

We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

6,900

Open access books available

185,000

International authors and editors

200M

Downloads

Our authors are among the

154

Countries delivered to

TOP 1%

most cited scientists

12.2%

Contributors from top 500 universities



WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index
in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com



Breast Cancer: Management and Survivorship

Bilal Rah, Shazia Ali, Mohd Ishaq Dar and Dil Afroze

Additional information is available at the end of the chapter

<http://dx.doi.org/10.5772/intechopen.82297>

Abstract

Breast cancer is one of the most common in female population worldwide and comprises about 22.9% of all cancers. Despite the prognosis and survival rates of breast cancer patients and survivors are comparatively better than other cancers, but their net outcome can be revealed by other factors like tumor grade, secondary effects of chemotherapy like insomnia and health behaviors, this distressing may decrease patient's life expectancy. In the backdrop of this, the need of the hour for the breast cancer survivors is to assess multifactorial nonpharmacological interventions and the management that includes physical exercise, psychological and complementary medicine, which could be cost effective, widely accessible and more promising for breast cancer patients and survivors apart from pharmacological interventions.

Keywords: breast cancer, management, survivorship, prognosis, chemotherapy

1. Introduction

Breast cancer is the most common noncutaneous form of cancer and principal cause of cancer related deaths among females worldwide [1, 2]. Globally with an estimation of more than 1.38 million new cases (around 23%), the breast cancer ranks second (10.9%) among all cancers [1, 3]. In 2017, approximately 252,710 women and 2470 men cases were diagnosed with breast cancer. Approximately around 40,610 women and 460 men were expected to die from breast cancer in 2017 [4]. The survival rates and prognosis for breast cancer are mostly dependent on the type of cancer, stages, treatment, and the ethnicity and location of the patient. High survival rates have been observed in breast cancer cases of western world as compared to developing countries where survival rates are less. More than 3.5 million women with a breast cancer are still alive in the United States and are either having cancer or undergoing

treatment [4, 5]. The incidence rates of breast cancer vary from 19.3 per 100,000 women in Africa to 89.7/100,000 women in Europe [6]. The highest incidence ($\geq 80/100,000$) in developed parts of the world (excluding Japan) and the lowest incidence ($\leq 40/100,000$) in most of the developing part the world [7, 9]. There are a number of factors responsible for causing breast cancer. Dietary factors, such as high-fat diet, alcohol intake, smoking, obesity, higher levels of cholesterol, and iodine deficiency have high risk of cancer occurrence. Due to the highest incidence of breast cancer in USA, Australia, New Zealand and UK, makes them top priority countries for breast cancer awareness [8, 9]. It is well documented that breast cancer is strongly related to age; only 5% of all breast cancers occur in women are less than 40 years of age and more than 80% of all female breast cancers arise among women aged 50 or more years [10]. In general the age of a woman is directly correlated with higher risk of developing breast cancer. The majority of breast cancers are not hereditary [11]. In about <5% of cases, breast-ovarian cancer syndrome occurs by inheritance including women having BRCA1 and BRCA2 mutation. The 90% of total genetics account to these mutations with a breast cancer risk of 60–80% affected cases. BRCA1 mutations predispose women to breast and ovarian cancers. BRCA1 in breast cancer has higher aneuploidy number than tumors, which do not have mutations in BRCA1. About 85% of breast cancers occur in women who have no family history of breast cancer [12].

From the recent past improved therapeutics have greatly increased the chance of survival. The median age at diagnosis of breast cancer is 61 years, whereas 43% are older than 65 years at diagnosis; therefore, cancer survivorship should be conduct in coordination with comorbidities related with aging [10, 12]. Around 61% will have confined disease, for which survival success are highest (5-year relative survival rates: 99% for localized-stage breast cancer vs. 25% for distant-stage breast cancer [13]. Long-term survival is common after breast cancer therapeutics, in the midst of a 5-year survival rate of approximately 90%; hence, addressing survivors' exclusive post-treatment requires decisive to providing quality health care [14].

The National Coalition for Cancer Survivorship and NIH defines individuals as survivors from the time of their diagnosis through the balance of their lives [15]. Owing to enhancement in cancer care, as well as earlier detection and improved therapeutics, the cancer survivors in the USA has been gradually mounting over the last 30 years (~12 million in 2007) and is likely to keep on to increase [16]. Cancer survivors also survive longer following cancer diagnosis (~5 million survive more than 10 years) and two-thirds are aged 65 years and above [17]. However, improved survival brings numerous challenges that varies from an high risk for cancer recurrence and the advanced development of second or other new primary cancers, to a host of chronic circumstances (e.g., osteoporosis, thromboembolic disease, and cognitive impairment, cardiovascular disease), and plethora of inconvenient physical and emotional symptoms [18]. Recent studies document that underlying pathophysiological changes in survivors' metabolic, immune, central nervous systems, and neuroendocrine including the sleep-wake cycle, contribute to these manifestations is emerging features in clinical practice is important for many reasons. First, breast cancer survivors make use of extra care during their

first 5 years after diagnosis than their age-matched controls, yet time and again report that their needs have not been met [19]. Second, poorly controlled features may lead to decreased adherence to adjuvant endocrine therapy [20]. Indeed, many reports document that only 50% adherence to completion of 5-year adjuvant endocrine therapeutic regimens, leading to poorer survival [21]. Third, although majority of the breast cancer survivors account comparable quality of life (QoL) with respect to age-matched controls and experience post-traumatic development after cancer, for a subset of survivors, physical and emotional features can upset their QoL [22].

Breast cancer survivors' success not only depends on their prognosis, but also on a host of other characteristics, including undesirable effects of cancer therapeutics, available to and accessibility of survivorship care, economic, social, medical care and cultural variables, QoL and health behaviors [23]. Considerable numbers of breast cancer survivors do not stick to approved health maintenance attract toward good health behaviors, such as avoid or low alcohol intake, cessation of smoking, maintaining good health and body weight and maintaining habit of physical activity, can drastically diminish survivors' risk of breast cancer recurrence [23]. However, benefits may be hampered by cancer-and therapeutics-associated morbidity, particularly, if the clinical features are causal to morbidity are not well regulated [24]. Therefore, of these improvement in cancer survivorship, many organizations for instance the US CDC have called for "public and medical health professionals to: (a) addressing the potential long-term and overdue effects of cancer and associated therapeutics on survivors' physical and psychosocial health, (b) offer survivors by means of harmonized care to deal with their several symptoms, and (c) foster the significance of healthy behaviors (e.g., cessation of smoking and physical exercise) to diminish the risk for new type or recurrent cancer and early detection to augment the chances of survival with new or recurrent cancer [2, 3]. QoL of enduring cancer survivors has been planned to be constituted of four principal domains of health: social, psychological, and spiritual physical. Given a number of inclusive overviews of the whole scenario of breast cancer survivorship QoL, we wanted to present an upgrade of the most recently published literature. Therefore, our focal point in this book chapter is to emphasize updated work in the field, of breast cancer survivorship and management, prioritizing from last few years of research, with intent of providing clinicians the realistic suggestion to enlighten their practices [25, 26].

