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4 - BREAST CANCER AS A MULTI-DIAGNOSIS SPECTRUM: IMPLICATIONS FOR PRACTICE AND FAMILIES

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Abstract

Breast cancer (BC) in women is the second most common cancer after lung cancer. It has been estimated that in developing nations 70 % of new BC cases would be seen by 2020. Breast cancer survivorship is a complex and dynamic process that starts from the moment of diagnosis and continues until the end of one's life. It has implications for both cancer survivors and their social networks, and medical practices. Provided the complex illness and treatment related symptoms, and patients' psychological responses to these, breast cancer can be treated nowadays as a multi-diagnosis spectrum, and not a single medical condition. However, some symptoms need years to develop, are omitted from medical protocols, remain unknown or unaddressed. Due to the increasing number of BC survivors, the medical practice needs a readjustment to be potentially able to enhance patient compliance with treatment and quality of life. This review aims to reconcile the existing evidence on BC and to heighten awareness of healthcare professionals to the current situation, with a view of improving the health care and education of BC women and their families.

***Cuvinte cheie:** cancer mamar, calitatea vieții, îngrijire medicală, familie*

***Keywords:** breast cancer, QoL, medical care, family*

1. INTRODUCTION

Improved prevention and detection methods, as well as progress in medical treatment, have increased the number of breast cancer (BC) survivors (ACS, 2009). It has been estimated that in developing nations 70 % of new BC cases would be

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seen by 2020 (Gonzalez-Angulo, Morales-Vasquez & Hortobagyi, 2007). BC as a long-term illness has contributed to a greater emphasis on rehabilitation and quality of life (QoL) (Reynolds et al., 2000). The main treatment modalities for BC are surgery, chemotherapy and radiotherapy. Systemic treatment includes cytotoxic, hormonal and immunotherapeutic agents used in the adjuvant, neoadjuvant and metastatic settings. In general, systemic agents are active at the beginning of therapy in 90% of primary cancers and 50% of metastases (Gonzalez-Angulo et al., 2007). The addition of taxanes increases the survival rate in patients with lymph node-positive disease. Hormone therapy reckons for approximately two thirds of the benefit of adjuvant therapy overall in women with hormone-receptor-positive BC (Gonzalez-Angulo et al., 2007). Tamoxifen has been accounted as the standard of care in premenopausal patients, while the aromatase inhibitor anastrozole has been proven to be superior to tamoxifen in postmenopausal women with early-stage BC. Over the last two decades QoL has been extensively used as an outcome in BC research (Hewitt, Herdman & Holland, 2004) and nursing practice. It explains the impact of cancer or treatment on a person's physical, psychological and social wellbeing. This review argues that, given the complex illness and treatment related consequences, and patients' responses to these, BC can be defined and approached nowadays as a multi-diagnosis spectrum, and not a single medical condition, for which medical practice needs (re)adjustment.

2. ILLNESS AND TREATMENT CONSEQUENCES

Although multiple studies have shown that adjuvant therapy for early-stage BC contributes to improvement in disease-free and overall survival, treatment benefits do not apply similarly to all patients or all life domains. That is, 5% of newly diagnosed cases of BC are metastatic, and 30% of treated patients have a systemic recurrence (Gonzalez-Angulo et al., 2007). Time of diagnosis, initial stages of adjuvant treatment and the months immediately following the end of treatment are transition times of poor adjustment and decreased QoL (Frost et al., 2000). Generally, women experience poorer QoL (physical, role, social, and cognitive functioning), decreased body image and anxiety at completion of treatment (Browall et al., 2008; Pandey et al., 2006) or later (Ganz et al., 2002; Heim, Valach & Schaffner, 1997; Engel et al., 2003; Montazeri, 2008). While some women experience improvements in all the domains of QoL (Bastani & Ahmad, 2011; Larsson, Mattsson & von Essen, 2010) for others only certain areas

of life improve (Montazeri, 2008). Some QoL domains reach the pre-treatment (Fairclough et al., 1999; Land et al., 2004) or even higher levels than baseline and remain stable over years (Glaspy, Bukowski & Steinberg, 1997).

