

# Pilot Testing of a New App for Prospective Evaluation of Health-related Quality of Life in Breast Cancer

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## Research

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## Abstract

**Background:** Given that BC patients now live longer and have a higher survival rate, long-term side effects of primary treatment and patients' Life Quality (LQ) have become a more central issue. The purpose of this study was to investigate whether Life Quality changes after primary BC treatment.

**Method:** A prospective cohort study was conducted including 149 Danish women with BC. Sixty had entered the date since chemotherapy termination and their daily measurement of QoL for mood in the app Bone@BC. All users can only enter the app with a Danish NemID and own mobile device. The app includes self-reported patient baseline characteristics related to BC treatment and simple self-reported data of LQ measured in mood, social life and wellbeing measured by fatigue, pain and appetite and physical activities.

**Results:** During the pilot test period, 149 BC survivors entered baseline data. Of the 149 BC survivors 60 (40%) have entered chemotherapy history and LQ data. The mean age of the BC survivors was  $58.2 \pm 9.6$  years (range 27-78 years). Days since chemotherapy termination was with a mean of 450 days (range 54-5.175 days). In group A (n=20) 35% reported 0-365 days and in group B (n=39) 65% reported more than 365 days since chemotherapy termination. In the whole group 65% reported neutral mood. By division into group A vs. B showed that mood improve over time measured by several in group B had a neutral mood achieved. Half (53%) had a good social life. Similar changes were reported for pain with 79% reporting mild to moderate pain in the whole group, group A vs. B showed an increasing level of pain over time with 24% reporting moderate to severe pain in group B vs. 13% in group A. Finally, it was observed that 58% reported mild to moderate appetite and it is decreasing over time, 64% reported mild to moderate appetite in group B vs. 50% in group A.

**Conclusion:** Our results indicate that BC survivors have impaired QoL up to several years after primary BC treatment but there is a trend of some improvement over time.

**Trial registration:** ClinicalTrials.gov:NCT03784651

## Background

Worldwide, an increasing number of people are affected by cancer. In 2018 18.1 million people were diagnosed with cancer with a mortality rate of 9.6 million (53%).(1) Breast cancer (BC) is one of the most common cancers worldwide and the most frequent cancer in Danish women with a high survival rate. On average 4.700 new cases are diagnosed in Denmark per year among a total population of 5.7 million citizens.(2)

The standard breast cancer care in Denmark is at a high prevention and intervention level including every second-year mammography from age 50-70 years in a national screening program and treatment are following evidence-based international recommendations.(3) However, concerning the rehabilitation and Life Quality measures in the first years after primary treatment of BC, the data are sparse and there is no evidence for specific follow-up or systematic knowledge of late-onset side effects.

It is well described that cancer in general have a psychosocial impact and affect the Quality of Life (QoL).(4) National and international data in patients with varying diagnosis of cancer on QoL in patients and especially evidence of improvement from disease onset shows conflicting results.(5)(6)(7)(8)

Currently, there is an increasing interest of the impact of BC disease and the self-perceived QoL after finalized oncologic treatment.(9) (10)(11)(12)(13) Several previous studies are focusing emotional distress which have highlighted physical side effects among BC survivors treated with surgery, chemotherapy, radiation and aromatase inhibitors.(14)(15)(16) Whereas physical and phycological side-effects are well investigated after surgery, chemotherapy and radiation.(17)(18)(19) Physical and psychological side effects severely impair women with BC psychological balance and self-perceived QoL. Indeed, several studies demonstrate the importance of traumatic factors, both for mental health and mood.(14)(20) In this review we are focusing QoL and our current knowledge of how it is related to endocrine treatment with anti-estrogen from a patient perspective and have tried to develop a tool for patient involvement collecting Patient Related Outcome Measures (PROMs).

Takai et al. found in their study of side effects from adjuvant endocrine therapy in BC survivors, that Health Related Quality of Life (HRQoL) was higher in BC survivors treated with Tamoxifen than those treated with Exemestane or Anastrozole.(21)

For several decades it has been accepted that patient perspective is paramount and listening to these perspectives can increase patient-empowerment and QoL.(22)(23)(24)

QoL is a complex, multifaceted concept which contains objective and subjective components. Patient-outcome assessment tools have direct relevance to mental health nursing in influencing the evidence based on which is practiced.(25) For many decades, HRQoL in BC survivors has been investigated.

