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Article

Racial and ethnic disparities in treatment-related heart disease mortality among US breast cancer survivors

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Abstract

Background: Racial and ethnic disparities in heart disease mortality by initial treatment type among breast cancer survivors have not been well described.

Methods: We included 739 557 women diagnosed with first primary invasive breast cancer between 2000 and 2017 (aged 18-84 years, received surgery, survived ≥1 year, followed through 2018) in the Surveillance, Epidemiology, and End Results–18 database. Standardized mortality ratios (SMRs; observed over expected) were calculated by race and ethnicity (non-Hispanic/Latina Asian American, Native Hawaiians, and other Pacific Islanders [AANHPI]; non-Hispanic/Latina Black [Black]; Hispanic/Latina [Latina]; and non-Hispanic/Latina White [White]) and initial treatment (surgery only; chemotherapy with surgery; chemotherapy, radiotherapy, with surgery; and radiotherapy with surgery) compared with the racial- and ethnic-matched general population, and by clinical characteristics. Cumulative heart disease mortality was estimated accounting for competing risks.

Results: SMRs were elevated for Black and Latina women treated with surgery only and chemotherapy with surgery (SMR range = 1.15-1.21) and AANHPI women treated with chemotherapy, radiotherapy, with surgery (SMR = 1.29; 95% confidence interval [CI] = 1.11 to 1.48), whereas SMRs were less than 1 for White women (SMR range = 0.70-0.96). SMRs were especially high for women with advanced (regional or distant) stage among Black women for all treatment (range = 1.15-2.89) and for AANHPI and Latina women treated with chemotherapy with surgery (range = 1.28-3.61). Non-White women diagnosed at younger than age 60 years had higher SMRs, as did Black and AANHPI women diagnosed with estrogen receptor–positive breast cancers. Black women had the highest 10-year cumulative risk of heart disease mortality: aged younger than 60 years (Black: 1.78%, 95% CI = 1.63% to 1.94%) compared with White, AANHPI, and Latina women (<1%) and aged 60 years and older (Black: 7.92%, 95% CI = 7.53% to 8.33%) compared with White, AANHPI, and Latina women (range = 3.90%-6.48%).

Conclusions: Our findings illuminated striking racial and ethnic disparities in heart disease mortality among Black, AANHPI, and Latina breast cancer survivors, especially after initial chemotherapy receipt.

In the United States, advances in breast cancer treatment have improved long-term survival; however, racial and ethnic disparities in mortality persist (1). Non-Hispanic Black women consistently have the lowest 5-year relative breast cancer survival across all stages and are more likely to be diagnosed at later stages than most other racial and ethnic groups (1,2), subsequently impacting treatment decisions and noncancer outcomes, such as heart disease. Breast cancer treatment practices have evolved over time with lower heart disease risks associated with radiotherapy because of increased precision to limit heart exposure and lower doses (3,4). Yet, certain breast cancer treatments such as anthracyclines, a known cardiotoxic chemotherapy, and trastuzumab, a targeted therapy for HER2–positive breast cancers used increasingly starting in the early 2000s (4,5), are still associated with elevated risk of heart disease, which can occur many years following completion of treatment (6,7). Recent studies have characterized higher cardiovascular disease mortality by treatment type for non-Hispanic Black breast cancer survivors compared with non-Hispanic White breast cancer survivors (8-10), but this question has not been assessed for Latina and Asian American, Native Hawaiian, and other Pacific Islander (AANHPI) breast cancer survivors. Because of disparities in breast cancer care and treatment affecting risk of heart disease (2) and heart disease mortality rates varying by race and ethnicity in the general population (11), a comprehensive evaluation of heart disease mortality among US breast cancer survivors by race and ethnicity is warranted. To examine treatment-related heart disease mortality, we assessed the role of initial breast cancer treatment on heart disease mortality among breast cancer survivors compared with mortality rates among their racial and ethnic counterparts in the

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general population using the Surveillance, Epidemiology, End Results (SEER) 18 Registries.

Methods

Study population

We included 739 557 women aged 18-84 years diagnosed with first primary invasive breast cancer between 2000 and 2017 (survived ≥1 year and followed through 2018) and treated with initial surgery within the SEER-18 database. The SEER-18 database covers 18 registries throughout the United States, represents approximately 23.6% to 62.4% of the population by race and ethnicity (Supplementary Table 1, available online), and leverages cancer registry data to characterize cancer incidence, treatment, and survival (12). Causes of death were ascertained using death certificates obtained from the US Mortality data, National Center for Health Statistics. Follow-up started 12 months after breast cancer diagnosis (to account for cancer treatment completion) and continued until date of death, last contact, or study end (December 31, 2018), whichever occurred first (Supplementary Figure 1, available online).

Outcome

The outcome of interest was heart disease mortality, a clinically relevant outcome for the selected treatments, defined using International Classification of Diseases–10 codes: I00-I09, I11, I13, I20-I51.

Exposures

Our primary exposures were 1) race and ethnicity, originally abstracted from medical records or death certificates, and categorized as non-Hispanic/Latina AANHPI, non-Hispanic/Latina Black (Black), Hispanic/Latina (Latina), and non-Hispanic/Latina White (White), and 2) first course of breast cancer treatment: surgery only (no or unknown chemotherapy and radiotherapy); chemotherapy with surgery (no or unknown radiotherapy); chemotherapy, radiotherapy, with surgery; and radiotherapy with surgery (no/unknown chemotherapy).

