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Please cite the final published version:

Johannsen, M., Christensen, S., Zachariae, R., & Jensen, A. B. (2015). Socio-demographic, treatment-related, and health behavioral predictors of persistent pain 15 months and 7–9 years after surgery: A nationwide prospective study of women treated for primary breast cancer. *Breast Cancer Research and Treatment*, 152 (3), 645–658. DOI: [10.1007/s10549-015-3497-x](https://doi.org/10.1007/s10549-015-3497-x)

Publication metadata

Title:	<i>Socio-demographic, treatment-related, and health behavioral predictors of persistent pain 15 months and 7–9 years after surgery: A nationwide prospective study of women treated for primary breast cancer</i>
Author(s):	<i>Maja Johannsen, Søren Christensen, Robert Zachariae, Anders Bonde Jensen,</i>
Journal:	<i>Breast Cancer Research and Treatment</i>
DOI/Link:	10.1007/s10549-015-3497-x
Document version:	Accepted manuscript (post-print)

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Breast Cancer Research and Treatment

Socio-Demographic, Treatment-related, and Health Behavioral Predictors of Persistent Pain 15 months and 7-9 years after Surgery - a Nationwide Prospective Study of Women Treated for Primary Breast Cancer --Manuscript Draft--

Manuscript Number:	
Full Title:	Socio-Demographic, Treatment-related, and Health Behavioral Predictors of Persistent Pain 15 months and 7-9 years after Surgery - a Nationwide Prospective Study of Women Treated for Primary Breast Cancer
Article Type:	Epidemiology
Keywords:	breast cancer; persistent pain; risk factors; cohort study
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Abstract:	<p>Purpose: To investigate and report prevalence and risk factors for persistent pain in breast cancer patients at 15 months and 7-9 years post-surgery.</p> <p>Methods: A nationwide inception cohort study including 3343 women treated for primary breast cancer between 2001-2004, who returned a questionnaire 3 months post-surgery. Socio-demographic and clinical information was obtained from registries. Questionnaire data on pain and health behaviors were obtained 15 months and 7-9 years post-surgery.</p> <p>Results: A total of 1905 women were eligible for analysis. At 15 months post-surgery, 32.7% reported pain "almost every day" or more frequently. At 7-9 years post-surgery the prevalence decreased to 20.4%. Socio-demographic (young age, lower education, lower income, lower occupational status), treatment-related (being lymph node positive, Axillary Lymph Node Dissection (ALND), post-menopausal endocrine treatment), and health behavioral factors (smoking >10 cigarettes/day, obesity (BMI >30 and <35), comorbidity, poor physical function) were significantly associated with pain at 15 months. Being physically active and moderate alcohol intake (<3 units/day) were negatively associated with pain. At 7-9 years after surgery, only ALND (OR:1.41, p=0.03), post-menopausal endocrine treatment (OR:1.62, p=0.01), poorer physical function (ORs:2.00-2.40, p=0.003), and weight training (h/week) at 15 months (OR:1.10, p=0.008) were significant predictors of pain when adjusting for age and pain 15 months post-surgery. No socio-demographic predictors remained statistically significant.</p> <p>Conclusion: Younger age, lower socio-economic status, more invasive surgery, endocrine treatment, and adverse health behaviors emerged as risk factors for</p>

	persistent pain. The influence of risk factors changed over time, suggesting a complex course of pain development and maintenance.	
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Funding Information:	The Aase & Ejnar Danielsen Foundation (106318)	Søren Christensen
	IMK Almene Fond (30206-215)	Søren Christensen
	The Danish Cancer Society (PP05020, PP03034)	Robert Zachariae

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TREATMENT

TITLE PAGE

Socio-Demographic, Treatment-related, and Health Behavioral Predictors of Persistent Pain 15 months and 7-9 years after Surgery – a Nationwide Prospective Study of Women Treated for Primary Breast Cancer

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Body text (excl. abstract, figures, tables, references): 3441 words

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ABSTRACT

Purpose: To investigate and report prevalence and risk factors for persistent pain in breast cancer patients at 15 months and 7-9 years post-surgery.

Methods: A nationwide inception cohort study including 3343 women treated for primary breast cancer between 2001-2004, who returned a questionnaire 3 months post-surgery. Socio-demographic and clinical information was obtained from registries. Questionnaire data on pain and health behaviors were obtained 15 months and 7-9 years post-surgery.

Results: A total of 1905 women were eligible for analysis. At 15 months post-surgery, 32.7% reported pain “almost every day” or more frequently. At 7-9 years post-surgery the prevalence decreased to 20.4%. Socio-demographic (young age, lower education, lower income, lower occupational status), treatment-related (being lymph node positive, Axillary Lymph Node Dissection (ALND), post-menopausal endocrine treatment), and health behavioral factors (smoking ≥ 10 cigarettes/day, obesity (BMI ≥ 30 and < 35), comorbidity, poor physical function) were significantly associated with pain at 15 months. Being physically active and moderate alcohol intake (< 3 units/day) were negatively associated with pain. At 7-9 years after surgery, only ALND (OR:1.41, $p=0.03$), post-menopausal endocrine treatment (OR:1.62, $p=0.01$), poorer physical function (ORs:2.00-2.40, $p=0.003$), and weight training (h/week) at 15 months (OR:1.10, $p=0.008$) were significant predictors of pain when adjusting for age and pain 15 months post-surgery. No socio-demographic predictors remained statistically significant.

Conclusion: Younger age, lower socio-economic status, more invasive surgery, endocrine treatment, and adverse health behaviors emerged as risk factors for persistent pain. The influence of risk factors changed over time, suggesting a complex course of pain development and maintenance.

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Keywords: breast cancer; persistent pain; risk factors; cohort study

INTRODUCTION

Persistent pain, lasting >3 months after surgery [1, 29], is a frequent complication after breast cancer treatment, with larger studies reporting prevalences between 29-42% [3–5]. Type of surgery has been associated with the development of pain with some studies [6, 7], but not all [1, 3], showing women who have received more invasive surgery (i.e. mastectomy) to report more pain than women who have received lumpectomy. Furthermore, women treated with Axillary Lymph Node Dissection (ALND) tend to report more pain compared to Sentinel Lymph Node Biopsy (SLNB) [1, 8, 9]. Another clinical risk factor is radiotherapy [1, 10, 11]. Although socio-demographic factors are less well-studied, younger age has consistently been found to be associated with higher incidence of pain [1, 4, 6, 9, 12].

