Author(s): Roine, Eija; Sintonen, Harri; Kellokumpu-Lehtinen, Pirkko-Liisa; Penttinen, Heidi; Utriainen, Meri; Vehmanen, Leena; Huovinen, Riikka; Kautiainen, Hannu; Nikander, Riku; Blomqvist, Carl; Hakamies-Blomqvist, Liisa; Saarto, Tiina

Title: Long-term health-related quality of life of breast cancer survivors remains impaired compared to the age-matched general population especially in young women : Results from the prospective controlled BREX exercise study

Year: 2021

Version: Published version

Please cite the original version:

Roine, E., Sintonen, H., Kellokumpu-Lehtinen, P.-L., Penttinen, H., Utriainen, M., Vehmanen, L., Huovinen, R., Kautiainen, H., Nikander, R., Blomqvist, C., Hakamies-Blomqvist, L., & Saarto, T. (2021). Long-term health-related quality of life of breast cancer survivors remains impaired compared to the age-matched general population especially in young women : Results from the prospective controlled BREX exercise study. Breast, 59, 110-116. https://doi.org/10.1016/j.breast.2021.06.012

The Breast 59 (2021) 110–116

Contents lists available at ScienceDirect

The Breast

journal homepage: www.elsevier.com/brst

Long-term health-related quality of life of breast cancer survivors remains impaired compared to the age-matched general population especially in young women. Results from the prospective controlled BREX exercise study

Eija Roine [a, *], Harri Sintonen [b], Pirkko-Liisa Kellokumpu-Lehtinen [c], Heidi Penttinen [a], Meri Utriainen [a], Leena Vehmanen [a], Riikka Huovinen [d], Hannu Kautiainen [e, f], Riku Nikander [g], Carl Blomqvist [a, h], Liisa Hakamies-Blomqvist [a], Tiina Saarto [a]

[a] Helsinki University Hospital, Comprehensive Cancer Center, and University of Helsinki, Faculty of Medicine, Helsinki, Finland
[b] University of Helsinki, Department of Public Health, Helsinki, Finland
[c] Tampere University, Faculty of Medicine and Medical Technology, and Tampere University Hospital, Cancer Center, Center of Research, Development and Innovation, Tampere, Finland
[d] Turku University Hospital, Department of Oncology, and University of Turku, Faculty of Medicine, Turku, Finland
[e] Kuopio University Hospital, Primary Health Care Unit, Kuopio, Finland
[f] Folkhälsan Research Center, Helsinki, Finland
[g] University of Jyväskylä, Faculty of Sport and Health Sciences, GeroCenter Foundation for Aging Research & Development, and Central Finland Hospital District, Department of Research & Education, Jyväskylä, Finland
[h] Örebro University Hospital, Department of Oncology, Örebro, Sweden

ARTICLE INFO

Article history:
Received 5 November 2020
Received in revised form
16 June 2021
Accepted 23 June 2021
Available online 26 June 2021

Keywords:
Breast neoplasms
Cancer survivors
Exercise
Follow-up studies
Health-related quality of life
Utility

ABSTRACT

Objective: To investigate long-term health-related quality of life (HRQoL) changes over time in younger compared to older disease-free breast cancer survivors who participated in a prospective randomized exercise trial.

Methods: Survivors (aged 35–68 years) were randomized to a 12-month exercise trial after adjuvant treatment and followed up for ten years. HRQoL was assessed with the generic 15D instrument during follow-up and the younger (baseline age ≤ 50) and older (age >50) survivors' HRQoL was compared to that of the age-matched general female population (n = 892). The analysis included 342 survivors.

Results: The decline of HRQoL compared to the population was steeper and recovery slower in the younger survivors (p for interaction < 0.001). The impairment was also larger among the younger survivors (p = 0.027) whose mean HRQoL deteriorated for three years after treatment and started to slowly improve thereafter but still remained below the population level after ten years (difference −0.017, 95% CI: −0.031 to −0.004). The older survivors' mean HRQoL gradually approached the population level during the first five years but also remained below it at ten years (difference −0.019, 95% CI: −0.031 to −0.007). The largest differences were on the dimensions of sleeping and sexual activity, on which both age groups remained below the population level throughout the follow-up.

