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Disparities in the occurrence of long term effects of bone marrow suppression after treatment in adolescent young adult breast cancer survivors

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Abstract

Background—Many adolescent and young adult (AYA) breast cancer (BC) patients receive adjuvant therapy as initial treatment with long-term bone marrow suppression as a potential complication, but no studies have evaluated the impact of race/ethnicity on the development of bone marrow suppression in AYA BC survivors.

Methods—Female patients ages 15-39 years diagnosed with BC (2006-2018) and surviving ≥2 years were identified from the California Cancer Registry and linked to statewide hospitalization data. We estimated the cumulative incidence of developing late effects of bone marrow suppression: leukopenia, anemia, thrombocytopenia, bleeding and infection/sepsis during hospital discharge diagnoses present ≥ 2 years after diagnosis. We examined the impact of sociodemographic and clinical factors on late effects using multivariate Cox proportional hazards regression.

Results—Of 11,293 patients, 42.8% were non-Hispanic (nH) White, 28.8% Hispanic, 19.5% Asian/Pacific Islander, and 7.5% nH Black. In multivariable analyses, nH Blacks had the highest risk (vs. nH Whites) of anemia [Hazard Ratio (HR) 1.72, 95% Confidence Interval (CI) 1.47-2.02], leukopenia [HR: 1.56, CI 1.14-2.13], thrombocytopenia [HR: 1.46, CI 1.08-1.99],

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Ethics Approval

This study was approved by the California Committee for the Protection of Human Subjects.

major infection/sepsis [HR: 1.64, CI 1.4-1.92], and bleeding [HR: 1.89, CI 1.39-2.58]. Hispanics had a higher risk of developing anemia, [HR: 1.17, CI 1.04-1.32] bleeding, [HR: 1.4, CI 1.12-1.76] and major infections/sepsis [HR: 1.36, CI 1.21-1.52]. Asian/Pacific Islanders had only a higher risk of developing bleeding [HR: 1.33, CI 1.03-1.72]. Patients from a low neighborhood socioeconomic status had a 20% higher risk of infection/sepsis [HR: 1.21, CI 1.1-1.34], but there were no associations for the other late effects.

Conclusions—We identified that AYAs of nH Black, Hispanic, and Asian/Pacific Islander race/ethnicity are at an increased risk of several late effects after adjuvant therapy compared with nH whites. From this data, providers can implement early/frequent screening of hematologic late effects in these high-risk survivors.

Keywords

Breast Cancer; Adolescent and young adult (AYA); bone marrow suppression; race/ethnicity; AYA breast cancer survivors

INTRODUCTION

Breast cancer (BC) is the most common cancer of adolescent and young adults (AYAs), defined as ages 15-39[1], in the United States, accounting for 30% of cancer diagnoses in this population.[2,3,4] There are 13,000 new cases of AYA BC diagnosed each year in the United States[4] and 5.6% of all invasive BCs occur in AYAs.[2] Compared to their older counterparts, they are more likely to have a familial cancer predisposition, larger tumors, and distant metastatic disease at diagnosis. The tumors have more unfavorable characteristics like higher grade, lymphovascular invasion, and more aggressive subtypes like luminal B, HER2 positive, and triple negative.[5] They are at a higher risk of adverse outcomes, including higher rates of recurrence.[2,5,6,7] In the AYA population, breast cancer is the most common cancer related death (22% of AYA cancer deaths in 2017)[8] which is thought to be due to the more aggressive tumor biology and lack of routine screening.[3] When compared to older women, AYA patients are 39% more likely to die from BC.[5] Due to this more severe disease, AYA breast cancer patients are often treated with adjuvant therapy,[2] including higher use of radiation[9] and 1.9 times the odds of receiving chemotherapy than patients in their forties ($p<0.001$).[5] However, due to their expected long-life span, long-term bone marrow suppression is a significant potential complication of the adjuvant treatments. Prior studies have shown a greater risk of long-term complications in the AYA population who receive chemotherapy, which is dependent on the cumulative dose.[10] However, no studies have evaluated how race/ethnicity is associated with the development of these long-term complications in AYA BC survivors.

Race and ethnicity are sociocultural categorizations that can capture groups experiencing structural racism and health inequities.[11] Racial and ethnic differences within the AYA population have been previously identified. Non-Hispanic (nH) Black AYAs have a 14% higher incidence of BC development then nH white AYAs, higher prevalence of triple negative tumors,[12] and a higher BC mortality rate.[8] Furthermore, the racial and ethnic disparity in breast cancer mortality is largest in the AYA population.[8] However, no population-based studies have addressed if the development of late effects after

chemotherapy for BC treatment differs by race/ethnicity, neighborhood socioeconomic status (SES), or health insurance. Addressing disparities in healthcare is incredibly important to better target patients who would most benefit from surveillance and intervention.

