ABSTRACT

Breast cancer is a common type of cancer among female human populations. Approximately, one million new cases are diagnosed per year and it is expected that this amount will increase in the future. In recent years, the common standard surgical procedures for the treatment of breast invasive carcinoma are breast-protective surgery and modified radical mastectomy. Residual tumor after surgery, stage T3–T4, metastases to 4 axillary lymph nodes or greater, and extracapsular axillary lymph node disease that is treated with adjuvant chemotherapy are indications of surgery. Post-mastectomy radiotherapy results in an increased disease-free condition and survival rate. With the improvement of survival rate, the procedure has been focused on quality of breast cancer survivors.

Keywords: Post Mastectomy, Pain, Phantom

Introduction

Breast cancer (BC) is a common type of cancer among female human populations (1). Approximately, one million new cases are diagnosed per year and it is expected that this amount will be increased in the future (2). In recent years, the common standard surgical procedures for the treatment of breast invasive carcinoma are breast-protective surgery and modified radical mastectomy. Residual tumor after surgery, stage T3–T4, metastases to four axillary lymph nodes or greater, and extracapsular axillary lymph node disease that is treated with adjuvant chemotherapy are indications of surgery. Post-mastectomy radiation therapy (PMRT) results in an increased disease-free condition and survival rate (3).

With the improvement of survival rate, the procedure has been focused on quality of BC survivors (4). Currently, 5-year survival occurs in over 80 percent of cases that entail rapid diagnosis and improved management (5). BC is the leading cause of women’s mortality in the United States, Canada, and Europe (2,6). One out of 10 women gets affected by BC (7). In addition, 23 percent of all women cancer cases are related to BC (8). The differences in the incidence rate as well as the mortality rate result from contributing factors, such as age, race, socioeconomic condition, lifestyle, reproduction history, family history, etc. (9). In developed countries, except Japan, BC incidence (>80 in 100000 cases) is high in comparison to developing countries (<40 in 100000 cases) (8). Almost always, BC cases are classified according to clinical staging during treatment by surgery (10).

Conservative surgery accounts for an increase of 40 percent in BC surgery cases and quadrantectomy, in which removing the primary tumor by a free margin is the most common occurrence. In certain cases, axillary lymphadenectomy by secondary incision in the region is important. Currently, quadrantectomy with the biopsy of the sentinel lymph node is a common less invasive method (7,10). Radical mastectomy surgery was developed in nineteenth century by Halsted; it is a non-conservative technique that includes removing the breast, skin, fat tissue, pectoralis major and minor, and the ipsilateral lymph nodes. In modified radical mastectomy, the pectoralis major muscle and, occasionally, pectoralis minor were preserved (11).

The goal of BC treatment included the achievement of the local control of tumor, optimal staging of the lymph node by minimal treatment—which is related to the mortality, good function, and maybe preservation of breast (12). Major factors can influence the quality of life of the survivors; adverse effects due to cancer treatment, such as lymphedema and post-mastectomy pain syndrome (PMPS), can occur among approximately 90 percent of patients during the treatment course and continue for months or years after the end of treatment (4,13). Chemotherapy, radiotherapy, and hormone-therapy can play a role in the development of these adverse effects, including upper-limb lymphedema, cognitive disorders, fatigue, sleep disorders, chronic pain...
in the breast zone, peripheral neuropathy, and cardiotoxicity (5).

All of these effects have negative impacts on the quality of life and the daily activities that result in non-compliant treatment and, finally, they influence prognostic outcome and survival (14). BC survivors suffer from one major problem: chronic persistent pain after BC. It is a common adverse effect with prevalence up to 50 percent. Persistent pain was originally reported by Wood in 1970. When pain is considered as chronic pain, its duration is longer than normal time for healing—three months at minimum (15,16). Several types of sensory disturbances may be seen, such as allodynia, hyperpathia, burning, and sensory loss. Chronic pain after the treatment of BC can be classified into four groups: 1) Phantom sensation or phantom pain, 2) Intercostobrachial neuralgia or post-mastectomy pain syndrome, which damages the intercostobrachial nerve, is the most common theory that accounts for neuralgia, 3) Pain, secondary to neuroma, including pain in the thorax or arm’s surgical scar, is triggered by strikes (Tinsel’s sign), and 4) Pain due to other nerve damages (17).

