Race/Ethnicity, Delay of Adjuvant Chemotherapy Initiation Following Breast Cancer Surgery and Associated Patient Survival: An Analysis of the United States National Cancer Database 2004-2016

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Abstract

Introduction: The relationship between survival and time to the start of adjuvant chemotherapy (AC) among breast cancer patients is unclear. Most breast cancer patients start adjuvant chemotherapy within a few weeks after surgery, but it is still unclear whether a delay in the initiation of chemotherapy will lead to adverse outcomes.

Methods: Women diagnosed between 2004 and 2016 with invasive breast cancer (stages I–III) and treated with surgery and adjuvant chemotherapy were selected from the National Cancer Database (n = 443,100). We evaluated factors associated with prolonged time to start adjuvant chemotherapy (≥60, ≥90, and ≥120 days after surgical resection) using multivariable log binomial models to estimate risk ratios (RRs) and 95% CIs. Cox proportional hazards model was used to investigate the effect of delay on survival.

Results: The average time to adjuvant chemotherapy was 47.93 days (±29.17 days). Non-Hispanic African American patients had higher risk of 60-day delay (RR, 1.41; 95% CI, 1.38 to 1.43), 90-day delay (RR, 1.55; 95% CI, 1.50 to 1.60), and 120-day delay (RR, 1.69; 95% CI, 1.61 to 1.78) compared with non-Hispanic white patients. Early initiation of chemotherapy, less than 1 month (RR, 0.893; 95% CI, 0.86 to 0.92), 1-2 month (RR, 0.80; 95% CI, 0.77 to 0.82), and 2-3 month (RR, 0.87; 95% CI, 0.84 to 0.90); was associated with decreased overall mortality. Non-Hispanic African Americans (RR, 1.16; 95% CI, 1.13 to 1.19) were associated with increased overall mortality compared to non-Hispanic whites.

Conclusion: Black breast cancer patients experience clinically relevant delays in the initiation of adjuvant chemotherapy more often than white patients, which may in part explain the increased mortality observed among black patients. Efforts should be made to reduce the time to surgery when possible to enhance overall survival.

Introduction

Breast cancer is among the highest mortality forms of cancer and is the most common form among women [1]. After lung cancer, breast cancer is the second leading cause of death among women in the United States [2]. The prevalence of breast cancer is increasing due to the population's growing exposure to a range of risk factors, including changes in the environment, healthcare access, and patient lifestyle. The lifetime risk of developing breast cancer is currently 12.4% in women [3, 4, 5] In 2018 over 2 million new cases were diagnosed, representing 23% of all cancers. It is now the most common cancer in developed and developing regions, though incidence varies widely with race and ethnicity [6, 7].

There is a wide array of treatment options for breast cancer. The preferred approach largely depends on the severity, malignancy, and other properties of the cancer given the disease's multifactorial nature. As with many cancers, the most common approaches are surgery, radiation therapy, chemotherapy, hormone therapy, and immunotherapy. Breast cancer consists of three subtypes based on estrogen/progesterone receptor expression and ERBB2 gene amplification, each with unique risk profiles and treatment approaches. For non-metastatic breast cancers, tumor resection (lumpectomy), followed by mastectomy and axillary lymph node surgery are coupled with systemic neoadjuvant or adjuvant therapies (preoperative and postoperative respectively) [8]. Nearly 90% of women will have an early-stage form of the disease, which presents with particularly high relapse risk. This finding is based on estimates from Mariotto et al. of roughly 150,000 women in the US living with metastatic breast cancer in 2017 [9]. Micrometastases have also shown an impact on long-term outcomes following a breast cancer diagnosis. Maibenco et al. demonstrated that 12-year survival was reduced among women with either solitary or multiple lymph nodes with micrometastases relative to cancer that has not spread to the lymph nodes (node-negative) [10]. Boer et al. found that isolated tumor cells or micrometastases in regional lymph nodes leads to reduced 5-year disease-free survival rate in women with favorable early-stage breast cancer without adjuvant therapy as well as significant increases in disease-free survival on receipt of adjuvant therapy [11]. Finally, Andersson et al. found that ten-year cancer-specific survival and overall survival were lower in cases of micrometastases relative to node-negative cases [12].