2.1. PHYSICAL IMPLICATIONS OF TREATMENT

Women undertaking medical treatment report poorer physical functioning, but they recover years after mastectomy (Osoba, 2011). Fatigue affects approximately 70% of women receiving active medication (Vogelzang et al., 1997). It is the most distressing side effect that persists for months or even years after treatment. Weight gain is a risk factor for disease recurrence. Although more rarely, women undergoing adjuvant therapy might be diagnosed with leukemia, which in turn leads to overwhelming complications of treatment (Curtis et al., 1992). Amongst major side-effects nausea, vomiting, alopecia, pain and feeling 'off color' (de Haes, van Oostrom & Welvaart, 1985; Satija et al., 2014) are predominantly faced by women. Nausea and vomiting seem the most time-consuming side effects (Mueller & Glennon, 2007), while alopecia is the most emotive one. Women treated over the chest might have symptoms of fatigue, skin irritation, anorexia, sore throat and cough. As treatment progresses, these symptoms are likely to be perceived as more intense (King et al., 1985). Minor side-effects include mouth ulcers, atypical sense of taste and smell, appetite alteration, indigestion, diarrhea, amenorrhea, cystitis, bone pain, headache, 'pins and needles', blurred vision, conjunctivitis, skin changes, broken nails and infections. Some women might experience fatigue, irritability, and drug-related morbidity (Palmer et al., 1980; Maguire et al., 1980) or severe ocular symptoms (the loss of eyelashes or eyebrows, retinal or conjunctival hemorrhages secondary to drug induced anemia) (Vizel & Oster, 1982). Some of these symptoms are short-term while others never return to the pre-surgical level (Wengström et al., 2000).

2.2. DEPRESSION AND ANXIETY

Treatment and BC are often associated with anxiety, depression, stress, difficulty in adjustment and poor social interactions (Vos et al., 2004). These responses are influenced by pain (Satija et al., 2014; Reddick et al., 2005), fear of recurrence, treatment physical side-effects, life stress (Low et al., 2006) and

lymphedema (McWayne & Heiney, 2005). Other causes of psychological problems are younger age, previous psychological problems and lack of social support (Stommel et al., 2004; Asmundson & Katz, 2009). Some women might experience the stress of limited communication with nurses (Demir et al., 2008) or how to cope with the illness in the family (Degi, 2009). Patients who show guilt and stigma are often depressed, blame themselves for their cancer and lack any initiative in trying to adapt to their diagnosis. This can disturb the continuity of treatment and post-treatment care.

For a distinct subset of survivors, cancer is a psychologically disabling event (Alfano & Rowland, 2006; Bloom, Peterson & Kang, 2007) and almost 17% meet severe changes in their jobs or roles, in work relationships or need special accommodation. Although emotional distress disappears in the majority of women one year after diagnosis (Maass et al., 2015), a small proportion of patients are at risk for severe long-term emotional distress (Bleiker et al., 2000). For a particular category of women, adjuvant chemotherapy associates with the risk of depression and anxiety only during treatment, but not after its completion (Bastani & Ahmad Kiadaliri, 2011). While some women might become depressed others can make a good psychological adaptation to their diagnosis. Some women present an aggregate of symptoms at once, while others experience different reactions to symptoms. Any woman might display a mixture at one time or pass through several stages.

There is a relation between stress, immunity and cancer occurrence or even mortality (Reich, Lesur & Perdrizet-Chevallier, 2008). It seems that anxiety characterizes diagnosis, whereas depression is more common after treatment⁵⁸. Frequently anxiety may be focused on one particular detail of the illness, such as surgery and its physical effects, treatment or family's reactions (Luutonen et al., 2011). Specific symptoms of anxiety are autonomic overactivity (palpitation and sweating) and anxious behaviour (restlessness and reassurance seeking) (Van Oers & Schlebusch, 2013). Prolonged anxiety has immunosuppressive effects and might impair the cognitive functioning when important health decisions must be made. The duration of symptoms, usually decisive in diagnosis, is difficult to estimate as anxiety may be labile and situational, making the onset of an episode difficult to define (Van Oers & Schlebusch, 2013). Organic anxiety is difficult to diagnose as its symptomatology is similar to those in cancer therapies. Associated somatic symptoms might be tremors, palpitations and dyspnoea resulting from the disease or treatment (Stark et al., 2002). Pain, asthenia, nausea, shortness of breath and

