

Full Length Research paper

Neuroimaging findings in breast cancer: A systematic qualitative review

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Accepted 18 March, 2020

Patients with breast cancer treated with chemotherapy may develop neuropsychiatric symptoms, including fatigue and depression. The authors discuss the potential use of structural neuroimaging in the identification of these patients. Findings from neuroimaging studies improve our understanding of the wide-ranging neurobiological changes in breast cancer patients. We set out to determine whether neuroimaging studies had identified brain abnormalities in association to the presence of breast cancer. A qualitative systematic review of all structural neuroimaging studies in subjects with breast cancer was carried out. Studies were identified using general medical and specific databases as well as search engine such as PUBMED, EMBASE and COCHRANE based on current contents and other secondary sources. Systematic review of results from ten studies led to the observation that different brain areas might be vulnerable to the presence of breast cancer. The most striking observation was the extreme variability of the results observed in different studies. Some variability in the results was associated to different imaging analysis, presence of neuropsychiatric symptomatology (depression and post traumatic stress) and use of co adjuvant chemotherapy. Evidence from neuroimaging studies has suggested areas of the brain that may be damaged by the presence of breast cancer or direct effect of chemotherapy. The clinical implications of these neuroimaging findings need to be investigated further, as they challenge traditional therapeutic approaches.

Key words: Breast cancer, neuroimage, depressive symptoms, chemotherapy, cognitive function.

INTRODUCTION

Breast cancer is the most frequently diagnosed cancer among women in industrialized countries and accounts for at least one third of all cancer cases. In aging populations, breast cancer among the elderly is a major public health concern (Bouchardy et al., 2003). With one million new cases in the world each year, breast cancer is the most common malignancy in women and comprises 18% of all female cancers (McPherson et al., 2000; American Cancer Society, 2007). Women who are diagnosed with breast cancer are at high risk for experiencing significant affective distress, with a subgroup manifesting

symptoms of anxiety and depression, meeting the criteria for psychiatric disorder up to several years post-diagnosis (Jesse et al., 2008). Nearly half of the women with early breast cancer had depression, anxiety, or both in the year after diagnosis, 25% in the second, third and fourth years, and 15% in the fifth year (Compas et al., 1999). Point prevalence was 33% at diagnosis, falling to 15% after one year. Almost the majority of those with recurrence experienced depression, anxiety, or both within three months of the diagnosis (Okamura et al., 2000). The data shows that cancer-related distress generally diminishes with time after diagnosis, increasing again after a possible recurrence (Okamura et al., 2005) and about 30% of post-operative breast cancer will recur within 10 years (Jenkins et al., 1991). Patients that experience significant distress and/or impairment of function,

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have the symptoms of distress persist for as long as 10 - 20 years after treatment (Kornblith et al., 2003; Luecken 2003; Luecken and Compas, 2002; Ahles, 2005; Hegel, 2006). The cost and prevalence, the impairment caused and the diagnostic and therapeutic uncertainty surrounding depressive symptoms among cancer patients make these conditions a priority for research (Pasquini and Biondi, 2007). Although the vulnerability factors involved in the development of neuropsychiatric symptoms in breast cancer have not been completely clarified, neuroimaging technologies provide a powerful approach to explore the genetic basis of individual differences in complex behaviors and vulnerability to neuropsychiatric illness (Bigos and Hariri, 2007). Although studies of neuroimaging reveal a variety of alterations in brain structure, the majority of them evaluate metastasis effects on brain, specific alteration in brain, despite the importance of the neuroimaging studies connected to clinic cases of patients with depression and breast cancer (Conill et al., 2007; Argyriou et al., 2006; Guruprasad et al., 2004).

This systematic review will improve the knowledge regarding brain mechanisms involved in the development of depressive symptoms in patients with breast cancer and therefore, will increase the likelihood of success of new treatments, leading to a significant improvement in the quality of life of these patients. This review critically examined structural and functional studies of the brain and also studies combining both modalities in breast cancer patients. Depressive and cognitive symptoms were examined in relation to neuroimaging findings, with case reports reviewed separately. Finally, the implications of these findings are discussed. We aimed to provide an overview of both functional and structural neuroimaging studies of breast cancer subjects with and without comorbid depressive symptoms.

