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ORIGINAL REPORT

Inflammatory Cytokines and Comorbidity Development in Breast Cancer Survivors Versus Noncancer Controls: Evidence for Accelerated Aging?

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A B S T R A C T

Purpose

The sequelae of cancer treatment may increase systemic inflammation and create a phenotype at increased risk of functional decline and comorbidities, leading to premature mortality. Little is known about how this trajectory compares with natural aging among peers of the same age without cancer. This longitudinal study investigated proinflammatory cytokines and comorbidity development over time among breast cancer survivors and a noncancer control group.

Methods

Women (N = 315; 209 with breast cancer and 106 in the control group) were recruited at the time of their work-up for breast cancer; they completed the baseline questionnaire, interview, and blood draw (lipopolysaccharide-stimulated production of interleukin [IL] -6, tumor necrosis factor-α, and IL-1β). Measures were repeated 6 and 18 months after primary cancer treatment (cancer survivors) or within a comparable time frame (control group).

Results

There were no baseline differences in comorbidities or cytokines between survivors and the control group. Over time, breast cancer survivors had significantly higher tumor necrosis factor-α and IL-6 compared with the control group. Survivors treated with surgery, radiation, and chemotherapy accumulated a significantly greater burden of comorbid conditions and suffered greater pain associated with inflammation over time after cancer treatment than did the control group.

Conclusion

Survivors who had multimodal treatment had higher cytokines and comorbidities, suggestive of accelerated aging. Comorbidities were related to inflammation in this sample, which could increase the likelihood of premature mortality. Given that many comorbidities take years to develop, future research with extended follow-up beyond 18 months is necessary to examine the evidence of accelerated aging in cancer survivors and to determine the responsible mechanisms.

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INTRODUCTION

The average five-year survival rates for patients with breast cancer is 89%,[1] and 3.1 million breast cancer survivors live in the United States alone.[2] These women experience continuing medical and psychosocial problems after breast cancer treatment—symptoms such as fatigue, depression, decreased cognitive and physical functioning, and adverse body composition changes, which increase the risk of obesity and sarcopenia.[3,4] They are also at risk of late effects of treatment, such as cardiac or other organ toxicity and neuropathy, that reduce functioning.[3] Furthermore, many women decrease their healthy behaviors during cancer treatment, including exercise, which never returns to premorbid levels.[5] All of this may increase inflammation and create a phenotype at risk of functional decline, comorbidity development, and mortality. However, without comparisons with healthy aging in cancer-free peers of the same age, it is unclear whether this represents a phenomenon akin to accelerated aging[6] in cancer survivors.

Although few studies have investigated accelerated aging in cancer survivors, investigators

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have looked at accelerated frailty as a sign of accelerated aging. Frailty is a clinical syndrome in which an individual cannot return to baseline functional status after a physical insult. Accelerated frailty has been linked to a greater comorbidity burden in childhood cancer survivors.[7] Accelerated aging was noted in the brains of adult survivors of pediatric lymphoid malignancies.[8] Among adults, the prevalence of frailty is higher in breast cancer survivors versus noncancer control groups, but this was measured at only one time point.[9]

Frailty is not a proxy for aging, because not all older adults become frail. Examining trends in comorbidity development is instructive in describing aging because comorbidity burden is linked to increased non–breast cancer mortality and all-cause mortality in breast cancer survivors.[10-15] Population-based Behavioral Risk Factor Surveillance System survey data document higher comorbidity and poorer health status in cancer survivors compared with control groups.[16] In the SEER-Medicare Health Outcomes Survey data set, 65% of breast cancer survivors reported having two or more comorbid conditions compared with 61% of those without a cancer history.[17] These data are cross sectional; thus, it is unknown whether cancer survivors had greater comorbidity before cancer or whether the excess comorbidity burden resulted from cancer treatment. One study that observed women older than 65 years of age over a span of 10 years suggests that older breast cancer survivors and control groups without cancer accumulate comorbid conditions at similar rates[12]; however, it is unknown whether the rate of comorbidity development differs among women younger than 65 years of age with and without cancer. A registry-based study of comorbidity in cancer survivors found that breast cancer survivors in particular were likely to report increased comorbidity development after cancer[18]; however, this study did not include noncancer control subjects.

