

Breast Cancer Survivorship: A Comprehensive Review of Long-Term Medical Issues and Lifestyle Recommendations

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Perm J 2015 Spring;19(2):48-79

<http://dx.doi.org/10.7812/TPP/14-241>

ABSTRACT

Long-term survival rates after a diagnosis of breast cancer are steadily rising. This is good news, but clinicians must also recognize that this brings new challenges to the medical community. As breast cancer becomes a chronic condition rather than a life-threatening illness owing to advances in early diagnosis and more effective treatments, health care practitioners must recognize and manage the long-term sequelae of the constellation of therapeutic modalities. Survivors of breast cancer represent a unique and extremely complex group of patients; not only do they have the challenge of dealing with multiple long-term side effects of treatment protocols, but many are also forced to address the preexisting comorbidities of their therapies, which often include multiple other issues. Therapies have additional and/or additive side effects that may interfere with treatments directed toward the new primary diagnosis of breast cancer. Our mandate is to establish a smooth transition from *patient* with breast cancer to *survivor* of breast cancer while providing ongoing and future guidance.

Certainly, the information and resources to accomplish this transition are readily available; however, they are scattered throughout the literature and therefore are not easily accessible or available to the primary care physician. It is imperative that the information available regarding survivorship issues be accessible in an organized and useful format. This article is a modest attempt to provide a comprehensive review of the long-term medical issues relevant to survivorship after the diagnosis and treatment of breast cancer. A predicted shortage of oncologists by 2020 is well-recognized. Therefore, the bulk of long-term care will become dependent on the primary care physician. This shift of care means that these physicians will need to be well educated in the long-term medical issues related to breast cancer treatment.

INTRODUCTION

It is estimated that there are approximately 2.5 million survivors of breast cancer in the US.¹ This figure will expand to 3.4 million in 2015, representing an increase of 31%.² The millions more worldwide are probably grossly underestimated because of the poor or inefficient reporting systems and the lack of reliable cancer registries in third-world countries.³ In 2006, the Institute of Medicine (IOM) issued a milestone comprehensive report, *From Cancer Patient to Cancer Survivor: Lost in Transition*.⁴ Of the 10 recommendations regarding cancer survivorship by the IOM, the issues receiving the utmost attention to date have been the provision

of a summary of diagnosis, treatment received (treatment summary), future follow-up care plans, and healthy lifestyle recommendations.⁵ A recent Special Series Overview⁶ eloquently described a number of major topics that have been addressed by world-renowned experts since the IOM recommendations were published.⁶ These include long-term cardiovascular issues secondary to treatment protocols,⁷ bone health,⁸ the increased risk of second primary malignancies (SPMs),⁹ the development of lymphedema,¹⁰ and other issues that, although extremely important, may not be life-threatening. Multiple other concerns have been inadequately addressed, including the increased risk of venous

thromboembolism in the setting of malignancy,¹¹⁻¹³ the failure of adherence and compliance to prescribed adjuvant hormonal therapies,¹⁴⁻¹⁶ and lifestyle changes with recommendations for effective modifications.

Although of major importance, issues regarding sexuality and fertility preservation are not addressed in this review. The reader is directed to excellent reviews of breast cancer and sexuality,^{17,18} as well as extensive guidelines regarding fertility preservation.¹⁹ In addition, non-specific symptoms secondary to treatment protocols (eg, fatigue, insomnia, pain, cognition) are omitted because recent and thorough reviews of these issues are readily available.²⁰ Furthermore, these are excluded because many are nonspecific symptoms and are not unique to a diagnosis of breast cancer.

Survivorship care programs provide an important component of the patient treatment pathway but fail in the elaboration and communication to the patient regarding many issues relevant to long-term survival. Most long-term care plans inadequately address the most important medical issues involving the long-term consequences of survivorship. Although the primary recommendations of the 2006 IOM report are sound,⁴ we would add the importance of patient education regarding some of the long-term sequelae of this disease and its treatment. These include the symptoms of the issues addressed in this article: cardiovascular diseases (CVDs) secondary to treatment modalities, bone health, SPMs, lymphedema, thromboembolic risks, long-term compliance with oral medications, and finally, lifestyle interventions.

Although most people with breast cancer will not die of breast cancer,

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their comorbidities (eg, obesity, hypertension, hyperlipidemia, and diabetes mellitus [DM]) will most certainly affect disease-free survival (DFS) and, ultimately, overall survival (OS). In this review we address lifestyle changes, which are largely dependent on body mass index (BMI) and include diet and exercise, and review recommendations regarding these issues. Survivors of breast cancer represent a unique group who must be cognizant of the long-term side effects of their treatment protocols and be given information to encourage a proactive approach to their overall health. Finally, a robust reference resource list is included in this article for those who wish to delve into specific issues in greater depth.

CARDIAC ISSUES

Although breast cancer is the most feared disease by most women in the US, it is far from the leading cause of death in women.^{21,22} CVD is the number 1 killer of women, claiming well over 400,000 lives each year. Sadly, nearly 50% of women are unaware that heart disease is the leading cause of death among women.²³ Survival of patients with breast cancer has dramatically increased in the last 2 decades, largely owing to earlier detection by advanced mammographic screening technologies, increased patient awareness, and of course more effective treatment modalities.²⁴ This success, however, may lead to an unintended increase in the incidence of mortality due to CVD. Although each year many women succumb to CVD, the risk of death due to CVD may be greatly increased in survivors of breast cancer by the addition of adjuvant therapies, regardless of cancer stage, at the time of diagnosis.

A further concern, demanding urgent attention, is that the rate of younger women (aged 35 to 44 years) who develop CVD is on the rise.^{25,26} Overlapping with this age group are the younger and younger women receiving a diagnosis of breast cancer. Therefore, the diagnosis, treatment, and long-term sequelae of treatment may be converging on patients who are currently facing a breast cancer diagnosis and are thus subjected to “modern” protocols. As with

the treatment of other malignancies occurring at young ages (eg, Hodgkin disease), the long-term sequelae of breast cancer treatment are just now, decades later, becoming fully realized. In fact, a subset of cardiologists in the US and internationally is focusing on a new subspecialty—cardio-oncology—a specialty in managing the long-term cardiovascular side effects of the treatment of malignancies.²⁷ Many survivors of breast cancer are at significantly increased risk of death caused by CVD, far exceeding their risk of death resulting from the initial cancer itself or from a recurrent cancer.^{21,22,28,29}

Chemotherapy

The development of multiple antineoplastic agents—many novel but also many older (decades old)—has dramatically increased breast cancer OS. Unfortunately, many of the chemotherapeutic agents used have the potential to cause cardiovascular complications, some acute but most chronic.^{30,31} The spectrum of CVD in the setting of breast cancer therapy includes congestive heart failure (CHF), myocardial ischemia, hypertension, arrhythmias, QT prolongation, bradycardia, pericarditis, acute coronary syndrome, and thromboembolic events (TEs).³¹⁻³⁴

Anthracyclines: Doxorubicin and Epirubicin: Anthracyclines bind to the DNA of malignant cells, interfering with the replication process and resulting in cellular death. Anthracycline therapy has been shown to increase the development of CHF and cardiomyopathy by 2%,³⁴⁻³⁹ doubling to 4% if used in conjunction or sequence with trastuzumab.^{34,39-43}

Of particular importance to the primary care physician, extensive data are available in the literature about the potential long-term sequelae of the cardiotoxicity of anthracycline-based therapy for survivors of breast cancer.³¹⁻³⁴ Furthermore, it should be noted that anthracycline therapy may not result in cardiotoxicity, particularly CHF, which is clinically evident for 10 to 20 years after treatment.^{33,44,45}

Alkylating Agents: Cyclophosphamide: Alkylating agents act by reacting with the proteins of the DNA of cancer cells

by adding an alkyl group to them. This disrupts effective DNA replication, resulting in the apoptosis of cancerous cells. Cyclophosphamide therapy can lead to cardiac damage, resulting in heart failure in nearly 30% of patients receiving the drug.⁴⁶⁻⁴⁸

As with most chemotherapeutic agents, the risk of cardiotoxicity appears to be dose related.^{33,47} In addition to dose, prior anthracycline therapy, a history of mediastinal radiation, and elderly age are further risk factors for cardiotoxicity.^{29,45-47,49,50}

Cytoskeletal Disruptors (Taxanes): Paclitaxel and Docetaxel: Cytoskeletal disruptors inhibit the process of cell division through the interruption of

Abbreviations

AET = antiestrogen therapy
AI = aromatase inhibitor
AML = acute myeloid leukemia
ATLAS = Adjuvant Tamoxifen Longer Against Shorter
aTTom = Adjuvant Tamoxifen Treatment Offers More
BCRL = breast cancer-related lymphedema
BCT = breast-conserving therapy
BMD = bone mineral density
BMI = body mass index
CHF = congestive heart failure
CVD = cardiovascular disease
DFS = disease-free survival
DM = diabetes mellitus
ER+ = estrogen receptor-positive
FRAX = Fracture Risk Assessment tool
HEALER = healthy eating, active living, and emotional resilience
HER2+ = human epidermal growth factor receptor 2-positive
IOM = Institute of Medicine
MDS = myelodysplastic syndrome
OS = overall survival
PE = pulmonary embolism
RT = radiation therapy
SEER = Surveillance, Epidemiology, and End Results
SERM = selective estrogen receptor modulator
SPM = second primary malignancy
SSRI = selective serotonin reuptake inhibitor
TE = thromboembolic event
WFPBD = whole-food, plant-based diet
WI = Wellness Index

microtubular functions, which are essential for cell division. Taxanes have been incorporated in the treatment of breast cancer only since the 1990s and, as such, their long-term cardiotoxic side effects may not yet have been adequately identified and reported. Furthermore, the multiple-combination chemotherapies used, which have included the addition of a taxane-based agent, make it difficult to decipher the true incidence of cardiotoxicity attributable to these drugs, particularly when administered alone.^{29,45,51-54}

Although the most common side effects of taxane therapies are related to arrhythmias, particularly bradycardia, myocardial ischemia has also been reported. The incidence with paclitaxel use is 0.5% to 5% and with docetaxel appears to approach 2%.³³ CHF resulting from docetaxel has ranged from 2.3% to 8%.^{51,55} It should be noted that most data for the development of cardiotoxicity has accumulated from the use of paclitaxel.⁵⁶

As noted previously, the cardiotoxicity of systemic therapies may become one of the most devastating consequences of the treatment itself, particularly when an additional comorbidity such as a history of coronary artery disease, hypertension, or smoking is added to the patient's active problem list (Table 1).^{45,56-58}

Radiation Therapy

The current standard of care for the treatment of early-stage breast cancer involves giving a patient an informed choice regarding surgical options.⁵⁹⁻⁶¹ The effectiveness of breast-conserving therapy (BCT), beginning in the 1970s with quadrantectomy vs mastectomy, has been fully verified with numerous studies, some reporting more than 2 decades of follow-up data.⁶²⁻⁶⁷ These findings have resulted in BCT as the primary surgical option for most patients during the past 2 decades. An integral part of BCT is the mandatory addition of adjuvant radiation therapy (RT).^{63,64,68} This surge in BCT has resulted in a large number of patients who receive adjuvant RT for early-stage breast cancer; rates of recurrence and death are markedly reduced.⁶⁹⁻⁷⁵

Cardiac injury resulting from RT to the thorax has long been recognized.

Table 1. Potential cardiotoxicity of therapeutic agents^a

Agent	Potential cardiotoxicity
Anthracyclines: doxorubicin and epirubicin	CHF, cardiomyopathy
Alkylating agents: cyclophosphamide	CHF
Taxanes ^b : paclitaxel and docetaxel	CHF, ischemia, arrhythmias
Targeted therapies: trastuzumab and lapatinib	CHF
Hormonal blockade: tamoxifen	TE

^a Long-term effects of conjunctive therapies may be additive.

^b Long-term cardiovascular toxicities are yet to be determined.
CHF = congestive heart failure; TE = thromboembolic events.

