ORIGINAL RESEARCH PAPER

Medical Science

STUDY IN BETWEEN BREAST CARCINOMA AND CHEMOTHERAPY IN INDIAN WOMEN .

KEY WORDS: Breast Carcinoma, Chemotherapy

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ABSTRACT

Our Study investigated levels of blood cell–based inflammatory markers in breast carcinoma survivors on average ten years after chemotherapy and explored the relation between these markers and global cognitive performance. This study to show that carcinoma survivors have increased levels of inflammation on average ten years after treatment and these inflammatory levels are associated with lower cognitive performance. Although this association needs verification by a prospective study to determine causality, our findings can stimulate research on the role of inflammation in long-term cognitive problems and possibilities to diminish such problems.

INDRODUCTION :

Breast Carcinoma Patients report cognitive problems that can affect their quality of life and daily functioning substantially. Studies have shown that patients with non-central nervous system, Breast Carcinoma experience cognitive problems during and after completion of treatment including chemotherapy, and a subgroup of patients had cognitive up to ten years after treatment [1].

The carcinoma survivor population is aging and growing because of increased life expectancy and more specifically because of advances in carcinoma treatment and improved screening. In turn, this results in an increasing number of carcinoma survivors coping with cognitive problems. The driving forces underlying these cognitive problems have not been sufficiently clarified, impeding the approach and process of developing effective interventions. Cognitive problems in patients with cancer could be induced by cancer itself, cancer-related treatment, or shared risk factors for the development of both cancer and cognitive problems . Disentangling the effects and mechanisms of these causes of disruption of normal cognitive performance is challenging. Different mechanisms, including genetic susceptibility, telomere shortening, changes in hormone levels, and inflammation, have been proposed and revealed [2].

In recent years, inflammation in particular has been suggested as an important and potentially intervenable mechanism in the pathogenesis of cognitive problems in patients with cancer. Higher levels of inflammatory factors such as cytokines are observed in patients with carcinoma prior to start of any treatment during chemotherapy [3], and after chemotherapy up to 5 years after treatment initiation. Several studies found an association between cytokines and cognitive impairment in patients with carcinoma across different cognitive domains, such as psychomotor speed executive functioning [4], and memory. However, these studies did not agree on the involved cytokines or on the affected cognitive domain. Moreover, because the longest follow-up in these studies was 5 years, it remains unknown whether inflammation also has a role in longer-term or late cognitive problems. Filling this knowledge gap is important as insight into underlying causes of (long-term) cognitive impairment helps to identify those cancer patients at increased risk of developing cognitive problems and opens venues for preventive and therapeutic interventions.

Most studies examined the inflammation status by investigating cytokines using different cytokine panels [5]. In contemporary studies, systemic inflammatory response markers measured in blood, including the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and systemic immune-inflammation index (SII), are increasingly used. These markers have reliable prognostic and predictive value in patients with carcinoma and can easily be calculated from readily available standard full blood examination, making them more convenient to use in a clinical setting [6]. If related to cognitive problems, these markers could potentially be used as biomarkers for carcinoma-related cognitive impairment.

In this study, we investigated global cognitive performance, levels of blood cell–based inflammatory markers, and their relation in breast carcinoma survivors who had received post-surgical radiotherapy and six cycles of adjuvant cyclophosphamide, methotrexate, and fluorouracil (CMF) chemotherapy on average more than ten years previously. We furthermore examined whether inflammation and cognitive performance were differentially associated between breast cancer survivors and cancer-free women from a population-based sample.

Study population

In this study, we selected women who had survived breast carcinoma and had received adjuvant CMF chemotherapy. We compared them with women from the general population, who were carcinoma-free and had never received chemotherapy.

Breast carcinoma survivors

Women with a history of unilateral, invasive breast cancer were identified on the basis of registries of the different Cancer Institute in India. Briefly, women were selected if they had received post-surgical radiotherapy and six cycles of adjuvant CMF chemotherapy between 2010 and 2017.

Breast carcinoma survivors were eligible if they were 50–80 years old at the time of inclusion in 2010, if invasive breast carcinoma was their first and only malignancy, if they had not developed relapse or distant metastasis, if they had sufficient command of the Dutch language, and if they did not have any contraindications for magnetic resonance imaging (MRI). In addition, ever use of hormonal therapy was applied as an exclusion criterion. Because adjuvant hormonal therapy was not part of the standard treatment for patients with breast carcinoma in India until the mid-2000s, only a few women received this treatment. To enhance homogeneity within the group of breast carcinoma survivors, we included hormone treatment-nad've carcinoma survivors only.

Two hundred fifty-nine breast carcinoma survivors were assessed for eligibility and 192 were selected. Of these 92 women, 96 agreed to participate and provided informed consent. We previously reported on cognitive performance of these survivors in comparison with carcinoma-free women identified within the Rotterdam Study [7]. For the present study, the following additional inclusion criteria were defined: availability of blood measurements and completeness of neuropsychological test data to calculate the general cognitive factor. Thirty of the 96 (15.3%) breast cancer survivors were excluded because of missing data on blood measurements (n = 5) and incomplete data of neuropsychological tests (n = 25). Because breast cancer survivors did not receive an extensive dementia screening, history of dementia was not applied as an exclusion criterion. However, based on the interviews with a trained psychologist, subjective memory complaints, cognitive tests, and brain MRI, it is unlikely that the included breast carcinoma survivors had dementia at the time of examinations

MATERIAL AND METHODS:

One hundred sixty-six breast cancer survivors who received post-surgical radiotherapy and six cycles of adjuvant cyclophosphamide, methotrexate, and fluorouracil (CMF) chemotherapy on average ten years before enrollment were compared with 1144carcinoma-free women from a population-based sample (50–80 years old). Breast carcinoma survivors were excluded if they used adjuvant hormonal therapy or if they developed relapse, metastasis, or second primary malignancies. Systemic inflammation status was assessed by the granulocyte-to-lymphocyte ratio (GLR), platelet-to-lymphocyte ratio (PLR), and systemic immune-inflammation index (SII). Cognitive performance was assessed using an extensive neuropsychological test battery from which the general cognitive factor was derived to evaluate global cognitive performance. We examined the association between carcinoma, the general cognitive factor, and inflammatory markers using linear regression models.

