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EPIDEMIOLOGY

Racial disparities in overall survival after the introduction of cyclin-dependent kinase 4/6 inhibitors for patients with hormone receptor-positive, HER2-negative metastatic breast cancer

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Abstract

Purpose CDK4/6 inhibitors (CDK4/6i) combined with endocrine therapy have improved HR + /HER2− metastatic breast cancer (MBC) outcomes. However, it is still unclear whether the response to CDK4/6i is similar for all races. Therefore, we aimed to assess overall survival (OS) trends stratified by race in patients with HR + /HER2− MBC after the approval of CDK4/6i, as part of the standard of care, in 2015.

Methods We performed a population-based study using the SEER database. Patients with HR + /HER2− MBC were divided into two time-based cohorts: 1) pre-CDK4/6i era (diagnosed in 2011–2013) and 2) post-CDK4/6i era (diagnosed in 2015–2017). We used propensity score matching and identified 2,684 patients in each cohort that matched in several characteristics. Kaplan–Meier methods were used to estimate 2-year OS. Association between cohort and OS was evaluated using marginal Cox proportional hazards models with robust sandwich variance estimator. We conducted competing risk analysis to estimate the risk of breast cancer death in both cohorts.

Results The 2-year OS rate was 65% for the post-CDK4/6i era and 62% for the pre-CDK4/6i era (stratified log-rank $p = 0.025$). The 2-year OS for non-Hispanic White (NHW) patients improved in the post-CDK4/6i era compared to the pre-CDK4/6i era (67% vs. 63%, $p = 0.033$). However, OS did not improve for non-Hispanic Black (NHB) (54% vs. 54%, $p = 0.876$) or Hispanic (67% vs. 65%, $p = 0.617$) groups. The risk of breast cancer death decreased in the post-CDK4/6i era as compared to the pre-CDK4/6i era (2-year risk of breast cancer death: 33% vs. 30%, $p = 0.015$); however, this effect was observed only in NHW (sHR 0.84, $p = 0.005$) women, but not in NHB (sHR 0.94, $p = 0.630$) or Hispanic (sHR 0.91, $p = 0.550$) women.

Conclusions Our study confirms that outcomes for HR + /HER2− MBC have improved after CDK4/6i were introduced in 2015. However, this effect is primarily driven by the improved OS in NHW patients, without significant improvement in OS in NHB or Hispanics.

Keywords Metastatic breast cancer · CDK4/6 inhibitors · Survival · SEER · Race

Abbreviations

OS	Overall survival
MBC	Metastatic breast cancer
HR	Hormone receptor
CDK4/6i	Cyclin-dependent kinase 4/6 inhibitors
SEER	Surveillance, epidemiology and end results
NHW	Non-Hispanic White
NHB	Non-Hispanic Black

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Background

Breast cancer is the most common malignancy and the leading cause of cancer mortality among women worldwide [1, 2]. Breast cancer outcomes have improved in the last three decades, primarily mediated by earlier detection and advances in therapeutic options. However, about 30% of women with early breast cancer develop metastatic breast cancer (MBC), an incurable disease with a 5-year overall survival (OS) rate of only 30%. Despite the widespread use of routine mammography screening, the incidence of de novo MBC has remained

relatively steady for decades suggesting that mammography screening does not eradicate the emergence of biologically aggressive MBC [3, 4]. Hormone receptor-positive (HR +)/Human epidermal growth factor receptor 2 negative (HER2−) is the most common breast cancer subtype, accounting for 70% of all breast cancer [5]. Endocrine therapy has been the cornerstone of systemic treatment for HR + /HER2− MBC; however, novel targeted therapies have emerged as treatment options for these patients.

Racial disparities in breast cancer exist. Despite a lower incidence, non-Hispanic Black (NHB) patients with HR + breast cancer have a 20% higher breast cancer mortality as compared to non-Hispanic White (NHW) patients [6–11]. In addition, NHB and Hispanic women have a higher incidence of de novo metastatic disease than NHW women [12–14]. Multiple etiologies have been proposed for racial disparities, such as biological [15–17] and socioeconomic factors [18–20]. Relative to NHW, HR + /HER2− tumors from NHB women are characterized by more aggressive molecular features, such as higher contributions from homologous recombination deficiency, TP53 mutations, and increased structural variation; furthermore, GATA3 mutations are more frequent in NHB regardless of breast cancer subtype [16, 21].

The addition of cyclin-dependent kinase 4/6 inhibitors (CDK4/6i) such as palbociclib, ribociclib, or abemaciclib to endocrine therapy (ET) has improved survival outcomes for patients with HR + /HER2− MBC. The landmark trial PALOMA-2 showed that adding the CDK4/6i palbociclib to letrozole as first-line treatment increased the median progression-free survival (PFS) by 10 months [22]. Subsequent studies demonstrated the clinical efficacy of CDK4/6i in patients with disease progression after endocrine therapy [23]. The Food and Drug Administration (FDA) approved CDK4/6i combined with endocrine therapy as first-line for patients with HR + /HER2− MBC in 2015, which became the standard of care for these patients [24]. Most patients enrolled in the CDK4/6i landmark trials were NHW. NHB patients were underrepresented in these studies representing less than 2% in CDK4/6i landmark trials; moreover, the proportion of Hispanic patients enrolled is unclear.

It is still unclear whether the response to CDK4/6i is similar for all races. Therefore, we aimed to assess OS trends, stratified by race, in patients with HR + /HER2− MBC before and after the approval of CDK4/6i as part of the standard of care in 2015.

Methods

Data collection

We used the Surveillance, Epidemiology, and End Results (SEER) research plus database (2021 submission) to identify eligible cases. The follow-up cut-off for this database is December 31st, 2019. We included patients diagnosed with de novo MBC from 2011 to 2017. Other inclusion criteria included age > 18 years, ER and/or PR positive, and HER2 negative. Exclusion criteria included patients diagnosed by autopsy or death certificate, prior malignancies, bilateral breast cancer, non-metastatic disease, unknown metastatic status, and unknown ER, PR or HER2 status. Since we aimed to assess outcomes after CDK4/6i approval, we created two time-based cohorts: 1) patients diagnosed in 2011–2013 (pre-CDK4/6i era), and 2) patients diagnosed in 2015–2017 (post-CDK4/6i era). The deidentified data were determined exempt from informed consent by the Albert Einstein Institutional Board review, which approved the study.

