

Neighborhood deprivation on increasing deficit accumulation in older breast cancer survivors and noncancer control individuals

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Abstract

Background: Neighborhood characteristics can affect aging and health. We tested the effects of neighborhood deprivation on deficit accumulation frailty scores in a prospective cohort of breast cancer survivors vs control individuals aged 60 to 98 years.

Methods: Newly diagnosed, nonmetastatic breast cancer survivors ($n = 477$) and frequency-matched control individuals ($n = 434$) were enrolled between 2010 and 2023, with up to 5-year follow-up through 2024. Deficit accumulation was measured using a 48-item index (scores of 0–1); a clinically meaningful deficit increase was defined by a 0.06 score increase. Neighborhood deprivation was assessed using the Area Deprivation Index (ADI) at enrollment census block group and categorized into tertiles. Cause-specific Cox models tested the association between ADI and risk of deficit accumulation increase.

Results: Participants living in more deprived areas (second and third tertiles of ADI) had a higher risk of increased deficit accumulation (adjusted hazard ratios = 1.38, 95% CI = 1.01 to 1.89, $P = .04$ and 1.46, 95% CI = 1.07 to 1.94, $P = .01$ vs first tertile, respectively). Independent of ADI, being a survivor (vs a control individual) was associated with greater risk of increased deficit accumulation (adjusted hazard ratio = 1.69, 95% CI = 1.32 to 2.17, $P < .001$). Patterns of cumulative incidence rates of increased deficit accumulation differed by ADI: Survivors treated with chemotherapy (with or without hormone therapy) living in more vs less deprived areas had a 20% higher incidence of increased deficit accumulation within 1 year ($P = .004$), while survivors receiving hormone therapy alone and noncancer control individuals had their most pronounced differences by 4 years (10%, $P = .32$ and 10%, $P = .05$, respectively).

Conclusions: Neighborhood deprivation may increase deficit accumulation, with an apparent acceleration of effects among older (≥ 60 years of age) breast cancer survivors treated with chemotherapy.

Introduction

Aging is characterized by gradual deficits in physical and cognitive function and the onset of aging-related diseases. These aging processes can be measured in many ways. Deficit accumulation indices are 1 well-validated approach to measure the cumulative

burden of deficits affecting physical, social, and psychological function; biological systems; and frailty in older adults.¹ Because deficit accumulation is a strong predictor of adverse health outcomes,^{2–7} growing efforts focus on identifying clinical and social factors that contribute to the deficit accumulation.

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Advancing age is the leading risk factor for cancer.⁸ In turn, cancer and its treatments can contribute to aging of these older adults by causing damage to biological systems and loss of function occurring due to symptoms of treatment-related toxicity.⁹ In fact, some cancer therapies have been associated with biomarker changes, suggesting age-related acceleration of 2 to more than 10 years.¹⁰⁻¹² Despite growing evidence linking cancer and its treatment to accelerated aging, assessment of deficit accumulation has been limited to determining ability to withstand treatment.¹³ Evidence about longitudinal post-treatment deficit accumulation is lacking, limiting long-term care management of cancer survivors. Breast cancer provides an important context for these questions because it is the most common cancer in women.⁸ In fact, with its high survival rates, breast cancer is the most prevalent cancer among women.¹⁴ Because most patients are diagnosed in midlife or later, survivorship overlaps with a period when aging processes become more pronounced, making this cancer particularly relevant for studying longitudinal deficit accumulation.

Beyond cancer and its therapies, aging and accumulation of deficits can be shaped by individual and area-level exposures, including where people live. Neighborhood deprivation, a composite measure of area-level income, education, employment, and housing quality, is 1 such area-level measure linked to health outcomes. Although some studies have examined the impact of neighborhood deprivation on risk of deficit accumulation,¹⁵⁻¹⁷ previous studies have focused solely on either cancer survivors¹⁵ or adults without cancer,^{16,17} but they have not assessed how neighborhood deprivation may differentially affect longitudinal deficit accumulation following cancer diagnosis and treatment in survivors vs comparable individuals without cancer.

We investigated the relationship between neighborhood deprivation and longitudinal change in deficit accumulation in older (≥ 60 years of age) female breast cancer survivors vs a frequency-matched noncancer control group. We hypothesized that individuals living in more deprived areas may be at greater risk of increases in deficit accumulation and that the effect of neighborhood deprivation on deficit accumulation may differ between cancer survivors and noncancer control individuals.

Methods

Study population

Data for this secondary analysis were derived from the Thinking and Living With Cancer (TLC) study, a prospective, multisite study designed to assess the impact of systemic therapy on cognition in older patients with breast cancer compared with matched noncancer control individuals (ClinicalTrials.gov identifier NCT03451383).^{18,19} Participants were recruited from the metropolitan Washington, DC, region; New York City; New Jersey; Los Angeles, California; and Indianapolis, Indiana. Eligibility criteria for survivors included being aged 60 years or older and having a recent diagnosis of nonmetastatic primary breast cancer; control individuals were enrolled through referral of survivors' friends or community recruitment and met the same eligibility criteria (Supplementary Methods). Control individuals were frequency-matched to survivors on age, racial and ethnic group, education level, and recruitment site.