Because of the increasing number of patients who have become long-term survivors of breast cancer thanks to BCT and RT, attention has now been directed to the late side effects of RT. These include direct damage to the myocardium and the coronary arteries, resulting in an increase in CHF and myocardial infarction compared with patients who do not receive RT.^{29,33,76}

Since the mid-1980s, the mean centigray cardiac exposure has decreased because of improved technologies, such as computed tomography for simulation for RT; nonetheless, even small amounts of radiation reaching the heart may be damaging.⁷⁷⁻⁸² It is estimated that each centigray exposure the heart receives increases the risk of death due to heart disease by 3%.^{83,84} The incidence and severity of cardiac morbidity and mortality risk are far greater for left-sided disease by virtue of human anatomy.^{81,85-88}

As with chemotherapy, the risk of death due to RT starts to rise 10 years after treatment and may not be fully manifest until the second decade after therapy.^{83,88} RT has a long-term effect; therefore, it is important to be cognizant of the lengthy delay in cardiac symptoms, particularly as the patient ages and becomes more vulnerable to the development of CVD.⁸⁹ Because RT has evolved over the years, incorporating new technologies, administration schedules, and delivery of centigray doses, the side effects for contemporary patients may be somewhat lessened, although long-term follow-up is not yet available.^{76,90-94}

Hormonal Blockade

Tamoxifen: Tamoxifen is a selective estrogen receptor modulator (SERM) and inhibits the growth of breast cancer cells

by its antiestrogenic activity through its competitive inhibition of estrogen binding to estrogen receptors.^{95,96} Since its introduction in the 1970s, tamoxifen has been shown to reduce the risk of breast cancer recurrence and mortality by more than 30%.^{97,98} Tamoxifen has been heralded as one of the most important advances in the treatment of breast cancer because approximately 70% of these patients have estrogen receptor-positive (ER+) cancer.⁹⁹⁻¹⁰³

The side effects of tamoxifen therapy are typically those that accompany the onset of menopause. These include hot flashes, mood swings, depression, loss of libido, and vaginal dryness.¹⁰¹ In addition, tamoxifen increases the risk of thromboembolic complications, including deep venous thrombosis, pulmonary embolism (PE), and cerebral vascular events.¹⁰⁴⁻¹⁰⁷ Tamoxifen has also been associated with an increase in the development of endometrial cancer.^{97,105}; therefore, women receiving this form of hormonal blockade who experience spotting require urgent gynecologic referral for uterine biopsy to rule out cancer. Because tamoxifen is a SERM, a beneficial effect is an apparent decrease in the incidence of myocardial infarction and CVD-related death as well as offering protection from osteoporosis and fracture risk in postmenopausal patients.¹⁰⁶⁻¹⁰⁸

A final but important consideration for patients receiving tamoxifen therapy centers on the recognized interactions with this drug in two common comorbid conditions: coagulation and depression. An aging population results in an increasing incidence of cardiac arrhythmias and other conditions resulting in the need for long-term anticoagulative therapy. Tamoxifen potentiates the

action of warfarin by competing with its metabolizing enzyme, cytochrome P4503A4, which may result in major hemorrhagic consequences.^{103,109}

Antidepressants are one of the most commonly prescribed medications in the US.¹¹⁰⁻¹¹² Commonly prescribed antidepressants classified as selective serotonin reuptake inhibitors (SSRIs) inhibit the enzyme CYP2D6 and thus may slow the metabolism of tamoxifen, resulting in a decrease of its potency and thereby increasing the risk of recurrence.¹¹³⁻¹¹⁶

Aromatase Inhibitors: Letrozole, Anastrozole, and Exemestane: Aromatase inhibitors (AIs) work by blocking the enzyme aromatase, which converts adrenal androgens into estrogens. Whereas tamoxifen is employed in premenopausal women who have ER+ tumors, AIs are the estrogen blocker of choice in postmenopausal women whose cancer is ER+. AIs have been established as an effective adjuvant treatment in the postmenopausal group.^{101,117-119} In women, AIs have similar side effects to tamoxifen regarding menopausal symptoms (eg, hot flashes, mood swings, vaginal dryness, and loss of libido).^{97,101-120} The risk of CVD, including myocardial infarction, CHF, hypertension, and hyperlipidemia, remains controversial because published studies have failed to adequately resolve these issues.^{106-108,121-126} Until more definitive data are available, it would be prudent to err on the side of caution and consider those patients who are also receiving long-term AI therapy to be at an increased risk for the development of CVD.

Although arthralgias are an important side effect of AI therapy,^{101,122,123} a potentially more clinically important side effect is the development of bone loss. Osteopenia (a decrease in bone calcium content) and osteoporosis (a decrease in the actual bony matrix) are well-recognized side effects of AI therapy.¹²⁷ Further discussion of bone loss are addressed in the section, Bone Health.

Targeted Biologic Therapies: Trastuzumab and Lapatinib

Targeted biologic agents are directed at protein kinases and the receptors that activate them. Approximately 15% to 30% of all breast cancers are

human epidermal growth factor receptor 2-positive (HER2+) and, as such, the HER2 receptor tyrosine kinase pathway has become an important therapeutic target.¹²⁸⁻¹³⁴ The main function of the *HER2/neu* oncogene (now also called *ERBB2*) is to promote the differentiation, growth, and survival of cells, thereby enhancing the aggressiveness of these breast cancers, resulting in an overall outcome that is inferior to those patients not overexpressing this oncogene.¹³⁵⁻¹³⁹ Multiple studies have demonstrated a reduction in mortality and an increase in OS in HER2+ patients when trastuzumab has been incorporated into their treatment regimens.¹⁴⁰⁻¹⁴² When used as a single treatment agent, trastuzumab increases the duration of survival, which is augmented by the administration of additional chemotherapeutic agents.^{128,138,143} The most severe complication of trastuzumab therapy has been its potential to adversely affect cardiac function; however, the exact mechanism of its cardiotoxicity remains unclear.^{31,144}

The risk of trastuzumab-related cardiac events, as with other cardiotoxic agents, increases when additional CVD risk factors are noted, especially a history of coronary artery disease or impaired left ventricular dysfunction.^{56,145} On a positive note, it appears that the cardiotoxic effects of trastuzumab are reversible as long as they are identified early through rigorous monitoring during administration.^{29,145-149}

Lapatinib, an orally administered medication, appears to be associated with a lower incidence of cardiotoxicity compared with trastuzumab.¹⁵⁰ It appears that the cardiotoxicity associated with lapatinib is not as severe and is also reversible.¹⁵¹ Lapatinib is a new targeted modality, and further clinical investigation is needed before definitive conclusions about its cardiac safety are made, especially in light of the fact that many treatment options employed in breast cancer therapy have been demonstrated to have delayed long-term toxicities. In addition, further follow-up studies need to be conducted to determine whether outcomes are comparable to those of trastuzumab therapy.^{146,152,153}

The cardiovascular complications of breast cancer treatment are an extremely

complex subject, involving numerous variables that may be difficult to isolate. The multifocal approach to treatment includes many chemotherapeutic agents, alone and/or in combination, as well as RT modalities, options for hormonal blockade depending on menopausal status, and targeted therapies. Dosages, sequence of administration, and concordant or tangential approaches further complicate a thorough understanding of both the short-term and long-term toxicity of the administered therapies. The cluster of therapies such as anthracycline-based chemotherapy, right- or left-sided RT, trastuzumab administration, and hormonal blockade with AIs may contribute to an increased incidence of CVD.^{39-48,62,67,153-156} In particular, there have been recent concerns calling for further investigation of targeted therapies used in combination with RT and the potential for long-term cardiovascular side effects.^{92,147,154,157} Table 1 summarizes the potential long-term cardiovascular side effects of chemotherapy.

Further complicating the multiple cardiotoxicities of breast cancer therapy are the long, well-recognized, preexisting conditions that predispose to CVD (obesity, hypertension, dyslipidemias, and DM). Patients with breast cancer, most of whom now are becoming long-term survivors, may harbor one or more of these comorbidities, all of which increase as the population ages. Because of the complexity of the long-term side effects of treatment modalities for breast cancer, those addressing survivorship care must be aware of the need to incorporate a multidisciplinary approach to issues surrounding assessment and management of CVD, which remains the leading cause of mortality in women.¹⁵⁸ Lifestyle changes that address these concerns are discussed in greater detail in the section, Lifestyle Management and Breast Cancer.

BONE HEALTH

Women with breast cancer are at an increased risk for the development of bone loss and osteoporosis because of adjuvant therapies; these changes may be extremely rapid in onset. Osteoporosis is a "silent disease" that is often not

recognized until a fracture event. Osteoporosis results in the deterioration of the bony microstructure, particularly in the vertebrae, ribs, and hips, culminating in fragility fractures and an increase in overall mortality. Maintenance of bone integrity is an important issue in breast cancer care because weakening of the bony matrix represents a major factor in OS. Current therapies profoundly influence the metabolic effectiveness of the skeletal structure.

Risk factors for osteoporosis, excluding the diagnosis of breast cancer, are well recognized and include both non-modifiable and modifiable variables, particularly in the elderly population.¹⁵⁹

Nonmodifiable risk factors include a family history of osteoporosis (genetically based), having a small, thin frame,^{160,161} increasing age, a prior fracture, and the early onset of menopause. These all contribute to the increased risk of osteopenia and osteoporosis (Table 2).¹⁶²⁻¹⁶⁷

In addition, indications for the treatment of other medical conditions necessitate certain pharmacologic interventions not specifically related to treatment of the breast cancer itself (Table 2). These include drugs commonly prescribed for gastrointestinal symptoms or diseases, psychotropic agents, glucocorticoids, hormonal therapies for

thyroidal malfunction, anticonvulsants, and anticoagulants for treatment of cardiac disease such as atrial fibrillation.

Gastrointestinal complaints, including those related to gastroesophageal reflux and peptic ulcer disease, result in one of the most commonly prescribed medications: proton pump inhibitors, which approach 150 million prescriptions annually.¹⁶⁸ These often-prescribed drugs decrease the intestinal absorption of calcium and therefore result in a decrease in bone mineral density (BMD), an effect that is reversible after discontinuation of therapy, usually within 12 months.¹⁶⁹⁻¹⁷¹

Nearly 10% of Americans are prescribed antidepressants annually.¹⁷² Second-generation antidepressants, SSRIs, are commonly dispensed and rank third in all drug classes prescribed in the US.¹⁷³ Serotonin receptors are present in all major bone cells and, as such, the neuroendocrine system of bony structures may be subjected to interference by the administration of SSRIs.¹⁷⁴⁻¹⁷⁷

Many survivors of breast cancer are prescribed medications for depression diagnosed either before or after their initial diagnosis of breast cancer. Patients with comorbidities such as depression are therefore at additional risk of BMD depletion. Add to this the compounding issues affecting depressed individuals, such as decrease in exercise, poor eating habits, lack of sun exposure, tobacco use, and an increase in alcohol intake, and the increased risk of fracture events rises even higher.^{178,179} Those caring for survivors of breast cancer must be aware of patients who are receiving antidepressants, particularly those receiving SSRIs, who may be at an increased risk of osteoporosis and subsequent fractures.¹⁷⁸

Long-term corticosteroid therapy, often employed in the treatment of multiple inflammatory and autoimmune diseases, is also a well-recognized risk factor for osteoporosis.^{164,179} Steroidal therapy leads to osteoporosis by decreasing bone formation through multiple and complex mechanisms, which are beyond the scope of this review.¹⁸⁰⁻¹⁸³ As with the proton pump inhibitors, the osteoclastic effect of corticosteroid therapy appears to decrease fracture risk after discontinuation of therapy.¹⁸⁴

Multiple other drugs prescribed for patients with breast cancer for concurrent diseases, including anticonvulsant and anticoagulation medications, may affect BMD, further contributing to osteoporotic fractures, particularly in the aging population. The literature is conflicting, but one should be aware that these classes of medications might increase the risk of fracture events (Table 2).¹⁸⁵⁻¹⁸⁷

Als, be they steroidal (exemestane) or nonsteroidal (anastrozole and letrozole), are associated with a substantial and often rapid decrease in BMD and an increased fracture risk.¹⁸⁸⁻¹⁹⁰ These medications appear to be significantly more effective than tamoxifen adjuvant therapy in ER+ tumors in postmenopausal patients, with longer overall DFS and without the additional risk of endometrial carcinoma.¹⁸⁵ Tamoxifen, classified as a SERM, acts like an antiestrogen in some tissues (breast) and an estrogen agonist in others (bone) and therefore is considered as a bone strengthener in women who are postmenopausal, an effect not seen in the premenopausal population.¹⁹¹⁻¹⁹⁵ As opposed to tamoxifen, AIs block the aromatization of androgens and thereby block their conversion to estrogens, resulting in bone loss. Recovery of BMD after completion of aromatase inhibiting therapy may be only partial, especially if exemestane (steroidal-based therapy) has been used as the initial choice of antiestrogen therapy (AET).^{164,185,194} Such reversible effects on bone density deterioration are similar to those reported with the discontinuation of other medications previously addressed.¹⁸⁴

Recent attention has been directed to patients who have been placed on a regimen of hormonal blockade therapy with tamoxifen, which is then discontinued after the appropriate duration. Postmenopausal women upon discontinuation of tamoxifen may suddenly experience an *estrogen deprivation* syndrome with respect to bone health; this results in the loss of the protective effects against the development of osteoporosis, with a subsequent increase in the risk of fracture.^{187-193,195} Thus, those providing long-term care for survivors of breast cancer must be aware that the abrupt discontinuation of tamoxifen requires

Table 2. Risk factors for osteoporosis	
Type of factor	Risk factor
Nonmodifiable	Age older than 50
	Family history
	Small, thin frame
	History of previous fracture
	Early-onset menopause
Modifiable	Sedentary lifestyle
	Poor nutrition <ul style="list-style-type: none"> • Excess protein, sodium, sugar intake • Inadequate calcium and vitamin D₃ intake
	Tobacco use
	Alcohol use
Concurrent medications	Aromatase inhibitors
	Glucocorticoids
	Proton pump inhibitors
	Psychotropic agents
	Antidepressants
	Thyroid replacement
	Anticoagulants
	Anticonvulsants

particular attention to bone fragility and its assessment.¹⁹⁵⁻¹⁹⁹ A further issue, yet to be adequately addressed, involves those patients in whom discontinuation of tamoxifen is followed by the administration of AIs, putting bone health and density at greater risk.