Statistical analyses

We estimated standardized mortality ratios (SMRs) for heart disease with exact Poisson-based 95% confidence intervals (CIs) in the multiple primary–SMRs session within SEER*Stat (version 8.3.9.2) (12). SMRs were calculated as the observed number of heart disease deaths among breast cancer patients divided by the expected number of heart disease deaths in the race- and ethnic-matched general female US population. Expected mortality rates were from the US Mortality data accounting for attained age (5-year groups) and calendar period (5-year groups). We assessed SMRs by race and ethnicity and initial treatment type and according to stage (localized, regional, distant), age at breast cancer diagnosis (18-59 years, 60-84 years), estrogen receptor (ER) status (positive, negative), and time since breast cancer diagnosis (latency: 1-4 years, 5-9 years, ≥10 years). SMR results with less than 10 events were suppressed.

To assess heterogeneity by race and ethnicity, we fit multivariable Poisson regression models (outcome: observed heart disease deaths; offset: log-transformed expected events) and adjusted for *a priori* selected covariates: year of diagnosis (2000-2004, 2005-2009, 2010-2017), stage (localized, regional or distant or unknown), and age at diagnosis (18-49, 50-54, 55-59, 60-64, 65-69, 70-74, 75-79, 80-84 years). Likelihood ratio tests assessed racial and ethnic heterogeneity in SMRs by initial treatment receipt.

To quantify the clinical burden, we estimated cumulative heart disease mortality by race and ethnicity and according to age at diagnosis and initial treatment receipt using competing risk methods accounting for nonheart disease deaths, using the stcompet package in Stata (13). Analyses were completed using Stata version 17 (StataCorp, College Station, TX, USA). All tests were 2-sided with statistical significance set at a *P* value less than .05, without multiple comparison corrections as the analyses were exploratory. Because of the use of deidentified and publicly available data, institutional review board approval and informed consent were not required.

Results

Descriptive characteristics

Among 739 557 breast cancer survivors, 8.2% were AANHPI, 10.3% were Black, 10.6% were Latina, and 70.9% were White breast cancer survivors. Median follow-up time was longest for White women (6.8 years, interquartile range [IQR] = 3.13-11.33 years) compared with AANHPI (5.96 years, IQR = 2.63-10.46 years), Black (5.46 years, IQR = 2.29-9.87 years), and Latina women (5.46 years, IQR = 2.34-9.87 years). There were 22 063 heart disease deaths of which 856 (3.9%) occurred among AANHPI, 2575 (11.7%) among Black, 1360 (6.2%) among Latina, and 17 272 (78.3%) among White women (Table 1). Patterns of treatment varied by race and ethnicity and stage at diagnosis (Supplementary Table 2, available online). Among women with localized breast cancer, AANHPI, Black, and Latina women were more likely to receive chemotherapy with surgery (15.3%-17.0%) or chemotherapy, radiotherapy, with surgery (15.8%-22.4%) compared with White women (11.2% and 14.9%, respectively). Receipt of chemotherapy with and without radiotherapy was also higher among non-White women at advanced stages. Overall deaths by race and ethnicity and year of breast cancer diagnosis are reported in Supplementary Table 3 (available online).

Overall heart disease SMRs and by breast cancer stage

SMRs for heart disease mortality were statistically significantly elevated for Black (SMR = 1.07, 95% CI = 1.03 to 1.11) and Latina (SMR = 1.09, 95% CI = 1.03 to 1.15) women, nonsignificantly elevated for AANHPI (SMR = 1.05, 95% CI = 0.98 to 1.12) women, but significantly decreased for White (SMR = 0.82, 95% CI = 0.81 to 0.83) breast cancer survivors relative to their racial and ethnic counterparts in the general population (Figure 1; Supplementary Table 4, available online). By initial treatment receipt, elevated heart disease SMRs were observed for Black and Latina women treated with surgery only and chemotherapy with surgery and AANHPI women treated with chemotherapy, radiotherapy, with surgery (SMRs range = 1.15-1.29), but heart disease SMRs were statistically significantly decreased for White women for all treatment types (SMRs range = 0.70-0.96; $P_{heterogeneity} < .0001$). Elevated heart disease SMRs were driven by higher SMRs after advanced (regional or distant) stage breast cancers. Black women diagnosed with regional or distant cancers had elevated heart disease mortality for all treatment types (SMRs range = 1.15-2.89). For AANHPI and Latina breast cancer survivors treated with chemotherapy with surgery, the risk of heart disease mortality was also elevated for advanced stages (for regional and distant stage, SMRs range = 1.28-3.61). In addition, among AANHPI women treated with chemotherapy, radiotherapy, with surgery, heart disease SMRs were elevated for localized (SMR = 1.39, 95%

Table 1. Descriptive characteristics by race and ethnicity among 739 557 women diagnosed with first primary breast cancer in 18 SEER registries from 2000 to 2017 and followed through 2018

