Chapter

Long-Term Survivors of Breast Cancer: A Growing Population

Nadeem Bilani, Elizabeth Blessing Elimimian, Leah Elson, Hong Liang and Zeina Nahleh

Abstract

Breast cancer represents the most common malignancy among women. However, due to effective public health campaigns and updated screening guidelines, the annual incidence of late stage diagnoses has fallen. This stage migration has allowed for better prognosis and more women achieving long-term survival. In this chapter, we review long-term survivorship – defined as 10 years from diagnosis – as reported in the United States and around the world. Additionally, we provide analysis for socio-demographic, clinical and pathologic factors associated with 10-year survival, using data from a large national registry. This chapter also utilizes historical case data to forecast stage migration patterns in breast cancer diagnoses, within the United States, to 2030. Finally, we discuss the effects of the novel coronavirus pandemic on breast cancer treatment and access to care, with a review of clinical considerations for the future.

Keywords: breast cancer, epidemiology, survivors, clinical considerations, forecasting

1. Introduction

In 2015, the World Health Organization reported that cancer ranked within the top four reasons for death, before the age of 70, in 113 of the 172 countries surveyed [1]. The impact of cancer on women's health is incontrovertible. An estimated 2.1 million individuals around the world were diagnosed with breast cancer in 2018, alone [2]. It is the most common malignancy in women, matched only in Sub-Saharan Africa by cervical cancer, due to an elevated prevalence of tumorigenic strains of the human papillomavirus [3].

The breast cancer disease burden is expected to increase, due to a number of socioeconomic risk factors, including: aging and growth of the population, nulliparity, later maternal age at first pregnancy, the use of exogenous hormones (i.e. oral contraceptive pills, hormonal replacement therapy), alcohol intake, and obesity [4].

In addition to this rising incidence rate, outcomes in breast cancer are improving over time. In the United States, mortality has dropped by 40% between 1989 and 2017 [5]. This is thought to be due to a combination of a) mass screening campaigns that allow caregivers to diagnose the disease at earlier stages, thus offering

better prognoses, and b) the evolution of targeted and increasingly-efficacious therapeutics.

The relative indolence of most non-metastatic breast neoplasms, compared to other malignancies with more acute courses, makes reports of 5-year overall survival less clinically relevant, except in patients who already have limited life expectancy. Additionally, certain breast cancers may be associated with a high rate of late recurrence. For instance, patients with primary tumors that are estrogen receptor (ER)-positive develop distant metastasis in 10–20% of cases, five or more years following initial diagnosis [6]. Therefore, there is great utility in surveying literature, which reports *long-term* survival outcomes in patients with breast cancer. For the purposes of this chapter, we define "long-term survival" as 10-year overall survival (OS).

We start by reporting national data from the United States, and exploring various socio-demographic, clinical, and pathologic characteristics significantly associated with 10-year OS. Next, we perform a literature review of epidemiologic studies from the United States, and around the world, to survey for trends in this growing population. Finally, we explore numerous clinical considerations in addressing the needs of this specific population, with lessons learned from the coronavirus disease 2019 (COVID-19) pandemic, and implications for future clinical care.

2. Prevalence of long-term survivorship in the United States

On an annual basis, the American Cancer Society (ACS) provides national survival data on breast cancer cases diagnosed within the United States. With respect to long-term survival, the society published that current "relative survival rates" for women diagnosed with breast cancer are 85% after 10 years and 80% after 15 years [7]. These rates are age- and race-adjusted; supported by the provided definition of "relative survival" as the "percentage of patients who will survive their cancer for a given period of time after diagnosis…compared to survival among people of the same age and race who have not been diagnosed with cancer" [8]. Despite high heterogeneity within the breast cancer population, the ACS did not stratify long-term survival rates by other socio-demographic, clinical, or pathologic characteristics in this publication. In order to add to ACS findings, we explored the impact of these factors in more granular detail, using OS as reported by the National Cancer Database (NCDB).

The NCDB is a United States-based registry which collects de-identified clinical, pathologic, and outcomes data on approximately 70% of all cancer diagnoses in the country [9]. Data on patients with breast cancer is uploaded into the NCDB from over 1,400 facilities, accredited by the Commission on Cancer and the American College of Surgeons. At the time of this publication, survival surveillance for patients in this repository included data collected through the year 2016. Therefore, in order to ensure adequate time had transpired to capture 10-year OS, we selected a cohort of patients diagnosed between 2004 and 2006. Univariate analysis was conducted to evaluate for independent factors (e.g., age, race, ethnicity, income, insurance status, facility type, co-morbidity index, clinical stage, grade, histology, oncotype, and treatment type) exhibiting significant association with 10-year survival. Subsequently, variables significant at the univariate level were selected for inclusion within one multiple logistic regression model also predicting 10-year survival. A p-value of <0.001 was considered significant, due to the very large sample size that may overpower correlative testing. A total of n = 515,610 patients with breast cancer were analyzed in this model. The results are depicted in **Table 1**, and explained as follows.