Variables

We obtained data on demographic variables such as age, sex, and race; this last variable was collected in combination with ethnicity leading to 4 racial groups: non-Hispanic White (NHW), non-Hispanic Black (NHB), Hispanic from all races, and other race/ethnic groups (non-Hispanic Asian/Pacific islander and non-Hispanic American Indian/Alaska Native). Socioeconomic variables included rurality and marital status. Rurality was obtained from the rural–urban continuum code from the SEER dataset and further dichotomized as metropolitan area or non-metropolitan (rural). We also collected information on breast cancer clinicopathological variables such as hormone receptor status (ER and PR), HER2 status, tumor grade, and metastatic sites (bone, brain, liver, or lungs). Treatment variables collected included surgery, chemotherapy, and radiation therapy. Breast cancer outcomes were assessed using vital status, survival in months, and cause of death.

Statistical analysis

We used the Pearson's *X*-square test in the overall cohort to assess the association between categorical variables and the student *t* test for continuous variables. Baseline characteristics variables were summarized with descriptive statistics.

Our cohorts differed in time and baseline characteristics. To decrease selection bias, we performed propensity score methods using complete case analysis to create matched cohorts. Then, we performed propensity score matching for the covariates sex, age, race, PR, ER, tumor grade, chemotherapy, surgery, radiation therapy, rurality, marital status, and metastasis to bone, brain, liver, and lungs. A 1-to-1 matching, without replacement, was performed using the nearest neighbor method with a caliper width equal to 0.1 standard deviations [25]. Matching was carried out using the Matchit package in R (version 4.3.3). We examined balance

in the baseline covariates in the matched data by using standardized mean differences and variance ratios [25]. Furthermore, a Love-plot was created to visualize covariate balance for all variables included in the propensity score.

We also compared baseline characteristics between both cohorts after matching. We used McNemar's or Friedman's test for categorical variables and paired student t tests for continuous variables.

Survival analysis

OS was defined as the time in months from MBC diagnosis to death from any cause. Since the follow-up time could be longer for the pre-CDK4/6i cohort, patients from both cohorts were censored at 24 months, and we proceeded to analyze the 2-year OS. We estimated OS in the pre-CDK4/6i and post-CDK4/6i cohorts using Kaplan–Meier methods in the matched data set and compared OS in both groups by using the log-rank test stratified on matched pairs. Association between cohort and OS was evaluated using marginal Cox proportional hazards models with a robust sandwich variance estimator to account for clustering within matched sets [26]. Hazard ratios (HRs) were estimated from these models.

We conducted a competing risk analysis to estimate the risk of breast cancer death in both cohorts. To compare the risk of breast cancer death between cohorts, we estimated cumulative incidence functions (CIFs) and marginal subdistribution hazard ratios (sHRs) from clustered Fine and Gray models that accounted for the within-pair clustering of outcomes [25].

We also assessed OS and breast cancer death risk among races by using stratified Cox proportional models and Fine and Gray models, respectively, which were adjusted for clinicopathological, treatment, and socioeconomic covariates such as age, hormone status, HER2 status, tumor grade, metastatic sites, chemotherapy, radiation therapy, surgery, rurality, and marital status.

Two-sided P values and 95% confidence intervals (CIs) are reported. An α equal to 0.05 was used for all hypothesis testing. Statistical analyses were performed in R (Version 1.4.1106).

Results

We identified 4,540 patients diagnosed with HR + / HER2− MBC in the pre-CDK4/6i era (2011–2013) and 4797 in the post-CDK4/6i era (2015–2017). Baseline characteristics for both cohorts were compared (Table 1). Patients in the pre-CDK4/6i era were slightly younger than the post-CDK4/6i era (≤ 65 years: 61% vs. 57%, $p < 0.001$). Tumor grade 3/4 was less common in the post-CDK4/6i era (30% vs. 27%, $p = 0.011$). Most patients in both cohorts had dual hormone receptor-positive tumors (80% and 81%). The pattern of metastasis was different between both cohorts. Brain (6% vs. 5%, $p = 0.003$) and liver (20% vs. 18%, $p = 0.004$) metastases were less common in the post-CDK4/6i era, whereas the presence of lung metastasis was similar in both cohorts (28% vs. 28%). There was no difference in the frequency of bone metastasis (74% vs. 75%, $p = 0.643$); however, bone-only MBC was more common in the post-CDK4/6i era (43% vs. 46%, $p = 0.031$). Treatment with surgery or radiation was less frequent in the post-CDK4/6i era (29% vs. 21% $p < 0.001$ and 34% vs. 31%, $p < 0.001$, respectively); however, chemotherapy was more frequently used in the post-CDK4/6i era (43% vs. 55%, $p < 0.001$). There was no difference in rurality or marital status between both cohorts. Likewise, racial distribution was different: NHW, NHB, Hispanic, and other race/ethnic groups represented 67, 14, 11, and 8% vs. 65, 13, 12 and 10% for the pre-CDK4/6i and post-CDK4/6i eras, respectively ($p = 0.022$).

Propensity score matching

From the overall cohort, 2684 patients in the pre-CDK4/6i era were matched with 2684 patients in the post-CDK4/6i era (Fig. 1). The distribution of baseline covariates was adequately balanced in the matched data set (Table 1). Absolute standardized mean differences were < 0.1 for all covariates, suggesting a negligible difference between both cohorts; indeed, the largest standardized mean difference was 0.04 in the matched data set. Baseline characteristics between both groups were compared after matching. We found no statistically significant difference between cohorts in age, sex, race, marital status, rurality, tumor grade, hormone receptor status, surgery, chemotherapy, radiation, or metastatic pattern. Matched cohorts were used for further survival analyses.

Overall survival in the pre-CDK4/6i and post-CDK4/6i eras

In the matched dataset, the 2-year OS rate was 62% in the pre-CDK4/6i era and 65% in the post-CDK4/6i era (stratified log-rank $p = 0.025$) (Table 2 and Fig. 2). The 2-year OS for NHW women improved in the post-CDK4/6i era compared to the pre-CDK4/6i era (63% vs. 67%, $p = 0.033$) (Table 2 and Supplementary information [SI] 1). However, there was no improvement for NHB (54% vs. 54%, $p = 0.876$), Hispanic (65% vs. 67%, $p = 0.617$), or other race/ethnic groups (69% vs. 67%, $p = 0.513$) (Table 2 and SI 1) Overall mortality was reduced in the post-CDK4/6i era with an estimated HR of 0.91 (95%CI 0.83–0.99). After adjustment for clinicopathological, treatment, and socioeconomic variables, the overall mortality was reduced in the post-CDK4/6i era for NHW (HR 0.87, 95%CI 0.78–0.97) (Table 3), whereas it was

Table 1 Subject demographics and clinical characteristics between pre-CDK4/6i and post-CDK4/6i era before and after propensity score matching

