CORRESPONDENCE



Socioeconomic status and left ventricular ejection fraction decline in breast cancer survivors following receipt of doxorubicin (*PREVENT WF-98213*)

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Abstract

Cancer survivors receiving doxorubicin may experience left ventricular ejection fraction (LVEF) decline during and following treatment; however, explanations for variations in decline beyond dosage differences, such as those related to socioeconomic status (SES), have not been fully examined. We conducted a retrospective analysis of a cohort of 215 breast cancer survivors receiving doxorubicin. SES factors (e.g., household income, education) were collected via a survey at a baseline and EF was assessed using magnetic resonance imaging. Linear regression models showed that prior to treatment, no SES factors were associated with LVEF. However, six months following treatment, survivors who were unemployed for reasons other than retirement and disability experienced greater LVEF declines compared to survivors who were employed ((b=2.79 [95% confidence interval (CI): 0.37-5.20; p=0.026). Our study demonstrated that non-clinical factors associated with social drivers of health, such as socioeconomic status, contribute to subclinical cardiovascular dysfunction and therefore supports further investigation of mechanisms behind these associations.

Trial registration NCT01988571 (WF-98213).

Keywords Breast cancer, Left ventricular ejection fraction, Socioeconomic status, Social drivers of health

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Background

Doxorubicin increases breast cancer survivors' risk for heart-related left ventricular (LV) dysfunction and heart failure, a leading cause of mortality among this group [1]. Data have attributed variations in the elevated risk of LV dysfunction and magnitude of LV ejection fraction (LVEF) decline to chemotherapy dose, presence of comorbid chronic conditions, and other clinical factors. However, while it is well established that one's socioeconomic status (SES), including income and education, is associated with poor cardiovascular health [2, 3], it is unknown if during cancer treatment it has a similar



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| Predictors | | Pre-treatment LVEF | | | 6-Month Change in LVEF | | |
|---------------------------------|------------|--------------------|-------------------------|-------|------------------------|-------------------------|-------|
| | N (%) | Estimates | 95% Confidence Interval | Р | Estimates | 95% Confidence Interval | Р |
| (Intercept) | | 54.67 | 48.68-60.72 | 0.000 | -42.33 | -54.7429.93 | 0.000 |
| Employment Status | | | | | | | |
| Unemployed - Retired | 25 (11.6) | 1.53 | -1.70-4.76 | 0.355 | 0.90 | -2.65-4.52 | 0.619 |
| Unemployed - Disabled | 9 (4.2) | 4.20 | -1.31–9.71 | 0.137 | -5.22 | -12.96–2.52 | 0.191 |
| Unemployed - Other | 43 (20.0) | 0.39 | -1.73–2.52 | 0.718 | 2.79 | 0.37-5.20 | 0.026 |
| Employed | 138 (64.2) | Ref | | | Ref | | |
| Family Income | | | | | | | |
| >\$75k | 102 (47.4) | 0.19 | -2.00-2.19 | 0.866 | -1.34 | -4.02- 1.34 | 0.032 |
| \$35-\$75k | 61 (28.4) | -0.53 | -2.98–1.93 | 0.675 | 0.29 | -2.55-3.14 | 0.840 |
| <\$35k | 52 (24.2) | Ref | | | Ref | | |
| Education | | | | | | | |
| Graduate or Professional School | 46 (21.4) | -0.48 | -2.66-1.71 | 0.668 | 1.62 | -0.83- 4.08 | 0.197 |
| High School | 44 (20.5) | -1.61 | -3.83–0.62 | 0.159 | 1.08 | -1.55-3.70 | 0.422 |
| College | 125 (58.1 | Ref | | | Ref | | |
| Group | | | | | | | |
| Statin | 110 (48.8) | 1.68 | -0.02-3.39 | 0.054 | 0.83 | -1.16-2.82 | 0.414 |
| Placebo | 105 (51.2) | Ref | | | Ref | | |

Table 1 Multivariable associations of patient characteristics with pre-treatment and LVEF change at 6 months among female breast cancer survivors (n = 215) receiving doxorubicin

Table 1 presents regression parameter estimates from a multiple linear regression model using multiple imputation for missing data, and adjusted for treatment group, ejection fraction at baseline, BMI, age, smoking status and hypertension status (defined by use of anti-hypertension medication or baseline systolic blood pressure of > 130)

impact on subclinical markers of cardiovascular disease, such as LV dysfunction. We examined the impact of SES factors on pre- and during doxorubicin treatment measures of LVEF.