Variable	No. (%)	10-year OS				
		%	OR	95% CI		p-value
Age						<.001
<50 (ref)	125,657 (24.4%)	54.1%	1.000	—	—	—
50–70	256,003 (49.7%)	53.0%	.946	.916	.978	.001
>70	133,950 (26.0%)	30.1%	.427	.407	.448	<.001
Race						<.001
White (ref)	440,048 (87.6%)	48.0%	1.000	—	—	—
Black	52,220 (10.4%)	40.7%	.821	.786	.858	<.001
Asian	9872 (2.0%)	51.9%	1.166	1.067	1.275	.001
Ethnicity						
Hispanic (ref)	445,220 (95.6%)	47.7%	1.000	—	—	—
Non-Hispanic	20,481 (4.4%)	44.4%	.936	.878	.998	.042
Income						<.001
<$30,000 (ref)	55,038 (11.0%)	41.8%	1.000	—	—	—
$30,000–$34,999	79,054 (15.8%)	44.9%	1.026	.977	1.078	.296
$35,000–$45,999	133,171 (26.6%)	46.7%	1.065	1.017	1.115	.008
>$46,000	233,078 (46.6%)	50.5%	1.126	1.076	1.178	<.001
Insurance status						<.001
Uninsured (ref)	10,440 (2.1%)	36.8%	1.000	—	—	—
Private insurance	284,063 (56.5%)	55.4%	1.552	1.417	1.701	<.001
Medicare	181,088 (36.0%)	36.5%	1.264	1.150	1.390	<.001
Medicaid/other governmental insurance	26,766 (5.3%)	41.8%	1.211	1.092	1.343	<.001

Variable	No. (%)	10-year OS				
		%	OR	95% CI		p-value
Facility type						<.001
Community cancer program (ref)	46,176 (9.4%)	43.8%	1.000	—	—	—
Comprehensive community cancer program	227,815 (46.5%)	47.7%	1.125	1.077	1.175	<.001
Academic/research program	142,123 (29.0%)	49.0%	1.063	1.015	1.113	.010
Integrated network cancer program	73,703 (15.0%)	44.6%	.819	.776	.865	<.001
Setting						.001
Metro (ref)	427,832 (85.6%)	47.6%	1.000	—	—	—
Urban	63,288 (12.7%)	47.4%	1.076	1.034	1.120	<.001
Rural	8534 (1.7%)	47.4%	1.091	.984	1.209	.099
Charlson/Deyo comorbidity index						.000
0 (ref)	450,329 (87.3%)	49.1%	1.000	—	—	—
1	52,983 (10.3%)	38.3%	.746	.717	.777	<.001
2	9425 (1.8%)	25.1%	.506	.459	.557	<.001
3	2873 (0.6%)	16.4%	.343	.280	.421	<.001
AJCC clinical staging						<.001
0 (ref)	59,736 (25.7%)	54.5%	1.000	—	—	—
1	87,698 (37.7%)	50.0%	.731	.703	.760	<.001
2	51,604 (22.2%)	42.4%	.526	.503	.551	<.001
3	18,871 (8.1%)	29.7%	.281	.264	.299	<.001
4	14,620 (6.3%)	6.1%	.073	.065	.082	<.001
Grade						<.001

Variable	No. (%)	10-year OS				
		%	OR	95% CI		p-value
Well-differentiated (ref)	94,046 (21.2%)	51.6%	1.000	—	—	—
Moderately-differentiated	184,976 (41.7%)	48.5%	.889	.860	.919	<.001
Poorly differentiated	164,490 (37.1%)	44.9%	.782	.752	.812	<.001
Histology						.007
Ductal carcinoma (ref)	367,409 (72.7%)	47.7%	1.000	—	—	—
Lobular carcinoma	79,387 (15.7%)	47.3%	.993	.957	1.031	.720
Other carcinoma	47,959 (9.5%)	49.1%	1.013	.966	1.061	.598
Epithelial-myoepithelial	1861 (0.4%)	42.1%	.898	.703	1.146	.385
Papillary	6005 (1.2%)	30.8%	1.054	.883	1.260	.559
Fibroepithelial	2058 (0.4%)	34.9%	.937	.755	1.162	.552
Mesenchymal	402 (0.1%)	21.4%	.713	0.309	1.645	427
Estrogen receptor status						
Negative (ref)	97,628 (21.9%)	43.9%	1.000	—	—	—
Positive	348,611 (78.1%)	48.6%	.908	.868	.949	<.001
Progesterone receptor status						
Negative (ref)	147,951 (33.6%)	44.0%	1.000	—	—	—
Positive	292,529 (66.4%)	49.3%	1.095	1.057	1.134	<.001
Type of surgery						.000
None (ref)	30,799 (6.0%)	15.8%	1.000	—	—	—
Lumpectomy	294,554 (57.3%)	52.6%	2.300	2.112	2.506	<.001
Mastectomy	188,531 (36.7%)	44.3%	2.320	2.134	2.523	<.001
Radiation						

Variable	No. (%)	10-year OS				
		%	OR	95% CI		p-value
No (ref)	239,355 (47.5%)	40.4%	1.000	—	—	—
Yes	264,681 (52.5%)	53.3%	1.385	1.341	1.430	<.001
Chemotherapy						
No (ref)	309,000 (62.9%)	46.0%	1.000	—	—	—
Yes	182,510 (37.1%)	49.2%	1.375	1.331	1.420	<.001
Hormonal therapy						
No (ref)	245,859 (51.0%)	42.3%	1.000	—	—	—
Yes	236,454 (49.0%)	51.9%	1.207	1.167	1.248	<.001
HER2-targeted therapy						
No (ref)	497,793 (99.6%)	47.2%	1.000	—	—	—
Yes	1862 (0.4%)	43.3%	1.273	1.236	1.311	<.001

Table 1.
Multiple logistic regression model for predictors of long-term overall survival in breast cancer in the United States, using data from the National Cancer Database (NCDB).