drug treatments (interferon, corticosteroids and morphine) are also associated with anxiety, while akathisia is commonly misdiagnosed as anxiety (Van Oers & Schlebusch, 2013). The toxicity of chemotherapy co-varies with anxiety and seems to be highest before the first infusion. Women undergoing magnetic resonance imaging and computer tomography may have panic attacks and acute anxiety, intensified by immobilization, the duration of the examination and the noise of the machine. Women presenting inoperable tumors and not receiving therapy show the highest levels of anxiety due to the perception that the decline cannot be avoided (Van Oers & Schlebusch, 2013). Women who complete radiotherapy might be highly anxious, potentially because of the perception of losing the protective effect of treatment (Stark, Kiely, Smith et al., 2002).

2.3. POST- TRAUMATIC STRESS DISORDER (PTSD) AND GROWTH

PTSD include cognitive avoidance, emotional reactivity, hypervigilance, sleep disruption, difficulties in concentration, intrusive thoughts related to cancer and its treatment, fear of recurrence, heart palpitations or nausea. PTSD prevalence was estimated to range from 3% to 35%, depending on assessment methods, populations studied and time since treatment (Alfano & Rowland, 2006). The risk factors include: persistent physical problems, poor psychosocial or familial adjustment, an avoidant coping style, low self-esteem, poor educational or financial resources, ailing premorbid physical and mental health, prior traumas or current or prior negative stressful life events, inadequate social support, cancer type and stage, fear of death and treatment severity.

Some women might experience renewed vigor, healthier social interactions, improved view of the self, positive life changes and outlook of life (Kornblith & Ligibel, 2003), greater valuation of life, reprioritization of values, growth in self confidence, and closer relationship with God, strengthened spirituality and greater interest in health behaviors.

2.4. RECURRENCE AND FEAR OF RECURRENCE

Even in the presence of treatment, breast cancer can spread to other parts of the body. Sometimes cancer returns after the entire tumor has been removed and nearby lymph nodes have been found to be cancer-free. Once metastases develop, the possibility of a cure is very limited or practically nonexistent. In this case, the 5-year survival rate is 20%, and the median survival duration varies from 12 to 24

months (Gonzalez-Angulo et al., 2007). Some women have an early recurrence although they have a diagnosis with good prognostic features and at a favorable stage. It is due to the resistance of tumor cells to therapy or resistant cell clones of micrometastatic disease. Other risk factors might be: stage of illness, location of the tumor and the surface that has been spread, gene expression, tumor size and shape, tumor markers, rate of cell division, the growing speed of tumor and whether the tumor is positive or negative hormone receptor. Despite advances in early detection and understanding of the molecular bases of BC biology, approximately 30% of all patients with early-stage BC have recurrent disease, which is metastatic in most cases (Gonzalez-Angulo et al., 2007).

The overall cumulative incidence of synchronous and metachronous contralateral BC ranges from 3% to more than 20% (Alfano, 2006). The range of local and systemic recurrence varies within different series, but in general, distant recurrences are dominant, supporting the hypothesis that BC is a systemic illness. Local recurrence may indicate a posterior systemic relapse in a considerable number of women within 2 to 5 years post-treatment (Alfano, 2006). Fear of recurrence is the highest concern of BC women. Some women might fear that the illness will recur or one of the family's members would be diagnosed with the same disease. Some patients are at high risk to develop a second BC.

