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

Raj Piyush Desai

University of Virginia

Aditya Narayan

University of Virginia

Sabrina Hsiao

University of Virginia

Rajesh Balkrishnan (✉ rbgws@yahoo.com)

University of Virginia School of Medicine <https://orcid.org/0000-0001-9363-9257>

Research Article

Keywords: Breast Cancer, Treatment Delay, United States, Disparities, Ethnicity, Surgery

Posted Date: March 15th, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-289142/v1>

License: © ⓘ This work is licensed under a Creative Commons Attribution 4.0 International License. [Read Full License](#)

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. Maibenko 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 weighted derived 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													<.01
Less than 1 month	97130	22.44	77821	23.32	4751	19.27	10867	19.06	2738	20.39	953	23.44	
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													<.01
18-49	120908	27.93	88425	26.50	9193	37.28	16962	29.75	4993	37.18	1335	32.84	
50-59	149204	34.47	113863	34.12	8444	34.25	20749	36.39	4648	34.61	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													<.01
Uninsured	10288	2.38	5214	1.56	2336	9.47	2080	3.65	508	3.78	150	3.69	
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													<.01
Northeast	88282	20.39	69648	20.87	5209	21.13	9451	16.57	3228	24.04	716	17.61	
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													<.01
I	139090	32.13	109545	32.83	6986	28.33	17078	29.95	4309	32.09	1172	28.83	
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													<.01
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													<.01
0	370017	85.48	289044	86.61	20816	84.42	44936	78.81	11846	88.22	3375	83.03	
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

Less than \$38,000	68777	15.89	39483	11.83	5906	23.95	21950	38.50	707	5.27	731	17.98
\$38,000 - \$47,999	93594	21.62	72768	21.81	5676	23.02	12856	22.55	1590	11.84	704	17.32
\$48,000 - \$62,999	115685	26.72	92629	27.76	6843	27.75	11894	20.86	3270	24.35	1049	25.81
\$63,000 +	154827	35.77	128833	38.61	6232	25.27	10320	18.10	7861	58.54	1581	38.89
Education												<.01
21% or more	67019	15.48	35952	10.77	11130	45.14	17017	29.84	2189	16.30	731	17.98
13% -20%	105698	24.42	75582	22.65	5729	23.23	20782	36.45	2613	19.46	992	24.40
7% - 12%	143104	33.06	118994	35.66	4965	20.14	13611	23.87	4287	31.93	1247	30.68
Less than 7%	117062	27.04	103185	30.92	2833	11.49	5610	9.84	4339	32.31	1095	26.94
Facility Category												<.01
Community Cancer program	41914	9.68	33681	10.09	2259	9.16	4381	7.68	1139	8.48	454	11.17
Comprehensive community cancer program	195456	45.15	158222	47.41	9042	36.67	21754	38.15	4885	36.38	1553	38.20
Academic/research program	133333	30.80	94029	28.18	9816	39.81	22150	38.85	5809	43.26	1529	37.61
Other specified types of cancer programs	62180	14.36	47781	14.32	3540	14.36	8735	15.32	1595	11.88	529	13.01
Urban setting												<.01
Large Metropolitan	233291	53.89	165986	49.74	17563	71.23	37170	65.19	10331	76.94	55.13	233291
Small Metropolitan	136317	31.49	111520	33.42	6015	24.39	14880	26.10	2792	20.79	1110	27.31
Suburban	46202	10.67	40793	12.22	831	3.37	3846	6.75	259	1.93	473	11.64
Rural	17073	3.94	15414	4.62	248	1.01	1124	1.97	46	0.34	241	5.93
Year of Diagnosis												<0.1
2004	27646	6.39	22439	6.72	1241	5.03	3124	5.48	661	4.92	181	4.45
2005	28221	6.52	22756	6.82	1353	5.49	3257	5.71	656	4.89	199	4.90
2006	30210	6.98	24243	7.26	1414	5.73	3573	6.27	738	5.50	242	5.95
2007	31452	7.27	24910	7.46	1640	6.65	3810	6.68	809	6.02	283	6.96
2008	31970	7.39	25028	7.50	1749	7.09	4044	7.09	858	6.39	291	7.16
2009	33939	7.84	26507	7.94	1813	7.35	4433	7.77	880	6.55	306	7.53
2010	34291	7.92	26369	7.90	1895	7.69	4646	8.15	1079	8.04	302	7.43
2011	36109	8.34	27583	8.27	2057	8.34	4915	8.62	1212	9.03	342	8.41
2012	36246	8.37	27518	8.25	2195	8.90	5004	8.78	1179	8.78	350	8.61
2013	37606	8.69	28334	8.49	2356	9.56	5207	9.13	1305	9.72	404	9.94
2014	36586	8.45	27362	8.20	2259	9.16	5234	9.18	1347	10.03	384	9.45
2015	35364	8.17	26212	7.85	2418	9.81	5010	8.79	1330	9.90	394	9.69
2016	33243	7.68	24452	7.33	2267	9.19	4763	8.35	1374	10.23	387	9.52
Distance to reporting facility, miles												
Mean	21.49		22.92		17.43		15.16		16.85		32.57	
SD	80.91		82.60		75.64		56.49		105.73		139.84	
Median	9.20		10.10		7.10		7.00		7.00		10.10	