	Before matching				After matching			
	pre-CDK4/6i ($n=4540$)	post-CDK4/6i ($n=4797$)	*P* value	Std. mean diff	pre-CDK4/6i ($n=2684$)	post-CDK4/6i ($n=2684$)	*P* value	Std. mean diff
Age, y, Mean ± SD	61.9 ± 13.9	62.9 ± 14.1	< 0.001	0.05	61.5 ± 14.0	61.6 ± 14.3	0.628	0.01
Age group, no. (%)			< 0.001				0.151	
≤ 65	2779 (61%)	2742 (57%)		NA	1667 (62%)	1617 (60%)		NA
> 65	1761 (39%)	2055 (43%)			1017 (38%)	1067 (40%)		
Sex, no. (%)			0.076				0.195	
Female	4486 (99%)	4718 (98%)		− 0.04	2650 (99%)	2638 (98%)		− 0.03
Male	54 (1%)	79 (2%)		0.04	34 (1%)	46 (2%)		0.03
Marital status, no. (%)			0.150				0.722	
Married	1952 (43%)	2113 (44%)		0.01	1268 (47%)	1282 (48%)		0.01
Unmarried	2330 (51%)	2452 (51%)		− 0.01	1416 (53%)	1402 (52%)		− 0.01
Unknown	258 (6%)	232 (5%)		NA	NA	NA		NA
Rurality, no. (%)			0.955				0.861	
Metro	4004 (88%)	4240 (88%)		− 0.01	2383 (89%)	2378 (89%)		− 0.006
No metro	528 (12%)	549 (11%)		0.01	301 (11%)	306 (11%)		0.006
Unknown	8 (0%)	8 (0%)		NA	NA	NA		NA
Race/ethnicity, no. (%)			0.022				0.609	
NH White	3039 (67%)	3134 (65%)		-0.03	1773 (66%)	1771 (66%)		-0.002
NH Black	635 (14%)	639 (13%)		-0.02	378 (14%)	363 (14%)		-0.02
Hispanic	507 (11%)	566 (12%)		0.02	302 (11%)	310 (12%)		0.009
Other	359 (8%)	458 (10%)		0.05	231 (9%)	240 (9%)		0.01
Grade, no. (%)			0.011				0.449	
Grade 1	421 (9%)	473 (10%)		0.02	329 (12%)	344 (13%)		0.02
Grade 2	1767 (39%)	1992 (42%)		0.06	1391 (52%)	1392 (52%)		< 0.001
Grade 3–4	1350 (30%)	1295 (27%)		− 0.08	964 (36%)	948 (35%)		− 0.01
Unknown	1002 (22%)	1037 (22%)		NA	NA	NA		NA
ER, no. (%)			< 0.001				0.888	
Negative	74 (2%)	40 (1%)		− 0.10	28 (1%)	26 (1%)		− 0.008
Positive	4461 (98%)	4757 (99%)		0.10	2656 (99%)	2658 (99%)		0.008
Unknown	5 (0%)	0 (0%)		NA	NA	NA		NA
PR, no. (%)			0.636				0.822	
Negative	771 (17%)	823 (17%)		0.01	430 (16%)	437 (16%)		0.007
Positive	3701 (82%)	3913 (82%)		− 0.01	2254 (84%)	2247 (84%)		− 0.007
Unknown	68 (1%)	61 (1%)		NA	NA	NA		NA
Hormone receptor status, no. (%)			0.001					
ER (+), PR (+)	3622 (80%)	3873 (81%)						
ER (+), PR (-)	839 (18%)	884 (18%)		NA	NA	NA	NA	NA
ER (-), PR (+)	79 (2%)	40 (1%)						
Bone met, no. (%)			0.643				0.924	
No	1077 (24%)	1122 (23%)		− 0.02	665 (25%)	669 (25%)		0.004
Yes	3380 (74%)	3598 (75%)		0.02	2019 (75%)	2015 (75%)		− 0.004
Unknown	83 (2%)	77 (2%)		NA	NA	NA		NA
Brain met, no. (%)			0.003				1.000	
No	4099 (90%)	4415 (92%)		0.01	2545 (95%)	2546 (95%)		0.002
Yes	258 (6%)	244 (5%)		− 0.01	139 (5%)	138 (5%)		− 0.002
Unknown	183 (4%)	138 (3%)		NA	NA	NA		NA
Liver met, no. (%)			0.004				0.594	

Table 1 (continued)

	Before matching				After matching			
	pre-CDK4/6i ($n=4540$)	post-CDK4/6i ($n=4797$)	*P* value	Std. mean diff	pre-CDK4/6i ($n=2684$)	post-CDK4/6i ($n=2684$)	*P* value	Std. mean diff
No	3471 (76%)	3799 (79%)		0.04	2179 (81%)	2163 (81%)		− 0.02
Yes	919 (20%)	870 (18%)		− 0.04	505 (19%)	521 (19%)		0.02
Unknown	150 (3%)	128 (3%)		NA	NA	NA		NA
Lungs met, no. (%)			0.014				0.735	
No	3095 (68%)	3318 (69%)		− 0.01	1925 (72%)	1937 (72%)		0.01
Yes	1257 (28%)	1334 (28%)		0.01	759 (28%)	747 (28%)		-0.01
Unknown	188 (4%)	145 (3%)		NA	NA	NA		
Bone met only, no. (%)			0.031					
No	1969 (43%)	2006 (42%)						
Yes	1972 (43%)	2209 (46%)		NA	NA	NA	NA	NA
Unknown	599 (13%)	582 (12%)						
Visceral met, no. (%)	2404 (53%)	2627 (55%)	0.204					
No	1969 (43%)	2006 (42%)		NA	NA	NA	NA	NA
Yes	167 (4%)	164 (3%)						
Unknown								
Surgery, no. (%)			< 0.001				0.372	
No	3179 (70%)	3761 (78%)		0.23	1849 (69%)	1876 (70%)		0.02
Yes	1327 (29%)	985 (21%)		− 0.23	835 (31%)	808 (30%)		− 0.02
Unknown	34 (1%)	51 (1%)		NA	NA	NA		NA
Chemotherapy, no. (%)			< 0.001				0.058	
No	2575 (57%)	2176 (45%)		− 0.26	1328 (49%)	1272 (47%)		− 0.04
Yes	1965 (43%)	2621 (55%)		0.26	1356 (51%)	1412 (53%)		0.04
Radiation, no. (%)			0.002				0.510	
No	2927 (64%)	3176 (66%)		0.10	1702 (63%)	1725 (64%)		0.02
Yes	1534 (34%)	1500 (31%)		− 0.10	982 (37%)	959 (36%)		− 0.02
Unknown	79 (2%)	121 (3%)		NA	NA	NA		NA

SD standard deviation, *Std. Mean Diff.* standard mean difference, *y* years, *NH* non-Hispanic, *ER* estrogen receptor, *PR* progesterone receptor, *NA* not applicable, *Met* metastasis, *Pos* positive, *Neg* negative, *Unk* unknown

no different for NHB (HR 0.98, 95%CI 0.79–1.22), Hispanic (HR 0.92, 95%CI 0.69–1.23), or other race/ethnic groups (HR 1.10, 95%CI 0.79–1.54) (Table 3 and SI 2).