Conclusions: HRQoL developed differently in younger and older survivors both regarding the most affected dimensions of HRQoL and the timing of the changes during follow-up. HRQoL of both age groups remained below the population level even ten years after treatment.

1. Introduction

The growing number of breast cancer survivors living long time beyond treatment has led to an emerging interest in evaluating, in addition to survival, late effects of treatments, and health-related

* Corresponding author. Comprehensive Cancer Center Helsinki University Hospital, P.O.Box 180 00029, HUS, Finland.
E-mail address: eija.roine@helsinki.fi (E. Roine).

https://doi.org/10.1016/j.breast.2021.06.012

quality of life (HRQoL). Some previous studies report that in comparison to general population peers, breast cancer survivors suffer from many limitations in functioning and symptoms even years after cancer treatment [1–4] while other studies have failed to detect any long-term difference in HRQoL between cancer survivors and controls without cancer [5].

Previous studies have reported a more severe impact of breast cancer on younger survivors' HRQoL and emotional well-being. A systematic review concluded that lower HRQoL and depressive symptoms were more frequent or severe in younger (≤50 years) survivors when compared to older (>50 years) survivors and that the mental, as opposed to physical functioning domains, were most severely impacted in the younger survivors [6]. Champion et al. reported that younger breast cancer survivors had more depression and fatigue, lower attention function, and lower sexual function than age-matched controls and older survivors, and more anxiety and sleep difficulty than the older ones several years after diagnosis [7]. Similarly, Marschner et al. found that younger, premenopausal patients reported a decrease in emotional well-being more often and more anxiety than postmenopausal patients [8].

HRQoL can be measured either with disease-specific instruments, which are sensitive in detecting impairments related to a certain disease and its treatment, or with generic HRQoL instruments intended for use across different diseases and conditions and allowing comparisons of results across different populations. Generic instruments produce a single index utility score, a profile, or both. Most of the cancer-specific HRQoL instruments that have been used in cancer survivorship studies have been developed to capture acute disease and treatment-related side-effects. Many of these side-effects are usually no longer relevant in the post-treatment survivorship in disease-free survivors [9]. A generic HRQoL measure, covering aspects of both physical and psychosocial health, serves well in the follow-up care of cancer survivors and enables a comparison to the general population revealing the stress that breast cancer and its treatment place on individuals. The 15D, a generic HRQoL measure, has been shown to have high discriminatory power and content validity in different states of breast cancer survivorship [10].

The BREX (BReast cancer and EXercise) study is an open, prospective, multicenter phase III randomized clinical trial investigating the effect of a supervised 12-month exercise intervention on HRQoL and bone health in disease-free breast cancer survivors. At baseline, the survivors had lower HRQoL compared to the age-standardized general female population both when measured with the generic 15D and with the cancer-specific EORTC QLQ-C30 instruments [11,12]. During the intervention (i.e., the first year after adjuvant treatment), the survivors' HRQoL improved in both the intervention and control groups measured with the EORTC QLQ-C30, but no effect of the exercise intervention on HRQoL was detected at one- or five-year follow-ups [13,14]. At five-year follow-up, the HRQoL of the survivors, measured with the 15D, still remained below the population level [15].

The aim of this report was to compare the mean HRQoL of younger and older breast cancer survivors to that of age-matched general Finnish female population during the nine years following the intervention, i.e., until ten years after primary treatment. The focus is on the effect of the patients' age at onset of illness on the changes of mean HRQoL over time.