Generally, the existing research is characterized by retrospective assessments, modest sample sizes, and considerable between-study variability in the operationalization of pain and the timing of assessment [1]. An exception is a large Danish study showing that 24.5% of patients reported moderate-severe pain 1.5-3.5 years after surgery [3] and that increased risk of pain was associated with receiving radiotherapy, ALND, and younger age. Recently, follow-up data on the same cohort showed that 16% of the women experienced moderate to severe pain at least weekly, 5 years after surgery [12]. While this study adds valuable information to our knowledge about the course of pain after breast cancer treatment, with the exception of age, the role of socio-demographic and health behavioral factors were not explored. Another relevant socio-demographic risk factor could be lower educational level which has been found associated with failure to return to work, higher sickness

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4 absence, and greater pain severity [13–16]. There are also indications that certain health behaviors
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6 may negatively influence long-term pain development. Smoking, for example, has been found asso-
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8 ciated with greater pain severity and higher levels of pain interference [17–20]. Physical activity
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10 and obesity have likewise been associated with the course of pain, with physical activity being in-
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12 versely associated with pain and obesity predictive of higher pain levels [16, 20, 21].
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17 To the best of our knowledge, no studies so far have prospectively investigated long-term pain after
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19 breast cancer treatment and included treatment-related, socio-demographic, as well as health behav-
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21 ioral risk factors. As pain has been associated with impaired Quality of Life [22, 23], psychological
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23 morbidity [24, 25], and appears to persist in a substantial number of women after treatment, identi-
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25 fication of patients at higher risk for developing persistent pain may offer valuable clinical infor-
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27 mation for the purpose of rehabilitation. We therefore investigated socio-demographic, treatment-
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29 related, and health behavioral predictors of persistent pain from 15 months to 7-9 years after breast
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31 cancer treatment in a large national cohort of women.
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38 **METHODS**

39 **Study design and sample**

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45 The Psychosocial Factors and Breast Cancer Cohort is a nationwide inception cohort study of 4917
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47 consecutively included Danish women treated for invasive breast cancer between 2001-2004 con-
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49 ducted in collaboration with the Danish Breast Cancer Cooperative Group (DBCG). Details of the
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51 cohort and recruitment procedure have been described elsewhere [26]. In brief, patient eligibility
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53 criteria at time of entry were: 18-70 years of age, histologically confirmed invasive breast cancer
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55 T1-3, N0-3, and M0 according to the TNM classification (27), and no history of other cancers, with
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the exception of non-melanoma skin cancer and carcinoma in situ of the cervix uteri. Further inclusion criteria included sufficient Danish language skills, ability to complete a questionnaire, and treated according to DBCG standard guidelines. Eligible women were identified by the DBCG and the surgical departments and informed about the study. At least 97% of all eligible women in Denmark during the inclusion period were identified [27]. Questionnaire packages were mailed out 3 months post-surgery and returned by 3343 women (68%) who thus constituted the original questionnaire cohort.

Eligibility in the present study

Additional data were collected 15 months and 7-9 years post-surgery in 2011. At 15 months, 3136 of the responders at 3 months were alive and had no recurrence or secondary cancer according to the DBCG and the Danish Cancer Registry. Of these, 2932 (94%) returned the questionnaire. At 7-9 years, 2289 women from the questionnaire cohort were still alive without signs of recurrence or new cancer, whereof 2070 (90.4%) returned the questionnaire. Eighty women who reported a recurrence or malign secondary cancer were excluded together with 85 women, who did not have complete data on pain measures at both assessments. A total 1905 women were eligible and available for analysis in the present study ([Figure 1](#)). The study was approved by the Regional Science Ethical Committees and the Danish Data Protection Agency.

(Insert Figure 1 near here)

Adjuvant treatment

The DBCG standard protocols 2001A-E and 2004C for adjuvant therapy were effective during the study period [29]. For pre-menopausal women, the available protocols were A: No adjuvant thera-

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py, B: 7 cycles of Cyclophosphamide, Epirubicin, and Fluorouracil (CEF) followed by Tamoxifen for 5 years, and D: 7 cycles of CEF. Post-menopausal women were treated according to protocols: A, C: 2.5 years of treatment with Tamoxifen, followed by 2.5 years of Exemestane, and E: 7 cycles of Cyclophosphamide, Methotrexate, and Fluorouracil (CMF). Exemestan was introduced in protocol C (2004C) from June 2004. Some women in this protocol had therefore been treated with Tamoxifen for up to 3.5 years before initiation of Exemestane treatment (2.5 yrs.). Women who had received lumpectomy and women with positive lymph node(s) were allocated to radiotherapy (a total dose of 48 Gy in 24 fractions). Lumpectomized women received radiotherapy on the residual breast tissue, whereas women with positive lymph node(s) received locoregional radiotherapy. Women <50 years of age had received additional boost treatment against the tumor bed with 10 – 16 Gy in 5 to 8 fractions. Mastectomized node-positive women received anterior thoracic radiotherapy (48 Gy in 24 fractions) [29].

Measures

Socio-demographic variables

Pre-cancer data concerning demographic factors, ethnicity, and socio-economic variables were obtained from the Danish longitudinal registries through a linkage serviced by Statistics Denmark [30] and included marital status, education, personal income, occupational status, and household net-wealth. Danish ethnicity was defined as Danish citizenship, being born in Denmark, and at least one parent a Danish citizen.

Clinical variables

Data on tumor characteristics and treatment were obtained through a linkage with the DBCG. The DBCG registry contains information on diagnosis, treatment, and follow-up reported by all depart-

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ments in Denmark involved in the treatment of breast cancer, including tumor-related variables (tumor size, estrogen receptor status, nodal status involvement), and treatment (DBCG treatment protocols, surgical procedures, chemo-, radiation-, and endocrine therapy) [29]. Information on subsequent recurrence and secondary cancers was obtained through DBCG and the Danish Cancer Registries.

Comorbidity

Comorbidity was assessed at the surgical department at the time of primary surgery with the Charlson Comorbidity Index (CCI), measuring 19 comorbid conditions shown to alter the risk of mortality in longitudinal studies [31, 32].

BMI and health behaviors at 15-month post-surgery

Body Mass Index (BMI) was calculated and categorized according to WHO guidelines [33]. Smoking status and alcohol intake were self-reported total consumption during the last week in units per day (e.g., number of cigarettes, beers, glasses of wine). Physical activity was assessed with the Physical Activity Scale for the Elderly (PASE) [34] and included the total number of hours spent on walking, light-, moderate-, and strenuous activities, and weight training during the previous week. To reduce patient burden, PASE was modified to exclude basic household activities. Physical workload was defined as total hours/day spent on non-sedentary work involving some or more arm movements.

Physical function (PF) at 15-month post-surgery

Physical function was assessed with the SF-36-PF subscale [35] measuring limitations in daily physical activities. Higher scores reflect higher levels of functioning (range 0-100).

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Pain medication

Use of pain medication was as assessed by self-report at 7-9 years post-surgery (yes/no response format). If yes, they were asked to indicate the number of days per week they had used pain medication.

Pain

Pain was assessed at 15 months and 7-9 years post-surgery. The women were asked how often they had experienced pain during the last month at two body locations (the arm/shoulder of the operated side and the surgical area) with the response categories "no pain" (0), "a few times a month" (1), "a few times a week" (2), "almost every day" (3), "several times every day" (4), and "all the time" (5). The women were also asked to rate the degree of pain burden with response options including "minimally" (0), "a little" (1), "some" (2), "much" (3), and "very much" (4). A combined pain frequency variable was constructed by selecting the highest pain score reported in *either* the operated side *or* the surgical area. Pain frequency was categorized as "high" and "low" pain frequency using a cut-off ≥ 3 (high pain frequency = "almost every day" or more frequently; low pain frequency = "no pain", "monthly pain" or "few days each week").

Statistical analysis

The data was analyzed with binary logistic regression, with pain frequency (high='1'; low='0') as the dependent variable. A strong correlation was found at 7-9 years between pain frequency and pain burden ($\rho=0.94; p<0.001$) indicating that participants did not distinguish between these aspects of their pain experience. To avoid redundancy, only results for pain frequency are reported. In our main analyses, we explored predictors of change in pain frequency from 15 months to 7-9 years

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presented as odds ratios (OR) adjusted for baseline pain (15 months) and age (both included as continuous variables), as both pain frequency and several potential predictors varied with age. In addition, results for socio-demographic-, clinical-, and health behavioral variables were presented separately for 15 months and 7-9 years as OR's (both unadjusted and age-adjusted analyses). The statistical analyses of systemic therapies were stratified according to menopausal status in order to eliminate possible confounding effects of age. Predictors were considered statistically significant ($p < 0.05$) if confirmed by the Wald statistic. Analyses were conducted with SPSS 19.0.0.1 (IBM SPSS Inc., Chicago, USA).