Understanding the trajectories of comorbidity development and the biologic mechanisms driving these effects in cancer survivors would point to targeted interventions to disrupt these processes. Biologic aging is characterized by changes in several domains that decrease organ reserve capacity across systems and increase the risk of comorbidity and mortality. These hallmarks of aging include genomic instability, telomere attrition, epigenetic alterations, loss of proteostasis, deregulated nutrient sensing, mitochondrial dysfunction, cellular senescence, stem cell exhaustion, and altered intercellular communication,[19] with the most prominent of these being chronic inflammation.[20] Inflammation is implicated in aging-related physical decrements and disability,[21-23] and chronic inflammation increases the risk of disability and mortality, including cancer mortality, even when clinical disease is not evident.[21,22,24,25] Overactivation of the inflammatory network is a mechanism believed to drive persistent fatigue in breast cancer survivors.[26] Several inflammatory biomarkers have been associated with breast cancer prognosis, especially with reduced survival.[27] However, because longitudinal research on inflammation and comorbidities in cancer survivors and control groups is lacking, the relationship between these variables is not understood.

This study investigated comorbidity development over time among breast cancer survivors relative to a noncancer control group in a longitudinal study and explored the role of inflammatory cytokines in comorbidity development.

METHODS

Study Methods

Women (N = 315) were identified from cancer clinics at The Ohio State University at the time of their work-up for breast cancer because of an initial test suggestive of cancer and were recruited into the parent longitudinal study of fatigue and immune dysregulation. As the result of one or more follow-up tests (ie, biopsy, fine-needle aspiration, magnetic resonance imaging, ultrasound, mammogram), participants received either a benign (noncancer control group) or a malignant (cancer survivor group) diagnosis. Recruitment occurred before knowledge of the diagnosis in benign women; women with breast cancer already knew their diagnosis. Individuals were ineligible if they had significant visual, auditory, or cognitive impairments or a history of cancer (excluding basal or squamous cell skin carcinomas). We did not include women who were found to have stage IV cancer. The Ohio State University Institutional Review Board approved the project, and all participants gave written informed consent.

Women completed the baseline questionnaire, interview, and blood draw at the time of their initial work-up for cancer. Cancer survivors' first post-treatment appointment occurred 6 months after the completion of surgery, radiation, or chemotherapy, whichever came last. The second post-treatment visit was 12 months later. Participants in the noncancer control group were scheduled within a comparable time frame using the average 6-month follow-up time of the breast cancer group. Participants completed the follow-up questionnaires, interviews, and blood draws at baseline and at both follow-up visits.

Figure 1 depicts the recruitment and retention of survivors and the control group. Overall, 315 women (209 women with breast cancer, 106 in the control group) completed the baseline assessment and blood draw; three hundred five women (202 with breast cancer, 103 in the control group) completed one or more follow-up assessments and blood draws and are included in the longitudinal analyses.

Measures

Comorbidity. Comorbidity was measured using the Charlson comorbidity index originally developed for patients with breast cancer.[28] The measure uses participants' self-reported health information to assign weights to 19 medical conditions (range, 1 to 37), with greater scores equal to greater comorbidity burden. Given known correlations between comorbidities and pain, we also included pain using the Rand 36-item Short Form Survey pain scale[29] (range, 0 to100, with greater scores equal to less pain).

Inflammatory cytokines. Fasting blood samples were collected between 7:00 and 9:00 AM to control for diurnal variation. We were interested in stimulated cytokine production, given that this process occurs upstream of circulating markers and that prior work has linked cytokine production to fatigue, physical function decline, disability, and death.[21,22,30,31] Lipopolysaccharide (LPS) -stimulated production of interleukin (IL) -6, tumor necrosis factor (TNF) -α, and IL-1β from isolated peripheral blood mononuclear cells was multiplexed and measured via the electrochemilluminescence method using Meso Scale Discovery kits (Meso Scale Diagnostics, Rockville, MD).[32] Each participant's frozen samples were assayed for all cytokines in one run using the same controls for all time points for each person. To capture overall inflammation, we also created a composite *z* score combining the IL-6, TNF-α, and IL-1β variables.

Covariates. Covariates included self-reported age, race/ethnicity, menopausal status, and cigarette smoking (never, former, current) at baseline. Breast cancer stage, hormone receptor status, and treatment information (surgery, chemotherapy, radiation, aromatase inhibitors, selective estrogen receptor modulators [SERMs]) were abstracted from medical records.