In this study, we sought to determine whether the development of late effects of bone marrow suppression after adjuvant therapies differed by sociodemographic factors. Using the population-based California Cancer Registry (CCR) data linked to healthcare data from the California Department of Healthcare Access and Innovation (HCAI), we analyzed associations between race/ethnicity and sociodemographic factors and late effects among AYA BC patients surviving 2 or more years. The purpose of this study was to identify groups at higher risk of late effects of bone marrow suppression to develop strategies to improve surveillance and long-term care for AYA BC survivors.

METHODS

Data Source and Study Population

Data for this analysis were provided by the California Cancer Registry (CCR) linked to the Department of Health Care Access and Information (HCAI). The CCR is one of the country's largest and most diverse registries by race/ethnicity and socioeconomic status (SES), capturing more than 99% of all invasive cancers diagnosed in the state of California. This linkage employed probabilistic algorithms of the CCR, utilizing social security number, date of birth, gender, and residential zip code. The HCAI hospital data contain detailed information for each discharge from any non-Federal (e.g., not military or Veterans Administration) hospitals in California, including hospitalization, emergency department, and ambulatory surgery visits. We used the International Classification of Diseases, Ninth or Tenth Revision, Clinical Modifications (ICD-9-CM/ICD-10-CM) to identify late effects of bone marrow suppression at each visit. Medical visits in the outpatient setting were not captured in HCAI.

Patients eligible for the study were persons aged 15-39 years who resided in California when diagnosed with primary invasive breast cancer during the period of 2006-2018, reported to the CCR from all non-Veterans Administration facilities, and surviving ≥2 years after diagnosis. We used International Classification of Disease for Oncology, 3rd Edition, (ICD-O-3) site codes C50.0–50.9 (excluding codes for sarcoma, melanoma, neuroendocrine tumors, sweat gland tumors, and lymphoma) to identify cases. Bilateral primary and inflammatory breast cancers were excluded. The final study population included 11,293 AYA breast cancer patients after exclusion of those diagnosed at autopsy or through death certificates, who died within 2 years or had invalid survival time (n=2,271), with secondary cancer within 60 days (n=16), or with non-adenocarcinoma histologies (n=93).

Demographics and Clinical Variables

For each patient, we obtained CCR information routinely recorded in the medical record at diagnosis including age, race/ethnicity nH White, Hispanic, nH Black, and Asian or Pacific Islander, other/unknown, neighborhood socioeconomic status (SES) based on patients' residential census-block group and categorized in tertiles,[13-15] health insurance [public

(Medicaid and other government-assisted programs), private/military (health maintenance organizations, preferred provider organizations, and managed care not otherwise specified), none, and unknown], American Joint Committee on Cancer (AJCC) stage, tumor grade, histology, tumor size, lymph node involvement, estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER-2) tumor-expression status, and first course of treatment modalities for the primary cancer (chemotherapy, radiation, primary surgery). Hormone receptor positive (HR+) indicates any combination of ER and PR positivity as well as HER2 negativity. HER2+ category indicated the patients are Her-2 positive but also hormone receptor negative.

Outcome Variables

The primary outcome in this study was the occurrence of late effects of bone marrow suppression: leukopenia, anemia, thrombocytopenia, bleeding and infection/sepsis during hospital discharge diagnoses present ≥ 2 years after diagnosis. While only the first diagnosis relative to each type of adverse health condition was noted, an individual could have multiple adverse events for each system recorded. Infectious disease was based only on a principal diagnosis to avoid overestimates. To examine the temporal relationship between breast cancer and long-term leukopenia, anemia, thrombocytopenia, bleeding, we excluded pre-existing medical conditions present before breast cancer diagnosis as outcomes. However, since infection/sepsis are acute and curable events, we did not apply this exclusion. All study protocols were overseen by the Institutional Review Board of the University of California, Davis and by the California Committee for the Protection of Human Subjects.