For the current study, eligibility was limited to TLC study participants enrolled between September 2010 and May 2023 who had had at least 1 follow-up appointment through May 2024 ($n = 1004$). Women were excluded if they had insufficient data to calculate a deficit accumulation score at baseline ($n = 47$) or at follow-up ($n = 30$) or if geocoding was not possible ($n = 16$). The

final study sample included 911 women (477 survivors; 434 control individuals) who completed questionnaires and provided consent to medical record review for cancer-related variables (survivors only) at baseline and at annual visits up to 60 months (Figure 1). The baseline deficit accumulation for survivors was assessed before systemic therapy to best reflect underlying deficit accumulation because systemic therapy is known to increase deficit accumulation.⁹ The final study sample reflected the overall TLC cohort, exhibiting a similar distribution of baseline characteristics (Table S1).

Study endpoints

The primary outcome was a clinically meaningful increase in the deficit accumulation score (0.06 increment) over time. Clinically significant small (0.02) or large (0.06) increases in scores correspond to 0.2 and 0.5 times of the SD of the index using a distribution-based method.²⁰ The small difference of 0.02 was used for sensitivity analysis.

The deficit accumulation score used to identify the primary outcome was calculated using a 48-item deficit accumulation index developed following the method described in Searle et al.^{5,21-23} Scores were calculated by summing across all items from the domains—including instrumental activities of daily living, physical health, emotional health, social health, general health, fatigue, diseases, weight, and polypharmacy—and dividing by the total number of items (range = 0-1) (Table S2). Scores from all annual visits, from enrollment through 60 months, were used to determine the primary outcome, defined as a 0.06 increase relative to the enrollment score.

Predictor variables

Neighborhood deprivation was measured using the Area Deprivation Index (ADI) according to each participant's residential address at study enrollment. The ADI is a measure that aggregates 17 factors (Table S3) at the US Census block group level, using data from the American Community Survey provided by the Neighborhood Atlas.²⁴ This index was created to inform health delivery and policy by providing a ranking for a specific Census block group relative to others in the United States (national-level ADI, ranging from 1 to 100, with 100 indicating the most deprived areas) or within the same state (state-level ADI, ranging from 1 to 10, with 10 indicating the most deprived areas).

We used state-level ADI as the primary variable due to differences in the cost of living and income between states (Figure S1). Because ADI data from 2015, 2020, and 2022 were available, we selected the ADI data for each participant's residential address closest to the date of TLC enrollment. We grouped data into tertiles to enhance statistical power and align with common practice.²⁵⁻²⁷

We included known covariates associated with age-related outcomes and deficit accumulation. These covariates consisted of age, race and ethnicity, education level, baseline deficient accumulation, and social well-being, as measured by the Functional Assessment of Cancer Therapy-General subdomain. Among survivors, additional covariates included American Joint Committee on Cancer, version 6, cancer stage, type of surgery, and systemic therapy (chemotherapy with or without hormone therapy vs hormone therapy only).

Statistical analysis

The baseline characteristics were summarized by ADI tertiles. Differences across the ADI tertiles were assessed using the

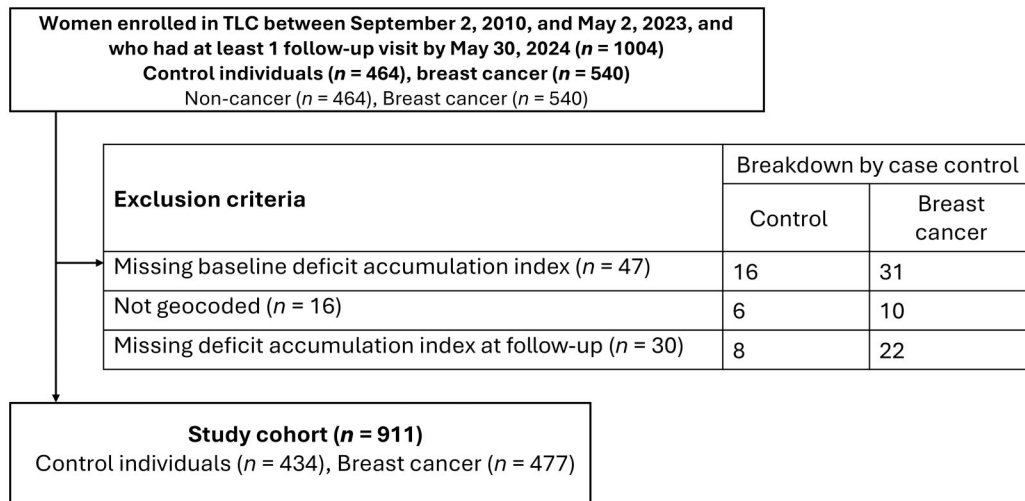


Figure 1. Cohort selection flowchart. TLC indicates Thinking and Living With Cancer.

Kruskal-Wallis test for continuous variables and the χ^2 test for categorical variables.

A multivariable, cause-specific Cox model was used to investigate the association between ADI tertiles and risk of having meaningful increases in deficit accumulation over time, considering competing risks of death.^{28,29} We assessed potential clustering among participants within the same census block groups using intraclass correlations and percentages of participants who shared the same census block. Noting the minimal intraclass correlation of 0.07 and very high singleton block (92%), clustering was not included in the final analysis.