2. Methods

Female breast cancer survivors (n = 573) were enrolled in the BREX study between September 2005 and 2007. Women aged from 35 to 68 years who had newly diagnosed locally invasive breast cancer (staged T1-4N0-3) and who had recently completed adjuvant chemotherapy or started endocrine and/or radiotherapy were included. Excluded were patients who had osteoporosis or disease affecting calcium and bone metabolism, severe cardiac disease, or other conditions contraindicating rigorous exercise training, as well as patients who had had a prior malignancy or were found to have hematogenous metastases.

The processes of recruitment, randomization, and the intervention have been reported in detail earlier [12,13,16,17]. The local Ethical Committee of the Helsinki University Hospital approved the study protocol and written informed consent was obtained from all participants. The trial has been registered in the Helsinki and Uusimaa Hospital District Clinical Trials Register (www.hus.fi) (trial number 210590) and on the clinical trials website http://www.clinicaltrials.gov/(identifier number NCT00639210).

The medical history of the survivors was assessed at the baseline visit. The survivors filled in questionnaires covering HRQoL, demographics, and lifestyle habits at baseline and thereafter at nine follow-up points until ten years. After the baseline visit, survivors were randomized either to a one-year supervised exercise training group or to a control group. The exercise intervention consisted of a 12-month weekly supervised aerobic exercise program and instructions for three times a week home exercise. The control group was encouraged to continue their previous exercise habits.

HRQoL was measured by the 15D, a generic, 15-dimensional, standardized, self-administered HRQoL instrument that can be used both as a profile and a single index utility score measure [18,19]. The health state descriptive system (questionnaire) is composed of the following dimensions: mobility, vision, hearing, breathing, sleeping, eating, speech (communication), excretion, usual activities, mental function, discomfort and symptoms, depression, distress, vitality, and sexual activity. For each dimension, the respondent chooses one of the five ordinal levels of severity best describing her state of health at the moment.

The valuation system is based on an application of the multi-attribute utility theory. The single index score (15D score), representing the overall HRQoL on a 0–1 scale (1 = full health, 0 = being dead) and the dimension level values, ranging from no problems on the dimension (=1) to being dead (=0), are calculated from the patient ratings on the questionnaire by using a set of population-based preference or utility weights. As deceased persons cannot fill in the questionnaire, they are assigned a 15D score of 0.

We included the 15D in the present study for two main reasons. Firstly, we had HRQoL data measured by the 15D available from a representative general population sample in Finland [20]. Secondly, the use of a generic HRQoL instrument like 15D in addition to a disease-specific instrument like EORTC QLQ-C30, also used in our study, enables comparisons across different diseases and cost-utility analyses. A recent study has ranked 15D first in sensitivity and construct validity among several generic instruments (AQoL, EQ-5D, HUI3 and SF-6D) in cancer patients [21].

Mean dimension level values are used to draw 15D profiles for groups. The minimum clinically important change or difference in the 15D score has been estimated to be ±0.015 on the basis that patients can on average feel such a difference [22]. The 15D was incorporated into the study during the second recruitment year. Thus, one third completed the 15D questionnaire at baseline and about half the patients at the 1-year follow-up visit. The mean HRQoL of the breast cancer survivors was compared to that of an age-matched representative sample of the general Finnish female population (n = 892) measured in the National Health 2011 Health Examination Survey [23].

After randomization, 36 survivors were excluded; 33 had osteoporosis, one had metastatic breast cancer, one had received endocrine treatment for more than four months, and one had primary lung cancer. Finally, 537 survivors were included in the study.

At the ten-year follow-up, 157 survivors had been excluded: 29 had a new malignancy, 77 had a breast cancer recurrence, 42 discontinued the study, one had deceased, and eight were excluded for other reasons or lost to follow-up. 15D data were available from n = 179 survivors at one year, n = 312 at two years, n = 327 at three years, n = 311 at five years, and n = 342 at ten years. A flow chart of patient inclusion in the present study is shown in supplemental Figure 1.