To further complicate the issue, recent studies suggest a beneficial effect in the extension of hormonal blockade, specifically tamoxifen, to ten years, exceeding the previously recommended years of therapy.^{198,199} Although these recommendations should be cautiously interpreted, the long-term suppression of bone density must be addressed. It is hoped that by the time patients who are just beginning hormonal blockade therapies reach their five-year mark, they will have a definitive answer and/or evidence-based medicine to strongly recommend continuing those therapies for an additional five years. Additional confounding variables, especially for long-term therapies, are adherence and compliance, which are discussed in the section, Adherence and Compliance.

Finally, an extensive variety of other medical conditions, diagnoses, and pharmacologic interventions have been implicated in contributing to the development or progression of decreasing BMD from osteopenia to osteoporosis.^{164,168,185,188} Many of these issues are addressed only by observational studies. Therefore, although these risk factors are important, their relevance to absolute risk increase awaits further results from ongoing trials.

Myriad medical conditions have been associated with the development of osteoporosis, but two particularly common diseases must be mentioned: thyroidal conditions and DM.

Hyperthyroidism is a common disorder affecting approximately 1 in 100 individuals, and it is often accompanied by the progression of osteoporosis, especially in postmenopausal women.²⁰⁰ Thyroidal disorders are often a comorbidity of patients with breast cancer, and thyroxine replacement therapy must be recognized because hyperthyroidism and the treatment of hypothyroidism may both result in bone resorption, resulting in an increased risk of osteoporosis.^{185,201,202} Conflicting results

have been reported regarding thyrotoxic conditions and the effect of thyroxine replacement therapy, suggesting that many patients are overmedicated for hypothyroidism and thus may be exposed to increasing their risk of osteoporosis.^{203,204} The relationship between thyroidal disease and osteoporosis remains controversial, and therefore, a diagnosis of thyroidal disease should be noted in addressing issues of survivorship in patients with breast cancer.^{185,205-208} Thyroidal dysfunction may be a risk factor for osteoporosis.^{209,210}

DM has emerged as a pandemic disease affecting more than 10% of the world population.²¹¹⁻²¹³ Many patients diagnosed with breast cancer enter the cancer “arena” with a preexisting diagnosis of DM. Both type 1 and type 2 DM have been associated with the exacerbation of osteoporosis²¹⁴; however, the mechanism of bone weakening appears to differ between the 2 diseases. Type 1 DM (insulin-dependent) is caused by insulin deficiency resulting in hyperglycemia in young patients, and it may lead to a decrease in BMD, particularly in the spine and hips, resulting in an increased risk of fracture.²¹⁵⁻²²² Conversely, the evidence for type 2 DM (non-insulin-dependent) for the increased risk of fracture appears somewhat conflicting for reasons unknown.^{215,223-225} It has been suggested that the comorbidities of type 2 DM (visual impairment, gait-related neuropathy, advanced age, and obesity) may offer clues to the increase in fracture risk.^{215,224} Multiple studies have reported contrary results when analyzing data regarding the association of type 2 DM and osteoporosis. Some studies suggest no differences in BMD and type 2 DM; some, a lower risk of osteoporosis with type 2 diabetes; and still others, a higher risk.^{214,226-228}

Many medical diagnoses have been identified as potential risk factors for osteoporosis. These include gastrointestinal diseases (celiac disease, malabsorption syndromes, and irritable bowel disease), autoimmune disorders (rheumatoid arthritis and lupus), and other diseases or syndromes.^{200,229} Because an abundance of information exists regarding the development of osteoporosis caused by coexistent morbidities,

patients with breast cancer must be thoroughly evaluated for potential comorbidities, particularly in the setting of hormonal blockade with AIs when used as long-term adjuvant therapy. Chronic conditions require the long-term use of medications that may further increase the risk of osteoporotic development. Extensive confusion surrounds the issue of osteoporotic comorbidities (both disease and drug related). Until further evidence is available, it would be prudent to consider these issues as potential risk factors for osteoporosis much the same as hypertension, dyslipidemias, and DM are regarded as risk factors for CVD and cerebral vascular diseases.

There are multiple modifiable risk factors for osteoporosis in the setting of breast cancer therapy. Most of these modifiable risk factors are related to lifestyle and include alcohol and/or tobacco use, nutritional concerns (including eating disorders), maintenance of a near normal BMI, and adequate physical activity.

The excessive consumption of alcohol, defined as greater than 2 U/day to 3 U/day (1 U equals a half-pint of beer [300 mL], a glass of wine [100 mL], 1 shot of distilled spirits [25 mL]), increases the risk of an osteoporotic fracture by up to 40% compared with those with moderate to no alcohol intake.²³⁰⁻²³² Excessive alcohol intake results in suppression of bone-forming cells and calcium metabolism. Alcoholism is also associated with multiple nutritional deficiencies, including vitamin D₃ deficiency, which results in the increased production of parathyroid hormone, thereby increasing bone resorption, thus further weakening BMD.^{232,233} Falls, resulting from chronic heavy drinking, further increase a patient’s risk of fracture events.

Tobacco use, both historic and current consumption, affects bone density and increases fracture risk, although the mechanism of action is not well understood.^{230,234,235} Inhibition of osteoblastic activity, excessive estrogen breakdown, and earlier onset of menopause have

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been suggested as possible causes of increased bone fragility in smokers.^{230,236}

Adequate nutrition plays a critical and complex role in bone health. Appropriate intake of calcium, phosphorus, and multiple other nutrients are essential in the maintenance of therapeutic levels of vitamin D₃.^{237,238} It was once thought that obesity was protective against osteoporosis,²³⁹ but recent evidence fails to support this belief.^{240,241} Assessment and monitoring of BMD has been established as an effective and appropriate predictor of fracture risk. Osteoporosis is currently defined on the basis of BMD as established by the World Health Organization in 1994 using T-scores.^{199,242}

Multiple technologies are available for assessing BMD; however, dual-energy x-ray absorptiometry is the most commonly employed. For each BMD value calculated, a T-score representing the average peak BMD in a young, normal reference population and a Z-score representing the standard deviation of the patient's calculated BMD from the patient's expected age-matched cohort are calculated. Osteopenia (decreased levels of calcium in the bones) is defined as a T-score between -1.0 and -2.5. Osteoporosis (decreased level of the bony matrix itself) is defined as a T-score equal to or less than -2.5.^{243,244}

To further delineate the risk of fracture incidence, the World Health Organization has developed the Fracture Risk Assessment tool (FRAX), which is a risk-assessment software program that attempts to further delineate the absolute risk by combining BMD measurements and clinical and historical factors.^{199,242} Table 2 summarizes risk factors for osteoporosis.

SECOND PRIMARY MALIGNANCIES

SPMs, those cancers that occur after the diagnosis of a primary cancer, now constitute one-sixth of all malignancies reported to the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) program.²⁴⁵

Because patients with breast cancer constitute nearly one-fourth of all long-term cancer survivors,^{246,247} the issue of SPMs is particularly germane. Commonly, SPMs occur in survivors

because of a genetic predisposition and increased susceptibility, caustic exposures to environmental toxins yet to be fully identified, and the carcinogenic proaccelerators of treatment modalities currently in use.^{9,248,249} Because survival rates for women with a breast cancer diagnosis continue to increase,^{250,251} the risk for development of SPMs also rises. Longer survival also increases the opportunity for SPMs to develop because increasing age is a well-recognized risk factor for all cancers.

The most important risk factor for SPMs appears to be age at the time of diagnosis. The younger one's age at diagnosis, the more likely the potential for the development of an SPM. Although the development of a new breast cancer may not qualify specifically as an SPM, it is the most common *second* malignancy in patients with a primary breast cancer; it accounts for nearly 40% of all new malignancies.²⁵² It may present in the ipsilateral or contralateral breast, but most often, such malignancies are found in the opposite breast, especially if the primary treatment of the initially diagnosed cancer included a mastectomy. The increased risk has been reported to approach 70% more than that of the general population during a 10-year follow-up period.²⁵² Again, younger

age at diagnosis has been identified as a predictor of increased risk.^{253,254}

Recurrence can be local, developing in or near the original site, resulting from a failure of primary treatment (even after mastectomy); regional, presenting as nodal involvement in the axillary, supraclavicular, or cervical anatomic locations; or distant, appearing in the bones, lung, liver, or brain. Most often, recurrence is predicated on the initial stage at the time of diagnosis; the higher the stage, the more likely a recurrence.²⁵⁵

An issue of major concern and debate centers on the differentiation of an ipsilateral tumor recurrence after BCT vs the development of a true new primary malignancy. The question is simple; the answer is complex. Approximately one in five patients with breast cancer who have completed a five-year course of adjuvant therapy will experience a recurrence vs an SPM. Technologies exist to distinguish between the two and result in the opportunity to offer better-advantage therapeutic approaches depending on the differentiation.^{253,254,256} In addition, time to occurrence has been demonstrated to be significantly shorter in patients with an ipsilateral recurrence compared with those diagnosed with a new SPM.²⁵⁷

Signs and symptoms of breast cancer, be they a new primary malignancy or a local-regional recurrence, include the following: a new lump in the breast or on the chest wall; dimpling of the skin; nipple retraction; a spontaneous clear or bloody discharge from the nipple; redness, scaling, or thickening of the nipple areolar complex; shrinking or swelling of the breast, especially if it is unilateral; a mass in the axilla; and a rash on the breast that does not resolve with antibiotics. Signs and symptoms of a distant recurrence may include the new onset of localized bone pain in the long bones, ribs, and/or spine lasting longer than two weeks; persistent chest pain with or without a cough; persistent headache and abdominal pain without intended weight loss; personality changes; new-onset seizures; and loss of consciousness. (See Sidebar: Signs and Symptoms of Breast Cancer.)

Follow-up of recommendations for patients who have completed therapy

Signs and Symptoms of Breast Cancer

Primary or recurrent/local-regional:

- Lump in the breast/chest wall/axilla
- Dimpling of the skin
- Nipple retraction
- Clear or bloody nipple discharge (spontaneous)
- Redness, scaling, thickening of nipple-areolar complex
- Rash on breast, unresponsive to antibiotics

Distant recurrence:

- New-onset localized bone pain lasting longer than 2 weeks (long bones, ribs, spine)
- Persistent chest pain, with or without cough
- Persistent abdominal pain
- Unintended weight loss
- Persistent headache
- Personality changes
- New-onset seizures
- Loss of consciousness

with a curative intent have been published by the American Society of Clinical Oncology.²⁵⁸ Regular physical examinations, varying from three to six months during the first three years and annually thereafter, are recommended. Mammograms are performed annually (with the exception of a six-month follow-up mammogram after completion of RT). Magnetic resonance imaging is indicated as an annual adjunctive screening tool in those patients who are *BRCA* gene positive and/or have a diagnosis of invasive lobular breast cancer.^{259,260} Follow-up in an asymptomatic patient does not call for regular bloodwork, advanced radiographic imaging, or surveillance with specific biomarkers.