Next, we estimated the cumulative incidence of having a meaningful increase in deficit accumulation scores by neighborhood deprivation using the Aalen-Johansen method while accounting for the competing risk of death.^{30,31} Given the substantially higher risk in the second and third ADI tertiles compared with the first tertile, we stratified cumulative incidence estimates using a binary ADI classification (first tertile vs all others combined). Differences in cumulative incidence between women from more and less deprived areas were assessed at first-year and fourth-year after diagnosis or enrollment, considering the follow-up time distribution. The Gray test was applied to test the statistical significance of cumulative risk differences.³¹⁻³³ Results were estimated for the overall sample of survivor and control groups combined and separately by group to examine the potential variations in the relationship between ADI and increases in deficit accumulation. Multiplicity was not considered for the exploratory analyses.

Sensitivity analyses

We conducted a series of sensitivity analyses examining variations in outcome definition, ADI categorization and type, and statistical approach. Regarding outcome definition, a 0.02 increase was evaluated because it captures a small yet clinically meaningful deficit accumulation.²⁰ We also explored an alternative outcome definition based on established categories, classifying individuals as robust (deficit accumulation score < 0.20), prefrail (0.20-0.34), or frail (≥ 0.35).²³ We assessed the time to progressive transitions, including robust individuals at baseline advancing to prefrail or frail status and prefrail individuals progressing to frailty over follow-up. Women who were frail at baseline were excluded from this sensitivity analysis because the focus was on transitions into frailty.

For alternative ADI categorization, consistent with prior studies on neighborhood deprivation and health outcomes, we dichotomized ADI at the 80th percentile (deprived) vs below (less deprived).¹⁶ Because most TLC participants were concentrated in the lower (less deprived) percentiles, however, only a small number of women fell into the 80th percentile category. We also examined state-level ADI deciles as a continuous variable and used national ADI to evaluate the robustness of the association between ADI and risk of clinically meaningful increases in deficit accumulation scores.

Given the discrete nature of the follow-up time (approximately 1 year), we employed a discrete hazard model as an alternative statistical model to relax a time-constant proportional hazard assumption and evaluate the robustness of the relationship between ADI and risk of increased deficit accumulation.

Statistical analyses were performed using the R, version 4.3.3, packages *prodlim*, *riskRegression*, and *discSurv* (R Foundation for Statistical Computing) for cumulative incidence plotting (based on the Aalen-Johansen estimator), the cause-specific Cox model, and the discrete hazard model, respectively. All statistical tests were 2 sided.

Results

The study participants were largely well educated, with nearly 60% holding graduate degrees, and primarily identified as non-Hispanic White (82.7%) (Table 1). The median follow-up period was 4.11 years (IQR, 2.0-5.0 years). Survivors and frequency-matched control individuals showed comparable distributions of ADI tertiles. At baseline enrollment, 20.8% of women were classified as prefrail or frail, with the highest prevalence (27.1%) observed among women living in the most deprived areas (third ADI tertile) compared with 16% to 17% in the first and second tertiles (Table 1).

Risk of increasing deficit accumulation, by neighborhood deprivation

Among all participants, more women residing in deprived areas had an increase in deficit accumulation than women in the least deprived area (85 and 114 of individuals living in the second and third ADI tertiles vs 80 among women in the first tertile) (Table 1). Women residing in more vs less deprived areas had a higher risk of having a clinically meaningful increase in deficit accumulation (adjusted hazard ratios [HRs] = 1.38, 95% CI = 1.01

Table 1. Participant characteristics, by tertiles of ADI.

