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Chemotherapy-Induced Biological Age Acceleration and Lifetime Outcomes in Breast Cancer Survivors

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Abstract

IMPORTANCE Growing evidence suggests some breast cancer survivors may experience accelerated aging (biological age in excess of chronological age) after receiving chemotherapy.

OBJECTIVE To quantify the range of lifetime changes in accelerated aging following chemotherapy.

DESIGN, SETTING, AND PARTICIPANTS This comparative effectiveness study used an established Cancer Intervention and Surveillance Modeling Network breast cancer model integrating biological aging with breast cancer epidemiology. Biological aging was modeled using data on distributions of postchemotherapy senescence measured by $p16^{INK4a}$ levels, and the model assumed chemotherapy-induced senescence only affected non–breast cancer mortality. The simulated population included US women diagnosed with breast cancer at ages 30 to 79 years between 1990 and 2030, with follow-up until death. Two model simulations were run; the first assumed all women who developed breast cancer received anthracycline, and the second assumed all received nonanthracycline treatment. Modeling was conducted from November 2025 to April 2026. Results were validated by comparing model-predicted trends with findings from the Anthracycline for Early Breast Cancer (ABC) trials.

EXPOSURES More vs less cytotoxic chemotherapy, using exemplar anthracycline-based vs nonanthracycline regimens.

MAIN OUTCOMES AND MEASURES Lifetime outcomes included the age at which the risk of non–breast cancer mortality exceeded the risk of breast cancer mortality by chemotherapy regimen, posttreatment life-years, and all-cause mortality by age group at diagnosis and median senescence levels.

RESULTS The study included a simulated population of 400 million US women aged 30 to 79 years diagnosed with breast cancer. Breast cancer survivors who received anthracycline lost 9.4 (IQR, 7.6-11.2) years of remaining life years. Overall, among anthracycline recipients, the risk of non–breast cancer mortality was projected to exceed breast cancer mortality 16 (IQR, 12-19) years earlier than expected based on chronological age. There was heterogeneity in results, with greater variability for women diagnosed at younger vs older ages. Women receiving more vs less cytotoxic regimens were estimated to lose a median difference of 7.6 (IQR, 7.0-8.0) more years of life due to earlier ages at onset of aging-related diseases. The model closely replicated all-cause and 8-year breast cancer survival trends in the ABC trials.

CONCLUSIONS AND RELEVANCE In this simulation model of chemotherapy-induced biological aging, increased breast cancer survival was seen with more (vs less) cytotoxic regimens, but this was paired with greater potential risk of earlier non–breast cancer mortality due to age acceleration.

(continued)

Key Points

Question What is the potential long-term effect of cancer therapy on biological aging of breast cancer survivors?

Findings This comparative effectiveness study used an established population-level simulation model and current data on chemotherapy's effects on cellular senescence to estimate differences in biological age acceleration in a simulated population of 400 million US women. The model estimated that the median difference in life years lost due to biological age acceleration was 7.6 years for anthracycline-based vs nonanthracycline treatment regimens.

Meaning These findings suggest that integrating knowledge about biological aging into survivorship care may help identify opportunities to deploy pharmaceutical and behavioral interventions that target aging-related processes.

+ Supplemental content

Author affiliations and article information are listed at the end of this article.

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Abstract (continued)

These results suggest the value of integrating knowledge about biological aging into survivorship care and could inform future research to address accelerated aging among breast cancer survivors.

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Introduction

Breast cancer survival rates have been steadily increasing over time due to advances in screening and the development of new therapeutic paradigms.[1] However, growing evidence suggests that some breast cancer survivors may experience long-term toxic effects of chemotherapy, including accelerated aging (biological age in excess of chronological age),[2-9] with declines in function and the development of chronic aging-related diseases such as cardiovascular disease and diabetes.[10-18]

One mechanism by which chemotherapy accelerates aging is through increases in the accumulation of senescent cells, defined as cells that have stopped dividing but are resistant to cell death.[19] These cells promote further aging through changes in tissue modeling and inflammation, contributing to excess non–breast cancer morbidity and mortality.[20-22] Several studies have documented increases in senescent cells in breast cancer survivors after chemotherapy.[23-26] Senescence has gained attention as a potential target for improving the health of the growing population of breast cancer survivors[27] given advances in the measurement of senescent cell burden (eg, $p16^{INK4a}$ levels and epigenetic markers of senescence), promising senolytic and other anti-aging drugs, and potentially effective behavioral interventions.[28-32]

Despite these advances, integrating the growing understanding of accelerated aging into survivorship care has been difficult due to heterogeneity in age acceleration among individual breast cancer survivors, variability in the effects of different regimens on aging, and limited tools to help clinicians assess and integrate information about accelerated aging into routine care and practice guidelines. To address this gap, we extended an established Cancer Intervention and Surveillance Modeling Network (CISNET) population model of breast cancer to include a novel systems biology module using $p16^{INK4a}$ biomarker levels to reflect the heterogeneity in senescent cell accumulation. The model was used to quantify the net population association of chemotherapy-related age acceleration with overall survivorship outcomes and to examine outcomes by age at breast cancer diagnosis, more vs less cytotoxic chemotherapy regimens, and level of precancer senescence. The results are intended to illustrate the use of simulation modeling for understanding the potential long-term implications of accelerated aging among breast cancer survivors.