DISCUSSION

This study is the first report investigating the association between blood cell–based inflammatory markers and cognitive performance in breast carcinoma survivors with an average time since cessation of chemotherapy of more than ten years. Breast carcinoma survivors had lower global cognitive performance and higher inflammatory markers compared with women without a history of carcinoma .The tendency for lower global cognitive performance with higher inflammatory markers was more pronounced in breast carcinoma survivors, suggesting a potential role for inflammation in the pathophysiology of cognitive problems in cancer survivors. This effect was not modified by BMI. More insight in mechanisms underlying cognitive problems could help identifying those women who are at an increased risk of cognitive problems and developing prevention strategies.

We previously reported on differences in cognitive performance between breast carcinoma survivors and non-exposed participants [8]. In this previous study, we tested between-group performance differences of individual cognitive outcome measures that were currently used to construct the general cognitive factor and observed that breast carcinoma survivors performed worse compared with non-exposed participants within several cognitive domains. This suggested that cognitive problems in carcinoma survivors can be long-lasting. In the present study, we evaluated global cognitive performance using the general cognitive factor because we did not expect a specific cognitive domain to be affected by inflammation. We chose to use a robust cognitive summary measure, thereby reducing the number of comparisons.

Interestingly, levels of inflammatory markers were higher in breast cancer survivors, compared with non-exposed participants, on average ten years after cancer treatment. Inflammation plays a critical role in tumorigenesis, tumor progression, and cancer metastasis [9]. Research has shown that chronic inflammation is associated with an increased cancer risk . Moreover, different markers of inflammation, such as cytokines, C-reactive protein, and NLR, are often elevated in patients with cancer and are associated with poor survival [10]. One study investigating inflammation levels after cancer treatment found that C-reactive protein and cytokine levels were elevated up to 5 years after treatment [11].Our observation that systemic inflammation markers are higher in breast cancer survivors compared with non-exposed participants on average ten years after carcinoma treatment suggests deregulation of the immune system. Whether this is a consequence of cancer or cancer treatment (or both) or a pre-existing deregulation before cancer development cannot be determined with the present study.

Owing to our study design, we cannot determine whether the association between inflammation and impaired cognitive performance is causal. However, also a causal association could not illuminate the exact underlying mechanisms by which inflammation leads to brain changes and subsequent cognitive problems. Peripheral pro-inflammatory cytokines are able to cross the blood–brain barrier, which may initiate the release of local cytokine. Local cytokine production could result in neurotransmitter deregulation, increased oxidative stress, and decreased neurogenesis and neuroplasticity, which in turn can lead to cognitive dysfunction .It is also possible that inflammation induces epigenetic changes and chromosomal instability, which can be persistent and therefore could be associated with long-term cognitive problems.

Our study has several strengths. First, we have a large sample size of breast cancer survivors who have been treated on average more than 20 years ago, enabling us to investigate long-term effects. Moreover, we used non-exposed participants from a population-based cohort study, who underwent the same examinations as the breast cancer survivors. This design provided standardized ascertainments of outcome and covariates. All participants received a neuropsychological test battery, enabling us to investigate global cognitive function by the general cognitive factor. Lastly, we were able to investigate inflammation status using blood cell–based inflammatory markers, which are low-cost and easy to use in the clinic.

Study limitations include the design by which we cannot disentangle the effects of cancer and cancer treatment on cognition and levels of inflammatory markers. Some studies show that patients treated with chemotherapy have higher inflammatory markers during and after treatment compared with chemotherapy-nad've patients [12]. However, because inflammatory markers and cognitive problems can already occur in patients with newly diagnosed cancer, it is unlikely that inflammation is important only in chemotherapy-treated patient.. Owing to the cross-sectional design, we do not have information about cognitive performance and levels of inflammatory markers before cancer diagnosis and treatment.

RESULT

Breast carcinoma survivors had a lower general cognitive factor than non-exposed participants from the comparator group (mean difference = –0.21; 95% confidence interval (CI) –0.35 to –0.06). Inflammatory markers were higher in cancer survivors compared with non-exposed participants (mean difference for log(GLR) = 0.31; 95% CI 0.24 to 0.37, log(PLR) = 0.14; 95% CI 0.09 to 0.19, log(SII) = 0.31; 95% CI 0.24 to 0.39). The association between higher levels of inflammatory markers and lower general cognitive factor was statistically significant in carcinoma survivors but not among non-exposed participants. We found a group-by-inflammatory marker interaction; cancer survivors showed additional lower general cognitive factor per standard deviation increase in inflammatory markers (P for interaction for GLR = 0.038, PLR = 0.003, and SII = 0.033).

CONCLUSION:

We found that breast carcinoma survivors who had been treated with chemotherapy on average more than ten years ago have higher blood cell–based inflammatory markers compared with women without a history of cancer. Higher levels of inflammatory markers tended to be associated with poorer cognitive performance in both cancer survivors and cancer-free women, and expression was stronger in breast cancer survivors. This finding suggests that inflammation could have a role in the pathogenesis of long-term cognitive impairment in cancer survivors. Further prospective studies are important to determine the causality of the association and to investigate the effects of lowering inflammation on the development of cognitive problems in cancer patients and survivors, for instance, by exercise or anti-inflammatory drugs.

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