Statistical Analyses

The 5-year cumulative incidence and associated 95% confidence intervals (CIs) of developing adverse late effects ≥2 years after diagnosis was calculated using nonparametric methods that account for death as a competing risk. Person-years of observation were compiled from two years after breast cancer diagnosis to date of first hospitalization with a medical condition, the date of last known contact, date of death or the study cut-off date (12/31/2020), whichever occurred first. Gray's K-sample test statistic was used to determine whether cumulative incidence of a medical condition differed by sociodemographic or clinical factors.[16]

To evaluate sociodemographic and clinical characteristics associated with the occurrence of each medical condition ≥2 years after diagnosis, we used multivariable flexible parametric models[17] to calculate hazard ratios (HR) and 95% CIs. A p-value <0.05 was used to indicate statistical analysis. All analyses were conducted using SAS version 9.4 software (SAS institute Inc., Cary, NC, USA).

RESULTS

Our study consisted of 11,293 AYA patients diagnosed with a primary, invasive breast cancer. As shown in Table 1, 42.8% were nH White, 28.8% Hispanic, 19.5% Asian/Pacific Islander, and 7.5% nH Black. Within the cohort, 49.1% lived in a high SES neighborhood

and 77.9% had private insurance. Of all patients, 72.9% had local or regional disease (27.9% stage I, 45% stage II). Most had surgical treatment (92.2%), 77.1% received chemotherapy, and 46.1% radiation therapy. Among AYAs with surgery treatment, 49% were also treated with radiation. In total, 9987 of patients were alive at the end of the study period, whereas 1306 had died from breast cancer.

The 5-year cumulative incidence for anemia (21.5% vs 17.4%), leukopenia (5.9% vs 4.0%), thrombocytopenia (6.5% vs 3.7%), and infection/sepsis (22.0% vs 16.9%) were greater following initial treatment with chemotherapy versus no chemotherapy ($p<0.0001$), but not bleeding ($p=0.1$) (Supplemental Table 1). This trend was mirrored for patients treated with radiation versus no radiation: anemia (21.7% vs 19.6%), leukopenia (6.6% vs 4.4%), thrombocytopenia (7.3% vs 4.6%), and infection/sepsis (22.2% vs 19.7%) were greater following initial treatment with radiation ($p<0.01$), but not bleeding ($p=0.3$). NH Blacks had the highest incidence of all late effects: anemia (30.4%), leukopenia (7.6%), thrombocytopenia (7.8%), infection/sepsis (28.6%), and bleeding (7.9%) (Figure 1a). Patients with public insurance had a significantly higher incidence of anemia (31.6% vs 17.9%), leukopenia (8.8% vs 4.6%), thrombocytopenia (9.3% vs 5%), infection/sepsis (36.4% vs 17%), and bleeding (9.1% vs 4.7%) than those with private insurance. With respect to neighborhood SES, patients residing in low SES neighborhoods had a significantly higher incidence of anemia (22.8% vs 18.3%), leukopenia (5.8% vs 5.1%), infection/sepsis (24.5% vs 17.1%), and bleeding (6.4% vs 4.7%). However, patients residing in a high SES neighborhood had a higher incidence of thrombocytopenia (6% vs 5.7%), but this did not reach statistical significance ($p=0.4$) (Figure 1b).

In multivariable models (Table 2), nH Blacks had the highest risk (vs. nH Whites) of anemia [Hazard Ratio (HR) 1.72, 95% CI 1.47-2.02], leukopenia [HR: 1.56, CI 1.14-2.13], thrombocytopenia [HR: 1.46, CI 1.08-1.99], major infection/sepsis [HR: 1.64, CI 1.4-1.92], and bleeding [HR: 1.89, CI 1.39-2.58]. Hispanics had a 17% higher risk of developing anemia, 89% bleeding, and 36% major infections/sepsis. Asian/Pacific Islanders had only a 33% higher risk of developing bleeding when compared to nH Whites. Patients from a low neighborhood SES had a 20% higher risk of infection/sepsis, but there were no associations with SES for the other late effects. AYAs with public insurance had significantly increased risk with respect to those with private health insurance by at least 1.5 times higher for all late effects studied. AYAs with breast cancer stage IV had significantly elevated risk compared to stage I by at least 3 times higher for all late effects.