No. of days from surgery to chemotherapy						
Mean	48.73	47.38	54.22	53.92	49.74	50.18
SD	29.56	28.04	34.71	34.28	29.82	32.62
Median	42.00	42.00	46.00	46.00	43.00	43.00

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		1.00		1.00	
\$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		1.00		1.00		1.00	
13% -20%	0.97	(0.95-99)	0.95	(0.93-0.97)	0.95	(0.92-0.99)	0.95	(0.90-1.01)
7% - 12%	0.95	(0.92-0.97)	0.91	(0.88-0.93)	0.87	(0.84-0.91)	0.88	(0.82-0.94)
Less than 7%	0.85	(0.83-0.88)	0.80	(0.77-0.82)	0.74	(0.70-0.78)	0.72	(0.66-0.77)
Facility Category								
Community Cancer Care	1.00		1.00		1.00		1.00	
Comprehensive community cancer program	0.91	(0.89-0.93)	0.88	(0.86-0.90)	0.83	(0.80-0.87)	0.80	(0.75-0.86)
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		1.00		1.00		1.00	
Small metropolitan	0.98	(0.96-0.99)	0.88	(0.86-0.89)	0.83	(0.81-0.86)	0.76	(0.73-0.79)
Suburban	1.01	(0.99-1.04)	0.92	(0.90-0.95)	0.83	(0.80-0.87)	0.75	(0.70-0.81)
Rural	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		1.00		1.00		1.00	
2005	1.04	(0.99-1.08)	1.04	(1.00-1.09)	1.04	(0.97-1.10)	1.09	(0.99-1.20)
2006	1.12	(1.08-1.16)	1.06	(1.02-1.10)	1.10	(1.04-1.17)	1.13	(1.03-1.24)
2007	1.16	(1.12-1.21)	1.12	(1.08-1.16)	1.09	(1.02-1.15)	1.10	(1.01-1.21)
2008	1.26	(1.21-1.31)	1.13	(1.09-1.17)	1.06	(0.99-1.12)	1.07	(0.98-1.18)
2009	1.32	(1.27-1.37)	1.08	(1.04-1.12)	1.04	(0.98-1.10)	1.02	(0.93-0.85)
2010	1.31	(1.26-1.36)	1.02	(0.98-1.06)	0.94	(0.88-0.99)	0.93	(0.85-1.02)
2011	1.19	(1.15-1.24)	0.91	(0.88-0.95)	0.87	(0.82-0.92)	0.84	(0.76-0.92)
2012	1.21	(1.17-1.26)	0.91	(0.88-0.95)	0.81	(0.76-0.86)	0.72	(0.65-0.79)
2013	1.21	(1.16-1.25)	0.90	(0.87-0.94)	0.80	(0.76-0.85)	0.75	(0.68-0.82)
2014	1.12	(1.08-1.16)	0.80	(0.77-0.83)	0.72	(0.68-0.77)	0.67	(0.61-0.74)
2015	1.15	(1.11-1.20)	0.80	(0.77-0.84)	0.71	(0.67-0.75)	0.63	(0.57-0.70)
2016	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 Data. 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

Funding

No funding or support was used for this study. The study was performed using UVA Cancer Center resources

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.