2.1 Overall survival by socio-demographic characteristics

Age at diagnosis was significantly associated with likelihood of long-term OS. The age distribution of our cohort was: n = 125,657 (24.4%) <50 years old, n = 256,003 (49.7%) between 50–70 years old, and n = 133,950 (26.0%) older than 70. Long-term OS rates were similar in patients diagnosed before 50 (54.1%) compared to those diagnosed between 50 and 70 years of age (53.0%). This may highlight the relative indolence of breast cancer as a primary malignancy, particularly when diagnosed and treated at early stages. However, a large drop in 10-year OS was seen in those diagnosed after 70 (30.1%), a cohort more likely to experience acute events due to the cumulative effect of chronic comorbidities such as hypertension, diabetes, and dyslipidemia. This is supported by the life expectancy of individuals in the United States which, in 2016, was estimated to be 78.9 years [10]. The distribution of survival, by age, may differ in other parts of the world, particularly in low- and middle-income countries, or those without mass screening programs.

Racial disparities continue to be a significant major healthcare challenge. In the 1980s, a marked divergence in death rates between White and Black women with breast cancer was first noted [11]. The implementation of mass screening programs disproportionately benefited areas wherein residents had access to favorably-resourced and accredited healthcare institutions [12, 13]; these communities were predominantly White. Additionally, hormonal therapy (e.g. tamoxifen), newly introduced to systemic treatment regimens for treatment of ER+ tumors, was not appropriate for many Black women, who are more likely to present with triple negative breast cancer (TNBC) – a type of breast cancer without ER, PR, or HER2 expression, which is unresponsive to tamoxifen regimens [14]. This is elaborated upon in Section 2.2.

Race-based survival disparity peaked in 2011, with mortality rates reported to be approximately 45% higher in Black versus White patients with breast cancer [5]. Despite improvements over the last decade, race continues to be an important predictor of 10-year OS ($p < 0.001$), as depicted in **Figure 1**. In our analysis, using data extrapolated from the NCDB, patients of Asian descent exhibited the highest long-term overall survival rate (51.9%), followed by White (48.0%) and then Black (40.7%) patients. Beyond access to healthcare, these race-based disparities are thought to be due to the complex interplay between multiple lifestyle factors (such as alcohol consumption and smoking), extent of comorbidity (including obesity, which is associated with worse outcomes in breast cancer due to increased estrogens and inflammatory mediators [15]), and genetics. Interestingly, from our analysis, ethnicity (defined in the NCDB as Hispanic vs. Non-Hispanic) was not determined to be a significant predictor of 10-year OS, even when adjusting for

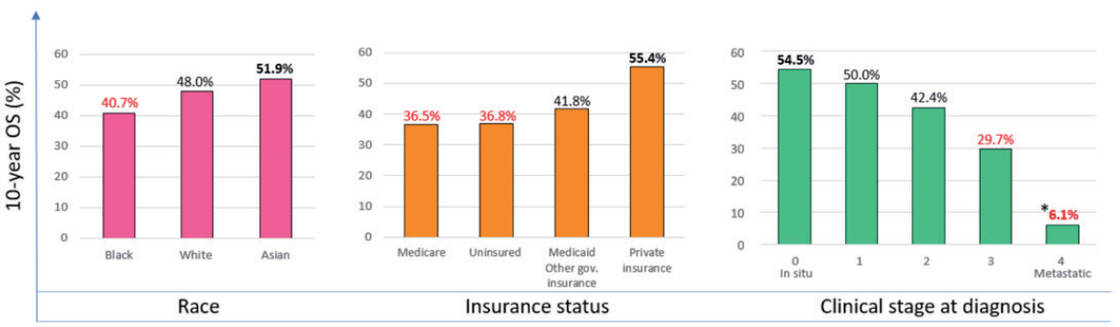

Figure 1.
Pictorial of key predictors of 10-year OS in the United States, through analysis of the National Cancer Database (NCDB).

relevant confounders such as age, race, comorbidity (Charlson/Deyo index), and AJCC clinical stage at diagnosis.

Measures of socioeconomic status – including annual income, insurance status, and treatment facility type – were also significantly associated with 10-year OS in this cohort ($p < 0.001$). Patients who were uninsured exhibited the lowest 10-year OS rates (36.8%), in contrast to patients who had private insurance (56.5%), as depicted in **Figure 1**. A study by Ko, et al., indicates that roughly half of all racial/ethnic disparity, associated with the risk of locally-advanced disease, can be attributed to insurance status as "uninsured" or "underinsured" [16]. Patients without healthcare coverage are less likely to effectively manage chronic comorbidities, including hypertension [17] and diabetes [18], which is likely a contributing factor of higher mortality observed in this subgroup. While setting (urban vs. rural) was not a significant predictor of long-term survival, facility type was ($p < 0.001$), with patients treated at academic cancer programs exhibiting the highest 10-year OS rate (49.0%), followed by those treated at comprehensive community cancer programs (47.7%) and those treated at community cancer programs (43.8%). This may be due to differences in time-to-diagnosis and time-to-treatment, determined by institution size, and care practices that may differ based on the accreditation of different cancer programs, as available to different communities [19].

2.2 Overall survival by clinical characteristics

As expected, the most important predictor of survival in breast cancer in our analysis was 'stage' at diagnosis, as depicted in **Figure 1**. Breast cancer stage represents the extent of spread of cancer in the body, expressed on a spectrum ranging from 0 (the earliest form, wherein cancer cells are restricted to the milk ducts of the breast, but have not invaded other breast tissue) to IV (the latest form, where the cancer has spread to another organ in the body, referred to as "metastatic"). Staging may be *clinical* (based on physical exam and imaging such as mammogram, ultrasound, or magnetic resonance imaging) or *pathologic* (based on evaluation of breast tissue and lymph nodes removed during surgery). We found that the widest disparity in long-term OS was associated with clinical stage of diagnosis (54.5% with stage 0, versus just 6.1% with stage IV disease, $p < 0.001$). As the majority of patients in the United States are diagnosed at early stages of disease (i.e. 0-II), this supports the positive, clinical impact of public health campaigns that target awareness of prevalence, risk factors, signs and symptoms of breast cancer.

