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Review article

Breast cancer treatment and its effects on aging

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ABSTRACT

Breast cancer is the most common cancer of women in the United States. It is also proving to be one of the most treatable. Early detection, surgical intervention, therapeutic radiation, cytotoxic chemotherapies and molecularly targeted agents are transforming the lives of patients with breast cancer, markedly improving their survival. Although current breast cancer treatments are largely successful in producing cancer remission and extending lifespan, there is concern that these treatments may have long lasting detrimental effects on cancer survivors, in part, through their impact on non-tumor cells. Presently, the impact of breast cancer treatment on normal cells, its impact on cellular function and its effect on the overall function of the individual are incompletely understood. In particular, it is unclear whether breast cancer and/or its treatments are associated with an accelerated aging phenotype. In this review, we consider breast cancer survivorship from the perspective of accelerated aging, and discuss the evidence suggesting that women treated for breast cancer may suffer from an increased rate of physical and cognitive decline that likely corresponds with underlying vulnerabilities of genome instability, epigenetic changes, and cellular senescence.

Contents

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1. Introduction

Breast cancer is the most frequent cancer amongst women in the United States and the second leading cause of cancer death for women [1]. An estimated 250,000 new cases of invasive breast cancer are diagnosed each year in the United States [1]. Patients with breast cancer are surviving longer as early detection measures improve and as advances in breast cancer treatment lead to increasingly improved survival outcomes. The five-year survival has risen from 75% in 1976 to 91% in 2017 [1]. With increased overall life expectancies, long-term breast cancer survivors are at risk for manifesting features of accelerated aging, the underpinnings of which likely involve overlapping hallmarks of aging and cancer development [2, 3]. While multiple epidemiological studies have highlighted long-term health complications associated with breast cancer treatments, the molecular mechanisms that underlie these apparent elevated health risks in breast cancer survivors have yet to be well elucidated.

From a clinical standpoint, careful evaluation and management of long-term and late side effects in patients with breast cancer are emerging as a critical challenge, particularly for patients who have undergone chemotherapy and require long-term adjuvant treatment [4–7]. Impairments in physical and cognitive functioning following treatment can considerably impact survivors' quality of life (QOL) [8–10] and treatment decision-making [11, 12]. Thus, the overall objective of this review is to begin to merge together two crucial fields of study in relationship to breast cancer long-term survival: 1) clinical studies that provide insight into how treatment affects patient-centered important health outcomes; and 2) laboratory studies that elucidate the underlying molecular mechanisms of aging, particularly in response to breast cancer treatments. While ground-breaking advances in breast cancer treatment and survival have occurred in the last 30 years, there is a still a lot of room to further improve therapeutic protocols by better understanding treatment effects on the rates of normal cellular aging.

As shown in Fig. 1, any pharmacologic treatment, targeted or not, also affects normal cells. Because of intrinsic differences in the genomes, epigenomes and transcriptomes between tumor cells and normal tissues, along with shifts in cellular metabolism and inherent genome instability that occurs in most tumors, cancer cells and normal cells in the body may respond quite differently to pharmacologic treatments in ways that could have profound long-term impact on health [2, 3, 13]. Importantly, unlike cancer cells that frequently lose tumor suppressor proteins, active tumor suppressive checkpoints remain in most normal cells, potentially leading to cell senescence, and possibly associated treatment induced cellular and organ damage that could contribute to accelerated aging.

Here, we examine the clinical health outcomes in patients treated with breast cancer in the context of well-described cellular and molecular hallmarks of aging that are likely affected by breast cancer cytotoxic therapies- summarizing the current state of the field and providing recommendations for future studies.