Analysis Plan

Baseline demographic and cancer-related characteristics were compared between breast cancer survivors and the control group using

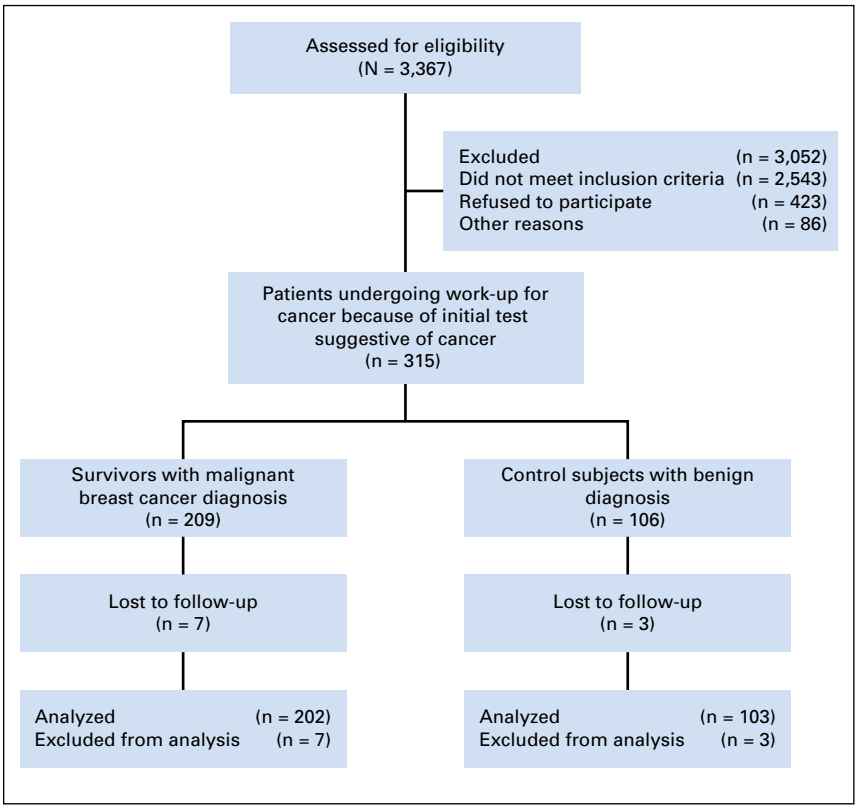

Fig 1. CONSORT diagram of participant recruitment.

t tests and χ^2 tests as appropriate. Linear mixed-effect models were used to test the differences in the trajectories over time of comorbidity, pain, and cytokines (LPS-stimulated IL-6, IL-1β, and TNF-α, and the cytokine *z* score) between cancer survivors and the control group. Fixed effects included visit, group (cancer, control), and their interaction. Random effects included a subject-specific random intercept, accounting for within-subject correlation, as well as an assay plate–specific random intercept (models with individual cytokines as outcomes), accounting for the variability among assay plates. To investigate differences in trajectories of comorbidity, pain, and inflammation over time by cancer treatment, these models were repeated with exposure groups defined by different stages of cancer versus the control group, or of different treatments (surgery, chemotherapy, radiation, aromatase inhibitors, SERMs) versus the control group. The Kenward-Roger adjustment to the degrees of freedom was used to control type 1 error rates.[33] The appropriateness of these models was assessed by examining residuals from all models; in all cases, the residuals were approximately normally distributed. To account for deviation in the time between baseline and visits two and three across participants, these models were repeated, adjusting for a variable indicating deviation from the group mean for the time between baseline and each visit. Analyses were unchanged from the unadjusted models; thus, we have presented the results without this adjustment.

Linear mixed-effect models were used to test the cross-sectional associations among cytokines, comorbidities, and pain. Data from all three visits were pooled to investigate the fixed effect of comorbidities and pain in relation to cytokines. There were no significant group-by-comorbidities interactions, indicating that the relationship between comorbidities and cytokines did not differ significantly between survivors and the control group, and thus, unadjusted models included only a fixed effect for group. Secondary analyses further controlled for potential confounders, such as age, race/ethnicity, menopausal status, and smoking status. As in the longitudinal analyses, random effects included a subject-specific random intercept and an assay plate–specific random intercept for models with individual cytokines.