Adjuvant treatment (treatment after surgery) is the primary mechanism of combating cancer relapse as well as metastases and involves radiation (local), cytotoxic chemotherapy (systemic), or endocrine approaches. Adjuvant therapy has led to decreased mortality, morbidity, and prevalence of breast cancer (30–40% based on the Early Breast Cancer Trialists’ Collaborative Group) [13]. Despite this demonstrated efficacy, there is minimal information regarding how the timing of administration impacts treatment outcomes [13, 14]. A recent meta-analysis by Zhan et al. found that a 4-week delay before adjuvant chemotherapy administration significantly decreased overall and disease-free survival [15]. Similarly, Biagi et al. performed a systematic review that found that a 4-week delay in adjuvant chemotherapy resulted in a significant decrease in overall and disease-free survival [16]. Several analogous studies have been performed for other types of cancer and stages of cancer, including late-stage colon cancer, early-stage breast cancer, gastric cancer, and pancreatic cancer [17–35]. The National Quality Forum, given such data, endorses chemotherapy initiation within 120 days of diagnosis or 90 days of surgery [36]. However, a number of studies describe a negligible difference: that delays in adjuvant therapy administration do not offer significant differences in treatment outcomes [37–40]. Collectively, these insights speak to the need for up-to-date, more conclusive data regarding treatment delays such that guidelines may be tailored to maximize survival rates for the highest-risk populations.

In considering risk factors, treatment delays have been shown to fall disproportionately along demographic lines. Gwyn et al. found potentially clinically significant differences in diagnosis and treatment delays between African American and white women between the ages of 20 and 54 [41]. Regarding adjuvant therapy administration specifically, over 2004–2006, Fedewa et al. found that most women received adjuvant chemotherapy
within 60 and 90 days of surgery (85.2% and 95.8%, respectively). However, African American and Hispanic patients were found to have a higher risk of delay at both time points compared to white patients — though the extent of these delays was variable, and further analysis was required to understand this variability [42]. Gorin et al. corroborated these results as they identified that the greatest diagnostic, treatment and clinical delays for breast cancer were identified for African American women among other demographics [43]. Ultimately, the relationship between survival and time to the start of adjuvant chemotherapy (AC) among breast cancer patients is unclear. Most breast cancer patients start adjuvant chemotherapy within a few weeks after surgery. However, it is still unclear whether a delay in the initiation of chemotherapy will lead to adverse outcomes and what mediating variables influence the relationship between AC and treatment outcomes.

Patients And Methods

Data was gathered from the National Cancer Database (NCDB), a cancer registry based on hospital care which is sponsored by the ACS and American College of Surgeons. The NCDB includes standardized data on patient insurance state, tumor characteristics, course of treatment, outcomes, demographics, socioeconomic data, and treatment facility data. The database includes roughly 70% of newly diagnosed cancer cases in the U.S. and contains over 34 million records across over 1500 facilities. The data is collected using CoC (Commission on Cancer) program registries and is coded using their Facility Oncology Registry Data Standards. Given that no hospital, provider, patient identifiers, or protected health information was used in this study, institutional review board approval was not required. Along with the NCDB’S classifications, The Charlson-Deyo Index Score is a weight derivative from the sum of scores for a list of conditions in the Charlson Comorbidity Score Mapping Table based on the ICD-9-CM (International Class of Disease, 9th edition, Clinical Modification). This was used to assess comorbidity.

Study Population

The patient population consisted of women diagnosed with invasive breast cancer (stages I-III) between January 1, 2004 and December 31st, 2016 from within the National Cancer Database (n = 432,883). Our analysis was restricted to women older than the age of 18.

In this study, we characterized four levels of adjuvant chemotherapy delay: Less than 1 month, 1–2 months, 2–3 months, and greater than 3 months. The time was defined based on the number of days following surgical resection to the start of adjuvant chemotherapy. In addition, the year of diagnosis was reported. Age was stratified into five groups: 18–49, 50–59, 60–69, 70–79, and over 80. Patient race was characterized as non-Hispanic White or non-Hispanic Black. The primary payer or insurance type held by the patient were classified by Medicaid, Medicare for patients between the ages of 18–64, Medicare for patients 65 and older, private health insurance (preferred provider organizations and health maintenance organizations), no insurance (self-pay, charity write-off, or those who are uninsured), and those with other or unknown data regarding insurance. Of note is the distinction between Medicare patients above the age of 65 and below the age of 65, as the latter is limited to those with permanent disabilities. Regions were categorized by the US Census Bureau Regions and Divisions, which divide the country into 9 different divisions: New England, Middle Atlantic, South Atlantic, East North Central, East South Central, West North Central, West South Central, Mountain, and Pacific. The regions were further classified into four regions: Northeast- Middle Atlantic, New England; Midwest- West North Central, East North Central; West-Pacific, Mountain; South- East South Central, West South Central, South Atlantic. The American Joint Commission on Cancer (AJCC) cancer stage was also included (Stage I, II or III). Based on the registry reporting of pre-existing comorbidities drawn from hospital discharge reports, the Charlson-Deyo comorbidity index was reported. Also related to the specific health status of the patient, their hormone receptor status (positive/borderline, negative, or no test available) was included in the analysis.