METHODS

Search strategy and selection criteria

We searched the Medline - The National Research Register, EMBASE and the Cochrane Controlled Trials Register of the Cochrane Library (edition 2002, no. 4) (1990 to 2009) using the following medical subject heading terms: depression, neuroimage, neuroimaging, Computed Tomography (CT) and Magnetic Resonance Imaging (MRI), Post Traumatic Stress Disorder (PTSD), Positron Emission Tomography (PET), Single-Photon Emission CT (SPECT), major depression, minor depression, voxel-based morphometry, brain MRI, cerebral blood flow; all combined with "breast cancer".

Inclusion criteria

The abstracts were screened and potentially relevant articles retrieved. These articles were included if they met the following criteria: 1) original article, written in English, on brain imaging in adult patients with breast cancer in comparison with control subjects; 2) diagnostic criteria for breast cancer indicated; 3) for CT

or MRI studies: specification of the method to map gray matter; 4) they addressed randomized clinical trials or case-control surveys designed to investigate neuroimaging in women with breast cancer and depression; 5) they assessed cognitive function using validated neuropsychological methods; 6) the reported data were suitable for analysis.

If multiple articles reported on the same imaging outcome measure from the same study population, the article with the most detailed data on brain imaging and/or the largest study population was included. Studies were evaluated according to their methods of investigation, data collection, sample characteristics, neuropsychological measures and interpretation of outcomes. The selected studies were screened to evaluate the methodological validity, including sampling, statistical design, measurements and power analysis.

To improve clarity, we therefore classified the included articles into the following main categories: 1) "Neuroimaging in breast cancer". This category included articles on both structural and functional neuroimaging findings in breast cancer subjects with and without comorbid neuropsychiatric symptoms; 2) "Neuroimaging in breast cancer in association to neuropsychiatric symptoms". This category included articles on both structural and functional neuroimaging findings in breast cancer subjects with depressive, anxiety symptomatology and cognitive assessment; 3) "Neuroimaging" in breast cancer and associated chemotherapy". This category included only articles on studies that evaluated structural and functional neuroimaging in breast cancer subjects with adjuvant chemotherapy.

RESULTS

The search strategy for MRI/ CT and PET/SPECT studies yielded 5455 articles that investigated neuroimaging abnormalities in women with breast cancer and depression. We identified 166 repeated papers. After evaluating paper titles, 5170 papers were excluded, and after evaluating the abstract 104 more were also excluded. Most of the excluded studies were related to the presence of metastasis rather than more subtle brain abnormalities. After selection process was completed, 12 original articles and 1 review were retrieved. Some of the selected studies have overlaps in their samples (Matsuoka et al., 2003; Nakano et al., 2002). We included 12 original papers that provided data for this review on brain abnormalities detected by imaging methodology in women with breast cancer. We reviewed and analyzed the data descriptively and did not perform meta-analyses. Table 1 summarizes the main findings of this review.

According to the classification, the category 1 "Neuroimaging abnormalities in breast cancer" congregated 12 articles. Those articles included structural and functional studies of the brain and also studies combining both modalities. The analysis of all data led to the observation that different brain areas might be vulnerable to the presence of breast cancer. The most striking observation was the extreme variability of the results observed in different studies. In the "Neuroimaging in breast cancer in association to neuropsychiatric symptoms" subgroup the most frequent finding observed in association to the presence of depressive symptoms and abnormalities in the amygdala volume (Yoshikawa et

Table 1. Neuroimaging abnormalities in breast cancer.