In addition to the risk of the development of contralateral disease, survivors of breast cancer are at an increased risk for the development of additional SPMs. It is estimated that an SPM will develop in 5% of patients within 10 years of diagnosis because chemotherapy has been linked, specifically, to the development of secondary acute myeloid leukemia (AML) and, more rarely, myelodysplastic syndromes (MDS).²⁶¹⁻²⁶⁷ The risk of AML or MDS appears to depend on the cumulative doses of anthracyclines and alkylating agents administered.^{262,266,268}

Recent controversies have questioned whether use of granulocyte colony-stimulating factors contributes to an increased risk of AML or MDS. The leukemogenic effect of granulocyte colony-stimulating factors is unknown at this time, but those involved in the long-term care of survivors of breast cancer should note that the addition of granulocyte colony-stimulating factors as part of the chemotherapy regimen may, in fact, increase the patient's potential for the development of AML or MDS.²⁶⁹⁻²⁷³ Although the absolute risk of the development of leukemia is likely to be low in survivors of breast cancer, it should be discussed with the patient, to educate about the potential signs and symptoms of these diseases.²⁶²

Recent studies have reported the increased risk of SPMs, with the authors hypothesizing that such malignancies are dependent on multiple other factors

in addition to treatment effects.^{274,275} The risk of developing an SPM, aside from a contralateral breast cancer, appears to be in the range of 5% to 7%.²⁷⁴⁻²⁷⁸ The most common sites for SPMs to develop are the pulmonary, gynecologic (endometrial and/or ovarian), colorectal, and integumentary (melanoma) systems.^{276,277} The fact that malignancies of the lung and the colon and rectum appear high on the list is not surprising because both are in the top 3 malignancies in women by incidence and mortality.²⁷⁹

Gynecologic malignancies are related to breast cancer through genetic predispositions (*BRCA1* and *BRCA2* genetic mutations) as well as conjoined risk factors, including obesity, nulliparity, delayed parity, and a history of hormone replacement therapy.^{280,281} Numerous epidemiologic studies have established the role of family history as an important risk factor for breast, ovarian, and other associated malignancies and have referred to this as "inherited cancer susceptibility syndromes." In the early 1990s, a genetic link was discovered between breast and ovarian cancers through the identification of the mutated forms of the *BRCA1* and *BRCA2* genes.^{282,283} These genes, when healthy, produce tumor suppressor proteins that help repair damaged DNA, but when mutated, the ability to repair DNA is rendered ineffective.

The harmful mutations in *BRCA1* or *BRCA2* can be inherited from a mother or father, further amplifying the importance of a thorough acquisition of the patient's family history. Although in the general population breast cancer will develop in about 1 in 8 women (12%) sometime in their lives, it will develop in 55% to 65% of women with a *BRCA1* mutation and 45% of women with a *BRCA2* mutation assuming they reach age 70 years.²⁸⁴⁻²⁸⁶ The general female population has slightly more than a 1% chance of ovarian cancer developing, in contrast to a 39% chance in those with a mutated *BRCA1* gene penetrance and an 11% to 17% chance if affected by the *BRCA2* mutation.²⁸⁴⁻²⁸⁶ Previous reports may have overstated the increased risk of breast and ovarian cancers associated with *BRCA1* and *BRCA2*. Carriers of

BRCA1 were reported to have a risk as high as 87%, and *BRCA2* carriers, a risk as high as 84%.^{287,288} The incidence of ovarian cancers has also been previously overestimated in families with a history of breast cancer.²⁸⁷ In addition, *BRCA1* and *BRCA2* mutations have been associated with an increased risk of fallopian tube and peritoneal cancers.²⁸⁸⁻²⁹²

Multiple other genes and their subsequent predisposition to the development of syndromes associated with the increased risk of breast cancer have been identified.^{293,294} Additional cancer susceptibility syndromes that have been noted are also an issue of concern deserving attention when providing care to long-term survivors of breast cancer. Nearly a dozen syndromes have been associated with hereditary breast (and ovarian) cancer mutations, and several excellent reviews of these issues are available.^{295,296} Other inherited susceptibility syndromes and/or genes that may predispose to the development of breast cancer include the Li-Fraumeni syndrome (soft tissue carcinoma, osteosarcoma, neurologic tumors, adrenocortical tumors, and leukemia),^{297,298} Cowden syndrome (multiple hematomas, tumors of the thyroid gland and uterus),^{296,299} and the Lynch syndrome (colon, uterus, pancreas, brain, gastrointestinal tract, and the integumentary system).²⁹⁵ Numerous other syndromes have been described in association with the increased incidence of breast cancer, but their penetrance and incidence appear minimal.^{295,296}

The most common gynecologic malignancy seen in survivors of breast cancer is uterine cancer, which is probably because of the common use of tamoxifen as an adjuvant therapy for ER+ tumors.^{97,105} Most studies have demonstrated that the increased relative risk of endometrial cancer in patients receiving tamoxifen is 2 to 3 times higher than that of an age-adjusted, cohort population.³⁰⁰⁻³⁰³ Furthermore, the association of uterine cancer and tamoxifen use appears to be dose dependent and also increases with duration of use.³⁰³⁻³⁰⁵ Despite the acknowledged increased risk

These genes, when healthy, produce tumor suppressor proteins that help repair damaged DNA, but when mutated, the ability to repair DNA is rendered ineffective.

of endometrial cancer in patients who receive tamoxifen therapy, the 5-year DFS rate for breast cancer approaches a 40% higher rate than patients not receiving the drug; therefore the risk-benefit ratio for significant increases in survival appears to far outweigh the risk of uterine cancer, which, in most cases, is cured by hysterectomy.^{300,305}

The development of colorectal malignancies has long been known to be increased in patients after the diagnosis of breast cancer.²⁵² However, the reported incidence rates of colorectal cancer in association with breast cancer vary widely.^{306,307} When investigation of the association of the *BRCA1* and *BRCA2* gene mutations is undertaken regarding a potential increased risk of colon cancer, current results are inconsistent and conflicting. Some studies have shown an elevated risk of colon cancers in *BRCA1* and *BRCA2* carriers, but these findings have not been confirmed by others.^{308,309} Further investigation must be undertaken to verify or to refute an association of *BRCA1* and *BRCA2* mutations with colorectal cancers.

There appears to be a reciprocally elevated risk of skin cancer occurring after the development of breast cancer, and vice versa.³¹⁰ The reverse increases in the development of breast cancer and melanoma range from a onefold to threefold increased incidence of developing the other malignancy.^{275,310-313} As with the increased incidence of SPMs, the incidence of cutaneous melanoma is also age dependent; the younger a woman is at time of diagnosis with one or the other malignancy, the higher her risk of the other malignancy.³¹⁰ These malignancies may share genetic predispositions such as *BRCA2* mutations^{275,281,310} and mutations in the *CDKN2A* gene, which have been identified as definitive risk factors for melanoma and thus may inversely increase the risk of breast cancer.³¹⁰⁻³¹⁴ Despite the conflicting results reported to date, one should note that the development of an SPM is associated with a significant decrease in OS, which is particularly concerning.²⁷⁶

Treatment of early-stage breast cancer saw a major paradigm shift in the 1990s from modified radical mastectomy with or without adjuvant therapy

to the increased use of BCT followed by radiation for control of local and/or local-regional recurrence.²⁵² With this change came the increased use of RT as the preferred adjunctive approach in procedures that aim to conserve the breast.⁵⁹⁻⁷⁵ Survival has increased with BCT and RT, and therefore the use of RT has grown exponentially. Long-term side effects of RT assume an increasingly important role in the development of SPMs.

Thoracic malignancies after RT for BCT have become an area of great concern as the role of RT in the treatment of breast cancer continues to rise. Lung cancer accounts for 5% of SPMs after breast cancer treatment; considering the high survival rate of breast cancer, lung malignancies, as a new SPM in these patients, are of concern because the survival rate of lung cancer is quite low.³¹⁵⁻³¹⁷ Lung SPMs appear to be significantly increased among women who are younger than age 50 years at their diagnosis. Strikingly, the increase in lung cancer appears as early as 1 year after treatment and the risk persists for an extended period of time. This phenomenon is perhaps not explained in the setting of RT and BCT because the long-term effects of RT have been well documented and follow a latent period of 5 to 10 years or longer.^{71,83,88,261,318-322} There may be an association in younger patients who have a higher increase in estrogen receptor negative tumors and an increased propensity for SPMs occurring as new lung malignancies.^{318,319,323}

Initially, RT was used as an adjuvant therapy for patients undergoing BCT. However, even in the setting of mastectomy, RT has been used as adjuvant therapy in patients with 4 or more axillary lymph nodes involved with metastases.^{324,325} There is clear and consistent, prospective, randomized data showing an absolute OS benefit approaching 10% in addition to fairly dramatic benefits in local and local-regional control in these patients. On the other hand, the ability to make solid recommendations for adjuvant RT in women with lesser node involvement has been more elusive. Some recent evidence points to the benefits of RT even in patients who undergo mastectomy but have minimal lymph node involvement (1 to 3

Risk Factors for Second Primary Malignancies

- Age at diagnosis
- Family history
- Genetic syndromes
- Adjuvant chemotherapy
- Use of granulocyte colony-stimulating factors
- Adjuvant radiation therapy
- Adjuvant antiestrogen therapy

positive lymph nodes) reported in the final pathologic synopsis.³²⁶

Thus, concerns about SPMs and RT in patients with breast cancer undergoing mastectomy with minimal nodal involvement will require future awareness and education for caregivers of survivors of breast cancer. As breast cancer survival continues to improve, and this improvement is largely attributable to adjuvant RT, understanding the long-term side effects of RT is assuming an increasingly important role. In addition to the commonly recognized SPMs, as described earlier, reports are beginning to emerge of less well-recognized SPMs secondary to RT, including the development of esophageal malignancies.^{315,327} The development of such malignancies has not been discussed in recent reports addressing SPMs, probably owing to their obscurity.²⁷⁶ Nonetheless, survivors of breast cancer and those providing follow-up care must be aware of these potential long-term complications, which have only recently been recognized. (See Sidebar: Risk Factors for Second Primary Malignancies.)

BREAST CANCER-RELATED LYMPHEDEMA

Breast cancer-related lymphedema (BCRL) is a serious, chronic, debilitating, and common consequence of breast cancer treatment and has been addressed as incurable, or at least as refractory, to conventional treatment modalities. Multiple lifelong morbidities include deformity, pain, a reduction in limb use, and extreme emotional distress often resulting in isolation.³²⁸⁻³³⁰ Many patients fear the development of lymphedema even more so than the diagnosis of the cancer itself or the loss of a

breast.^{328,329,331-333} Upwards of one in five patients may face the consequences of this irreversible, lifelong condition.³³⁰ In BCRL, there is an ongoing, progressive accumulation of protein-rich fluids and subsequent fibrosis in the affected limb because of the disruption of lymphatic anatomy.^{10,334-337} This condition remains poorly understood despite extensive research directed in attempts to identify its exact etiology.^{10,335,338}

BCRL is a well-recognized sequela of the treatment of breast cancer, including surgery and adjuvant therapies employed.^{10,339} The risk of the development of BCRL is a lifetime risk. Fibrosis may be slow to develop, which may account for the delay in the development of BCRL.^{334,337} BCRL may develop at any time after treatment; however, the condition develops in most patients within the first two to three years after treatment.^{332,340-342}

The incidence of BCRL, as reported, is incredibly misleading and quite confusing because it varies from 6% to 62%. This range represents an enormous variation and underscores our poor understanding of the condition.^{331,338,343-345} Some estimates of the incidence of BCRL even exceed 80%.³³² Discrepancy of the reported incidence of BCRL appears to result from multifactorial variations of the definition of the condition, the absence of any standardized uniform measurements, the lack of patient symptom reporting, inadequate follow-up of complaints relating to BCRL symptoms, varying follow-up periods, weak study designs, and finally, poor documentation by health care professionals involved in the treatment of patients with BCRL.^{10,338,346-348} In addition, BCRL may develop in other regions, including the chest wall and/or the remaining breast tissue, an issue that has received little attention in the medical community.³⁴⁹⁻³⁵²

Numerous predisposing risk factors for BCRL have been identified. These risks can be stratified into two major categories: disease specific (factors beyond the patient's control) and lifestyle risks (factors that may be influenced or controlled by the patient's proactive involvement). Although some of these risk factors may overlap, many nonmedical

factors remain beyond the patient's control. Factors beyond the patient's control include the age at diagnosis, stage of disease, extent of surgical manipulation, need for adjuvant therapies, development of postoperative infections, and formation of seromas.^{10,353,354} Age has been addressed in several studies, and the evidence for this as being a definitive risk factor for the development of BCRL remains conflicting.^{10,353,354} An urgent and more recent concern is that breast cancer is being diagnosed in younger women. Because development of BCRL is a lifelong risk, the long-term survival of younger patients may result in an increased risk of BCRL over time, as with the risk of CVD.^{25,26}

The surgical treatment of breast cancer appears to be the primary predisposing factor for the development of BCRL. Therefore, the risk of BCRL may differ depending on the initial surgical option chosen by the patient. Mastectomy, as opposed to lumpectomy, may result in a significantly higher risk (a twofold to sixfold increase) of BCRL.^{341,355,356} The extent of axillary dissection and the ratio of positive to negative lymph nodes have also been identified as factors that may increase the potential for BCRL development.^{330,338,357-359}