We conducted a multivariable analysis to assess factors associated with OS (combined cohorts) (Table 4). Older patients experienced worse OS (HR 1.34, 95%CI 1.25–1.43). Among tumor-related factors, higher tumor grade was associated with adverse outcomes (HR 1.24, 95%CI 1.06–1.46 for grade 2; and HR 1.91, 95%CI 1.62–2.25 for grade 3/4). Single hormone-receptor positivity was associated with worse OS than dual hormone-receptor positivity (HR 1.86, 95%CI 1.67–2.07 for ER+/PR−; HR 3.34, 95%CI 2.42–4.63 for ER−/PR+). Among metastatic patterns, brain metastasis had the worse OS (HR 2.23, 95%CI 1.90–2.62), followed by liver (HR 2.02, 95%CI 1.82–2.24), lung (HR 1.33, 95%CI 1.21–1.47), and bone (HR 1.12, 95%CI 1.01–1.24) metastasis (Table 4). All treatment modalities were associated with improved OS (HR 0.52, 95%CI 0.46–0.59 for surgery; HR 0.56, 95%CI 0.51–0.62 for chemotherapy; and HR 0.87, 95%CI 0.79–0.97 for radiation therapy). Married status was associated with improved OS (HR 0.77, 95%CI 0.70–0.85), whereas living in a rural area was associated with worse OS (HR 1.16, 95%CI 1.01–1.33).

Risk of breast cancer death before and after CDK4/6i approval

We used competing risk analysis to assess the risk of breast cancer death. The cumulative incidence function (CIF) curve for breast cancer death is depicted in Fig. 3. The estimated probability of breast cancer death at 2 years was 33% and 30% for the pre-CDK4/6i and post-CDK4/6i eras, respectively ($p=0.015$) (Fig. 3). The risk of breast cancer death was reduced in the post-CDK4/6i era with an estimated

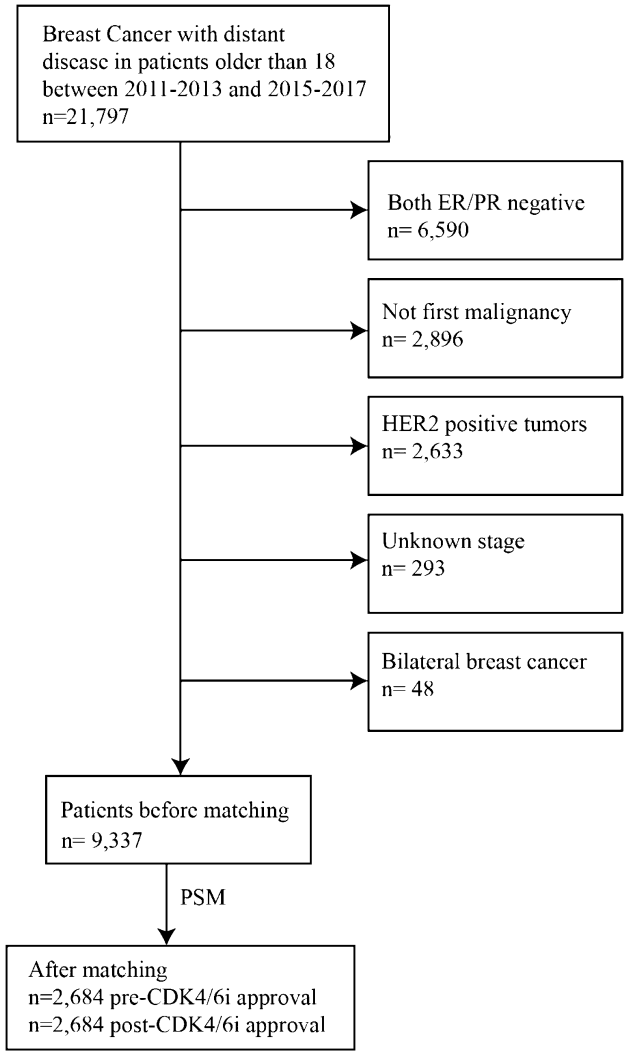

Fig. 1 Consort Diagram. From the Surveillance, Epidemiology, and End Results (SEER) research plus database, we identified 21,797 patients. Subsequently, patients with both estrogen and progesterone receptor-negative breast cancer, patients with HER2-positive tumors, and patients with unknown stage and bilateral breast cancer were excluded. A propensity score matching method was used to obtain two matched cohorts with 2,684. Abbreviation: PSM: Propensity score matching

sHR of 0.89 (95%CI, 0.81–0.98) (Table 5). After adjustment for clinicopathological, treatment, and socioeconomic factors, the risk of breast cancer death was reduced in the post-CDK4/6i era for NHW (sHR 0.84, 95%CI 0.74–0.95), whereas it was no different for NHB (sHR 0.94, 95%CI 0.75–1.19), Hispanic (sHR 0.91, 95%CI 0.67–1.24), and other race (sHR 1.16, 95%CI 0.81–1.67) groups (Table 6 and SI 3).

In addition, we conducted competing risk analyses to identify factors associated with the risk of breast cancer death (both cohorts combined) (Table 5). Older age (sHR 1.25, 95%CI 1.16–1.34), high tumor grade (sHR 1.97, 95%CI 1.65–2.36), and single hormone-receptor positivity (sHR 1.84, 95%CI 1.63–2.08 for ER + /PR−, and sHR 2.93, 95%CI 2.02–4.27 for ER−/PR +) were associated with increased risk of breast cancer death. Among metastatic sites, liver metastasis had the higher risk of breast cancer death (sHR 2.07, 95%CI 1.85–2.33), followed by brain (sHR 1.94, 95%CI 1.59–2.37), lung (sHR 1.32, 95%CI 1.19–1.47), and bone metastasis (sHR: 1.24, 95%CI 1.10–1.40). While chemotherapy (sHR 0.62, 95%CI 0.56–0.69) and surgery (sHR 0.54, 95%CI 0.48–0.61) decreased the risk of breast cancer death, radiation therapy had no effect on it (sHR 0.94, 95%CI 0.84–1.04). Married status was associated with decreased risk of breast cancer death (sHR 0.81, 95%CI 0.73–0.89,), whereas living in a rural area was associated with an increased risk of breast cancer death (sHR 1.22, 95%CI 1.05–1.40) (Table 5).