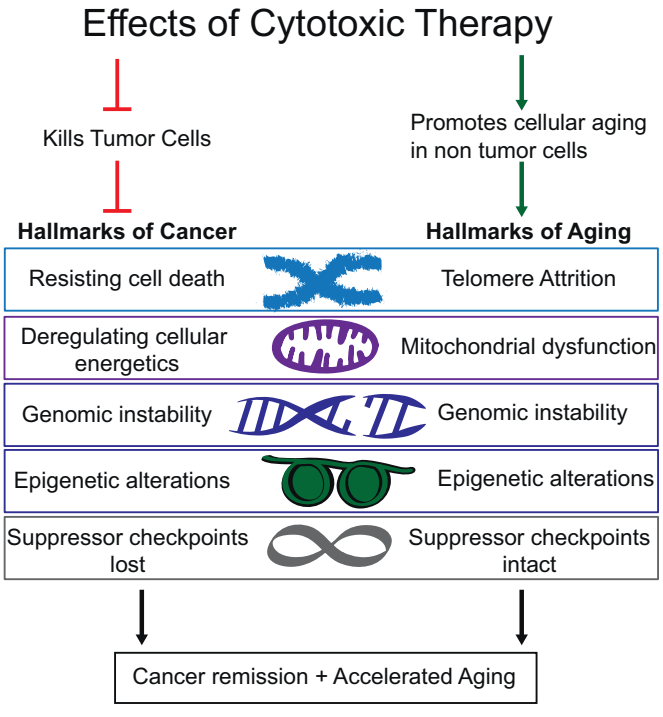

Fig. 1. Cytotoxic therapy effects on tumor versus normal cells.

2. Clinical Manifestations of Advanced Physiologic Aging in Breast Cancer Survivors

2.1. Breast Cancer Therapies and Physical Health

A number of studies of the physical, functional and cognitive changes following breast cancer diagnosis and treatment reveal a landscape of challenges experienced by breast cancer survivors. Although the potential contribution of accelerated aging to cancer initiation cannot be excluded [14, 15], the cumulative data indicate, unequivocally, that breast cancer treatments are associated with either transient or long-lasting physical dysfunction and an accelerated aging phenotype. Currently, the treatment associated accelerated aging phenotype is an inescapable consequence of life-saving therapy. However, understanding the processes that contribute to this phenotype could shed new light on potential interventions that mitigate, or possibly even eliminate these adverse long-term health effects.

2.1.1. Accelerated Reproductive Aging

Though the exact cellular mechanisms and their relation to what patients experience post-chemotherapy has not been well delineated, the clinical manifestations may in part result from accelerated physiologic aging. Perhaps the clearest example is treatment-induced reproductive aging. Young women experience unavoidable and irreversible amenorrhea, infertility, and early hormonally-induced menopause as a consequence of ovarian chemotoxicity. Age is the most relevant biological factor influencing chemotherapy related amenorrhea; however, type of chemotherapy and schedule of administration may influence premature ovarian failure [16]. While imperative to treat the breast cancer, the induction of early menopause may have other long-term

implications. For example, in a large observational study of 16,251 women, later age of natural menopause and longer reproductive lifespan was significantly associated with increased longevity [17], suggesting that longer reproductive capacity may reflect more favorable cellular aging.

2.1.2. Compromised Cardiopulmonary Fitness

Cardiorespiratory fitness may be one of the best markers of physiological age that tends to decline over time, and evidence suggests that patients with breast cancer treated with adjuvant therapies may age more quickly. In a recent review of 27 breast cancer studies that included randomized controlled trials, exercise interventions or observational studies of cardiorespiratory fitness assessed by V02 max, there was a strong consensus that compared to pre-adjuvant therapy or healthy sedentary controls, those who had received adjuvant therapy had the worst performance [18].

Early clinical trials demonstrate that adjuvant chemotherapy, especially anthracyclines, can cause short-term cardiotoxicity; however, the clinical benefit of decreased annual breast cancer death rates by 20–38% are the reason for continued use [19–22]. Pre-treatment cardiac screening and dose adjustment have served to improve clinical outcomes with decreased cardiac toxicity, but there remain concerns about possible long-term cardiac sequelae. While some smaller studies suggested no long-term cardiac complications associated with anthracycline use, the largest to date of 43,338 women demonstrated an increased number of heart failure cases in older breast cancer survivors who received anthracyclines compared with other treatments [23]. Aromatase inhibitor therapy, which increases bone turnover and decreases bone mineral density, increases the risk of fractures and osteoporosis [24–27]. Peripheral neuropathy and neuropathic pain are other common chemotherapy related adverse effects and in particular, neuropathy may be very debilitating for older survivors as it may precipitate falls and fractures [28]. Taken together, an abundance of evidence suggests that some of the breast cancer therapies may increase the rate of physiological aging, with long-term adverse health consequences.