2. Role of primary care providers (PCPs) in breast cancer survivors

Depending on number of survivor's, primary care physicians should have access to the evidence and be able to provide care and follow up. Breast cancer prevalence rates are alarming due to the growth and aging of the population [27]. Women are able to survive with breast cancer after treatment that follows up routinely to detect any recurrence and manage late and long-term outcomes of treatment [28]. Breast cancer survivors are

growing in number with increase in cost for their well-being, follow up and other medical care facilities [29]. The role of primary care providers is increasingly being taken up for follow-up care and same should be maintained as we have limited secondary care facilities [30]. There should be a systematic registry and data maintenance that follow up is being done and breast cancer survivors are effectively treated in primary care [3]. There is a short and long term side effect on health of breast cancer survivors including physical, emotional, sexual and social consequences such as pain, depression, fatigue, weakness [31]. The loss of confidence in leading a normal life is one of the increasing factors which is treated by primary care system and are involved more as compared to control patients [32]. It is important that PCPs should provide good and maximum care to cancer survivors and need of patient's should be satisfied. PCPs prefer to guide on disease recurrence and risk management involved in cancer treatment and survival of patient [32]. The evidence based recommendations are provided to PCPs for cancer survivors and are available for clinical practice guidelines [32]. Most of the recommendation is available on how recurrences occurs in a breast cancer patient and are concerned with diagnosis [3, 33]. Mammography has been recommended to breast cancer patients on follow-up in five guidelines and physical examination of breast in three of them [3, 33]. Ultrasound is recommended in one of the guideline while undergoing mammography [33]. All these guidelines advise genetic counseling for risk factors and patients are educated enough to know about signs and symptoms of recurrence or any other underlying cause and sign, how to resolve it and inform your medical advisor [3, 33].

3. Management strategies for breast cancer

Despite the prolonged survival and improved lifespan, there are a few manifestations that breast cancer survivors' physical utility might diminish more rapidly than that of their peers. These survivors might facilitate from an approach that is frequently applied in the aging population [34]. First, survivors encounters several, congregate and chronic features. Second, survivors display psychological, physical, and behavioral variations that may hamper their efficient status and lead to dependence and impairment, as revealed by higher fall risk, reduced physical exercise and distinguishes limitations in both basic and highly developed activities of daily living [3]. Thus, a subset of characteristic breast cancer survivors set to benefit from a management approach that is regularly applied in the elderly medicine situations, one that is: multidisciplinary (e.g., behavioral and physical factors); multifactorial (i.e., one intervention targets multiple symptoms simultaneously); augmented use of nonpharmacological treatment intervention options; and setting therapeutic goals (i.e., recognizing that complete resolution may not be achieved, but improvement is likely) [35] (**Table 1**). Various pharmacological and nonpharmacological interventions are used for the therapeutics of breast cancer as well as post therapeutics are shown in **Figure 1**. In a below section, we will demonstrate this concept by stressing basic measurement and management principles that apply evenly across numerous frequently

observed physical and emotional features in breast cancer survivors, such as adjustment disorder, cognitive dysfunction, or other vasomotor symptoms, psychosocial distress, and fatigue and insomnia.

Treatment type	Long-term shortcomings	Late shortcomings
Surgery	Loss of dermal sensation. Body shape change. Sexual disturbance. Impaired movement. Motion poor weakness	Lymphedema Neurological disorder
Radiation therapy to the breast including chest adjacent wall lymphatic nodes	Weakness Skin is sensitive to pain Impaired pain Pain Pneumonitis Poor dressing sense Breast atrophy Lymphedema Impaired pain or weakness of the upper limb	Skin color change Asymmetric breast Sexual disturbance Ataxia telangiectasia- Neural dysfunction lymphedema Breast volume not same in both affected and normal Difficulty in breath fibrosis Cardiovascular disease Second primary cancers arise of soft-tissue thorax, cervical, shoulder, lung cancer
Chemotherapy	Sexual disturbance fertility decreased Gain of body weight and mass, fat accumulation increases, neurological disorders, weight gain, oral, hair loss Weakness Ovarian dysfunction	Osteoporosis/osteopenia Cardiovascular risk factors at increased level increased risk of (cardiomyopathy, congestive heart failure) with chemotherapy Leukemic malignancies at increased risk with alkylating agents, anthracyclines, other topoisomerase II inhibitors
<i>Hormonal therapy</i>		
Tamoxifen	Hot flashes, menstrual cycle irregular, mood swings Increased triglycerides	Increased cardiovascular diseases, cervical cancer, blood clotting, bone malformation in premenopausal women
Aromatase inhibitors	Vaginal dryness, sexual dysfunction, muscle pain, neurological disorder, cholesterol increased	Osteoporosis, bone malformation, bone fracture
<i>Targeted therapy</i>		
Trastuzumab	Cardiac arrest, cardiac dysfunction	
Psychosocial long-term and late shortcomings	Mental depression, tension, headache, unpleasant behavior, social distress, physically un well, pain, end of life bad dreams, death fear, social difficulties, sexual problems, relations problems, financial shortcomings	

Table 1. Long term and short term shortcomings of breast cancer therapeutic interventions.

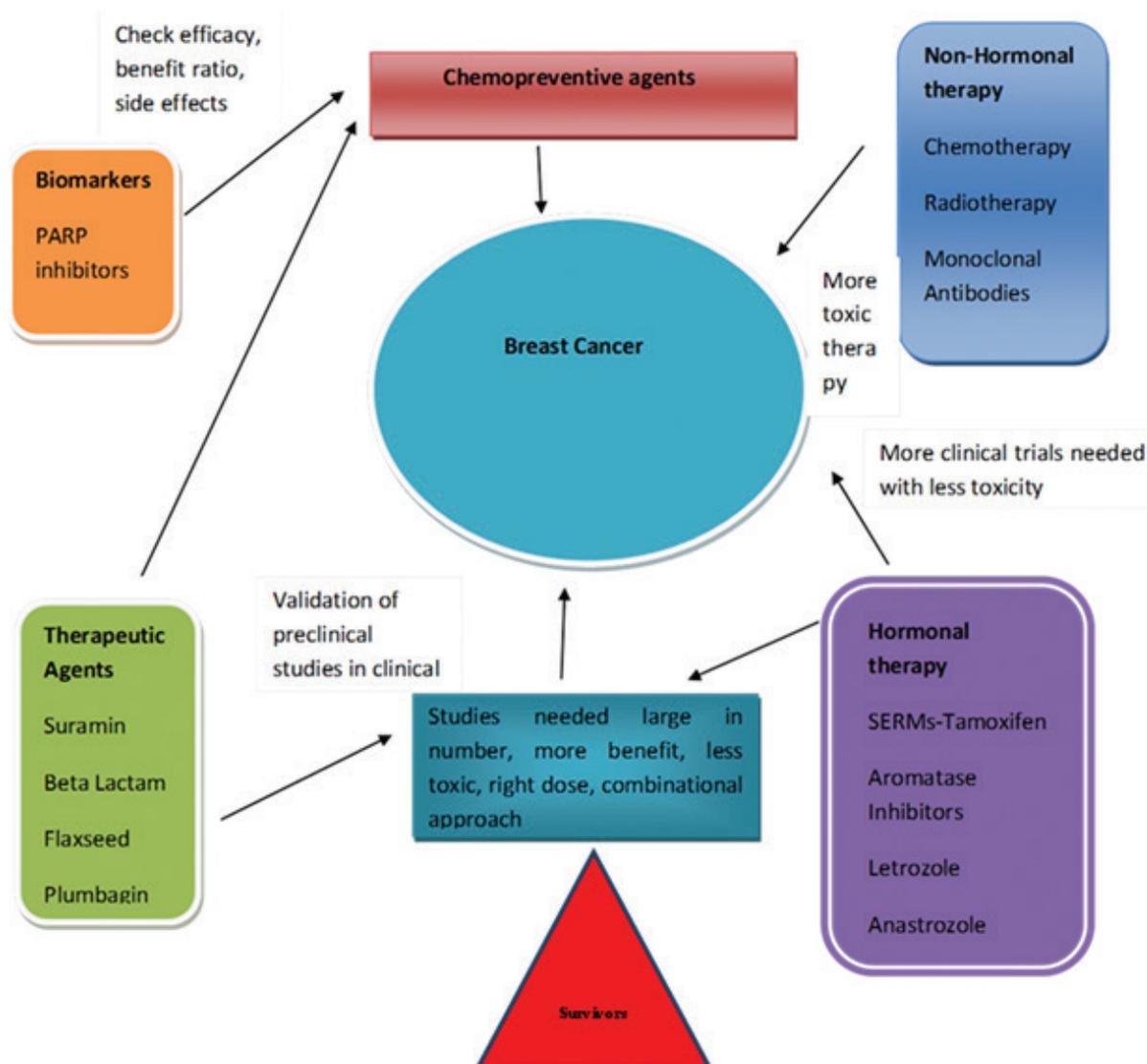


Figure 1. Different therapeutic targets in breast cancer treatment explain role of each new agent, its benefit to survivors.