RESULTS

At 15 months, 3136 women were identified as eligible, with 2923 (93.2%) having completed the pain measure. Of these, a total of 2129 (72.8%) reported pain during the last month (no further data shown). Of 2289 eligible women approached at 7-9 years follow-up with no signs of recurrence or new cancer, a total of 1905 women (83.2%) had completed the pain assessments at both 15 months and 7-9 years post-surgery and were thus available for analysis. For this sample ($n = 1905$), the median age at 15 months post-surgery was 56.5 years (range: 27.3-71.2). Mean time from surgery was 15.2 months (SD: 0.8) and 7.1 years (SD: 0.7) at the first and second pain assessments respectively. Analyses of women who dropped out from 15 months to 7-9 years post-surgery ($n = 167$) revealed no differences in pain frequency ($p = 0.10$) or age ($p = 0.85$) at 15 months between completers and dropouts.

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Pain prevalence

Of the 1905 women who completed questionnaires at both time points, a total of 1384 women (72.7%) reported monthly or more frequent pain 15 months post-surgery. At 7-9 years post-surgery, 1100 women (57.7%) reported pain at least monthly (Table 1). Pain in the surgical area and pain in the arm/shoulder on the operated side were highly correlated ($r=0.61; p<0.001$). However, pain was slightly more frequently reported in the arm/shoulder region of the side operated than in the surgical area at both time points (60.6% vs. 59.1% at 15 months; 49.2% vs. 43.4% at 7-9 years). The prevalence of high pain frequency decreased from 32.7% at 15 months to 20.4% at 7-9 years post-surgery. In all, 10.3% women changed status from low pain frequency at 15 months to high pain frequency at 7-9 years, while 58.9% reporting high pain frequency at 15 months reported pain corresponding only to low pain frequency at 7-9 years post-surgery.

(Insert Table 1 near here)

Use of pain medication at 7-9 years post-surgery

A total of 1881 women completed the items concerning use of pain medication. Of these, a total of 658 women (35.0%) reported having used pain medication during the previous month. More women in the high frequency pain group (216; 56.4%) reported using pain medication during the previous months than in the low frequency pain group (442; 29.5%) ($p<0.001$). The Inter Quartile Range (IQR, the 25-75% percentile) for weekly use of pain medication was 0-4 days per week in the high frequency pain group and 0-1 days per week in the low pain frequency group.

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Predictors of high pain frequency 15 months post-surgery

As seen in Table 2, younger age was associated with a higher pain frequency. Adjusting for age, higher pain frequency was associated with lower education, lower occupational status, lower personal income, and negative net-wealth. Adjusted for age, ALND, axillary node positive status, and endocrine treatment for post-menopausal women were significantly associated with pain (Table 3). Smoking ≥ 10 cigarettes/day, obesity (BMI:30-34), poorer physical function, and comorbidity were also associated with high pain frequency at 15 months in the age adjusted analyses. Factors associated with lower pain frequency were moderate alcohol consumption (>0 and <3 units of alcohol/day, moderate exercise, strenuous activities, and performing non-sedentary work (Table 4)).

(Insert Table 2, 3, and 4 near here)

Predictors of high pain frequency 7-9 years after surgery

Except from physical functioning, all health behavioral predictors measured at 15 months post-surgery ceased to be significantly associated with pain 7-9 years post-surgery, whereas socio-demographic and clinical risk factors associated with pain at 15 months were significantly predictive of pain at 7-9 years (unadjusted).

Predictors of change in pain frequency from 15 to 7-9 years after surgery

When investigating possible predictors of change in pain frequency from 15 months to 7-9 years post-surgery by adjusting for age and pain at 15 months, no socio-demographic predictors reached statistical significance (Table 2). Of the treatment-related variables, ALND (vs. SNLB) and endocrine treatment (vs. no endocrine treatment) in post-menopausal women both showed to be statistically significant predictors of more frequent pain from 15 months to 7-9 years post-surgery (Table

3). Smoking, BMI, alcohol consumption, and physical workload did not reach statistical significance (Table 4), while poorer physical function proved to be a significant predictor of more frequent pain over time when compared to women with better physical functioning. Physical activity was related to pain in the opposite direction than the associations observed at 15 months with walking and weight training being statistically significant associated with increased risk of pain from 15 months to 7-9 years post-surgery. In order to identify possible independent predictors among types of physical activity (PASE), we conducted a multivariate regression analysis including all the PASE components while adjusting for age and pain at 15 months. In this model, weight training (h/week) emerged as the only independent statistically significant predictor (OR=1.09; CI:1.01-1.19) (no further data shown). A result in the opposite direction was also found for comorbidity, with comorbidity predicting lower pain frequency from 15 months to 7-9 years post-surgery.

DISCUSSION

In this large nationwide follow-up study, one out of every five women treated for breast cancer reported pain almost every day or more frequently 7-9 years after surgery. Our results suggest that socio-demographic, treatment-related, and health-behavioral factors influence the risk of developing pain in different ways over time, suggesting a complex course of persistent pain after breast cancer treatment.

At 15 months post-surgery, younger patients with lower socio-economic status (SES), i.e., lower education, income, and net wealth, were more likely to report pain. This is supported by previous reports with respect to young age [1, 4, 6, 9, 12] and, although less well-studied, low education [4, 36] and low income [22, 36]. At 7-9 years post-surgery, however, none of the socio-demographic

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variables remained statistically significant when adjusting for pain 15 months post-surgery, suggesting that socio-demographic risk factors add no predictive value over time.

As previously observed [1, 8, 9], ALND proved a strong treatment-related predictor of pain. Our results show that this risk persists even 7-9 years after surgery. Although associations between pain and type of surgery [6, 7] and radiotherapy [1, 3, 4, 6, 10], have previously been reported, we could not replicate these results. With respect to radiotherapy, it is possible that the influence on pain may already have declined when assessed at 15 months. However, other studies reporting radiotherapy as a predictor of persistent pain have used similar assessment points exceeding 13 months (e.g. [3,4]). Our results also revealed that post-menopausal women receiving endocrine treatment were at higher risk of pain at 15 months, a risk which persisted at 7-9 years post-surgery. This could partially be explained by the addition of AIs after 2.5 yrs initial treatment with Tamoxifen in post-menopausal women, as AIs have indicated a stronger association with pain compared to Tamoxifen [37–39].