2.2. Breast Cancer Therapies and Cognitive Decline

Cognitive impairment is one of most common symptoms among breast cancer survivors [29–31]. Impairments can range from subtle to severe and last for up to 20 years following treatment [32–34]. While the high prevalence of cognitive impairment among breast cancer survivors is well documented, data are conflicting regarding the extent to which cognitive deficits are related to treatment. A summary of relevant studies of cognitive function and cognitive imaging in patients with breast cancer is provided (see Table 1) where the study findings have been compared and contrasted in different age groups, classified by outcome, treatment modality, and study design [33, 35–47]. A meta-analysis by Jim et al. [48] that analyzed results of 17 studies found cognitive deficits in verbal and visuospatial abilities in patients treated with chemotherapy. This is consistent with results of several previous meta-analyses reporting significant impairments across multiple domains among patients with cancer treated with chemotherapy [49–53]. However, some longitudinal studies have found weak or null associations between chemotherapy and objectively measured neurocognitive deficits or self-reported cognitive concerns [54, 55]. Likewise, evidence for a negative association between endocrine therapy and cognition is mixed [56–59], with at least one longitudinal study finding significant improvements in neurocognitive performance after completion of endocrine therapy [60] or both chemotherapy and endocrine therapy [61]. A recent prospective study found that while chemotherapy was linked to self-reported cognitive concerns, those who received aromatase inhibitors alone did not report clinically meaningful concerns [59]. Other research has shown that cognitive deficits are not limited to those undergoing adjuvant treatment. Some studies have found pre-treatment impairments in objectively measured cognition [52, 62, 63]. A meta-analysis by Ono et al. [53] reported that levels of neurocognitive impairment in chemotherapy versus non chemotherapy treated patients did not significantly differ, providing evidence that factors other than treatment regimen may influence risk of cognitive impairment.

2.2.1. Influence of Age on Models of Cognitive Decline After Breast Cancer

Another important factor contributing to cognitive decline among cancer survivors may be increasing age [64, 65]. Aging is a strong risk factor for cancer [66] and older adults (age 65 years or older) represent the majority of cancer cases [67]. Cognitive impairment among breast cancer survivors may result from common risk factors for both the development of cancer and age-related cognitive decline [30, 68, 69]. Mandelblatt et al. [40] and Ahles et al. [70] describe two possible trajectories of cognitive impairment after cancer treatment relative to age-related decline. The *phase shift hypothesis* asserts that patients with cancer experience post-treatment cognitive declines that are slightly worse than those without cancer (or its treatment), but parallel the non-cancer population over time. Conversely, the *accelerated aging hypothesis* proposes that cancer and/or its treatment may accelerate normal aging, that is, patients with cancer may experience steeper and earlier declines in cognitive function compared to non-cancer populations [40, 70, 71]. Mandelblatt and colleagues [45] performed trajectory group analysis on a cohort of 1280 breast cancer survivors aged 65–91 years, assessed at six months post-treatment and annually for up to seven years. Over the follow-up period, 42.3% of survivors maintained high self-reported cognitive scores, 50.1% showed a phase shift pattern, and 7.6% showed accelerated decline. While age was not directly related to trajectory, age-related characteristics (having >2 vs ≤ 2) comorbidities and frailty, respectively) were associated more strongly with the accelerated aging group than the phase shift group. These results demonstrate that impairment among breast cancer survivors does not follow a uniform course but rather, may result from a complex synergy of age, comorbidities, cancer treatment, and cancer itself [72].

2.2.2. Breast Cancer Treatments and Self-reported and Objective Cognition

Although mixed, several studies show that breast cancer survivors exhibit impaired neurocognitive functioning compared to age-matched controls [40, 41, 73]. Breast cancer survivors have self-reported greater cognitive concerns compared to age-matched controls. In one of the largest published longitudinal studies of 581 breast cancer survivors, 36.5% of patients with breast cancer self-reported meaningful cognitive decline at six months, compared with only 13.6% of age-matched controls [74]. Longitudinal objective assessments are useful to determine whether age-associated declines in cognitive function in breast cancer survivors mirror adults without a cancer history and two that assessed patients six months or longer post-treatment reported that cancer survivors had lower scores on tests of processing speed and executive function [42, 75]. Taken together, these studies lend support to a prevailing hypothesis that cognitive impairments may be a symptom of accelerated aging caused by cancer and/or its treatments.