2.5. 'CHEMO BRAIN'

Cognitive impairment following cancer treatment, commonly referred to as 'chemo brain', is one of the most frequently reported post-chemotherapy symptoms (Boykoff, Moieni & Subramanian, 2009). It might be diffuse, affecting all of these processes, although difficulty in attention and concentration, learning new information and recalling recently learned information are the most frequently reported deficits during active treatment. These deficits are similar to those observed in normal cognitive aging, and might be subtle or dramatic, temporary or permanent and stable or progressive. The direct contributing factors might be metastases and primary tumors of central nervous system (CNS). The indirect factors are medical therapies, infections, fevers, nutritional deficiencies, metabolic and endocrinologic abnormalities, hematologic abnormalities, medications (analgesics, antiemetics and antidepressants), advancing age, menopausal status, depression, anxiety and sleep disorders (Bender, Paraska & Sereika, 2001).

Underlying mechanisms are connected with peripheral and CNS and chemotherapeutic agents administered as part of adjuvant therapy regimens. Although neurologic toxicities are not a common sequel of standard dose therapy, they have been described in response to high-dose chemotherapy. Higher doses of chemotherapy are associated with penetration of medical agents across the blood brain barrier leading to neurotoxicity. The decrease in metabolic activity in the brain, due to methotrexate, may lead to encephalopathy, which in turn causes lethargy, somnolence and, infrequently, seizure activity. Some women may be at great lifetime risk for deterioration in learning, memory and attention due to their exposure to reduced levels of estrogen following adjuvant chemotherapy (Bender, Paraska & Sereika, 2001). Nearly one third of patients receiving adjuvant chemo-hormonal therapy experience some form of cognitive impairment (Olin, 2001) often lasting more than two years beyond treatment. Women with non-CNS malignancies treated with chemotherapy have been found to have an increased risk of cognitive problems (Bender, Paraska & Sereika, 2001). Given concurrently with radiation, chemotherapy increases the risk of cognitive deficits compared with radiotherapy alone.

2.6. BC WOMEN AND THEIR SEXUALITY

Women who no longer menstruate after chemotherapy report the greatest diminution of sexual functioning (Ganz et al., 1998; Lebel, Rosberger, Edgar et al., 2008) due to an estrogen-deficient state. Premature menopause in young women may contribute to increased cardiovascular morbidity. Chemotherapy-related amenorrhea may be reversible, with some women resuming their menstrual function months or years after treatment. The vast majority of women who remain amenorrheic one year after treatment are likely to not regain ovarian function (Partridge, Burstein & Winer, 2001).

2.7. ADJUVANT MEDICATIONS FOR DEPRESSION, ANXIETY AND PAIN

Most serotonin reuptake inhibitors (SSRIs) could be prescribed to women with multiple comorbidities, due to their tolerability and lack of interaction with other receptors, such as histaminic, cholinergic, dopaminergic and noradrenergic (Ferguson, 2001). As Table 1 indicates, adjuvant medication, if provided,

contributes the multi-diagnosis spectrum of BC. Gastrointestinal disturbances are the most frequent symptoms, with fluvoxamine leading to the highest frequency. Sertraline and fluoxetine are most often associated with anxiety, agitation and insomnia. Citalopram is the best tolerated SSRI followed by fluoxetine and sertraline, while paroxetine and fluvoxamine result in the most side-effects and the highest discontinuation percentage (Dewan & Anand, 1999). The most distressing adverse effects of long-term SSRI therapy are sexual dysfunction, weight gain and sleep problems. Discontinuation syndrome is reported by women who withdraw SSRI treatment and is caused by neurophysiologic readjustment in the CNS to compensate the pharmacologic effects of the therapy. Symptoms include dizziness, nausea, lethargy, headache, anxiety and agitation (Dewan & Anand, 1999). More disabling side-effects are falls and absence from work, but all these symptoms are resolved once the SSRI therapy is reinstated. Alternatively, psychosocial interventions are beneficial for those with a lower QoL who derive greater benefit from enhanced coping.