4. Surgical treatment of breast cancer

Primary management of breast cancer is surgery. Most of the women diagnosed with early breast cancer underwent surgery. It may be wide local excision or mastectomy. Mastectomy is indicated when there is a presence of polycentric invasive cancer spots, inflammatory carcinoma, intraductal carcinomas, large primary tumors and patient preference [36]. Skin-sparing mastectomies followed by immediate reconstruction are now one of the most popular forms of reconstruction [36]. The status of the axillary lymph nodes is an important prognostic factor in early stages of breast cancer. During the operation, the lymph nodes in the axilla are also considered for removal. Axillary lymph node dissection remains the standard of care for patients with clinically palpable or positive histological confirmed lymph nodes [36]. Sentinel lymph node biopsy (SLNB) is an advanced technique and is very helpful in the management of axilla [37]. SLNB technique is based on the observations that tumor cells migrate from the primary cancer site to one of the nearby lymph nodes before moving to other distant lymph nodes [38]. In patients with a negative

lymph node biopsy, there is no requirement of axillary lymph node dissection (ALND) [39]. This in turn reduces the risk of lymphedema and other complications such as nerve injury and muscular problems, associated with the axillary lymph node dissection surgery [40].

5. Pharmacological interventions

5.1. Adjuvant chemotherapy for breast cancer management

Some patients with early breast cancer relapse with stage IV breast cancer even after surgery, reason may be the presence of micrometastatic disease present before the surgery [2]. For this reason in breast cancer patients adjuvant systemic therapy are used to halt the process of cancer recurrence [2]. It has been shown and proved by several trials that 6 months anthracycline therapy following surgical treatment of cancer results in about 40% reduction in mortality rates from breast cancer in women below age of 50 years and 20% reduction in between 56 and 69 age group [2, 41]. Further analysis showed that the addition of taxane based chemotherapy to anthracycline based regimen reduced mortality rate by further 15% [2, 41].

5.2. Adjuvant trastuzumab monoclonal antibody

At least 18–20% of breast cancer patients tumor cells overexpress HER-2 proteins [42]. In these patients trastuzumab (monoclonal antibody) is given as an adjuvant therapy [2, 42]. Full course of 52 treatments are given to woman with breast cancer [42]. Trastuzumab is well tolerated at therapeutic doses but may result in cardiac toxicity in patients initially given anthracycline regimen or in patients having baseline cardiac problem [43]. Left ventricular dysfunction and heart failure is reported in some patients by administration of trastuzumab [42]. All breast cancer patients should have scheduled cardiac monitoring before and during administration of therapy [2, 42].

5.3. Adjuvant endocrine therapy and breast cancer management

The majority of breast cancers are estrogen receptor (ER) positive [2, 42]. In those women with ER positive breast cancer, adjuvant endocrine therapy is routinely offered [2, 42]. The addition of endocrine therapy following either adjuvant chemotherapy or radiotherapy confers a further reduction in mortality rates [2, 42]. Tamoxifen is the mainstay of endocrine treatment in premenopausal woman [2, 42]. In post-menopausal woman aromatase inhibitors are the agents of choice [2, 42].

6. Non-pharmacological interventions

6.1. Psychophysiological symptoms

A thorough approach to evaluate the symptom management is to investigate in detail whether symptoms can be accredited to cancer and associated therapeutics and other procedures

including anesthesia or to additional contributing factors that are capable to be reversible [44]. These various factors might include anemia, vitamin deficiencies, organ dysfunction, metabolic, intracranial or endocrine abnormalities. The suitable investigations for various deficiencies can be assessed by methods which include imaging studies, blood work and/or neuropsychological testing. Additionally, the sensible and careful listening to survivors, education and multifactorial assistance from other disciplines (e.g., physical and behavioral medicine) associated to survivors may contribute to therapeutics significantly [45].

Management comprises of pharmacological therapeutic intervention (e.g., antidepressants or stimulants) in combination with a range of nonpharmacological interventions, for example psychological support, physical therapy, complementary medicine and nutritional counseling [46, 47]. The other choice to pharmacological therapeutic intervention for managing these side effects is psychological therapeutic interventions [48, 49]. Various behavioral interventions are linked with the diathesis stress model. This model explains how acute symptoms might develop into well-established or long lasting. However, many patients have predisposing factors to make them more susceptible to the event of insomnia. Such as, under the precipitating factor like stress, biologically older female patients sleep very less and make them prompt for low threshold for developing insomnia [50]. Owing to the cancer diagnosis and its therapeutics, undoubtedly accumulates more stress and advance in the development of acute insomnia. In an effort to mitigate their symptoms, patients may draw in behaviors that eventually perpetuate their insomnia. Cognitive Behavioral Therapy for Insomnia (CBT-I) proposed by Spielman provide the foundation of this model [25]. For instance a patient may initiate to spend more time in bed or take more naps throughout the day in the hopes that this would lessen her tiredness or fatigue, when in fact it may intensify his/her insomnia by disturbing the sleep wake and circadian cycles [51]. A behavioral therapeutic intervention aims these perpetuating behaviors to decrease sleeplessness problems and assist patients develop a more regular and standard sleep schedule. A behavioral therapist would support the patient to circumvent compensatory methods, such as sleeping during the course of day or lounging in bed, or would initiate stimulus control methods, such as reserving bed for sleep and sex only to decrease the number of relations with bed that are not conducive for sleep (watching TV, worrying, staying awake). Some of these therapies influence multiple symptoms, which is the need of hour [1]. For example, increasing physical exercises not only develops functional status, strength and survival, but also facilitates improved QoL, emotional, cognitive and physical symptoms and on the whole cancer-associated mortality [52]. A sensible and well knowledgeable discussion can assist to delineate an individualized management approach that accounts for aforementioned therapeutics, patient preferences and insurance coverage. Pursuing nonpharmacological treatment management can be formidable, as it frequently entails more dynamic involvement of the survivor (e.g., time and expense). For example, cancer survivors might be challenged in their pursuit to commence, continue or enhance the height of physical exercise by logistical difficulties, attained physical constraints or a fear of injury. In these occasions, a proficient cancer exercise trainer or a physical therapist is an important resource. Cancer survivors may undergo discouraged when misery with long lasting symptoms, and even though most breast cancer survivors manage well, some survivors become significantly laden by symptoms, and in this case, a brief course of psychological therapy focused on empowerment, increased self-care and coping skills may prove helpful [53, 54].