DISCUSSION

In this large population-based study of over 11,293 AYA breast cancer survivors, we show that AYAs of nH Black, Hispanic, and Asian/Pacific Islander race/ethnicity are at an increased risk of several late effects of bone marrow suppression compared to nH whites. AYAs with BC are a vulnerable population due to their stage of life and overall poorer prognosis.[18] The AYA population has been historically understudied, but now are recognized to have unique needs including more severe disease, requiring more advance treatment modalities,[2,5] cognitive impairments, alterations in growth and development, longer life spans, and quality of life issues.[19,20] These factors put them at greater risk for

the long effects of bone marrow suppression compared to their older counterparts. This also means that survivorship programs are incredibly important for this group to help minimize the negative effects that exist for this population. This includes screening for secondary malignancies, chronic conditions, premature aging, and psychosocial support.[19] This study's findings demonstrate the need for additional surveillance in survivorship programs for AYA BC survivors from racial/ethnic minority backgrounds, with public insurance, or residing in lower neighborhoods, including physical exams and laboratory monitoring, to diagnose long-term effects of bone marrow suppression earlier and prevent clinical worsening like hospitalizations.

In general, BC is treated with a combination of surgery, endocrine therapy, radiation, and chemotherapy. Due to more aggressive breast cancer in the AYA population, they receive more aggressive surgery, like mastectomy, and adjuvant therapies, including chemotherapy and radiation.[5,23] In this study, we found that AYA patients treated with chemotherapy and radiation had a higher incidence of late effects. For hormone receptor positive BC, Oncotype Dx and MammaPrint are used to preserve chemotherapy for those most likely to benefit. However, the adoption in the AYA population has lagged behind older patients,[24] resulting in the higher use of chemotherapy in this age group. Also, chemotherapy randomized control trials rarely include the AYA population resulting in chemotherapy treatment relying on data from their older counterparts.[25] This leads to an understudied area of how adjuvant treatments should be used in this age group and associated long-term effects. Prior work has shown chemotherapy in this group can be harmful, leading to premature aging syndrome[26] and other complications.[10] Our study adds that long-term effects of bone marrow suppression occur frequently for patients in the AYA group and surveillance for these late effects should be part of survivorship programs.

Prior work in this age group has shown there are racial and ethnic inequities, with nH Black AYAs having higher BC mortality.[8] Our work now adds that this group has a higher incidence of late effects of bone marrow suppression, which can affect overall survival and quality of life. This is likely multifactorial, including higher proportions of more severe BC subtypes and the low use of the 21-gene recurrence score (Oncotype Dx) for the most common subtype, hormone receptor positive BC. Prior work in nH Black adult patients has shown they are less likely to receive Oncotype Dx testing compared to their nH White counterparts.[27-30] When testing is done, there is evidence these tests do not have as high prognostic accuracy in nH Black compared to nH White patients leading to misuse of chemotherapy and higher mortality within similar score strata.[31] This difference in prognostic accuracy suggests tumor biology differences between racial/ethnic groups. Also, prior work has shown there are differences in tumor genomics and microenvironments across racial/ethnic groups that contribute to disease severity and treatment susceptibility.[32,33] We need a better understanding of how to interpret these genomic assays in different racial/ethnic populations to improve chemotherapy utilization and survival. Hispanic and Asian/Pacific Islander patients are also less likely to receive Oncotype Dx testing compared to nH white patients[27] and this is likely mirrored in the AYA population. While these racial/ethnic categories are encompassing a wide range of patient groups, these findings are important to highlight patient groups that may need more consistent surveillance to reduce health inequities.

Despite the importance of survivorship programs, the AYA population has historically been less engaged in health care surveillance after treatment.[21] Qualitative work in AYA cancer survivors identified six themes to improve care: use of digital health tools, raising awareness about late effects, increasing access to supportive services, improving communication/coordination, increased support for healthcare transitions and adapting survivorship models for AYA groups.[22] Using these recommendations should hopefully improve AYA survivorship compliance in the future, but more work will need to be done to continue successfully aiding this population. AYA BC survivors with public/no insurance are at an even greater disadvantage due to poor access of survivorship care.[34] Our studyfound that AYA BC survivors with public, versus private, insurance had a higher incidence of all late effects of bone marrow suppression indicating an even greater need to find strategies to engage this group. Among the AYA patients without health insurance, studies have shown there is an “illness-driven care”, where patients only seek medical care when they have developed symptoms versus having long term preventative medical care.[19] This patient group also frequently loses their insurance after treatment completion leading to poor survivorship care.[35] Lacking adequate insurance can lead to less access of appropriate survivorship monitoring and result in more hospitalizations from late effects. AYA breast cancer survivors from a low SES neighborhood had a higher incidence of many of the late effects of bone marrow suppression. Cancer has a well-known financial impact for patients, particularly AYA survivors who are faced with medical bills and often are not employed or have ways to earn an income.[36] This group has also been shown to forego care due to cost concerns.[37] This aligns with the findings in our study, highlighting the additional burden this group has leading to poor surveillance and more “illness-driven care”.[19] This highlights the need vulnerable populations have to being set up with survivorship programs that are accessible and affordable. Future work should work on outreach to continually engage this group.