Additional social determinants of health were included in the collected patient data. Patient income was grouped into less than $38,000, $38,000-$47,999, $48,000-$62,999, and $63,000 +. Further, the proportion of the population in a particular ZIP Code, based on prior census data, which did not attain a high school diploma was included in the collected data. Patients were grouped according to 21% or more, 13% -20%, 7%-12%, and less than 7%. Finally, given the issues faced by geographic barriers to accessing care, the data includes information on the patient's distance from the reporting facility.

Statistical Analysis

Women diagnosed between 2004 and 2016 with invasive breast cancer (stages I to III) who were treated with surgery and adjuvant chemotherapy were selected from the national cancer database. Descriptive statistics for and bivariate associations between groups were reported. We evaluated factors associated with prolonged time to start adjuvant chemotherapy (≥ 60, ≥ 90, and ≥ 120 days after surgical resection) using multivariable log binomial models to estimate risk ratios and associated confidence intervals. Cox proportional hazards model was used to investigate the effect of delay on survival. All tests were two sided and a p-value of < 0.05 was considered significant. The statistical analysis was performed using SAS version 9.4 (SAS Institute, Cary NC).

Results

The demographics and clinical characteristics of the study cohort are summarized in Table 1. There were significant differences across different racial groups with respect to delay of adjuvant chemotherapy. The average number of days from surgery to initiation chemotherapy was 48.73 days (± 29.56 days) among all patients. Black patients had an average of 53.92 days, whereas Nonhispanic Whites averaged 47.38 days. Black patients
were found to have the highest risk of mortality in the 120 day delay group ([HR], 1.69; 95% CI, (1.61–1.78). Medicaid usage was more profound in non-hispanic Black communities (13.86%) than whites (5.10%), and it was highest in the Hispanic communities. There was a notable difference in regions between Nonhispanic Whites and Blacks for the South and West regions. The highest Charlson Deyo Score was found for black patients in comparison to the other five groups.