Characteristics	Asian American, Native Hawaiian, and other Pacific Islanders (n = 60 583) No. (%)	Black (n = 76 244) No. (%)	Latina (n = 78 407) No. (%)	White (n = 524 323) No. (%)
Overall	60 583 (100.00)	76 244 (100.00)	78 407 (100.00)	524 323 (100.00)
Treatment				
Surgery only	17 110 (28.24)	18 872 (24.75)	20 882 (26.63)	146 849 (28.01)
Chemotherapy with surgery	11 891 (19.63)	16 185 (21.23)	17 595 (22.44)	81 813 (15.60)
Chemotherapy, radiotherapy, with surgery	16 113 (26.60)	25 165 (33.01)	22 611 (28.84)	130 262 (24.84)
Radiotherapy with surgery	15 469 (25.53)	16 022 (21.01)	17 319 (22.09)	165 399 (31.55)
Stage				
Localized	40 126 (66.23)	44 554 (58.44)	46 451 (59.24)	352 434 (67.22)
Regional	19 087 (31.51)	29 247 (38.36)	29 716 (37.90)	160 776 (30.66)
Distant	973 (1.61)	1959 (2.57)	1541 (1.97)	8443 (1.61)
Unknown or missing	397 (0.66)	484 (0.63)	699 (0.89)	2670 (0.51)
Age at breast cancer diagnosis, y				
18-59	36 878 (60.87)	45 065 (59.11)	49 704 (63.39)	249 501 (47.59)
60-84	23 705 (39.13)	31 179 (40.89)	28 703 (36.61)	274 822 (52.41)
ER status				
Positive	47 082 (77.71)	48 626 (63.78)	57 059 (72.77)	409 795 (78.16)
Negative	10 354 (17.09)	22 454 (29.45)	15 777 (20.12)	82 209 (15.68)
Unknown or missing	3147 (5.19)	5164 (6.77)	5571 (7.11)	32 319 (6.16)
PR status				
Positive	40 659 (67.11)	40 139 (52.65)	48 784 (62.22)	353 642 (67.45)
Negative	16 030 (26.46)	30 208 (39.62)	23 014 (29.35)	133 106 (25.39)
Unknown or missing	3894 (6.43)	5897 (7.73)	6609 (8.43)	37 545 (7.16)
HER 2 status[a]				
Positive	5636 (17.62)	6173 (16.41)	6917 (16.84)	31 042 (13.39)
Negative	24 367 (76.16)	29 243 (77.74)	31 225 (76.01)	188 491 (81.34)
Unknown or missing	1991 (6.22)	2200 (5.85)	2936 (7.15)	12 213 (5.27)
Breast cancer subtype[a]				
HR+/HER2+ (luminal B)	3769 (11.78)	4169 (11.08)	4788 (11.66)	22 467 (9.69)
HR−/HER2+ (HER2 enriched)	1851 (5.79)	1988 (5.28)	2107 (5.13)	8493 (3.66)
HR+/HER2− (luminal A)	21 827 (68.22)	21 903 (58.23)	26 612 (64.78)	167 548 (72.30)
HR−/HER2− (triple negative)	2514 (7.86)	7300 (19.41)	4559 (11.10)	20 693 (8.93)
Unknown or missing subtype	2033 (6.35)	2256 (6.00)	3012 (7.33)	12 545 (5.41)
Calendar year of diagnosis				
2000-2004	12 960 (21.39)	18 395 (24.13)	16 774 (21.39)	149 260 (28.47)
2005-2009	15 629 (25.80)	20 233 (26.54)	20 555 (26.22)	143 317 (27.33)
2010-2017	31 994 (52.81)	37 616 (49.34)	41 078 (52.39)	231 746 (44.20)
Attained age, y[b]				
Younger than 50	18 223 (30.08)	21 316 (27.96)	25 974 (33.13)	101 591 (19.38)
50-69	41 432 (68.39)	51 314 (67.30)	51 817 (66.09)	340 209 (64.89)
70-84	20 219 (33.37)	25 839 (33.89)	24 166 (30.82)	251 234 (47.92)
85 and older	3730 (6.16)	4462 (5.85)	4192 (5.35)	59 489 (11.35)
Latency years since diagnosis[b]				
1-4 y	60 583 (100.00)	76 244 (100.00)	78 407 (100.00)	524 323 (100.00)
5-9 y	38 872 (64.16)	46 158 (60.54)	47 778 (60.94)	359 465 (68.56)
≥10 y	19 683 (32.49)	22 230 (29.16)	22 899 (29.21)	194 000 (37.00)

[a] Restricted to breast cancer patients diagnosed from 2010 onward. CI = confidence interval; ER = estrogen receptor; HR = hormone receptor; PR = progesterone receptor; SEER = Surveillance, Epidemiology, and End Results.
[b] No. indicates number entering interval.

CI = 1.04 to 1.81) and regional stage cancers (SMR = 1.62, 95% CI = 1.30 to 1.99).

Heart disease SMRs by age at breast cancer diagnosis

SMRs for heart disease mortality were higher and the disparities were wider for younger breast cancer survivors (aged younger than 60 years) (Figure 2; Supplementary Table 5, available online), with markedly elevated heart disease SMRs for surgery only among Black (SMR = 1.46, 95% CI = 1.25 to 1.69), AANHPI (SMR = 1.58, 95% CI = 1.10 to 2.19), and Latina (SMR = 1.62, 95% CI = 1.27 to 2.05) women. After receipt of chemotherapy with surgery, younger Black women had 38% (SMR = 1.38, 95% CI = 1.18 to 1.60) higher risk of heart disease mortality, and younger AANHPI women had a 57% (SMR = 1.57, 95% CI = 1.06 to 2.24) higher risk compared with their racial- and ethnic-matched general population, and for younger AANHPI women treated with chemotherapy, radiotherapy, with surgery, the risk was 2.2-fold (SMR = 2.20, 95% CI = 1.68 to 2.84). In older women (aged 60 years and older), Black and Latina women treated with surgery only and chemotherapy with surgery also had elevated heart disease mortality (SMRs range = 1.16-1.21).