Methods

This secondary analysis utilized data from a multi-site double-blind randomized placebo-controlled (atorvastatin versus placebo) clinical trial (WF-98213) coordinated by the Wake Forest NCI Community Oncology Research Base (NCORP) and Alliance (A221501) [4]. The study was approved by the Institutional Review Board at Virginia Commonwealth University and informed consent was obtained from all study participants. The trial enrolled adult breast cancer and lymphoma survivors scheduled to receive doxorubicin, who were not candidates to receive a statin for primary or secondary prevention of a future cardiovascular event. Participants received LVEF assessments via cardiovascular magnetic resonance at baseline (pre-cancer treatment) and following six months of treatment, and factors associated with SES (i.e., employment status, family income, education) were collected via survey at baseline. Protocol details may be found elsewhere [4]. This analysis only included female breast cancer survivors (n = 215). Univariable statistics (e.g., percentages, mean, standard deviation) were employed for categorical and continuous variables. We used factor analysis to reduce the dimension of risk factors including use of hypertension medications, body mass index (BMI), age, smoking status, systolic blood pressure (BP), diastolic BP, C-reactive protein (CRP), total cholesterol and low-density lipoprotein (LDL) at baseline into three factors, which allowed us to better fit our models with limited data. Linear regression models assessed associations of the SES factors with baseline LVEF and changes in LVEF from baseline to six months. Statistical analyses were conducted in R version 4.10.

Results

Among the 215 women the age averaged 50 ± 12 years; the majority were White (83.3%) and employed (64.2%). Pre-doxorubicin, LVEF averaged $62.7 \pm 5.5\%$; six months after initiating treatment, the LVEF declined by $4.6 \pm 6.8\%$.

Accounting for age, body mass index (BMI), smoking, hypertension, and treatment arm, employment status was associated with LVEF change six months after initiating cancer treatment (Table 1). When compared to women who were currently employed, women who were unemployed for reasons other than retirement and disability had significantly greater LVEF declines (b = 2.79 [95% confidence interval (CI): 0.37–5.20; p = 0.026). No other SES factors were significantly associated with either outcome.

Discussion

These study findings support the relevance of SES on cardiovascular outcomes following a breast cancer diagnosis. Moreover, this study highlights the potential impact of SES on early indicators of poor cardiovascular health. While our study is the first to report on this finding within the context of LVEF and breast cancer treatment, a study by Dupre et al. in the general population found a greater risk of acute myocardial infarction in unemployed individuals compared to employed individuals [5].

Although women who were unemployed for reasons other than retirement and disability were not required to report their "other" status, some responses included being a caretaker, "out of work due to illness" and "not working while getting chemotherapy." The mechanism for the association between unemployment and LVEF declines is uncertain. This association may be related to non-traditional CV risk factors including perceived psychosocial stress or physical inactivity, and may be salient for cancer survivors in whom emotional distress and physical inactivity are known to be common [6]. During breast cancer therapy, some patients may find it difficult to work due to the side effects of treatment and/or because of logistical issues (e.g., a job that does not allow for paid time off). Ultimately, this difficulty may result in financial strain and consequent social and emotional distress.

These study results provide opportunities for further exploration, particularly in the context of social drivers of health (SDoH) and cardiovascular outcomes in cancer survivors. Future studies could consider collecting more detailed data regarding employment and other SES factors as there are nuances in the definition of employed versus unemployed. One may be employed, but not working at the moment because of an illness. Conversely, individuals are considered unemployed if they are not working *and* are not looking for work. In summary, our findings highlight the need for further investigation into the mechanisms by which SES and other SDoH impact LVEF during treatment for breast cancer.

Abbreviations

| BMI | Body mass index |
|------|------------------------------------|
| CI | Interval confidence |
| LVEF | Left ventricular ejection fraction |
| SES | Socioeconomic status |

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N/A

Author contributions

ALS conducted analyses and drafted the main manuscript text. NSO conducted analyses and assisted with the manuscript draft. ARL, KCO, KWR,

and VBS reviewed the manuscript. BK, KJR, and KEW carried out the study and reviewed the manuscript. WGH devised the idea, wrote the grant, carried out the study, and drafted the manuscript.

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Data availability

Data are available upon reasonable written request to the Wake Forest NCORP Research Base (ncorp@wakehealth.edu).

Declarations

Ethics approval and consent to participate

A statement about participant consent is in the main text of the manuscript.

Consent for publication

IRB# IRB00024197, R01HL118740.

Competing interests

The authors declare no competing interests.

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