Priestman TJ and Baum M were the first to PROMs for advanced breast cancer patients back in 1976.(26) Based on the pioneering work by Priestman and Baum the today's updated evaluation method are Patient Reported Outcomes (PROs). PROs are the accepted gold standard for collecting data of patients own assessment of their HRQoL.(27)

Based on the pioneering work through decades The World Health Organization (WHO) defines QoL as an: *"Individual's perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns. It is a broad ranging concept affected in a complex way by the person's physical health, psychological state, personal beliefs, social relationships and their relationship to salient features of their environment"*.(28)

HRQoL is divided into different domains such as health, physical functioning/activities, mental health, social functioning, fatigue and pain. One of the major PROs for measurement HRQoL in patients with breast cancer is provided by the European Organization for Research and Treatment of Cancer (EORTC). The EORTC QLQ-C30 as a modular approach is available in more than 100 languages and is used to assess HRQoL in patients with breast cancer within the scope of clinical trials, as well as in daily routine.(29) Another major PROs for measurement are provided by The Medical Outcomes Study (MOS). The short form health survey (SF-36) is available in more than 40 languages and is used to assess HRQoL in patients with different diseases among others BC. It is a generic instrument and used in the scope of clinical trials as well as in daily routine.(28) The transition from paper-based evaluated PROMs to electronic based evaluated e-PROMs is relative new.(30) The development of digitalization in medicine, validation of electronic versions of well-established PRO instruments are essential and might contribute to comprehensive and holistic oncology care and to ensure high quality BC research. Paper-based questionnaires are however still the predominating standard. Knowledge about electronic patient reported outcome ePRO is still sparse and ePRO is not yet validated.(27)

Willingness of BC patients to utilize innovative mobile applications for monitoring their own health has been increasing in parallel to the enhanced possibilities for using private mobile devices.(27)(31)

Patients own assessments of their QoL and HRQoL make it possible to assess the patients benefit from a total patient care perspective. Optimal communication of PRO-data to different health care professionals in diverse departments are of great importance for symptom management and improvement of the QoL of the individual patient with BC. Electronic self-reporting tools might be of major importance for QoL and patient empowerment.(32)(33)(34)

A variety of instruments are being used to capture and measure symptoms as well as for examine the complexity of caring for patients e.g. treating, managing their symptoms and evaluate the QoL for cancer patients.(35)

Riis et al. concluded in a recent review of prospective studies with PROs during patient follow-up in early BC, including only a few and low-medium impact studies that: *"The limited evidence available suggests that PROs may be useful for providing a more complete picture of the patient's symptoms and problems, possibly leading to improvements in symptom management"*.(36)

The aim of this prospective small cohort pilot study was to evaluate if Quality of Life change after primary breast cancer treatment in a small sample primarily to evaluate the usability of the patient app Bone@BC.

## **Main Text**

### **Methods**

The study is conducted as a prospective cohort pilot study at the Center for Cancer and Organ Diseases, Copenhagen University Hospital, the Dept. of Endocrinology, Rigshospitalet, the Capital Region of Denmark in collaboration with Center for Cancer and Organ Diseases, Copenhagen University Hospital, the Dept. of Oncology, Rigshospitalet, the Capital Region of Denmark. The study is blinded for the assessors.

## Study participants

Women from all over Denmark with a personal registration number are eligible for data-entrance given the diagnosis of breast cancer.