To explore longitudinal relationships between inflammation and comorbidity and pain development, logistic regression models tested whether the magnitude of change in cytokines from baseline to visit two predicted an increase in comorbidities from baseline to visit three (1 was equal to an increase; 0 was equal to no change), controlling for the number of baseline comorbidities, baseline cytokine levels, and group. Similarly, linear regression models were used to test whether cytokine change from baseline to visit two predicted change in pain from baseline to visit three, while controlling for baseline pain and cytokine levels, age, race/ethnicity, menopausal status, smoking status, and group.

RESULTS

Characteristics of the Sample

Table 1 lists the baseline characteristics of breast cancer survivors versus the control group. On average, participants were 55 years of age, postmenopausal, predominately white, and more than 25% had some postgraduate education. There were no demographic differences between breast cancer survivors and the control group. Two thirds of breast cancer survivors had been diagnosed with stage I or II cancers, and 30% were treated with surgery only. Most had estrogen receptor– and/or progesterone receptor–positive tumors. A minority were treated with aromatase inhibitors (41% of survivors) or SERMs (32% of survivors).

Differences in Trajectories of Comorbid Conditions and Pain in Breast Cancer Survivors Versus the Control Group During and After Primary Breast Cancer Treatment

There were no baseline differences between survivors and the control group in terms of comorbidities or pain (Table 1 and Fig 2).

Table 1. Baseline Demographic and Clinical Characteristics of Breast Cancer Survivors and Control Group

Characteristic	Control Group (n = 103)	Survivors (n = 202)	*P*
Age, years, mean (SD)	55.3 (10.7)	55.8 (11.6)	.75
Race			.63
White	84 (82)	158 (78)	
Black	15 (15)	31 (15)	
Other	4 (3)	13 (7)	
Current smoker	9 (9)	27 (13)	.26
Education level			.56
High school or less	26 (25)	57 (28)	
Some college	19 (19)	43 (21)	
College graduate	32 (31)	48 (24)	
Postgraduate	25 (25)	54 (27)	
Income level, $			.55
0-25,000	17 (17)	35 (17)	
25,000-50,000	19 (19)	44 (22)	
50,000-75,000	19 (19)	26 (13)	
75,000-100,000	11 (11)	26 (13)	
> 100,000	21 (21)	52 (26)	
No report	14 (14)	19 (9)	
Cancer stage			
0	NA	37 (18)	
I	NA	92 (46)	
IIA	NA	33 (16)	
IIB	NA	19 (9)	
IIIA	NA	16 (8)	
IIIB	NA	1 (1)	
IIIC	NA	3 (1.5)	
Cancer treatment			
Surgery only	NA	62 (30.9)	
Radiation + surgery	NA	54 (26.9)	
Chemotherapy + surgery	NA	33 (16.4)	
Radiation + chemotherapy + surgery	NA	52 (25.9)	
Type of surgery			
Lumpectomy	NA	69 (34.5)	
Mastectomy	NA	131 (65.5)	
Estrogen receptor status			
Negative	NA	42 (21.3)	
Positive	NA	155 (78.7)	
Progesterone receptor status			
Negative	NA	55 (28.1)	
Positive	NA	141 (71.9)	
Ever on aromatase inhibitors	NA	67 (41.1)	
Ever on selective estrogen receptor modulators	NA	52 (31.5)	
Time from baseline visit to visit 2, days, mean (SD)	392.5 (139.5)	414.9 (169.0)	.33
Time from baseline visit to visit 3, days, mean (SD)	765.9 (156.7)	768.0 (191.8)	.60
Postmenopausal	68 (67)	126 (63)	.46
Charlson comorbidity score, mean (SD)	0.5 (0.9)	0.5 (0.9)	.62
Pain scale, mean (SD)	77.8 (22.6)	79.4 (22.7)	.48
Stimulated TNF-α, mean (SD)	5,487.4 (2,192.0)	5,202.4 (1,965.2)	.36
Stimulated IL-6, mean (SD)	15,869.2 (6,513.0)	16,049.8 (5,857.4)	.79
Stimulated IL-1β, mean (SD)	5,163.1 (3,475.8)	4,486.1 (2,904.4)	.20
Cytokine *z* score, mean (SD)	0.3 (2.7)	−0.1 (2.4)	.20

NOTE. Data are presented as No. (%) unless indicated otherwise.
Abbreviations: IL, interleukin; NA, not applicable; SD, standard deviation; TNF, tumor necrosis factor.