Intuitively, it appears to make sense that the number of lymph nodes removed and, furthermore, those that are found to be involved with metastatic disease would increase the chance of BCRL developing owing to the disruption of the anatomic flow of lymph. Several studies do not support this concept and, in fact, offer little evidence for the mechanism of this pathologic event.^{339,354,360} A potential explanation offered is the fact that lymph node involvement early in the disease process allows the development of collateral channels for lymphatic drainage.³⁶⁰ On the other hand, multiple additional studies lend support to the hypothesis that the extent of nodal dissection or involvement with the disease are, indeed, factors that increase the propensity for the BCRL.^{330,338,340,357-359,361} Replacing the radical axillary dissections of decades ago, sentinel lymph node sampling is now the currently accepted, minimally invasive, approach to breast cancer

treatment in early-stage disease.^{328,362} Compared with traditional axillary dissection, multiple studies have well documented that sentinel lymph node biopsy for assessing and staging breast cancer results in a significant reduction in the development of BCRL.^{328,355,363-366} Nonetheless, despite the rapid adoption of sentinel lymph node biopsy, BCRL remains a concern; according to recent data, there is still more than a 7% or 8% chance of BCRL developing within the first 6 months after the biopsy procedure.^{328,353,367}

Chemotherapy has been well documented as an extremely effective adjuvant therapy to decrease recurrence and increase the OS of patients with breast cancer.^{368,369} Interestingly, the percentage of patients receiving such adjuvant therapies as related to the development of BCRL is poorly documented because of incomplete information gathering and secondarily, in large part, because of the outpatient administration of chemotherapy.³⁷⁰ The addition of chemotherapy to the breast cancer treatment regimen and its relationship to the incidence of BCRL remains largely unresolved. As the multidisciplinary approach to breast cancer increases, it is becoming increasingly difficult to separate various therapies and their long-term consequences. This is particularly true in the setting of BCRL. Polyagent therapies have been implicated with an increase in the incidence of BCRL.³⁷¹⁻³⁷³ Particular attention has focused on the anthracycline-based therapies.³⁷⁴ It remains unclear why the addition of chemotherapy to the treatment of breast cancer may increase the incidence of BCRL. The issue of more advanced disease requiring adjuvant chemotherapy may skew the population that is more likely to experience BCRL. No studies, to our knowledge, have addressed or isolated a primary association. Therefore, it seems wise to be aware of the fact that chemotherapy, particularly anthracycline-based regimens, should be considered as a potential contributing risk factor for BCRL.

As previously mentioned, RT has become a mainstay in the adjuvant treatment of breast cancer.⁵⁹⁻⁷⁵ Although the ultimate role of adjuvant

RT in the development of BCRL is currently under review, substantial evidence has been reported supporting the idea that axillary RT increases the risk of BCRL.^{335,338,375,376} Presumably, RT-induced fibrosis results in scarring of the lymphatic system, resulting in further lymphatic flow disruption and the subsequent development of BCRL. Other studies have reported no increase in the incidence of BCRL after adjuvant axillary RT.³⁷²⁻³⁷⁴ Contemporary therapy involves sophisticated computed tomographic planning for appropriate simulation and allows for a more exact “targeted” zone for RT. As such, the potential for BCRL secondary to RT will, one hopes, be minimized in the near future.

Additional risk factors for BCRL include the postoperative complications of infection and seroma formation.^{336,352,355} Trauma, such as a shearing chest wall injury or dermal intrusion secondary to activities such as gardening and hiking, may also predispose a patient to the development of late-onset BCRL. Furthermore, surgery on the dominant side may also increase the incidence of BCRL.³⁷⁷

Lifestyle issues that are modifiable by a patient’s behavior may also play an important role in BCRL risk. The most important modifiable risk factor is related to obesity as determined by BMI.^{330,338,354,355} A sedentary lifestyle contributes to obesity, and therefore increasing physical activity may help decrease a patient’s BMI. In fact, multiple studies have demonstrated the benefits of exercise to not only decrease BMI but also to decrease the risk of BCRL.^{10,354,378-380} In addition, exercise

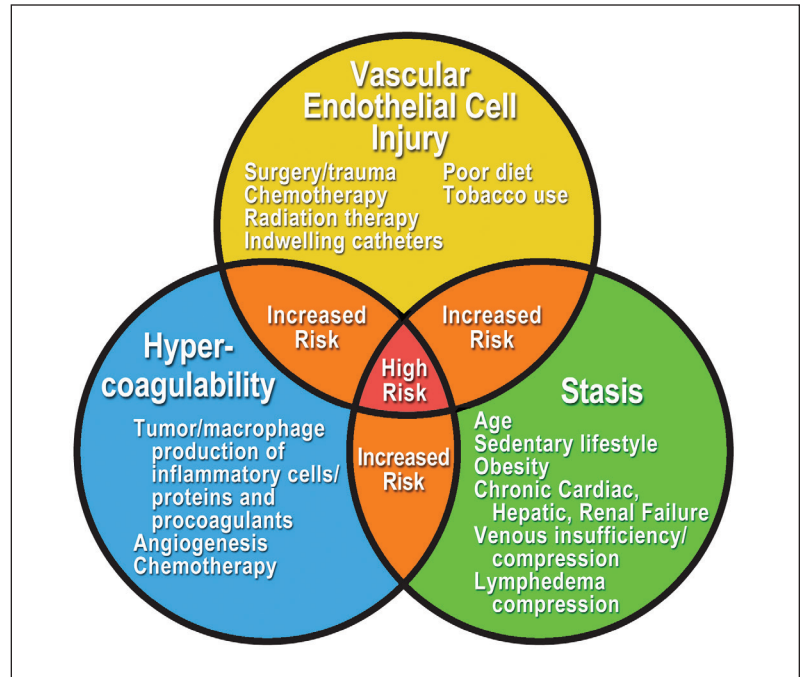


Figure 1. Virchow's triad.

CHF = congestive heart failure.

has been shown to have significant beneficial effects in cancer rehabilitation and, when coupled with an effective diet, including high vegetable and fruit consumption, has been shown to increase OS after breast cancer.³⁸¹⁻³⁸³ Finally, DM and hypertension, both associated with an increased BMI, have been identified as potential risk factors for BCRL, and these conditions may be altered by an effective diet and exercise program.^{10,338,354,355,381,383} Obesity, DM, and hypertensive states also increase the risk of CVD as previously discussed. (See Sidebar: Risk Factors for Breast Cancer-Related Lymphedema.)

THROMBOEMBOLIC EVENTS

TEs, such as deep venous thrombosis and PE, are uncommon but serious potential consequences related to all malignancies, breast cancer being no exception.³⁸⁴ Cancers are prothrombotic states, and the association of malignancies and the development of hypercoagulability have been well recognized for more than 150 years. Initially described by Rudolf Virchow,³⁸⁵ this association has come to be known as the triad of Virchow or Virchow's triad: damage

to endothelial cells, hypercoagulability (elaboration of procoagulants), and stasis (alteration in blood flow)^{12,386,387} (Figure 1).

The risk of TE in cancer-affected patients is estimated to range from 15% to 20% and is the second-leading cause of death in those with cancer, although it is often seen in conjunction with multiple additional comorbidities.^{384,388} The incidence of TE appears to be on the rise because of improved diagnostic imaging technologies, advanced and more effective therapeutic interventions, and, most importantly, increased long-term survival (DFS rates, measured in years after diagnosis and treatment).³⁸⁹ Multiple risk factors for TE in patients with cancer have been identified as significantly affecting morbidity and mortality. It has been estimated that patients in whom a malignancy was diagnosed have a 4- to 7-fold higher risk of TE compared with individuals without a cancer diagnosis.^{390,391}

In addition to the diagnosis of cancer, which itself is a thrombogenic and prothrombotic state,³⁹²⁻³⁹⁴ other risk factors for TE have been identified. As with all diseases, age older than 40 years remains

Risk Factors for Breast Cancer-Related Lymphedema

- Age at time of diagnosis
- Stage of disease
- Extent of axillary surgical manipulation
- Postoperative infection/seroma formation
- Adjuvant chemotherapy
- Adjuvant radiation therapy
- Trauma to chest wall after therapy
- Obesity
- Comorbid conditions: diabetes mellitus, hypertension

a primary risk factor for TE.³⁹⁵ Stage of disease at the time of diagnosis has also been associated with an increased risk of TE. The more aggressive the disease, the higher the chance of experiencing an episode of TE.^{390,391,396,397} Stage of disease dictates, in large part, further and more aggressive therapeutic interventions, including the more frequent use of invasive technologies and advanced chemotherapeutic regimens, which further increase the risk of TE.^{390,398-400} Chemotherapy increases TE risk through multiple pathways and mechanisms involving multifactorial issues, which are beyond the scope of this article. Several excellent reviews on the complex interactions of the association between chemotherapy and the increased risk of TE are available in the references provided.^{13,292,392} Again, it is important to mention that advanced and/or metastatic disease places patients at an increased risk of TE.⁴⁰⁰

Most patients with breast cancer (upwards of 70%) have ER+ status, meaning their tumors are being fueled by endogenous estrogen.^{99-103,401,402} Having an ER+ tumor is important for 2 reasons. First, ER+ tumors tend to be less aggressive, and second, such tumors can be treated with an array of AETs. Tamoxifen has long been considered the primary antiestrogenic drug of choice for ER+ breast cancers. A major side effect, recognized early after its implementation, has been the increased incidence of TE.¹⁰⁴⁻¹⁰⁷ The risk of TEs in patients receiving tamoxifen as adjuvant therapy is 1% to 2%^{105,403} and appears to be highest in the initial 2 years of treatment, although the risk remains throughout all years of therapy.^{390,404}

The recognition of the extremely effective role of AET in the treatment of most breast cancers has resulted in the so-called "third generation" of AETs, the AIs (letrozole, anastrozole, and exemestane).^{188-190,405} As previously stated, the effects of AIs on the circulatory system remain controversial.^{106-108,121-126} What seems to have been resolved is the incidence of AIs and TEs. Multiple studies have now documented the decreased incidence of TEs with the use of AIs in direct comparison to tamoxifen.^{127,406,407} Thus, it now appears

that AIs do not increase the risk of TE in patients with breast cancer. What remains controversial are the long-term effects of AIs on lipid levels, which may affect cardiovascular profiles, and subsequent risk factors, which may contribute to CVD.^{106-108,121-126} Clearly, for those women with a history of TE, AIs are the drug of choice for adjuvant AET in the postmenopausal patient with an ER+ breast cancer.

Additional risk factors for TE exist in patients with breast cancer. Many contemporary patients receive long-term intravenous therapies, which extend beyond the short-term chemotherapy regimen. These include a one-year cycle of trastuzumab and/or pertuzumab as well as bisphosphonates for bone metastasis and protection against fractures. For the comfort of the patients, indwelling catheters are often placed for administration of such medications as well as to provide easy vascular access to monitor whole blood cell counts. Indwelling catheters may lead to thrombotic complications, the incidence of which is poorly documented in the literature.^{384,400,408,409} Additional risk factors for TE are not unique to patients with breast cancer but are often identified along with their comorbidities. These include any history of cardiac disease (myocardial infarction, CHF) and a history of TE.^{395,410} Obesity and its impact on breast cancer is described in the section, Lifestyle Management and Breast Cancer. Relating to the development of TE, obesity is a well-recognized risk factor.^{395,411,412} Overweight and obesity are often associated with a sedentary lifestyle and general immobility (lack of exercise). It is a modifiable lifestyle risk factor in most patients. Exceptions include increased immobilization caused by hemiplegia after nonfatal cerebral vascular events and fractures of the lower extremities and hips.^{164,384,392,413}

The mechanism by which malignant tumors cause a hypercoagulable state is incompletely understood and is likely multifactorial in nature. Numerous abnormalities in blood composition have been identified, including increased levels of clotting factors, excessive tumor production of inflammatory

proteins (cytokines, tumor necrosis factor- α , interleukin-1 β), C-reactive protein, and tissue factor from vascular endothelial cells, which all interfere with the normal hemostatic mechanism.^{387-389,393,414,415}

Angiogenesis (the formation of new blood vessels) has been identified recently as a process that may also interfere with the coagulation cascade because both tissue factor and vascular endothelial growth factor are produced by tumorous cells that acquire their own vascular supply.^{13,388,416,417} In fact, detection of tissue factor in breast cancer vascular endothelium has been shown to be proportionally related to the initiation of new blood vessel formation.⁴¹⁸ Further linking angiogenesis and TE are the well-described role of platelet aggregation and the production of platelet-derived growth factor. As such, these also contribute to the risk of TE development.^{56,392,418} Angiogenesis may also result in the formation of blood vessel structures that are abnormal in their basic anatomic scaffolds and appearance and that display aberrant blood flow patterns.³⁸⁴ Such flow discrepancies may have a role in the development of TE.