## Methods

We developed a new electronic questionnaire and report on the pilotesting of this new app version of the questionnaire named Bone@BC. The technical development of the app was performed in close collaboration with the Oncological Department, Rigshospitalet and IT-company ZiteLab ApS. Our app Bone@BC was released May 1, 2018 from the Dept. of Endocrinology, Rigshospitalet, the Capital Region of Denmark. The app has been officially approved by the Danish Breast Cancer Patients Society and the unified Danish eHealth Portal. The app is compatible with android mobile phone, iPhone, iPad and computer, as it is built in HTML5. The app enables patient-centered and real-time data. The text version is available in a Danish and English version. Videos are solely published with Danish speak. Registrations are bound on self-reported user data. The app is released in Denmark, Germany and Sweden, but can only be used if the user has a Danish NemID (national electronic personal ID). The users of the app are using their own device. The NemID secure patient accept of participation with analyzed data

**Eligibility criteria included:** All women from all over Denmark with a personal registration number, all users who have entered chemotherapy termination date and the daily HRQoL measurement mood, some have also entered other daily HRQoL measurements in the pilot test period May 1, 2018 to August 31, 2019.

## App data collection

Data were collected via Bone@BC, version 1, in the pilot test period from May 1, 2018 to August 31, 2019.

The App includes some questions from the Medical Outcomes Study Short Form 36 (SF-36) and EORTC QLQ-C30, the European Organization for Research and Treatment of Cancer Quality of Life Core Questionnaire.

The app includes self-reported patient baseline characteristics related to breast cancer treatment. Furthermore, the app includes simple prospective self-reported data of HRQoL measures on mood (5-point scale, multiple choice), social life (4-point scale, multiple choice) and wellbeing measured by fatigue (Visual analogue scale (VAS) 0-10 point scale), pain (VAS 0-10 scale), appetite (VAS 0-10 point scale) and physical activity (0-90 minutes/day). Physical activity is self-reported and divided into different types of physical activity such as gardening, cycling, cleaning etc. All the questions and possible answers in the Bone@BC app are presented in figure 1.

HRQoL questionnaires are divided into generic and disease-specific instruments. The Medical Outcomes Study Short form 36 (SF-36) questionnaire is a generic instrument that has been widely used for assessment of HRQoL in studies on different diseases among others breast cancer.(28) The European Organization for Research and Treatment of Cancer Quality of Life Core Questionnaire (EORTC QLQ-C30) is disease-specific and has been the instrument of choice in studies on breast cancer disease.(37) The EORTC QLQ-C30 is a cancer-specific 30-item HRQoL questionnaire and consist of 30 questions.(29) Twenty-four questions form nine multi-item scales presenting various aspects of HRQoL, whereas the remaining six are single-item scales describing cancer-relevant symptoms. The SF-36 consists of 36 questions that form eight multi-item scales.(38) The two instruments are quite similar and have five domains in common: Pain, social functioning, fatigue/vitality, mental health/emotional functioning and physical functioning. When the SF36 and the EORTC QLQ-C30 have been compared in cancer populations both instruments displayed satisfactory psychometric properties and the correlation (measured from Cronbach's alpha) between the five domains covered by both instruments ranged from respectively 0.70-0.81 and 0.50-0.70.(39)(40)

## Statistics

Values of parametric character following a normal distribution are summarized by mean and standard deviations (SD). Values of non-parametric character, not following a normal distribution are given by median and interquartile range (IQR). Generation of normal distribution were mainly applied by visual checking scatterplot.

Categorical variables are summarized as percentages.

First, the successive levels of each categorical item are numbered increasingly. For instance, a common scheme with five-category items is to grade responses such as patient mood: Excellent, happy, neutral, sad, unhappy decoded as 1-5 respectively.

Cronbach's alpha estimates how reliable are the responses of a questionnaire and is a common indicator for internal consistency.(41)  
(42) Cronbach's alpha is calculated on the three domains: Mood/social functioning, mental health and physical functioning.

Values for patient mood and social life are calculated with scatterplot and Generalized Linear Model (GLM) univariate.

Values for fatigue, pain, appetite and physical activity are calculated with scatterplot and linear regression and residual plot.

We have used chemotherapy termination date and only the latest input in the mood item for the statistical analysis.

For all domains we always reported combined but also divided and compared into two groups, group A and B. Group A represented patients with BC from 0-365 days since chemotherapy termination and group B 365-5.175 days since chemotherapy termination. In the total group it is only reported when more than 10 participants have reported and in group A and B when more than 8 participants have reported in group A.