As illustrated in Figure 2A, in longitudinal models, there was a nonsignificant trend over time ($P = .06$) for higher comorbidity in survivors compared with the control group (by visit three, mean difference [MD] = 0.17). There was a significant trend over time in pain; survivors reported worse pain by visit three compared with the control group (Fig 2B; MD = −7.36; $P = .02$). In models with exposure groups defined by different stages of cancer or by different treatments versus the control group, trajectories of comorbidities were worse in those with higher-stage (II to III) cancers ($P < .001$, results not shown). There were significant differences in the trajectories of comorbidity scores ($P = .02$) and pain scores ($P = .05$) by treatment groups (Figs 2C and 2D), with more comorbidities and worse pain scores over time among survivors treated with a combination of surgery, radiation, and chemotherapy. Trajectories of comorbidity scores were higher in survivors versus the control group regardless of whether survivors took aromatase inhibitors or SERMs. Worse pain scores over time were noted in survivors who took aromatase inhibitors ($P = .008$; results not shown).

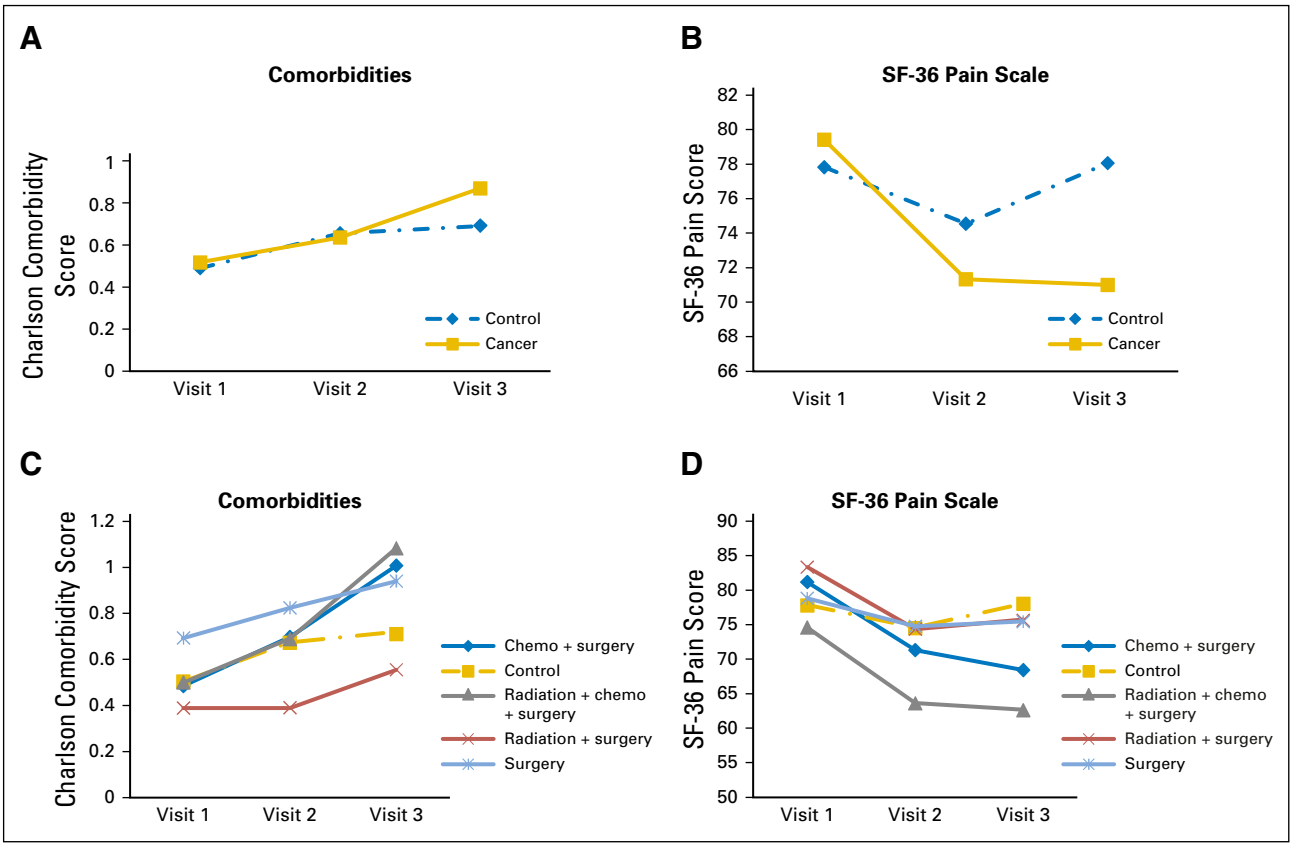

Fig 2. Charlson comorbidity score and SF-36 pain score over time in cancer survivors versus control group. (A) Charlson comorbidity score over time. (B) SF-36 pain score over time. Note that higher scores indicate less pain. (C) Charlson comorbidity score over time by cancer treatment type. (D) SF-36 pain score over time by cancer treatment type. chemo, chemotherapy; SF-36, Rand 36-item Short Form Survey.

Differences in Trajectories of Inflammatory Cytokines in Breast Cancer Survivors Versus the Control Group During and After Primary Breast Cancer Treatment

There were no significant baseline differences between survivors and the control group in LPS-stimulated TNF-α, IL-6, or IL-1β cytokines, or in the cytokine *z* score (Table 1 and Fig 3). Over time, there were significant trends for survivors to have greater LPS-stimulated TNF-α and IL-6 at visits two and three relative to the control group (Figs 3A to 3D; TNF-α: $MD_{visit2} = 888.62$, $P = .0046$; $MD_{visit3} = 808.06$, $P = .015$; IL-6: $MD_{visit2} = 2{,}873.18$, $P = .001$; $MD_{visit3} = 1{,}509.19$, $P = .096$). There was no difference in LPS-stimulated IL-1β over time in survivors compared with the control group. Overall, survivors had significantly higher inflammation on the cytokine *z* score compared with the control group over time ($MD_{visit2} = 1.12$, $P = .005$; $MD_{visit3} = 0.95$, $P = .02$). In models with exposure groups defined by different stages of cancer or different treatments compared with the control group, survivors of higher-stage cancer (stage IIB to III) had greater increases in stimulated cytokines over time (all $P < .05$; results not shown). There were significant differences in the trajectories of stimulated cytokines over time by treatment group (all $P < .05$; results not shown), with survivors treated with a combination of surgery, radiation, and chemotherapy having the highest increases in stimulated cytokines. Inflammation was higher in survivors than in the control group regardless of whether the survivors took aromatase inhibitors; however, there were significant trends for survivors who took SERMs to have increased stimulated cytokines over time (all $P < .01$; results not shown).

Inflammatory Cytokines in Relation to Comorbidity and Pain

Comorbidities and cytokines. In cross-sectional models relating stimulated cytokines to comorbidity, the comorbidities score was significantly related to greater LPS-stimulated TNF-α (β = 193.54; $P = .04$), and greater cytokine composite *z* scores (β = 0.25; $P = .04$). In models adjusted for age, race/ethnicity, menopausal status, and smoking, the comorbidities score was significantly associated with the cytokine composite *z* score (β = 0.25; $P = .04$); however, the relationships between comorbidities score and LPS-stimulated TNF-α (β = 168.04; $P = .07$), and Il-6 (β = 476.74; $P = .06$) became nonsignificant.

In longitudinal models, change in LPS-stimulated IL-6 from baseline to visit two was significantly related to an increase in comorbidities from baseline to visit three (odds $ratio_{100units} = 1.008$; 95% CI, 1.0007 to 1.02; $P = .029$), with similar but nonsignificant results for TNF-α ($P = .07$).

Pain and cytokines. Pain scores were not related to stimulated cytokines or to the cytokine *z* score in unadjusted or adjusted models or in longitudinal models of cytokine and pain change over time.