We also found health behavioral variables to be associated with risk of persistent pain, particularly in the shorter term. Moderate alcohol consumption was thus associated with less pain at 15 months, whereas smoking >10 cigarettes per day and being obese ($BMI \geq 30$) was associated with more pain, but only at 15 months post-surgery. That smoking is associated with increased pain is in general concordance with existing research [17–19], while the results are mixed with respect to obesity [9, 14, 20, 21]. Our results suggest an adverse effect of obesity on pain, which, however, does not appear to persist over time. Furthermore, the relationship between pain and obesity appeared to be non-linear, with only obesity, and not severe obesity, reaching statistical significance. However, due to the small number of severely obese, this could be a statistical power issue. Poorer physical function was strongly associated with pain at both 15 months and 7-9 years post-surgery. However, as

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no pre-morbid assessments of the participants were available, the direction of causality is less clear. While several studies have found that being physically active is associated with less pain [16, 20, 21, 40], our results suggest the need for a more complex understanding of the influence of exercise. At 15 months, high-intensity activities (i.e., moderate and strenuous exercise) and performing a job with physical requirements were associated with a lower frequency of pain. At 7-9 years post-surgery, this was no longer the case, with weight training measured at 15 months now being associated with an increased risk of pain over time. This information may be relevant when counseling patients regarding health behaviors, as it suggests moderation in advising patients unequivocally to exercise and indicates that some types of exercise may be more relevant than others at different time points after treatment. The role of comorbidity also appeared to change over time. While comorbidity was associated with an increased risk of pain 15 months after surgery, comorbidity was also a predictor of less frequent pain from 15 months to 7-9 years post-surgery. One could hypothesize that although pain in cancer patients in general seems to be undertreated [41, 42], patients with comorbidities may have more contacts with the healthcare system over time, possibly increasing the likelihood that their pain is identified and targeted in treatment.

With respect to possible limitations, we did not include a validated pain questionnaire, e.g. The McGill Pain Questionnaire [43]. However, the pain prevalence reported in the present study is comparable to the prevalence found in a similar large, nationwide cohort study [12]. Although the two studies used different methods to operationalized pain, the comparable prevalence rates tentatively suggest that pain frequency is a reliable and relevant measure of pain. It should also be noted that we have previously found some indications of response bias in our cohort [26], with responders tending to be younger, more wealthy, and more well-educated than the cohort as a whole, which may slightly overestimate the reported pain prevalence, as younger age has consistently been shown

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to predict pain [1, 4, 6, 9, 12]. While a common issue in questionnaire-based studies, this may limit the generalizability of the results. In addition, being a longitudinal study with 7-9 years follow-up, the treatment regimens have been revised since the time of data collection (e.g., implementation of Trastuzumab and taxanes). Finally, although a prospective study, no pre-morbid or pre-surgical information on health behaviors and pain were available, thereby limiting conclusions with respect to causality.

Despite these limitations, major strengths of our study are its longitudinal design, that it is based on a large nationwide cohort, the high response rates at follow-up, and the availability of comprehensive pre-cancer socio-demographic data as well as disease- and treatment-related information, allowing for estimations of a wide range of possible socio-demographic, clinical, and health-related risk factors.

CONCLUSION

Taken together, our results showed that a large proportion of women was found to experience persistent pain after breast cancer treatment, with approximately one in five women reporting high pain frequency even after 7-9 years post-surgery. Our results have several clinical implications. First, younger women with low SES, poorer physical function, and women who receive ALND and AI treatment appear to be at higher risk for developing persistent pain. Second, caution should be used regarding excessive weight training. Our results underline the importance of offering interventions for pain soon after patients present pain symptoms, as it appears to become a long-term problem for a substantial number of women.

LEGENDS

Fig 1 Flow diagram of patient selection

ACKNOWLEDGEMENTS

We thank the participating women and the Danish Breast Cancer Cooperative Group (DBCG), Rigshospitalet, Copenhagen University Hospital, for providing the clinical data.

Acknowledgements of research support: This research was generously supported by The Danish Cancer Society (PP05020, PP03034), IMK Almene Fond (30206-215) and The Aase and Ejnar Danielsen Foundation (106318).

Disclaimers: The authors declare that they have no conflicts of interest.

REFERENCES

1. Andersen KG, Kehlet H (2011) Persistent Pain After Breast Cancer Treatment: A Critical Review of Risk Factors and Strategies for Prevention. *J Pain* 12(7):725–46.
2. Kehlet, Jensen TS, Woolf CJ (2006) Persistent postsurgical pain: risk factors and prevention. *Lancet* 367:1625–8.
3. Gärtner R, Nielsen J, Ewertz M, et al (2009) Prevalence of and Factors Associated With Persistent Pain Following Breast Cancer Surgery. *JAMA* 302(18):1985–92.
4. Peuckmann V, Ekholm O, Rasmussen NK, et al. (2009) Chronic pain and other sequelae in long-term breast cancer survivors: Nationwide survey in Denmark. *Eur J Pain* 13(5):478–85.
5. Anderson KO, Reyes-Gibby CC (2013) Biopsychosocial approach to persistent post-mastectomy pain: What can we conclude? *Pain* 154(5):623–4.
6. Poleschuk EL, Katz J, Andrus CH, et al. (2006) Risk Factors for Chronic Pain Following Breast Cancer Surgery: A Prospective Study. *J Pain* 7(9):626–34.
7. Fernández-Lao C, Cantarero-Villanueva I, Fernández-de-las-Peñas C, et al. (2011) Widespread Mechanical Pain Hypersensitivity as a Sign of Central Sensitization after Breast Cancer Surgery: Comparison between Mastectomy and Lumpectomy. *Pain Med* 12(1):72–8.
8. Bianco PD, Zavagno G, Burelli P, et al. (2008) Morbidity comparison of sentinel lymph node biopsy versus conventional axillary lymph node dissection for breast cancer patients: results of the sentinella-GIVOM Italian randomised clinical trial. *Eur J Surg Oncol* 34(5):508–13.
9. Steegers MA, Wolters B, Evers AW, et al (2008) Effect of Axillary Lymph Node Dissection on Prevalence and Intensity of Chronic and Phantom Pain After Breast Cancer Surgery. *J Pain* 9(9):813–22.
10. Jung BF, Ahrendt GM, Oaklander AL, et al (2003) Neuropathic pain following breast cancer surgery: proposed classification and research update. *Pain* 104:1–13.
11. Levy MH, Chwistek M, Mehta R (2008) Management of Chronic Pain in Cancer Survivors. *Cancer J* 14(6):401–9.
12. Mejdahl M, Andersen K, Gärtner R, et al (2013) Persistent pain and sensory disturbances after treatment for breast cancer: six year nationwide follow-up study. *BMJ* 1865(April):1–14.
13. Noeres D, Park-Simon T-W, Grabow J, et al. (2013) Return to work after treatment for primary breast cancer over a 6-year period: results from a prospective study comparing patients with the general population. *Support Care Cancer* 21(7):1901–9.