Diagnosis of breast cancer is typically confirmed with a biopsy, during which a tumor tissue sample is sent for evaluation by specialists in pathology. Through microscopy, and the use of staining techniques, numerous pathophysiological characteristics of the neoplasm can be determined. Important among them, is the 'breast cancer subtype', referring to the molecular profile of the tumor, based on the expression of three receptors on the surface of breast cancer cells: 1) the estrogen receptor (ER), 2) progesterone receptor (PR), and the 3) human epidermal factor growth factor 2 (HER2) receptor. The combination of these receptors forms the basis for clinical decision-making regarding targeted therapy in breast cancer. For instance, if the primary tumor is ER+/PR+, 'endocrine' or 'hormonal' therapy can be administered (e.g. selective estrogen receptor modulators, or SERMs, like tamoxifen, that directly modulate these hormonal receptors, or aromatase inhibitors, which decrease the natural conversion of androgens to estrogens in the body); if the tumor exhibits HER2+ status, the monoclonal antibody trastuzumab is given to block this receptor subtype.

The NCDB did not routinely document HER2 receptor status in cases diagnosed before 2009, thus the impact of this receptor expression on 10-year OS could not be evaluated in this multivariate model. However, the analysis did include ER status and PR status, demonstrating that positivity of either receptor significantly predicted long-term survival. This finding underscores progress made in the improvement of patient outcomes as treatment modalities become more targeted (prior to endocrine therapy, non-targeted chemotherapy was the gold standard for treatment of even hormone receptor positive breast cancer). This is also strongly reflected in one of our previous analyses, indicating that patients with tumors which were negative for all three receptors (TNBC), exhibited the lowest rate of 5-year OS (71%), followed by the ER-, PR-, HER2+ subtype (77%), the ER/PR+, HER2+ subtype (83%), and a highest 5-year OS rate seen in the ER/PR+, HER2- subtype (84%) [20].

Interestingly, HER2 overexpression, occurring in around 20% of breast cancers, is associated with worse natural prognosis due to increased growth and marked metastatic potential of these tumors [21]. However, we have shown that survival outcomes in ER/PR-, HER2+ breast cancer, in the United States, have surpassed TNBC due to the advent of HER2-targeted regimens. Therefore, HER2+ status may be predictive of treatment efficacy in breast cancer. This may not be the case globally, particularly in low- and middle-income countries which may exhibit limitation in drug funding. In 2012, the Union for International Cancer Control and the Dana-Farber Cancer Institute filed an application with the World Health Organization to add trastuzumab (a HER2-targeted therapy) to the essential medications list [22], an advisory list of the minimum medicine needs for basic healthcare systems. This was not approved until May 2015 [23]. Current literature still reports trans-national disparities in the availability of HER2-targeted therapeutics, and advocates for the distribution of more affordable trastuzumab biosimilars in order to address this ongoing need [24, 25].

Pathologists will also assign a 'grade' to the tumor under evaluation using a method of classification known as the Nottingham modification of the Scarff-Bloom-Richardson system [26]. Grading in breast cancer designates how "abnormal" neoplastic cells appear, and is based on the extent of glandular/tubular differentiation, nuclear pleomorphism, and mitotic count [27]. Grade 1 tumors are "well differentiated", meaning their growth is slower and appears most similarly to normal breast tissue. Grade 3 tumors, on the other hand, are "poorly differentiated", appearing "dysplastic" (very different from normal cells) and have a higher growth potential. Grade 2, tumors have "moderate" differentiation, and fall between Grade 1 and Grade 3 in prognostic implication. While not predictive of the same breadth of overall survivorship as tumor staging, we found in our NCDB analysis that tumor grade was still a statistically significant predictor of 10-year OS: patients with Grade 1 tumors exhibited a 10-year OS rate of 51.6% (unadjusted for stage at diagnosis) versus those with Grade 2 tumors (48.5%) and those with Grade 3 tumors (44.9%). Finally, we also showed that while 'histological subtype' (referring to the tissue type a neoplasm originated from) was not a statistically-significant predictor of long-term overall survival ($p > 0.001$), the highest 10-year OS rates were seen in the most common subtypes: ductal carcinoma (47.7%, not adjusted for stage at diagnosis) and lobular carcinoma (47.3%). Patients with some rare histologies exhibited lower rates of 10-year OS, including epithelial-myoepithelial (42.1%), fibroepithelial (34.9%), papillary (30.8%), and mesenchymal (21.4%) breast cancers. The scarcity of these subtypes has limited the ability to study these unique histologies in a high-throughput manner. However, recent studies suggest that tumor histology should be considered when determining the optimal treatment approach for each patient [28–30].

3. Prevalence of long-term survivorship globally

Survival rates for breast cancer vary considerably in different parts of the world. The 5-year OS rate – which is more commonly reported and can thus be compared when controlling for confounders such as race, stage at diagnosis, age at diagnosis, etc. – varies from over 80% in developed countries, to less than 60% in low- and middle-income countries [31]. However, less is known about 10-year OS in low- and middle-income countries. We conducted a systematic search using MEDLINE, via PubMed and Google Scholar, from inception until December 2020. We included observational cohort studies also reporting OS rates if published in the English language. The search strategy involved a combination of free text searches, as well as medical subject headings (MeSH), as follows: ("Breast Neoplasms" [MeSH], OR "breast cancer" OR "breast tumor") AND ("Survival" [MeSH] OR "Survival Rate" [MeSH] OR "Life Tables" [MeSH] OR "Kaplan–Meier Estimate" [MeSH] OR "Hazard Ratio" OR "Cox regression") AND ("Cohort Studies" [MeSH] OR "Retrospective Studies" [MeSH] or "Prospective Studies" [MeSH] OR "follow-up" or "longitude").