Factor	Total	ADI tertile ^a			P
		First	Second	Third	
Total, No. (%)	911 (100)	282 (31.0)	263 (28.9)	366 (40.2)	
Follow-up time, median (IQR)	4.11 (2.0-5.0)	4.18 (2.0-5.1)	4.10 (2.1-5.0)	4.06 (2.0-5.0)	
Breast cancer status, No. (%)					
No (noncancer control individuals)	434 (47.6)	127 (45.0)	127 (48.3)	180 (49.2)	.56
Yes (Breast cancer survivors)	477 (52.4)	155 (55.0)	136 (51.7)	186 (50.8)	
Patient age at enrollment, mean (SD), y	67.9 (6.2)	68.0 (6.0)	67.3 (5.9)	68.2 (6.4)	.22
Race or ethnicity, No. (%)					
Black	68 (7.5)	10 (3.5)	19 (7.2)	39 (10.7)	
Hispanic	51 (5.6)	8 (2.8)	18 (6.8)	25 (6.8)	
White	753 (82.7)	254 (90.1)	208 (79.1)	291 (79.5)	<.01
Race not otherwise specified	39 (4.3)	10 (3.5)	18 (6.8)	11 (3.0)	
Education level, No. (%)					
High school graduate	115 (12.6)	19 (6.7)	30 (11.4)	66 (18.0)	<.01
College graduate	252 (27.7)	49 (17.4)	74 (28.1)	129 (35.2)	
Graduate school or more	544 (59.7)	214 (75.9)	159 (60.5)	171 (46.7)	
Marital status, No. (%)					
Married	367 (40.3)	100 (35.5)	97 (36.9)	170 (46.4)	<.01
Other	544 (59.7)	182 (64.5)	166 (63.1)	196 (53.6)	
Social well-being at enrollment, No. (%)					
Good (Functional Assessment of Cancer Therapy-General ^b ≥16)	345 (37.9)	107 (37.9)	96 (36.5)	142 (38.8)	.85
Poor	566 (62.1)	175 (62.1)	167 (63.5)	224 (61.2)	
Site, No. (%)					
Georgetown University	192 (21.1)	103 (36.5)	36 (13.7)	53 (14.5)	<.01
Memorial Sloan Kettering Cancer Center	156 (17.1)	65 (23.0)	47 (17.9)	44 (12.0)	
Moffit Cancer Center	251 (27.6)	22 (7.8)	91 (34.6)	138 (37.7)	
City of Hope	136 (14.9)	27 (9.6)	50 (19.0)	59 (16.1)	
John Theurer Cancer Center	36 (4.0)	8 (2.8)	11 (4.2)	17 (4.6)	
Indiana University	140 (15.4)	57 (20.2)	28 (10.6)	55 (15.0)	
Baseline deficit accumulation index at enrollment, No. (%)					
Robust (score <0.2)	722 (79.3)	234 (83.0)	221 (84.0)	267 (73.0)	<.01
Prefrail (score 0.2-0.34)	173 (19.0)	44 (15.6)	39 (14.8)	90 (24.6)	
Frail (score >0.34)	16 (1.8)	4 (1.4)	3 (1.1)	9 (2.5)	
Clinically significant Deficit Accumulation Frailty Index increase (a 0.06 increment) during follow-up, No. (%)					
Yes	279 (30.6)	80 (28.4)	85 (32.3)	114 (31.1)	.87
No	632 (69.4)	202 (71.6)	178 (67.7)	252 (68.9)	
Breast cancer survivors only					
Stage of breast cancer at diagnosis, No. (%)					
Early stage (stages 0 and I)	365 (76.5)	121 (78.1)	110 (80.9)	134 (72.0)	.16
Advanced (stage II and III)	112 (23.5)	34 (21.9)	26 (19.1)	52 (28.0)	
Molecular subtype, No. (%)					
Hormone receptor negative/ERBB2 negative	36 (7.5)	13 (8.4)	8 (5.9)	15 (8.1)	.02
Hormone receptor negative/ERBB2 positive	9 (1.9)	2 (1.3)	2 (1.5)	5 (2.7)	
Hormone receptor positive/ERBB2 negative	360 (75.5)	129 (83.2)	97 (71.3)	134 (72.0)	
Hormone receptor positive/ERBB2 positive	36 (7.5)	8 (5.2)	12 (8.8)	16 (8.6)	
Missing	36 (7.5)	3 (1.9)	17 (12.5)	16 (8.6)	
Chemotherapy use, No. (%)					
Yes (with or without hormone therapy)	111 (23.3)	30 (19.4)	28 (20.6)	53 (28.5)	.04
No (hormone therapy alone)	366 (76.7)	125 (80.6)	108 (79.4)	133 (71.5)	
Type of chemotherapy regimen, No. (%)					
Not treated with chemotherapy	366 (76.7)	125 (80.6)	108 (79.4)	133 (71.5)	
AC	6 (1.3)	1 (0.6)	2 (1.5)	3 (1.6)	.50
AC followed by T	41 (8.6)	8 (5.2)	10 (7.4)	23 (12.4)	
ATC	49 (10.3)	18 (11.6)	11 (8.1)	20 (10.8)	
A-CMF	9 (1.9)	2 (1.3)	3 (2.2)	4 (2.2)	
AT	3 (0.6)	1 (0.6)	1 (0.7)	1 (0.5)	

(continued)

Table 1. (continued)

Factor	Total	ADI tertile ^a			P
		First	Second	Third	
Type of hormone therapy, No. (%)					
Not treated with hormone therapy	89 (18.7)	21 (13.5)	20 (14.7)	48 (25.8)	.01
Anastrozole	257 (53.9)	79 (51.0)	79 (58.1)	99 (53.2)	
Exemestane	17 (3.6)	9 (5.8)	4 (2.9)	4 (2.2)	
Letrozole	67 (14.0)	24 (15.5)	21 (15.4)	22 (11.8)	
Tamoxifen citrate	42 (8.8)	22 (14.2)	9 (6.6)	11 (5.9)	
Other	4 (0.8)	0 (0)	2 (1.5)	2 (1.1)	
Type of surgery, No. (%)					
Breast-conserving surgery	322 (67.5)	117 (75.5)	90 (66.2)	115 (61.8)	.03
Mastectomy	154 (32.3)	38 (24.5)	46 (33.8)	70 (37.6)	

Abbreviations: A-CMF = adriamycin plus cyclophosphamide followed by methotrexate and fluorouracil; AC = adriamycin (doxorubicin) plus cyclophosphamide; AC followed by T = adriamycin (doxorubicin) plus cyclophosphamide followed by taxane (paclitaxel or docetaxel); ADI = Area Deprivation Index; ATC = adriamycin, taxane, and cyclophosphamide (sometimes used in sequence or combination); AT = adriamycin plus taxane.