Methods

This comparative effectiveness study adapted a well-validated CISNET breast cancer model.[33-35] CISNET models have been previously used to inform clinical guidelines and practice,[33] conduct clinical trial simulations of omitting radiotherapy for low-risk breast cancers,[36] determine contralateral breast cancer risk by endocrine therapy regimens,[37] create clinical decision aids,[38] and project US mortality trends.[39,40] We used one CISNET model, Model GE, to model chemotherapy effects on senescence.[41] This study followed the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) reporting guideline.[42] The institutional review board at University of Wisconsin, the CISNET Breast Group Coordinating Center, determined that this study was exempt from review and informed consent because it did not constitute human participant research.

General Model Approach

Model GE is a population-level Monte Carlo simulation model that has been described elsewhere.[38,41] For this study, we adapted the treatment and survivorship portion of the model to integrate a

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systems biology model of senescent cell accumulation as measured by cyclin-dependent kinase inhibitor 2A messenger RNA ($p16^{INK4}$) levels.[43] $p16^{INK4a}$ is one of the most commonly reported senescence biomarkers in the oncology literature.[44-46] In this study, we use $p16^{INK4a}$ interchangeably with the terms *senescence* and *senescence level*.

As depicted in **Figure 1**, we began with the distribution of $p16^{INK4a}$ levels by chronological ages of women in the general population.[21,22] We then used published clinical data on the increase of $p16^{INK4a}$ levels after chemotherapy[23,25,26] to simulate the altered level of senescence for the remaining lifetime of breast cancer survivors. The senescence level was used to derive a biological age that was then used, instead of chronological age, to determine non–breast cancer mortality rates. We made the simplifying assumption that only chemotherapy affected senescence levels and did not explicitly model any effects of local or other systemic therapy regimens (eg, breast radiation, hormonal therapy, targeted therapy, or immunotherapy) on senescence, since there were limited data for these modalities.[26,47,48]

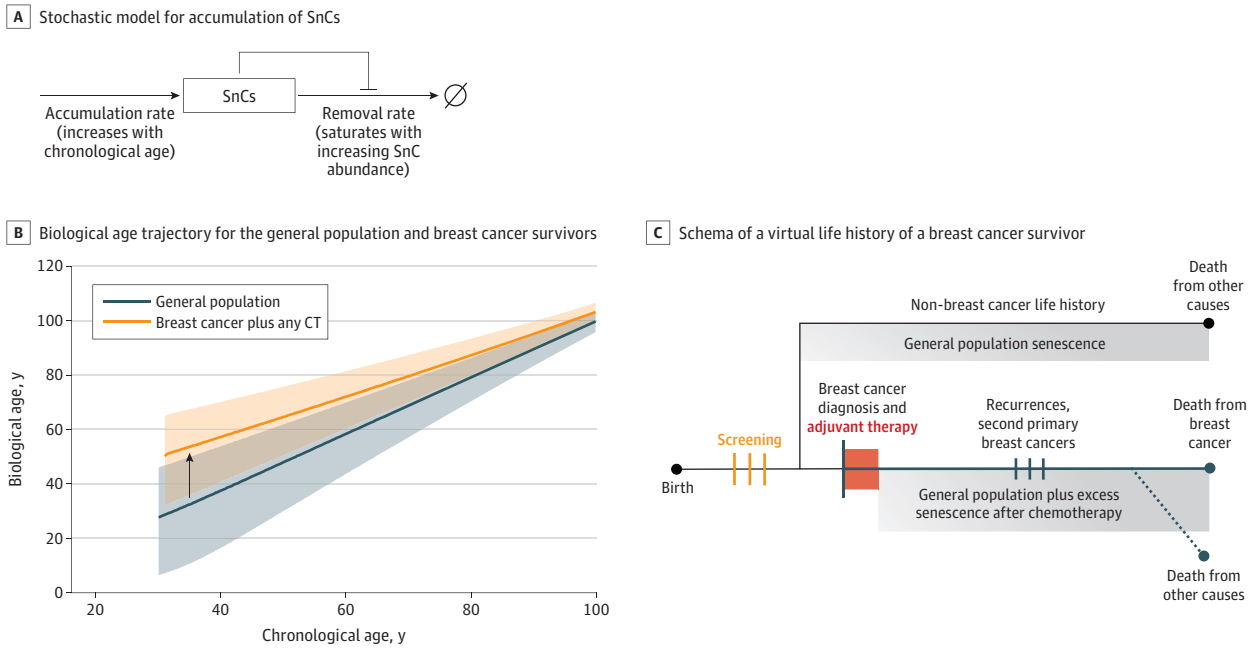
Population

We simulated a multicohort population of US women, using birth year distribution from 1890 to 2010, followed from birth to death. We summarized results for the population of women aged 30 to 79 years who developed a primary breast cancer between 1990 and 2030 and were treated with adjuvant or neoadjuvant chemotherapy. We chose this age range to reflect treatment exposures among survivors alive at the time of the analysis. We did not include women diagnosed before age 30 years due to low incidence and high rates of mutation-related cancers.