2.2.3. Breast Cancer Treatments and Neuroimaging Findings

Impairments observed through self-reported and objective neurocognitive testing are supported by evidence of physiological changes to the brain. Neuroimaging studies in breast cancer survivors have revealed structural alterations in both grey and white matter [76–78]. Functional changes including abnormal activation in frontal regions during cognitive tasks [35, 79] and reduced brain network resilience to attacks [38] have been reported in most, but not all studies [80]. fMRI changes in brain areas involved in executive control, memory, and emotional regulation were determined to be different between breast cancer survivors and healthy, age, education and intelligence matched controls [124]. However, the most compelling evidence of an ill effect from breast cancer treatments comes from magnetic resonance imaging (MRI) measurements of grey matter volume before and after

Table 1
Studies of cognitive function and aging among breast cancer survivors, by study design.

Authors	Study objectives	Study population	Mean age (SD, range)	N[a]	Treatments	Main study findings	Comments
Cross-sectional							
Conroy SK et al. [35]	Examine structural and functional effects of chemo and post-chemotherapy interval (PCI), and relationship of neuroimaging to neurocognitive testing, self-reported cognition, and oxidative DNA damage	24 breast cancer survivors, PCI mean 6.4, range 3–10 years 23 age- and education-matched controls	Cases: 57.8 (9.6) Controls: 61.2 (9.9)	47	100% C	PCI was positively correlated with structural and functional changes on MRI, which were related to neurocognitive performance. Compared to controls, breast cancer survivors had increased neurocognitive impairment (memory dysfunction), cognitive complaints, and DNA damage	Potential clinical significance of imaging results underscored by association with neurocognitive testing
De Ruiter MB et al. [36]	Assess brain activation and cognitive performance ~10 years after high-dose chemo	34 breast cancer survivors: 19 treated with chemo 15 not treated with chemo	Breast cancer survivors treated with chemo: 56.3 (5.5) Breast cancer survivors not treated with chemo: 58.2 (5.8)	34	Among those treated with chemo 100% H 100% R 100% S Among those not treated with chemo: 6.6% H 100% R 100% S	~10 years after treatment, high dose chemo was associated with long-term cognitive impairments including decreased responsiveness of brain regions related to executive functioning and memory encoding	Comparisons with non-breast cancer controls are necessary to assess trajectory of cognitive decline over time
Kesler SR et al. [37]	Examine differences in prefrontal-executive functioning between breast cancer survivors with and without treatment with chemotherapy compared to control, and to assess relationships between prefrontal cortex deficits and behavioral impairments	44 breast cancer survivors: 25 treated with chemo 19 not treated with chemo 18 healthy controls	Breast cancer survivors treated with chemo: 56.2 (7.8) Breast cancer survivors not treated with chemo 58.1 (6.5) Controls: 55.6 (9.4)	62	Among those treated with chemo: 56% H 56% R Among those not treated with chemo: 53% H 68% R	Women treated with chemo had significant reduced left caudal lateral prefrontal cortex activation, increased perseverative errors, and reduced processing speed compared to non-chemo breast cancer survivors or controls. Older age was associated with greater executive functioning impairment in patients treated with chemo	Chemotherapy may interact with increasing age to accelerate cognitive decline
Kesler SR et al. [38]	Use brain network models to study the effects of chemo on white matter organization and connectivity, and brain network tolerance	34 breast cancer survivors 36 matched healthy controls	Cases: 56.9 (7.6, 43.8–72.7) Controls: 56.9 (8.2, 42.8–73.4)	70	100% C 60% H 80% R 100% S	Cases showed reduced brain network tolerance (brain resilience) to simulated neurodegeneration, which was associated with neurocognitive deficits. Despite larger overall impacts of attacks on brain network among cases, both groups experienced similar rate of decline.	Findings support phase shift (parallel) rather than accelerated decline among breast cancer survivors treated with chemo
Lange M et al. [39]	Assess cognitive functioning among elderly breast cancer patients before adjuvant treatment	123 breast cancer patients	70 (4.1, 65–83)	123	100% S	41% of patients had cognitive impairment before any adjuvant treatment, significantly higher than what is reported in normative data based on age and education. Proportion of patients reporting pre-treatment impairments was higher than published rates of pre-treatment impairments in younger survivors.	Older patients may be more sensitive to the effects of cancer on cognition, but longitudinal studies are needed to determine if cancer treatment accelerates normal cognitive aging
Mandelblatt JS et al. [40]	Determine if older breast cancer patients show cognitive impairment before systemic treatment	164 breast cancer patients (pre-treatment) 182 age-matched non-cancer controls	Cases: 68.1 (6.7, 60–98) Controls: 67.3 (6.5, 60–90)	346	100% S	No differences in unadjusted rates of neurocognitive impairment in breast cancer patients (14%) before systemic treatment compared to age-matched controls (15%)	Results do not support an effect of cancer on pre-treatment cognition.
Von Ah D et al. [8]	Examine the frequency of clinically significant cognitive dysfunction in breast cancer survivors and possible associations with treatment	52 breast cancer survivors 52 individually matched healthy	Cases: 58.2 (9.2) Controls: 59.0 (9.0)	104	55.8% C 79% H 80.8% R 100% S	Breast cancer survivors exhibited impaired neurocognitive functioning compared to age-matched controls. Exploratory analysis	Longitudinal studies needed to examine long-term trajectory of cognitive decline