Author and date	Sample	Findings
Findings involving limbic areas		
Yoshikawa et al. 2006	22 breast cancer depression (11 major depression + 11 minor depression) 29 breast cancer without depression	Reduced gray matter volume in the left amygdala in breast cancer and depression
Matsuoka et al. 2003	35 breast cancer with cancer-related intrusive recollections; 41 breast cancer without such history	Reduced gray matter volume in the amygdala in subjects with a history of intrusive recollections
Eberling et al. 2004	10 breast cancer taking tamoxifen (TAM); 15 women taking estrogen (ERT+); 15 women not taking estrogen or tamoxifen (ERT-).	Reduced gray matter volume in right hippocampus in women with breast cancer + TAM
Nakamo et al. 2002	28 breast cancer positive to distressing memories regarding to cancer 39 breast cancer negative to distressing memories regarding to cancer	Reduced gray matter volume in left hippocampus with intrusive recollections
Inagaki et al. 2006	51 breast cancer survivors exposed to adjuvant chemotherapy (C+) 55 breast cancer survivors unexposed (C -)	Reduced gray matter volume in parahippocampal gyrus in breast cancer and chemotherapy
Hara et al. 2008	15 breast cancer with pos traumatic stress disorder (PTSD) 39 breast cancer without PTSD	Inverse correlation of PTSD scores and hippocampal volume
Findings involving the basal ganglia		
Ernst et al. 2002	16 breast cancer and tamoxifen 27 without breast cancer that received estrogen 33 control group	Decrease mio-inositol (MI) in basal ganglia in breast cancer with tamoxifen
Silverman et al. 2007	11 breast cancer chemotherapy and tamoxifen 5 breast cancer chemotherapy 5 breast cancer survivors control 3 non breast cancer survivor control	Reduced glucose metabolism in basal ganglia in tamoxifen + chemotherapy
Findings in others brain region		
Inagaki et al. 2006	51 breast cancer exposed to chemotherapy (C+) 55 breast cancer unexposed (C -)	Reduced gray matter volume prefrontal and precuneus in the exposed breast cancer women
Silverman et al. 2007	11 breast cancer chemotherapy and tamoxifen 5 breast cancer chemotherapy 5 breast cancer survivors control 3 non breast cancer survivor control	Reduced glucose metabolism in frontal cortex and cerebellum in subjects with chemotherapy
Kim et al. 2008	12 breast cancer with major depressive symptoms 12 breast cancer without depressive symptoms	Reduced glucose metabolism in prefrontal cortex in association to depressive symptoms
Negative findings		
Yoshikawa et al. 2005	44 breast cancer with chemotherapy 31 breast cancer without chemotherapy	No hippocampal differences

Table 1. Contd.

Author and date	Sample	Findings
	Negative findings	
Inagaki et al. 2004	17 breast cancer with first major depressive after cancer diagnosis 51 subjects without major depressive episode	No hippocampal differences
Matsuoka et al. 2006	28 breast cancer survivor with intrusive recollections; 39 breast cancer survivor without intrusive recollections; 52 women without history; of cancer diagnosis	The frequency of any CSP in the cancer survivors with intrusive recollections was not different in the both groups

al., 2006; Inagaki et al., 2004) and the presence of recollected memory (associated to post traumatic stress) and abnormalities localized in hippocampus volume (Inagaki et al., 2004; Silverman et al., 2007; Eberling et al., 2004 ; Nakano et al., 2002). In the "Neuroimaging in breast cancer and associated chemo-therapy" subgroup, there was no general agreement among the studies, which showed extreme variability (Inagaki et al., 2007; Yoshikawa et al., 2005; Ernst et al., 2002; Silverman et al., 2007; Eberling et al., 2004).

Studies of brain structure in patients with breast cancer

The most prevalent alteration observed in structural studies that examine gray matter abnormalities in association to breast cancer was reduction in volume of structures located at limbic area such as amygdala and hippocampus (Yoshikawa et al., 2006; Inagaki et al., 2004; Inagaki et al., 2007; Yoshikawa et al., 2005; Ernst et al., 2002; Silverman et al., 2007; Eberling et al., 2004; Matsuoka et al., 2003; Nakano et al., 2002; Matsuoka et al., 2006).

Studies of brain spectroscopy in patients with breast cancer

Spectroscopy studies can provide information about alterations in several compounds in the human brain. One study described the presence of reduced mio-inositol located in basal ganglia in association to the use of tamoxifen in breast cancer women (Ernst et al., 2002).

Studies of brain function in patients with breast cancer

A few studies have now demonstrated the involvement of the brain metabolism and function in association to chemotherapy, however the results showed extreme variability. Most of the studies investigated the effect of chemotherapy in brain metabolism and the results were

mostly controversy, involving basal ganglia (Silverman et al., 2007), prefrontal (Kim et al., 2008) and frontal (Silverman et al., 2007) cortex.

DISCUSSION

The analysis of studies results indicates that breast cancer is associated with brain abnormalities observed in both structural and functional neuroimaging in the absence of metastasis. The main finding was the reduction of gray matter volume in the hippocampus and amygdala. This finding was mostly associated to the presence of depressive symptoms in breast cancer women, as well as the presence of comorbid cognitive deficits in those same women (Yoshikawa et al., 2006; Inagaki et al., 2007; Eberling et al., 2004; Matsuoka et al., 2003; Nakano et al., 2002). Possible reasons for the differences in the patterns of brain metabolism and structure assessed in imaging studies may be related to the study design, the control group utilized, presence of other comorbid medication in use, treatment effects or neurodevelopmental plasticity and the presence of other psychiatric disorders, including alcohol and substance misuse.