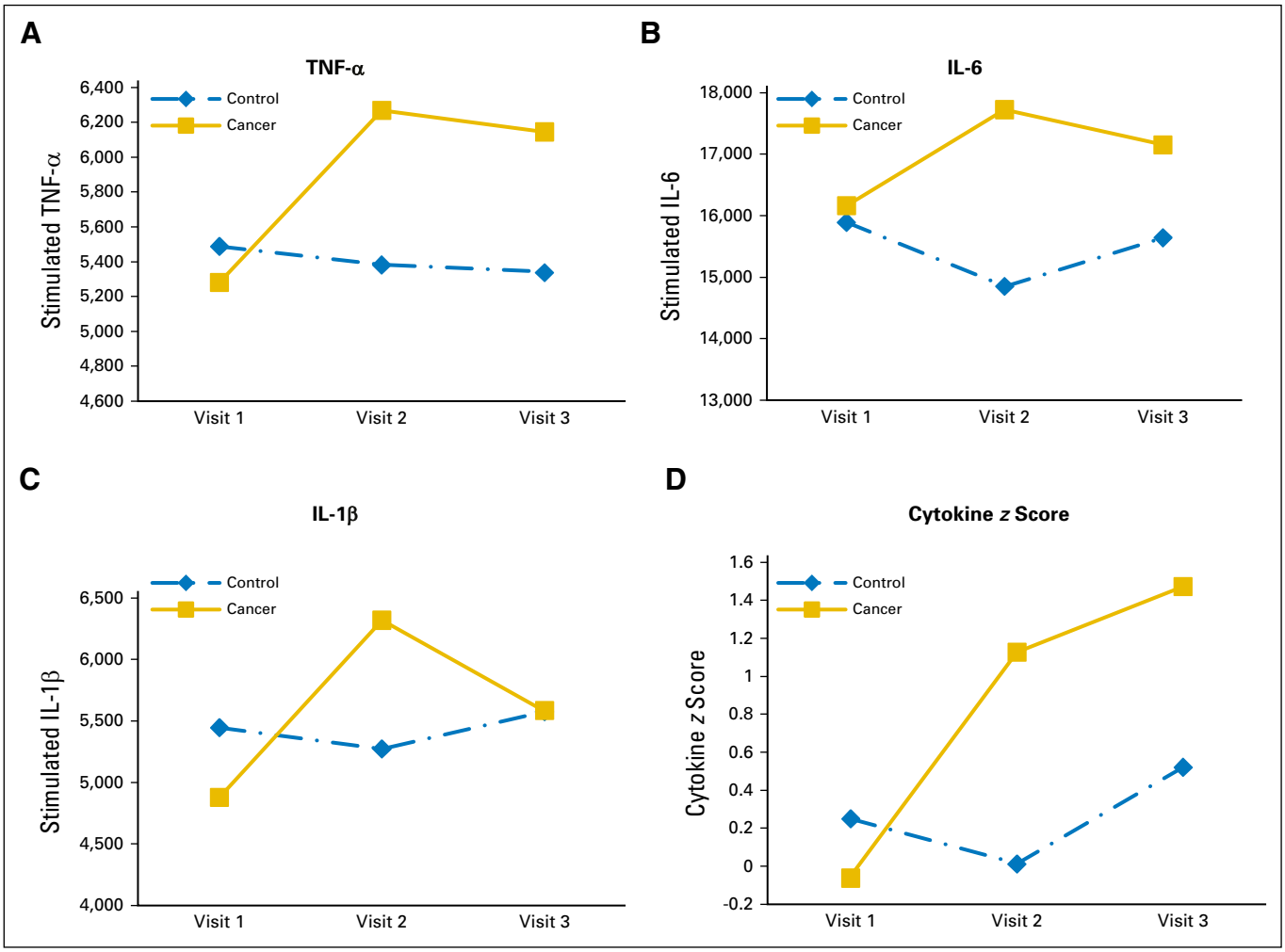

Fig 3. Lipopolysaccharide-stimulated cytokines over time in cancer survivors versus control group. (A) Lipopolysaccharide-stimulated TNF-α over time. (B) Lipopolysaccharide-stimulated IL-6 over time. (C) Lipopolysaccharide-stimulated IL-1β over time. (D) Overall inflammation over time as measured by the cytokine *z* score. IL, interleukin; TNF, tumor necrosis factor.