Heart disease SMRs by ER status

Statistically significantly elevated heart disease SMRs were observed for Black women diagnosed with ER-positive breast

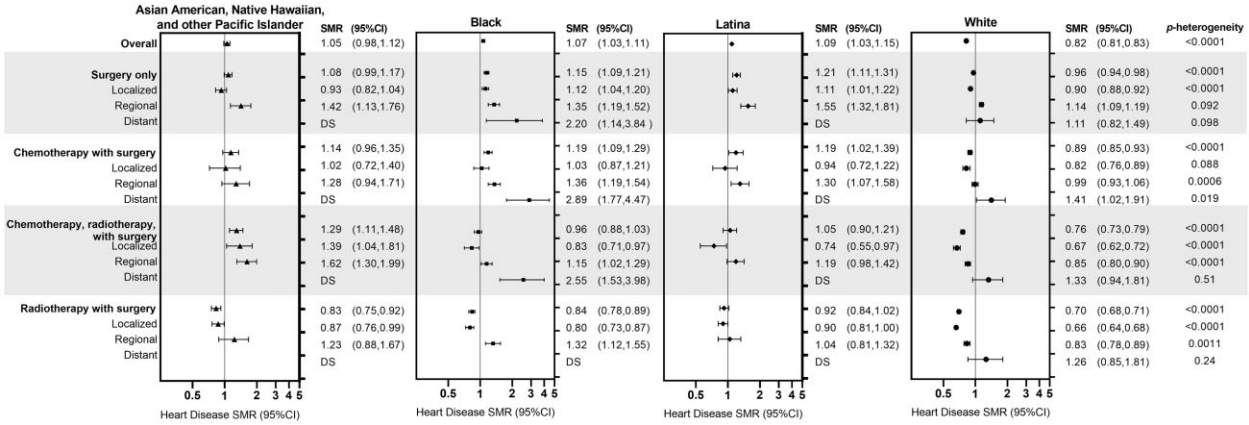

Figure 1. Standardized mortality ratios (SMRs) and 95% confidence intervals (CIs) for heart disease by race and ethnicity according to initial treatment and stage among 739 557 women diagnosed with first primary breast cancer in 18 Surveillance, Epidemiology, and End Results registries from 2000 to 2017 and followed through 2018. DS = data suppressed; indicates unreported SMR and 95% confidence interval because of less than 10 events. $P_{heterogeneity}$ calculated based on likelihood ratio tests comparing Poisson regression models (outcome = observed events, offset = log-transformed expected events) by race and ethnicity, adjusted for age and year of breast cancer diagnosis. SMRs for unknown stage are not reported (AANHPI: n = 397, 0.66%; Black: n = 484, 0.63%; Latina: n = 699, 0.89%; White: n = 2670, 0.51%). Observed and expected events reported in Supplementary Table 4 (available online). AANHPI = Asian American, Native Hawaiian, and other Pacific Islander.

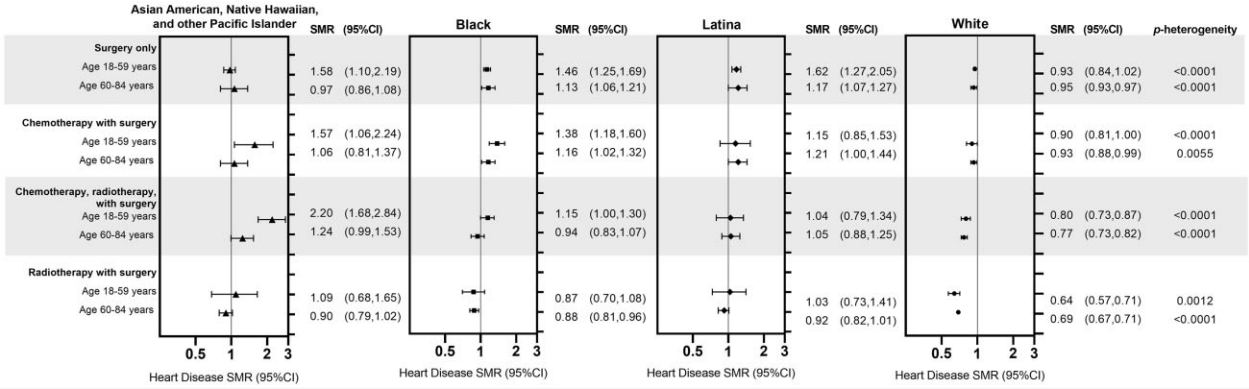

Figure 2. Standardized mortality ratios (SMRs) and 95% confidence intervals (CIs) for heart disease by race and ethnicity according to initial treatment and age at breast cancer diagnosis among 739 557 women diagnosed with first primary breast cancer in 18 Surveillance, Epidemiology, and End Results registries from 2000 to 2017 and followed through 2018. $P_{heterogeneity}$ calculated based on likelihood ratio tests comparing Poisson regression models (outcome = observed events, offset = log-transformed expected events) by race and ethnicity, adjusted for age, year of breast cancer diagnosis, and stage. Observed and expected events reported in Supplementary Table 5 (available online).

