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Original article

Fatigue, anxiety and depression overrule the role of oncological treatment in predicting self-reported health complaints in women with breast cancer compared to healthy controls

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ABSTRACT

Background: Women with breast cancer often attribute their health problems as side effects caused by oncological treatments. The aim of the study was to examine and compare self-reported health complaints (SHC) in postmenopausal patients with breast cancer to healthy controls.
Method: Women with breast cancer ($N = 196$) filled in 5 questionnaires 1–2 years after surgery; SHC Inventory, Functional Assessment of Cancer Therapy-Endocrine Subscale (FACT-ES), Fatigue – Functional Assessment of Cancer Therapy-Fatigue subscale (FACIT-F), Fatigue Visual Analog Scale (Fatigue VAS), and Hospital Anxiety and Depression Scale (HADS). Controls comprised 101 blood donors who reported on the questionnaires except for HADS. Bonferroni adjustment and $p < 0.0017$ was considered statistically significant for SHC Inventory, $p < 0.05$ for the remaining questionnaires.
Results: The patients, mean age 58.0 (SD 9.5), reported significantly more self-reported health complaints, whereof 6 of 29 complaints were significantly elevated compared to the controls, mean age 57.0 (SD 5.8) ($p < 0.001$). HADS scores in patients fell into normal range, mean 6.3 (SD 5.7). A subgroup of 48 patients experienced more frequent and severe symptoms in all the questionnaires compared to the remaining 148 patients, and the 101 controls. Among the patients, fatigue, anxiety and depression explained 49% of the total variance in self-reported health complaints ($p \leq 0.001$).
Conclusion: Most women with breast cancer (76%) reported health complaints equal to the healthy controls. Fatigue, anxiety and depression, not oncological treatments, were significant predictors for the complaints.

Introduction

Adjuvant chemotherapy and endocrine therapy, i.e. tamoxifen (Tam) and aromatase inhibitors (AIs) prevent recurrence in estrogen receptor-positive breast cancer patients [1]. Treatment works by blocking the stimulatory effect of estrogen on the estrogen receptor level, or by suppressing the total body estrogen levels [1], both creating a menopausal transition [1]. Early menopause

Abbreviations: SHC, Subjective Health Complaints; FACT-ES, Functional Assessment of Cancer Therapy-Endocrine Subscale; FACIT-F, Fatigue – Functional Assessment of Cancer Therapy-Fatigue subscale; Fatigue VAS, Fatigue Visual Analog Scale; HADS, Hospital Anxiety and Depression Scale; FEC, Flourouracil + Epirubicin + Cyclofosfamid; SD, Standard Deviation; OR, Odds Ratio; CI, Confidence Intervals; Tam, Tamoxifen; AI, Aromatase Inhibitor.

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caused by chemotherapy has been reported in 40% of 40 year old women, and close to 100% in women after the age of fifty [2]. Women who become post-menopausal at a younger age are more likely to have bothersome symptoms compared to older women [3].

Side effects of hormone blockade are typically those that accompany onset of menopause; heat flushes, sleep disturbance, fatigue, vaginal dryness and depression [4–6]. Fatigue is described as an unusual or extreme sensation of tiredness that is not easily overcome by rest or sleep, and afflicts the whole human being [7]. Attacks of fatigue that recur or persist for more than 6 months are classified as chronic [7,8]. Prevalence of cancer-related fatigue is approximately 60%–90%, and may persist for months to years after the completion of therapy [8]. Interrupted sleep is also a substantial problem in breast cancer patients [9]. In addition, between 30% and 50% of cancer patients report anxiety and depression [9], which may increase mortality risk when elevated symptoms [10]. Individuals with concomitant depression have a greater non-adherence to endocrine treatment compared to patients without depression [11]. Many healthy postmenopausal women often report health complaints like the patients [3]. However, Amir et al. [12], found that the breast cancer treatments, like chemotherapy and endocrine therapy, may lead to a higher risk of developing the same health complaints. Though, the physiology of the menopause is complex, and may vary considerably both among patients and healthy women [13,14].

Self-reported health complaints, are defined as symptoms or complaints that, despite thorough examination, cannot be fully explained [15]. The Subjective Health Complaints Inventory (SHC Inventory) is a validated instrument commonly used in different populations and countries, examining self-reported health complaints during the last month [15,16]. Self-reported health complaints are very common, and the most frequently reported complaints are muscle and joint pain, gastrointestinal problems, tiredness and sleep disorders [15,17]. Studies suggest that subgroups of breast cancer patients report several postmenopausal complaints [13,18]. In clinical practice, patients with breast cancer often wonder whether the symptoms are a result of treatment or due to aging. However, there are few studies examining these complaints in women with breast cancer compared to post-menopausal healthy controls.