2.8. PATIENTS' CHARACTERISTICS

Advancing age has been the most critical risk factor in the BC development, with one in ten women over the age of 65 being likely to develop it (Yoo, Levine, Aviv et al., 2010). Young age (prior to the age of 35 years) has been associated with illness recurrence after breast conserving surgery (Ganz et al., 2002), emotional distress at diagnosis (Andritsch, 2007), depressive symptoms and anxiety (Burgess et al., 2005), economic problems (Ganz et al., 2002) and deterioration in the mental health and well-being at four and ten months after diagnosis. Younger women might have a worse prognosis even when treated with mastectomy, as it is likely to be more invasive and mutilating. Older women might experience comorbidities related to old age, as cardiovascular problems, dyspnea and sexual functioning. Toxicity of treatment and recovery might be more severe in older women as they might have fewer supportive networks. While some elderly women are likely to be offered less chemotherapy as they are less able to endure the toxicity (Browall et al., 2008), younger patients are exposed to more side-effects because of induction of an early menopause and potential infertility.

Women with a higher educational achievement have better overall QoL, fewer arm and breast symptoms after mastectomy and better social well-being. These women are more trained about how to look after themselves. However, it seems

that there is a category of survivors for who education has no influence on how they cope with the illness (Ganz et al., 2002; Mols et al., 2005). Years of education might lead to more avoidance at diagnosis or to cancer related anxiety (Fafouti et al., 2010). Access to education, screening and care depends on area of residence. Urban women have better QoL than rural ones (Waldmann, Pritzkeleit & Raspe, 2007; Hall, Holman & Hendrie, 2004). Rural women might have unique and supplementary concerns, such as disruption to family life, work and financial insecurity, and need to travel twice the distance to treatment centers. It seems that having children predicts less breast symptoms at six months for married women after mastectomy. Married women might have a better sexual functioning, while single BC mothers who have children might have higher levels of illness-related concerns (Northouse et al., 1999). Unmarried women are likely to have poorer QoL and global health status (King et al., 2000). Women describing a poor quality of their marriage are likely to have a worse QoL than the divorced ones (Jassim & Whitford, 2013)

Table 1 Comorbidities of adjuvant medication for cancer pain and psychological dysfunctions

Drug category	Example	Side-effects
Selective serotonin reuptake inhibitors	Paroxetine, Citalopram, Fluoxetine, Fluvoxamine, Sertraline	Reduced effectiveness of tamoxifen, nausea, sleep disturbances, sexual dysfunction, appetite changes, headache, dry mouth
Serotonin-norepinephrine reuptake inhibitors	Venlafaxine	All of the side effects of the SSRIs, hypertension, tachycardia
Tricyclic antidepressants	Amitriptyline, Desipramine, Doxepin, Imipramine, Clomipramine, Trimipramine, Desipramine, Nortriptyline, Protriptyline	Constipation, blurred vision, dry mouth, urinary retention, tachycardia, cognitive decline, orthostatic hypotension
Triazolopyridines	Trazodone, Nefazodone	Constipation, dizziness, altered sense of taste, sedation, hives, difficulty breathing, blurred vision, eye pain or swelling, panic attacks, hyperactivity, higher depression/ anxiety
Anti-convulsants	Gabapentin	Weight gain, ataxia, dizziness, somnolence, fatigue
Multiple receptor antidepressants	Mirtazapine	Drowsiness, weight gain, hypercholesterolemia
Miscellaneous	Bupropion	Negligible
Local anaesthetics	Mexilitine	Nausea, dizziness
Corticosteroids	Prednisolone, Dexamethasone	Gastrointestinal discomfort, immunosuppression, hyperglycaemia
Bisphosphonates*	Clodronate, Pamidronate, Zoledronic acid, Ibandronate	Bone/joint/ muscle pain, bisphosphonate-associated osteonecrosis

*The possibility of side effects depends on the duration of therapy - *Source*: Adapted from Ferguson (2001)