With the consideration of BC surgery-induced chronic pain, differentiation between non-painful phantom sensation and phantom pain is important (16). The conception of phantom pain is the included pain in the region of the body that does not exist. It was originally described by the French military in the early sixteenth century (18). Phantom breast pain is the pain that takes place in the breast that has been previously removed. Phantom sense makes a person feel like the breast that was removed is still in its place. Phantom sensation, either painful or non-painful, can occur after the removal of every part of the innervate organs of the body (16).

Characteristics of Phantom Breast Syndrome (PBS)

Phantom breast syndrome (PBS) is a condition in which the patient experiences phantom pain or a sensation or both of them (19). This syndrome, including the spectrum of syndromes, results from varying non-painful breast sensations to extremely painful distressing conditions. It may be localized in the nipple and then expand to the whole breast. Patients may sense pain or discomfort, itching, tingling, pressure or burning, throbbing, stabbing, and even the sensation of tingling, lancinating, electrical shock, and premenstrual-type discomfort in the removed breast (19-23).

PBS was firstly considered by Mitchell, but it is not still completely understood (1). Phantom pain characteristics have been classified into the four following groups: 1) Severity of pain, 2) Attack frequency, 3) Duration of attack, and 4) Pain description (21).

PBS begins over three months after surgery and usually occurs in the first year after mastectomy; the highest prevalence rate was seen over one month after the operation. The pain may be sensed in all parts of the breast or merely in the nipple (22). It usually occurs as intermittently as every 2–4 weeks (21,22). This chronic pain has serious impacts on the emotional situation of the patients, their daily activities, social life, and health system costs (2). Pre-amputation pain has a strong relationship with phantom sensation, rather than phantom pain; but there are considerable similarities between the characteristics of pre- and post-mastectomy pains. The association of phantom pain and pre-amputation pain is relevant during six months after mastectomy. It seems that phantom pain after mastectomy is less severe than after limb amputation, probably because of the breast kinesthetic and small cortical response (22). Its incidence varies among different studies, perhaps because of the uncertainty between the phantom pain and sensation (19,21). Also, patients may be afraid of reporting the pain in an organ that does not exist (12).

Based on the 95% confidence interval of prevalence, the studies did not overlap, thus indicating important differences in prevalence; this may be due to different evaluation methods in study design and a different studied population (24). Variations in the prevalence of phantom pain and sensation are substantial; varying from 10–55% for the phantom sensation (12).

Mechanisms and Theories

Phantom pain and sensation usually exist together, but they are induced by different mechanisms; treatment of one cannot improve the other. The phantom sensation is eliminated after removing the cortex, but the phantom pain remains (22).

Both the peripheral and central mechanisms have been contributed to these issues. Central mechanisms were classified at the spinal and supraspinal level. It is proposed that the peripheral nerves are cut during amputation (peripheral mechanisms), and neuronal and tissue damage result in the disruption of afferent perineural input to the spinal cord; this is followed by deafferentation (25). In the proximal part of the cutting nerve, neuromas are created. The accumulation of the sodium channel expression accelerates molecules in these neuromas induced hyper-excitability and spontaneous discharges. It seems that the abnormal peripheral activity is a source of phantom pain (26). Phantom pain has greater intensity in patients, which has a high probability after the toleration of the chronic pain of undergoing amputation due to neuroma preformation with excess mechanical and chemical stimulation (22).

Under stress circumstances and emotional and peripheral (cold) stimulation, norepinephrine secretion is increased from sympathetic afferent endings and in a neuroma, norepinephrine can augment phantom pain. Furthermore, similar changes in the cells of the dorsal horn can take place as the neuroma induces phantom pain.

The spontaneous activity of neurons, increased metabolic activity of the spinal cord, and increased level of sensory perception induce increased spinal sensitivity and anatomic changes in the dorsal horn of the spinal cord. Then, a lack of peripheral sensation of lost extremity (amputated), increased the activity in the dorsal horn of the spinal cord, starts and sense as attack discharges. The treatment of phantom pain with anticonvulsant and the
impairment of the nigra body supports this spinal mechanism (22).

Furthermore, the actions of the NMAPA receptors increased, followed by the wind-up phenomenon (i.e., the upregulation of receptors in this region) (27). However, this may have occurred by decreasing the local intersegment’s inhibitory mechanisms at a spinal level. Damage to the spinal cord during amputation can result in the beginning of axonal regeneration and induce hyper-excitability in regions such as the neuromas. Increased pain due to emotional distress or exposure to cold may induce sympathetic discharges and circulating catechol amines (22). However, this mechanism cannot solely explain phantom pain, especially in extremities, because spinal anesthesia and Cordotomy cannot completely eliminate pain.