References

1. Momenimovahed Z, Salehiniya H (2019) Epidemiological characteristics of and risk factors for breast cancer in the world. *Breast Cancer: Targets Therapy* 11:151–164. doi:10.2147/bctt.s176070
2. Desantis CE, Ma J, Gaudet MM et al (2019) Breast cancer statistics, *CA: A Cancer Journal for Clinicians*. 2019;69(6):438–451. doi:10.3322/caac.21583
3. Hortobagyi GN, de la Garza Salazar J, Pritchard K et al (2005) ABREAST Investigators The global breast cancer burden: variations in epidemiology and survival. *Clinical Breast Cancer* 6(5):391–401
4. Parkin DM, Fernández LM (2006) Use of statistics to assess the global burden of breast cancer. *Breast J* 12(s1):S70–S80
5. Desantis CE, Ma J, Goding Sauer A, Newman LA, Jemal A (2017) Breast cancer statistics, 2017, racial disparity in mortality by state. *CA Cancer J Clin* 67(6):439–448
6. Zaidi Z, Dib HA (2019) Abstract 4191: The worldwide female breast cancer incidence and survival, 2018. *Epidemiology*. doi:10.1158/1538-7445.sabcs18-4191
7. DeSantis C, Ma J, Bryan L, Jemal A (2014) Breast cancer statistics, 2013. *CA Cancer J Clin* 64(1):52–62
8. Waks AG, Winer EP (2019) Breast Cancer Treatment: A Review. *JAMA* 321(3):288–300. doi:10.1001/jama.2018.19323
9. Mariotto AB, Etzioni R, Hurlbert M et al (2017) Estimation of the number of women living with breast cancer in the United States. *Cancer Epidemiol Biomarkers Prev* 26(6):809–815. doi:10.1158/1055-9965.EPI-16-0889
10. Maibenko DC, Dombi GW, Kau TY, Severson RK (2006) Significance of micrometastases on the survival of women with T1 breast cancer. *Cancer* 107(6):1234–1239. doi:10.1002/cncr.22112
11. Boér K (2010) A gyógyszeres kezelés szerepe a korai emlőrák kezelésében [Adjuvant chemotherapy of early stage breast cancer]. *Orv Hetil* 151(9):344–353. doi:10.1556/OH.2010.28824
12. Andersson Y, Bergkvist L, Frisell J, Boniface JD (2018) Long-term breast cancer survival in relation to the metastatic tumor burden in axillary lymph nodes. *Breast Cancer Res Treat* 171(2):359–369. doi:10.1007/s10549-018-4820-0
13. Early Breast Cancer Trialists' Collaborative Group (EBCTCG), Peto R, Davies C et al. Comparisons between different polychemotherapy regimens for early breast cancer: meta-analyses of long-term outcome among 100,000 women in 123 randomised trials. *Lancet*. 2012;379(9814):432–444. doi:10.1016/S0140-6736(11)61625-5
14. Rossi L, Stevens D, Pierga J-Y et al. Impact of Adjuvant Chemotherapy on Breast Cancer Survival: A Real-World Population. *Plos One*. 2015;10(7). doi:10.1371/journal.pone.0132853
15. Zhan Q-H, Fu J-Q, Fu F-M, Zhang J, Wang C (2017) Survival and time to initiation of adjuvant chemotherapy among breast cancer patients: a systematic review and meta-analysis. *Oncotarget* 9(2):2739–2751. doi:10.18632/oncotarget.23086
16. Biagi JJ, Raphael MJ, Mackillop WJ, Kong W, King WD, Booth CM (2011) Association between time to initiation of adjuvant chemotherapy and survival in colorectal cancer: a systematic review and meta-analysis. *JAMA* 305(22):2335–2342