All analyses were conducted with IBM® SPSS® Statistics version 26.

## Results

### *Analysis of psychometric properties for the data collection.*

The app as a data instrument displayed satisfactory psychometric properties and correlation in the three domains measured from Cronbach's alpha (CA): Mood and social functioning (2 items) CA: 0.81, mental health (3 items) CA: 0.60 and physical functioning (5 items) CA: 0.70.

### *Patient entered results*

149 BC survivors have downloaded the app and entered baseline data. Of the 149 BC survivors 60 (40%) have entered chemotherapy history and regularly entered daily HRQoL data.

Demographic data for the BC survivors are presented in table 1. The BC survivors that entered data are with a mean age of 58.2 ±9.6 years (range 27-78 years). The median weight was 69.5 kg and the height 168.0 cm. The data shows that our participating BC survivors have a widely distributed observation time since chemotherapy termination with a mean of about 450 days (range 54-5.175 days).

### **Table 1 Demographics of BC patients from the Bone@BC app**

	(n=60)	
Age [mean (SD)] range	58.2 ±9.62 (27-78)	
Weight [median (IQR)]	69.50 (19.00)	
Height [median (IQR)]	168.0 (9.00)	
BMI kg/m <sup>2</sup> [median (IQR)]	24.69 (6.29)	
<b>Nutrition n (%)</b>		
Whole meal	34 (58)	
Vegetarian	3 (5)	
Impaired meat consumption	16 (27)	
Vegan	1 (2)	
n/a	5 (8)	100
<b>Coffein n (%)</b>		
Tea	10 (17)	
Coffee	16 (27)	
Both	29 (48)	
n/a	5 (8)	100
<b>Smoking n (%)</b>		
Current smoker	2 (3)	
Former smoker	29 (48)	
Non-smoker	21 (35)	
n/a	8 (14)	100
<b>Alcohol consumption n (%)</b>		
0 ml alcohol pr. Week	4 (7)	
< 105 ml pr. Week	38 (63)	
105-225 ml alcohol pr. week	5 (8)	
>225 ml alcohol pr. Week	1 (2)	
n/a	12 (20)	100
<b>Daily activity level in the last 4 weeks n (%)</b>		
Always	34 (57)	
Sometimes	25 (41)	
Never	0 (0)	
n/a	1 (2)	100
<b>Physical activity of either 10.000 steps/day or 2x20 min. moderate training/week n (%)*</b>		
Yes	37 (61)	
No	22 (37)	
n/a	1 (2)	100
<b>Social contact today n (%)</b>		

Yes	50 (83)	
No	9 (15)	
n/a	1 (2)	100
<b>Menopause n (%)</b>		
Yes	16 (27)	
No	4 (6)	
n/a	40 (67)	100

\* Recommendation from The Danish Health Authority <https://www.sst.dk/da/Viden/Fysisk-aktivitet>

Among the BC survivors almost all participants are non-smoking, only two are current smokers (3%), whereas almost every second (48%) are former smokers.

The BC survivors included are in general physical active and about 6 of 10 (57%) report high level physical active by either walking 10,000 steps/day or doing 2 x 20 minutes of moderate exercise/week.

Furthermore, two thirds (83%) respond that they feel that they have good social support from their daily network.

Baseline characteristics of the participating patients with BC are presented in table 2. One of 60 participants did not enter relevant data in full and are excluded. One third of our patients included (34%) reported on lymph nodes removal.

**Table 2 Breast cancer characteristics of BC patients**

(n = 60)		
<b>Diseases n (%)</b>		
Breast cancer	60 (100)	
Metabolic disease	4 (7)	
Previous cancer	8 (13)	
Other cancer	0 (0)	
<b>Mamma surgery n (%)</b>		
Mastectomy	16 (28)	
Lumpectomy	37 (62)	
Double mastectomy + ovariectomy	3 (5)	
n/a	1 (2)	100
<b>Operation n (%)</b>		
Right	26 (43)	
Left	26 (43)	
Both	7 (12)	
n/a	1 (2)	100
<b>Lymphnode surgery n (%)</b>		
Yes	20 (33)	
No	39 (65)	
n/a	1 (2)	100
<b>Chemotherapy treatment n (%)</b>		
Yes	38 (63)	
No	21 (35)	
n/a	1 (2)	100
<b>Radiation therapy n (%)</b>		
Yes	47 (78)	
No	12 (20)	
n/a	1 (2)	100
<b>Aromatase inhibitors n (%)</b>		
Yes	45 (75)	
No	14 (23)	
n/a	1 (2)	100
<b>Anti estrogen treatment n (%)</b>		
Letrozol	26 (43)	
Anastrozol	2 (3)	
Exemestan	4 (7)	
Tamoxifen	12 (20)	