The central nervous system mechanism was noted as the common cause for the induction or enhancement of phantom pain (18). It seems that cortical reorganization is the most important mechanism of phantom pain and sensation. The high rate of the extremity of phantom pain, in comparison to the ipsilateral breast, is related to the differences of the primary sensory cortex. Foot and hand, in relation to the breast, attribute the further portion of the sensory and motor cortex and extremities also have a greater dependency on deep and superficial sensation. Women may not, however, easily express their phantom pain or sensation after mastectomy (24).

Through the use of sophisticated scanning techniques, it was observed that the sensory cortex remaps after amputation (28). Accordingly, the start time of this postoperative effect has been reported in different ways in several studies and this means that remapping in the reorganization of peripheral and cortical inputs may be rapidly induced after the operation. Furthermore, the presentation of such cortical plasticity during several days after a surgery can indicate some evidence of unmasking the extant non-functional connections (16). Flor suggested the model of inducing phantom pain of the limb for its perpetuation by peripheral factors and guidance for recent studies about the phantom breast. In his model, the presence of pre-amputation pain can cause cortical pain memory that induces cortical reorganization after amputation. Nervous impulse cycling from peripheral nerves repeat and, therefore, a person may have the sensation of the lost portion. In the absence of amputated limb findings, the patterns of induced abnormal stimulations are interpreted as painful stimuli (19). The reorganization of the amputated zone is perpetuated in the somatosensory cortex by peripheral inputs, including the ectopic discharges of the central and peripheral neurons, activation of sympathetic system, and the absence of nociceptive inputs. Supraspinal mechanism is a neuromatrix theory that was suggested by Melzeck (2001). The neuromatrix consists of neuronal plexus, extending throughout the brain. The repeated cycling process of the neural peripheral impulses in the neuromatrix showed a characteristic pattern: neurosignature. The patient may have some kind of sense on part of the body in absence of peripheral input (18, 29). Other mechanisms are based on the body scheme that was originally stated by Head and Holmes. The body scheme originates from the whole body in the brain and any change in the body (amputation) can cause phantom pain (30).

One cause of the lower incidence of phantom breast pain in relation to a limb is that in contrast to the limbs, the breast does not mediate the kinesthetic sensory and somatosensory zone; representing the somatosensory zone of the breast is relatively more limited. Stimulations, such as emotional stresses, exercise, and palpitations usually stimulate pain. Phantom pain is commonly reduced two years after mastectomy (31). One important question exists about future studies—whether the cortical reorganization is induced by phantom pain or whether cortical reorganization is a result and experience of phantom pain. Nevertheless, it is expected that the association between phantom pain and cortical reorganization varies (16). Ramchandran (1998) stated that cortical reorganization is possibly a valuable mechanism in the perception of phantom pain and sensation. The higher prevalence of phantom pain and sensation in amputated pain in relation to the amputated breast may be a result of the different cortical representation of the limb and primary sensorimotor cortex of the breast. Both arms and legs are represented in the larger zones of the primary sensorimotor cortex, rather than the breasts. Limb perception potently relies on sensory submodalities, such as proprioception and, sensibly, this means that PBS, after breast amputation, is lower than the amputated limb (24).

The evidence showed that the motor and somatosensory cortex, after amputation, had neuroplastic changes. In the articles, cortical areas account for the representation of amputated extremities taken over neighbors and represented zones, which are primarily associated with the motor (M1) and somatosensory (SI) cortex (32-36). Patrick Wall is a suggestive of plasticity in adult’s central nervous system and on the other hand, cortical organization depends on the size of different areas. In the description of cortical reorganization, Ramachandran, using magneto encephalography, showed that the motor sensory cortex in humans can be minimally organized 2–3 cm in the adult human brain (37). The assessment of phantom pain must rule out pathologic findings, such as skin damage, vascular disorders, skin and subcutaneous infection, or neuroma (22).

Risk Factors:

In the survey of Hansen, there was an association between PBS and age, breast zone pain, chemotherapy, radiotherapy, and aggregated link and node protection (ALNP). Chemotherapy and radiotherapy were not common risk factors for phantom pain, such as neuropathic pain syndromes after mastectomy, including acute postoperative pain and the further use of analgesic activity (38). Therefore, the relief of acute severe pain
may decrease the risk of chronic pain (39). Preoperative pain of the breast has a correlation with increased pain and phantom sensation (40). Other risk factors included pre-amputation pain, permanent pain, and stump pain. The occurrence of phantom pain had no association with the type of tumor histology and the affected side (40).