Discussion

Our study shows that the OS has improved for patients with HR + /HER2− MBC in the post-CDK4/6i era as compared to those in the pre-CDK4/6i era (2-year OS rate 65% vs. 62%, $p = 0.025$); however, this improvement was seen only for NHW patients (HR 0.87, $p = 0.016$), with no improvement for NHB (HR 0.98, $p = 0.864$) or Hispanic (HR 0.92, $p = 0.578$) women. The risk of breast cancer death decreased in the post-CDK4/6i era as compared to the pre-CDK4/6i era

Table 2 Two-year overall survival rates in the pre-CDK4/6i and post-CDK4/6i era

	pre-CDK4/6i era (2011–2013)				post-CDK4/6i era (2015–2017)				
	No. subjects	No. events	Survival rate %	95% CI	No. subjects	No. events	Survival rate %	95% CI	*P* value
All	2684	1006	62	60–64	2684	927	65	63–67	0.025
NH White	1773	662	63	60–65	1771	588	67	64–69	0.033
NH Black	378	171	54	49–59	363	165	54	49–60	0.876
Hispanic	302	105	65	60–71	310	97	67	62–73	0.617
Other	231	68	69	64–76	240	77	67	61–73	0.513

No number, *CI* confidence interval, *NH* non-Hispanic

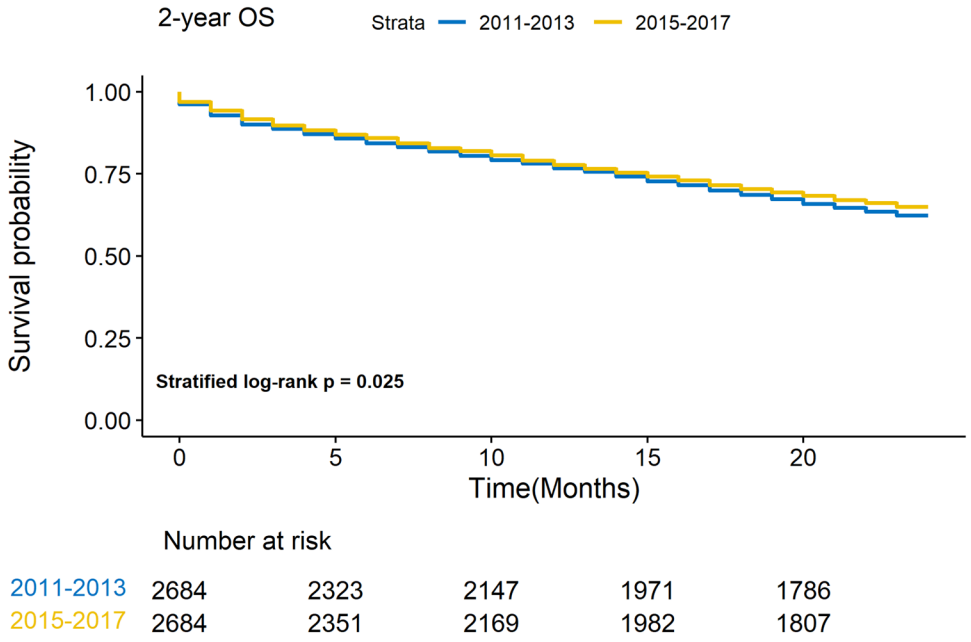

Fig. 2 2-year overall survival (OS) for all races in the pre-CDK4/6i and post-CDK4/6i era. The blue line represents the pre-CDK4/6i era (2011–2013) and the yellow line represents the post-CDK4/6i era (2015–2017)

(2-year risk of breast cancer death: 33% vs. 30%, $p=0.015$); however, this effect was observed only in NHW (sHR 0.84, $p=0.005$) women, but not in NHB (sHR 0.94, $p=0.630$) or Hispanic (sHR 0.91, $p=0.550$) patients.

Our data suggest racial disparities in OS after the introduction of CDK4/6i in patients with HR + /HER2− MBC. Racial disparities in breast cancer outcomes have been well recognized [27]. Prior studies have demonstrated that Black women are diagnosed at more advanced stages [28] and are more likely to discontinue chemotherapy [29]. Studies have reported that early discontinuation of therapy, clinicopathological characteristics, and insurance might not completely explain the survival differences between NHB and NHW women [9, 30]. In a population study, Huang reported that patients with MBC in the lowest socioeconomic status (SES) quintile had a significantly increased risk of breast cancer death compared to those in the highest SES quintile (sHR 1.22, 95%CI 1.17–1.26). Compared to NHW women, NHB and Hispanics experienced increased (sHR 1.15, 95%CI 1.11–1.19) and similar risk (sHR 1.03, 95%CI 0.99–1.07) of breast cancer-specific mortality, respectively. Among women with HR + MBC, residing in areas with the lowest SES quintile was associated with an increased risk of breast cancer mortality among NHW (sHR 1.19, 95%CI 1.12–1.26), Black (sHR 1.21, 95%CI 1.05–1.39), and Hispanic (sHR 1.18, 95%CI 1.02–1.37) women [31]. These results suggest that socioeconomic factors affect the risk of breast cancer death in patients with MBC. In our database, we only had access to information about rurality and marital status; therefore, we could not assess the full effect of SES on OS trends. Rurality has been associated with MBC outcomes, possibly mediated by distance to healthcare centers and access to screening and treatment [3, 4, 32]. A meta-analysis including 21 studies showed that women living in rural areas were 1.2 times more likely to be diagnosed with MBC when compared to women living in urban areas [33]. Our study also found that rurality was associated with worse OS (HR 1.16, $p=0.032$). However, despite adjustment for rurality, only NHW demonstrated improvement in OS and breast cancer death in the post-CDK4/6i era.