n/a	16 (27)	100
<b>Herceptin treatment n (%)</b>		
Yes	16 (27)	
No	4 (6)	
n/a	40 (67)	100

Two third of the BC survivors (63%) have received chemotherapy treatment. Radiation therapy was received by 47 of 59 BC survivors (80%). Furthermore have 45 of 59 BC survivors (76%) reported aromatase inhibitor treatment.

### ***Time of analysis***

The data points based on observation time are distributed for the three main areas; mood and social functioning, mental health and physical activities, as follows:

35% reported 0-365 days since chemotherapy termination, (group A (n=20)) and 65% are more than 365 days after chemotherapy termination, (group B (n=39)). BC survivors in group A are with a mean age of 57.4 ±8.8 years (range 37-78 years) and in group B with comparable mean age of 59.0 ±10.3 years (range 27-76 years) (ns). Overall, in the three domains evaluated, we observed a positive correlation for mood ( $R^2 = 0.005$ ,  $P = 0.58$ ) and social functioning ( $R^2 = 0.039$ ,  $P = 0.30$ ). A negative correlation for fatigue ( $R^2 = 0.040$ ,  $P = 0.06$ ) and appetite ( $R^2 = 0.003$ ,  $P = 0.68$ ) and a positive correlation for pain ( $R^2 = 0.003$ ,  $P = 0.72$ ). There is generally positive correlation for all questions regarding physical activities, none of which is statistically significant.

### ***Mood and social functioning***

#### ***Mood***

All 59 BC survivors reported prospectively on today's mood. Our data shows that over time from chemotherapy termination the mood of the BC survivors are improving. In most of our participants (65%) the mood is reported as neutral.

When we compare the 2 groups of participants with short observation time since chemotherapy termination, group A ((n=20) and 0-365 days since chemotherapy termination (mean 240 days)) to the group of participants with longer time since chemotherapy termination, group B ((n= 39) and 365-5.175 days since chemotherapy termination (mean 1114 days)) we observe that the mood significantly improved and more participants have gained a neutral mood (group B (67%) vs. group A (60%)).

#### ***Social functioning***

Fifty-seven BC-survivors of 59 BC survivors have answered the question about daily social life. Almost half of the BC survivors that participate (53%) reported a good social life since the end of chemotherapy.

When we compare the groups group A (n=19) and group B (n=39) we observe that social life significantly improves, and more participants reported social wellbeing (group B 57% vs. 42% in group A).

#### ***Mental health***

##### ***Fatigue***

Forty-four BC-survivors of 59 BC survivors have answer the question about daily fatigue (76%). More than half reported fatigue to be mild to moderate (57%). There are a negative association between fatigue and days since chemotherapy termination. For every 1000 days increase since chemotherapy termination date the reported level of fatigue for the BC survivors decrease. The two variables fatigue and days since chemotherapy termination are linearly related. There is negative linearity and there is variance homogeneity. When we compare group A (n=16) to group B (n=29) we observed that fatigue decreased. In group A half of the participants reported mild to moderate fatigue and the other half reported moderate to strong fatigue. In group B a little bit more than half (62%) of the participants reported mild to moderate fatigue.