Model Input Parameters

The model input parameters are summarized in eTable 1 in Supplement 1. Parameters that were newly developed for this study are described here.

Figure 1. Diagrams and Line Graph Showing Biological Age Acceleration Due to Chemotherapy and Implications for Breast Cancer Epidemiology



A, Reaction network diagram illustrating a stochastic model for senescent cells (SnC) accumulation, originally developed Karin et al[22] using the $p16^{INK4a}$ messenger RNA expression data from mice and human mortality rate data. B, Biological age trajectory with 95% CIs for the general population, and the accelerated biological aging trajectory in breast cancer survivors after receiving chemotherapy at age 30 years. The blue shaded area represents the general population, the yellow shaded area represents survivors with accelerated biological aging, and the overlapping shaded area represents overlap between the 95% CIs. The arrow depicts the level of biological age acceleration due to chemotherapy. C, Schema of a virtual life history of a breast cancer survivor in Cancer Intervention and Surveillance Modeling Network population-level simulation model; this study used the Georgetown University-Albert Einstein College of Medicine model (Model GE).[42]

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Senescence Accumulation Model

To simulate the accumulation of senescent cells with age among women, we used the stochastic differential equation model developed by Karin et al (Figure 1A; eMethods in Supplement 1).[22] Based on Karin's model, we simulated 1 million women in order to develop a robust distribution of $p16^{INK4a}$ senescence expression level for each chronological age. These data were used to randomly assign women to a senescence level, independent of cancer molecular subtype and stage. We then made the simplifying assumption that $p16^{INK4a}$ expression does not increase the risk of breast cancer mortality.

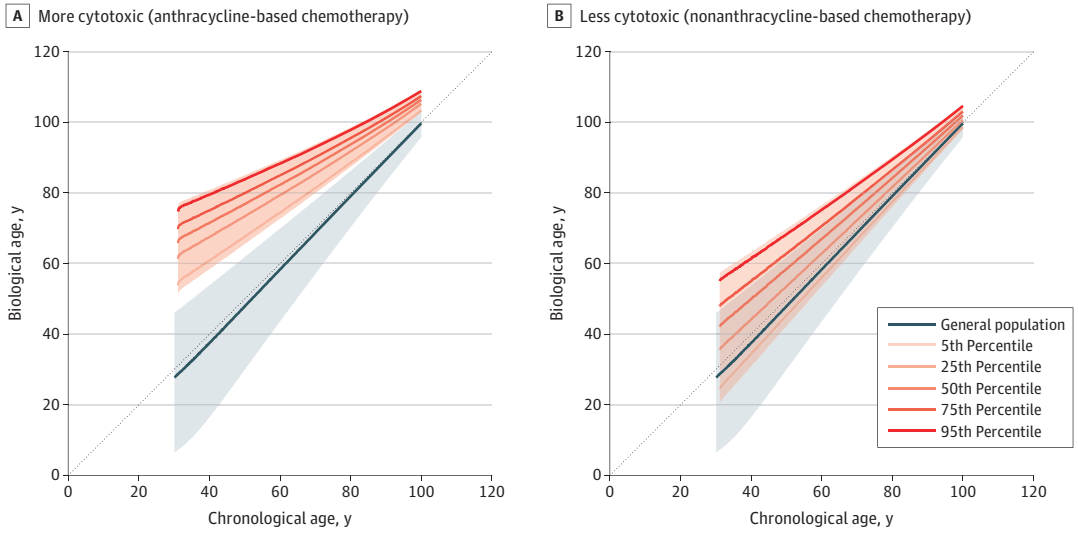
Chemotherapy and $p16^{INK4a}$ Expression

Using the best available data, we estimated the absolute change in the level of $p16^{INK4a}$ expression after chemotherapy with more vs less cytotoxic regimens, using anthracycline and nonanthracycline regimens as exemplars because they had the most data available at the time of this study (eTable 1, eMethods, and eFigure 1 in Supplement 1).[23,25,26] This change in $p16^{INK4a}$ level was used to modify senescence for the remaining lifetime of survivors from that seen in the general population. The modified senescence distribution was used to estimate a woman's biological aging conditional on chemotherapy regimen and age at diagnosis and treatment (**Figure 2**; eMethods in Supplement 1). Based on existing data on persistence of $p16^{INK4a}$ levels after chemotherapy,[23,25,26,49-51] we assumed that the effects of chemotherapy on $p16^{INK4a}$ persisted for survivors' entire remaining lifetimes and that women remained at the same biological aging distribution for the remainder of their lives.