This study has an important limitation due to HCAI only collecting hospitalization, emergency department, and ambulatory surgery data. Therefore, any long-term effects treated as an outpatient would not be collected. This could lead to underestimated incidence. As cancer registries do not collect details on treatment, including chemotherapy agents and doses, future studies should consider specific systemic therapies and their cumulative effects that place different patient populations at increased risk. While our population data is from California, which is a large and sociodemographic diverse state, it is important for other states to look at their population data to confirm these associations with late effects of bone marrow suppression. Despite these limitations, our large population-based study provides the first look at the disparities in late effects of bone marrow suppression among AYA breast cancer survivors.

CONCLUSIONS

Our study identifies that long-term effects of bone marrow suppression occur frequently for patients in the AYA group and AYAs of racial/ethnic minority groups, with public insurance and residing in lower SES neighborhoods are at an increased risk of several late effects of bone marrow suppression. AYA BC patients are a vulnerable group often presenting with more advanced cancers requiring adjuvant treatment. Accessible survivorship programs

are incredibly important, with providers implementing early/frequent screening of these hematologic late effects in high-risk populations.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Data availability statement

The data that support the findings of this study are available from the CCR and the California Department of HCAI. Access to these data sources is granted through an application process by the management or data custodians.

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SYNOPSIS

Our study found adolescent and young adult breast cancer patients of Black, Hispanic, and Asian/Pacific

Islander race/ethnicity have an increased risk of bone marrow suppression late effects. Survivorship programs should implement early/frequent screening of these hematologic effects in high-risk survivors.

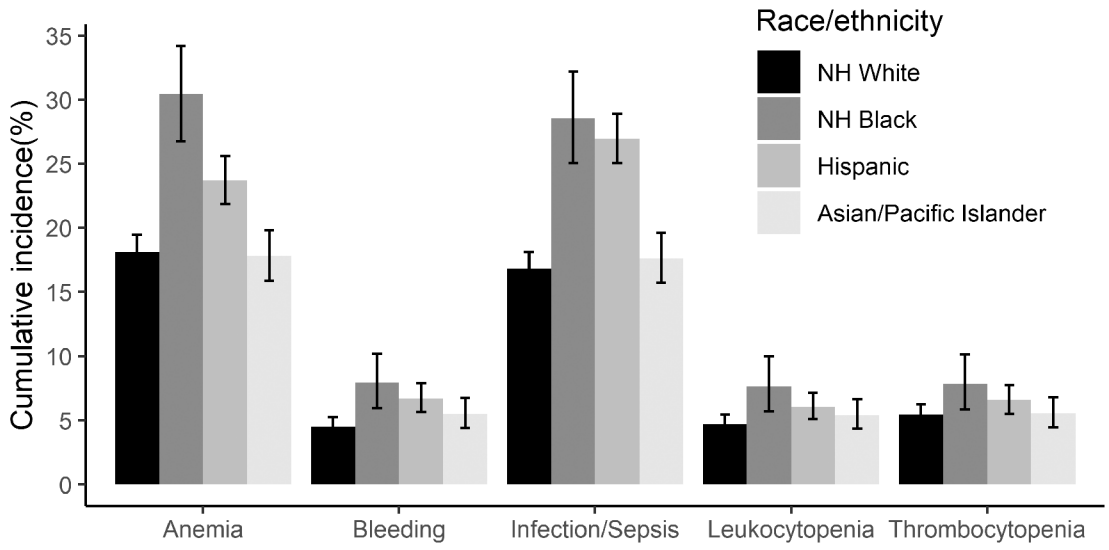

Figure 1a:

Cumulative incidence of late effects of bone marrow suppression at 5 years after diagnosis among 2-year Adolescent and Young Adult Breast Cancer Survivors by race/ethnicity

