The Breast xxx (2014) 1–8

Contents lists available at ScienceDirect

The Breast

journal homepage: www.elsevier.com/brst

Original article

Development in self-reported arm-lymphedema in Danish women treated for early-stage breast cancer in 2005 and 2006 – A nationwide follow-up study

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ARTICLE INFO

Article history:
Received 23 December 2013
Received in revised form
18 February 2014
Accepted 3 March 2014

Keywords:
Breast cancer
Lymphedema
Development
Prevalence
Associated factors

ABSTRACT

The main purpose of this nationwide follow-up study was to examine the development of self-reported lymphedema in the population of women with early-stage breast cancer in Denmark. In 2008 and 2012 two identical questionnaires were sent to the women aged 18–70 years treated for unilateral primary breast cancer in 2005 and 2006. 2293 women (87%) reported on lymphedema in 2008 and 2012. Overall 37% reported lymphedema in 2008 while 31% reported lymphedema in 2012 and severity of symptoms decreased. 50% of women treated with SLNB and reporting lymphedema in 2008 did not report symptoms by 2012 in contrast to 30% treated with ALND. However, 19% of women treated with ALND and not reporting lymphedema in 2008 had developed lymphedema by 2012. In conclusion lymphedema remains a frequent problem, years after treatment for breast cancer, though, number of women reporting lymphedema and overall severity of symptoms decreased.

Introduction

Due to improved survival, the number of breast cancer survivors is increasing steadily, now approaching 3 million women in the US [1]. Lymphedema is among the most feared complications after breast cancer surgery with substantial impact on function [2–4], body image [5], social activities [6], and psychological well-being [3,6–9]. Thus the importance of well-conducted studies providing clinicians with information regarding risk of late development of lymphedema for their patients and providing them with arguments for clinical follow-up on lymphedema and early treatment when dealing with health authorities is warranted.

Breast cancer related arm lymphedema is caused by damage to the lymphatic vessels due to surgery and radiotherapy, or more rarely due to recurrence of cancer [2,10–12]. Lymphedema develops when the lymph drainage capacity is exceeded causing accumulation of lymph protein rich fluid in the interstitial tissue of the arm [13,14]. Most common symptoms are sensations of swelling and/or heaviness of the arm [15].

The incidence of lymphedema reported in the literature varies considerably, from 2% to 65% [16]. A most resent systematic review pooled data from clinical measurements of lymphedema and found an overall incidence of 16.6% or 21.4% when restricted to data from prospective cohort studies [17]. Some of the variation between studies can be ascribed to methodological differences in assessment and definition, while true differences may exist between treatment modalities and patient characteristics. In addition, the incidence may vary with time since surgery, the risk being highest during the first years [13,18–21]. Lymphedema can, however, develop several years after the end of breast cancer treatment [13,18–21]. In a population-based prospective study of 631

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http://dx.doi.org/10.1016/j.breast.2014.03.001
0960-9776/

randomly selected breast cancer patients, there was a cumulative incidence of lymphedema of 42% with 80% of the cases occurring within 2 years of diagnosis [20]. In another prospective study of 622 women with follow-up every 6 months, the cumulated proportion of women ever experiencing lymphedema after breast cancer treatment stabilized on 54% after 3 years and a prevalence between 23 and 29% at all times [21].

In a nationwide population-based study from 2008 we asked 3253 women with early-stage breast cancer about symptoms of arm lymphedema. 13–65% of women had symptoms of lymphedema 1–3 years after treatment, depending on the surgical and adjuvant treatment regimen [2]. Using the same assessment methodology, the primary aim of the present follow-up study is to examine the development of self-reported arm lymphedema from 2008 to 2012 in the population of women who participated in the 2008-study by following the course of symptoms for every single individual. The impact of surgery and adjuvant therapy on development in self reported arm lymphedema and prevalence of lymphedema 5–7 years after surgery are also addressed.

Material and methods

The present nationwide follow-up study on development of self-reported arm-lymphedema was based on two identical questionnaires sent out in 2008 and 2012. In 2010 we reported the results regarding lymphedema of the questionnaire sent out in 2008 [2]. The questionnaire also dealt with chronic pain and sensory disturbances [22]. Follow-up on this data is reported elsewhere [23].