We found n = 37 studies reporting 10-year OS rates, as presented in **Table 2**. The majority were from high income countries (n = 27, 73%), while n = 10 (27%) reported data from low- and middle-income countries. It was found that high income countries have been reporting long-term OS data over a longer period of time (1978–2020), while data from low- and middle-income countries have been published more recently (2008–2020). Additionally, cohorts used in studies from high income countries were larger (mean sample size: n = 1,573) than those from low- and middle-income countries (mean sample size: n = 268). In comparing data published since the year 2000, the mean 10-year OS rate from high-income country studies was 72%, versus the mean 10-year OS rate from low- and middle-income countries studies, which was 64%. However, these comparisons do not control for the impact of patients age at diagnosis (most studies did not report a

First author	Year of publication	Country	Sample size	Mean age y +/– SD	10-year survival
Low- and middle-income countries					
Mai TTX et al.	2019	Korea	206	47 +/– 9	0.88
Dolatkhah R et al	2019	Iran	4989	50.4 +/– 13	0.65
Bender MPF et al	2015	Brazil	264	63 +/– 13	0.41
Ziaei JE et al	2013	Iran	271	48	0.76
Li BJ et al	2012	China	84	57 +/– 11	0.63
Gokce T et al	2011	Turkey	1746	51	0.79
Xia LP et al	2010	China	70	NR	0.73
Heydari ST et al	2009	Iran	877	47 +/– 12	0.46
Rajaeefard AR et al	2009	Iran	310	NR	0.53
Yaghmaei et al	2008	Iran	50	52 +/– 14	0.47
High-income countries					
Wu SC et al	2020	Taiwan	2,002	NR	0.78
Ameijide A et al	2019	Spain	10,195	NR	0.41

First author	Year of publication	Country	Sample size	Mean age y +/− SD	10-year survival
Ignatov A et al	2018	Germany	12,053	NR	0.82
Yoshimura A et al	2018	Japan	63,348	NR	0.79
Park EH et al	2017	Korea	109,988	NR	0.85
Plichta JK et al	2016	USA	584	NR	0.86
Campbell ID et al	2015	New Zealand	101,824	NR	0.84
Fong Y et al	2014	England	1,712	NR	0.77
Hamadeh RR et al	2014	Bahrain	1,005	51	0.49
Hauth EA et al	2012	Germany	222	NR	0.96
Marchal F et al	2009	France	116	66 +/− 12	0.52
Thalib L et al	2009	Sweden	300,011	NR	0.64
Ueno M et al	2007	Japan	559	NR	0.75
Jayasinghe UW et al	2005	Australia	393	54	0.69
Tejler G et al	2004	Sweden	7,892	NR	0.54
Minelli L et al	2004	Italy	2,460	NR	0.47
Jensen AR et al	2003	Denmark	1,573	56	0.66
Twelves CJ et al	2001	Scotland	1,617	NR	0.52
Barchielli A et al	1999	Italy	1,182	NR	0.53
Fakhro AE et al	1999	Bahrain	93	50	0.36
Wallgren A et al	1997	Sweden	75	NR	0.54
Sariego J et al	1995	USA	81	NR	0.49
Sant M et al	1991	Italy	1,991	NR	0.5
Toikkanen S et al	1990	Finland	461	NR	0.37
Isard HJ et al.	1988	USA	70	57	0.7
Adami HO et al	1985	Sweden	12,319	NR	0.38
Heller KS et al	1978	USA	304	65	0.62

Table 2.
Review of global cohort data reporting long-term overall survival rates of breast cancer.

mean age), disease stage at diagnosis (though all cohorts reported individuals from all four stages of breast cancer), race, or the presence of comorbidities in these cohorts. Therefore, more information will be needed to calculate pooled estimates of global survival, by region or country. This review of studies reveals a stark disparity in the availability of long-term outcomes data from different regions around the world.

4. Forecasting stage of diagnosis in the United States to 2030

As mentioned, the strongest predictor of 10-year survival outcomes, in breast cancer, is stage at diagnosis. As diagnostic capabilities continue to facilitate earlier identification of disease, it is important to understand how stage migration is

predicted to change in the future – an important metric for allocation of resources and services needed for this growing group of survivors.

In order to understand future stage migration patterns, in a cohort of long-term survivors of breast cancer, there is utility in forecasting the predicted proportion of cases that are expected to be early stage (0, I or II) versus late stage (III or IV) based on historical trends. To do this, we extracted annual incidence data from the NCDB from 2004–2016, stratifying by cases that were diagnosed at early stage versus those at late stages. This data was analyzed via time-series forecasting, specifically autoregressive integrated moving averages (ARIMA) modeling, which considers annual variation and accounts for temporal correlation in analysis of historical data [32]. The performance of ARIMA models has been found to be comparable to other time series models in its capacity to forecast healthcare data, such as the Bayesian shared two-component model [33].

Multiple ARIMA models were generated using the Statistical Package for the Social Sciences (SPSS) Version 27.0 software (IBM Corp, Armonk, NY) using different combinations of the autoregressive parameters for 'p', the order of the autoregressive model, 'd', the degree of differencing and 'q', the order of the moving average (p, d, q). The most predictive model was selected using the lowest Bayesian Information Criteria, and mean absolute percentage error, and this was the (0, 1, 0) ARIMA model. **Figure 2** depicts 1) the historical incidence of breast cancer in the United States (black curve), stratified by stage at diagnosis (blue for early-stage and red for late-stage) for the years 2004–2016, and 2) forecasted incidence of total, early stage and late stage cases to the year 2030. The annual proportion of new cases diagnosed at late-stage is highlighted on as an emboldened numerical figure in red. Tabulated numerical data of these forecasts can be found in **Table 3**.