Table 1. Patient Characteristics by Race, NCDB, 2004-2016 (n = 432,883)
| Characteristic | Total (n= 432,883) | White (n=333,713) | Hispanic (n=24,657) | Black (n=57,020) | Asian (n=13,428) | Other/Unknown (n=4,065) | P |
|---------------|-------------------|------------------|---------------------|------------------|------------------|-----------------------|---|
|                | N | %  | N | %  | N | %  | N | %  | N | %  | N | %  |
| **Delay**     |   |     |   |     |   |     |   |     |   |     |   |     |   |     |
| Less than 1 month | 97130 | 22.44 | 77821 | 23.32 | 4751 | 19.27 | 10867 | 19.06 | 2738 | 20.39 | 953 | 23.44 | <.01 |
| 1-2 month      | 230512 | 53.25 | 180573 | 54.11 | 12057 | 48.90 | 28580 | 50.12 | 7311 | 54.45 | 1991 | 48.98 |     |
| 2-3 month      | 73203 | 16.91 | 53670 | 16.08 | 5092 | 20.65 | 11314 | 19.84 | 2376 | 17.69 | 751 | 18.47 |     |
| Beyond 3 months | 32038 | 7.40 | 21649 | 6.49 | 2757 | 11.18 | 6259 | 10.98 | 1003 | 7.47 | 370 | 9.10 |     |
| **Age group, years** |   |     |   |     |   |     |   |     |   |     |   |     |   |     |
| 18-49          | 120908 | 27.93 | 88425 | 26.50 | 9193 | 37.28 | 16962 | 29.75 | 4993 | 37.18 | 1335 | 32.84 | <.01 |
| 50-59          | 149204 | 34.47 | 113863 | 34.12 | 8444 | 34.25 | 20749 | 36.39 | 4648 | 36.41 | 1500 | 36.90 |     |
| 60-69          | 115556 | 26.69 | 92396 | 27.69 | 5252 | 21.30 | 14137 | 24.79 | 2852 | 21.24 | 919 | 22.61 |     |
| 70-79          | 41873 | 9.67 | 34540 | 10.35 | 1581 | 6.41 | 4613 | 8.09 | 860 | 6.40 | 279 | 6.86 |     |
| 80+            | 5342 | 1.23 | 4489 | 1.35 | 187 | 0.76 | 559 | 0.98 | 75 | 0.56 | 32 | 0.79 |     |
| **Insurance status** |   |     |   |     |   |     |   |     |   |     |   |     |   |     |
| Uninsured      | 10288 | 2.38 | 5214 | 1.56 | 2336 | 9.47 | 2080 | 3.65 | 508 | 3.78 | 150 | 3.69 | <.01 |
| Medicaid        | 32284 | 7.46 | 17014 | 5.10 | 5122 | 20.77 | 7905 | 13.86 | 1724 | 12.84 | 519 | 12.77 |     |
| Medicare for patients age 18-64 years | 18427 | 4.26 | 12556 | 3.76 | 1092 | 4.43 | 4355 | 7.64 | 260 | 1.94 | 164 | 4.03 |     |
| Medicare for patients age 65 years and older | 78393 | 18.11 | 65342 | 19.58 | 2701 | 10.95 | 8504 | 14.91 | 1354 | 10.08 | 492 | 12.10 |     |
| Private         | 282360 | 65.23 | 225792 | 67.66 | 12533 | 50.83 | 32469 | 56.94 | 9180 | 68.36 | 2386 | 58.70 |     |
| Other/Unknown   | 11131 | 2.57 | 7795 | 2.34 | 873 | 3.54 | 1707 | 2.99 | 402 | 2.99 | 354 | 8.71 |     |
| **Region**     |   |     |   |     |   |     |   |     |   |     |   |     |   |     |
| Northeast      | 88282 | 20.39 | 69648 | 20.87 | 5209 | 21.13 | 9451 | 16.57 | 3228 | 24.04 | 716 | 17.61 | <.01 |
| Midwest        | 113188 | 26.15 | 96532 | 28.93 | 2555 | 10.36 | 11552 | 20.26 | 1846 | 13.75 | 703 | 17.29 |     |
| South          | 167020 | 38.58 | 119770 | 35.89 | 9531 | 38.65 | 33496 | 58.74 | 2771 | 20.64 | 1452 | 35.72 |     |
| West           | 64423 | 14.88 | 47763 | 14.31 | 7362 | 29.86 | 2521 | 4.42 | 5583 | 41.58 | 1194 | 29.37 |     |
| **Disease stage** |   |     |   |     |   |     |   |     |   |     |   |     |   |     |
| I              | 139090 | 32.13 | 109545 | 32.83 | 6986 | 28.33 | 17078 | 29.95 | 4309 | 32.09 | 1172 | 28.83 | <.01 |
| II             | 212337 | 49.05 | 161990 | 48.54 | 12545 | 50.88 | 28875 | 50.64 | 6817 | 50.77 | 2110 | 51.91 |     |
| III            | 81456 | 18.82 | 62178 | 18.63 | 5126 | 20.79 | 11067 | 19.41 | 2302 | 17.14 | 783 | 19.26 |     |
| **Hormone status** |   |     |   |     |   |     |   |     |   |     |   |     |   |     |
| Negative       | 129426 | 29.90 | 289044 | 86.61 | 7138 | 28.95 | 24592 | 43.13 | 3658 | 27.24 | 1138 | 28.00 |     |
| +ve/Borerline  | 302546 | 69.89 | 240163 | 71.97 | 17425 | 70.67 | 32293 | 56.63 | 9744 | 72.56 | 2921 | 71.86 |     |
| No test        | 911 | 0.21 | 650 | 0.19 | 94 | 0.38 | 135 | 0.24 | 26 | 0.19 | 6 | 0.15 |     |
| **Charlson-Deyo score** |   |     |   |     |   |     |   |     |   |     |   |     |   |     |
| 0              | 370017 | 85.48 | 289044 | 86.61 | 20816 | 84.42 | 44936 | 78.81 | 11846 | 88.22 | 3375 | 83.03 | <.01 |
| 1              | 52024 | 12.02 | 37144 | 11.13 | 3252 | 13.19 | 9674 | 16.97 | 1393 | 10.37 | 561 | 13.80 |     |