^a A higher tertile of the ADI indicates greater deprivation.

^b The Functional Assessment of Cancer Therapy-General is a 27-item questionnaire designed to assess 4 domains of health-related quality of life in patients with cancer. Eight of these items were used to evaluate social well-being.

to 1.89, $P = .04$ and 1.46, 95% CI = 1.07 to 1.94, $P = .01$ for the second and third tertiles vs the least deprived area [first ADI tertile], respectively) (Table 2). Independent of neighborhood deprivation (ADI), being a breast cancer survivor vs a control individual (adjusted HR = 1.69, 95% CI = 1.32 to 2.17, $P < .001$) and older age at enrollment (adjusted HR = 1.03 per 1-year increase in age [95% CI = 1.01 to 1.05, $P = .01$]) were statistically significantly associated with risk of increased deficit accumulation (Table 2).

Cumulative incidence of increased deficit accumulation, by neighborhood deprivation

Among all participants, the cumulative incidence of having a clinically meaningful increase in deficit accumulation score was consistently higher among women residing in more vs less deprived areas (second or third tertile vs first tertile) across all follow-up time points (Figure 2, A); this difference was statistically significant at year 1 (difference = 5%; $P = .04$) and year 4 (difference = 7%; $P = .04$) (Figure 2, A).

Among survivors, the cumulative incidence of increased deficit accumulation was higher than among control individuals across all time points, reaching nearly 50% by year 4 compared with 35% in noncancer control individuals (Figure 2, B and C), with statistically significant differences at year 1 (difference = 10%; $P < .001$) and year 4 (difference = 14%; $P \leq .001$) (Figure S2). The difference in cumulative incidence by ADI was statistically significant for control individuals at year 4 (difference = 10%; $P = .04$), but no such statistical difference was observed among survivors, despite consistently higher rates of increased deficit accumulation in women from more deprived areas (Figure 2, B and C).

In separate analyses for survivors only (Figure 3), however, survivors treated with chemotherapy (with or without hormone therapy) living in more vs less deprived areas had a statistically significantly higher cumulative incidence of deficit accumulation increase, with the most pronounced difference by year 1 (20%; $P = .004$) (Figure 3, B). Women who received hormone therapy alone exhibited a pattern similar to noncancer control individuals, with a more pronounced difference by ADI emerging at later follow-up (Figure 3, C).

Sensitivity analysis

The association between higher neighborhood deprivation and an increase in deficit accumulation remained consistent across multiple sensitivity analyses (Table S4). Using an alternative outcome definition based on a smaller increase in the deficit

Table 2. Association between neighborhood deprivation and clinically significant deficit accumulation frailty increase score increase^a among women in the TLC study

Factor	Adjusted hazard ratio (95% CI)	P
ADI		
First tertile (least deprived)	(Referent)	
Second tertile	1.38 (1.01 to 1.89)	.04
Third tertile (most deprived)	1.46 (1.07 to 1.94)	.01
Age at enrollment, per 1 y in age	1.03 (1.01 to 1.05)	.01
Race or ethnicity		
Black	0.74 (0.43 to 1.26)	.27
Hispanic	0.53 (0.28 to 1.01)	.05
White	(Referent)	
Race not otherwise specified	1.04 (0.60 to 1.78)	.88
Breast cancer status		
No (noncancer control individuals)	(Referent)	
Yes (breast cancer survivors)	1.69 (1.32 to 2.17)	<.001
Social well-being ^b at enrollment		
Poor (score <16)	(Referent)	
Good (score ≥ 16)	0.81 (0.63 to 1.04)	.09
Baseline deficit accumulation index		
Robust (score <0.2)	(Referent)	
Prefrail (score 0.2-0.34)	0.85 (0.62 to 1.15)	.29
Frail (score >0.34)	1.30 (0.57 to 3.00)	.52
Education attainment		
High school graduate	(Referent)	
College graduate	0.98 (0.63 to 1.51)	.91
Graduate school or more	1.32 (0.89 to 1.96)	.15

Abbreviations: ADI = Area Deprivation Index; TLC = Thinking and Living With Cancer.

^a A 0.06 increment over time, associated with statistically significant differences in overall mortality.

^b Social well-being was measured using the Functional Assessment of Cancer Therapy-General subdomain for social well-being and classified as poor when scores were below 16.

accumulation score (≥ 0.02) nearly doubled the overall event rate compared with the primary definition (≥ 0.06) and showed similar but attenuated associations between ADI and the risk of increased deficit accumulation. An additional outcome definition, based on progression across predefined deficit accumulation categories (eg, from robust to prefrail or frail or from prefrail to frail) also similarly demonstrated higher risk associated with greater neighborhood deprivation.