The objectives of this study were; (1) examine the validity of SHC Inventory in women with breast cancer, (2) compare self-reported health complaints in patients with breast cancer, 1–2 years after surgery, to healthy controls, (3) identify differences in self-reported health complaints in the patient group, and (4) factors that explain the variance in these complaints.

Material and methods

Participants

Women with breast cancer were recruited from two university hospitals between 2012 and 2013 [19]. The study population were consecutive patients receiving curative breast cancer treatment (surgery, chemotherapy, radiation, and/or endocrine therapy). Demographic information like age, body-mass index (BMI), marital status, and education was obtained, and medical records were used to confirm cancer-related data. 209 patients, 1–2 years (median 18 months) after surgery responded to 5 questionnaires about health problems. Thirteen patients dropped out due to; long travel distance (n = 8), unknown reasons (n = 4), and dead (n = 1). As a result, 196 (94%) patients were included. After curative treatment, none of the patients self-reported regained menstruation, and consequently, they were all in a postmenopausal state.

The controls were 315 female blood donors coming to a university hospital during the spring of 2014. The women were given information about the study and asked to participate by filling in 4 of the 5 questionnaires, and giving the same demographic information as the patients. All the controls accepted the participation. Those 101, who self-reported a postmenopausal state, were included in this study.

The patients and controls were Norwegian women more than 18 years of age.

Measures

SHC Inventory was the core instrument to examine subjective health complaints, and is not previously tested in a breast cancer population. Therefore, three validated breast cancer- and one generic questionnaire were used to substantiate the results in the SHC Inventory. The instrument measures 29 subjective, somatic and psychological complaints experienced during the last month, and has a satisfactory validity and reliability [16]. Severity of each complaint is rated on a 4-point Likert scale; 0 = “no” complaints to 3 = “severe complaints” (range 0–87). The questionnaire evaluates five domains; *musculoskeletal pain* (headache, neck pain, upper back pain, low back pain, arm pain, shoulder pain, migraine, and leg pain, range 0–24), “*pseudoneurology*” (tiredness, sleep problems, anxiety, sadness/depression, extra heartbeats, heath flushes, and dizziness, range 0–21), *gastrointestinal problems* (gas discomfort, stomach discomfort, diarrhea, constipation, gastritis/ulcer, heartburn, and stomach pain, range 0–21), *allergy* (allergies, breathing difficulties, eczema, and asthma, range 0–15) and *flu* (cold/flu and coughing, range 0–6) [16]. In a previous study using SHC Inventory, 86% from the general population and 96% of the healthy controls [17] reported a score below 20, which was considered as normal. We therefore used a SHC-score of 20 as cut-off value to dichotomize patients into subgroups.

Functional Assessment of Cancer Therapy – Endocrine Subscale, version 4 (*FACT-ES*) contains 19 statements examining self-reported menopausal and sexual symptoms related to breast cancer endocrine therapy during the last week. A license had to be obtained before using the FACT-ES (http://www.facit.org/). The scores range from 0 = “not at all” to 4 = “very much”, range 0–76. According to the guidelines, all the questionnaires are drafted in a way that higher scores represent improved quality of life [20], therefore, higher scores must represent fewer symptoms. When translating the FACT-ES from English to Norwegian, the FACIT Translation Project Team's methodology was followed [21]. Cronbach's alpha for the Norwegian version of FACT-ES was 0.86 in patients, and 0.83 in controls.

Functional Assessment of Cancer Therapy – Fatigue Subscale, version 4 (FACIT-F), is a validated self-assessment scale consisting of 13 items measuring physical and mental fatigue affecting daily life during the last week [22]. Each item is rated on a 5-point scale (0 = “not at all” to 4 = “very much”, range 0–52) and higher scores represent fewer symptoms [22]. Cronbach's alpha in the patients and controls were 0.84 and 0.81 respectively.

Fatigue Visual Analog Scale (Fatigue-VAS) is a 100 mm line where the far left is 0 = “no problems with fatigue and exhaustion”, and the far right is 10 = “so much fatigue and exhaustion that is possible to experience”, during the last week [23]. The scale examines the intensity of fatigue reported by the patients during the clinical investigation.

HADS is a self-assessment mood scale consisting of 14 items, 7 for HADS-A (anxiety) and 7 for HADS-D (depression) [24]. Each item is rated from 0 = “not present” to 3 = “maximum”. The scale