TREATMENT

14. Miaskowski C, Cooper B, Paul SM, et al (2012). Identification of patient subgroups and risk factors for persistent breast pain following breast cancer surgery. *J Pain* 13(12):1172–87.
15. Eaker S, Wigertz A, Lambert PC, Bet al. (2011) Breast cancer, sickness absence, income and marital status. A study on life situation 1 year prior diagnosis compared to 3 and 5 years after diagnosis. *PLoS One* 6(3):e18040.
16. Rief W, Barwell WA, Dimsdale JE, et al. (2011) Long-term course of pain in breast cancer survivors: a 4-year longitudinal study. *Breast Cancer Res Treat* 130:579–86.
17. Ditre JW, Gonzalez BD, Simmons VN, et al. (2011) Associations between pain and current smoking status among cancer patients. *Pain* 152(1):60–5.
18. Ditre JW, Brandon TH, Zale EL, et al. (2011) Pain, nicotine, and smoking: research findings and mechanistic considerations. *Psychol Bull* 137(6):1065–93.
19. Patterson AL, Gritzner S, Resnick MP, et al (2012) Smoking cigarettes as a coping strategy for chronic pain is associated with greater pain intensity and poorer pain-related function. *J Pain* 13(3):285–92.
20. Sipilä R, Estlander AM, Tasmuth T, Ket al (2012) Development of a screening instrument for risk factors of persistent pain after breast cancer surgery. *Br J Cancer* 107(9):1459–66.
21. Forsythe LP, Alfano CM, George SM, et al (2013) Pain in long-term breast cancer survivors: the role of body mass index, physical activity, and sedentary behavior. *Breast Cancer Res Treat* 137(2):617–30.
22. Caffo O, Amichetti M, Ferro A, et al. (2003) Pain and Quality of Life after Surgery for Breast Cancer. *Breast Cancer Res Treat* 80(1):39–48.
23. MacDonald L, Bruce J, Scott NW, et al. (2005) Long-term follow-up of breast cancer survivors with post-mastectomy pain syndrome. *Br J Cancer* 92:225–30.
24. Jim HSL, Small BJ, Minton S, et al. (2012) History of Major Depressive Disorder Prospectively Predicts Worse Quality of Life in Women with Breast Cancer. *Ann Behav Med* 43(3):402–8.
25. Bair MJ, Robinson RL, Katon W, et al. (2003) Depression and pain comorbidity: A literature review. *Arch Intern Med* 163(20):2433–45.
26. Christensen S, Zachariae R, Jensen AB, et al. (2009) Prevalence and risk of depressive symptoms 3–4 months post-surgery in a nationwide cohort study of Danish women treated for early stage breast-cancer. *Breast Cancer Res Treat* 113(2):339–55.
27. Singletary S (2002) Revision of the American Joint Committee on Cancer Staging System for Breast Cancer. *J Clin Oncol* 20(17):3628–36.

TREATMENT

- 1
- 2
- 3
- 4 28. Rostgaard K, Holst H, Mouridsen HT, et al. (2000) Do clinical databases render population-
- 5 based cancer registers obsolete? The example of breast cancer in Denmark. *Cancer Causes*
- 6 *Control* 11(7):669–74.
- 7
- 8 29. Møller S, Jensen M, Ejlersen B, et al. (2008) The clinical database and the treatment
- 9 guidelines of the Danish Breast Cancer Cooperative Group (DBCG); its 30-years experience
- 10 and future promise. *Acta Oncol (Madr)* 47(4):506–24.
- 11
- 12
- 13 30. Gjerstorff ML (2011) The Danish Cancer Registry. *Scand J Public Health* 39(7 Suppl):42–5.
- 14
- 15
- 16 31. Charlson ME, Pompei P, Ales KL, et al. (1987) A new method of classifying prognostic
- 17 comorbidity in longitudinal studies: Development and validation. *J Chronic Dis* 40(5):373–
- 18 83.
- 19
- 20 32. Extermann M (2000) Measurement and impact of comorbidity in older cancer patients. *Crit*
- 21 *Rev Oncol Hematol* 35(3):181–200.
- 22
- 23
- 24 33. World Health Organization (WHO) (2000) Obesity. Preventing and managing the global
- 25 endemic. Geneva: Technial Report Series no 894.
- 26
- 27
- 28 34. Washburn RA, Smith KW, Jette AM, et al. (1993) The Physical Activity Scale for the
- 29 Elderly (PASE): Development and Evaluation. *J Clin Epidemiol* 46(2):153–62.
- 30
- 31 35. Ware JE, Sherbourne CD (1992) The MOS 36-Item Short-Form Health Survey (SF-36). *Med*
- 32 *Care* 30(6):473–83.
- 33
- 34
- 35 36. Ashing-Giwa KT, Lim J (2009) Examining the Impact of Socioeconomic Status and
- 36 Socioecologic Stress on Physical and Mental Health Quality of Life Among Breast Cancer
- 37 Survivors. *Oncology* 36(1):79–88.
- 38
- 39
- 40 37. Jakesz R, Jonat W, Gnant M, et al. (2005) Switching of postmenopausal women with
- 41 endocrine-responsive early breast cancer to anastrozole after 2 years' adjuvant tamoxifen:
- 42 combined results of ABCSG trial 8 and ARNO 95 trial. *Lancet* 366(9484):455–62.
- 43
- 44
- 45 38. Presant CA, Bosserman L, Young T, et al (2007) Aromatase inhibitor-associated arthralgia
- 46 and/ or bone pain: frequency and characterization in non-clinical trial patients. *Clin Breast*
- 47 *Cancer* 7(10):775–8.
- 48
- 49
- 50 39. Crew KD, Greenlee H, Capodice J, et al. 82007) Prevalence of joint symptoms in
- 51 postmenopausal women taking aromatase inhibitors for early-stage breast cancer. *J Clin*
- 52 *Oncol* 25(25):3877–83.
- 53
- 54
- 55 40. Alfano CM, Smith AW, Irwin ML, et al. (2007) Physical activity, long-term symptoms, and
- 56 physical health-related quality of life among breast cancer survivors: a prospective analysis. *J*
- 57 *Cancer Surviv* 1(2):116–28.
- 58
- 59
- 60
- 61
- 62
- 63
- 64
- 65

**RUNNING HEAD: PREDICTORS OF PERSISTENT PAIN AFTER BREAST CANCER
TREATMENT**

41. Kwon JH (2014) Overcoming barriers in cancer pain management. *J Clin Oncol* 32(16):1727–33.
42. Deandrea S, Montanari M, Moja L, et al. (2008) Prevalence of undertreatment in cancer pain. A review of published literature. *Ann Oncol* 19(12):1985–91.
43. Melzack R (1975) The McGill Pain Questionnaire: Major Properties and Scoring Methods. *Pain* 1(1):277–99.

RUNNING HEAD: PREDICTORS OF PERSISTENT PAIN AFTER BREAST CANCER TREATMENT

Table 1

Pain prevalence at 15 months and 7-9 years after surgery^a

Pain symptoms during previous month, N (%)	Surgical area		Arm/shoulder on the operated side	
	15 mo.	7-9 yrs.	15 mo.	7-9 yrs.
No pain	777 (40.9)	1075 (56.6)	750 (39.4)	966 (50.8)
A few times a month	438 (23.0)	447 (23.5)	331 (17.4)	383 (20.1)
A few times a week	305 (16.0)	171 (9.0)	279 (14.6)	218 (11.5)
Almost every day	200 (10.5)	117 (6.2)	239 (12.5)	182 (9.6)
Several times a day	115 (6.0)	49 (2.6)	202 (10.6)	88 (4.6)
All the time	66 (3.5)	40 (2.1)	104 (5.5)	66 (3.5)

^a A total of 1905 women completed pain questionnaires at both 15 mo. and 7-9 yrs follow-up and were eligible for analysis. Missing observations are not shown when ≤ 2 % and totals may therefore differ slightly

RUNNING HEAD: PREDICTORS OF PERSISTENT PAIN AFTER BREAST CANCER TREATMENT

Table 2

Socio-demographic predictors of high pain frequency at 15 months and 7-9 years after surgery in a national cohort of women treated for breast cancer^a