17. Gao P, Huang X-Z, Song Y-X et al. Impact of timing of adjuvant chemotherapy on survival in stage III colon cancer: a population-based study. *BMC Cancer*. 2018;18(1). doi:10.1186/s12885-018-4138-7
18. Sen F, Pilanci KN (2016) Adjuvant Systemic Therapy in Stage II and III Colon Cancer. *Colorectal Cancer - From Pathogenesis to Treatment*. doi:10.5772/63208
19. Salner AL, Smith S, Yu PP (2018) Timing of adjuvant chemotherapy administration for early breast cancer. *J Clin Oncol* 36(30_suppl):62–62. doi:10.1200/jco.2018.36.30_suppl.62
20. Bos A, Erning FV, Gestel YV, Creemers G, Punt C, Oijen MV, Lemmens V (2015) Timing of adjuvant chemotherapy and its relation to survival among patients with stage III colon cancer. *Eur J Cancer* 51(17):2553–2561. doi:10.1016/j.ejca.2015.08.016
21. Kennedy RD, Bylesjo M, Kerr P et al (2011) Development and independent validation of a prognostic assay for stage II colon cancer using formalin-fixed paraffin-embedded tissue. *J Clin Oncol* 29(35):4620–4626. doi:10.1200/JCO.2011.35.4498
22. Huang S-M, Chen Y-C, Chen W-Y et al (2019) Optimal Timing for Postsurgical Adjuvant Therapy in Patients with Gastric Cancer: A Propensity Score Matching Study. *J Cancer* 10(2):332–340. doi:10.7150/jca.27753
23. Ma SJ, Oladeru OT, Miccio JA, Iovoli AJ, Hermann GM, Singh AK. Association of Timing of Adjuvant Therapy With Survival in Patients With Resected Stage I to II Pancreatic Cancer. *JAMA Network Open*. 2019;2(8). doi:10.1001/jamanetworkopen.2019.9126
24. Kim HW, Lee J-C, Lee J, Kim JW, Kim J, Hwang J-H. Early versus delayed initiation of adjuvant treatment for pancreatic cancer. *Plos One*. 2017;12(3). doi:10.1371/journal.pone.0173960
25. Mönig SP, Bonino MA (2019) Delay in initiation adjuvant S-1 monotherapy for gastric cancer: important prognostic factor. *Translational Gastroenterology Hepatology* 4:61–61. doi:10.21037/tgh.2019.07.03
26. Yu K-D, Fan L, Qiu L-X, Ling H, Jiang Y-Z, Shao Z-M (2016) Influence of delayed initiation of adjuvant chemotherapy on breast cancer survival is subtype-dependent. *Oncotarget* 8(28):46549–46556. doi:10.18632/oncotarget.10551
27. Farolfi A, Scarpi E, Rocca A et al (2015) Time to initiation of adjuvant chemotherapy in patients with rapidly proliferating early breast cancer. *Eur J Cancer* 51(14):1874–1881. doi:10.1016/j.ejca.2015.07.003
28. Pronzato P, Campora E, Amoroso D, Bertelli G, Botto F, Conte PF, Sertoli MR, Rosso R (1989) Impact of administration-related factors on outcome of adjuvant chemotherapy for primary breast cancer. *Am J Clin Oncol* 12(6):481–485. <https://doi.org/10.1097/00000421-198912000-00004>
29. Gagliato Dde M, Gonzalez-Angulo AM, Lei X, Theriault RL, Giordano SH, Valero V, Hortobagyi GN, Chavez-Macgregor M. Clinical impact of delaying initiation of adjuvant chemotherapy in patients with breast cancer. *J Clin Oncol*. 2014 Mar 10;32(8):735 – 44. doi: 10.1200/JCO.2013.49.7693. Epub 2014 Jan 27. PMID: 24470007; PMCID: PMC3940536