Non–Breast Cancer Mortality

In our past modeling, non–breast cancer mortality has always been a function of chronological age.[37,52] For this study, at each chronological age, survivors were assigned a corresponding biological age based on senescence levels to determine their non–breast cancer mortality. These biological age–dependent mortality rates were used to determine left-truncated survival functions for

Figure 2. Line Graphs of Variability in the Accelerated Biological Aging of Breast Cancer Survivors After Chemotherapy



The panels show the biological age acceleration curves for (A) the more cytotoxic regimen (anthracycline-based chemotherapy) and (B) the less cytotoxic regimen (nonanthracycline chemotherapy). The distribution of biological age after chemotherapy was divided into 5 different groups, centered at the 5th, 25th, 50th, 75th, and 95th percentiles of the full distribution of biological age. The primary outcomes were the median (50th percentile) and IQR (25th and 75th percentiles). The blue line and 95% CI (blue shaded area) represent the biological age distribution in the general population, which was not affected by chemotherapy. The x-axis represents chronological age at breast cancer diagnosis, starting at 30 years, and the y-axis represents biological age based on senescence as measured by $p16^{INK4a}$ biomarker levels. These graphs represent biological age acceleration only for breast cancer diagnosis at age 30 years; however, our simulation study included breast cancer diagnosis at ages 30 through 79, and we generated biological age acceleration curves starting from those ages to use in our population-level simulation model.

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non–breast cancer mortality starting from the date of completion of chemotherapy. The survival functions were then used to sample the time to death from non–breast cancer causes. The biological age–dependent survival functions were calibrated to match the age-adjusted US non–breast cancer mortality rate in breast cancer survivors (eFigure 2 in Supplement 1).

Validation

We simulated a population of 100 million women and selected a sample of breast cancer survivors (n = 40 166) from this population to match the patient demographic and clinical characteristics, years of diagnoses (2007-2013), and follow-up period (8 years), as reported in the Anthracycline in Early Breast Cancer (ABC) trials (eTable 1 in Supplement 1).[53] We compared model-predicted all-cause, breast cancer, and non–breast cancer survival after anthracycline-based vs nonanthracycline-based chemotherapy with the results of the trial.

Statistical Analysis

Modeling was conducted from November 2025 to April 2026. We modeled the entire population of US women, first assuming that all women who developed breast cancer received anthracycline. We then repeated the model simulations for the population assuming that all women with breast cancer received nonanthracycline, analogous to a clinical trial. In each scenario, we applied the treatment-specific hazards of breast cancer and non–breast cancer death. We simulated 400 million women to minimize stochastic variation as in our prior studies.[33,40]

The primary outcomes included the cumulative risk of breast cancer vs non–breast cancer death, life-years lived after chemotherapy, and all-cause survival based on biological age for more vs less toxic chemotherapy regimens and 6 age groups at diagnosis: 30 to 39, 40 to 49, 50 to 59, 60 to 69, 70 to 79 years, and combined 30 to 79 years. Based on observed distributions of senescence in the population, we reported medians and IQRs as our primary outcomes; data for the 5th and 95th percentiles were included as supplemental outcomes.

Results

Model Validation

The validation analysis included a simulated population of breast cancer survivors aged 30 to 79 years whose characteristics matched those of the participants in the ABC trials (n = 40 166). The model demonstrated the same pattern of outcomes as the ABC trials: breast cancer survival was higher with anthracycline-based vs nonanthracycline-based regimens, but all-cause mortality did not differ in 8 years of follow-up (**Figure 3**). The anthracycline-based chemotherapy in the ABC trials was anthracycline plus taxane, and the nonanthracycline-based regimen was cyclophosphamide plus taxane. There was a small absolute difference of 10 percentage points in the model results for breast cancer mortality in the general population of trial-eligible breast cancer survivors (77.6%) vs the population treated in the clinical trial (87.3%).

Chemotherapy-Associated Biological Aging and Non–Breast Cancer vs Breast Cancer Mortality Risk

Among a simulated population of 400 million women and breast cancer diagnosis at ages 30 to 79 years between 1990 and 2030, we found that survivors faced competing risks of breast cancer and non–breast cancer mortality. In general, as women aged, the risk of non–breast cancer mortality became higher than the risk of breast cancer mortality. With biological age acceleration, this transition occurred at earlier ages than expected based on chronological age (**Figure 4**). For example, for women diagnosed at ages 40 to 49 years, the point at which non–breast cancer mortality exceeded breast cancer mortality occurred at a median difference of 19 (IQR, 16-23) years earlier, with biological aging associated with more cytotoxic chemotherapy. This effect was lower among women diagnosed at ages 60 to 69 years (Figure 4). For all ages combined, the