## *Pain*

Thirty-nine BC survivors of 59 BC survivors have answered the question about daily pain (68%). A little less than four fifths (79%) reported mild to moderate pain. There are a positive association between pain and days since chemotherapy termination. For every 1000 days increase since chemotherapy termination the reported level of pain for the BC survivors increase. The two variables pain and days since chemotherapy are linearly related. There is positive linearity and there is variance homogeneity. When we compare the group A (n=15) to group B (n=25) we observed that pain significantly increased. In group A more than two thirds (87%) reported mild to moderate pain and in group B a little less than three fourths (76%) reported mild to moderate pain and 24% reported moderate to strong pain in group B vs. 13% in group A.

## *Appetite*

Fifty-three BC survivors of 59 BC survivors (92%) have answered the questions about daily appetite. About half have responded that their appetite today has been mild to moderate (58%). There are a negative association between appetite and days since last chemotherapy. For every 1000 days increase since chemotherapy termination the reported level of appetite for the BC survivors decrease. The two variables appetite and days since chemotherapy termination are linearly related. There is linearity and there is variance homogeneity. When we compare group A (n= 18) and group B (n=36) we observed that appetite significantly decreased in group A half (50%) of the participants reported mild to moderate appetite and in group B 64% of the participants reported mild to moderate appetite.

## ***Physical functioning***

*Gardening* was reported by 13 BC survivors of the 59 BC survivors. There was a positive association between physical activity - gardening and days since last chemotherapy. For every 1000 days increase since chemotherapy termination the reported level of physical activity -gardening for the BC survivors increase. The two variables physical activity -gardening and days since chemotherapy termination are linearly related.

*House cleaning* was reported by 27 BC survivors of 59 BC survivors. There was an association between physical activity – house cleaning and days since last chemotherapy. For every 1000 days increase since chemotherapy termination the reported level of physical activity – house cleaning for the BC survivors increase. The two variables physical activity -cleaning and days since chemotherapy termination are linearly related. When we compare group A (n= 9) to group B (n= 19) we observed that physical activity-house cleaning inconclusive increase.

*Bicycling* was reported by 17 BC survivors of 59 BC survivors (29%). There is a positive association between physical activity - bicycling and days since last chemotherapy. For every 1000 days increase since chemotherapy termination the reported level of physical activity - bicycling for the BC survivors increase. The two variables physical activity - cycling and days since chemotherapy termination are linearly related.

*Walking* was reported by 45 BC survivors of 59 BC survivors (78%). There was a positive association between physical activity - walking and days since last chemotherapy. For every 1000 days increase since chemotherapy termination the reported level of physical activity - walking for the BC survivors increase. The two variables physical activity - walk and days since chemotherapy termination are linearly related. Group A (n= 15) vs. group B (n= 31) showed that physical activity- walking significantly increased over time group A (mean  $34.00 \pm 18.34$ ) vs. group B (mean  $45.48 \pm 27.24$ ).

## **Discussion**

Our current pilot study indicates that the BC survivors seem willing to report on daily life quality and continues to enter data over time. Further hereto, our preliminary data from a small sample indicate that the mood among BC survivors seem to improve over time and is reported neutral even long time after chemotherapy termination. The pilot study also indicate that the social support improves over time and is reported neutral even long time after chemotherapy termination.

Pain and appetite loss are the most frequent reported observations in our pilot study.

Our preliminary data showed surprisingly that BC survivors complained about loss of appetite and that this loss of appetite were more severe even long time after last chemotherapy. To our knowledge this is the first indication in a report of even continuous loss of

appetite in BC survivors. Our data are based on prospective patient data compared to former published data on this issue. Furthermore, pain seem to increase over time and the intensity is mild to moderate pain. We find an increasing number of patients reporting moderate to strong pain (24%) over time. Several studies have suggested that the pain occurs as a result of surgery or as a result of lymphedema.(43) Several studies have also concluded that the pain may develop partly into chronic pain and the chronic pain are being partly the most frequently reported consequence of BC treatment.(43)(44)(45) In our study we find a strong correlation between reported pain and the self-perceived HRQoL in BC survivors which is in line with former studies.(46)(12)(47)(48) Although pain affects BC survivors self-perceived HRQoL, we found that BC survivors still are increasing their physical activity and in our dataset about half of the patients reported that they either walk 10,000 steps daily or twice a week exercise moderate exercise in 20 minutes. This observation is not in line with other studies as studies show that BC survivors several years post-treatment are still less physically active.(49)(50)(51) On the other hand, studies have shown the importance of BC survivors being physically active as it can help the effects such as fatigue, pain and loss of appetite that BC survivors experience after treatment.(52)(53)