(continued on next page)

Table 1 (*continued*)

Authors	Study objectives	Study population	Mean age (SD, range)	N[a]	Treatments	Main study findings	Comments
		controls				showed no association between exposure to chemo or hormonal therapy and neurocognitive function	
Case-control							
Koppelmans V et al. [33]	Examine if chemo is associated with worse cognitive performance in breast cancer survivors more than 20 years after treatment	196 breast cancer survivors (avg. 21.2 years since diagnosis) 1509 controls	Cases: 64.1 (6.4) Controls: 57.9 (5.4)	1705	100% C	Up to 20 years later, women exposed to chemo performed significantly worse on neurocognitive tests (memory, processing speed, executive functioning, psychomotor speed) and had greater self-reported memory impairment	Lack of baseline or interim cognitive scores limits comment on rate of decline compared to healthy controls. Longer longitudinal studies are needed to understand cognitive trajectories over time.
Prospective longitudinal							
Ahles TA et al. [42]	Examine, longitudinally, the impact of age and cognitive reserve on cognition among breast cancer patients receiving adjuvant treatment	132 breast cancer survivors: 60 treated with chemo 72 not treated with chemo 45 healthy controls	Breast cancer survivors treated with chemo: 51.7 (7.1, 31–66) Breast cancer survivors not treated with chemo: 56.6 (8.3, 37–69) Controls: 52.9 (10, 30–68)	177	Among those treated with chemo: 80% H 81% R Among those not treated with chemo: 66% H, 72% R	Breast cancer survivors showed lower scores on neurocognitive tests (processing speed and executive function) compared to healthy controls. Older survivors and those treated with chemo performed poorest. Age was related to post-treatment decline in women exposed to chemo.	Influence of cancer treatment on cognitive functioning may vary by age
Collins B et al. [43]	Examine neurocognitive outcomes in breast cancer patients pre-treatment, during treatment, and 1 year after completion of chemo	60 breast cancer patients 60 healthy, age, education, and language-matched controls	Cases: 51.8 (7.8) Controls: 51.3 (7.7)	120	100% C 84% H 100% S	48% of breast cancer survivors showed steady cognitive decline during and immediately post-chemo, with partial recovery in cognitive function (working memory) at 1 year follow-up. Higher proportion of patients (22%) showed persistent impairment at follow-up compared to the control group (6%).	A sub-set of breast cancer patients show long-term treatment-related cognitive decline. Findings provide some support for accelerated aging hypotheses
Lepage C et al. [44]	Assess relationship between grey matter attenuation via functional magnetic resonance imaging (fMRI) and neurocognitive function in breast cancer patients prior to treatment, during chemo, one month following chemo, and one year after completion of treatment	19 breast cancer survivors 19 controls	Cases: 50.2 (8.6, 35–64) Controls: 49.3 (9.0, 31–61)	38	Among cases: 100% C 52.6% H 68.4% R 100% S	Cases showed reduced grey matter volume one month post-chemo, with a partial recovery one year post-treatment. Neurocognitive testing showed similar pattern, with poorest processing speed scores one month post-treatment and some improvement at one year. These changes were not observed in controls.	Changes in brain volume observed through neuroimaging had a similar trajectory to neurocognitive deficits. Partial recovery does not support accelerated aging hypothesis
Mandelblatt JS et al. [45]	Determine long-term trajectories of self-reported cognitive function and test the effects of chemo on cognitive trajectories among older breast cancer survivors 6 months post-chemo and annually for up to 7 years	1280 breast cancer survivors	72.7 (6.6)	1280	67.6% S 40.5% C (with or without H) 53.7% H only	Through follow-up, 42.3% maintained high self-reported cognitive scores, 50.1% showed a phase shift (parallel) pattern, and 7.6% showed accelerated decline. While age was not directly related to trajectory, age-related traits (having >2 vs ≤ 2) comorbidities and frailty, respectively) were associated more strongly with the accelerated aging group than the phase shift group.	Cognitive impairment in breast cancer survivors varies and may result from the complex interaction of age, cancer treatment, and cancer itself.
Schagen SB et al. [46]	Assess the effects of high vs. standard dose chemo on cognitive function up to 12 months post-treatment	124 breast cancer patients 60 healthy controls	Cases: High dose: 45.2 (5.8) Standard dose: 45.5 (6.6) No chemo:	184	High dose: 22.6% (100% H) Standard dose: 31.5% (97% H)	Greater proportion of high-dose chemo patients, compared to controls, exhibited deterioration of cognitive functioning over time. No difference for standard dose or controls	Results support the notion that breast cancer survivors treated with high-dose chemo may experience accelerated cognitive decline compared to controls