Here we report the HRQoL of the 342 breast cancer survivors who filled in the 15D at ten-year follow-up and at least one other follow-up point between one- and ten-year follow-up. As there was no difference between the exercise and the control groups measured by the EORTC-QLQC30 at one- or five-year follow-ups [13,14], the survivors are analyzed here as one group. A separate analysis in pre- and postmenopausal women was pre-planned in the study protocol. While determining menopausal status was challenging due to e.g., hysterectomy, endocrine therapy, and menopausal changes during chemotherapy, we used the age of 50 years as a cut-point. An age limit instead of baseline menopausal state was chosen for several reasons. Firstly, most of the previous literature on quality of life (QoL) in breast cancer patients use an age limit (most commonly 50) [6,24]. Secondly, since 15D measurements in most patients started at the one-year follow-up visit, baseline menopausal state was considered to be of minor relevance in the present study, since most of the previously premenopausal patients had already experienced a drug-induced menopause. Moreover, determination of menopausal status in premenopausal patients under endocrine therapy was not part of the BREX exercise study. To investigate the effect of age at diagnosis on HRQoL, younger (≤50 years at baseline) and older (>50 years) survivors were compared to their age-matched general population.

The descriptive statistics are presented as means with standard deviations (SD) or as counts with percentages. Age-matching was performed with five-year age cohorts at each follow-up point.

The effect of age group, time, and their interaction on HRQoL scores was analyzed using generalizing estimating equations (GEE) models with an unstructured correlation structure. Two sets of analyses were made, the first of the absolute HRQoL measures of the two age groups, the second of the difference between the survivors' HRQoL measures and those of the age-matched women. GEE models take into account the correlation between repeated measurements in the same subject, they do not require complete data and can be fit even when individuals do not have observations at all the time points. The normality of variables was evaluated graphically and using the Shapiro–Wilk W test. Stata 16.1 (StataCorp LP, College Station, TX, USA) was used for the analysis. A significance level of <0.05 was used for testing the HRQoL score. A Bonferroni adjustment for multiple testing was used in the analysis of the 15 dimensions of the 15D instrument (p-value limit 0.0033).

3. Results

The baseline characteristics of the 342 breast cancer survivors who participated in the ten-year follow-up are presented in Table I.

There was no significant difference between younger (baseline age ≤ 50 years) and older (>50 years) survivors in mean HRQoL in the direct comparison during follow-up (p = 0.90) (Fig. 1a). Compared to the age-matched general female population, the mean HRQoL was significantly more impaired in the younger than in the older survivors during the ten-year follow-up (p = 0.027) (Fig. 1b). The change of mean HRQoL during follow-up was significantly different in the younger and older survivors (p for interaction < 0.001) (Fig. 1b). The younger survivors' mean HRQoL deteriorated for up to three years after adjuvant treatment, and although improving considerably between five and ten years of the follow-up, it remained, both statistically and clinically, significantly below the population level at ten years (difference −0.017, 95% CI: −0.031 to −0.004). The older survivors' mean HRQoL gradually approached the population level during the first five years but also remained significantly lower than that of the population at ten years (difference −0.019, 95% CI: −0.031 to −0.007) (Fig. 1b). The older survivors showed a subtle decrease in HRQoL between five and ten years of follow-up in contrast to the improvement in younger survivors.

Fig. 2 demonstrates age-matched mean scores of the different dimensions of the 15D for the younger and older survivors during the ten-year follow-up. Both younger and older survivors were significantly worse off than the general population in sleeping and sexual activity throughout the ten-year follow-up (Fig. 2). Mental function was also significantly impaired throughout the follow-up, except for the older women at the last follow-up. Younger survivors had significantly lower scores in vision, hearing, and sleeping. Discomfort and symptoms improved during follow-up. The interaction between age and time was highly significant for sleeping, eating, and excretion, and barely significant (p = 0.003) for depression (Fig. 2). Tables of values corresponding to means and confidence intervals depicted in Figs. 1 and 2 are included as supplement tables.