	<u>Study co- hort</u> N (%)	<u>Frequency (%)</u> Almost every day or more frequently Prevalence= 32.7%	15 months		<u>Frequency (%)</u> Almost every day or more frequently Prevalence= 20.4%	7-9 years	
			OR (95% CI) Unadjusted	OR (95% CI) Age-adjusted		OR (95% CI) Unadjusted	OR (95% CI) Adjusted for pain at 15 months and age
Age^b			P<0.001	-		P<0.001	P=0.06 ^c
60–71	666 (35.0)	25.5	1 Ref	-	15.3	1 Ref	1 Ref
50–59	760 (39.9)	36.1	1.65 (1.31-2.07)	-	21.3	1.50 (1.14-1.97)	1.20 (0.89-1.62)
40–49	400 (21.0)	36.5	1.68 (1.28-2.19)	-	26.3	1.97 (1.45-2.68)	1.59 (1.14-2.23)
<40	79 (4.2)	41.8	2.09 (1.30-3.38)	-	24.1	1.75 (1.00-3.06)	1.32 (0.72-2.42)
Marital Status			P=0.58	P=0.51		P=0.45	P=0.51
Divorced, widow, single (not cohabiting)	420 (22.1)	33.8	1.07 (0.85-1.34)	1.08 (0.86-1.36)	21.7	1.11 (0.85-1.44)	1.10 (0.82-1.48)
Married or Cohabiting	1485 (78.0)	32.4	1 Ref	1 Ref	20.0	1 Ref	1 Ref
Children			P>0.99	P=0.65		P=0.77	P=0.87
No	208 (10.9)	32.7	1 Ref	1 Ref	21.2	1 Ref	1 Ref
Yes	1697 (89.1)	32.7	1.00 (0.74-1.36)	1.08 (0.79-1.47)	20.3	0.95 (0.67-1.35)	0.97 (0.66-1.43)
Education (ISCED 97 Based)			P=0.04	P=0.03		P=0.001	P=0.09
Tertiary Master Degree (≥18 yrs)	97 (5.1)	24.7	1 Ref	1 Ref	10.3	1 Ref	1 Ref
Tertiary < Master Degree (14–17 yrs)	485 (25.5)	29.7	1.28 (0.78-2.12)	1.34 (0.81-2.21)	17.3	1.82 (0.91-3.65)	1.68 (0.80-3.52)
Upper Secondary (11– 13 yrs)	766 (40.2)	35.1	1.65 (1.01-2.67)	1.79 (1.10-2.92)	22.6	2.54 (1.29-4.99)	2.14 (1.04-4.39)
Lower Secondary General (8–10 yrs)	254 (13.3)	36.6	1.76 (1.04-2.98)	1.85 (1.09-3.14)	26.4	3.12 (1.53-6.35)	2.50 (1.17-5.34)
Lower Secondary General (7 yrs)	284 (14.9)	29.2	1.26 (0.74-2.13)	1.68 (0.97-2.89)	17.6	1.86 (0.90-3.83)	1.94 (0.88-4.25)
Occupational Status (ISCO-88 Based)			P=0.01	P<0.001		P=0.03	P=0.70
Manager or employee – Medium or upper level	574 (30.1)	29.3	1 Ref	1 Ref	18.1	1 Ref	1 Ref

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Employee – Basic level, in education, or others	774 (40.6)	35.7	1.34 (1.06-1.69)	1.39 (1.10-1.75)	23.1	1.36 (1.04-1.78)	1.21 (0.90-1.63)
Unemployed, recipient of temporary allowance-, cash- or pre-retirement benefits etc.	339 (17.8)	29.8	1.03 (0.76-1.38)	1.41 (1.02-1.94)	17.4	0.95 (0.67-1.35)	1.08 (0.72-1.63)
Old age pension	81 (4.3)	25.9	0.85 (0.50-1.44)	1.53 (0.86-2.73)	14.8	0.79 (0.41-1.50)	1.23 (0.58-2.64)
Recipients of early retirement pension, rehabilitation- or sickness benefits	133 (7.0)	40.6	1.65 (1.12-2.44)	2.14 (1.43-3.22)	25.6	1.55 (1.00-2.42)	1.32 (0.79-2.21)
Personal Income (US \$)^d			P=0.29	P=0.006		P=0.24	P=0.51
>55.000	373 (19.6)	29.8	1 Ref	1 Ref	18.8	1 Ref	1 Ref
>40.000 and ≤55.000	532 (28.0)	30.5	1.03 (0.77-1.38)	1.03 (0.77-1.38)	20.1	1.09 (0.78-1.52)	1.02 (0.71-1.48)
>30.000 and ≤40.000	398 (20.9)	35.7	1.31 (0.97-1.77)	1.38 (1.01-1.87)	24.1	1.38 (0.97-1.95)	1.23 (0.84-1.80)
>20.000 and ≤30.000	358 (18.8)	34.4	1.24 (0.91-1.69)	1.55 (1.12-2.14)	17.9	0.94 (0.65-1.37)	0.89 (0.58-1.35)
≤20.000	240 (12.6)	34.2	1.23 (0.87-1.73)	1.65 (1.15-2.38)	21.3	1.17 (0.78-1.75)	1.19 (0.75-1.90)
Household Net wealth per person (US \$)^d			P<0.001	P=0.01		P=0.001	P=0.15
≥120.000	399 (21.0)	26.6	1 Ref	1 Ref	19.0	1 Ref	1 Ref
≥55.000 and <120.000	438 (23.0)	31.5	1.27 (0.94-1.72)	1.23 (0.91-1.66)	17.6	0.91 (0.64-1.29)	0.76 (0.52-1.11)
≥20.000 and <55.000	372 (19.6)	30.1	1.19 (0.87-1.63)	1.09 (0.80-1.50)	18.8	0.99 (0.69-1.41)	0.83 (0.56-1.25)
≥0 and <20.000	333 (17.5)	33.3	1.38 (1.01-1.90)	1.24 (0.90-1.72)	18.3	0.95 (0.66-1.39)	0.68 (0.45-1.04)
<0	359 (18.9)	42.6	2.05 (1.51-2.79)	1.76 (1.28-2.41)	29.0	1.73 (1.24-2.43)	1.05 (0.71-1.57)
Ethnicity			P=0.22	P=0.25		P=0.08	P=0.14
Immigrant or descendant	49 (2.6)	24.5	1 Ref	1 Ref	10.2	1 Ref	1 Ref
Non-immigrant or non-descendant	1853 (97.3)	32.9	1.51 (0.78-2.92)	1.47 (0.76-2.86)	20.7	2.29 (0.90-5.82)	2.08 (0.78-5.55)

^a A total of 1905 women completed pain questionnaires at both 15 mo. and 7-9 yrs follow-up and were eligible for analysis. Missing observations are not shown when ≤ 2 % and totals may therefore differ slightly. OR = Odds Ratio, CI = 95% Confidence Interval

^b Age at 15 months post surgery

^c Adjusted for pain at 15 months (baseline) only.

^d The amounts were converted from Danish Kroner to US \$ based on the exchange rate of 31/12-2003. A full description has been published elsewhere [26].