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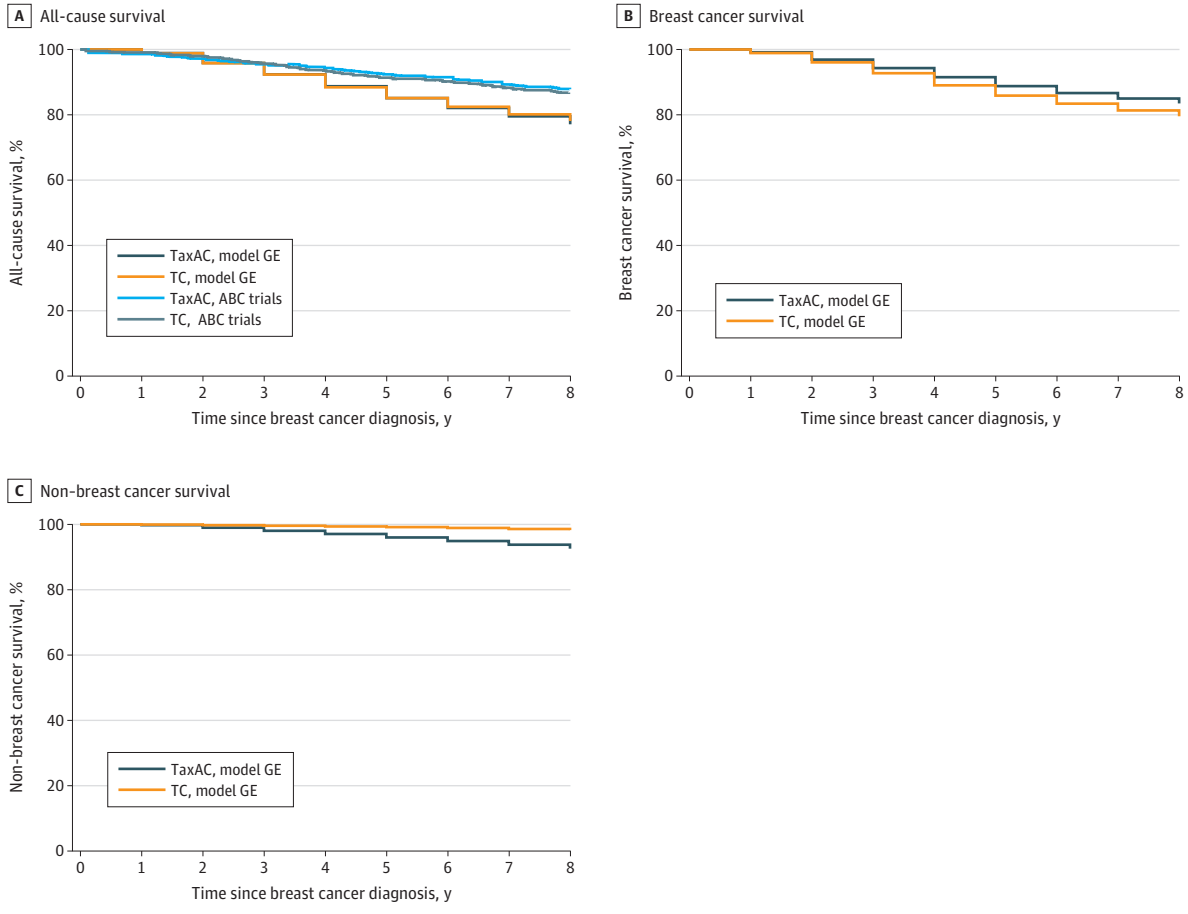
non–breast cancer mortality risk based on chronological age exceeded breast cancer mortality risk 33 years after diagnosis (eFigures 3 and 4 in Supplement 1). However, biological age acceleration due to more cytotoxic chemotherapy caused this transition at a median of 16 (IQR, 12-19) years earlier.

Chemotherapy-Associated Biological Aging and Life-Years

The median difference in posttreatment life-years lost due to biological age acceleration was projected to be 7.6 (IQR, 7.0-8.0) years for the more vs less cytotoxic treatment regimens (**Table**). The 50th percentile absolute life years (Table, column 7) most closely approximate the median seen in clinical studies, where breast cancer survivors have a distribution of biological ages at the same chronological age, with many having lower than average biological age and others having higher than average biological age. The impact of biological age acceleration on the difference in remaining life-years lost after more vs less cytotoxic treatment regimens varied by age. The greatest potential years of life lost occurred among women diagnosed and treated at ages 30 to 39 years. Based on chronological age, women treated at ages 30 to 39 years would be expected to live 50.4 years; when modeling the influence of the more cytotoxic chemotherapy on age acceleration, these

Figure 3. Cumulative Risk Curves Showing Comparison of the 8-Year Follow-Up of All-Cause, Breast Cancer, and Non–Breast Cancer Survival With the Results of the Anthracycline in Early Breast Cancer (ABC) Trials



A, All-cause survival from the ABC trials and Model GE. The blue and gray lines represent the 8-year survival percentages from the ABC trials, captured using image analyzing software.[54] The teal and orange lines are 8-year survival percentages from Model GE simulation of a population with the same characteristics as the ABC trials. B, Breast cancer survival from Model GE. C, Non-breast cancer survival from Model GE. Compared with the ABC trial (N = 4181),[54] the simulation study started with a population of 100 million and selected women that matched the patient characteristics of the ABC trial. This resulted in 40 166 breast cancer survivors, or N = 40 166 for the Model GE curves presented in all panels. TaxAC indicates anthracycline-based chemotherapy regimen (anthracycline plus taxane); TC, nonanthracycline-based regimen (cyclophosphamide plus taxane).