We found that, based on historical trends, the proportion of cases diagnosed at advanced stages of disease is projected to fall to 10.7%, compared to the historical proportion, in 2004, of 19.8%. Based on this projected stage migration, we can expect the number of long-term survivors in the United States to continue to grow. In Section 5, we discuss the impact of the COVID-19 pandemic on mass screening, and implications for staging and care of patients diagnosed during 2020.

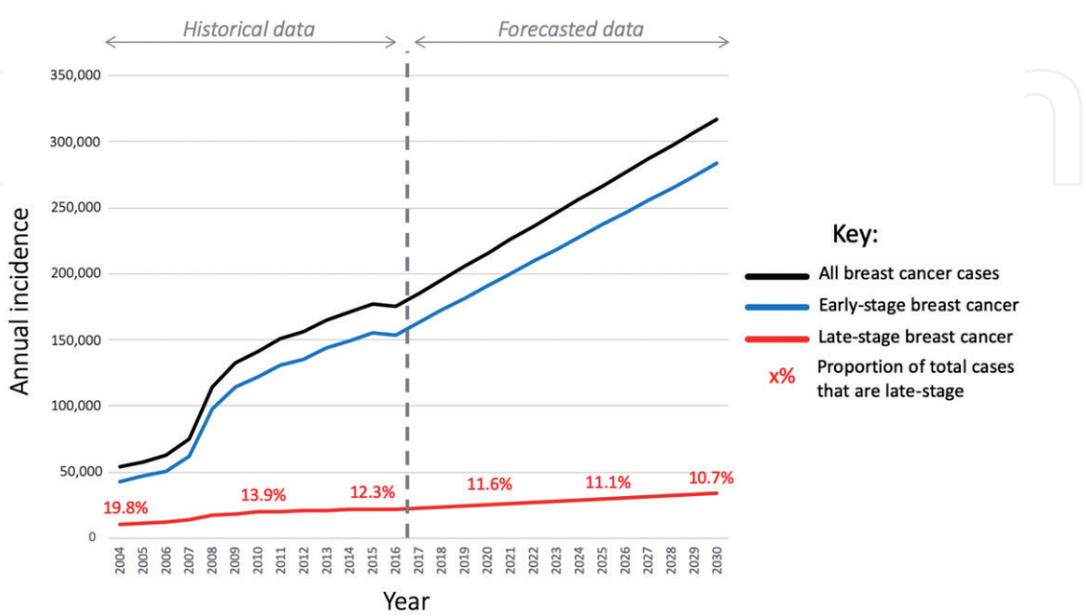

Figure 2.
ARIMA forecasts of breast cancer incidence in the United States to the year 2030, stratified by stage at diagnosis, using the NCDB.

	Year	Total Incidence	Incidence Diagnosed at Early Stages (0–2)	Incidence Diagnosed at Late Stages [3–4]	% of Cases Diagnosed at Advanced Stages
Historical data from the NCDB	2004	53,551	42,970	10,581	19.76%
	2005	57,902	46,792	11,110	19.19%
	2006	62,412	50,503	11,909	19.08%
	2007	75,251	61,786	13,465	17.89%
	2008	114,666	97,699	16,967	14.80%
	2009	132,520	114,357	18,163	13.71%
	2010	141,328	121,716	19,612	13.88%
	2011	151,081	130,967	20,114	13.31%
	2012	156,102	135,506	20,596	13.19%
	2013	164,902	143,840	21,062	12.77%
	2014	171,275	149,422	21,853	12.76%
	2015	177,569	155,709	21,860	12.31%
	2016	175,293	153,924	21,369	12.19%

	Year	Total Incidence	Incidence Diagnosed at Early Stages (0–2)	Incidence Diagnosed at Late Stages [3–4]	% of Cases Diagnosed at Advanced Stages
Forecasted data using (0,1,0) ARIMA modeling	2017	185,438	163,170	22,268	12.01%
	2018	195,583	172,416	23,167	11.85%
	2019	205,728	181,662	24,066	11.70%
	2020	215,873	190,908	24,965	11.56%
	2021	226,018	200,154	25,864	11.44%
	2022	236,164	209,401	26,763	11.33%
	2023	246,309	218,647	27,662	11.23%
	2024	256,454	227,893	28,561	11.14%
	2025	266,599	237,139	29,460	11.05%
	2026	276,744	246,385	30,359	10.97%
	2027	286,889	255,631	31,258	10.90%
	2028	297,035	264,878	32,157	10.83%
	2029	307,180	274,124	33,056	10.76%
	2030	317,325	283,370	33,955	10.70%

Table 3.
Historical incidence and forecasted incidence to 2030 of breast cancer in the United States, using data from the National Cancer Database (NCDB).

5. Impact of the COVID-19 pandemic

5.1 COVID-19: Epidemiology & healthcare impacts

The COVID-19 pandemic is now a defining feature of the year 2020. This novel coronavirus was identified in 2019, as the etiology of a pneumonia diagnosis in Wuhan, in the Hubei province in China [34]. Genomic sequencing and phylogenetic analysis indicated that the coronavirus that causes COVID-19 is of the same subgenus as the severe acute respiratory syndrome (SARS) virus [35, 36]. This led to the determination that COVID-19 is due to severe acute respiratory syndrome coronarivurs-2. Following its discovery, the outbreak of this disease spread rapidly: on January 10, 2020, the genomic sequence of SARS-CoV-2 was released and shared globally by China [37]; by February of 2020, COVID-19 had quickly spread through the Hubei province [38]; and On March 11,2020, the World Health Organization, had declared the COVID-19 outbreak a global emergency and pandemic [38].