Analyses incorporating alternative ADI categorizations and types as well as those employing an alternative statistical approach such as discrete hazard models supported the

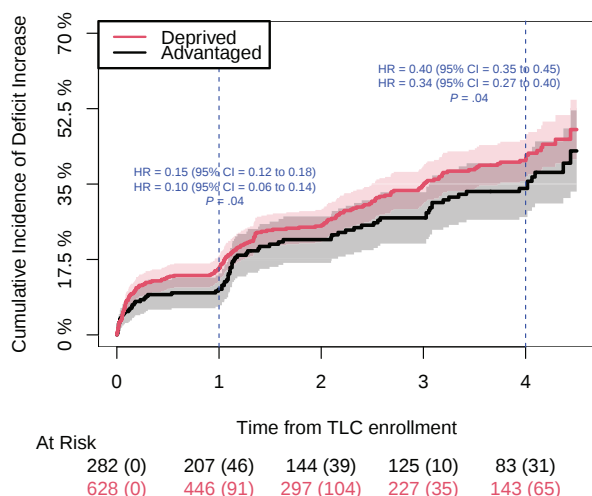
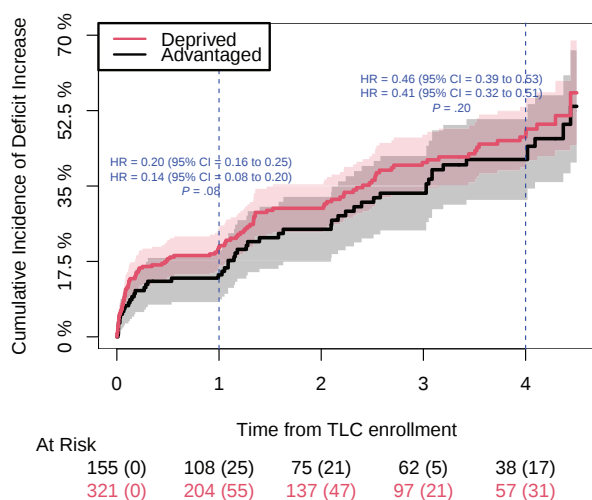
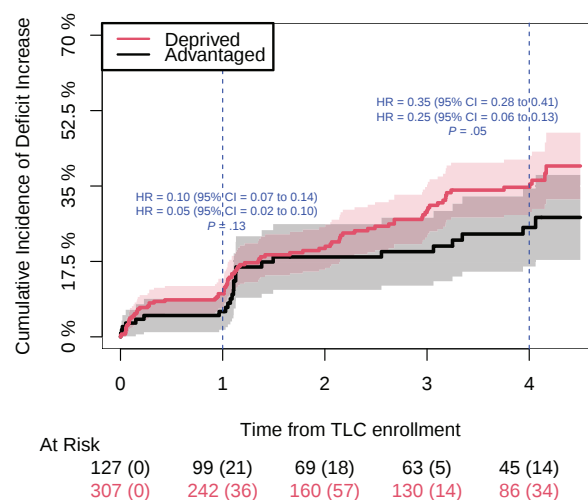
A Overall by Neighborhood Deprivation**B Breast Cancer Survivors by Neighborhood Deprivation****C Control by Neighborhood Deprivation**

Figure 2. Cumulative incidence of a clinically meaningful increase in deficit accumulation (≥ 0.06 score increase) among all women, by neighborhood deprivation,^a (A) among all women in the TLC study ($n = 911$), (B) among breast cancer survivors ($n = 477$), and (C) among noncancer control individuals ($n = 434$). The number below each year (x-axis) indicates the number of individuals at risk, by neighborhood deprivation, including individuals who were censored in parentheses. Abbreviations: HR = hazard ratio; TLC = Thinking and Living With Cancer.

^aNeighborhood deprivation was categorized as advantaged (first tertile) vs deprived (second and third tertiles). P values are from the Gray test for the difference in cumulative incidence at given time points.

relationship between neighborhood deprivation and higher risk of deficit increase (Table S4).

Discussion

This is the first multisite, longitudinal study of older breast cancer survivors and matched noncancer control individuals to examine how the area women lived in may have affected deficit accumulation, a clinically useful marker of aging-related declines in health. We found that women residing in more deprived neighborhoods faced a higher risk of meaningful increases in deficit accumulation and that being a survivor (vs a control individual) independently increased this risk. There were also different patterns of cumulative incidence of increased deficit accumulation by neighborhood deprivation: survivors treated with chemotherapy (with or without hormone therapy) living in

more vs less deprived areas had deficit accumulation increases within 1 year of diagnosis, while area deprivation had the greatest impact on women receiving hormone therapy or noncancer control individuals at 4 years. These findings suggest that neighborhood deprivation may increase risk of deficit accumulation differentially depending on cancer diagnosis and treatment vs noncancer populations, highlighting the need for tailored interventions to mitigate accelerated deficit accumulation.

Consistent with previous studies that have linked neighborhood disadvantage to phenotypic frailty or deficit accumulation index scores,¹⁵⁻¹⁷ our results extend these findings to illustrate the substantial impact of living in deprived areas on the incidence of deficit accumulation increases over time. Although earlier research examined this relationship either in community-dwelling older adults without cancer^{16,17} or exclusively among cancer survivors,¹⁵ we observed distinct patterns in how