| ≥ 2            | 10842 | 2.50 | 7525 | 2.25 | 589 | 2.39 | 2410 | 4.23 | 189 | 1.41 | 129 | 3.17 |     |
| **Income**     |   |     |   |     |   |     |   |     |   |     |   |     |   |     |
| <.01 |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
| Facility Category | Less than 7% | 7% - 12% | 13% - 20% | 21% or more | <.01 | <.01 | <.01 | <.01 |
|-------------------|-------------|----------|-----------|-------------|------|------|------|------|
| Education         | 67019       | 15.48    | 35952     | 10.77       | 11130| 45.14| 17017| 29.84|
|                    | 302         | 21.62    | 7268      | 21.81       | 5676 | 23.02| 12856| 22.55|
| Education         | 105698      | 24.42    | 75582     | 22.65       | 5729 | 23.23| 20782| 36.45|
|                    | 143104      | 33.06    | 118994    | 35.66       | 4965 | 20.14| 13611| 23.87|
| Less than 7%      | 117062      | 27.04    | 103185    | 30.92       | 2833 | 11.49| 5610  | 9.84  |
| Facility Category | 41914       | 9.68     | 33681     | 10.09       | 2259 | 9.16 | 4381  | 7.68  |
| Community Cancer program | 195456 | 45.15 | 158222 | 47.41 | 9042 | 36.67 | 21754 | 38.15 |
| Academic/research program | 133333 | 30.80 | 94029 | 28.18 | 9816 | 39.81 | 22150 | 38.85 |
| Other specified types of cancer programs | 62180 | 14.36 | 47781 | 14.32 | 3540 | 14.36 | 8735  | 15.32 |
| Urban setting     | 233291      | 53.89    | 165986    | 49.74       | 17563| 71.23| 37170| 65.19 |
| Large Metropolitan | 136317    | 31.49    | 111520    | 33.42       | 6015 | 24.39| 14880| 26.10 |
| Small Metropolitan | 46202     | 10.67    | 40793     | 12.22       | 831  | 3.37 | 3846  | 6.75  |
| Suburban          | 17073       | 3.94     | 15414     | 4.62        | 248  | 1.01 | 1124  | 1.97  |
| Rural             | 22746       | 6.39     | 22439     | 6.72        | 1241 | 5.03 | 3124  | 5.48  |
| Year of Diagnosis | 28221       | 6.52     | 22756     | 6.82        | 1353 | 5.49 | 3257  | 5.71  |
| 2004              | 30210       | 6.98     | 24243     | 7.26        | 1414 | 5.73 | 3573  | 6.27  |
| 2005              | 31452       | 7.27     | 24910     | 7.46        | 1640 | 6.65 | 3810  | 6.68  |
| 2006              | 31970       | 7.39     | 25028     | 7.50        | 1749 | 7.09 | 4044  | 7.09  |
| 2007              | 33939       | 7.84     | 26507     | 7.94        | 1813 | 7.35 | 4433  | 7.77  |
| 2008              | 34291       | 7.92     | 26369     | 7.90        | 1895 | 7.69 | 4646  | 8.15  |
| 2009              | 36109       | 8.34     | 27583     | 8.27        | 2057 | 8.34 | 4915  | 8.62  |
| 2010              | 36246       | 8.37     | 27518     | 8.25        | 2195 | 8.90 | 5004  | 8.78  |
| 2011              | 37606       | 8.69     | 28334     | 8.49        | 2356 | 9.56 | 5207  | 9.13  |
| 2012              | 36586       | 8.45     | 27362     | 8.20        | 2259 | 9.16 | 5234  | 9.18  |
| 2013              | 35364       | 8.17     | 26212     | 7.85        | 2418 | 9.81 | 5010  | 8.79  |
| 2014              | 33243       | 7.68     | 24452     | 7.33        | 2267 | 9.19 | 4763  | 8.35  |
| 2015              | 21.49       | 22.92    | 17.43     | 15.16       | 16.85| 32.57|       |      |
| Distance to reporting facility, miles | SD  | 80.91 | 82.60 | 75.64 | 56.49 | 105.73 | 139.84 |      |
| Mean              | 9.20        | 10.10    | 7.10      | 7.00        | 7.00 | 10.10|      |      |
Table 2 demonstrates multivariable risk ratios for 30, 60, 90, and 120 day delays based on the characteristics of Table 1: patient demographics, age, area-level SES, insurance status, and facility-level characteristics. The non-hispanic African American patients had the highest risk of mortality compared to non-hispanic whites as the number of delay days for each group increased. Older ages were associated with increased risk of mortality across all delay groups. Patients with a more advanced cancer stage had an increased mortality risk at each stage relative to stage one cancer in the 30-day delay group.
Table 2. Multivariate Regression Analysis of Factors Related 30-, 60-, 90-, and 120-Day Chemotherapy Delay, Patients with Breast Cancer, NCDB, 2004-2016 (n= 432,883)