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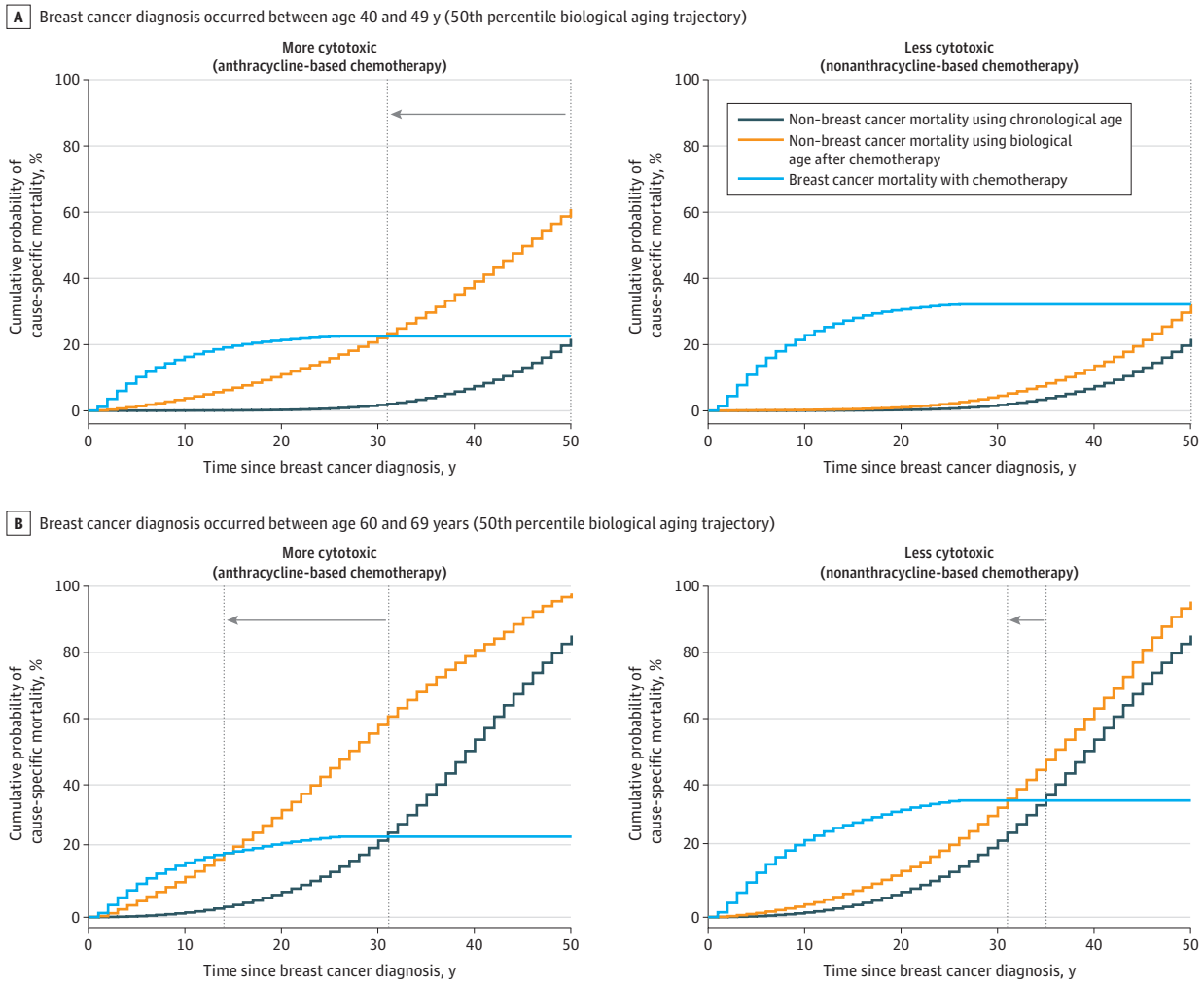
women were projected to live a median of 38.7 (IQR, 36.3-41.3) years due to earlier death from non–breast cancer mortality, for a net loss of 11.7 years. In contrast, if these women had less cytotoxic therapy, they would have lost a median of 2.1 (IQR, 1.1-4.1) years due to age acceleration, for a median difference of 9.6 (IQR, 8.0-10.0) life-years lost with more vs less cytotoxic treatment. Because older women have a shorter life expectancy than younger women, the impact of age acceleration was less.

All-Cause Survival in the Overall Breast Cancer Survivor Population

For all ages and biological age levels, the age acceleration seen with more cytotoxic regimens became more pronounced over time (eFigure 5 in Supplement 1). During the first 5 to 10 years after chemotherapy, all-cause survival for more vs less cytotoxic regimens were within 5% of each other. However, after 20 years, all-cause mortality rates were 10% to 25% higher among breast cancer survivors who received more vs less cytotoxic regimens due to higher levels of competing non–breast cancer mortality.

Figure 4. Cumulative Risk Curves of Non–Breast Cancer Mortality (vs Breast Cancer Mortality) With and Without Excess Biological Aging for Breast Cancer Diagnosis at the 50th Percentile of Biological Aging



A, Cumulative risk curves for breast cancer survivors diagnosed and treated at age 40 to 49 years. B, Cumulative risk curves for breast cancer survivors diagnosed and treated at age 60 to 69 years. The gray arrows represent the shift in the time point at which the risk of non–breast cancer mortality starts to dominate the risk of breast cancer mortality, due to biological age acceleration. The plots for other age groups and all ages combined are in eFigures 3 and 4 in Supplement 1, respectively.