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Table 3

Treatment-related predictors of high pain frequency at 15 months and 7-9 years after surgery in a national cohort of women treated for breast cancer^a

	Study co- hort N(%)	Frequency (%) Almost every day or more frequently Prevalence= 32.7%	15 months		7-9 years		
			OR (95% CI) Unadjusted	OR (95% CI) Age-adjusted	Frequency (%) Almost every day or more frequently Prevalence= 20.4%	OR (95% CI) Unadjusted	OR (95% CI) Adjusted for age and pain at 15 months
Tumor size			P=0.75	P=0.75		P=0.29	P=0.29
≤ 20 mm	1252 (65.7)	32.3	1 Ref	1 Ref	19.6	1 Ref	1 Ref
> 20 mm ≤ 50 mm	610 (32.0)	33.8	1.07 (0.87-1.31)	1.07 (0.87-1.31)	22.5	1.19 (0.94-1.51)	1.17 (0.90-1.52)
> 50 mm	37 (1.94)	29.7	0.89 (0.43-1.82)	0.87 (0.42-1.78)	16.2	0.80 (0.33-1.93)	0.63 (0.24-1.65)
Tumor grade			P=0.31	P=0.25		P=0.86	P=0.92
I	513 (26.9)	33.3	1 Ref	1 Ref	20.5	1 Ref	1 Ref
II	694 (36.4)	34.7	1.06 (0.84-1.35)	1.04 (0.82-1.33)	21.0	1.04 (0.78-1.37)	1.10 (0.81-1.51)
III	329 (17.3)	31.6	0.92 (0.69-1.24)	0.85 (0.63-1.14)	20.4	0.99 (0.71-1.40)	1.00 (0.68-1.46)
Non-ductal carcinoma	357 (18.7)	29.1	0.82 (0.61-1.10)	0.82 (0.61-1.10)	18.8	0.90 (0.64-1.26)	1.04 (0.71-1.51)
Lymph node status			P<0.001	P=0.001		P<0.001	P=0.05
Lymph node negative	1011 (53.1)	29.1	1 Ref	1 Ref	17.5	1 Ref	1 Ref
Lymph node positive	894 (46.9)	36.8	1.42 (1.17-1.72)	1.40 (1.15-1.70)	23.6	1.46 (1.16-1.82)	1.28 (1.00-1.64)
ER/PR receptor status			P=0.51	P=0.39		P=0.57	P=0.47
Negative	299 (15.7)	31.1	1 Ref	1 Ref	19.1	1 Ref	1 Ref
Positive	1595 (83.7)	33.0	1.09 (0.84-1.43)	1.13 (0.86-1.47)	20.5	1.10 (0.80-1.50)	1.14 (0.80-1.61)
Type of surgery			P=0.11	P=0.09	P=0.08	P=0.10	P=0.29
Mastectomy	965 (50.7)	34.4	1 Ref	1 Ref	21.9	1 Ref	1 Ref
Lumpectomy	940 (49.3)	31.0	0.86 (0.71-1.04)	0.85 (0.70-1.03)	18.8	0.83 (0.66-1.04)	0.88 (0.69-1.13)
Surgical lymph node procedure			P<0.001	P<0.001		P<0.001	P=0.03
SLNB	1332 (69.9)	21.5	1 Ref	1 Ref	13.5	1 Ref	1 Ref
ALND	437 (22.9)	36.3	2.08 (1.61-2.68)	2.05 (1.59-2.64)	23.1	1.93 (1.42-2.61)	1.41 (1.02-1.97)
Not reported	136 (7.14)	33.8	1.87 (1.22-2.85)	1.89 (1.23-2.88)	15.4	1.17 (0.68-2.01)	0.85 (0.47-1.52)
Chemotherapy							
<i>Pre-menopausal</i>			P=0.25	P=0.33		P=0.82	P=0.70
No	134 (17.7)	32.1	1 Ref	1 Ref	23.1	1 Ref	1 Ref

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Yes	623 (82.3)	37.4	1.26 (0.85-1.88)	1.22 (0.82-1.83)	24.1	1.05 (0.68-1.64)	0.91 (0.55-1.49)
<i>Post-menopausal</i>			P=0.33	P=0.24		P=0.10	P=0.12
No	944 (85.7)	30.4	1 Ref	1 Ref	18.8	1 Ref	1 Ref
Yes	158 (14.3)	26.6	0.83 (0.57-1.21)	0.79 (0.54-1.17)	13.3	0.66 (0.41-1.08)	0.66 (0.39-1.12)
Radiotherapy			P=0.07	P=0.10		P=0.31	P=0.77
No	394 (20.7)	28.9	1 Ref	1 Ref	18.5	1 Ref	1 Ref
Yes	1511 (79.3)	33.7	1.25 (0.98-1.59)	1.22 (0.96-1.56)	20.8	1.16 (0.87-1.54)	1.05 (0.77-1.43)
Endocrine treatment^b							
<i>Pre-menopausal</i>			P=0.20	P=0.21		P=0.59	P=0.33
No	247 (32.6)	33.2	1 Ref	1 Ref	25.1	1 Ref	1 Ref
In treatment	510 (67.4)	38.0	1.24 (0.90-1.70)	1.23 (0.90-1.69)	23.3	0.91 (0.64-1.29)	0.82 (0.55-1.22)
<i>Post-menopausal</i>			P=0.005	P=0.004		P=0.002	P=0.01
No	394 (35.8)	24.6	1 Ref	1 Ref	13.2	1 Ref	1 Ref
In treatment	708 (64.3)	32.8	1.49 (1.13-1.97)	1.51 (1.14-2.00)	20.6	1.71 (1.21-2.41)	1.62 (1.11-2.35)
DBCG protocol^c							
<i>Pre-menopausal</i>			P=0.40	P=0.45		P=0.64	P=0.59
A	134 (7.03)	32.1	1 Ref	1 Ref	23.1	1 Ref	1 Ref
B	510 (26.8)	38.0	1.30 (0.87-1.95)	1.26 (0.84-1.89)	23.3	1.01 (0.64-1.59)	0.87 (0.52-1.44)
D	113 (5.9)	34.5	1.12 (0.66-1.90)	1.05 (0.61-1.81)	27.4	1.26 (0.71-2.24)	1.12 (0.58-2.17)
<i>Post-menopausal</i>			P=0.02	P=0.02		P=0.009	P=0.04
A	236 (12.4)	23.3	1 Ref	1Ref	13.1	1 Ref	1 Ref
C	708 (37.2)	32.8	1.60 (1.14-2.25)	1.59 (1.13-2.24)	20.6	1.72 (1.13-2.61)	1.58 (1.00-2.49)
E	158 (8.3)	26.6	1.19 (0.75-1.90)	1.13 (0.71-1.81)	13.3	1.01 (0.56-1.84)	0.95 (0.50-1.81)

^a A total of 1905 women completed pain questionnaires at both 15 mo. and 7-9 yrs follow-up and were eligible for analysis. Missing observations are not shown when $\leq 2\%$ and totals may therefore differ slightly. OR = Odds Ratio, CI = 95% Confidence Interval

^b At the time of data collection, protocols prescribed endocrine treatment as follows: pre-menopausal women were treated with Tamoxifen for 5yrs (protocol B), post-menopausal women were treated with Tamoxifen for 2.5 yrs (at minimum), followed by 2.5 years with AI treatment (protocol C)

^c **A**= No adjuvant therapy, **B**= 7 cycles of chemotherapy (CEF) + endocrine treatment (Tamoxifen) for 5 yrs, **C**= endocrine treatment for 5 yrs (Tamoxifen + AI treatment), **D**= 7 courses of chemotherapy with CEF, **E**= 7 cycles of chemotherapy with CMF

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Table 4

Health behavioral predictors of high pain frequency at 15 months and 7-9 years after surgery in a national cohort of women treated for breast cancer^a