6.2. Physical activity

Physical exercise has been proved to have potential to counter numerous cancer-associated therapeutic side effects. Scientific world has documented that proper physical exercise strongly related with improved outcomes. Various reports and meta-analysis revealed that proper and well managed physical exercise have many health benefits and could ameliorate anxiety, improved quality of life such as blood circulation, physical fitness, depression, improving body shape, remove depression, good impact on quality of life, cognitive impairment and decreases inflammation as well as diminishes toxicities stemming from deleterious cancer therapeutics [55]. Breast cancer survivors should be recommended to revisit to normal daily activities as quickly as possible after diagnosis and to continue engaging in regular physical activity [3, 55]. The guidelines recommended for cancer patients and cancer survivors reported in American College of Sports Medicine documents that one should perform moderate intensity aerobic activity includes gardening, walking and ballroom dancing for 150 min or strenuous aerobic exercise which includes jogging, race walking or hiking uphill for 75 min in a week and 20–30 min of moderate-intensity anaerobic muscle strengthening activity for at least twice a week [2, 3, 55]. Additional details about the amount of time required for each entire training session is less clear. More importantly cancer patient and survivor should inquire about the advice of oncologist and/or primary care clinician prior to initiate a new activity. However working with professional trainers who are skilled to perform such type of exercise for cancer patients and survivors, and acquire individualized exercise directions that account for different types of cancer, disease progression, comorbidities, physical limitations, age, and other appropriate factors [3]. Additionally preliminary reports document the fact that proper regular exercise from well trained person could confer a survival benefit and is related with or increase overall quality of life significantly across the cancer patients and cancer survivors. It is worth to mention that up to 70% of breast cancer survivors do not meet these ACSM public health recommendations and have not taken any opinion to discuss activity with respective oncology care team [56]. About 32% of cancer survivors meet the recommendations for physical activity. Observational evidence advocates greater amounts of physical exercise may be needed, even though the data is insufficient to make it an approval at this time; aerobic exercise of 3 h or more per week may possibly be needed to improve breast cancer survival [57]. However, reports revealed that cancer survivors of entire ages would like their oncologist to start discussion about activity and formulate suitable referrals timely in the therapeutic course [57]. Given the benefits of physical activity during and after the cancer therapeutics, schedule discussions about exercise between the oncologist team and cancer patients and survivors in combination with referrals to a trainer exercise physiologist could considerably advance cancer therapy adherence, side effect burden, recovery, quality of life, as well as disease-free and overall survival in breast cancer patients and survivors [3, 57].

6.3. Nutrition

The diet characterized by high content of vegetables, fruits, whole grains, and legumes (vs a typical Western diet) has been related with a low risk (range, 15–43%) in all-cause mortality. Only 18–34% of breast cancer survivors report eating five or more fruit and vegetables daily [58]. Data from the two large RCTs of diet therapy in breast cancer survivors and patients

suggest that the dietary change adequately result in weight loss and may possibly be required to favorably impact breast cancer recurrence and prognosis [3]. As per ACS nutrition and physical activity guidelines, alcohol consumption should be limited to no more than one drink per day for women, as in the general population [3]. Data are not consistent but advocate that breast cancer survivors who consume more than three to four drinks per week are at high risk for breast cancer recurrence. Various studies revealed that the carcinogenic ingredient of alcohol consumption augments the risk of developing numerous types of cancers irrespective of the type (i.e., wine, beer, etc.), and recommended limits [3]. About 7% of breast cancer survivors revealed the excessive drinking of alcohol. Based on these facts, survivors should be counseled to: achieve a dietary pattern that is high in vegetables, fruits, whole grains, and legumes; limit alcohol intake to no more than one drink per day; and follow the ACS guidelines on nutrition and physical activity for cancer survivors with intend on successful weight management [3, 59].

6.4. Musculoskeletal symptoms

Despite other deleterious effects, breast cancer survivors may account intricacies with the ipsilateral upper end after surgery, as well as decreased range of motion, rotator cuff injury, adhesive capsulitis (“frozen shoulder” with firmness and pain in the shoulder joint), and axillary web syndrome (“cording” in the skin of the inner arm with ambience of pain and stiffness that emerge as a web or a corded rope) [3]. These malformations can lead to a decline capability to perform exercise of daily living and can effect employment [1, 3]. Other therapies like systemic therapy may also be associated with the progression of musculoskeletal symptoms in breast cancer survivors [1, 3]. Musculoskeletal symptoms are very common in the midst of breast cancer survivors, whether due to aromatase inhibitor therapy, menopause or chemotherapy. The incidence of musculoskeletal symptoms in breast cancer patients differs significantly: these include restricted shoulder range of motion (range, 1.5–50% of patients), musculoskeletal pain (range, 12–51% of patients), upper limb tiredness (range, 18–23% of patients), and immobility or numbness (range, 29–81% of patients). Above 50% of breast cancer survivors endure a musculoskeletal syndrome on initiation of an aromatase inhibitor, generally as either new or worsened diffuse arthralgias or myalgias, which most often develop within 2–3 months. Around 30% of breast cancer survivors entail to stop early adjuvant aromatase inhibitor therapy due to deleterious effects (~25% because of musculoskeletal symptoms) [1, 3, 60, 61]. In particular, up to 50% of postmenopausal women undergo therapeutics with aromatase inhibitor medications report arthralgias (joint pain) and myalgias (muscle pain) that are intense enough in 20% of women to lead to therapeutics discontinuation [1, 61]. These aromatase inhibitor-related musculoskeletal symptoms are frequently not receptive to nonsteroidal anti-inflammatory drugs or acetaminophen [1, 61]. Another option for treatment is alternative therapy that is replacement of one antiestrogen therapy with another. More than 40% of the patients who discontinue the drug may tolerate a distinct aromatase inhibitor or a discrete formulation of the aromatase inhibitor. The rest usually tolerate tamoxifen. Poor compliance/adherence to therapeutics has revealed the high risk of breast cancer recurrence, therefore serving breast cancer patients and survivors management and their symptoms and supporting drug compliance has utmost importance [1, 61]. Albeit a underlying relationship is possibly to be due to cancer therapeutics or

menopausal transition, new diagnostics, such as autoimmune or crystalline arthritis, should not be ignored. Treatment modalities are similar to those of osteoarthritis and may cover nonpharmacological methods such as physical therapy, local heat and/or acupuncture, in combination with pharmacological therapy, such as immediate short-term administration of NSAIDs, either systemically or topically [1, 3, 62, 63].

Besides arthralgia-type symptoms, breast cancer survivors may also progress fibrosis, rotator cuff pathology and distorted body habits, thereby leads to pain, limited range of motion and malfunctions in daily life, which are considered to be consequences of loco-regional treatment with surgery, with or without radiation therapy. Axillary web syndrome is the most extreme presentation of these symptoms. Physical and massage therapists are of great value as they are able to provide symptom relief by administering an intense regimen of massage, stretching and exercises that minimizes the need for surgical therapy. Physical therapy, including stretching and other exercises, has been reported to be efficient for managing postsurgical musculoskeletal symptoms. Recent reports from the hormones and physical exercise trial, a prospective cohort study, revealed that contribution in an intensive exercise regimen resulted in a 20% reduction in aromatase inhibitor-related pain. So far, only acupuncture and physical exercise have been revealed statistically significant improvement in aromatase inhibitor-related symptoms. Additionally psychological support may help patients cope with pain and can also be helpful [1, 3, 62, 63].