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Discussion

This study is the first to integrate a systems biology model of aging with an established simulation model to quantify the potential effects of cancer and aging on breast cancer survivorship outcomes. The results suggest the potential importance of considering biological age in the care of all breast cancer survivors. Survivors diagnosed at early ages and/or treated with the most cytotoxic regimens were projected to have the greatest biological age acceleration, with increased risk of death from non–breast cancer causes at earlier chronological ages than expected in general populations. This age acceleration could result in potential losses of life-years. Additionally, there was variation in outcomes based on the population distribution of senescence. These results suggest the potential of population modeling to complement clinical survivorship research on cancer and aging.

Most prior studies of age acceleration among cancer survivors have focused on survivors of childhood, adolescent, and young adult cancers,[18,54] with survivors having a level of disease and decline in function at 30 years comparable to that of a 63-year-old individual (ie, 33 years of accelerated aging).[55] There are fewer longitudinal studies among breast cancer survivors.[23,25,26] Our results for age acceleration among breast cancer survivors show the complexities of clinical care, including potential trade-offs between maximizing breast cancer survival and accelerating biological aging as well as the effects accelerated aging on life expectancy due to earlier onset of aging-related diseases.

While concern about aging-related outcomes has been primarily focused on women diagnosed at age 65 years or older,[56-59] our results highlight suggest that women treated with chemotherapy at earlier ages have more potential years of life to lose due to age acceleration than women treated at older ages. This finding is important because rates of chemotherapy use are higher in younger vs older women, in part because younger women have a higher risk of aggressive tumor subtypes that often require highly cytotoxic therapies.[60,61] Since the goal of treatment is to improve breast cancer survival, oncologists should not modify treatment decisions based on potential for accelerated aging, but our results suggest the need for awareness of possible age acceleration. Additionally, since the

Table. Life-Years After Diagnosis Among Breast Cancer Survivor Who Received Chemotherapy by Regimen, Age, and Distribution of Senescence-Related Biological Age Acceleration

Age at diagnosis, y	Life-years using chronological age[a]	Life-years using biological age acceleration by percentile subgroups of breast cancer survivors[b]									
		5th Percentile[c]		25th Percentile		50th Percentile		75th Percentile		95th Percentile	
		Absolute	Lost	Absolute	Lost	Absolute	Lost	Absolute	Lost	Absolute	Lost
More cytotoxic chemotherapy with anthracycline											
30-39	50.4	44.8	−5.6	41.3	−9.1	38.7	−11.7	36.3	−14.1	32.6	−17.8
40-49	45.1	39.3	−5.8	35.9	−9.2	33.6	−11.5	31.2	−13.9	28.2	−16.9
50-59	36.3	31.0	−5.3	28.1	−8.2	26.3	−10.0	24.5	−11.8	21.9	−14.4
60-69	28.9	24.2	−4.7	22.0	−6.9	20.5	−8.4	18.9	−10.0	16.9	−12.0
70-79	20.2	16.9	−3.3	15.2	−5.0	14.2	−6.0	13.2	−7.0	11.9	−8.3
All ages	34.4	29.4	−5.0	26.8	−7.6	25.0	−9.4	23.2	−11.2	20.9	−13.5
Less cytotoxic chemotherapy with nonanthracycline											
30-39	43.6	43.7	0.1	42.5	−1.1	41.5	−2.1	39.5	−4.1	37.7	−5.9
40-49	39.8	40.9	1.1	39.1	−0.7	37.7	−2.1	36.1	−3.7	33.9	−5.9
50-59	31.6	32.6	1.0	31.1	−0.5	29.8	−1.8	28.4	−3.2	26.3	−5.3
60-69	24.9	26.1	1.2	24.3	−0.6	23.2	−1.7	21.9	−3.0	20.3	−4.6
70-79	17.9	18.3	0.4	17.4	−0.5	16.5	−1.4	15.7	−2.2	14.6	−3.3
All ages	31.5	32.5	1.0	30.9	−0.6	29.7	−1.8	28.3	−3.2	26.4	−5.1

[a] Using the average non–breast cancer mortality hazard rate among women in the US without considering variability in biological aging. This column shows the estimated remaining life-years if using chronological age to determine the hazard of non–breast cancer mortality.

[b] Each percentile column contains 2 subcolumns showing the remaining life-years (absolute) and life-years lost due to biological age acceleration (lost).

[c] Biological aging trajectory of breast cancer survivors with less cytotoxic chemotherapy in the 5th percentile group is lower than chronological age, resulting in a higher number of life-years when compared with life-years at chronological age.

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therapeutic landscape is always evolving, our results suggest that biological age acceleration might be a useful endpoint in correlative studies in trials of new agents.