A TE significantly decreases long-term survival rates in patients with cancer.^{384,400} Patients with a malignancy who experience a TE have a fourfold to eightfold higher risk of dying of TE than those who do not have a concurrent malignancy.⁴¹⁹⁻⁴²² Without doubt, patients with malignancies and an episode of TE have a poor prognosis. Furthermore, the risk of a recurrence of TE after an initial episode of TE is higher in patients who have a diagnosis of malignancy. The development of TE is well documented to lead to significantly decreased long-term survival in patients with breast cancer.^{405,423} and malignancies resulting in death often involve a thrombotic component.

Numerous abnormalities in blood composition have been identified, including increased levels of clotting factors, excessive tumor production of inflammatory proteins (cytokines, tumor necrosis factor- α , interleukin-1 β), C-reactive protein, and tissue factor from vascular endothelial cells, which all interfere with the normal hemostatic mechanism.

Surprisingly, as high as the incidence of TE is, nearly three-fourths of Americans surveyed were unaware of the condition and its long-term sequelae.^{413,424} Because TE is a lifetime risk factor after breast cancer,³⁹¹ it is incumbent on the survivorship care team to educate patients with breast cancer on the signs and symptoms of TE. Usually DVT is heralded by the sudden onset of pain, swelling, tenderness, and occasionally redness and/or warmth in an extremity. A PE, sometimes the sequela of untreated DVT, is heralded by the sudden onset of shortness of breath, chest pain exaggerated by deep breathing, a rapid or irregular pulse, lightheadedness, and occasionally hemoptysis. Education of patients regarding these symptoms can be lifesaving.^{425,426} (See Sidebar: Risk Factors for Thromboembolic Events.)

ADHERENCE AND COMPLIANCE

Many patients who are given prescriptions for medications fail to take them as directed or for the length of time recommended. Adherence and compliance are a concern in the management of malignancies because oral chemotherapeutic agents are increasingly being developed and used in long-term management.⁴²⁷ Of the nearly 400 antineoplastic agents in various stages of development, nearly one-fourth are planned as oral agents.⁴²⁸ Clearly, the increasing percentage of cancer patients who are prescribed or will be prescribed oral therapies will affect current oncologic treatment patterns. Breast cancer survivorship is on a steady rise,^{427,428} and this cancer is no longer thought of as an acute illness but rather a chronic condition. Therefore, long-term therapies are being increasingly used. Foremost of these interventions is the oral administration of drugs in the outpatient setting, allowing patients to medicate themselves with appropriate dosages and scheduling.

This major advance in cancer treatment comes with new concerns: adherence and compliance. Although adherence and compliance are ultimately related, they are distinct parameters of therapy. *Adherence* defines the taking of medication as prescribed, whereas *compliance* more specifically addresses taking the medication for the full term

Risk Factors for Thromboembolic Events

- Diagnosis of malignancy
- Age older than 40 years
- History of thromboembolic events
- Stage of disease at time of diagnosis
- Adjuvant chemotherapy
- Adjuvant antiestrogen therapy (long-term administration)
- Obesity
- Sedentary lifestyle

recommended. Compliance is also often referred to as “persistence.”^{429,430} Some have called for the dismissal of the term *compliance* because it connotes an onus and dependence on the patients for their ultimate outcomes.⁴³¹

Regardless of definitions and disparities, the ultimate measure of outcome is OS.⁴³² Although developments in oncology have resulted in major advances in survivorship, many are dependent on long-term administration protocols. As such, the issue of adherence and/or compliance to therapies recommended has become the latest oncologic challenge. This also provides increased impetus for survivorship programs to assume a major role in the care of these patients, that is, follow-up with adherence and compliance.

Adherence and compliance are important for women who are prescribed AET. AET has been definitively demonstrated for more than 30 years to decrease both recurrence and mortality in ER+ patients.^{15,97,98} Five years of AET, with either tamoxifen or AIs, results in a greater than 30% reduction in breast cancer recurrence and increased OS.^{97,98,433} Despite the strong documentation of the effectiveness of AET, it is both surprising and disappointing to note the incredibly high rates of noncompliance to a 5-year regimen, which range from 30% to 70%.⁴³⁴ Less than 80% compliance at 2.5 years has been associated with increased mortality.¹⁴ Nearly 25% of patients discontinue AET within the first year, and 50% become noncompliant by Year 4,^{433,435} despite multiple trials that have shown higher recurrence rates and decreased survival.^{14,436,437}

Another point of major concern is that women younger than age 45 years have a greater risk of recurrence owing to more aggressive, higher grade tumors, and yet this group is most likely to discontinue therapy.¹⁵ Multiple studies have noted this,^{435,438,439} yet the issue of age has not been adequately addressed. Patients who are premenopausal when their breast cancer is diagnosed have a higher recurrence rate and increased mortality than those diagnosed in the postmenopausal state.

The poor adherence and compliance to 5 years of AET presents a major challenge. Although this is a large enough issue, we now face new reports strongly supporting a 10-year regimen. Results from the Adjuvant Tamoxifen Longer Against Shorter (ATLAS) trial and the Adjuvant Tamoxifen Treatment Offers More (aTTom) trial have clearly demonstrated improved outcomes by doubling the 5-year recommendation for AET.^{198,440} The ATLAS trial concluded that recurrence and mortality were lowered in patients given an additional 5 years of tamoxifen. Ten-year recurrence rates decreased by 29% in 6846 patients. Similar findings were reported in aTTom, which followed 6934 women with early-stage breast cancer. Although AIs have been clearly demonstrated to decrease recurrence rates in postmenopausal women with breast cancer,¹⁸⁹ their indications for extended length of therapy are less clear and are currently undergoing further investigation. These reports demonstrate the increasing need for adherence and compliance for AET maintenance. Extensions of AET must also take into consideration the long-term side effects of these therapies. Risks of PE were noted in the ATLAS trial as well as the development of endometrial cancer; however, the risk of mortality was lower than the mortality due to breast cancer itself.^{441,442} Long-term side effects of the AIs have yet to be determined. Particular attention must focus on bone health and osteoporosis as well as the CVD risk associated with AIs.^{126,443} Clearly, poor adherence and compliance result in less effective disease outcomes and increased mortality.⁴⁴⁴

AET is one of the most important recent advances in cancer treatment. As

simple a treatment as it is, via oral administration, a large number of patients do not take advantage of this intervention. Numerous barriers to adherence and compliance have been identified. These barriers are multifactorial, complex, and often interrelated. Medication side effects are the primary reason for discontinuation of AET. Of patients receiving AET, 94% report mild to severe symptoms directly attributable to AET. These include hot flashes, bone and joint pain, muscle aches, mood swings, loss of libido, dyspareunia, and other menopause-related symptoms.⁴⁴⁵ Each year, more than 80,000 postmenopausal women begin the 5-year regimen with AIs in an effort to decrease recurrence.⁴⁴⁶ A major reason for the discontinuation of AIs is the development of incapacitating bone pain and arthralgias in a group that, because of age, has the comorbidity of arthritis.⁴⁴⁷ Strategies to encourage continuation of AIs include switching to different AIs and the promotion of exercise.^{448,449}

Additional reasons cited for noncompliance include a poor understanding by the patient of the importance of taking the medication to offset recurrence and mortality.⁴⁵⁰ This has been attributed to inadequate communication by health care practitioners regarding risk vs benefit of the regimens and, in general, poor clinician-patient relationships.⁴³² Patients who fail to understand the importance of their oral medications are likely not to take them as directed. Furthermore, as years of treatment progress and there are no overt symptoms of a malignancy or disease, patients may develop a sense of complacency, resulting in further noncompliance.⁴³¹ Finally, the cost of medications may play a factor in noncompliance.^{15,431,432} Those with poor health care coverage or high copayments may not be able to afford the costs of oral agents for an extended time. Although most intravenous medications are a covered benefit, the same is not so for oral therapies. Oral

parity legislation has been enacted by multiple states to guarantee payment for outpatient chemotherapy, putting it on par with infusion therapies. The federal government is considering such legislation but has failed to implement such a law. The American College of Surgeons Commission on Cancer's Advocacy Committee (of which the senior author [BB] is a member) has been active in attempting to push oral parity legislation in Washington, DC. The unequal copay for oral anticancer agents needs correction, as does the poor adherence and compliance in patients with breast cancer receiving AET.

Practices to improve the dismal adherence and compliance rates for AET need to be developed. Interventions should involve a multifaceted approach, beginning with the attending physician and then extending to pharmacists and navigators. Pharmacists, in particular, have the opportunity to expand their scope of practice by actively participating in

A CALL TO ACTION

We, as caregivers, are letting our patients die by not taking a strong, proactive role in promoting healthy eating and an active lifestyle, and encouraging emotional resilience. These principles are the cornerstone of the rapidly emerging subspecialty known as lifestyle medicine. Current medical practice is reactive: surgery or a prescription for every illness. This needs to change. A paradigm shift to lifestyle medicine must be implemented immediately.

Dramatic effects using lifestyle interventions have been demonstrated in patients with chronic conditions, which now include breast cancer. Several large studies have conclusively shown that diet and exercise modifications can significantly improve total health.¹⁻⁶ One prospective study of 23,000 participants evaluated adherence to 4 recommendations: no tobacco use, 30 minutes of exercise 5 times per week, maintaining a body mass index less than 30 kg/m², and eating a healthy diet (high consumption of fruits, vegetables, legumes, and whole grains, and low consumption of meat).⁵ People who adhered to these 4 recommendations had an overall 78% lower risk for development of a chronic condition during an approximately 8-year timeframe.⁵ Furthermore, in those adhering to the recommendations, there was a 93% reduced risk of diabetes mellitus, an 81% reduced risk of myocardial infarction, and a 36% reduction in the risk of cancer.⁵

Ample evidence exists to support the avocation of a diet based on the recommendations noted in Table 1.^{1-3,7-12} In addition, a whole-food, plant-based diet tends to promote a healthy body mass index, which is associated with, yet again, a lower risk of all

Table 1. Daily dietary recommendations	
Decrease or eliminate	Increase or consume heavily
Bad carbohydrates <ul style="list-style-type: none"> • Refined grains (white bread, crackers) • Processed foods (cakes, cookies, chips)^a • Added/refined sugar (soft drinks, cereals) 	Good carbohydrates <ul style="list-style-type: none"> • Fruits • Vegetables • Legumes • Beans/lentils • Whole grains (bread, cereal, pasta) • Natural soy products
Bad fats <ul style="list-style-type: none"> • Saturated fats • Trans fats 	Good fats <ul style="list-style-type: none"> • Omega-3 fatty acids • Flaxseed • Nuts
Salt	
Meat <ul style="list-style-type: none"> • Red meat, beef, poultry, pork • Processed meats^a 	
Dairy	
Alcohol	

^a Processed foods are stripped of nutrients and include unhealthy additives. It is important to remove these from the diet completely.

common cancers.¹³ Dietary principles cannot be fully addressed without consideration of caloric density. *Caloric density* refers to foods that may or may not provide high amounts of vitamins and nutrients, but contain higher levels of calories. High-nutrient foods have fewer calories per pound in contrast to low-nutrient

(Continued on next page.)

patient education regarding the importance of taking medications and appropriate scheduling. Navigators can play an important role as well. Regular telephone or texting conversations to check on a patient's adherence can not only evaluate the patient for compliance but also serve as a motivator for the patient. Although it would appear intuitive that education for patient and family members about the importance of consistent oral therapy would improve compliance, this has not been fully validated.⁴³² Reminder letters and telephone calls have demonstrated only a minor increase in adherence rates.⁴⁵¹ Other studies have noted no improvement in patients given additional education materials or increased support services.^{452,453} Going forward, technologic advances such as

the widespread use of electronic medical records, sophisticated prescription bottles with built-in reminder timers, and effective pharmacy tracking systems may lead to further improvements. Simplified dosing regimens, as well as seamless access to refills, may also help improve compliance. Clearly, many women are not taking their AET as prescribed, and this remains an issue of major concern. Prescribed medications are useless if the patient does not take them. (See Sidebar: Barriers to Adherence and Compliance.)

LIFESTYLE MANAGEMENT AND BREAST CANCER

In 2014, the American Institute for Cancer Research reported in their latest review of global research that diet,

Barriers to Adherence and Compliance
Medication side effects or intolerance
Lack of oral parity in health care coverage
Poor understanding of importance of therapy
Inadequate patient education
Complacency
Cost of medications

physical activity, and weight management play a major role in survival among patients with breast cancer.⁴⁵⁴ Research indicates that a lower BMI and eating a whole-food, plant-based diet (WFPBD), high in fiber and low in fats, improves survival in breast cancer. Maintaining health after a diagnosis

(Continued from previous page.)

foods (Figure 1). A healthy diet should remain in the green zone as much as possible and constitute the bulk of food intake.