6.5. Infertility, sexual dysfunction and urinary complaints

Infertility as a consequence of chemotherapeutics is a potential enduring deleterious effects faced by younger breast cancer survivors (younger than age 45 years). More than half of breast cancer survivors, especially those on adjuvant endocrine therapy suffer from sexual dysfunction [1, 3, 64–68] and urinary symptoms [1, 69]. Sexual dysfunction may be caused due to vaginal atrophy, diminished libido or feeling of pain during intercourse [1, 3]. Changes in libido have multiple causes, including mood disorder, pain, fatigue, estrogen deprivation and issues in relationship [1, 3]. Sexual issues can be partially subsided by using non-hormonal approaches i.e. by using moisturizers, lubricants, vitamin E and low doses of topical estrogens [1, 3]. Pelvic floor muscles exercises, gynecologic, vaginal dilatational measures and psychological care are also very helpful [1, 3]. Treatment with aromatase inhibitors usually cause vaginal dryness, menopausal symptoms, and loss of sexual desire [1, 3]. Radiation therapy can often cause skin fibrosis, loss of sexual sensitivity of the skin, and, uncommonly, cardiac and respiratory damage, all of which negatively impacts on sexual desire and response [1, 3, 70]. It is important to counsel patients concerning possible sexual dysfunction remedies, including treatments for vaginal dryness [1, 3]. Nonhormonal, water-based lubricants and moisturizers remain the primary treatment [1, 3, 71]. Silicone based products or glycerin-based products also show very good results [3]. Hormonal therapies, such as a low-dose estrogen vaginal tablets or an estradiol vaginal ring, may be recommended for vaginal dryness because of urogenital atrophy, although better results are shown approximately after 6–12 week treatment [1, 3, 71, 72]. Urinary issues include overactive bladder with urgency with and without incontinence [1, 3]. Urinary complications can usually be reduced by pelvic floor muscle exercises, topical estrogen and, in some cases, by consulting a urogynecologist

[1, 3]. It is recommended that primary care clinicians should refer survivors of child bearing age who experience infertility to a specialist reproductive endocrinologist [1]. Infertility as a result of breast cancer treatment is a potential long-term side effect faced by younger breast cancer survivors. Infertility can have a profound impact on a survivor's physical and social character [1, 3]. Chemotherapy can be gonadotoxic, leading to reduced fertility or early menopause secondary to premature ovarian failure [1, 3, 73]. Many of the most frequently used chemotherapy agents in the treatment of breast cancer (e.g., alkylating agents and taxanes) are also those that most often lead to premature ovarian failure [1, 3, 74]. The incidence of chemotherapy-related amenorrhea has shown to be increased with age due the reason that the female ovarian reserve is nonrenewable and usually diminishes steadily with age [1, 3]. Primary care clinicians should involve the medical oncologist in any discussion related to the time for pregnancy after breast cancer treatment completion [1, 3]. Premenopausal women who desire pregnancy and are having difficulty conceiving for 6 months or more should be referred to a fertility specialist [1, 3]. Timely referral is crucial because of the rapid loss of ovarian reserve in these women [1, 3].

6.6. Management of bone health

It is estimated that osteoporosis affects one in every three postmenopausal women, with a 40% lifetime risk of fracture and approximately 21% risk of 1-year mortality after hip fracture [3, 75]. Breast cancer survivors are at very high risk of bone loss due to chemotoxic effects on the bones, due to treatment induced hypogonadism, due to supportive steroid therapies and due to vitamin D deficiency [3, 69]. Simple measures, such as weight-bearing exercises, avoiding of consumption of nicotine/alcohol and an adequate intake of calcium and vitamin D (600 mg/400 IU twice daily), are very essential for fracture risk reduction [1]. Breast cancer survivors should be monitored by dual-energy X-ray absorptiometry scans every 2 years [3]. Postmenopausal women treated with aromatase inhibitors are at increased risk of osteoporosis and should have periodic dual-energy X-ray absorptiometry scans [3]. All postmenopausal women or premenopausal women which are under GnRH agonist induced ovarian suppression therapy are at higher risk for developing osteoporosis and should be screened for postmenopausal osteoporosis diagnosis and treatment [1, 3]. In addition to lifestyle and nutritional interventions, pharmacologic options should be considered in patients, which are at high risk for bone loss [1, 3]. Bisphosphonates or denosumab can prevent bone loss and are good and established treatment options for osteoporosis [1, 3, 76, 77]. However, these drugs do have side effects and risks, so that the risk versus benefit must be considered in a careful manner [3]. Estrogen receptor modulators raloxifene and tamoxifen could also be used because of their antiresorptive nature.

6.7. Obesity concerns after treatment

About 62% of breast cancer survivors are overweight, of which 30% are classified as obese [2, 3]. Various research studies have presented obesity as a risk factor for postoperative complications, risk of recurrence, development of diabetes, and other issues [78]. Conversely, weight

loss subsides symptoms and improves QoL. Weight gain during breast cancer treatment is a serious problem [78]. Breast cancer survivors should avoid inactivity and return as soon as possible to normal activities after surgery and therapy [79]. American Society of Clinical Oncology (ASCO) has issued a statement that guides oncologists to counsel their patients about the benefits a healthy weight [80]. Primary care clinicians should also counsel cancer survivors to achieve or maintain a healthy weight as well as counsel survivors, to limit consumption of high calorie foods, beverages, to increase physical activity and maintain healthy weight [1, 3]. Various research studies have shown that heavier survivors are more likely to die of cancer due to recurrence [3, 81]. Various suggestions and diet charts for getting back to healthy weight in breast cancer survivors have been recommended. E.g. eating at least 2 cups of vegetables and fruits, more usage of whole grain foods like brown rice, less intake of saturated fats, preference of chicken and fish over red meat and moderate aerobic exercise of 150 min per week has shown to reduce and subside the complications associated with breast cancer treatment [81].

6.8. Cardiovascular issues in breast cancer survivors

Breast cancer survivors are at increased risk of cardiovascular disease and the collective incidence rate is 33% [82] Breast cancer patients after treatment experience cardiotoxicity and it may also lead to cardiac issues like cardiomyopathy, thrombosis, pericardial disease and arrhythmias [82]. It is important to control and assess cardiovascular risk factors including weight, physical fitness, lipid profile and glucose tolerance [83]. A dietitian, psychologist and personal trainer may help facilitate these efforts [3]. It is recommended that primary care clinicians should monitor lipid levels, provide cardiovascular monitoring and should also educate breast cancer survivors on healthy lifestyle modifications, potential cardiac risk factors [3]. Radiation, chemotherapy, and endocrine therapy with aromatase inhibitors have been associated with an increased risk of cardiovascular disease in patients with breast cancer [84]. The risk of heart disease increases in postmenopausal women, as endogenous estrogens in younger women contribute to the low prevalence of cardiovascular disease in that population [3]. Various studies have shown that breast cancer patients who experience treatment-related early menopause are at higher risk for development of heart disease [3]. The chemotherapeutic agents epirubicin and doxorubicin are associated with an increased risk of cardiomyopathy [85]. Similarly, trastuzumab is associated with an increased risk of cardiac dysfunction, most notably when taken together with anthracycline [2, 3, 85]. Aromatase inhibitors are known to raise cholesterol levels and the increase the risk of diabetes in breast cancer patients after or during treatment [3]. Excessive weight gain may lead to hypertension and insulin resistance, which further elevate the risk of cardiovascular disease [3]. Primary care clinicians and physicians should monitor lipid levels as well as monitor cardiovascular changes in cancer patients after treatment [3]. It is very essential to educate breast cancer survivors about daily lifestyle modifications, like smoking cessation, diet, and exercise that may be helpful in reducing severity and risks of cardiotoxicity [3]. Patients should be advised to be aware of the potential cardiotoxicity risk and also advised to report symptoms such as shortness of breath or fatigue to their health care provider [3].