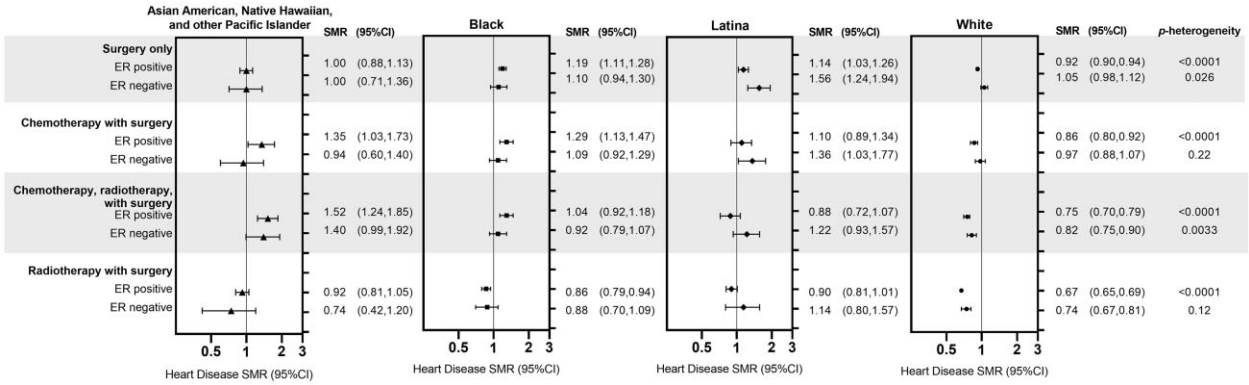

Figure 3. Standardized mortality ratios (SMRs) and 95% confidence intervals (CIs) for heart disease by race and ethnicity according to initial treatment and estrogen receptor (ER) status among 739 557 women diagnosed with first primary breast cancer in 18 Surveillance, Epidemiology, and End Results registries from 2000 to 2017 and followed through 2018. $P_{heterogeneity}$ calculated based on likelihood ratio tests comparing Poisson regression models (outcome = observed events, offset = log-transformed expected events) by race and ethnicity, adjusted for age, year of breast cancer diagnosis, and stage. SMRs for unknown or missing ER status are not reported (AANHPI: n = 3147, 5.19%; Black: n = 5164, 6.77%; Latina: n = 5571, 7.11%; White: n = 32 319, 6.16%). Observed and expected events reported in Supplementary Table 6 (available online). AANHPI = Asian American, Native Hawaiian, and other Pacific Islander.

cancers treated with surgery only and chemotherapy with surgery (SMR range = 1.19-1.29) but not for ER-negative cancers (Figure 3; Supplementary Table 6, available online) compared with their racial- and ethnic-matched general population. This pattern by ER status was similar for AANHPI women, with elevated heart disease mortality for ER-positive breast cancer treated with chemotherapy with surgery (SMR = 1.35, 95% CI = 1.03 to 1.73) and chemotherapy, radiotherapy, with surgery (SMR = 1.52, 95% CI = 1.24 to 1.85). For Latina women with ER-negative cancers, elevated heart disease mortality was observed after receipt of surgery only (SMR = 1.56, 95% CI = 1.24 to 1.94) and chemotherapy, radiotherapy, with surgery (SMR = 1.36, 95% CI = 1.03 to 1.77).

Heart disease SMRs by latency period

With respect to latency, SMRs increased modestly after 5-9 years and were highest 10 or more years post breast cancer diagnosis (Figure 4; Supplementary Table 7, available online). Notably, heart disease mortality was elevated after 5 years for Black women who received chemotherapy with surgery (SMR range = 1.29-1.31), after 10 years for AANHPI and Latina women who received chemotherapy with surgery (SMR range = 1.37-1.50) and chemotherapy, radiotherapy, with surgery (SMR range = 1.53-1.90), and after 10 years for AANHPI women who received radiotherapy with surgery (SMR = 1.27, 95% CI = 1.04 to 1.53) compared with their racial- and ethnic-matched general population.

Cumulative heart disease mortality by age at diagnosis and initial treatment receipt

Black breast cancer survivors diagnosed at younger than age 60 years had the highest 10-year cumulative mortality (CM) (CM = 1.78%, 95% CI = 1.63% to 1.94%) compared with White (CM = 0.62%, 95% CI = 0.59% to 0.66%), AANHPI (CM = 0.49%, 95% CI = 0.40% to 0.59%), and Latina (0.54%, 95% CI = 0.46% to 0.63%) women (Table 2). Similar disparities were evident among Black women diagnosed at age 60 years or older (CM = 7.92%, 95% CI = 7.53% to 8.33%) compared with White (CM = 6.48%, 95% CI = 6.36% to 6.60%), AANHPI (3.90%, 95% CI = 3.56% to 4.26%), and Latina (CM = 5.29%, 95% CI = 4.94% to 5.66%) women. By treatment receipt, women treated with surgery only had the highest CM across all race and ethnicity groups after age 60 years.

Discussion

This large population-based cohort of US breast cancer survivors provided the first comprehensive evaluation of racial and ethnic disparities in heart disease mortality using SMRs to account for the race- and ethnic-matched general population mortality rates. First, we observed that Black and Latina breast cancer survivors had higher heart disease mortality rates than the Black and Latina general population. Second, we detected clear racial and ethnic disparities and statistically significant heterogeneity in heart disease mortality rates for nearly all treatment groups, but especially after receipt of chemotherapy among Black, Latina, and AANHPI women, persisting across stage, age, ER status, and latency.

To our knowledge, no previous study has examined racial and ethnic heterogeneity in heart disease mortality by treatment receipt among a diverse group of breast cancer survivors and specifically for AANHPI and Latina breast cancer survivors. Further, this is the first study to use SMRs to describe disparities in heart disease mortality among Black breast cancer survivors, accounting for the underlying heart disease mortality rates in the Black general population. Three previous studies have characterized disparities in cardiovascular disease mortality among Black breast cancer survivors (8,9,14), and 1 study reported lower cardiovascular disease mortality among disaggregated AANHPI ethnic groups compared with White breast cancer survivors (15). One study examined cardiovascular disease incidence among Latina breast cancer survivors (16), but none focused on mortality. We expanded on these previous findings by examining the role of treatment and focusing on death from heart disease, as it may provide insight into potential synergistic adverse effects of multimodality treatments for breast cancer (eg, chemotherapy and radiotherapy) and risk factors for heart disease.

