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Original article

Severe fatigue after treatment of ductal carcinoma in situ: A comparison with age-matched breast cancer survivors and healthy controls☆

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ABSTRACT

Purpose: Severe fatigue after treatment of ductal carcinoma in situ (DCIS) has not been studied before. The current study examined (i) the prevalence of severe fatigue in DCIS patients versus breast cancer survivors (BCS) and healthy controls (HC), (ii) quality of life and functioning of severely versus non-severely fatigued DCIS patients and BCS, and (iii) the association of fatigue with psychosocial and behavioral factors in DCIS patients.
Methods: 89 patients treated for DCIS were matched on age and gender to 67 BCS and 178 HC (ratio 1:1:2). Fatigue was measured with the Fatigue Severity subscale of the Checklist Individual Strength.
Results: 23% of DCIS patients, 25% of BCS, and 6% of HC were severely fatigued (DCIS versus HC: $p < 0.001$). Severely fatigued DCIS patients had a lower quality of life and were more impaired in all domains of functioning than non-severely fatigued DCIS patients. Sleep problems, dysfunctional cognitions regarding fatigue, avoidance of activities, all-or-nothing behavior, perceived lack of social support, DCIS-related coping problems, and fear of future cancer occurrence were related to fatigue.
Conclusions: The prevalence of severe fatigue in DCIS patients was similar to BCS, but higher than in HC. Severely fatigued DCIS patients had a lower quality of life and more functional impairments. The psychosocial and behavioral fatigue-related factors in DCIS patients are known to perpetuate fatigue in BCS. These factors can be targeted in interventions for cancer-related fatigue. Our findings suggest that the same treatment elements might be applicable to severely fatigued DCIS patients.

1. Introduction

Since the introduction of breast cancer screening programs in western countries in the nineties, the number of detected cases of ductal carcinoma in situ (DCIS) has increased rapidly [1]. Nowadays, an estimated proportion of 1 in 33 women will be diagnosed with an in situ diagnosis in her lifetime [2]. It cannot be predicted in which cases DCIS will be harmless, and in which cases it will develop into breast cancer [3]. To prevent any progression, DCIS is generally treated with a mastectomy or breast-conserving surgery followed by radiotherapy [4].

This means that although DCIS is non-invasive, it is treated with

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the same treatment modalities as breast cancer. This paradox can make DCIS a confusing diagnosis for patients [5]. So far, the influence of DCIS on patients' lives has been examined in a limited number of studies. A recent large study showed that the overall quality of life does not differ between DCIS patients and age-matched women without a history of a breast disease [6]. Nevertheless, the diagnosis and treatment of DCIS can have significant impact on psychosocial functioning.

A subgroup of DCIS patients has increased distress levels and poor mental health during and after treatment completion, and coping problems frequently occur [7–9]. Patients are often unsure about their diagnosis, for example about whether DCIS is cancer [9]. Despite the favorable prognosis of DCIS, many patients overestimate their actual risk on the occurrence of breast cancer or metastases [8,10,11]. Anxiety plays a main role in this overestimation [8].

In contrast to the limited number of studies on sequelae of DCIS treatment, numerous studies examined this subject in breast cancer survivors (BCS). In these studies, severe fatigue emerged as one of the most troublesome cancer-related symptoms, occurring in approximately one in four BCS and diminishing patients' quality of life [12,13]. Thus far, the prevalence of severe fatigue and its consequences have not been studied in DCIS patients.

Guidelines on cancer-related fatigue assume that fatigue is related to cancer and its treatment [13]. However, these triggers are no longer present after treatment completion. At that point, factors that maintain fatigue come into play [14]. There is evidence for multiple psychosocial and behavioral factors that can perpetuate fatigue in cancer survivors: sleep problems, perceived lack of social support, low physical activity levels, dysfunctional cognitions regarding fatigue, heightened fear of cancer recurrence, and poor coping with the diagnosis cancer and being treated for cancer [14,15]. Though DCIS-related coping problems and worries about future cancer occurrence are also common in DCIS patients [8,10,11], it is unknown if these factors are related to fatigue. The other factors and their association with fatigue have not been explored in DCIS patients yet.

In this study, we examined (i) the prevalence of severe fatigue in DCIS patients compared to BCS and healthy controls (HC), (ii) quality of life and functioning of severely versus non-severely fatigued DCIS patients and BCS, and (iii) the association of fatigue with psychosocial and behavioral factors in DCIS patients.