6.9. Lymphedema associated with breast cancer treatment

About 40% women breast survivors face a very higher risk of developing lymphedema [1, 3, 86]. Breast cancer related lymphedema results from obstruction of the lymphatic system due to removal of lymph nodes and tissue damages caused by radiotherapy [87]. Survivors personal habits like obesity and overweight can increase the chances of lymphedema [88]. Lymphedema has associated psychosocial problems that hamper day to day lives of breast cancer survivors [89]. Infections can trigger and worsen and the symptoms of lymphedema, so it is important to have good personal hygiene in order to reduce the risk of infection [3]. All patients in which lymphedema has developed should be referred to a physical or occupational therapist or to lymphedema specialists [3]. Management of lymphedema remains a major challenge for patients and health care professionals [3]. Routine check-ups for lymphedema management, physical therapy, use of bandages, special lotions and frequent infections creates a huge financial burden not only to breast cancer survivors but also to the health care system [86]. Breast cancer-related lymphedema can occur in shoulders, breast, and thoracic area [86]. Treatments include pharmacological therapy and adjuvant therapies [3, 86]. Drugs included in the pharmacological management of lymphedema are benzopyrones, flavonoids, diuretics, hyaluronidase and selenium [86]. Surgical treatment for lymphedema in breast cancer survivors included lympholymphatic anastomoses, debulking and liposuction [3, 86]. Chronic lymphedema in breast cancer survivors sometimes lead to formation of excess subcutaneous adipose tissue which can be removed by liposuction [86]. Liposuction increases the blood flow in skin capillaries without damaging already compromised lymph transport capacity in breast cancer survivors with lymphedema [1, 3, 86].

7. Strategies to improve breast cancer survivorship symptom care

7.1. Survivorship care plan

There has undoubtedly been a call from all over the globe to stress on the importance of largely on cancer survivorship and care. In recent past, first cancer survivorship symposium was held by ASCO, and highlights the crucial issues faced by cancer survivors and patients with numerous cancers following treatment. Survivorship care strategies are recommended as crucial tool to assist communication and distribution of responsibility during the course of transition from active therapeutics to survivorship care. This care plan directs recommendations for the type and timing of follow-up imaging, laboratory tests, and other office visits. In addition cancer survival plan should incorporate necessary information regarding the deleterious effects of chemotherapy and what to watch for specifically based on the type of cancer and treatment received. Ideally, the oncology team should also work with the patient to develop an individualized cancer survivorship care plan for breast cancer survivors. A brief outline of a patient's diagnosis and treatment received should be presented by the oncologist team when a patient with breast cancer transitions care to other providers; a treatment outline should explain the type and stage/side of the cancer, type of surgery, the name of the chemotherapy/hormones/biologics and collective doses of chemotherapy, and the types and collective doses of radiation therapy, together with the fields and extent of the radiation. However, the field of oncology in context with cancer survivorship and care plan is mostly struggling with how to excellently meet this recommendation and in categorize the

specific benefits of such care plans. Various tools and strategies to assist the creation and distribution of these care plans are being actively considered for all tumor sites, including breast cancer. Currently, challenges in workflow and tools make this difficult, but the field is working toward a sustainable solution. Patients can start the building of a cancer survivorship care plan course on the ASCO website (cancer.net/survivorship/follow-care-after-cancer-treatment/asco-cancer-treatment-and-survivorship-care-plans; at journeyforward.org/or livestrongcareplan.org/).

8. Conclusion and future perspective

Despite the increasing number and longevity of breast cancer survivors the symptomology associated to therapeutics can be burdensome, multifaceted and long lasting and usually undertreated. Recent data suggest that management symptomology of these survivors could improvement of QoL, while evidence about its ability to reduce healthcare utilization is scarce. Cancer survivorship programmes help breast cancer survivors organize and remember their appointments. Communication and cooperation among providers and survivors are critical in the management and survivorship of breast cancer patients after treatment. Oncology teams all are working to develop a cancer survivorship care plan for breast cancer survivors. This care plan should guide survivors about the future laboratory tests, cardiovascular diseases, musculoskeletal issues, psychosocial issues, and other issues from which they usually suffer after treatment. The care plan should include information on the risk for late effects of treatment. To summarize, cancer survivorship care is need of a hour to allow better care for a larger number of breast cancer survivors in a financially sustainable manner.

Acknowledgements

We thank Director Dr. O.J. Shah and H.O.D Dr. Z.A. Shah for encouraging us to complete this work.

Conflict of interest

The authors declare no conflicts of interest.

Author details

Bilal Rah[†], Shazia Ali[†], Mohd Ishaq Dar[†] and Dil Afroze*

*Address all correspondence to: afrozedil@gmail.com

Department of Immunology and Molecular Medicine, Sher-i-Kashmir Institute of Medical Sciences, Srinagar, J&K, India

[†] These authors contributed equally.

References

- [1] Van Londen G, Beckjord EB, Dew MA, Cuijpers P, Tadic S, Brufsky A. Breast cancer survivorship symptom management: Current perspective and future development. *Breast Cancer Management*. 2013;**2**(1):71-81
- [2] Ring A, Parton M, editors. *Breast Cancer Survivorship: Consequences of Early Breast Cancer and Its Treatment*. Springer; 2016
- [3] Runowicz CD, Leach CR, Henry NL, Henry KS, Mackey HT, Cowens-Alvarado RL, et al. American cancer society/American society of clinical oncology breast cancer survivorship care guideline. *CA: A Cancer Journal for Clinicians*. 2016;**66**(1):43-73
- [4] Coleman C. Early detection and screening for breast cancer. In: *Seminars in Oncology Nursing*. Vol 33. WB Saunders, Elsevier; 2017. pp. 141-155
- [5] Siegel R et al. Cancer treatment and survivorship statistics. *CA: A Cancer Journal for Clinicians*. 2012;**62**(4):220-241
- [6] Chalkiadaki C, Martin A. Exploring the usefulness of social media and patient forums in identifying indirect costs of a disease. *Value in Health*. 2014;**17**(7):A628
- [7] Boffetta P, Boccia S, La Vecchia C. Distribution, causes and prevention of individual neoplasms. In: *A Quick Guide to Cancer Epidemiology*. Cham: Springer; 2014. pp. 15-75
- [8] Torre LA et al. Global cancer statistics. *CA: A Cancer Journal for Clinicians*. 2012;**65**(2):87-108
- [9] Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, et al. Cancer incidence and mortality worldwide: Sources, methods and major patterns in GLOBOCAN 2012. *International Journal of Cancer*. 2015;**136**(5):E359-E386
- [10] Saslow D et al. American Cancer Society guidelines for breast screening with MRI as an adjunct to mammography. *CA: A Cancer Journal for Clinicians*. 2007;**57**(2):75-89
- [11] Petrucelli N, Daly MB, Pal T. *BRCA1-and BRCA2-Associated Hereditary Breast and Ovarian Cancer*; 2016
- [12] Haber G, Ahmed NU, Pekovic V. Family history of cancer and its association with breast cancer risk perception and repeat mammography. *American Journal of Public Health*. 2012;**102**(12):2322-2329
- [13] Torre LA, Goding Sauer AM, Chen MS Jr, Kagawa-Singer M, Jemal A, Siegel RL. Cancer statistics for Asian Americans, Native Hawaiians, and Pacific Islanders, 2016: Converging incidence in males and females. *CA: A Cancer Journal for Clinicians*. 2016;**66**(3):182-202
- [14] Loon CS. *The Development of a Work-directed Intervention on Return to Work for People Living with Colorectal Cancer*; 2016
- [15] Cappiello M et al. Breast cancer survivors: Information and support after treatment. *Clinical Nursing Research*. 2007;**16**(4):278-293