Dijkstra suggested that age was a potential risk factor for PBS. One explanation for the impact of age on PBP was that the breast was probably a symbol of feminization, sexuality, and body image in female surgery (24). While sensation of anxiety is a strong risk factor in eliciting of PBS, the feeling of well-being is usually considered as a reducing factor. It seems that psychological factors play an important role in the appearance and elimination of PBS (33). A recent report in the Anesthesiology annual meeting (ASA) meeting stated that depression and fear of cancer recurrence are higher in women with phantom pain (39). Moreover, Wallake showed that the most common prevalence of post-mastectomy pain occurred in women undergoing mastectomy and reconstruction without an implant or mastectomy without reconstruction (41). Phantom pain and other pain syndromes strictly impact the quality of life; phantom pain influences the quality of life through its impact on physical disabilities and stresses (39).

Also, Jamison reported that prevalence rate of phantom pain was 60–80 percent. As a general fact, phantom pain has negative deep influences on physical and psychological aspects (42). In one study, about half of the patients after BC surgery reported some implications on life activities and one quarter of them noted that the pain has moderate to severe effects on their daily life (16). Pulinsky showed that pain influences work and home (34). On the other hand, some patients have both phantom pain and the sensation and fear of reporting them due to the fear of being considered insane. The time interval after mastectomy to PBS prevalence is different in several studies and varies in the range of the first month till years after mastectomy (24,35). Hansen showed the association between low age and PBS in his study. This association is already unknown, but various studies demonstrated the degeneration of peripheral nerves with age; this may be a physiological explanation that decreased with increased age (24). However, young individuals in relation to old people are probably focused on body signals. In Hansen’s study, no association existed between PBS occurrence, chemotherapy, and radiotherapy (36). Women who received afterglow luminescent nanoparticles (ALNP) had low PBS, rather than solid lipid nanoparticles (SLNP). One explanation may be that women undergoing SLNP have greater sensitivity than women undergoing ALNP due to the lower occurrence of major symptoms in SLNP (38).

**Prevention**

Certain risk factors can cause induction or exacerbation of chronic neuropathic pain and ambiguous pain after BC-induced mastectomy. Despite new dependent and independent approaches to neuropathic pain, the evaluation of risk factors and their possible associations might be unknown due to lack of sufficient evidences. In common literatures referring to the perioperative breast, severe postoperative pain and further usage of analgesics are important risk factors that contribute to phantom pain reduction. It seems that therapeutic and prophylactic measures may resolve pain in the preoperative and postoperative periods; in addition, they will decrease the prevalence of chronic pain after an operation. Psychological stresses could enhance pain and its related risk factors, it means that controlling of them might help to treat the pain. According to the incomplete available evidence, goals and prophylactic strategies will be optimal targets (39).

**Treatment**

However, the novel treatment regimen needs to be evaluated. Oral agents, such as antidepressants, anticonvulsants, opioids or N-methyl-d-aspartate (NMDA) antagonists, calcineurine, topical lidocaine, cannabinoids, capsaicin, glycine antagonists, clonidine, ketamine, amitriptyline, and calcitonin can also be used. Evidence showed that opioids induce decreased cortical organization, which may cause phantom limb pain (PLP) (18).

Using lidocaine plus prilocaine 5% (EMLA)(a eutectic mixture of 25 mg of prilocain+25 mg of lidocaine) in the preoperative period can decrease the need for postoperative analgesia, incidence, and the severity of chronic pain; but its results may need further studies to be confirmed (5). Using these approaches for BC survivors is more common than patients with other cancers. With the consideration of subjective and objective elements in the treatment of cancer, cognitive behavior was efficiently used by many patients with BC, including different techniques (e.g., relaxation training, progressive muscle relaxation, hypnosis, distraction, and guided imagery) (22).

Transcutaneous electrical nerve stimulation (TENS) application in treatment of post-mastectomy pain is effective; the mechanisms of this application include inhibition of pain impulses transmission through spinal cord by sending electrical impulses from skin, releasing of endogenous opioids such as endorphins from spinal cords or brain, and also deep brain and spinal cord stimulation with various degrees of success (18).

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**Conflict of Interest**

Authors declared no conflict of interests.

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