3. CONCLUSION

As BC is now often viewed as curable, there is an inevitable tension between treatment related constraints, side effects and patient's desire to maintain a normal life (Magai et al., 2008). Given the increasing figures of BC diagnoses and survival rates, it is important to raise awareness with regard to related comorbidities and thereby improve diagnostic and treatment (Burgess et al., 2005; Van Oers & Schlebusch, 2013). To provide effective treatment with low toxicity, it is necessary to select therapies based on the patient and the clinical and molecular characteristics of the tumor. The variation observed in rates of BC incidence, treatment side-effects, as well as mortality and illness progression, is due to medical history, age, race, education, socio-economic status, life style, reproductive history, family history, area of residence, *etc* (Gonzalez-Angulo et al., 2007). The risk for depression in the 5 years survival is influenced more by the patient rather than the disease or its treatment (Burgess et al., 2005). These factors should be involved in the treatment protocol and clinical practice (Gonzalez-Angulo et al., 2007).

The difficulty of the treatment process lived simultaneously with the hope of relief from the disease often lead to conflicting psychological states among patients (Lim, Devi & Ang, 2011). Often, psychological needs are left unaddressed (Asmundson & Katz, 2009; Caplette-Gingras & Savard, 2008) since the physical impact of the diagnosis is seen as an immediate target for intervention (Jassim et al., 2015). Women experiencing minor symptoms might not be referred for further consultations. Sometimes symptoms need years to develop. Some patients might have limited access to information or benefit from insufficient explanations from their doctors. Oncologists might not be aware of the prevalence of co-morbid psychological distress or late sexual and cognitive side-effects. Often, diagnostic and treatment protocols omit such information (Degi, 2009). On the other side, it is difficult for busy healthcare practitioners and nurses to review the extensive literature (Burgess et al., 2005). If patients feel reluctant to talk about their problems, healthcare providers might feel guilty to ask about them. Some questions might be perceived as unethical or distressing (Postavaru, 2014). This form of shared avoidance can block patients, and their caregivers from understanding one another's perspective and achieving good medical treatment. There is a need of further education of oncology healthcare professionals and family practitioners with regard to at-risk patients, and the importance of a psychological work-up

within an overall diagnosis. In this way, the shortcomings of the “disease first” approach can be counteracted. Medical protocols should be based on the joint efforts of a multidisciplinary team and knowledge of the benefits and potential acute and late toxic effects of each of the therapy regimens (Gonzalez-Angulo et al., 2007). Medical encounters should include the patient in the treatment related decisions. Symptoms are differently assessed by patients, healthcare professionals and family members. It seems that health care providers tend to rate their patients’ QoL as more poorly than patients themselves do (Sneeuw et al., 1997). These decisions should take into account the existing reviews and consider a (re)adjustment of medical practice and patient education.

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REZUMAT

Cancerul mamar (BC) la femei înregistrează cea mai mare incidență după cancerul la plămâni. Se estimează că în țările în curs de dezvoltare rata cazurilor noi va fi de 70% până în anul 2020. Supraviețuirea în urma cancerului mamar reprezintă un proces dinamic care începe din momentul diagnosticării și continuă până la finalul vieții. Implicațiile sunt atât pentru persoanele diagnosticate și rețelele sociale, cât și pentru practicile medicale. Dată fiind compexitatea simptomelor asociate bolii și tratamentului, precum și răspunsurile psihologice ale pacientelor față de acestea, cancerul mamar poate fi tratat astăzi ca o combinație de diagnostice și nu ca o singură condiție medicală. Cu toate acestea, unele simptome au nevoie de ani pentru a se dezvolta, sunt omise din protocoalele medicale, rămân necunsocute sau netratate. Ca urmare a numărului crescând de supraviețuitoare ale cancerului de sân, practica medicală necesită o reajustare pentru a putea îmbunătăți, cel mai probabil, complianța pacientelor la tratament și calitatea vieții. Această recenzie a literaturii își propune să reunească datele cu privire la cancerul mamar și să sprijine conștientizarea din partea cadrelor medicale a situației actuale, cu viziunea de a îmbunătăți serviciile medicale și educația femeilor diagnosticate și a familiilor acestora.