- [16] Smith RA et al. American Cancer Society guidelines for breast cancer screening: Update 2003. *CA: A Cancer Journal for Clinicians*. 2003;**53**(3):141-169
- [17] Parkin DM. Global cancer statistics in the year 2000. *The Lancet Oncology*. 2001;**2**(9):533-543
- [18] Bodai BI, Tusso P. Breast cancer survivorship: A comprehensive review of long-term medical issues and lifestyle recommendations. *The Permanente Journal*. 2015;**19**(2):48
- [19] Maly RC, Liu Y, Liang L-J, Ganz PA. Quality of life over 5 years after a breast cancer diagnosis among low-income women: Effects of race/ethnicity and patient-physician communication. *Cancer*. 2015;**121**(6):916-926
- [20] Kimmick G et al. Adjuvant hormonal therapy use among insured, low-income women with breast cancer. *Journal of Clinical Oncology*. 2009;**27**(21):3445
- [21] Ruddy KJ, Partridge AH. Adherence with Adjuvant Hormonal Therapy for Breast Cancer. Oxford University Press. 2009:401-402
- [22] Paraskevi T. Quality of life outcomes in patients with breast cancer. *Oncology Reviews*. 2012;**6**(1)
- [23] Ganz PA et al. Breast cancer survivors: Psychosocial concerns and quality of life. *Breast Cancer Research and Treatment*. 1996;**38**(2):183-199
- [24] Wang XS. Pathophysiology of cancer-related fatigue. *Clinical Journal of Oncology Nursing*. 2008;**12**(5 Suppl):11
- [25] Shin W-K, Song S, Jung S-Y, Lee E, Kim Z, Moon H-G, Noh D-Y, Lee JE. The association between physical activity and health-related quality of life among breast cancer survivors. *Health and Quality of Life Outcomes*. 2017;**15**(1):132
- [26] Paskett ED et al. Breast cancer survivors' health-related quality of life. *Cancer*. 2008;**113**(11):3222-3230
- [27] Nekhlyudov L, O'Malley DM, Hudson SV. Integrating primary care providers in the care of cancer survivors: Gaps in evidence and future opportunities. *The Lancet Oncology*. 2017;**18**(1):e30-e38
- [28] Rojas MP et al. Follow-up strategies for women treated for early breast cancer. *Cochrane Database of Systematic Reviews*. 2005;**1**(1):CD001768
- [29] Spronk I, Korevaar JC, Schellevis FG, Albrecht T, Burgers JS. Evidence-based recommendations on care for breast cancer survivors for primary care providers: A review of evidence-based breast cancer guidelines. *BMJ Open*. 2017;**7**(12):e015118
- [30] Vahdat S, Hamzehgardeshi L, Hessem S, Hamzehgardeshi Z. Patient involvement in health care decision making: A review. *Iranian Red Crescent Medical Journal*. 2014;**16**(1)
- [31] Stein KD, Syrjala KL, Andrykowski MA. Physical and psychological long-term and late effects of cancer. *Cancer*. 2008;**112**(S11):2577-2592

- [32] Tol A, Alhani F, Shojaezadeh D, Sharifirad G, Moazam N. An empowering approach to promote the quality of life and self-management among type 2 diabetic patients. *Journal of Education and Health Promotion*. 2015;**4**
- [33] Hiramaneek N. Breast cancer recurrence: Follow up after treatment for primary breast cancer. *Postgraduate Medical Journal*. 2004;**80**(941):172-176
- [34] Rowland JH, Bellizzi KM. Cancer survivorship issues: Life after treatment and implications for an aging population. *Journal of Clinical Oncology*. 2014;**32**(24):2662
- [35] Leclerc A-F, Jerusalem G, Devos M, Crielaard J-M, Maquet D. Multidisciplinary management of breast cancer. *Archives of Public Health*. 2016;**74**(1):50
- [36] Benson JR et al. Early breast cancer. *The Lancet*. 2009;**373**(9673):1463-1479
- [37] Apple SK. Sentinel lymph node in breast cancer: Review article from a pathologist's point of view. *Journal of Pathology and Translational Medicine*. 2016;**50**(2):83
- [38] Langer I et al. Morbidity of sentinel lymph node biopsy (SLN) alone versus SLN and completion axillary lymph node dissection after breast cancer surgery: A prospective Swiss multicenter study on 659 patients. *Annals of Surgery*. 2007;**245**(3):452
- [39] Guenther JM et al. Axillary dissection is not required for all patients with breast cancer and positive sentinel nodes. *Archives of Surgery*. 2003;**138**(1):52-56
- [40] Kwan W et al. Chronic arm morbidity after curative breast cancer treatment: Prevalence and impact on quality of life. *Journal of Clinical Oncology*. 2002;**20**(20):4242-4248
- [41] Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: An overview of the randomised trials. *The Lancet*. 2005;**365**(9472):1687-1717
- [42] Urquhart L. *A Nurse's Guide to Caring for Cancer Survivors: Breast Cancer*. Jones & Bartlett Learning; 2010
- [43] Wood WC et al. Malignant tumors of the breast. In: DeVita V, Hellman S, Rosenberg S, editors. *Cancer: Principles and Practice of Oncology*. 7th ed. Philadelphia: Lippincott Williams & Wilkins; 2005. pp. 1422-1423
- [44] Ganz PA et al. Quality of life at the end of primary treatment of breast cancer: First results from the moving beyond cancer randomized trial. *Journal of the National Cancer Institute*. 2004;**96**(5):376-387
- [45] Cherny NI. The management of cancer pain. *CA: A Cancer Journal for Clinicians*. 2000;**50**(2):70-116
- [46] Baqutayan SMS. The effect of anxiety on breast cancer patients. *Indian Journal of Psychological Medicine*. 2012;**34**(2):119
- [47] İzci F, İlğün AS, Fındıklı E, Özmen V. Psychiatric symptoms and psychosocial problems in patients with breast cancer. *The Journal of Breast Health*. 2016;**12**(3):94
- [48] Zainal NZ, Nik-Jaafar NR, Baharudin A, Sabki ZA, Ng CG. Prevalence of depression in breast cancer survivors: A systematic review of observational studies. *Asian Pacific Journal of Cancer Prevention*. 2013;**14**(4):2649-2656

- [49] Su J-A, Yeh D-C, Chang C-C, Lin T-C, Lai C-H, Hu P-Y, et al. Depression and family support in breast cancer patients. *Neuropsychiatric Disease and Treatment*. 2017;**13**:2389
- [50] Krychman ML, Katz A. Breast cancer and sexuality: Multi-modal treatment options (CME). *The Journal of Sexual Medicine*. 2012;**9**(1):5-13
- [51] Barbaric M, Brooks E, Moore L, Cheifetz O. Effects of physical activity on cancer survival: A systematic review. *Physiotherapy Canada*. 2010;**62**(1):25-34
- [52] Forbes CC, Blanchard CM, Mummery WK, Courneya KS. Prevalence and correlates of strength exercise among breast, prostate, and colorectal cancer survivors. *Oncology Nursing Forum*. 2015;**42**(2):118-127
- [53] Chalasani P, Livingston R. Differential chemotherapeutic sensitivity for breast tumors with "BRCAness": A review. *The Oncologist*. 2013;**18**(8):909-916
- [54] Curigliano G, Cardinale D, Suter T, Plataniotis G, De Azambuja E, Sandri MT, et al. Cardiovascular toxicity induced by chemotherapy, targeted agents and radiotherapy: ESMO Clinical Practice Guidelines. *Annals of Oncology*. 2012;**23**(suppl_7):vii155-vii166
- [55] Kangas M, Bovbjerg DH, Montgomery GH. Cancer-related fatigue: A systematic and meta-analytic review of non-pharmacological therapies for cancer patients. *Psychological Bulletin*. 2008;**134**(5):700
- [56] Markes M, Brockow T, Resch K-L. Exercise for women receiving adjuvant therapy for breast cancer. *Cochrane Database of Systematic Reviews*. 2006;**4**
- [57] World Health Organization. National Cancer Control Programmes: Policies and Managerial Guidelines. World Health Organization; 2002
- [58] Heidemann C et al. Dietary patterns and risk of mortality from cardiovascular disease, cancer, and all causes in a prospective cohort of women. *Circulation*. 2008;**118**(3):230-237
- [59] Doyle C et al. Nutrition and physical activity during and after cancer treatment: An American Cancer Society guide for informed choices. CA: A Cancer Journal for Clinicians. 2006;**56**(6):323-353
- [60] Bell LN, Nguyen ATP, Li L, Desta Z, Henry NL, Hayes DF, et al. Comparison of changes in the lipid profile of postmenopausal women with early stage breast cancer treated with exemestane or letrozole. *The Journal of Clinical Pharmacology*. 2012;**52**(12):1852-1860
- [61] Dumas JA, Makarewicz J, Schaubhut GJ, Devins R, Albert K, Dittus K, et al. Chemotherapy altered brain functional connectivity in women with breast cancer: A pilot study. *Brain Imaging and Behavior*. 2013;**7**(4):524-532
- [62] Irwin ML, Cartmel B, Gross CP, Ercolano E, Li F, Yao X, et al. Randomized exercise trial of aromatase inhibitor-induced arthralgia in breast cancer survivors. *Journal of Clinical Oncology*. 2015;**33**(10):1104
- [63] Crew KD, Capodice JL, Greenlee H, Brafman L, Fuentes D, Awad D, et al. Randomized, blinded, sham-controlled trial of acupuncture for the management of aromatase inhibitor-associated joint symptoms in women with early-stage breast cancer. *Journal of Clinical Oncology*. 2010;**28**(7):1154-1160