2. Methods

2.1. Participants and procedure

A cross-sectional study was conducted in two general hospitals in the Netherlands: hospital Gelderse Vallei (Ede) and hospital Pantein (Boxmeer). All patients who were treated for DCIS or breast cancer between January 2010 and September 2015 were registered in anonymous patient registries. DCIS patients and BCS were selected from these registries. Ethical approval was obtained from the medical ethic committees of both hospitals.

DCIS patients were eligible if treatment for DCIS was completed up to five years ago. DCIS patients were excluded if (i) a current or former malignant tumor, or (ii) a somatic comorbidity that can cause severe fatigue was reported in their medical records. All eligible DCIS patients were selected from the patient registries, and invited to participate by mail. If they were willing to participate, they were asked to return a participation form and to indicate if they preferred to complete the questionnaires by e-mail or by mail. Subsequently, participants received the questionnaires in the preferred way, as well as an informed consent with a self-addressed envelope by mail.

To determine if the prevalence of fatigue in DCIS patients differed from women who have had a malignant breast tumor and healthy women, two control groups were selected. Each DCIS patient was matched to one BCS and two HC (ratio 1:1:2) with respect to gender and age, based on categories of 5-year strata. Matched BCS were selected from the patient registries of the participating hospitals. All matched BCS (i) had completed breast cancer treatment up to five years ago (except for hormone therapy), (ii) were disease-free, and (iii) had no somatic comorbidities that could cause severe fatigue according to their medical records. To equalize type of treatment, DCIS patients were only matched to BCS who had not received chemotherapy. A recent meta-analysis of our research group indicated chemotherapy as a potential risk factor for severe fatigue in BCS [12]. For this reason, BCS who had received chemotherapy were excluded. Matched BCS received questionnaires by mail. They were asked to return the questionnaires and an informed consent if they were willing to participate.

Matched HC were derived from CentERdata, a cohort of over 2000 Dutch adults who represent the general Dutch population [16]. Precision matching on age and gender was performed with the procedure Coarsened Exact Matching (CEM) using STATA/SE 12.1. Being healthy was defined as zero days of sick leave in the past month, and no self-reported limitations in daily activities, social activities and work due to health problems.

2.2. Measures

Data on the clinical variables stage of DCIS, type of surgery, radiotherapy, and date of diagnosis were retrieved from medical records. Data on the latter two variables were also available in BCS. Data on the socio-demographic variables partner and work status, educational level, medical problems, and recent significant life events were gathered with self-report questionnaires. Educational level was also available in HC and categorized into low, medium and high, according to the Dutch national public health compass [17].

The level of fatigue was measured in DCIS patients, BCS and HC with the subscale Fatigue Severity of the Checklist Individual Strength (CIS-fatigue; 8 items, 7-point scale, range 8–56) [18,19]. Higher score indicate higher levels of fatigue. The established cut-off score for severe fatigue is 35 or higher, which is two standard deviations above the mean score in HC [18, 19]. The CIS-fatigue has good psychometric properties [20,21], and was used in previous research on cancer patients and survivors [14,15,22].

Quality of life and functioning were measured in DCIS patients and BCS with the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC-QLQ-C30; 30 items, 4-point scale) [23]. This questionnaire consists of function scales (physical, social, cognitive, emotional, and role functioning) and a global quality of life scale. Higher scores indicate better functioning. The EORTC-QLQ-C30 has adequate validity and reliability [24].

Questionnaires on behavioral and psychosocial factors were only administered in DCIS patients. *Sleep quality* was measured with the Sleep/Rest subscale of the Sickness Impact Profile-8 (SIP-8). Higher scores indicate more sleep problems [25].

Activity patterns were assessed with the two subscales of the Cognitive and Behavioral Responses to Symptoms Questionnaire (CBRSQ): avoidance of activities and fluctuating activity patterns (i.e., all-or-nothing behavior). Higher scores indicate a more dysfunctional activity pattern [26].

Cognitions regarding fatigue were measured with the Self-Efficacy Scale (SES). Higher scores indicate a lower sense of control with regard to fatigue [27]. Focusing on fatigue was measured with the Illness Management Questionnaire (IMQ). Higher scores