Table 1 (*continued*)

Authors	Study objectives	Study population	Mean age (SD, range)	N[a]	Treatments	Main study findings	Comments
			50.5 (7.7) Controls: 48.8 (6)				
Schilder CM et al. [47]	Examine the influence of tamoxifen and exemestane on cognitive functioning 1 year post-treatment in postmenopausal breast cancer patients	179 breast cancer patients:80 tamoxifen	Cases: Tamoxifen: 68.7 (7.6, 51–84) Exemestane: 68.3 (6.8, 50–82)	299	Tamoxifen: 100% H 58.8% R 100% S Exemestane:100% H 20.2% R 100% S	At one year, compared to controls, those treated with tamoxifen showed cognitive impairments, while exemestane group did not. Among tamoxifen group, older survivors (> 65 yrs) showed greater deficits than younger survivors (≤ 65 yrs)	Tamoxifen may be associated with persistent decline and effects may be age-dependent
		99 exemestane 120 healthy controls	Controls: 66.2 (7.9, 49–86)				

Acronyms: C- Chemotherapy H- Hormonal therapy. R- Radiation therapy. S- Surgery.
[a] N = number of study participants.

chemotherapy. Compared to a matched cohort of healthy women, MRI scans of breast cancer survivors demonstrate an initial reduction in grey matter volume, which tends to improve by one year post-treatment. Neuropsychological tests revealed that the grey matter changes correlated with some level of cognitive impairment, specifically in the processing speed domain [81].

3. Molecular Mechanisms of Normal Cellular Aging in Patients with Breast Cancer

The pathology behind cancer cells and aging is most simply defined as the accumulation of cellular damage; whereas cancerous mutations provide advantages in certain cells for growth, cellular damage causes loss of fitness in aging cells. We use cytotoxic treatments to inhibit tumor growth; however, this treatment is indiscriminate and also affects the non-tumor cells. Describing the cellular and molecular hallmarks of aging including: 1) telomere attrition; 2) mitochondrial dysfunction; 3) genomic instability; 4) epigenetic alterations; and 5) cellular senescence, we discuss how each may be affected in the setting of normal aging versus breast cancer and its related treatments.