4. Discussion

The results of the present study are in line with earlier findings showing that living through breast cancer and its treatments is a difficult experience affecting many important aspects of health-related quality of life even several years after the treatment. By comparing the survivors to an age-matched general female population we found that age at diagnosis influenced the effect on the HRQoL patterns of younger and older survivors. The younger survivors had a steeper drop in mean HRQoL during the first three years compared to the flatter curve of the older ones. After five years the younger survivors' mean HRQoL improved, while the older survivors showed a decrease. In both age groups, HRQoL remained below the population level at the last follow-up. Regardless of age group, the largest differences, compared to the general population throughout the study period, were on the dimensions of sleeping and sexual activity.

Our results are in line with earlier reports indicating that HRQoL impairments are largest during the first years after diagnosis [1,4,25,26]. Two cross-sectional studies reported that HRQoL approached the level of the general population or controls without cancer after approximately five years [4,25]. Several longitudinal studies with longer follow-up periods extending up to ten years post-diagnosis, however, have reported that a new downward shift in HRQoL was seen after an initial improvement in the first years and that survivors had lower HRQoL, more symptoms, and decreased functions even ten or more years after treatment [2,3,27,28]. A delayed decline in HRQoL might reflect late effects resulting from cancer and its treatment, such as cardiac, respiratory, or musculoskeletal problems that may appear more than five years after treatment [29,30].

In addition to the difference in the change of HRQoL over time, there were differences between the age groups on certain dimensions of the 15D. Younger women scored worse for vision, hearing, and sleeping. While the difference between the survivors and the age-matched population was relatively small for vision and hearing, the scores for sleeping were considerably lower in both age groups. The younger survivors approached the population on all dimensions at ten years while the older ones diverged from the population on several dimensions after five years of follow-up. We found a significant interaction between age and time-course for

Table 1
Baseline characteristics of the breast cancer survivors who participated in the ten-year follow-up.

Variables	Younger survivors (n = 116)	Older survivors (n = 226)	All survivors (n = 342)
Age, years, mean (range)	45.0 (35–50)	57.6 (51–69)	53.3 (35–69)
Years of education, mean (SD)	15.0 (2.9)	13.6 (3.5)	14.0 (3.4)
Menopausal status, n (%)			
• Premenopausal	110 (94.8)	44 (19.5)	154 (45.0)
• Postmenopausal	6 (5.2)	182 (80.5)	188 (55.0)
Marital status, n (%)			
• Married/Co-habiting	80 (69.0)	148 (65.5)	228 (66.7)
• Unmarried	15 (12.9)	30 (13.3)	45 (13.2)
• Divorced	18 (15.5)	32 (14.2)	50 (14.6)
• Widowed	1 (0.9)	13 (5.8)	14 (4.1)
• Information missing	2 (1.7)	3 (1.3)	5 (1.5)
Breast surgery, n (%)			
• Mastectomy	66 (56.9)	106 (46.9)	172 (50.3)
• Breast conserving surgery	50 (43.1)	120 (53.1)	170 (49.7)
Axillary operation, n (%)			
• Axillary dissection	80 (69.0)	167 (73.9)	247 (72.2)
• SNB	36 (31.0)	59 (26.1)	95 (27.8)
Adjuvant treatments, n (%)			
• Chemotherapy	107 (92.2)	203 (89.8)	310 (90.6)
• Radiotherapy	89 (76.7)	174 (77.0)	263 (76.9)
• Endocrine treatment	93 (80.2)	191 (84.5)	284 (83.0)
BMI, n (%)			
• <25 (normal weight)	68 (58.6)	95 (42.0)	163 (47.7)
• 25–30 (overweight)	36 (31.0)	92 (40.7)	128 (37.4)
• >30 (obese)	12 (10.3)	39 (17.3)	51 (14.9)
Any reported disease, n (%)	43 (37.1)	142 (62.8)	185 (54.1)
Smoker, n (%)	9 (7.8)	19 (8.4)	28 (8.2)