Sadly, because profit motives play a large role in the business of health care, the delivery of care and the care of patients is often politicized. Most chronic conditions are influenced by lifestyle and account for more than 75% of health care costs.¹⁴ Since 2009,

more than 17% of the US gross national product has been spent on health care, amounting to more than \$2 trillion.¹⁵ Few, if any, of these dollars have been spent on identifying the true underlying etiologies of these chronic conditions. Lifestyle changes have taken a backseat to disease treatment. If we continue on the pathway of treating risk factors and developed disease, we will bankrupt the health care system in the near future.¹⁴ Costs for care will continue to escalate; lives will continue to be lost.

It is time for the medical community to intervene and to intervene aggressively. We are not providing the proper treatment when confronting conditions that can be prevented and may even be reversed with lifestyle change and education. Current and future physicians must be trained in lifestyle medicine. The neglect of both the root cause of disease and corrective interventions continues to further the development of chronic conditions and ultimately demise (Figure 2). Lifestyle management courses should be required annual training for all health care employees, optimally as we do annual training for corporate compliance. It is time to prevent disease in all aspects of our lives and the lives of the people we love. It is time to change our health destiny by changing our hearts and minds from an unhealthy lifestyle to a total health lifestyle. It is time to move from disease to health where we live, learn, work, pray, and play. It is time to eat healthy, be active, and resolve conflict.

The evidence is irrefutable and the message is clear. We are charged with providing patients with the information they need to live a long, healthy life, which can readily be accomplished through lifestyle education. We, as caregivers, owe them that. ♦

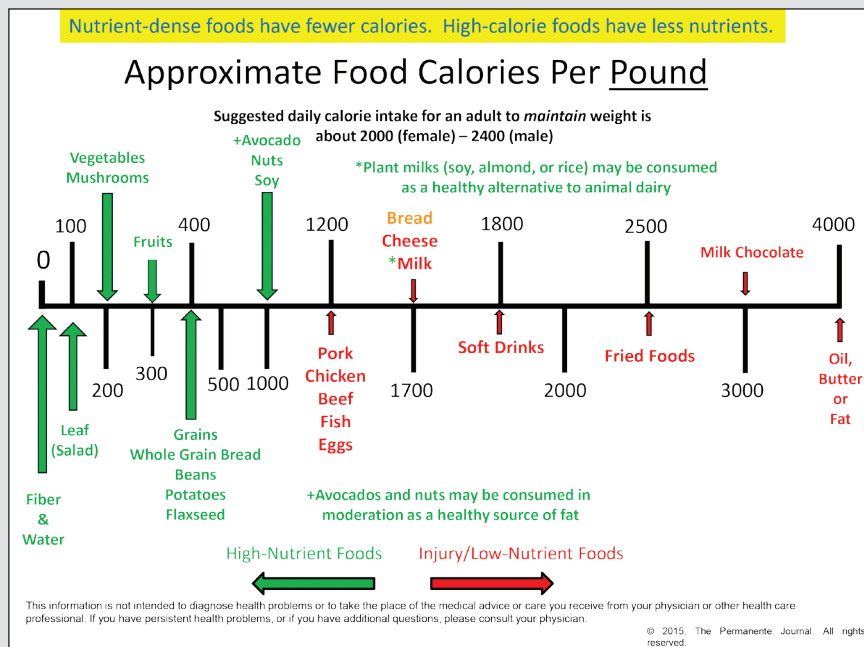


Figure 1. Approximate food calories per pound. Green indicates nutrient-rich foods that should be a major part of a healthy diet; red indicates foods that are low in nutrition and high in calories and should be eliminated completely or consumed in smaller amounts; yellow indicates foods that may be nutrient rich or calorie dense.

of breast cancer requires a lifestyle transformation that helps fight cancer and prevents the development of other diseases that may lower survival. Thus, all patients should consider developing a lifestyle that includes a focus on the vital signs of health called the Wellness Index (WI).⁴⁵⁵ (The WI is shown in the Sidebar: The Breast Cancer Wellness Index.)

The goal of the WI is to determine the current state of health and then use the index to identify areas of opportunity to achieve total health during and after treatment. Achieving total health includes a focus on healthy eating, active living, and emotional resilience (HEALER). (See Sidebar: Healthy Eating, Active Living, and Emotional Resilience Goals.) Surviving breast

cancer moves one into the HEALER zone, where patients maximize their abilities to prevent cancer recurrence while simultaneously optimizing their ability to treat and prevent chronic diseases such as obesity, DM, hypertension, hyperlipidemia, tobacco and/or alcohol abuse, and coronary artery disease. The WI appears in two parts. The first part is an objective measure of biometrics. This includes a report on BMI, blood pressure, blood glucose and hemoglobin A_{1c}, and any current history of tobacco use or alcohol abuse. Biometrics is an objective measure of current health status. The second part, HEALER, subjectively assesses what lifestyle changes the patient is making to improve survival.

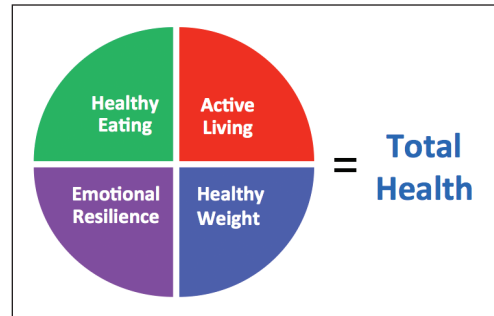


Figure 2. The essential components of total health.

Biometrics

Surviving breast cancer involves a total-health care strategy. Women with breast cancer who are otherwise healthy have a better chance of survival than do unhealthy women. Biometrics and

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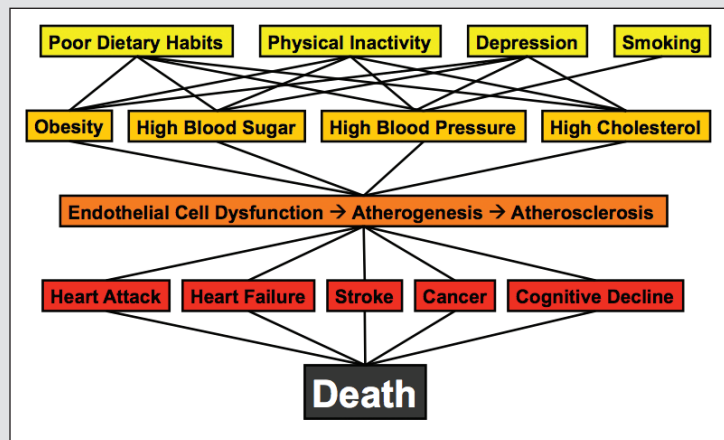


Figure 2. Relationship between lifestyle management and death. The measurement and treatment of high cholesterol, high blood pressure, and depression are a key strategy to prevent disease and death. Heart attacks, heart failure, strokes, cancer, and cognitive impairment are influenced by unhealthy behaviors and lifestyle. Unhealthy lifestyle choices subsequently lead to endothelial cell injury, endothelial cell dysfunction, and atherosclerosis. Atherosclerosis leads to organ damage and disease that can be prevented and treated through healthy lifestyle interventions. Therefore, basic lifestyle habits—healthy eating, active living, cessation of smoking, and developing emotional resilience—may be a future upstream strategy to help us prevent preventable disease, lower health care costs, and save lives.

HEALER are considered total-health balance factors (Figure 2) because they describe the relationship of our current wellness state and our future lifestyle approaches. Healthy eating, active living, and BMI describe an energy balance that is the relationship between energy consumed (healthy eating), energy expended (physical activity), and energy stored (fat). BMI is defined as weight in kilograms divided by height in meters squared. In general, underweight is a BMI below 20 kg/m², normal weight is a BMI of 21 to 25 kg/m², overweight is a BMI of 25 to 29.9 kg/m², and obesity refers to a BMI above 30 kg/m².⁴⁵⁶

A positive energy balance results when energy intake exceeds energy expended (BMI increased); negative energy balance results when energy intake is less than energy expended (BMI decreased). Obesity, inactivity, and unhealthy eating are linked to decreased overall and cancer-specific survival in patients with breast cancer. Studies have demonstrated that interventions to maximize healthy eating and active living can improve quality of life and survival in patients with breast cancer.

Obesity

Obesity is associated with an increased risk of postmenopausal breast cancer in population-based studies.⁴⁵⁷ Obesity at the time of diagnosis may limit the reduction in breast cancer mortality attainable through the detection and treatment of early-stage disease.⁴⁵⁸ In addition, obesity at diagnosis is associated with inferior outcomes in ER+ operable breast cancers.⁴⁵⁹ Obesity is a risk factor for breast cancer recurrence and mortality and an important outcome measure for overall health. Maintaining a healthy weight through programs such as HEALER is one of the most important interventions a patient with breast cancer can make to reduce the risk of breast cancer recurrence, mortality, and development of other chronic diseases.

A systematic literature review and meta-analysis of 82 follow-up studies on the relationship between BMI and breast cancer survival was reported in 2014.⁴⁵⁶ The report included 213,075 survivors of breast cancer and 41,477 deaths (23,182 deaths were attributed to breast cancer).

For each 5 kg/m² increment of BMI before breast cancer diagnosis, less than 12 months after diagnosis, and 12 or more months after diagnosis, increased risks were observed, respectively, of 17%, 11%, and 8% for overall mortality and 18%, 14%, and 29% for breast cancer-specific mortality. The authors concluded that obesity is associated with poorer OS and breast cancer survival regardless of when BMI is ascertained.⁴⁵⁶

Despite abundant data linking obesity to a poor prognosis in early-stage breast cancer, there have been relatively few studies evaluating the efficacy and potential benefits of weight loss interventions in survivors of breast cancer. In 2002, researchers performed a systematic review of 5687 literature citations to explore associations among survival and/or recurrence and obesity at diagnosis or weight gain after diagnosis of breast cancer. Results of this observational study showed that women with breast cancer who are overweight or gain weight after diagnosis are found to be at higher risk of breast cancer recurrence and death. The authors concluded that weight loss interventions should be considered in the total-health management of patients with breast cancer.⁴⁶⁰

Data from the Health, Eating, Activity, & Lifestyle Study suggest that increasing physical activity and decreasing body fat may be a reasonable intervention to decrease insulin and leptin levels, thereby potentially influencing breast cancer prognosis.⁴⁶¹ Preventing weight gain by regular aerobic exercise in these women may be important in preventing recurrent disease.⁴⁶² The strongest evidence that physical activity leading to weight loss and weight maintenance is associated with better outcomes of breast cancer comes from the Nurses' Health Study.⁴⁶³ Weight management with diet and lifestyle changes should be an integral part of the follow-up of women with breast cancer.

Besides BMI, other biometrics are important for health. Women treated for cancer are also at risk of chronic diseases later in life. Controlling blood pressure, cholesterol, and fasting blood glucose/hemoglobin A_{1c} and avoidance of tobacco and excessive alcohol consumption will help decrease the

The Breast Cancer Wellness Index

Biometrics goals:

- Body mass index 21 to 25 kg/m² (be as lean as possible without becoming underweight)
- Blood pressure < 140/90 mm Hg
- Total blood cholesterol < 200 mg/dL
- Fasting blood glucose < 99 mg/dL; hemoglobin A_{1c} < 7.0%
- Tobacco use: no smoking
- Alcohol abuse: no more than 1 drink/day for women

risk of death caused by chronic disease. For these reasons, women with a breast cancer diagnosis should also monitor and control the other biometrics listed to maintain good health. The HEALER interventions will help maintain a healthy BMI and reduce risks factors associated with the other chronic conditions mentioned.

Epidemiologic evidence shows that the risk of premature death due to coronary artery disease is increased in women who have uncontrolled hypertension, hyperlipidemia, and an elevated hemoglobin A_{1c} level, and in those who smoke tobacco. The strong association observed between mortality and major cardiovascular risk factors makes the undertaking of multifactorial prevention strategies important. Lifestyle strongly influences the development of high blood pressure, high cholesterol, and DM in women. Therefore, women with uncontrolled risk factors for CVD should be seen by their primary care physician and treatment should be initiated to reduce the risk of CVD.⁴⁶⁴ Because some studies suggest that all types of alcohol may increase the risk of cancer, women with breast cancer should also limit alcohol intake.⁴⁶⁵

Women who smoke should stop. The relationship between breast cancer risk and active cigarette smoking remains controversial because of unresolved issues of confounding (alcohol intake) and dose response. To investigate these issues further, researchers analyzed data from 73,388 women in the American Cancer Society's Cancer Prevention Study II Nutrition Cohort.⁴⁶⁶ Analyses were based on 3721 patients with invasive breast cancer identified during a median follow-up of 13.8 years. The

results showed that breast cancer rates were higher in current and former smokers than in never smokers. In addition, the data showed that the risk of invasive breast cancer was highest in women who began smoking at an earlier age.⁴⁶⁶

Because a large portion of the life of a patient with breast cancer may be spent in survivorship, lifestyle interventions could have time to make a difference and should be included in the overall treatment plan of all patients who receive a breast cancer diagnosis. Assessing biometrics will help us understand opportunities for improvement that can be made as described in the next intervention, which includes healthy eating, active living, and developing emotional resilience as it relates to survivorship.