Our study findings of statistically significant racial and ethnic disparities in heart disease mortality by receipt of initial cancer treatment could be related to disparities in access to care and treatment practices for both the original breast cancer diagnosis and subsequent heart disease. Non-White women are more likely to have disparities in access to health care including longer delays between abnormal screening and follow-up (17-19), more likely to experience health-care system failures (defined as treatment recommended and not refused by patient but did not ensue) (20), less likely to receive guideline concordant care or receive care at lower-quality hospitals (21,22), and have unequal

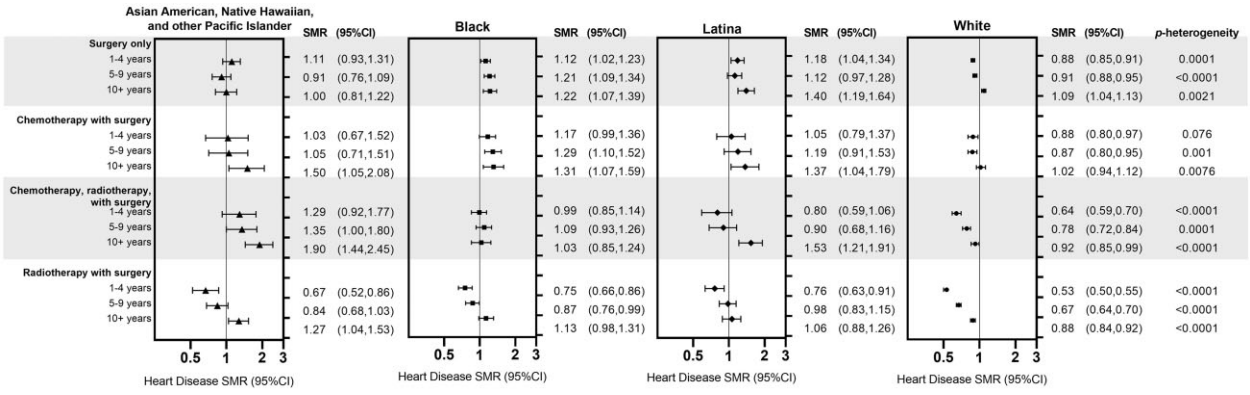

Figure 4. Standardized mortality ratios (SMRs) and 95% confidence intervals (CIs) for heart disease by race and ethnicity according to initial treatment and time since breast cancer diagnosis (latency) among 739 557 women diagnosed with first primary breast cancer in 18 Surveillance, Epidemiology, and End Results registries from 2000 to 2017 and followed through 2018. $P_{heterogeneity}$ calculated based on likelihood ratio tests comparing nested Poisson regression models (outcome = observed events, offset = log-transformed expected events) by race and ethnicity, adjusted for age at breast cancer diagnosis and stage. Observed and expected events reported in Supplementary Table 7 (available online).

Table 2. Cumulative mortality (CM) and 95% confidence interval (CI) of heart disease by race and ethnicity and initial treatment receipt, according to age at breast cancer diagnosis[a]