DISCUSSION

We investigated the evidence for an accelerated aging phenotype in breast cancer survivors characterized by the accumulation of excess comorbidities relative to peers of the same age without cancer. We also examined the associations between inflammation and this phenotype. The findings support our hypothesis that cancer treatment may trigger an accelerated aging process in some cancer survivors. There were no baseline differences in comorbidities before cancer treatment. Although the increase in survivors' comorbidities over time after treatment versus that of the control group was nonsignificant overall, it was also accompanied by significantly greater pain. In particular, this study found significantly greater increases in comorbidity among survivors of higher-stage cancers and those who were treated with a combination of surgery, chemotherapy, and radiation. Our data suggest that survivors treated with this multimodal therapy may face the highest risk of accelerated comorbidity development. Although mean pain scores in this sample were nearly two standard deviations better than the age-matched US population mean of 48[34] and although the mean Charlson comorbidity score was low to moderate,[35] our results are concerning because a one-unit increase on the Charlson comorbidity index is associated with twice the 1-year mortality rate.[36] Furthermore, because the last measurement of comorbidity was only 18 months after cancer treatment and because many comorbidities caused or exacerbated by cancer treatment may take years to develop (eg, heart failure from cardiotoxicity), this may be an early signal that cancer survivors face a higher burden of comorbid conditions that could accelerate their functional decline and lead to premature mortality. Our longitudinal findings are consistent with prior cross-sectional work from the Behavioral Risk Factor Surveillance System survey that documented higher comorbidity and poorer health status in cancer survivors compared with control groups[16] and from SEER-Medicare Health Outcomes Survey data that demonstrate that breast cancer survivors specifically have more comorbid conditions than control groups.[17] However, our results disagree with a 10-year study of women older than 65 years of age that found equivalent rates of comorbid conditions in breast cancer survivors and the control groups without cancer.[12] The difference may be a result of the fact that

the 10-year study only included women older than 65 years of age or that the women were 5 years post–breast cancer. Our effect may be indicative of comorbidity accumulation early after treatment.

The mechanisms that drive accelerated aging or comorbidity burden and subsequent health and longevity in cancer survivors are not understood. This study investigated the associations between inflammatory cytokines and comorbidity development. Although there were no baseline differences in cytokines between survivors and the control group, survivors had significantly greater inflammation at visits two and three relative to the control group. In particular, survivors of higher-stage cancers treated with surgery, chemotherapy, and radiation, and those treated with SERMs had greater increases in inflammation. Inflammation was significantly related to the increased comorbidity seen in survivors. It may be that the combination of these cancer treatments elevates the inflammatory system, which increases comorbidity. Or, it may be that the pathophysiology of these conditions reduces physical functioning or physical activity, which increases subsequent inflammation. Of concern, given longer follow-up time, this excess inflammation may contribute to poorer health and premature mortality in the cancer survivor group. These results underscore the need for breast cancer survivorship care to include screening for and treatment of comorbid conditions, as well as recommendations for exercise, diet, and weight-management programs to prevent comorbidity development, as described in the new American Cancer Society and American Society of Clinical Oncology breast cancer survivorship care guidelines.[37,38] Monitoring is particularly important for women treated with multimodal therapy and SERMs.

Key study strengths are the inclusion of the measurement of comorbidities and inflammatory cytokines longitudinally in women with breast cancer and the noncancer control group. But the study also has limitations. The study was not designed to measure accelerated aging per se; thus, other biologic mechanisms of aging (eg, telomere length) were not measured. Participants were not observed for longer than 18 months after treatment to determine the longer-term trajectories of comorbidity and cytokines. Our control group had all been evaluated for breast cancer and may not be representative of all women without a breast cancer history. Our sample size was not sufficient to investigate differences in cytokines, comorbidities, and pain by chemotherapy regimen, radiation dose, surgical factors, treatment-induced menopause, physical activity, body mass index, or other mediating factors that may drive these problems among cancer survivors or to characterize patterns in the types of comorbidities developing in the survivors. Future research using large cohorts of cancer survivors and control groups with frequent longitudinal assessments are needed to further investigate these hypotheses.

In conclusion, this study found that, compared with peers of the same age without cancer, breast cancer survivors treated with surgery, chemotherapy, and radiation have increased inflammatory cytokines, pain, and comorbidity burden that are not evident before cancer treatment but are detected by 18 months after treatment. The increased comorbidity burden was related to increased inflammation in this sample. Although it is possible that cancer treatment may trigger an accelerated aging process in cancer survivors, longer follow-up is needed to confirm this hypothesis and to determine the biologic drivers of these effects.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at ascopubs.org/journal/jco.

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Final approval of manuscript: All authors

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