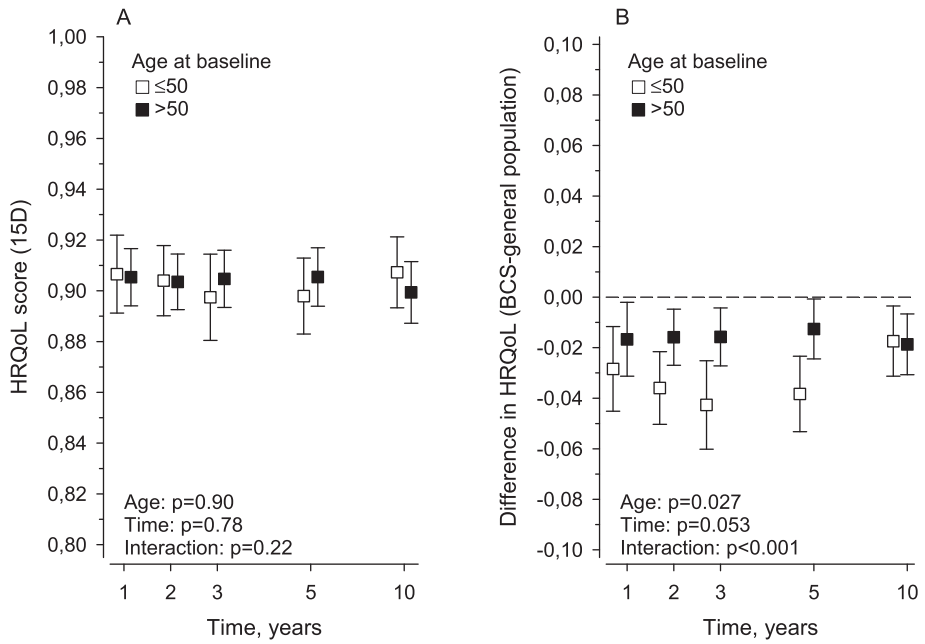

Fig. 1. a. Mean HRQoL and 95% confidence intervals of the younger and older breast cancer survivors during the ten-year follow-up. A difference of ±0.015 in the HRQoL score is considered clinically important. **1b.** The difference in mean HRQoL between the breast cancer survivors (BCS) and the age-matched general female population during the ten-year follow-up. The mean values of the general population are presented with a dashed line. A difference of ±0.015 in the HRQoL score is considered clinically important.

sleeping, eating, excretion, and depression. The dimensions of sleeping, excretion, and to some extent depression, seemed to explain most of the difference in the change over time of HRQoL between the age groups. The clinical relevance of the statistically significant interaction for eating is difficult to interpret since the mean scores were high and close to the population values throughout the study period in both age groups.

We have not been able to find any previous long-term breast cancer survivor study utilizing the 15D questionnaire. However, a number of previous studies have investigated the different aspects of HRQoL using other quality of life (QoL) instruments. The different QoL subscales in these questionnaires do not necessarily correspond exactly to those in 15D, making comparisons difficult. Many studies have indicated anxiety and depression to be more common in younger survivors [6,7,31,32]. In several studies also a more pronounced HRQoL impairment and a more devastating effect on emotional functioning in younger survivors has been reported [3,6,7,24,31–33]. Thus, these studies confirm our findings that