NHB and Hispanic women were underrepresented in the landmark CDK4/6i trials; consequently, there is scarce literature on the response to CDK4/6i among different racial groups. In a meta-analysis of 4 trials that evaluated CDK4/6i as first-line therapy, there was an interaction between treatment effect on PFS and ethnicity (HR 0.56 for all, HR 0.9 for Asian, HR 0.62 for non-Asian, p for interaction = 0.002) [34]. However, this study was focused on Asian vs. non-Asian groups and did not provide information about NHB or Hispanic patients. PALOMA-3 and MONARCH-2 trials evaluated CDK4/6i after progression on ET and found no racial differences in PFS; however, their analyses were focused on White and Asian patients [35, 36]. A real-world study by Agrawal and colleagues found that the median PFS for Indian women treated with palbociclib and letrozole was 20.2 months in the first line and 12 months in the second line, suggesting similar effectiveness to other real-world evidences [37]. Our study focused on NHW, NHB, and Hispanic patients. Asian composed only a small group of patients; therefore, they were combined with the other race group/ethnic in our study. We found no improvement in OS or breast cancer death risk from the pre-CDK4/6i to the post CDK4/6i era for the other race/ethnic group.

Table 3 Multivariable models for overall survival by Cox regression method stratified by Race

Characteristic	Non-Hispanic White ($n=3544$)			Non-Hispanic Black ($n=741$)			Hispanic ($n=612$)		
	HR	95% CI	*P* values	HR	95% CI	*P* values	HR	95% CI	*P* values
Cohort									
pre-CDK4/6i	Reference			Reference			Reference		
post-CDK4/6i	0.87	0.78–0.97	0.016	0.98	0.79–1.22	0.864	0.92	0.69–1.23	0.578
Age (years)									
≤65	Reference			Reference			Reference		
>65	1.38	1.27–1.50	<0.001	1.30	1.10–1.54	0.003	1.80	1.44–2.26	<0.001
Marital status									
Unmarried	Reference			Reference			Reference		
Married	0.75	0.67–0.84	<0.001	0.90	0.69–1.17	0.425	0.95	0.71–1.27	0.723
Rurality									
Metro	Reference			Reference			Reference		
No Metro	1.22	1.04–1.42	0.013	0.89	0.60–1.31	0.541	0.85	0.34–2.10	0.725
Grade									
Grade 1	Reference			Reference			Reference		
Grade 2	1.20	0.99–1.45	0.058	1.63	0.99–2.70	0.055	1.08	0.63–1.83	0.784
Grade 3–4	1.73	1.43–2.10	<0.001	2.83	1.72–4.65	<0.001	2.07	1.21–3.54	0.008
Hormone receptor									
ER (+), PR (+)	Reference			Reference			Reference		
ER (+), PR (−)	1.86	1.63–2.13	<0.001	1.51	1.17–1.94	0.002	2.42	1.74–3.37	<0.001
ER (−), PR (+)	3.77	2.37–5.98	<0.001	3.43	1.72–6.82	0.069	5.72	2.65–12.36	<0.001
Bone met									
No	Reference			Reference			Reference		
Yes	1.06	0.93–1.21	0.396	1.34	1.03–1.75	0.028	1.18	0.85–1.64	0.312
Brain met									
No	Reference			Reference			Reference		
Yes	2.15	1.76–2.64	<0.001	2.71	1.83–4.01	<0.001	2.35	1.46–3.78	<0.001
Liver met									
No	Reference			Reference			Reference		
Yes	1.86	1.63–2.12	<0.001	2.39	1.87–3.05	<0.001	2.36	1.69–3.28	<0.001
Lung met									
No	Reference			Reference			Reference		
Yes	1.31	1.16–1.48	<0.001	1.37	1.10–1.73	0.006	1.38	1.02–1.86	0.037
Surgery									
No	Reference			Reference			Reference		
Yes	0.50	0.43–0.58	<0.001	0.55	0.41–0.74	<0.001	0.54	0.38–0.77	<0.001
Chemotherapy									
No	Reference			Reference			Reference		
Yes	0.56	0.50–0.64	<0.001	0.50	0.39–0.63	<0.001	0.60	0.44–0.82	0.001
Radiation									
No	Reference			Reference			Reference		
Yes	0.84	0.74–0.96	0.008	0.97	0.77–1.23	0.801	0.91	0.66–1.25	0.553

HR hazard ratio, *CI* confidence interval, *ER* estrogen receptor, *PR* progesterone receptor, *Met* metastasis, + positive, - negative

A single institution study of CDK4/6i by Knudsen et al. included Black patients in the non-European group accounting for ~ 8% of patients. The non-European group experienced shorter PFS than patients of European descent ($p<0.002$). However, Black patients entered treatment with CDK4/6i disproportionately with more recurrent disease and treatment with fulvestrant, both of which are associated with shorter PFS [38]. Isaacs combined NHB and Hispanic patients enrolled in PALOMA-2 ($n=65$) and PALOMA-3 ($n=48$) trials, and conducted a survival analysis [39]. In the

Table 4 Univariate and multivariable model for overall survival by Cox regression model including all races ($n = 5368$)

Characteristic	Univariate			Multivariable (all races)		
	HR	95% CI	*P* values	HR	95% CI	*P* values
Cohort						
pre-CDK4/6i	Reference			Reference		
post-CDK4/6i	0.91	0.83–0.99	0.044	0.91	0.83–0.99	0.044
Age (years)						
≤ 65	Reference			Reference		
> 65	1.49	1.40–1.59	< 0.001	1.34	1.25–1.43	< 0.001
Sex						
Female	Reference			Reference		
Male	1.05	0.74–1.49	0.797	NA	NA	NA
Marital status						
Unmarried	Reference			Reference		
Married	0.66	0.60–0.72	< 0.001	0.77	0.70–0.85	< 0.001
Rurality						
Metro	Reference			Reference		
No metro	1.13	0.99–1.29	0.075	1.16	1.01–1.33	0.032
Race						
NH White	Reference			Reference		
NH Black	1.35	1.20–1.53	< 0.001	NA	NA	NA
Hispanic	0.92	0.79–1.07	0.271	NA	NA	NA
Other	0.85	0.72–1.01	0.069	NA	NA	NA
Grade						
Grade 1	Reference			Reference		
Grade 2	1.24	1.06–1.46	0.009	1.24	1.06–1.46	0.009
Grade 3–4	1.86	1.59–2.19	< 0.001	1.91	1.62–2.25	< 0.001
Hormone receptor						
ER (+), PR (+)	Reference			Reference		
ER (+), PR (−)	1.91	1.71–2.12	< 0.001	1.86	1.67–2.07	< 0.001
ER (−), PR (+)	3.42	2.49–4.70	< 0.001	3.34	2.42–4.63	< 0.001
Bone met						
No	Reference			Reference		
Yes	0.97	0.88–1.08	0.612	1.12	1.01–1.24	0.047
Brain met						
No	Reference			Reference		
Yes	2.57	2.20–3.00	< 0.001	2.23	1.90–2.62	< 0.001
Liver met						
No	Reference			Reference		
Yes	2.01	1.82–2.22	< 0.001	2.02	1.82–2.24	< 0.001
Lung met						
No	Reference			Reference		
Yes	1.63	1.49–1.79	< 0.001	1.33	1.21–1.47	< 0.001
Bone met only						
No	Reference					
Yes	0.48	0.44–0.53	< 0.001	NA	NA	NA
Visceral met						
No	Reference					
Yes	2.06	1.89–2.26	< 0.001	NA	NA	NA
Surgery						
No	Reference			Reference		
Yes	0.42	0.37–0.47	< 0.001	0.52	0.46–0.59	< 0.001