| Factor                      | 30-Day Delay | 60-Day Delay | 90-Day Delay | 120-Day Delay |
|-----------------------------|--------------|--------------|--------------|---------------|
|                             | RR 95% CI    | RR 95% CI    | RR 95% CI    | RR 95% CI     |
| Race                        |              |              |              |               |
| White                       | 1.00         | 1.00         | 1.00         | 1.00          |
| Hispanic                    | 1.15 (1.11-1.20) | 1.33 (1.29-1.37) | 1.38 (1.32-1.44) | 1.47 (1.37-1.58) |
| Black                       | 1.29 (1.26-1.32) | 1.41 (1.38-1.44) | 1.55 (1.50-1.60) | 1.69 (1.61-1.78) |
| Asian                       | 1.14 (1.09-1.19) | 1.06 (1.02-1.11) | 1.02 (0.95-1.08) | 1.01 (0.91-1.13) |
| Other/Unknown               | 0.97 (0.90-1.04) | 1.22 (1.14-1.31) | 1.31 (1.18-1.46) | 1.37 (1.16-1.62) |
| Age, years                  |              |              |              |               |
| 18-49                       | 1.00         | 1.00         | 1.00         | 1.00          |
| 50-59                       | 1.13 (1.11-1.15) | 1.09 (1.07-1.11) | 1.05 (1.02-1.08) | 1.02 (0.97-1.07) |
| 60-69                       | 1.31 (1.28-1.34) | 1.21 (1.19-1.24) | 1.16 (1.12-1.20) | 1.13 (1.07-1.19) |
| 70-79                       | 1.48 (1.43-1.54) | 1.37 (1.33-1.42) | 1.34 (1.27-1.42) | 1.37 (1.26-1.49) |
| 80-99                       | 1.46 (1.36-1.57) | 1.61 (1.50-1.72) | 1.67 (1.51-1.84) | 1.90 (1.64-2.20) |
| Insurance status            |              |              |              |               |
| Private                     | 1.00         | 1.00         | 1.00         | 1.00          |
| Uninsured                   | 1.36 (1.29-1.43) | 1.43 (1.37-1.50) | 1.50 (1.41-1.60) | 1.72 (1.57-1.90) |
| Medicaid                    | 1.30 (1.26-1.34) | 1.52 (1.48-1.56) | 1.67 (1.60-1.73) | 1.85 (1.74-1.96) |
| Medicare for patients age 18-64 years | 1.25 (1.20-1.30) | 1.37 (1.32-1.42) | 1.51 (1.44-1.59) | 1.67 (1.54-1.80) |
| Medicare for patients age 65 years and older | 1.11 (1.08-1.14) | 1.10 (1.07-1.13) | 1.12 (1.07-1.16) | 1.16 (1.08-1.24) |
| Other/unknown               | 0.77 (0.74-0.80) | 1.07 (1.03-1.12) | 1.23 (1.15-1.32) | 1.26 (1.13-1.41) |
| Region                      |              |              |              |               |
| South                       | 1.00         | 1.00         | 1.00         | 1.00          |
| Northeast                   | 1.33 (1.30-1.36) | 1.22 (1.20-1.25) | 1.23 (1.20-1.27) | 1.21 (1.16-1.27) |
| Midwest                     | 0.99 (0.98-1.02) | 0.87 (0.86-0.89) | 0.82 (0.80-0.85) | 0.79 (0.75-0.83) |
| West                        | 1.19 (1.16-1.22) | 1.09 (1.07-1.12) | 1.12 (1.08-1.16) | 1.17 (1.11-1.24) |
| Stage                       |              |              |              |               |
| III                         | 1.00         | 1.00         | 1.00         | 1.00          |
| II                          | 1.31 (1.29-1.34) | 1.11 (1.09-1.13) | 0.99 (0.96-1.03) | 0.90 (0.86-0.95) |
| I                           | 1.61 (1.57-1.64) | 1.13 (1.27-1.32) | 1.16 (1.13-1.20) | 1.10 (1.04-1.16) |
| Hormone status              |              |              |              |               |
| Negative                    | 1.00         | 1.00         | 1.00         | 1.00          |
| Positive                    | 1.55 (1.52-1.57) | 1.46 (1.44-1.49) | 1.45 (1.41-1.49) | 1.45 (1.39-1.51) |
| Unknown                     | 1.17 (1.00-1.35) | 1.75 (1.52-2.02) | 1.80 (1.47-2.21) | 1.97 (1.46-2.65) |
| Charlson-Deyo score         |              |              |              |               |
| 0                           | 1.00         | 1.00         | 1.00         | 1.00          |
| 1                           | 1.18 (1.15-1.20) | 1.12 (1.10-1.14) | 1.13 (1.10-1.17) | 1.12 (1.06-1.18) |
| ≥2                          | 1.30 (1.24-1.37) | 1.34 (1.28-1.39) | 1.39 (1.31-1.48) | 1.39 (1.26-1.53) |
Table 2. Multivariate Regression Analysis of Factors Related 30-, 60-, 90-, and 120-Day Chemotherapy Delay, Patients with Breast Cancer, NCDB, 2004-2016 (n= 432,883)