It is important to discuss the physiology of brain circuits associated with mood regulation and then compare it with the pathophysiology of mood disorders. Normal regulation of mood may depend on the integrity of pathways linking the paralimbic frontal cortex and the basal ganglia (Campbell, 2004). The hippocampus is intimately connected with the amygdala, besides being involved in learning and in consolidation of explicit memories, from short-term to long term memory cortical storage (Campbell, 2004; Joca et al., 2007). Hippocampus has a critical role in memory functioning, is damaged by chronic stress (Astur, 2006) and is also involved in spatial and non-spatial learning and memory processes. Indeed, many studies have demonstrated that exposure to stressful events and corticosteroid hormones affect hippocampal-dependent learning and memory processes (Alfarez and Wiegert Okrugers, 2006). Hippocampus has recently received significant attention in mood disorders research and, although it is not solely responsible for the myriad of symptoms observed in

depression, the highly plastic, stress-sensitive hippocampal region may play a central role in depressive illness (Troson, 2008). The amygdala complex has long been known as part of the neural circuitry critical for emotion (LeDoux, 2000). Amygdala damage demonstrates its importance in emotional learning, whereby cues acquire significance through association with rewarding or aversive events. Other recent research has advanced the concept that the amygdala regulates additional cognitive processes, such as memory or attention (Gallagher and Chiba, 1996). The amygdala is comprised of a number of subnuclei, which can be divided into two broad categories: the basal/lateral complex. The basolateral complex neurons have primarily ascending projections that innervate areas involved in higher cognitive processes, such as the evaluation of emotional stimuli and goal-directed behavior (Gray et al., 2002).

The most frequent alteration seen in patients with depression in general, no with breast cancer, are abnormal blood flow and glucose metabolism in several regions relevant to social cognition, including the amygdala, the rostral anterior cingulate, the orbitofrontal cortex and the dorsolateral prefrontal cortex (DLPFC) (LeDoux, 2000). Typically, areas involved in higher cognitive function (for example, the DLPFC) are deactivated, while structures mediating emotional and stress responses (for example, the amygdala) are abnormally activated. Drevets has suggested that increased activity in the amygdala may reflect stimulations of cortical structures involved in declarative memory, thus accounting for the tendency for depression, therefore, appears to associate with abnormal functioning in both higher cognitive and limbic domains (LeDoux, 2000). A limbic-cortical deregulation model has been proposed to account for the pathophysiology of depression (Gallagher and Chiba, 1996). In summary, depression is associated with altered functional activity in the amygdala, anterior cingulate, and DLPFC- all regions hypothesized to be critical for social cognition (Gray et al., 2002).

Our systematic review of neuroimaging studies in breast cancer has shown that the most replicated finding in this population is the reduced gray matter in the hippocampus and amygdala, as well as the presence or development of depressive symptoms, indicating both reduced gray matter and cerebral blood flow in limbic areas (Yoshikawa et al., 2006; Inagaki et al., 2007; Eberling et al., 2004; Matsuoka et al., 2003; Nakano et al., 2002). However, it has been unclear whether these abnormalities precede the development of depression or are caused by the depressed state (Stephan, 2005). The possibility of a pre-existent depressed state can not be ruled out, as well as the recurrence of a previous depressive episode trigger by a stress and the presence of co-morbid breast cancer.

Furthermore, we acknowledged that we discussed the selected studies applying a similar level of evidence. Even though each study may be different because of its

methodology, sampling, power, design or measurements the present topic had been scarcely investigated, leading to a great variability of findings. In addition, studies controlling for past and current treatment and the presence or absence of co-morbidity are needed to determine the relative contributions. This would allow the pooling of data or a meta-analysis that would compensate for individually small studies. Finally, it should be noted, that some of the selected studies have samples partially overlapped (Matsuoka et al., 2003; Nakano et al., 2002). These aspects should be considered in the interpretation of the findings due to a possibility of type I error (alpha error).

The clinical implication of this review is that, in breast cancer patients, there are more subtle brain changes, in the absence of metastasis, involving both structure and function encompassing several areas. Although, our results implicate different areas, the hippocampus and amygdala may be key areas to present or develop depressive symptom in these population..

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