In an attempt to flatten the epidemiologic growth curve of new COVID-19 diagnoses, public health departments implemented targeted social measures to decrease transmission rates. This included emphasis on social distancing, stay-at-home mandates, a requirement of face masks worn in public, and hand hygiene [39]. Additionally, in order to reduce mortality and relieve the case-load pressure on clinical care providers, many healthcare systems were forced to change clinical practice. While there has been much investigation into the pathology and biologic effects of COVID-19, the overall impact of COVID-19 on management of chronic health outcomes – including breast cancer management and overall survival – is still evolving.

Due to the COVID-19 pandemic, the mechanism for healthcare delivery has changed substantially. One of the changes seen in the United States, was the broad adoption of telemedicine and the upheaval of the in-person visit. Prior to the year 2020, the use of telemedicine was unsubstantial [40]. However, telemedicine visits increased from 1.1% during the second quarter (Q2) of 2019, to 35.3% in Q2 of 2020 [41]. Correspondingly, as the rise in the rate of remote visits increased, the number of in-person visits decreased – the number of office-based health care visits in Q2 of 2020, decreased by 50.2% compared with the previous year [41]. While helping to slow the dissemination of COVID-19, this decrease of in-person visits has made the full-spectrum of care for patients with breast cancer challenging, because physical exams and in-person evaluations have also declined. As a result, co-morbidity management may have also suffered: during Q2 of 2020, blood pressure assessments decreased by 50.1%, while cholesterol assessments decreased by 35.3% [41].

The overall effect of COVID-19 on delays in cancer diagnosis, disruptions in treatment, and modifications to therapeutic regimens is still being evaluated. One report, including 609 patients with breast cancer, identified treatment delays for 44% of the study population, aged 45 years and younger [42]. Another study suggests a higher death rate in cancer patients in receipt of recent therapy, however the proportion of patients reported on active therapy, in this study, was marginal and thus conclusive correlation cannot be determined [43–45]. Literature has shown that patients with cancer, when compared to those without cancer, are at increased susceptibility to infection, secondary to systemic immunosuppression from their cancer or anticancer therapy [46–49]. Initial reports suggested patients with cancer experienced more frequent COVID-19 complications [43, 50, 51]. As a result, physicians and patients must strategically balance the risks of cancer advancement, cancer relapse, etc. with the risks of hospitalization or death secondary to a COVID-19-related complication. Through diagnoses to management, special concern for patients with cancer is warranted due to the pandemic.

Patients with breast cancer might be at an increased risk for treatment-related complications and other health issues during the COVID-19 pandemic. The CDC reports that having cancer increases your risk of severe illness from COVID-19 [52]. Several studies have been conducted with respect to the effects of COVID-19 on patients with cancer. One multicenter study was conducted to evaluate the clinical characteristics of COVID-19-infected patients who died within 28 days of hospitalization in the intensive care unit [53]. This study reported 784 deaths after 28 days, 60 of these deaths (7.7%) were among those with active cancer; their multivariable model revealed that active cancer was associated with increased COVID-19-driven mortality (odds ratio (OR), 2.15; 95% CI, 1.35–3.43) [53]. An additional multi-institutional study was performed to evaluate the impact of COVID-19 on patients with active or prior malignancies [54]. The primary end point of this analysis was all-cause mortality, within 30 days of a COVID-19 diagnosis. Within this population, 22% had hematologic malignancies, and the remainder were previously diagnosed with solid tumors [54]. This study did *not* find an association between increased COVID-19-related mortality and cancer type, anticancer therapy, or recent surgery. There were several factors associated with increased 30-day mortality: male sex (OR, 1.63 [95% CI, 1.07–2.48]), older age (per 10 years) (partially adjusted OR, 1.84 [95% CI, 1.53–2.21]), increased comorbidities (≥2) (OR, 4.50 [95% CI, 1.33–15.28]), a previous smoking status (OR, 1.60 [95% CI, 1.03–2.47]), Eastern Cooperative Oncology Group performance status 2 (OR, 3.89 [95% CI, 2.11–7.18]) or more (OR, 5.66 [95% CI, 2.79–11.47]), and progressive cancer (defined as no longer responding to treatment) (OR, 5.20 [95% CI, 2.77–9.77]) [54].

5.2 Relationship between COVID-19 and breast cancer

The increased risk of severe illness, secondary to COVID-19, in patients with breast cancer [52] might be multifaceted. Both cancer, and cancer treatment, can cause a significant physiologic strain on protective mechanisms of the human body. The immune system is intrinsically linked to breast cancer pathogenesis via inflammatory pathways, immune surveillance, and adaptive immunity [55]. Chronic inflammatory activity has been discovered in all breast cancers, regardless of breast cancer subtype [56]. This chronic inflammation can lead to damaged breast cells, which may support continued tumor progression, with some breast cancer models revealing CD4+ T lymphocytes indirectly promoting invasion and metastasis [57].

An additional reason for a potentially increased risk of serious complications, including death, secondary to COVID-19, in breast cancer patients, is impaired immunity due to chemotherapy. Treatment, with chemotherapy or radiation therapy, can lead to chronic pain, immune suppression, treatment-related toxicities, failure to thrive, and decreased physical and cognitive abilities [58]. Chemotherapy has been shown to induce neutropenia and lymphopenia in patients [59]. Women with breast cancer, who were treated with adjuvant therapy that consisted of chlorambucil, methotrexate, and 5-fluorouracil had decreased peripheral blood lymphocytes [60]. Similarly, other studies report decreased CD4+ cell counts along with concurrent pneumocystis pneumonia in patients with breast cancer who had received multi-agent chemotherapy and radiation therapy [61].