| Factor                          | 30-Day Delay | 60-Day Delay | 90-Day Delay | 120-Day Delay |
|--------------------------------|--------------|--------------|--------------|---------------|
|                                | RR  95% CI    | RR  95% CI    | RR  95% CI    | RR  95% CI    |
| Income                         |              |              |              |               |
| $63,000 +                       | 1.00 (1.00-1.05) | 1.03 (1.00-1.05) | 1.07 (1.00-1.05) | 1.13 (1.09-1.16) |
| $48,000 - $62,999               | 1.03 (1.00-1.05) | 1.01 (0.99-1.03) | 0.99 (0.96-1.03) | 0.97 (0.92-1.03) |
| $38,000 - $47,999               | 1.07 (1.04-1.09) | 1.04 (1.01-1.07) | 1.02 (0.98-1.06) | 0.98 (0.92-1.05) |
| Less than $38,000               | 1.13 (1.09-1.16) | 1.08 (1.04-1.11) | 1.06 (1.01-1.11) | 1.03 (0.96-1.12) |
| Education                       |              |              |              |               |
| 21% or more                     | 1.00 (0.95-0.99) | 0.95 (0.93-0.97) | 0.95 (0.92-0.99) | 0.95 (0.90-1.01) |
| 13% -20%                        | 0.97 (0.92-0.97) | 0.91 (0.88-0.93) | 0.87 (0.84-0.91) | 0.88 (0.82-0.94) |
| 7% - 12%                        | 0.95 (0.83-0.88) | 0.80 (0.77-0.82) | 0.74 (0.70-0.78) | 0.72 (0.66-0.77) |
| Less than 7%                    |               |               |               |               |
| Facility Category               |              |              |              |               |
| Community Cancer Care           | 1.00 (0.89-0.93) | 0.88 (0.86-0.90) | 0.83 (0.80-0.87) | 0.80 (0.75-0.86) |
| Comprehensive community cancer program | 0.91 (1.08-1.14) | 1.11 (1.08-1.14) | 1.07 (1.03-1.12) | 1.05 (0.99-1.12) |
| Academic/research program       | 1.11 (1.08-1.14) | 1.11 (1.08-1.14) | 1.07 (1.03-1.12) | 1.05 (0.99-1.12) |
| Other specified types of cancer programs | 1.00 (0.97-1.03) | 0.96 (0.93-0.99) | 0.92 (0.88-0.96) | 0.89 (0.82-0.96) |
| Urban Setting                   |              |              |              |               |
| Large metropolitan              | 1.00 (0.96-0.99) | 0.88 (0.86-0.89) | 0.83 (0.81-0.86) | 0.76 (0.73-0.79) |
| Small metropolitan              | 1.01 (0.99-1.04) | 0.92 (0.90-0.95) | 0.83 (0.80-0.87) | 0.75 (0.70-0.81) |
| Suburban                        | 1.03 (0.99-1.08) | 0.90 (0.86-0.93) | 0.77 (0.73-0.83) | 0.74 (0.67-0.83) |
| Year of diagnosis               |              |              |              |               |
| 2004                            | 1.00 (0.99-1.08) | 1.04 (1.00-1.09) | 1.04 (0.97-1.10) | 1.09 (0.99-1.20) |
| 2005                            | 1.04 (1.08-1.16) | 1.06 (1.02-1.10) | 1.10 (1.04-1.17) | 1.13 (1.03-1.24) |
| 2006                            | 1.12 (1.21-1.21) | 1.12 (1.08-1.16) | 1.09 (1.02-1.15) | 1.10 (1.01-1.21) |
| 2007                            | 1.26 (1.21-1.31) | 1.13 (1.09-1.17) | 1.06 (0.99-1.12) | 1.07 (0.98-1.18) |
| 2008                            | 1.32 (1.27-1.37) | 1.08 (1.04-1.12) | 1.04 (0.98-1.10) | 1.02 (0.93-0.85) |
| 2009                            | 1.31 (1.26-1.36) | 1.02 (0.98-1.06) | 0.94 (0.88-0.99) | 0.93 (0.85-1.02) |
| 2010                            | 1.19 (1.15-1.24) | 0.91 (0.88-0.95) | 0.87 (0.82-0.92) | 0.84 (0.76-0.92) |
| 2011                            | 1.21 (1.17-1.26) | 0.91 (0.88-0.95) | 0.81 (0.76-0.86) | 0.72 (0.65-0.79) |
| 2012                            | 1.21 (1.16-1.25) | 0.90 (0.87-0.94) | 0.80 (0.76-0.85) | 0.75 (0.68-0.82) |
| 2013                            | 1.12 (1.08-1.16) | 0.80 (0.77-0.83) | 0.72 (0.68-0.77) | 0.67 (0.61-0.74) |
| 2014                            | 1.15 (1.11-1.20) | 0.80 (0.77-0.84) | 0.71 (0.67-0.75) | 0.63 (0.57-0.70) |
| 2015                            | 1.12 (1.08-1.17) | 0.83 (0.80-0.86) | 0.76 (0.71-0.80) | 0.70 (0.63-0.77) |

