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Cognitive impairment in the first year after breast cancer diagnosis: A prospective cohort study

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ABSTRACT

Objectives: The objective of this study was to assess the relation between cancer treatments and incident cognitive impairment in breast cancer patients, taking into account the levels of anxiety before treatment.
Materials and methods: We conducted a prospective cohort study with 418 newly diagnosed breast cancer patients with no cognitive impairment, defined as values at least 1.5 standard deviations below age- and education-adjusted cut-offs in the Montreal Cognitive Assessment (MoCA), at baseline. The Hospital Anxiety and Depression Scale and MoCA were used for evaluations before treatment and at 1-year after diagnosis. We used Poisson regressions to compute adjusted relative risks (RR) and corresponding 95% confidence intervals (95%CI) to identify predictors of cognitive impairment.
Results: The median (Percentile 25, Percentile 75) MoCA score before treatment was 24 (21, 26). A total of 8.1% (95%CI: 5.8, 11.2) of the patients presented incident cognitive impairment during the follow-up. There was a statistically significant interaction between anxiety at baseline and the effect of chemotherapy on the incidence of cognitive impairment (P for interaction = 0.028). There was a significantly increased risk of incident cognitive impairment among patients with no anxiety prior to treatment with schemes including doxorubicin and cyclophosphamide (adjusted RR = 4.22, 95%CI: 1.22, 14.65).
Conclusion: There was a statistically significant association between chemotherapy and cognitive impairment, but only among women with no anxiety at baseline.

1. Introduction

Worldwide, breast cancer is the leading cause of malignant neoplasms among women, with an estimated 1.67 million new cases in 2012 [1]. Due to improved access to early diagnosis and effective treatments [2,3], breast cancer survival increased over the past years, with the most recent 5-year relative survival estimates surpassing 80% in several developed countries [4]. The growing number of women surviving breast cancer for longer periods highlights the need for a comprehensive assessment of the burden related to cancer treatment, especially regarding conditions that may be associated with some degree of incapacity throughout life.

Breast cancer and its treatment may be accompanied by several neurological complications [5], which may affect the patients' capacity to accomplish their daily life activities [6]. Although cognitive impairment has been documented among breast cancer patients, its aetiology and determinants remain unclear. Chemotherapy has been the treatment more consistently associated with cognitive impairment among breast cancer patients [7–10], and the pattern of cognitive dysfunction associated with it was named "chemobrain" [11]. However, heterogeneous results across studies may reflect, to some extent, methodological differences, namely regarding the definition of the outcome, the characterization of the exposure and the control of confounding factors [12,13].

In addition to chemotherapy, many other treatments and conditions have been postulated to be related to cognitive impairment, namely radiotherapy [14,15], endocrine therapy [16,17], para-

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neoplastic syndromes [18], increased levels of pro-inflammatory cytokines, especially interleukin 1 and 6, and tumour necrosis factor [19] and also anxiety and depression [10]; however, findings are inconsistent.

Although anxiety has not been consistently proven to be a risk factor for cognitive impairment [10,20,21], cognitive interference theories suggest that high levels of anxiety are associated with poorer performance in cognitive tests, due to decreasing attentional control [22,23]. Therefore, we hypothesized that anxiety prior to treatment may influence the estimated role of potential risk factors for cognitive impairment; this may also contribute to inconsistent findings across studies, and should be taken into account in the interpretation of results. We aimed to quantify the association between cancer treatments and incident cognitive impairment, in early stage breast cancer patients during the first year of follow-up, taking into account the levels of anxiety before treatment.

2. Methods

We conducted a prospective cohort study of women with newly diagnosed breast cancer, followed for 1-year, as previously described in detail [24].

2.1. Assembling of the cohort

Participants were consecutively recruited in 2012, among women aged 18 years or older, admitted to the Breast Clinic of the Portuguese Institute of Oncology of Porto (IPO-Porto), Portugal, with a potential diagnosis of breast cancer ($N = 961$). We considered eligible those who were proposed for surgery, with histologically confirmed breast cancer diagnosed in the previous three months, not treated with chemotherapy and/or radiotherapy in the chest or axillary areas for other primary cancers, and capable of understanding the purpose of the study ($N = 588$). We excluded those who refused to participate ($N = 2$), those with a Montreal Cognitive Assessment (MoCA) score at least 1.5 standard deviations below age- and education-adjusted cut-offs for possible cognitive impairment at baseline [25] ($N = 165$), and those with stage IV cancer ($N = 2$). We further excluded one woman with missing data on anxiety at baseline. Data from 418 participants was therefore available for the present analysis.

2.2. Data collection

Sociodemographic data was collected at baseline, using a structured questionnaire. Information on breast cancer stage and treatment were collected from clinical records.