Fatigue was shown to decrease over time in our pilot study, although more than half of the BC survivors report that they experience mild fatigue to moderate fatigue. Studies point out that fatigue affects BC survivors Quality of Life.(48)(13) Separovic et al. finds in their cross-sectional study that precisely fatigue, pain and loss of appetite contribute most to BC survivors having a lower Quality of Life.(54)

Only two of the BC survivors were current smokers in this pilot test and about half were former smokers. In general, the studies over the past years have not been able to show a correlation between BC and smoking. It is different to other cancers as lung cancer where there is a strong association between the cancer and smoking. Over the years, several studies have discussed how smoking might affect the risk of BC development and breast cancer mortality. The studies do not agree; however, several studies indicate that there is a positive association between current smokers and breast cancer mortality. Furthermore, several studies have shown that women who smoke after being diagnosed with BC and treatment for breast cancer have a higher mortality risk from both breast cancer and other causes. Some studies report a slightly increased risk in women who smoke compared to women who have never smoked to develop breast cancer.(55)(56)(57)(58)

When looking at the age composition of the total pilot study group, group A and group B of BC survivors, then group A is younger than group B, as expected. The total group is expected to show an average age of 58.2 years, an average age which is consistent with having estrogen sensitive breast cancer and thus, 76% (45 of 59) have received aromatase inhibitor treatment.

There is nothing in this study that indicate that the impaired HRQoL we find on these BC survivors is age-related.

In general, it is difficult to compare with previous studies, as our data is obtained prospectively and not retrospectively, which benefits from no recall-bias. We asked BC survivors while sitting at home on the couch about their Quality of Life parameters exactly on this day, avoiding any recall-bias. Others have performed retrospective studies and asked questions via paper-based questionnaires when patients have been under control. Both SF-36 and EORTC QLQ-C30 questionnaires ask retrospectively.

## Conclusion

Our study tested the usability among BC survivor's in a small cohort in order to evaluate Life Quality changes after primary BC treatment. Our test showed that the BC survivors continued using the app. The pilot test of a small cohort indicates some trends that are of clinical relevance for BC survivors. Our data indicate that BC survivors might change their HRQoL, in the form of experiencing more pain and less appetite. Furthermore, the study indicate that BC survivors might achieve a more neutral level of mood and might experience improvement of social life over time. Furthermore, BC survivors seems to be more physically active over time, as well as having less fatigue over time. This pilot test highlight that more large-scale prospective studies are needed to further elucidate long time Quality of Life among BC survivor's and our electronic application Bone@BC might be of value for this purpose.

## Study Limitations

Our pilot study has several limitations. The most essential limitation is the small number of participants and thereby the limited number of prospective data points leading to large variance in the responses. Further hereto, the use of self-reported HRQoL data might be early terminated by the participants, and we observed in this study that about 40% of the participants continued entering data after the initial data registration. This might significantly influence our results and preliminary conclusions.

Our data are based on patient self-reporting and therefore there is a risk of recall-bias. In fact, there is a recall-bias in our research in the form of BC survivors responding to their chemotherapy termination date, but 35% responded that they did not receive chemotherapy. There may be several reasons for this, one of them may be that they do not remember or know if they have received chemotherapy and another reason might be that they have answered no to chemotherapy, but yes to Herceptin treatment. It might be a wording problem in the app questions. We have focused that in our up-date of the app that is intended to use in large scale studies.

We conclude that the current demographic data also lacks information and need to include among others educational level, marital status and date of cancer diagnosis.

In the current questionnaire some questions are too few to reflect all nuances of i.e. mood and social functioning. Currently there are only two items related hereto and should be improved. The ideal in relation to correlation calculated by Cronbach's alpha, would be at least three items in each domain. This is in our dataset a significant limitation.