Insurance type was associated with survival outcomes among patients with later delays. Patients who were uninsured or who were enrolled in Medicaid or Medicare had an increased risk of mortality in the 60, 90, and 120 day delay groups. Notably, this trend was not consistent with the
privately insured 30 day delay group who showed a decreased risk of mortality. The facility type was associated with a decreased risk of mortality across all delay groups. The only increase in risk relative to the community cancer care was found within the academic research programs. The hormone receptor-positive status was associated with a higher risk of mortality across the delay groups relative to hormone receptor-negative (1.55, 1.46, 1.45, 1.45). For the Charlson Deyo score, each of the varying day groups had the highest risk relative to the Charlson Deyo score of 2.

Table 3 demonstrates Cox Hazard ratios that do not change over time to assess the impact of treatment delay post surgery on mortality. In comparison to delayment of treatment, there was an increase in associated risk found among all studied groups. Those with medicare for both age groups had a decreased associated risk relative to privately insured individuals, whereas those without insurance and had medicaid had a decreased survival rate.

Discussion

The study determined the suggested effect of delayed adjuvant chemotherapy for breast cancer treatment among five groups. The findings were consonant with previous research that used varied locations and samples. Prior studies have indicated a higher risk of mortality among women receiving adjuvant chemotherapy with increased days of delay after surgery [44]. This suggests clinical and nonclinical factors as important and providers should avoid delays.

Low socioeconomic status and lack of health insurance coverage combined have been cited as a predictor of delay in many previous studies [45]. These results were replicated using the California Cancer Registry database [46]. Similar to our findings, the young women patients of lower income and a longer delay treatment have a significantly increased risk of mortality compared with those with a shorter number of delays. This adverse impact on survival was more pronounced in African American women, those with public or no insurance.

The study found Black and Hispanic women and women without private insurance were more likely than white women with private insurance to be at risk. This suggests these women with public or no insurance compared with those with private insurance and women with low socioeconomic status compared with those with high socioeconomic status were shown to have longer initiated delay of treatment [47]. This suggests the need to initiate and diagnose prior to the issue exacerbating which can be addressed through more local options to get diagnosed, with or without insurance. As an example, it has suggested that a mobile mammogram has been an effective measure for addressing racial diversity and resulting in a higher recall rate [48].

It is well supported that areas with lower socioeconomic status have decreased opportunities to get education [49]. Decreased education and access to quality facilities has been associated with a higher risk of mortality for those affected by breast cancer [50]. Women with higher education levels attend breast cancer screening to a greater extent than less educated women [51] [52].

The findings on delay in breast cancer diagnosis and treatment suggest decreased quality of care among African American and Hispanic patients. A patient's environment such as a rural setting may be less likely to have specialized equipment or trained personnel. For treatment to be effective, there must be attention for how the provider reaches out to patients post-treatment [53] [54]. Whether for screening or diagnostic purposes, many studies' results suggest the health system must support training for following up with patient effective communication and providing feedback [55]. This supports this paper's findings similarly suggesting different regions' facilities contribute to a decreased ability to go in for screenings and thus delay treatment.

The findings on delay in breast cancer diagnosis and treatment suggest Black and Hispanic groups had decreased access to quality of care, services, and education. Quality of care relates to distrust. Previous studies have assessed distrust and adjuvant cancer treatment with increased risk of mortality due to delayed adjuvant treatment for breast cancer among patients [56] [57] [58]. The study suggests since there is a difference in allocating resources and communities for White patients when treating the disease, they can more easily recover because they trust their provider about the benefits of chemotherapy. This suggests the need to include ways to educate providers about assessing medical distrust among different communities as a way to promote cultural competence.

The study's interpretations are limited by the given design of the National Cancer Database. The NCDB provides a holistic, comprehensive picture for its samples, including a number of less commonly available details that enable subtle cultural differences among each group to be studied. NCDB is a comprehensive source, approximately 70% of newly diagnosed cancer cases in the United States reported [59] and 34 million cases reported, however, it does not qualify as population-based because if a patient happens to choose a different hospital, one that is not an NCDB participant, his or her data are not included. This data additionally was limited to the time span of 2004 to 2016. Since NCDB is a hospital-based registry, findings may not be generalizable to all patients in the United States. Analysis of a study from a population-based data source in comparison to the findings presented could allow for further analysis of delayed treatment of breast cancer.

Declarations

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Conflicts of interest

All authors declare that they have no conflicts of interest.

Author Contributions

Conceptualization: Desai and Balkrishnan Data and Analysis: Desai and Balkrishnan Paper Writing Desai, Narayan and Hsiao Critical Revision: All authors

Ethics approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

The study protocol was exempted by the UVA IRB

Consent to participate

The study uses an extant database. All participants consented for their data to be collected.

Consent for publication All authors have reviewed the manuscript and consented to its submission for publication.

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