Table 4 (continued)

Characteristic	Univariate			Multivariable (all races)		
	HR	95% CI	*P* values	HR	95% CI	*P* values
Chemotherapy						
No	Reference			Reference		
Yes	0.55	0.50–0.60	< 0.001	0.56	0.51–0.62	< 0.001
Radiation						
No	Reference			Reference		
Yes	0.76	0.69–0.83	< 0.001	0.87	0.79–0.97	0.010

HR hazard ratio, *ER* estrogen receptor, *PR* progesterone receptor, *NA* not applicable, *Met* metastasis, + positive, - negative, *CI* confidence interval

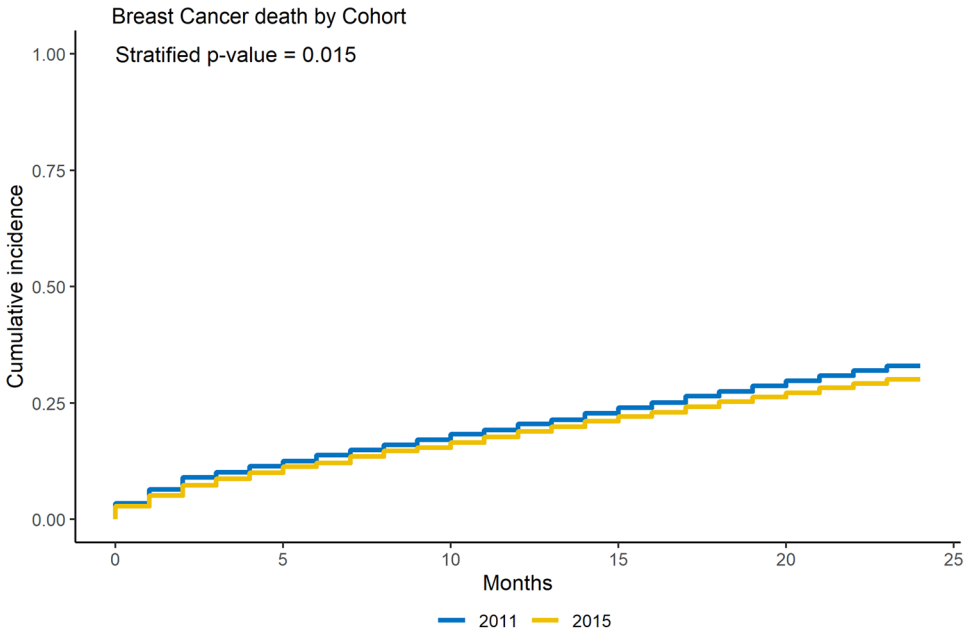

Fig. 3 Cumulative risk of breast cancer death. The blue line represents the pre-CDK4/6i era (2011–2013) and the yellow line represents the post-CDK4/6i era (2015–2017)

PALOMA-2 trial, the PFS did not improve (HR 0.61, 95%CI 0.31–1.2) with the addition of Palbociclib. OS was not reported. For the PALOMA-3 trial, adding palbociclib did not improve PFS (HR 0.56, 95%CI 0.28–1.14) but improved OS (HR 0.48, 95%CI 0.23–0.97). It is noteworthy that this study combined NHB and Hispanic patients in the same group. Historically, Hispanics and NHB patients have better and worse survival outcomes than NHW patients, respectively. Therefore, combining them in the same group may lead to biased results. In addition, HRs for all comparisons were not adjusted for clinicopathological variables since they were estimated from the unstratified Cox proportional hazards model; therefore, results must be interpreted cautiously. A single institution study by Schreier included the highest proportion of Black patients for analysis of response to CDK4/6i reported in the literature. This study included 182 patients, 46% Black and 56% non-Black, and reported no difference in PFS for Black vs. non-Black patients (316 vs. 407 days, $p = 0.51$)[40]. It is noteworthy that this was a single-center study in an academic center in the Bronx, NY; and the study population reflects the racial distribution of The Bronx population, demonstrating similar access to CDK4/6i for both racial groups. These results suggest that similar access to CDK4/6i leads to similar outcomes for Black and non-Black patients treated with CDK4/6i.

Furthermore, population studies in the US have demonstrated that Hispanics have lower breast cancer incidence and mortality compared to NHW women [41]. Nevertheless, our study suggests that the OS has not improved after introducing CDK4/6i for Hispanics. Hispanic is a very heterogeneous group of patients from different countries, which can also lead to different OS among Hispanic subgroups. Currently, there is scarce literature about disparities in breast cancer outcomes for Hispanic women treated with CDK4/6i.

Our study has certain limitations. First, this is an observational study that is still subject to unmeasured confounding despite a large sample size. Second, a 24-month follow-up is a relatively short period to assess survival differences;

Table 5 Competing risk for breast cancer-specific survival (Fine and Gray model) including all races ($n=5368$)