Finally, we do not have a non-cancer comparison group, so it is not possible to disentangle changes due to aging e.g. the issues of the impact of chronic disease on both mental and physical wellbeing from those due to cancer. By including a healthy test group would enable us to compare the dataset to an age matched healthy control group although the most essential observations for the patients with BC are to show if time since last chemotherapy will lead closer to normality on wellbeing and HRQoL.

### **Perspective**

The development of an app version for mobile phones might improve prospective everyday data entrance from patients on PROs as the device are closer to the patient. Our next step will be to validate the method to paper questionnaires and to establish a large scale prospective PRO study on Quality of Life in BC long time survivors in order to learn more about the long-time consequences of the disease and treatment.

## **Abbreviations**

App: Application; BC: Breast cancer; CA: Cronbach's alpha; EORTC: The European Organization for Research and Treatment of Cancer; EORTC-QLQ-C30: The European Organization for Research and Treatment of Cancer Quality of Life Core Questionnaire; ePRO: Electronic patient reported outcomes; GLM: Generalized Linear Model; HRQoL: Health-Related Quality of Life; IQR: Interquartile Range; LQ: Life Quality; MOS: The Medical Outcomes Study; n: Population size; NemID: National electronic personal ID; ns.: Not statistically significant; P: P-value; PRO: Patient Reported Outcome; PROMs: Patient Related Outcome Measures; PROs: Patient Reported Outcomes; QoL: Quality of Life; R<sup>2</sup>: R-squared; SD: Standard Deviations; SF-36: The short form Health Survey ; VAS: Visual Analogue Scale; vs.: Versus; WHO: The World Health Organization.

## **Declarations**

### **Acknowledgements**

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### **Authors Contributions**

TLJ and PS designed the study. TLJ and PS conducted the study. TLJ analyzed the data. TLJ wrote the first draft of the manuscript. TLJ and PS revised and finalized the manuscript.

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Læge Sofus Carl Emil og Hustru Olga Doris Friis Legat.

### **Availability of data and materials**

All the necessary data are presented herewith. However, if needed, raw data on excel format can be availed on reasonable request from the corresponding author.

## Ethics approval and consent to participate

All personal information regarding the participants are protected by the Danish Act of Data Protection and Health Act. The protocol is in accordance with the Declaration of Helsinki II and has been approved by the Data Protection Agency and the Ethics Committee, the Capital Region of Denmark Journal-nr.: H-18016600. The Bone@BC app have as the standard all data reviewed and registered in the Capital Region of Denmark (notification and registration of data) journal-nr.: I-suite nr.: 6203, local Journal-nr.: RH-2018-38 and in Pactius jr.nr.: P-2020-520. All participants have given a signed informed consent by NemID (national electronic personal ID) before data-entrance and approved electronically in the Bone@BC app that data will be used for scientific purpose. The project is registered at ClinicalTrials.gov: NCT03784651. Data are downloaded from secured storage in the Region Capital of Denmark to Microsoft Excel (Office 365 PRO+/Office 2016, Microsoft, Redmond, Washington).

## Consent for publication

All participants gave electronic consent for use of data and publication.

## Competing interests

The authors declare to have no conflicts of interest.

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## Figures

Question	Possible answers
1. Which word describes your mood today?	Excellent Happy Neutral Sad Unhappy
2. Which word describes your social life today?	Excellent Good Okay Bad
3. Have you felt tired today?	VAS-scale 0-10
4. How much pain have you had today?	VAS-scale 0-10
5. How has your appetite been today?	VAS-scale 0-10
6. How many minutes have you cleaned today?	0-90 minutes
7. How many minutes have you spent in your garden today?	0-90 minutes
8. How many minutes have you walk today?	0-90 minutes
9. How many minutes have you been cycling today?	0-90 minutes

**Figure 1**

The questions in the Bone@BC app and possible answers

Question	Possible answers
1. Which word describes your mood today?	Excellent Happy Neutral Sad Unhappy
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3. Have you felt tired today?	VAS-scale 0-10
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7. How many minutes have you spent in your garden today?	0-90 minutes
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9. How many minutes have you been cycling today?	0-90 minutes

**Figure 1**

The questions in the Bone@BC app and possible answers