30. Downing A, Twelves C, Forman D, Lawrence G, Gilthorpe MS (2014) Time to begin adjuvant chemotherapy and survival in breast cancer patients: a retrospective observational study using latent class analysis. *Breast J* 20(1):29–36. doi:10.1111/tbj.12209
31. Lohrisch C, Paltiel C, Gelmon K et al (2006) Impact on survival of time from definitive surgery to initiation of adjuvant chemotherapy for early-stage breast cancer. *J Clin Oncol* 24(30):4888–4894. doi:10.1200/JCO.2005.01.6089
32. Chavez-MacGregor M, Clarke CA, Lichtensztajn DY, Giordano SH (2016) Delayed Initiation of Adjuvant Chemotherapy Among Patients With Breast Cancer. *JAMA Oncol* 2(3):322–329. doi:10.1001/jamaoncol.2015.3856
33. Hershman DL, Wang X, McBride R, Jacobson JS, Grann VR, Neugut AI (2006) Delay of adjuvant chemotherapy initiation following breast cancer surgery among elderly women. *Breast Cancer Res Treat* 99(3):313–321. doi:10.1007/s10549-006-9206-z
34. Nurgalieva ZZ, Franzini L, Morgan RO, Vernon SW, Liu CC, Du XL (2013) Impact of timing of adjuvant chemotherapy initiation and completion after surgery on racial disparities in survival among women with breast cancer. *Med Oncol* 30(1):419. doi:10.1007/s12032-012-0419-1
35. Altundag M, Çelik I, Özişik Y (2000) Is there a range of time for initiation of adjuvant chemotherapy in patients with malignancy? *Ann Oncol* 11(9):1209. doi:10.1023/a:1008339804441
36. Desch CE, Mcniff KK, Schneider EC et al (2008) American Society of Clinical Oncology/National Comprehensive Cancer Network Quality Measures. *J Clin Oncol* 26(21):3631–3637. doi:10.1200/jco.2008.16.5068
37. Buzdar AU, Smith TL, Powell KC, Blumenschein GR, Gehan EA (1982) Effect of timing of initiation of adjuvant chemotherapy on disease-free survival in breast cancer. *Breast Cancer Res Treat* 2(2):163–169. doi:10.1007/bf01806452
38. Cold S, Düring M, Ewertz M, Knoop A, Møller S (2005) Does timing of adjuvant chemotherapy influence the prognosis after early breast cancer? Results of the Danish Breast Cancer Cooperative Group (DBCG). *Br J Cancer* 93(6):627–632. doi:10.1038/sj.bjc.6602734
39. Sánchez CJ, Ruiz A, Martín M et al (2006) Influence of Timing of Initiation of Adjuvant Chemotherapy Over Survival in Breast Cancer: A Negative Outcome Study by the Spanish Breast Cancer Research Group (GEICAM). *Breast Cancer Res Treat* 101(2):215–223. doi:10.1007/s10549-006-9282-0
40. Shannon C, Ashley S, Smith I (2003) Does Timing of Adjuvant Chemotherapy for Early Breast Cancer Influence Survival? *J Clin Oncol* 21(20):3792–3797. doi:10.1200/jco.2003.01.073
41. Gwyn K, Bondy ML, Cohen DS et al (2004) Racial differences in diagnosis, treatment, and clinical delays in a population-based study of patients with newly diagnosed breast carcinoma. *Cancer* 100(8):1595–1604. doi:10.1002/cncr.20169