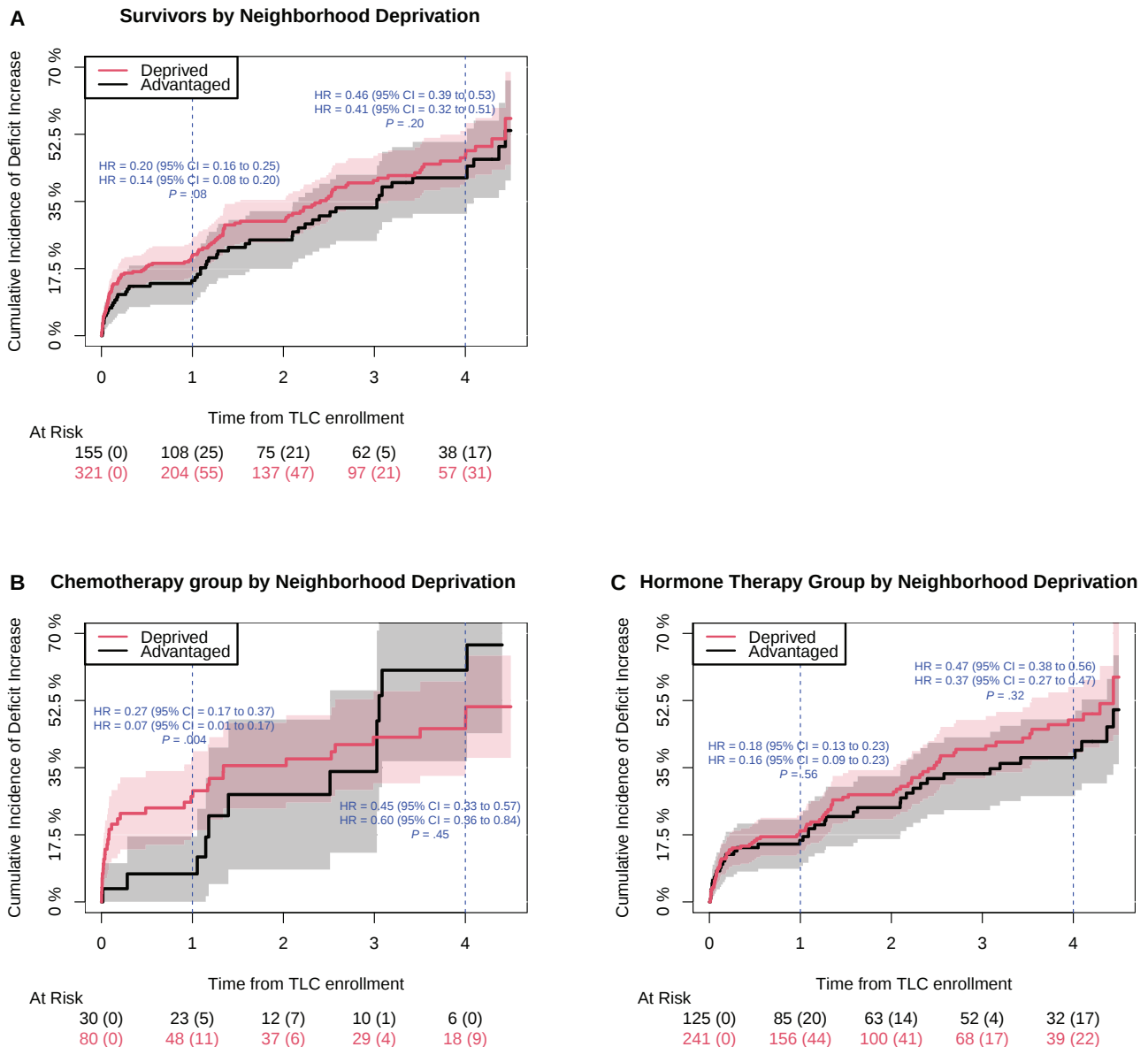


Figure 3. Cumulative incidence of a clinically meaningful increase in deficit accumulation (≥ 0.06 score increase) among breast cancer survivors, by neighborhood deprivation,^a (A) among all breast cancer survivors ($n = 477$), (B) among breast cancer survivors treated with chemotherapy (with or without hormone therapy) ($n = 111$), and (C) among breast cancer survivors on hormone therapy alone ($n = 366$). The number below each year (x-axis) indicates the number of individuals at risk by neighborhood deprivation, including individuals who were censored in parentheses. Abbreviations: HR = hazard ratio; TLC = Thinking and Living With Cancer.

^aNeighborhood deprivation was categorized as advantaged (first tertile) vs deprived (second and third tertiles). P value from the Gray test for the difference in cumulative incidence at given time points.

neighborhood deprivation affects the accumulation of deficits based on cancer status. The strong impact of cancer chemotherapy combined with living in a disadvantaged community on deficit accumulation increase was immediate—within the first year following diagnosis—while the impact on survivors receiving hormone therapy alone or control individuals occurred much later, at 4 years. This pattern suggests that the negative effects of chemotherapy on aging patterns in survivors may be intensified by poor neighborhood quality. It remains to be determined whether this finding partially reflects unmeasured factors such as restricted access to supportive care, inadequate symptom management, or poor psychosocial status, which are common concerns in disadvantaged communities.³⁴⁻³⁶ These findings, however, suggest the need for targeted disease and symptom

management during survivorship care visits using structured symptom monitoring. The results also suggest that solutions include community-based supportive care programs and psychosocial counseling during and immediately after chemotherapy.