Race and ethnicity	Events	No.	5-year CM (95% CI)	10-year CM (95% CI)
Asian American, Native Hawaiian, and other Pacific Islander				
Age 18-59 y	146	36 878	0.18% (0.14% to 0.23%)	0.49% (0.40% to 0.59%)
Surgery only	35	8424	0.19% (0.11% to 0.32%)	0.49% (0.31% to 0.73%)
Chemotherapy with surgery	30	8772	0.18% (0.10% to 0.31%)	0.35% (0.22% to 0.54%)
Chemotherapy, radiotherapy, with surgery	59	12 332	0.18% (0.12% to 0.28%)	0.62% (0.43% to 0.78%)
Radiotherapy with surgery	22	7350	0.18% (0.09% to 0.33%)	0.41% (0.24% to 0.66%)
Age 60-84 y	710	23 705	1.51% (1.34% to 1.70%)	3.90% (3.56% to 4.26%)
Surgery only	319	8686	2.16% (1.83% to 2.53%)	4.84% (4.26% to 5.47%)
Chemotherapy with surgery	60	3119	0.68% (0.41% to 1.07%)	2.76% (2.00% to 3.72%)
Chemotherapy, radiotherapy, with surgery	86	3781	1.11% (0.77% to 1.56%)	2.65% (1.99% to 3.46%)
Radiotherapy with surgery	245	8119	1.31% (1.04% to 1.64%)	3.89% (3.30% to 4.54%)
Black				
Age 18-59 y	676	46 065	0.80% (0.71% to 0.89%)	1.78% (1.63% to 1.94%)
Surgery only	179	8486	1.09% (0.87% to 1.35%)	2.39% (2.02% to 2.82%)
Chemotherapy with surgery	177	11 497	0.72% (0.57% to 0.91%)	1.89% (1.59% to 2.22%)
Chemotherapy, radiotherapy, with surgery	233	18 405	0.71% (0.59% to 0.86%)	1.55% (1.33% to 1.78%)
Radiotherapy with surgery	87	6677	0.69% (0.49% to 0.94%)	1.32% (1.00% to 1.72%)
Age 60-84 y	1899	31 179	3.58% (3.36% to 3.82%)	7.92% (7.53% to 8.33%)
Surgery only	882	10 386	5.11% (4.66% to 5.59%)	10.37% (9.65% to 11.12%)
Chemotherapy with surgery	236	4688	3.02% (2.51% to 3.60%)	6.23% (5.37% to 7.18%)
Chemotherapy, radiotherapy, with surgery	241	6760	2.07% (1.70% to 2.48%)	5.14% (4.43% to 5.92%)
Radiotherapy with surgery	540	9345	3.02% (2.64% to 3.43%)	7.68% (6.96% to 8.46%)
Latina				
Age 18-59 y	215	49 704	0.19% (0.15% to 0.24%)	0.54% (0.46% to 0.63%)
Surgery only	71	10 716	0.25% (0.16% to 0.38%)	0.85% (0.64% to 1.13%)
Chemotherapy with surgery	49	13 515	0.16% (0.10% to 0.26%)	0.48% (0.34% to 0.67%)
Chemotherapy, radiotherapy, with surgery	57	17 562	0.18% (0.12% to 0.26%)	0.34% (0.24% to 0.47%)
Radiotherapy with surgery	38	7911	0.25% (0.14% to 0.41%)	0.72% (0.49% to 1.03%)
Age 60-84 y	1145	28 703	2.25% (2.06% to 2.45%)	5.29% (4.94% to 5.66%)
Surgery only	539	10 166	3.36% (2.98% to 3.77%)	7.15% (6.49% to 7.85%)
Chemotherapy with surgery	123	4080	1.56% (1.18% to 2.04%)	3.89% (3.12% to 4.78%)
Chemotherapy, radiotherapy, with surgery	125	5049	0.99% (0.72% to 1.35%)	3.15% (2.50% to 3.91%)
Radiotherapy with surgery	358	9408	1.98% (1.67% to 2.33%)	5.01% (4.41% to 5.66%)
White				
Age 18-59 y	1609	249 501	0.27% (0.25% to 0.29%)	0.62% (0.59% to 0.66%)
Surgery only	430	53 564	0.33% (0.28% to 0.39%)	0.77% (0.68% to 0.86%)
Chemotherapy with surgery	336	53 983	0.26% (0.22% to 0.31%)	0.60% (0.53% to 0.68%)
Chemotherapy, radiotherapy, with surgery	511	87 782	0.25% (0.22% to 0.29%)	0.55% (0.49% to 0.61%)
Radiotherapy with surgery	332	56 172	0.23% (0.19% to 0.27%)	0.60% (0.53% to 0.69%)
Age 60-84 y	15 663	274 822	2.66% (2.59% to 2.72%)	6.48% (6.36% to 6.60%)
Surgery only	7706	93 285	4.18% (4.04% to 4.32%)	9.10% (8.87% to 9.32%)
Chemotherapy with surgery	1095	27 830	1.79% (1.63% to 1.97%)	4.42% (4.11% to 4.73%)
Chemotherapy, radiotherapy, with surgery	1327	44 480	1.23% (1.12% to 1.35%)	3.40% (3.18% to 3.63%)
Radiotherapy with surgery	5535	109 227	2.10% (2.00% to 2.20%)	5.80% (5.62% to 5.99%)

[a] CM calculated accounting for non-heart disease deaths.

access to high-quality and timely health care and treatment (23-25). These factors may contribute to advanced (or delayed) breast cancer diagnoses and the higher observed proportions of chemotherapy (with and without radiotherapy) among Black, AANHPI, and Latina women in this study, potentially resulting in increased use of cardiotoxic cancer treatment (eg, anthracycline-based chemotherapy or trastuzumab) (4,5,26,27). Our findings could also suggest that differential confounding by indication by race and ethnicity could be present, whereas treatment receipt may vary based on race and ethnicity because of clinical indications or contraindications, warranting further investigation. Additionally, the intersection of cancer and heart disease is a complex clinical specialty (28), and elevated heart disease mortality could be in part related to lack of recommended cardiovascular screening, surveillance after receipt of cardiotoxic treatment, and insufficient cardiovascular treatment and management for cancer treatment–related heart disease (4,5,26). Elevated heart disease mortality risks for ER-positive breast cancer were unexpected, and this finding warrants further investigation into individualized risk assessment and monitoring during endocrine therapy and examining potential overtreatment of cardiotoxic chemotherapy for ER-positive breast cancers among Black and AANHPI women. Providers might be more vigilant with treatment decision making for ER-negative cancers. Because breast cancer is a screen-detected cancer, lower risk of heart disease mortality among White breast cancer survivors could be related to the healthy screening bias, especially for White women with ER-positive breast cancers (29). A recent SEER study demonstrated higher cardiovascular disease mortality among breast cancer survivors who lived in lower socioeconomic or rural counties compared with those in higher socioeconomic and more urban counties, indicating the importance of access to care (30). Further, White women are more likely to receive a biopsy after abnormal breast screening compared with non-White women, and delays are longest among Black women (19). These delays could potentially result in more aggressive treatment and late effects such as heart disease. Among AANHPI breast cancer survivors, our findings of elevated heart disease

mortality when treated with chemotherapy were novel and attributable to using AANHPI in the general population as the reference. Using White women as the reference group, as previous studies have done (15), would have masked treatment-related disparities.