Characteristic	Univariate			Multivariable		
	sHR	95% CI	*P* values	sHR	95% CI	*P* values
Cohort						
pre-CDK4/6i	Reference			Reference		
post-CDK4/6i		0.81–0.98	0.021	0.89	0.80–0.98	0.015
Age (years)						
≤65	Reference			Reference		
>65	1.55	1.41–1.70	<0.001	1.25	1.16–1.34	<0.001
Marital status						
Unmarried	Reference			Reference		
Married	0.70	0.64–0.77	<0.001	0.81	0.73–0.89	<0.001
Rurality						
Metro	Reference			Reference		
No Metro	1.16	1.01–1.34	0.036	1.22	1.05–1.40	0.008
Grade						
Grade 1	Reference			Reference		
Grade 2	1.26	1.06–1.51	0.011	1.23	1.03–1.47	0.023
Grade 3	1.99	1.67–2.37	<0.001	1.97	1.65–2.36	<0.001
Hormone receptor						
ER (+), PR (+)	Reference			Reference		
ER (+), PR (−)	1.93	1.73–2.16	<0.001	1.84	1.63–2.08	<0.001
ER (−), PR (+)	3.18	2.25–4.51	<0.001	2.93	2.02–4.27	<0.001
Bone met						
No	Reference			Reference		
Yes	1.08	0.96–1.21	0.190	1.24	1.10–1.40	<0.001
Brain met						
No	Reference			Reference		
Yes	2.38	2.01–2.82	<0.001	1.94	1.59–2.37	<0.001
Liver met						
No	Reference			Reference		
Yes	2.11	1.90–2.34	<0.001	2.07	1.85–2.33	<0.001
Lung met						
No	Reference			Reference		
Yes	1.60	1.45–1.77	<0.001	1.32	1.19–1.47	<0.001
Surgery						
No	Reference			Reference		
Yes	0.44	0.39–0.49	<0.001	0.54	0.48–0.61	<0.001
Chemotherapy						
No	Reference			Reference		
Yes	0.61	0.55–0.67	<0.001	0.62	0.56–0.69	<0.001
Radiation						
No	Reference			Reference		
Yes	0.81	0.74–0.90	<0.001	0.94	0.84–1.04	0.230

sHR sub-distribution hazard ratio, *ER* estrogen receptor, *PR* progesterone receptor, *NA* not applicable, *Met* metastasis, + positive, - negative, *CI* confidence interval

however, we used the last update of the SEER database, which contained a decent number of events to allow our planned survival analysis. Future studies with longer follow-up are required to confirm our results. Third, the SEER database does not provide information about treatment with CDK4/6i; therefore, we cannot assess the specific effect of CDK4/6i on survival trends for the entire population or race-stratified groups. Fourth, the SEER database does not provide information about endocrine therapies, which can directly affect our survival in our study population. Fifth,

Table 6 Competing risk for breast cancer-specific survival (Fine and Gray model) by race

Characteristic	Non-Hispanic White ($n=3544$)			Non-Hispanic Black ($n=741$)			Hispanic ($n=612$)		
	sHR	95% CI	*P* values	sHR	95% CI	*P* values	sHR	95% CI	*P* values
Cohort									
pre-CDK4/6i	Reference			Reference			Reference		
post-CDK4/6i	0.84	0.74–0.95	0.005	0.94	0.75–1.19	0.630	0.91	0.67–1.24	0.550
Age (years)									
≤65	Reference			Reference			Reference		
>65	1.31	1.20–1.44	<0.001	1.21	1.01–1.45	0.036	1.39	1.07–1.81	0.013
Marital status									
Unmarried	Reference			Reference			Reference		
Married	0.79	0.70–0.90	<0.001	0.96	0.72–1.27	0.760	0.93	0.69–1.27	0.660
Rurality									
Metro	Reference			Reference			Reference		
No Metro	1.30	1.11–1.52	0.001	0.92	0.61–1.39	0.680	1.02	0.38–2.74	0.970
Grade									
Grade 1	Reference			Reference			Reference		
Grade 2	1.18	0.96–1.45	0.110	1.67	0.93–2.99	0.084	1.05	0.60–1.84	0.860
Grade 3–4	1.81	1.47–2.24	<0.001	3.00	1.69–5.31	<0.001	1.73	0.98–3.07	0.059
Hormone receptor									
ER (+), PR (+)	Reference			Reference			Reference		
ER (+), PR (−)	1.82	1.57–2.12	<0.001	1.55	1.19–2.03	0.001	2.31	1.60–3.33	<0.001
ER (−), PR (+)	3.94	2.46–6.31	<0.001	2.15	0.94–4.89	0.069	4.09	1.68–9.96	0.002
Bone met									
No	Reference			Reference			Reference		
Yes	1.22	1.05–1.41	0.011	1.35	1.01–1.79	0.041	1.23	0.86–1.77	0.260
Brain met									
No	Reference			Reference			Reference		
Yes	1.79	1.39–2.31	<0.001	2.52	1.61–3.93	<0.001	2.18	1.26–3.77	0.005
Liver met									
No	Reference			Reference			Reference		
Yes	2.03	1.76–2.35	<0.001	2.41	1.86–3.13	<0.001	2.13	1.48–3.07	<0.001
Lung met									
No	Reference			Reference			Reference		
Yes	1.31	1.14–1.49	<0.001	1.22	0.96–1.57	0.110	1.39	0.99–1.95	0.058
Surgery									
No	Reference			Reference			Reference		
Yes	0.51	0.44–0.60	<0.001	0.60	0.44–0.81	0.001	0.59	0.42–0.84	0.003
Chemotherapy									
No	Reference			Reference			Reference		
Yes	0.59	0.52–0.68	<0.001	0.56	0.43–0.71	<0.001	0.76	0.55–1.07	0.110
Radiation									
No	Reference			Reference			Reference		
Yes	0.89	0.78–1.02	0.100	1.04	0.81–1.34	0.740	1.01	0.73–1.41	0.940

sHR sub-distribution hazard ratio, *ER* estrogen receptor, *PR* progesterone receptor, *NA* not applicable, *Met* metastasis, + positive, -, negative, *CI* confidence interval

SEER dichotomizes information about chemotherapy (yes or no) but does not provide details about specific chemotherapy regimens or the number of chemotherapy lines patients received, which could influence our survival analysis. Sixth, we were unable to include more socioeconomic variables that could lead to differences in treatments, or access to them, for both cohorts, such as insurance status, household income, social deprivation index, and many other factors.

In conclusion, our study confirms that the OS in patients with HR + /HER2− MBC has improved after CDK4/6i was introduced in 2015. However, this effect is primarily driven by the improved OS in NHW patients, without significant improvement in OS in NHB, Hispanics, or other race patients. Studies with larger sample sizes and longer follow-up are required to confirm our results. Further studies need to assess whether a biological etiology could lead to differences in response to novel therapeutic agents (such as CDK4/6i) in some racial groups or if socioeconomic factors may affect access to these novel therapeutic agents in some racial groups.

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Data availability This study was conducted using matrices obtained from SEER*Stat 8.4.0.1. We used the SEER database research plus the 2021 submission to collect the data. The spreadsheet created for the data analysis is available for the public after a request for the SEER software from the NCI is granted. The selection criteria necessary to obtain the matrix we used for this study are specified in the methods section of the manuscript.

Declarations

Competing interests Alvaro Alvarez, Ana M. Bernal, and Jesus Anampa declare no conflict of interest during the preparation of this manuscript.

Ethical approval This study was approved by the Institutional Board Review (IRB) of Albert Einstein College of Medicine. Due to the retrospective nature of this study, no informed consent was required.

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