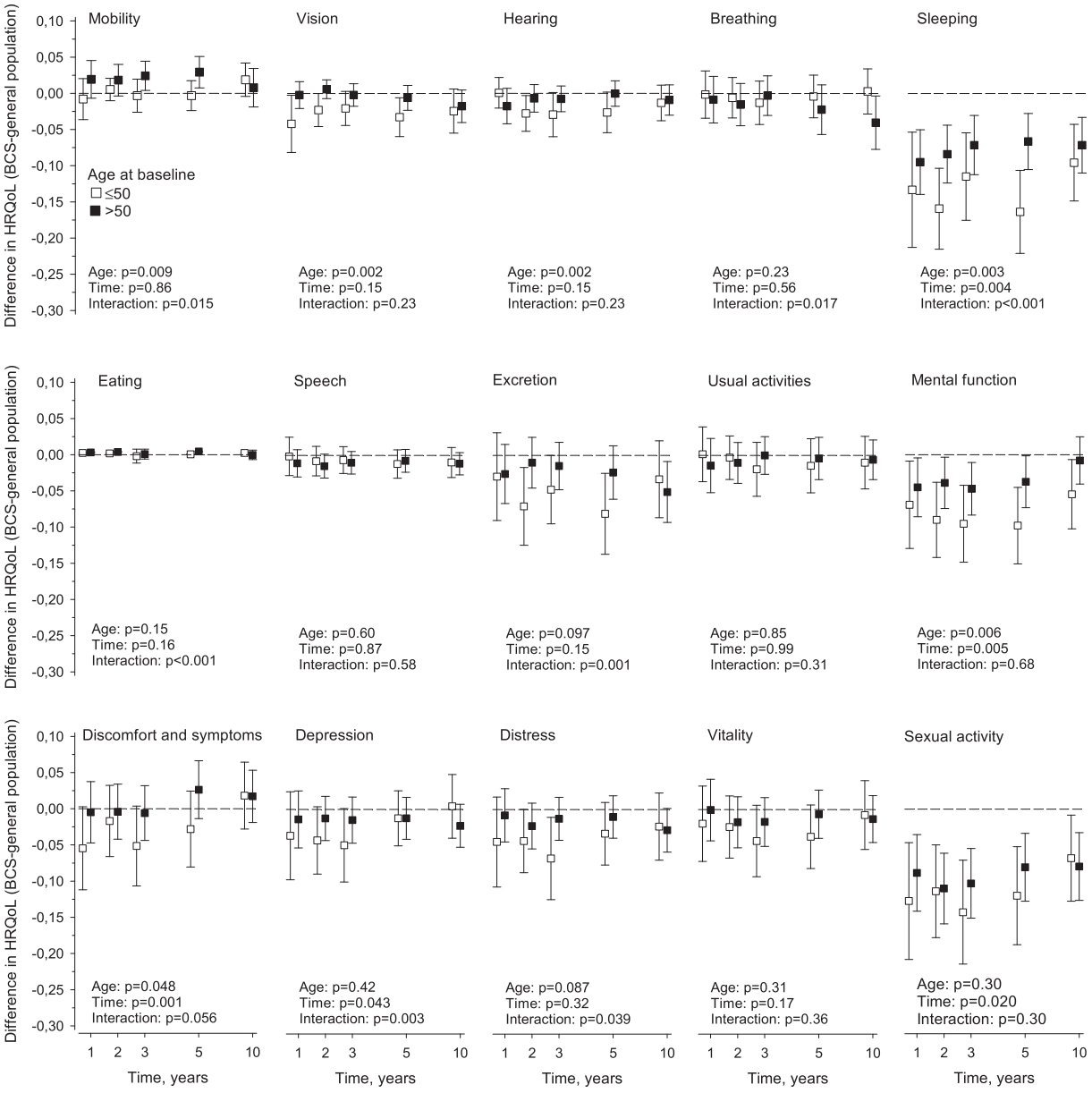

Fig. 2. Difference in mean 15D dimension scores between the breast cancer survivors (BCS) and the general population during follow-up. The black squares represent the older survivors and the white ones the younger survivors. Bonferroni corrected 95% confidence intervals are presented with whiskers. The mean values of the general population are presented with a dashed line.

depression is more severe in younger women, a finding that may be related to the fact that younger women suffer more from trouble with sleeping. An investigation of associations between different dimensions of HRQoL could reveal possible causal relationships between these. This type of analysis requires extensive statistical methods and was not within the scope of the present study. We are, however, conducting in a separate study a statistical network analysis in the BREX study on the different subscales of the EORTC QLQ-C30 questionnaire which may be better suited for this type of analysis in breast cancer survivors, since it focuses more specifically on symptoms related to cancer.