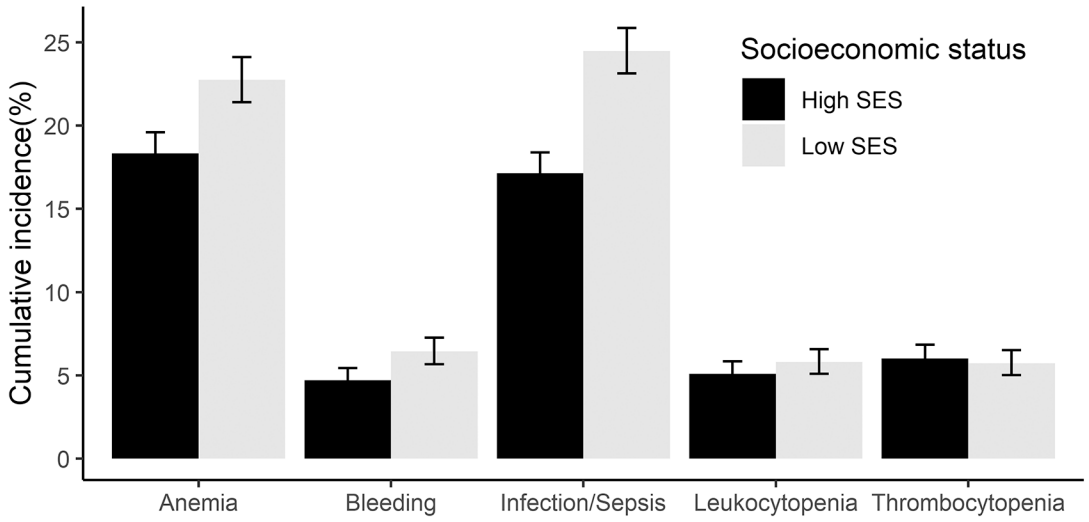

Figure 1b:

Cumulative incidence of late effects of bone marrow suppression at 5 years after diagnosis among 2-year Adolescent and Young Adult Breast Cancer Survivors by Socioeconomic status

Table 1:

Selected Sociodemographic and Clinical Characteristics of 2-year Adolescent and Young Adult Breast Cancer Survivors (N=11,293), California, 2006-2018

Characteristics	Total N=11,293 N (%)
Race/ethnicity	
NH White	4,830 (42.8)
NH Black	848 (7.5)
Hispanic	3,254 (28.8)
Asian/Pacific Islander	2,205 (19.5)
Other/unknown	156 (1.4)
Age	
15-24	175 (1.5)
25-29	1,092 (9.7)
30-34	3,179 (28.2)
35-39	6,847 (60.6)
Year of diagnosis	
2006-2009	3,595 (31.8)
2010-2012	2,694 (23.9)
2013-2015	2,638 (23.4)
2016-2018	2,366 (21.0)
Neighborhood socioeconomic status	
Low SES	5,746 (50.9)
High SES	5,547 (49.1)
Payment	
Private/military	8,792 (77.9)
Public/Medicaid/Medicare	2,056 (18.2)
Uninsured/self-pay	109 (1.0)
Unknown	336 (3.0)
AJCC Stage	
Stage I	3,155 (27.9)
Stage II	5,082 (45.0)
Stage III	2,102 (18.6)
Stage IV	596 (5.3)
Unstage/unknown	358 (3.2)
Chemotherapy	
No/unknown	2,583 (22.9)
Yes	8,710 (77.1)
Radiation	
No/unknown	6,087 (53.9)
Yes	5,206 (46.1)
Surgery	

Characteristics	Total N=11,293 N (%)
Lumpectomy	3,679 (32.6)
Mastectomy	6,736 (59.6)
None	830 (7.3)
Grade	
Grade I	947 (8.4)
Grade II	3,899 (34.5)
Grade III	5,764 (51.0)
Undifferentiated	121 (1.1)
Histology	
Ductal	9,484 (84.0)
Lobular	1,149 (10.2)
Other	660 (5.8)
Histology	
Ductal carcinoma	9,484 (84.0)
Lobular carcinoma	286 (2.5)
Mixed lobular/ductal carcinoma	863 (7.6)
Medullary	76 (0.7)
Mucinous	194 (1.7)
Papillary	33 (0.3)
Carcinoma NOS	357 (3.2)
T category	
T1a:<=0.5cm	518 (4.6)
T1b:0.5-1cm	754 (6.7)
T1c:1-2cm	3,006 (26.6)
T2:2-5cm	5,041 (44.6)
T3:>5.00 cm	1,541 (13.6)
Diffuse	49 (0.4)
No mass/tumor found/unknown/missing	384 (3.4)
Lymph node involvement	
Regional lymph nodes involvement	4,347 (38.5)
No lymph node involvement	4,464 (39.5)
Unknown	2,482 (22.0)
Regional nodes examined	
Sentinel Lymph Node Biopsy	5,754 (51.0)
Axillary lymph node dissection	4,808 (42.6)
No nodes examined/unknown	731 (6.5)
Tumor marker	
Hormone Receptor positive	5,498 (48.7)
Her-2 Positive	835 (7.4)
Triple Negative	1,791 (15.9)
Triple Positive	2,078 (18.4)