Study population

Women aged 18–70 years and treated for unilateral primary breast cancer in Denmark in 2005 and 2006 were identified from the Danish Breast Cancer Cooperative Group, (DBCG) [24,25]. Information on mortality was obtained from the Danish Civil Registration System. Women who had reconstructive or corrective breast surgery, who had emigrated, died, developed a new primary or a contra-lateral breast cancer, recurrence or other malignant disease were excluded.

Treatment

Breast cancer treatment was divided into 12 major categories according to type of surgery (breast conserving or mastectomy); sentinel lymph node biopsy (SLNB) or axillary lymph node dissection (ALND); type of adjuvant radiotherapy (breast alone (BRT)); anterior thoracic radiotherapy after mastectomy (ATRT); locoregional radiotherapy to periclavicular nodes; nodes at axillary level 3, and for right-side breast cancers, the internal mammary nodes (LRRT)), and chemotherapy with 6 cycles of cyclophosphamide, epirubicin and fluorouracil (Table 1). Further treatment details are described elsewhere [22].

Data collection

Two identical questionnaires were sent out in 2008 and 2012 [2]. On February 1, 2012, the questionnaire was sent to all eligible patients. Those who did not respond received a second questionnaire on March 5, 2012. To minimise selection bias, a second reminder was sent on March 30, 2012, to the patients not responding to the second questionnaire. Data collection ended on May 8, 2012.

Questionnaire

In order to asses Lymphedema a questionnaire was developed and content validated in the breast cancer population [22].

Lymphedema was defined by a sensation of swelling or heaviness. To determine the prevalence of perceived lymphedema, a dichotomous “yes“ or “no” question was used: “Does the armpit, the arm or the back of the hand, on the side where you were operated, sometimes or always feel swollen or heavy?”.

Severity was rated in two regions: clustering the axilla with the upper arm, and the forearm with the back of the hand. To estimate the severity, a numeric rating scale from 0 to 10 was used, where 0 was “no swelling/heaviness“ and 10 “worst imaginable swelling/heaviness”. 1–3 was categorized as light, 4–6 as moderate and 7–10 as severe swelling/heaviness. “Worst swelling/heaviness” was defined as the highest score of the 2 regional scores.

Frequency of symptoms was assessed by a 3-point verbal categorical scale: 1) every day or almost every day, 2) 1–3 days a week, 3) more rarely.

Statistical analysis

Univariate analyses were carried out to test for significant associations between covariates and outcomes using Wald χ^2 test. Multivariate logistic regression models were then used to examine the simultaneous influence of age and treatment modalities on lymphedema and the development of lymphedema. Factors included in the models were age ($\leq$49,50–59,60–69,70$\leq$) type of surgery (mastectomy vs. breast conserving surgery), extent of axillary surgery (ALND vs. SLNB), radiotherapy (LRRT + BRT/ATRT or BRT alone vs. none), chemotherapy vs. none. Adjusted odds ratios (ORs) and 95% confidence intervals (CIs) were calculated, and the Wald χ^2 test was used to test the overall significance of each parameter. Patients not reporting lymphedema and patients reporting lymphedema in 2008 were analysed in separate logistic regression analyses for the subsequent development of lymphedema. All ORs reported in the text are adjusted values. The adjusted number needed to be exposed (NNE) and exposure impact number (EIN) for ALND vs. SLNB were calculated using the method suggested by Bender et al. [26]. All statistical methods were computed using SPSS version 19 (IBM, NY, USA).

Ethics

The conduction of the present study complies with the current ethical rules and laws for medical studies in Denmark and was approved by the Data Protection Agency no. 2007-41-1530, and the Regional Bioethics committee of the capital region in Denmark, H-D-2007-0099. The study is registered in clinicaltrials.gov no. NCT01543711.

Results

Participants

In 2005 and 2006, 5119 women aged 18–70 years were identified from the Danish Breast Cancer Cooperative Group, (DBCG) [24] as being treated for unilateral primary breast cancer in Denmark.

Study enrolment, response rates and loss to follow-up

In 2008, after a mean follow-up of 26 months, a questionnaire was sent to 3754 eligible patients having excluded 1365 patients whose primary surgery included reconstructive or corrective breast

Please cite this article in press as: Gärtner R, et al., Development in self-reported arm-lymphedema in Danish women treated for early-stage breast cancer in 2005 and 2006 – A nationwide follow-up study, The Breast (2014), http://dx.doi.org/10.1016/j.breast.2014.03.001