3.1. Telomere Attrition

Telomeres are particularly prone to age-related DNA damage [82] and most somatic cells do not express telomerase, limiting their ability to replicate the terminal ends of chromosomes [83]. Thus, telomere de-protection and shortening have been cited as a Hallmark of Aging [2]. In patients with breast cancer, the treatments given could contribute to accelerated aging at least in part by its effects on telomeres [84]. One recent systematic review of telomere length (TL) included 33 studies that reported on TL measured in blood, tumor and normal tissues in relation to prognostic factors [85]. The authors reported that with the exception of one negative study, there was an overall trend toward a positive association of longer telomeres in breast tissue with a better prognosis. It was notable that in peripheral blood, blood TL was not associated with chemotherapy in three out of four studies [85]. Apart from TL, telomere deprotection mechanisms are potentiated by anti-mitotic therapies such as colcemid, vinblastine, Taxol, and Velcade [86].

3.2. Cellular Energetics

Declines in mitochondrial function and corresponding somatic mtDNA mutations have been reported in normal human aging [87, 88]. Specifically, insulin/IGF-1 and rapamycin (TOR) signaling pathways that regulate cellular aging have been linked to dysfunctional mitochondria [89–91]. How cancer therapies affect cellular energetics as they relate to rate of aging is unclear, but mitochondrial energetics appear to play an important role in cancer metabolism and growth, Somatic mitochondrial DNA alterations allow cancer cells to adapt to the tumor microenvironment of hypoxic and acidic conditions, and some have proposed a mechanism of metabolic coupling between cancer cells and stromal cells. Tumor cells induce reprogramming in surrounding non-tumor cells to undergo mitophagy, reducing the number of mitochondria, resulting in conversion to glycolytic metabolism (the Warburg phenotype). These stromal fibroblasts generate excessive lactate and ketones; producing fuel for anabolic cancer cells ('reverse Warburg') [92, 93]. Additionally, mitochondrial dysfunction may promote breast cancer malignancy as dysregulated mitochondria may affect oncogenic regulation by elevated ROS, decreased apoptosis and resistance to chemotherapeutic agents [94–96].

3.3. Genome Instability

Genome instability is a hallmark of cancer and it is also a hallmark of aging, as DNA damage accumulates in normal cells over time, primarily though endogenous processes such as replication errors and reactive oxygen species-induced DNA damage [3]. Many of the cytotoxic chemotherapies used to treat cancer, including microtubule poisons, alkylating agents, anti-metabolites, topoisomerase inhibitors and DNA cross-linking agents, as well as radiation therapy, are designed to kill tumor cells by causing lethal DNA damage. Indeed, these exogenous agents also damage DNA in normal cells, but the presence of intact tumor suppressive checkpoints and competent DNA repair pathways in non-cancer cells, as well as their generally lower proliferation rate, usually result in preferential tumor cell death. However, these treatments greatly accelerate the rate of nuclear and mitochondrial DNA damage, also synergizing with endogenous mechanisms of DNA damage such as elevated ROS levels, potentially contributing to accelerated aging [97, 98].

3.4. Epigenetic Alterations

Epigenetic alterations are also likely to contribute to the aging phenotype, and may be accelerated in breast cancer survivors. Sehl et al. have examined the breast tissue and peripheral blood of 40 patients with breast cancer and found that breast cancer tissue had a higher epigenetic age, with the difference diminishing with advancing chronological age [99]. Certainly, changes in DNA methylation, post-translational modification of histones, and alterations of chromatin remodeling complexes are characteristic of aging [100], and could potentially be impacted by cancer treatment. Although some of the key regulators of these processes have begun to be identified, including DNA and histone methylases and demethylases, histone acetylases and de-acetylases and chromatin remodelers, how they regulate the changes in aging through alteration of global transcriptional programs, remains to be elucidated.