42. Fedewa SA, Ward EM, Stewart AK, Edge SB (2010) Delays in adjuvant chemotherapy treatment among patients with breast cancer are more likely in African American and Hispanic populations: a national cohort study 2004–2006. *J Clin Oncol* 28(27):4135–4141. doi:10.1200/JCO.2009.27.2427
43. Gorin SS, Heck JE, Cheng B, Smith SJ (2006) Delays in breast cancer diagnosis and treatment by racial/ethnic group. *Arch Intern Med* 166(20):2244–2252. doi:10.1001/archinte.166.20.2244
44. Fedewa SA, Ward EM, Stewart AK, Edge SB (2010) Delays in Adjuvant Chemotherapy Treatment Among Patients With Breast Cancer Are More Likely in African American and Hispanic Populations: A National Cohort Study 2004–2006. *J Clin Oncol* 28(27):4135–4141. doi:10.1200/jco.2009.27.2427
45. Lannin DR (1998) Influence of Socioeconomic and Cultural Factors on Racial Differences in Late-Stage Presentation of Breast Cancer. *JAMA* 279(22):1801. doi:10.1001/jama.279.22.1801
46. Smith EC, Ziogas A, Anton-Culver H (2013) Delay in Surgical Treatment and Survival After Breast Cancer Diagnosis in Young Women by Race/Ethnicity. *JAMA Surgery* 148(6):516. doi:10.1001/jamasurg.2013.1680
47. Berrian JL, Liu Y, Lian M, Schmaltz CL, Colditz GA. Relationship between insurance status and outcomes for patients with breast cancer in Missouri. *Cancer* Published online November 17, 2020. doi:10.1002/cncr.33330
48. Stanley E, Lewis MC, Irshad A et al (2017) Effectiveness of a Mobile Mammography Program. *Am J Roentgenol* 209(6):1426–1429. doi:10.2214/ajr.16.17670
49. Taheri M, Tavakol M; Akbari ME, Almasi-Hashiani A, Abbasi M Relationship of Socio Economic Status, Income, and Education with the Survival Rate of Breast Cancer: A Meta-Analysis. *Iranian journal of public health*. 2019;48(8). Accessed November 17, 2020. <https://pubmed.ncbi.nlm.nih.gov/32292725/>
50. Ramachandran A, Freund KM, Bak SM, Heeren TC, Chen CA, Battaglia TA (2015) Multiple Barriers Delay Care Among Women with Abnormal Cancer Screening Despite Patient Navigation. *Journal of Women's Health* 24(1):30–36. doi:10.1089/jwh.2014.4869
51. Hussain SK, Altieri A, Sundquist J, Hemminki K (2007) Influence of education level on breast cancer risk and survival in Sweden between 1990 and 2004. *Int J Cancer* 122(1):165–169. doi:10.1002/ijc.23007
52. Wu T-Y, Lee J (2019) Promoting Breast Cancer Awareness and Screening Practices for Early Detection in Low-Resource Settings. *European Journal of Breast Health* 15(1):18–25. doi:10.5152/ejbh.2018.4305
53. Gorin SS, Ashford AR, Lantigua R et al (2006) Effectiveness of Academic Detailing on Breast Cancer Screening among Primary Care Physicians in an Underserved Community. *The Journal of the American Board of Family Medicine* 19(2):110–121. doi:10.3122/jabfm.19.2.110
54. Bastani R, Yabroff KR, Myers RE, Glenn B (2004) Interventions to improve follow-up of abnormal findings in cancer screening. *Cancer* 101(S5):1188–1200. doi:10.1002/cncr.20506
55. Ginsburg O, Yip C, Brooks A et al (2020) Breast cancer early detection: A phased approach to implementation. *Cancer* 126(S10):2379–2393. doi:10.1002/cncr.32887
56. Dean LT, Moss SL, McCarthy AM, Armstrong K (2017) Healthcare System Distrust, Physician Trust, and Patient Discordance with Adjuvant Breast Cancer Treatment Recommendations. *Cancer Epidemiology Biomarkers Prevention* 26(12):1745–1752. doi:10.1158/1055-9965.epi-17-04791
57. Jassem J, Ozmen V, Bacanu F et al (2013) Delays in diagnosis and treatment of breast cancer: a multinational analysis. *Eur J Pub Health* 24(5):761–767. doi:10.1093/eurpub/ckt131
58. Heath J, Paulishak M, Kasales C, Schubart J, Kass R. Reasons symptomatic breast cancer patients delay seeking medical care. *Journal of Unexplored Medical Data*. 2019;2019. doi:10.20517/2572-8180.2018.011
59. National Cancer Database. American College of Surgeons. Published 2020. Accessed February 19 (2021) <https://www.facs.org/quality%20programs/cancer/ncdb>

Figures

Figure 1

Derivation of the study population, National Cancer Database 2004 to 2016