Prior to clinical translation of our population-level model results into clinical practice with individual survivors, research will be needed to test the impact of biological age assessment and management of biological age acceleration on survivorship outcomes. Evidence-based behavioral interventions that slow age acceleration in general populations, such as physical activity or maintaining good sleep,[62] are currently recommended for all breast cancer survivors.[63-68] Knowledge about the risks of accelerated aging among women exposed to chemotherapy may help motivate lifestyle changes.[68,69] Further, as evidence on the safety and utility of senolytic and other anti-aging drugs evolves, modeling may help identify populations of survivors at risk for age acceleration who might benefit from pharmacologic intervention.[48,70,71]

Our population model results confirm and extend those from the ABC trial results comparing 8-year survival with anthracycline-based vs nonanthracycline-based regimens.[53] We found similar 8-year results. We also found that over the lifetime, although an anthracycline-based regimen was associated with higher breast cancer survival, non–breast cancer survival was lower, and all-cause survival was similar in the anthracycline and nonanthracycline groups. Further, our lifetime projections indicate that at periods of 20 years or longer, all-cause survival may be higher in survivors who had nonanthracycline regimens. There are also small differences between our results, with higher non–breast cancer survival rates in the ABC trials compared with the model. This difference is likely due to the fact that the model used non–breast cancer mortality rates for the general population of women in the US, while participants enrolled in clinical trials, such as the ABC trials, are likely healthier than the general population.

Strengths and Limitations

This modeling study has some strengths, including expansion of a well-validated and established CISNET model, use of the most current literature to inform input parameters, and application of a novel methodology. There are also several limitations should be considered when interpreting our results. First, biological age acceleration was modeled based on a single biomarker of aging, $p16^{INK4a}$. Although $p16^{INK4a}$ expression level is well-validated to predict aging-related outcomes,[46,72] neither it nor other biomarkers of aging, such as DNA methylation,[73,74] genomic instability,[75] mitochondrial dysfunction[76] and other biomarkers,[19] are routinely used in clinical practice. As clinical translation of these markers evolves,[6,77,78] the model can be updated with inputs for new markers. Alternatively, future studies could link data on $p16^{INK4a}$ to more commonly used measures of aging, including geriatric assessment, deficit accumulation indexes, or C-reactive protein; these latter approaches have been used for estimating biological age from UK Biobank and other datasets.[58,79,80] Second, we modeled the same population under 2 hypothetical scenarios (more vs less cytotoxic regimens), similar to a randomized trial. However, in clinical settings, women may be selected for treatment based on differences in clinical and social factors that are not captured in the model but may also affect survival. Therefore, the results from this study may not be representative of outcomes in different groups of women. Third, we modeled 2 exemplar regimens that varied in cytotoxic effects and for which data on biological age acceleration were available.[23,25,68] However, we did not have sufficient data on biological aging specific for hormonal therapy or new regimens, such as immunotherapy. Fourth, we assumed baseline $p16^{INK4a}$ levels were independent of the probability of developing breast cancer. As evidence evolves, future modeling should test other assumptions, because current data regarding this assumption are inconsistent.[25,44] Fifth, we assumed that biological aging persisted without recovery after chemotherapy.[51] To test this assumption, it will be important to include biological aging assessments in long-term follow-up of trials, and prospective studies should refine knowledge of biological aging trajectories. Sixth, although we used robust general population data on the distribution of senescence and the effects of chemotherapy on senescence, none of the existing data have been stratified by social and environmental exposures or stressors, constraining our ability to capture individual-level heterogeneity in aging.[81,82] This will be

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an important area for future model refinement. Overall, our results should be considered as illustrative of how simulation modeling may be used as an in silico laboratory to understand the potential population impact of cancer and aging inter-relationships. Given the flexible structure of our model, we will be able to update inputs as new data emerge, enhancing clinical translation.

Conclusions

The results of this comparative effectiveness study offer evidence that biological age acceleration may substantially influence postchemotherapy survivorship outcomes. As data from cancer and aging studies evolve, future applications of our model could be used to inform survivorship care guidelines personalized to biological rather than chronological age.[70,83,84] Because breast cancer is the most prevalent cancer among female cancer survivors,[85] developing and testing strategies based on mechanisms of aging could improve survivors' quality and quantity of life.

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Author Contributions: Dr Sarkar had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Concept and design: Sarkar, Carroll, Mandelblatt.

Acquisition, analysis, or interpretation of data: All authors.

Drafting of the manuscript: Sarkar, Muss, Mandelblatt.

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SUPPLEMENT 1.

eMethods

eFigure 1. Senescence Expression Accumulation and Biological Aging Trajectories for Breast Cancer Survivors Receiving Specific Chemotherapy Regimens

eFigure 2. Age-Adjusted Breast Cancer and Non–breast Cancer Mortality Rates From Simulation Including Biological Age Acceleration Due to Chemotherapy

eFigure 3. Cumulative Risk Curves of Breast Cancer Mortality and Non–breast Cancer Mortality (With and Without Biological Age Acceleration) for Different Age Groups of Diagnosis and Percentiles of Biological Aging Trajectories

eFigure 4. Cumulative Risk Curves of Breast Cancer Mortality and Non–breast Cancer Mortality (With and Without Biological Age Acceleration) for All Age Groups of Diagnosis (30-79 Years) and Different Percentiles of Biological Aging Trajectories

eFigure 5. All-Cause Survival in the Overall US Female Breast Cancer Survivor Population in the Anthracycline-Based (vs Nonanthracycline-Based) Chemotherapy Group, With and Without Biological Age Acceleration

eTable 1. Input Parameters for Breast Cancer Life History Simulations Using CISNET's Model GE

eReferences

SUPPLEMENT 2.

Data Sharing Statement

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