Characteristics	Total N=11,293 N (%)
Unknown	1,091 (9.7)

NH nonHispanic *SES* socioeconomic status *AJCC* American Joint Committee on Cancer

Table 2:

Multivariate adjusted hazard ratios (HR) and associated 95% confidence interval estimates for the association between sociodemographic and clinical characteristics with late effects of bone marrow suppression among 2-year Adolescent and Young Adult Breast Cancer Survivors

Characteristics	Late Effects				
	Leukocytopenia	**Infection/sepsis**	**Anemia**	**Thrombocytopenia**	**Bleeding**
Race/ethnicity					
NH White	Reference				
NH Black	1.56 (1.14, 2.13)	1.64 (1.40, 1.92)	1.72 (1.47, 2.02)	1.46 (1.08, 1.99)	1.89 (1.39, 2.58)
Hispanic	1.16 (0.93, 1.46)	1.36 (1.21, 1.52)	1.17 (1.04, 1.32)	1.10 (0.88, 1.37)	1.40 (1.12, 1.76)
Asian/Pacific Islander	1.08 (0.84, 1.40)	0.98 (0.86, 1.12)	1.01 (0.88, 1.15)	1.07 (0.84, 1.37)	1.33 (1.03, 1.72)
Other/unknown	1.10 (0.49, 2.51)	1.46 (1.01, 2.10)	0.84 (0.53, 1.33)	0.33 (0.08, 1.33)	1.62 (0.79, 3.33)
Age					
15-24	Reference				
25-29	1.12 (0.55, 2.27)	1.02 (0.72, 1.44)	0.95 (0.67, 1.35)	0.89 (0.45, 1.75)	1.38 (0.66, 2.87)
30-34	0.92 (0.47, 1.82)	0.82 (0.59, 1.15)	0.82 (0.59, 1.15)	0.83 (0.43, 1.58)	0.88 (0.43, 1.81)
35-39	0.82 (0.42, 1.60)	0.82 (0.59, 1.14)	0.81 (0.58, 1.12)	0.84 (0.44, 1.58)	0.99 (0.49, 2.01)
Year of diagnosis					
2006-2009	Reference				
2010-2012	1.16 (0.92, 1.45)	1.11 (0.99, 1.24)	1.07 (0.95, 1.20)	1.12 (0.89, 1.40)	1.11 (0.88, 1.40)
2013-2015	1.25 (0.96, 1.64)	1.25 (1.09, 1.42)	1.17 (1.03, 1.34)	1.35 (1.04, 1.74)	1.46 (1.13, 1.88)
2016-2018	1.73 (1.22, 2.46)	1.45 (1.21, 1.74)	1.34 (1.12, 1.60)	1.70 (1.20, 2.41)	1.28 (0.86, 1.90)
Neighborhood socioeconomic status					
Low SES	1.01 (0.83, 1.22)	1.21 (1.10, 1.34)	1.08 (0.97, 1.19)	0.88 (0.73, 1.06)	1.09 (0.90, 1.32)
High SES	Reference				
Payment					
Private/military	Reference				
Public/Medicaid/Medicare	1.52 (1.23, 1.88)	1.94 (1.75, 2.16)	1.60 (1.43, 1.79)	1.59 (1.29, 1.95)	1.71 (1.38, 2.11)
Uninsured/self-pay	0.79 (0.30, 2.13)	1.41 (0.96, 2.08)	1.45 (0.99, 2.12)	2.01 (1.07, 3.78)	1.89 (0.97, 3.68)
Unknown	1.39 (0.89, 2.18)	1.53 (1.22, 1.92)	1.30 (1.02, 1.66)	1.32 (0.85, 2.06)	1.21 (0.75, 1.95)
AJCC Stage					