The relationship between the uses of immune check point inhibitors (ICIs) in breast cancer patients is another new area of interest during the COVID-19 pandemic. Several ICIs have been developed targeting breast cancer; some of the most clinically-advanced are those that target programmed cell death-1 (PD-1) and programmed cell death ligand-1 (PD-L1) [62]. Anti-PD-1/PD-L1 agents are an emerging treatment modality with encouraging results for aggressive breast tumors, like

triple negative breast cancers [63]. These ICI therapies, however, are associated with several significant side effects -- one of which includes inflammatory syndromes like pneumonitis, which targets the lungs [64, 65]. These treatments have also been associated with increased inflammation and tissue damage [66, 67]. Currently, reports evaluating the relationship between anti-PD-1/PD-L1 agents and COVID-19 are ongoing. But, some preclinical studies reveal that viral clearance is accelerated by PD-1/PDL-1 pathways and, thus blocked by immune check point inhibitors [68]. Other reports have associated COVD-19 with increased T-cell exhaustion when there is increased expression of PD-1 and PDL-1 [69].

As the effect of COVID-19 on breast cancer patients in receipt of ICIs is still being evaluated, members of the medical community defer to historical trends between ICIs and other viruses for clinical decision making. For instance, the checkpoint inhibitor, pembrolizumab has demonstrated efficacy in a subset of patients with progressive multifocal leukoencephalopathy caused by JC virus infection [70]. Additionally, some studies have noted that ICIs exacerbate viral lung infections, with increased toxicities observed in the winter months when the majority of the population are diagnosed with colds and the flu [71, 72].

Although there are increased risks and side effects associated with the use of chemotherapy and ICIs during the COVID-19 pandemic, the benefits of these treatment modalities could outweigh the risks. The OS of breast cancer patients has improved significantly over the last three decades, due in part to improvements in systemic chemotherapy, endocrine therapy, targeted therapy, and recently the application of ICIs [73, 74]. Therefore, while breast cancer therapies may be associated with negative side effects, recovery is possible with appropriate management, dependent upon tumor burden and the overall health status of the patient [75–77]. In order to maximize the clinical efficacy of these treatment modalities, while limiting COVID-19-related health risks, additional research is needed to guide practice.

6. Clinical considerations of a growing cohort of long-term survivors

While outcomes following treatment of invasive breast cancer have become increasingly favorable, survivors remain at-risk for recurrence of disease, either loco-regionally or at a distant site. In one large cohort of 9,514 women diagnosed with breast cancer under the age of 75, 10.4% developed distant metastasis, most commonly at a bony site [78]. Patients were more likely to experience recurrence in the period 5–10 years after diagnosis, if they presented with primary tumors that were ER-positive, lymph-node positive, or larger than 20 mm in size [78]. Women with ER-negative tumors, however, have a lower risk during this period. The development of multigene sequencing panels predicting outcomes in ER-positive tumors can guide clinicians to ensure at-risk patients receive the appropriate adjuvant therapy.

Survivors of breast cancer should undergo regular follow-up for surveillance and management of treatment-related effects, as well as breast-specific and other indicated imaging to evaluate for malignant recurrence, or new disease. This management necessarily includes a wide range of disciplines in medicine. Breast surgery or radiation therapy can result in chronic pain, fibrosis, fat necrosis, or recurrent skin infections in the chest wall [79, 80]. Patients are also at long-term-risk for cardiovascular dysfunction, including congestive heart failure [81], ovarian failure [82], and even the development of secondary cancers [83]. For this reason, the care of long-term survivors of breast cancer should be based on collaboration between multiple subspecialties. Patients should also continue to receive age-appropriate screening as indicated for the general population with respect to conditions other than breast cancer.

Cancer diagnoses are also associated with increased patient distress and anxiety [84]. Therefore, clinicians are strongly encouraged to consider psychosocial support for long-term breast cancer survivors, as an important complement to clinical monitoring. Providing integrated care that is directed to the overall wellness of the patient, maximizes the potential to increase patient satisfaction, increase patient medical compliance, and preserve quality of life [85–87]. Interestingly, it has also been found that ethnic minority groups, who typically report poorer quality of life and worse distress after diagnosis, may derive more acute benefit from integrated modalities like art therapy [88]. It is also of importance to note that effective psychosocial support programs have been shown to be significantly associated with favorable clinical outcomes [84, 89–92].

7. Conclusions

The advancement of screening modalities and novel therapies has led to more favorable prognoses in patients with breast cancer. As a result, long-term breast cancer survivors are a large and continually-growing group, globally. This group is also projected to increase, substantially, within coming years. While these trends are favorable and clinically promising, patients with breast cancer should undergo regular follow-up for surveillance and management of treatment-related effects, as well as potential disease recurrence. In the time of the COVID-19 pandemic, it is also important to note a potential combinatorial effect of possible complications secondary to cancer treatment received, and possible impact on screening and treatment delays imposed by the novel coronavirus, on both communities and health care delivery systems.

Conflict of interest

The authors declare no conflict of interest.

Abbreviations

ACS	American Cancer Society
ARIMA	Autroregressive integrated moving average
COVID-19	Coronavirus disease 2019
ER	Estrogen receptor
HER2	Human epidermal growth factor 2
ICI	Immune checkpoint inhibitor
NCDB	National Cancer Database
OS	Overall survival
PR	Progesterone receptor
PD-1	Programmed cell death-1
PD-L1	Programmed cell death ligand
SARS	Severe acute respiratory disorder
TNBC	Triple negative breast cancer

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Author details

Nadeem Bilani, Elizabeth Blessing Elimimian, Leah Elson, Hong Liang and Zeina Nahleh*
Cleveland Clinic Florida, Weston, Florida, USA

*Address all correspondence to: nahlehz@ccf.org

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