3.5. Suppressor Checkpoints for Cellular Senescence

In normal tissues, the $p16^{INK4A}$/Rb and $p19^{ARF}$/p53 pathways are two critical regulatory pathways that are usually suppressed, but become activated to prevent cells with damaged DNA from replicating [101, 102]. In cancer cells, one or both of these pathways is commonly disrupted, enabling tumor cells bearing markedly damaged DNA to proliferate. These dysregulated pathways can be targeted by cytotoxic chemotherapies, resulting in preferential cell death of tumor cells, but how these treatments also affect normal cells with intact $p16^{INK4a}$/Rb and $p19^{ARF}$/p53 pathways is unclear.

DNA damage accumulates over the lifespan with a corresponding increase of $p16^{INK4a}$/Rb and $p19^{ARF}$/p53 noted with advancing chronological age [103]. In breast cancer survivors, including those undergoing cytotoxic chemotherapy, the levels of p16 and p19, potential biomarkers of accelerated aging, are markedly increased and the extent of accelerated aging was calculated to be equivalent to 14.7 years of chronological aging [104]. Additionally $p16^{INK4a}$ expression at later time points found that the increased levels of $p16^{INKa}$ persisted for at least several years after initial chemotherapy exposure [104].

3.6. Other Markers of Cellular Senescence

In one longitudinal study of 315 women, 209 were diagnosed and treated for breast cancer and 106 were diagnosed with benign disease. At baseline there were no differences in cellular senescence or comorbidities; however, after follow-up of eighteen months, patients with breast cancer treated with surgery, radiation, and chemotherapy had elevated IL-6 and tumor necrosis factor-alpha levels as compared to controls [105]. Importantly, compared to controls, there was a significant increase in comorbidities in survivors, who were treated with multimodal therapy, suggesting that they may be at highest risk of accelerated aging and comorbidity development.

4. Concluding Remarks

Integrated DNA, RNA, epigenetic and immunohistochemical analyses [106–110] are reshaping the understanding of the molecular underpinnings of breast cancer. Increasingly sophisticated molecular classification systems are emerging [111] that promise to further improve outcomes by helping match the right patient with the right drug or combination of drugs. This is welcome news for women with breast cancer; however, as they survive, they experience an array of health challenges that need to be better understood. In addition to the risk of developing second malignancies that could be related to germline vulnerabilities or post-treatment effects, survivors experience chronic health problems characteristic of accelerated aging [112], including chemotherapy related amenorrhea, decreased cardiorespiratory fitness, increased risk of fracture, osteoporosis and neuropathy, and cognitive decline which can persist for months to years following treatment [33, 113].

As more women become long-term breast cancer survivors, the accumulated toll of treatment-induced damage to normal cells becomes increasingly significant. In this review, we have highlighted five of nine previously described cellular hallmarks of aging that have been described in the context of cytotoxic breast cancer treatments [2].The biology of aging in itself is an active area of investigation and understanding how perturbations such as cytotoxic therapies affect the rate of aging could lend to the development of novel therapeutics. As an example, $p16^{INK4a}$ is now being used a biomarker of chemotherapy toxicity to identify chemotherapy induced senescent (TIS) cells [114]. With development of blood-based biomarkers, new senolytic drugs, such as ABT-263, have shown promise in human cells and mouse studies by selectively eliminating TIS, leading to better outcomes such as reduced bone marrow suppression and less cardiac toxicity [114, 115].

By solving the problem of immediate survival for the vast majority of patients with breast cancer we now face new challenges. Scientists and clinicians together should make efforts to combine their expertise so that each can be aware of the emerging technologies in the context of real live patient experiences. Ideally, longitudinal mechanistic studies should be designed to identify the molecular basis of accelerated cancer aging in tandem with assessing clinically important outcomes so that interventions can be developed to maximize therapy anti-tumor effects while also optimizing the long-term health of breast cancer survivors.

Contributions

Study conception: Chang L, Jeste D, Kado D; Study design: Chang L, Kado D; Data acquisition and quality control: Chang L, Weiner L, Hartman S, Kado D; Data analysis and interpretation: Chang L, Weiner L, Hartman S, Mischel P, Horvath S, Kado D; Statistical analysis: N/A; Manuscript preparation, editing and review: All authors.

Conflicts of Interest

The authors have no conflicts of interest to declare.

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