project administration. **A.S. Raghavendra:** Resources, data curation, investigation, methodology, project administration, writing–review and editing. **S. Pasyar:** Data curation, software, formal analysis, investigation, methodology, writing–review and editing. **R.L. Bassett:** Data curation, software, formal analysis, investigation, methodology, writing–review and editing. **D. Tripathy:** Validation, writing–review and editing. **C.H. Barcenas:** Validation, writing–review and editing. **K.M. Basen-Engquist:** Validation, writing–review and editing. **B.K. Arun:** Conceptualization, supervision, validation, investigation, project administration, writing–review and editing.

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## Note

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