Healthy Eating, Active Living, and Emotional Resilience

Each year breast cancer is diagnosed in more than 240,000 women in the US. A high proportion of these patients are both obese and sedentary.⁴⁶⁷ Therefore, lifestyle interventions may be needed to improve health outcomes and prognosis. Recent studies demonstrate that weight loss interventions in breast cancer result in significant weight loss at 6, 12, and 18 months after diagnosis.⁴⁶⁸ A single-variable analysis in 2007 looked at the association between healthy eating, active living, and obesity with breast cancer survival in a prospective study that included 1490 women who underwent treatment of breast cancer.³⁸¹ The results showed an association between reduced mortality and higher vegetable-fruit consumption, increased physical

activity, and a BMI that was neither underweight nor obese.

An analysis of 85 studies that included more than 164,000 women worldwide demonstrated that the survival of patients with breast cancer may be associated with healthy eating, active living, and a healthy weight.⁴⁶⁹ These findings support the recommendation that all survivors of breast cancer eat a WFPBD, maintain a healthy weight, and get regular exercise.⁴⁷⁰ Research suggests that women who have a healthy weight and are physically active have a better chance of surviving breast cancer.

Healthy Eating: On the basis of the aforementioned evidence, women with a breast cancer diagnosis should enroll in a course on lifestyle management. This course should include advice from a WFPBD-trained lifestyle specialist. Consultation should include a discussion on a variety of issues outlined in the Sidebar: The Breast Cancer Wellness Index, including a focus on total health⁴⁷¹ and a WFPBD with a substantial reduction, and possibly complete elimination, of all animal-based foods. The dietary focus should emphasize the importance of fruits, vegetables, whole grains, and legumes as the basis for a healthy diet.^{472,473} Also included in a WFPBD is the elimination of energy-dense foods such as sugary drinks and processed foods high in added sugar, salt, and fat. These types of foods contain more calories per ounce and increase the risk of weight gain. Low-energy-dense foods, like those found in a WFPBD, allow patients to actually eat more food but consume fewer calories. A WFPBD

results in decreased intake of foods that increase the risk of coronary artery disease⁴⁷⁴ and increased intake of foods that may prevent angiogenesis, or the growth of new blood vessels, to cancer cells.⁴⁷⁵

A large, multiple-database review (MEDLINE, Embase, and The Cochrane Library) to examine and to quantify the potential dose-response relation between fruit and vegetable consumption and the risk of all-cause, cardiovascular, and cancer mortality was reported in 2014.⁴⁷⁶ The researchers looked at prospective cohort studies that reported mortality risk estimates by levels of fruit and vegetable consumption. Sixteen prospective cohort studies were eligible in this meta-analysis, with follow-up periods ranging from 4.6 to 26 years in which there were 56,423 deaths (including 11,512 deaths caused by CVD and 16,817 due to cancer) among 833,234 participants. Higher consumption of fruits and vegetables was significantly associated with a lower risk of all-cause mortality. The researchers found that there was a threshold at 5 servings of fruits and vegetables per day, after which the risk of all-cause mortality was not further reduced. The results support current recommendations to increase consumption of fruits and vegetables to promote health and overall longevity. Other studies have shown that a diet rich in fruits and vegetables and low in fat lowers blood pressure and reduces the risk of stroke and type 2 DM.⁴⁷⁷⁻⁴⁸⁰ One meta-analysis of prospective cohort studies demonstrated that increased consumption of fruits and vegetables from fewer than 3 servings per day to more than 5 servings per day is related to a 17% reduction in CVD risk.⁴⁷⁹

In laboratory studies, many individual minerals, vitamins, and phytochemicals demonstrate anticancer effects, yet evidence suggests it is the synergy of compounds working together in the overall diet that offers the strongest cancer protection. No single food or food component can protect against cancer by itself, but strong evidence shows that a diet filled with a variety of plant foods (vegetables, fruits, whole grains, and beans) helps lower the risk of many cancers. A recent meta-analysis of prospective

Healthy Eating, Active Living, and Emotional Resilience Goals

Healthy eating

- Eat a whole-food, plant-based diet that includes at least 5 servings of fruits and vegetables per day, legumes, and whole grains
- Limit consumption of salty foods and foods processed with salt
- Avoid calorie-dense foods, which include sugary drinks
- Limit consumption of red meats (eg, beef, pork, and lamb) and avoid all processed meats
- Avoid supplements purported to protect against cancer

Active living

- Be physically active for at least 30 minutes 5 days per week
- Limit sedentary habits

Emotional resilience

- Evaluation for depression and treatment of depression, if needed

studies reported that a high intake of fruits and vegetables was associated with a reduction in the risk of breast cancer.⁴⁸¹ Further data show that there may be an inverse association between dietary fiber intake and breast cancer risk.⁴⁸² Finally, reducing dietary fat intake, with a modest influence on body weight, may improve relapse-free survival rates of patients with breast cancer receiving conventional cancer treatment.⁴⁸³

Fruits and vegetables contain large amounts of polyphenols. These nutrients have been shown in epidemiologic studies and meta-analyses to offer some protection against the development of cancers, CVD, and DM.^{484,485} Polyphenols may fight cancer by inhibiting carcinogenesis.⁴⁸⁶ For example, resveratrol, found in grapes, has been shown to inhibit the growth of a variety of cancer cells. Studies have shown that resveratrol has the potential to modulate all three stages of carcinogenesis (initiation, promotion, and progression), in both chemically and ultraviolet B-induced skin carcinogenesis in mice, as well as in various murine models of human cancers.⁴⁸⁷

A number of studies have demonstrated that consumption of polyphenols limits the incidence of coronary artery diseases.⁴⁸⁸ Atherosclerotic lesions may be present and silent for decades before becoming active and causing cardiovascular events.⁴⁸⁸ Polyphenols may be protective against CVDs by improving endothelial cell function, inhibiting oxidation of low-density lipoproteins, inhibiting platelet aggregation, and preventing macrophage activation and subsequent thrombosis.^{489,490}

Although the association between breast cancer risk and dietary factors has long been identified, the complex relationship between obesity and breast cancer is poorly understood. Obesity in women presenting with breast cancer may be a marker of unhealthy eating and inactivity. However, recent data suggest that even more important than obesity status, women who eat at least five servings of fruits and vegetables per day have a survival advantage over women who do not.⁴⁷⁶

Active Living: A prospective observational study to determine whether physical activity among women with

breast cancer decreases the risk of death caused by breast cancer compared with more sedentary women has demonstrated the relationship between breast cancer survival and physical activity.⁴⁹¹ The study was based on responses from 2987 female registered nurses in the Nurses' Health Study who were diagnosed with Stage I, II, or III breast cancer. Results showed that women who were inactive had a higher risk of death than women who were physically active. The greatest benefit occurred in women who performed the equivalent of walking 3 to 5 hours per week. The authors concluded that physical activity after a breast cancer diagnosis may reduce the risk of death; thus, women with breast cancer who follow physical activity recommendations may improve their survival.⁴⁶³

Additional studies have shown that women who increased physical activity after a breast cancer diagnosis reduce their overall risk of death by 45%, whereas women who decreased physical activity after diagnosis had a 4-fold greater risk of death.^{492,493} Other studies suggest that exercise after breast cancer diagnosis may improve overall quality of life⁴⁹⁴ and DFS.⁴⁹⁵ Healthy eating and active living interventions for women with breast cancer will require behavior change.⁴⁹⁶ Therefore, strategies for behavior change should be part of lifestyle management programs designed to improve survival in this population. Finally, physical activity has been shown to improve quality of life and balance of life after a breast cancer diagnosis.⁴⁹⁷

Emotional Resilience: Depression is a major public health problem and often is undiagnosed and untreated in women with breast cancer.⁴⁹⁸⁻⁵⁰⁰ Untreated, depression can cause amplification of physical symptoms, poor treatment adherence, and increased functional impairment.^{501,502} Physicians are now more aware of the importance of screening and treating depression while managing a particular chronic disease such as breast cancer.^{503,504} Important advances include routine depression screening at the time of breast cancer diagnosis,⁵⁰⁵ as well as early interventions and counseling specifically designed to treat

depression in patients with cancer.^{506,507} Cognitive therapy appears to be particularly helpful in treating depression in patients with breast cancer.⁵⁰⁸ In addition, cognitive therapy may be used to help women with breast cancer achieve the biometric outcomes and weight loss goals associated with improved survival.⁵⁰⁹ Tamoxifen is commonly used in the treatment of women with breast cancer. As previously mentioned, certain antidepressants, including paroxetine, fluoxetine, and bupropion, may interfere with the metabolism of tamoxifen and should be avoided. Venlafaxine, desvenlafaxine, and mirtazapine do not appear to affect the metabolism of tamoxifen and may be considered the safer choice for the treatment of depression in patients with breast cancer who are receiving tamoxifen.¹¹⁶

Summary of Lifestyle Recommendations

Diet, physical activity, and weight play a major role in survival among patients with breast cancer.⁴⁵⁴ Looking at improving long-term survival in breast cancer encompasses a total-health strategy that includes a focus on healthy eating, active living, healthy weight, and emotional resilience.⁴⁷¹

Five-year breast cancer survival rates have increased, and a total-health care plan will reduce a woman's risk of cancer recurrence, new cancer formation, and CVD.⁴⁵⁷

HEALER is a total-health approach to wellness that includes treating the mind, body, and spirit of a patient with breast cancer. Our long-term goal is to help patients with breast cancer understand the importance of energy balance.⁵¹⁰ By helping patients with breast cancer achieve a healthy weight and healthy biometrics, we can maximize their chances for long-term survival.

CONCLUSION

Breast cancer survivorship has become a major issue, particularly in the last decade, as early detection and more effective therapies have led to an ever-increasing number of those transitioning from *patient* to *survivor*. These successes present a new challenge to the medical community, which must now deal with the long-term complications of past and current treatment modalities.

Although extremely effective in curative intent, many of these therapies result in long-term side effects. Current therapies, which often include polychemotherapeutic agents, RT, and AET, can challenge the cardiovascular system. Cardiovascular disease remains the number one cause of mortality in women in the US, although breast cancer is the most feared.^{21,22} Bone strength is affected secondary to prolonged estrogen blockade. As younger patients are receiving a breast cancer diagnosis, the incidence of SPMs is becoming more frequently recognized. Thromboembolism risk increases after a cancer diagnosis, and some therapies increase its risk, resulting in death secondary to embolic events.

Advanced therapies call for extended administration of recently developed oral chemotherapy agents. The medical community has been challenged to enforce a five-year regimen for estrogen blockade, and recent findings suggest that doubling the therapy to ten years may decrease recurrence and increase survival. Adherence and compliance for just five years of oral therapy have been poor, and extending such recommendations to ten years appears to be the next challenge for oncologists.

Lifestyle changes, largely focused on reducing BMI, have been demonstrated to play a significant role in extending OS after breast cancer treatment. HEALER provides a tool for clinicians to evaluate the status of survivors of breast cancer. HEALER also summarizes the proactive role that patients may take to enhance their survival.

There is a well-recognized predicted shortage of oncologists by 2020.⁵¹¹ Therefore, the bulk of long-term care will become dependent on the primary care physician. This shift of care means that these physicians will need to be well educated in the long-term medical issues related to breast cancer treatment. Our intent is to share the present information with all those who will be charged with survivorship care in the coming years. ❖

Disclosure Statement

The author(s) have no conflicts of interest to disclose.

Acknowledgment

The authors wish to acknowledge the assistance of Helene Wolf in the preparation of this manuscript, the assistance of Stephen Beebe in creating the Virchow's triad figure, and the editorial assistance and support provided by Max L. McMillen, ELS.

Kathleen Loudon, ELS, of Loudon Health Communications provided editorial assistance.

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A Much Brighter Future

In 50 cases operated upon by what we call the complete method we have been able to trace only three local recurrences [6%] ... In 34 (73%) ... there has never been a local or regional recurrence, 24 are living and 10 are dead. In 43 of 46 cases (93%) there has been no true local recurrence These statistics are so remarkably good that we are encouraged to hope for a much brighter ... future for operations for cancer of the breast.

— Halsted WS. I. The results of operations for the cure of cancer of the breast performed at the Johns Hopkins Hospital from June 1889, to January 1894. *Ann Surg* 1894 Nov;20(5):497-555