Our findings also underscore the importance of longitudinal deficit accumulation assessment in breast cancer survivors because cumulatively, over 5 years, approximately 50% of survivors experienced a clinically meaningful deficit accumulation increase, exceeding the 30% rate observed among matched non-cancer control individuals. Specific frailty or deficit accumulation indices are not used in routine oncology care, and clinical geriatric assessments are recommended only at the time of cancer diagnosis for treatment decisions and deescalation.^{37,38} Our results suggest that longitudinal assessments of deficit accumulation in

older breast cancer survivors may be warranted using tools such as geriatric assessment. Such assessments may help identify patients on a trajectory toward progression to frailty and could inform interventions, including tailored physical or occupational therapy programs, provision of durable medical equipment, home safety modifications, in-home social services, nursing or rehabilitation services, and caregiver support.^{23,39-41}

The robust association between neighborhood deprivation and an increase in deficit accumulation, even after adjusting for key individual-level covariates and across multiple sensitivity analyses, suggests that ADI captures additional influences beyond individual-level factors. Given the uneven distribution of built and natural environmental exposures across neighborhoods, such as air pollution, green space, traffic, noise, crime, and healthcare access,⁴²⁻⁴⁵ a more systematic approach will be needed to identify their specific impact.^{46,47} Future research should focus on disentangling the role of neighborhood factors in driving aging to inform targeted interventions that maintain and improve health.

Our study has several limitations. First, it considered participants' addresses at baseline enrollment because residential history data were unavailable. Second, there may be left-censoring due to the exclusion of individuals at high risk of frailty or mortality from eligibility in the TLC study. Third, the current data did not include emerging therapeutic agents because the sample was primarily enrolled before their general use. The gradual rise in deficit accumulation among patients receiving hormone therapy may reflect cumulative effects of endocrine therapy. Future studies with detailed treatment information will be needed to determine the long-term impact of newer chemotherapeutic regimens and whether their effects on deficit accumulation interact with hormone therapy. Also, the TLC study sample is well educated and mainly White, limiting generalizability to the broader population of older women in the United States. Future studies using larger datasets, such as Surveillance, Epidemiology, and End Results Program-Medicare, may provide more robust long-term estimates and allow for a more precise evaluation of factors associated with differential effects across population subgroups defined by cancer status and treatment.

In conclusion, we found that living in more deprived neighborhoods may contribute to clinically meaningful increases in deficit accumulation among older breast cancer survivors, with a short-term immediate effect in survivors who received chemotherapy vs a longer-term sustained effect in other survivors. Identifying specific, modifiable neighborhood-level factors linked to aging-related and cancer-related deficit accumulation is crucial for guiding targeted interventions at the clinical, regional, and guideline levels. Such measures could potentially counterbalance accelerated aging and deficit accumulation seen in the growing population of older cancer survivors, fostering healthier aging within communities.

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Author contributions

Junji Choi (Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Validation, Visualization, Writing—original draft, Writing—review & editing), Wanting Zhai (Data curation, Writing—review & editing), Jaeh Ahn (Formal analysis, Writing—review & editing), Tim A. Ahles (Writing—review & editing), Ashley L. Artese (Writing—review & editing), Iwalola Awoyinka (Writing—review & editing), Judith E. Carroll (Resources, Writing—review & editing), Harvey J. Cohen (Writing—review & editing), Kathleen Van Dyk (Writing—review & editing), Deena Graham (Writing—review & editing), Heather S. L. Jim (Writing—review & editing), Brenna C. McDonald (Writing—review & editing), Zev M. Nakamura (Writing—review & editing), Sunita K. Patel (Writing—review & editing), Kelly E. Rentscher (Writing—review & editing), James C. Root (Writing—review & editing), Andrew J. Saykin (Writing—review & editing), Brent J. Small (Writing—review & editing), Yiwey Shieh (Writing—review & editing), Jeanne S. Mandelblatt (Conceptualization, Resources, Supervision, Writing—review & editing), and Traci N. Bethea (Supervision, Writing—review & editing)

Supplementary material

[Supplementary material](#) is available at JNCI: Journal of the National Cancer Institute online.

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Conflicts of interest

J.S.M., who is a deputy editor and is co-author on the manuscript, was not involved in the editorial review or decision to publish the manuscript. J.S.M. is a co-inventor on a pending invention patent application (PCT/US2022/028741) filed by Georgetown University titled "Use of RAGE inhibitors to Treat Cancer-Related Cognitive Decline" and licensed to Cantex Pharmaceuticals. J.S.M. has

waived her rights and will not receive any remuneration, consideration, or revenue generated from this license or the patents and patent applications licensed thereunder. This patent is unrelated to the content of the current study. B.J.S., who is a JNCI Editorial Board member and co-author on this article, was not involved in the editorial review or decision to publish the manuscript.

Data availability

The TLC data are available for sharing following the National Institutes of Health requirements and FAIR (Findability, Accessibility, Interoperability, Reproducibility) principles for data access. The deidentified datasets generated during or analyzed during the current study are available from the corresponding author using the TLC data use agreements at <https://tlcage.georgetown.edu/>. TLC data inquiries can also be sent by a request to the Infrastructure for Research in Equity, Aging, Cancer and Health Data Core at <https://ireach.georgetown.edu/>. The SAS code and data for the analyses included in the article are available upon request within the constraints of the TLC institutional review board requirements.

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