15 months					7-9 years		
Study cohort N (%)	Frequency (%) Almost every day or more frequently Prevalence= 32.7%	OR (95% CI) Unadjusted	OR (95% CI) Age-adjusted		Frequency (%) Almost every day or more frequently Prevalence= 20.4%	OR (95% CI) Unadjusted	OR (95% CI) Adjusted for age and pain at 15 months
Assessed at 15 mo.:							
Smoking status		P=0.001	P=0.003			P=0.11	P=0.57
Never Smoker	767 (40.3)	29.5	1 Ref	1 Ref	19.3	1 Ref	1 Ref
Ex-smoker	597 (31.3)	32.8	1.17 (0.93-1.47)	1.16 (0.92-1.47)	21.1	1.12 (0.86-1.46)	1.05 (0.79-1.41)
1-9 per day	131 (6.9)	26.7	0.87 (0.58-1.32)	0.91 (0.60-1.38)	16.0	0.80 (0.48-1.32)	0.84 (0.48-1.45)
10-19 per day	224 (11.8)	42.0	1.73 (1.27-2.35)	1.71 (1.25-2.32)	20.5	1.08 (0.75-1.57)	0.81 (0.54-1.21)
≥ 20 per day	154 (8.1)	40.3	1.61 (1.13-2.31)	1.55 (1.08-2.22)	27.9	1.62 (1.09-2.41)	1.20 (0.77-1.87)
Alcohol (pr. day)		P=0.008	P<0.008			P=0.12	P=0.66
No alcohol	410 (21.5)	39.8	1 Ref	1 Ref	23.2	1 Ref	1 Ref
> 0 and < 1 drinks	620 (32.6)	32.6	0.73 (0.57-0.95)	0.70 (0.54-0.91)	21.9	0.93 (0.69-1.26)	1.08 (0.77-1.50)
≥ 1 and < 2 drinks	515 (27.0)	29.7	0.64 (0.49-0.84)	0.64 (0.48-0.84)	19.4	0.80 (0.58-1.10)	1.00 (0.70-1.42)
≥ 2 and < 3 drinks	243 (12.8)	27.6	0.58 (0.41-0.81)	0.60 (0.43-0.85)	16.5	0.65 (0.43-0.98)	0.83 (0.53-1.31)
≥ 3 drinks	113 (5.9)	32.7	0.74 (0.48-1.15)	0.79 (0.51-1.24)	15.0	0.59 (0.33-1.03)	0.75 (0.40-1.38)
BMI		P=0.03	P=0.02			P=0.12	P=0.63
Normal weight (≥18.5 and < 25)	1071 (56.2)	30.8	1 Ref	1 Ref	19.6	1 Ref	1 Ref
Underweight (≤ 18.5)	34 (1.8)	38.2	1.39 (0.69-2.81)	1.41 (0.70-2.87)	17.6	0.88 (0.36-2.15)	0.68 (0.26-1.79)
Overweight (≥ 25 and < 30)	558 (29.3)	33.3	1.12 (0.90-1.40)	1.15 (0.92-1.44)	20.4	1.05 (0.82-1.36)	0.97 (0.73-1.29)
Obese (≥ 30 & < 35)	160 (8.4)	43.8	1.75 (1.25-2.45)	1.80 (1.28-2.54)	28.7	1.65 (1.14-2.41)	1.30 (0.85-1.97)
Severely obese (≥35)	49 (2.6)	30.6	0.99 (0.53-1.84)	1.02 (0.54-1.90)	18.4	0.92 (0.44-1.93)	0.86 (0.38-1.94)
PASE components^{b,c}							
Walking ^d	1696 (89.0)		P=0.41	P=0.82		P=0.09	P=0.02
		32.5	0.99 (0.97-1.01)	1.00(0.98-1.02)	20.4	1.02 (1.00-1.05)	1.03 (1.01-1.06)
Mild ^d	337 (17.7)		P=0.88	P=0.89		P=0.29	P=0.27
		31.5	1.00 (0.94-1.05)	1.00 (0.94-1.05)	20.8	1.03 (0.97-1.09)	1.04 (0.97-1.12)
Moderate exercise ^d	905 (47.5)		P=0.001	P=0.002		P=0.98	P=0.07
		28.2	0.94 (0.91-0.98)	0.94 (0.91-0.98)	20.0	1.00 (0.97-1.04)	1.04 (1.00-1.08)

RUNNING HEAD: PREDICTORS OF PERSISTENT PAIN AFTER BREAST CANCER TREATMENT

Strenuous exercise ^d	643 (33.8)		P<0.001	P<0.001		P=0.66	P=0.16
		25.8	0.88 (0.82-0.94)	0.88 (0.82-0.94)	18.5	0.99 (0.93-1.058)	1.04 (0.98-1.04)
Weight training ^d	330 (17.3)		P=0.22	P=0.29		P=0.08	P=0.008
		32.1	0.96 (0.89-1.03)	0.96 (0.90-1.03)	23.9	1.06 (0.99-1.13)	1.10 (1.03-1.19)
Physical workload ^e	731 (38.4)		P=0.23	P=0.009		P=0.08	P=0.07
		31.1	0.97 (0.93-1.02)	0.94 (0.90-0.99)	21.2	1.04 (1.00-1.09)	1.05 (1.00-1.11)
SF-36 PF^f			P<0.001	P<0.001		P<0.001	P=0.003
100 (Best)	488 (25.6)	13.3	1 Ref	1 Ref	7.8	1 Ref	1 Ref
> 90 and < 100	409 (21.5)	20.8	1.71 (1.20-2.43)	1.73 (1.21-2.47)	17.4	2.49 (1.64-3.78)	2.00 (1.29-3.11)
>80 and ≤ 90	448 (23.5)	38.2	4.02 (2.91-5.55)	4.29 (3.09-5.95)	23.4	3.63 (2.44-5.39)	2.08 (1.36-3.19)
>70 and ≤ 80	267 (14.0)	53.6	7.51 (5.26-10.70)	7.79 (5.44-11.17)	32.2	5.63 (3.70-8.56)	2.40 (1.52-3.79)
≥ 0 and ≤ 70 (Worst)	274 (14.4)	56.6	8.48 (5.95-12.08)	9.87 (6.87-14.19)	31.0	5.33 (3.51-8.09)	2.00 (1.25-3.20)
CCI^g			P=0.04	P=0.01		P=0.21	P=0.04
No comorbidity	1736 (91.1)	32.0	1 Ref	1 Ref	20.7	1 Ref	1 Ref
Comorbidity	163 (8.6)	39.9	1.41 (1.01-1.96)	1.54 (1.10-2.15)	16.6	0.76 (0.49-1.17)	0.62 (0.39-1.00)

^a A total of 1905 women completed pain questionnaires at both 15 mo. and 7-9 yrs follow-up and were eligible for analysis. Missing observations are not shown when ≤ 2 % and totals may therefore differ slightly. OR = Odds Ratio, CI = 95% Confidence Interval

^b The Physical Activity Scale for the Elderly³⁴

^c The PASE components are treated as dichotomous variables when reporting Study Cohort (n) and Frequency (%). The Frequency (%) reported for each component refers to the percent of women engaged in the activity the previous 7 days (compared to the percent of women *not* engaged in the activity). In the logistic regressions, component scores are treated as continuous variables

^dHours per week

^eHours per day

^f The SF-36 Physical Function subscale³⁵

^g Charlson Comorbidity Index^{31,32}. Assessed at time of surgery

Figure1
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Socio-Demographic, Treatment-Related and Health Behavioral Predictors
Article title (first few words) *of persistent pain*

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