Characteristics	Late Effects				
	Leukocytopenia	Infection/sepsis	Anemia	Thrombocytopenia	Bleeding
Stage I	Reference				
Stage II	1.49 (1.08, 2.07)	1.26 (1.09, 1.44)	1.28 (1.11, 1.48)	1.42 (1.05, 1.92)	0.94 (0.72, 1.22)
Stage III	3.02 (2.10, 4.33)	1.71 (1.44, 2.02)	2.00 (1.69, 2.38)	2.78 (1.97, 3.91)	1.31 (0.95, 1.81)
Stage IV	8.26 (5.55, 12.28)	3.04 (2.46, 3.76)	4.27 (3.48, 5.24)	6.24 (4.24, 9.17)	3.42 (2.34, 4.99)
Unstage/unknown	2.40 (1.34, 4.28)	1.82 (1.40, 2.35)	1.93 (1.47, 2.54)	2.34 (1.36, 4.02)	1.65 (1.00, 2.73)
Chemotherapy					
No/unknown	Reference				
Yes	1.04 (0.79, 1.37)	1.13 (0.99, 1.29)	0.98 (0.86, 1.12)	1.27 (0.96, 1.67)	1.02 (0.79, 1.31)
Radiation					
No/unknown	Reference				
Yes	1.48 (1.21, 1.81)	1.17 (1.06, 1.30)	1.18 (1.06, 1.31)	1.59 (1.30, 1.94)	1.19 (0.98, 1.46)
Surgery					
None	1.75 (1.13, 2.70)	1.47 (1.17, 1.85)	1.47 (1.17, 1.84)	2.23 (1.48, 3.35)	1.43 (0.91, 2.23)
Lumpectomy	Reference				
Mastectomy	1.46 (1.16, 1.85)	1.24 (1.11, 1.39)	1.32 (1.18, 1.49)	1.38 (1.10, 1.73)	1.27 (1.02, 1.58)
Unknown	2.09 (0.74, 5.87)	1.63 (0.93, 2.88)	1.51 (0.80, 2.86)	2.19 (0.79, 6.12)	0.98 (0.24, 4.05)
Grade					
Grade I	Reference				
Grade II	1.27 (0.83, 1.95)	1.03 (0.85, 1.26)	1.19 (0.96, 1.46)	1.50 (0.96, 2.33)	0.92 (0.63, 1.34)
Grade III	1.55 (1.01, 2.39)	1.11 (0.91, 1.36)	1.31 (1.06, 1.62)	1.66 (1.06, 2.59)	1.23 (0.84, 1.79)
Undifferentiated	1.47 (0.63, 3.46)	1.02 (0.67, 1.56)	1.47 (0.98, 2.19)	2.28 (1.09, 4.75)	1.70 (0.85, 3.41)
Unknown	0.98 (0.54, 1.79)	1.09 (0.83, 1.44)	0.93 (0.69, 1.25)	1.23 (0.68, 2.21)	0.73 (0.41, 1.29)
Histology					
Ductal	Reference				
Lobular	1.26 (0.96, 1.64)	1.19 (1.03, 1.38)	1.32 (1.15, 1.51)	1.35 (1.04, 1.75)	1.25 (0.94, 1.65)
Other	0.86 (0.56, 1.30)	0.99 (0.82, 1.20)	0.87 (0.71, 1.08)	0.94 (0.64, 1.38)	1.17 (0.82, 1.67)
Regional nodes examined					
Sentinel Lymph Node Biopsy	Reference				

Characteristics	Late Effects				
	Leukocytopenia	**Infection/sepsis**	**Anemia**	**Thrombocytopenia**	**Bleeding**
Axillary lymph node dissection	1.13 (0.90, 1.41)	1.09 (0.97, 1.21)	1.06 (0.95, 1.19)	0.96 (0.77, 1.19)	1.08 (0.87, 1.34)
No nodes examined/unknown	1.37 (0.93, 2.04)	1.15 (0.93, 1.42)	1.23 (1.00, 1.52)	1.32 (0.91, 1.91)	1.16 (0.77, 1.76)
Tumor marker					
HR positive	Reference				
Her-2	0.60 (0.42, 0.86)	1.01 (0.85, 1.19)	0.89 (0.75, 1.07)	0.79 (0.57, 1.10)	1.08 (0.79, 1.49)
TNBC	0.70 (0.52, 0.94)	0.98 (0.85, 1.13)	0.95 (0.83, 1.10)	0.96 (0.73, 1.25)	0.90 (0.68, 1.18)
TPBC	0.68 (0.53, 0.87)	0.88 (0.77, 1.00)	0.85 (0.75, 0.97)	0.66 (0.51, 0.85)	0.86 (0.67, 1.11)
Unknown	0.84 (0.56, 1.25)	0.97 (0.79, 1.19)	1.00 (0.82, 1.23)	0.87 (0.58, 1.29)	0.99 (0.66, 1.47)

NH nonHispanic *SES* socioeconomic status *AJCC* American Joint Committee on Cancer *HR* hormone receptor *TNBC* triple negative breast cancer *TPBC* triple positive breast cancer

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