- [64] Ghezzi P et al. Impact of follow-up testing on survival and health-related quality of life in breast cancer patients: A multicenter randomized controlled trial. *JAMA*. 1994;**271**(20):1587-1592
- [65] Henry LN, Hayes DF, Ramsey SD, Hortobagyi GN, Barlow WE, Gralow JR. Promoting quality and evidence-based care in early-stage breast cancer follow-up. *Journal of the National Cancer Institute*. 2014;**106**(4):dju034
- [66] Ruddy K, Mayer E, Partridge A. Patient adherence and persistence with oral anticancer treatment. *CA: A Cancer Journal for Clinicians*. 2009;**59**(1):56-66
- [67] Ahles TA, Saykin AJ, McDonald BC, Li Y, Furstenberg CT, Hanscom BS, et al. Longitudinal assessment of cognitive changes associated with adjuvant treatment for breast cancer: Impact of age and cognitive reserve. *Journal of Clinical Oncology*. 2010;**28**(29):4434
- [68] Kohli S et al. The effect of modafinil on cognitive function in breast cancer survivors. *Cancer*. 2009;**115**(12):2605-2616
- [69] Fobair P, Spiegel D. Concerns about sexuality after breast cancer. *The Cancer Journal*. 2009;**15**(1):19-26
- [70] Berkey FJ. Managing the adverse effects of radiation therapy. *American Family Physician*. 2010;**82**(4):381-388
- [71] Mazzarello S, Hutton B, Ibrahim MFK, Jacobs C, Shorr R, Smith S, et al. Management of urogenital atrophy in breast cancer patients: A systematic review of available evidence from randomized trials. *Breast Cancer Research and Treatment*. 2015;**152**(1):1-8
- [72] Pruthi S, Simon JA, Early AP. Current overview of the management of urogenital atrophy in women with breast cancer. *The Breast Journal*. 2011;**17**(4):403-408
- [73] Kort JD, Eisenberg ML, Millheiser LS, Westphal LM. Fertility issues in cancer survivorship. *CA: A Cancer Journal for Clinicians*. 2014;**64**(2):118-134
- [74] Andersen BL, Rowland JH, Somerfield MR. Screening, assessment, and care of anxiety and depressive symptoms in adults with cancer: An American Society of Clinical Oncology guideline adaptation. *Journal of Oncology Practice*. 2014;**11**(2):133-134
- [75] Irwin ML, McTiernan A, Manson JE, Thomson CA, Sternfeld B, Stefanick ML, et al. Physical activity and survival in postmenopausal women with breast cancer: Results from the women's health initiative. *Cancer Prevention Research*. 2011;**4**(4):522-529
- [76] Gralow JR et al. NCCN task force report: Bone health in cancer care. *Journal of the National Comprehensive Cancer Network*. 2009;**7**(Suppl 3):S1-S32
- [77] Greenspan SL et al. Effect of once-weekly oral alendronate on bone loss in men receiving androgen deprivation therapy for prostate cancer: A randomized trial. *Annals of Internal Medicine*. 2007;**146**(6):416-424
- [78] Rock CL, Byers TE, Colditz GA, Demark-Wahnefried W, Ganz PA, Wolin KY, et al. Reducing breast cancer recurrence with weight loss, a vanguard trial: The exercise and nutrition to

enhance recovery and good health for you (ENERGY) trial. *Contemporary Clinical Trials*. 2013;**34**(2):282-295

- [79] Wolin KY, Schwartz AL, Matthews CE, Courneya KS, Schmitz KH. Implementing the exercise guidelines for cancer survivors. *The Journal of Supportive Oncology*. 2012;**10**(5):171
- [80] Ligibel JA, Alfano CM, Courneya KS, Demark-Wahnefried W, Burger RA, Chlebowski RT, et al. American Society of Clinical Oncology position statement on obesity and cancer. *Journal of Clinical Oncology*. 2014;**32**(31):3568
- [81] Kushi LH, Doyle C, McCullough M, Rock CL, Demark-Wahnefried W, Bandera EV, et al. American Cancer Society guidelines on nutrition and physical activity for cancer prevention: Reducing the risk of cancer with healthy food choices and physical activity. *CA: A Cancer Journal for Clinicians*. 2012;**62**(1):30-67
- [82] Schmitz KH, Prosnitz RG, Schwartz AL, Carver JR. Prospective surveillance and management of cardiac toxicity and health in breast cancer survivors. *Cancer*. 2012;**118**(S8):2270-2276
- [83] Mehta LS, Watson KE, Barac A, Beckie TM, Bittner V, Cruz-Flores S, et al. Cardiovascular disease and breast cancer: Where these entities intersect: A scientific statement from the American Heart Association. *Circulation*. 2018;**137**(8):e30-e66
- [84] Abdel-Qadir H, Amir E, Fischer HD, Fu L, Austin PC, Harvey PJ, et al. The risk of myocardial infarction with aromatase inhibitors relative to tamoxifen in post-menopausal women with early stage breast cancer. *European Journal of Cancer*. 2016;**68**:11-21
- [85] Valachis A, Nilsson C. Cardiac risk in the treatment of breast cancer: Assessment and management. *Breast Cancer: Targets and Therapy*. 2015;**7**:21
- [86] Fu MR. Breast cancer-related lymphedema: Symptoms, diagnosis, risk reduction, and management. *World Journal of Clinical Oncology*. 2014;**5**(3):241
- [87] Wanchai A, Armer JM, Stewart BR, Lasinski BB. Breast cancer-related lymphedema: A literature review for clinical practice. *International Journal of Nursing Sciences*. 2016;**3**(2):202-207
- [88] Mehrara BJ, Greene AK. Lymphedema and obesity: Is there a link? *Plastic and Reconstructive Surgery*. 2014;**134**(1):154e
- [89] Dominick SA, Natarajan L, Pierce JP, Madanat H, Madlensky L. The psychosocial impact of lymphedema-related distress among breast cancer survivors in the WHEL study. *Psycho-Oncology*. 2014;**23**(9):1049-1056