The Hospital Anxiety and Depression Scale (HADS) [26,27] was used to characterize anxiety and depression at baseline and at 1-year of follow-up; scores range from 0 to 21, and scores greater than or equal to 11 in the respective subscales were considered indicative of clinically significant anxiety and/or depression, as applicable.

The MoCA test was used to evaluate cognitive performance, at baseline and at the 1-year follow-up evaluation. Incident cognitive impairment was considered to have occurred during the first year after the initial assessment when the patient's MoCA score (ranging from 0 to 30) decreased to values at least 1.5 standard deviations below age- and education-adjusted cut-offs for possible cognitive impairment [25].

2.3. Statistical analysis

Sample characteristics are presented as counts and proportions for categorical variables, and median and percentiles 25 and 75 (P25, P75) for quantitative variables, taking into account the asymmetry of the corresponding distributions.

We computed cumulative incidence estimates, and the corresponding 95% confidence intervals (95%CI), for cognitive impairment at the 1-year follow-up. Adjusted relative risks (RR) and

Table 1
Sociodemographic and clinical characteristics of breast cancer patients with normal cognitive function for their age and education at baseline ($N = 418$).

	N (%)
Age[a], years	
≤55	200 (47.8)
>55	218 (52.2)
Education[b], years	
≤4	198 (47.4)
5-9	110 (26.3)
≥10	110 (26.3)
Anxiety[c]	159 (38.0)
Depression[d]	34 (8.1)
Cancer stage	
0	29 (6.9)
I	197 (47.1)
II	132 (31.6)
III	60 (14.4)
Breast surgery[e]	
Breast-conserving	212 (50.7)
Mastectomy	206 (49.3)
Axillary surgery[f] [$N = 404$]	
SLNB	265 (65.6)
ALND	139 (34.4)
Chemotherapy	242 (57.9)
Timing	
Neoadjuvant	25 (10.3)
Adjuvant	217 (89.7)
Schemes	
Doxorubicin + cyclophosphamide[g]	50 (20.7)
Doxorubicin + cyclophosphamide + docetaxel[h]	24 (9.9)
5-FU + epirubicin + cyclophosphamide[i]	20 (8.3)
5-FU + epirubicin + cyclophosphamide + docetaxel[j]	144 (59.5)
Others[k]	4 (1.6)
Radiotherapy	303 (72.5)
Brachytherapy	82 (19.6)
Endocrine therapy	351 (84.0)
Immunotherapy	55 (13.2)

ALND, Axillary lymph node dissection; SLNB, Sentinel lymph node biopsy; 5-FU, 5-Fluorouracil.

[a] Range: 27–87 years.

[b] Range: 2–22 years.

[c] Defined as a score ≥11 in the anxiety subscale of the Hospital Anxiety and Depression Scale. The median (Percentile 25, Percentile 75) of the whole sample was 9 (6, 12).

[d] Defined as a score ≥11 in the depression subscale of the Hospital Anxiety and Depression Scale. The median (Percentile 25, Percentile 75) of the whole sample was 5 (2, 8). Within the group of patients with depression, four patients did not present anxiety (11.8%) but the remaining 30 cases reached a clinically significant score in the anxiety subscale (88.2%).

[e] Patients who had both breast-conserving surgery and mastectomy are reported as mastectomy.

[f] Patients who had both SLNB and ALND are reported as ALND; does not sum 100.0% because 14 patients only performed breast surgery.

[g] Four cycles of concomitant doxorubicin (60 mg/m^2) and cyclophosphamide (600 mg/m^2).

[h] Four cycles of concomitant doxorubicin (60 mg/m^2) and cyclophosphamide (600 mg/m^2), followed by four cycles of docetaxel (100 mg/m^2).

[i] Six cycles of concomitant 5-FU (500 mg/m^2), epirubicin (100 mg/m^2), and cyclophosphamide (500 mg/m^2).

[j] Three cycles of concomitant 5-FU (500 mg/m^2), epirubicin (100 mg/m^2) and cyclophosphamide (500 mg/m^2), followed by three cycles of docetaxel (100 mg/m^2).

[k] Four cycles of concomitant doxorubicin (60 mg/m^2) and cyclophosphamide (600 mg/m^2), followed by four cycles of Paclitaxel (80 mg/m^2) ($N = 1$), Four cycles of concomitant cyclophosphamide (600 mg/m2) and docetaxel (75 mg/m^2) ($N = 1$), Six cycles of concomitant docetaxel (75 mg/m^2) and carboplatin (212 mg/m^2) ($N = 1$) and Six cycles of concomitant 5-FU (600 mg/m^2), cyclophosphamide (600 mg/m^2) and methotrexate (40 mg/m^2) ($N = 1$).