We also observed heterogeneity by race and ethnicity among women treated with radiotherapy with surgery, which was elevated for Black women with regional stage breast cancer and AANHPI women after 10 years. Risk of heart disease mortality after radiotherapy increases 5-30 years after exposure and rises with higher dose, especially for advanced disease (4,31,32). We previously reported declining trends in heart disease mortality among breast cancer survivors after radiotherapy (3); however, inequities in treatment access, such as advances and modern techniques in radiotherapy treatment (eg, deep inspiratory breath hold, lateral decubitus positioning, or proton therapy) (33) to reduce damage to the heart, could contribute to the observed racial and ethnic disparities in heart disease mortality. Another interesting finding was elevated heart disease mortality risk among women who received surgery only for certain characteristics. Because surgery is not a risk factor for heart disease, elevated risk among women treated with surgery only could be related to underascertainment of treatment in SEER especially for advanced stages or preexisting heart disease that would contraindicate use of certain cardiotoxic chemotherapy and radiotherapy. Unfortunately, data on heart disease prevalence and risk factors are not available in SEER and should be considered in future studies.

Clinical implications from this study include the importance of culturally appropriate care for education, prevention, and monitoring of heart disease and its risk factors among breast cancer survivors, especially for Black, AANHPI, and Latina women diagnosed at younger ages and more advanced stages. Language barriers and health literacy should also be considered for non-English speaking and lower socioeconomic status patients undergoing complex cancer and cardiac care (34,35). Additionally, future studies are needed to examine nonfatal heart disease outcomes, preexisting comorbid conditions and risk factors, treatment patterns, and the impact of socioeconomic status among diverse breast cancer survivors to understand barriers to health care, disparities in treatment receipt, and potential confounding by indication. Lastly, it is crucial to recognize the heterogeneity in heart disease and cancer incidence and risk factor prevalence (36) among Latina groups [who represent different countries, cultures, and immigration experiences (37)] and AANHPI individuals [who comprise an ethnically diverse group representing more than 30 different countries and more than 100 languages (38,39), with heterogenous and rising ER-positive breast cancer incidence (40)].

A major strength of this study is the robust, large population-based cohort of diverse breast cancer survivors and the comparison to their racial and ethnic counterparts in the general population instead of the traditional use of White patients as a reference group, which masks disparities in heart disease mortality patterns between White women and other racial and ethnic groups. Further, underlying differences by race and ethnicity (eg, cardiovascular risk factors) are indirectly accounted for by using this SMR approach. Although White patients were the largest group representing more than 70% of the cohort, this cohort included a large number of AANHPI, Black, and Latina breast cancer survivors with proportions consistent with the US demographics. Further, SEER is considered generalizable to the US population with coverage by race and ethnicity ranging from 23.6% to 62.4% (41). Limitations of this study are related to the registry-based design and include potential misclassification of the cause of death on death certificates [under- or overreporting of heart disease, which mostly likely would have biased the SMRs toward the null (42)] but would unlikely differ by race and ethnicity (43), cancer treatment data limitations (ie, first course of treatment only, lack of detailed chemotherapy agents, and known underascertainment of radiotherapy and chemotherapy), and lack of prevalent risk factor data (eg, history of hypertension, smoking, obesity, dyslipidemia, diabetes) (44). Importantly, for treatment in SEER, sensitivity is considered moderate (chemotherapy: 69%; radiotherapy: 80%), and positive predictive value is considered high (chemotherapy: 91%; radiotherapy: 98%) (45). Additionally, the lack of specific chemotherapy agents (eg, anthracyclines) could underestimate the risk of heart disease as some agents are not cardiotoxic. Longer follow-up is required to evaluate whether there are racial and ethnic disparities related to radiotherapy given the long latency period after treatment (4,31,32). We were unable to present data on heart disease mortality among American Indian and Alaska Native women because of small sample sizes. Another limitation of SEER is the inability to compare rates in disaggregated data for AANHPI and Latina patients with their ethnic-matched general population. Regardless, we provided an initial account of heart disease mortality for AANHPI and Latina breast cancer survivors, which can serve as a basis for future research.

This study comprehensively evaluated heart disease mortality among a large racially and ethnically diverse cohort of breast cancer survivors and illuminated striking disparities among Black, Latina, and AANHPI breast cancer survivors. Inequities during cancer care and subsequent heart disease may contribute to persistent differences and heterogeneity observed by race and ethnicity across most treatment types and clinical characteristics. Future studies are needed to examine racial and ethnic disparities in heart disease mortality by detailed treatment, lifestyle risk factors, and interventions for diverse breast cancer survivors. These novel findings establish that racial and ethnic disparities persist throughout breast cancer survivorship and within heart disease mortality outcomes.

Data availability

All data used in this work is publicly available from the US Surveillance, Epidemiology, and End Results (SEER) Program of the National Cancer Institute. Specifically, this work used data from the SEER-18 registries database. These data can be downloaded using the software SEER*Stat, which may be downloaded from https://seer.cancer.gov/seerstat/.

Author contributions

Jacqueline B Vo, PhD, RN, MPH (Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Writing – original draft); Cody Ramin, PhD, ScM (Conceptualization; Formal analysis; Methodology; Writing – review & editing); Wayne R Lawrence, DrPh (Writing – review & editing); Ana Barac, MD, PhD (Writing – review & editing); Katherine L Ho, MPH (Writing – review & editing); Jongeun Rhee, ScD (Writing – review & editing); Lene HS Veiga, PhD (Methodology; Writing – review & editing); and Amy Berrington de González, DPhil (Conceptualization; Formal analysis; Methodology; Supervision; Writing – review & editing).

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Conflicts of interest

The authors declare no conflicts of interest.

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JB Vo had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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