Results on how long the more pronounced HRQoL impairment in younger survivors lasts vary [3,6,24,31,33]. A study with survivors ten years from diagnosis found significant restrictions on nearly all functioning and symptom scales of the EORTC-QLQC30 when compared to the general population, and the differences were largest for younger survivors who had impairments on all scales [3]. In that study, about one-fifth of the survivors had a breast cancer recurrence while we included only disease-free survivors, and more survivors had been treated with axillary dissection, which may explain some of the differences in the findings. Another study with survivors treated with breast-conserving surgery and radiotherapy reported that younger survivors had lower HRQoL than older ones in the first year after radiotherapy, although of limited clinical relevance. Three years after radiotherapy the younger survivors had HRQoL values equal to the general population [24]. The survivors in that study had, however, less severe disease and thus had received fewer adjuvant treatment modalities and less invasive surgery than our study population, which might have contributed to their more rapid recovery.

The reason why younger survivors suffer relatively more during the early years was not explicitly addressed in the present study.

Younger women are, however, often diagnosed with more severe disease, and as younger age as such is a risk factor for worse prognosis, they are more likely to receive systemic treatment. Systemic treatment induces premature menopause, either by damaging the ovaries or altering the uptake of estrogen, and is associated with a high acute risk of transient or permanent amenorrhea and menopausal symptoms [34–36]. Menopausal symptoms such as hot flashes, disturbed sleep, vaginal dryness, and dyspareunia are more frequent and severe when menopause occurs abruptly because of cancer treatment than after natural menopause [37–39]. This could contribute to the fact that younger survivors show a more pronounced impairment compared to the general population in the early years, while at the ten-year follow-up the age-matched population has also become peri- or postmenopausal and the difference has evened out.

We compared the two age groups of survivors with respect to how they compared to their respective age-matched general populations. Like the juxtaposition of Fig. 1a and b shows, comparing the age groups directly would be meaningless, since age effects would confound the effects of cancer on survivors of different ages. The prevalence of chronic illnesses likely to affect HRQoL increases with age. The younger a breast cancer patient is at diagnosis, the more drastic is the change in HRQoL, i.e., the more she has to lose. When an older woman, already possibly suffering from one or more conditions affecting her HRQoL, is diagnosed with breast cancer, the added relative loss of HRQoL is smaller. Also, the older population to which they are compared has on average a higher prevalence of illnesses affecting their HRQoL. Thereby the comparison of HRQoL values between the survivors and the population may be more lenient for the older group.

The main limitation of the BREX study pertains to the selection of participants with a healthy lifestyle and good physical performance. Like in all behavioral studies, physically active and healthy people are more willing to participate. Merely the opportunity of participating in an exercise study further activates the participants irrespective of the study group [13]. Even though the recruitment rate of eligible women was high (78%), the exclusion criteria, e.g., musculoskeletal disorders, osteoporosis and cardiovascular disease prevented participation in the study. These health issues become more frequent with increasing age, which may have led to a more pronounced selection of healthier and physically fit survivors especially in the older group. This may indeed affect the absolute levels of the different dimensions of 15D to the benefit of the older group but can hardly have any bearing on the different curve shapes of the change of HRQoL between the age groups during the ten-year follow-up. The main strengths of the present study are the long follow-up time and the large number of patients.

5. Conclusions

In the present study, breast cancer survivors were followed for more than ten years after diagnosis. HRQoL changed differently during follow-up in younger and older survivors both regarding the most affected dimensions of HRQoL and the timing of the changes.

Our findings suggest that the age of onset of illness may affect the need for integrating a rehabilitation plan including psychosocial support, during the treatment phase and follow-up/survivorship care, to reduce HRQoL impairments over time.

Declaration of competing interest

Harri Sintonen is the developer of the 15D.

Acknowledgements

The BREX study was supported by the Cancer Society of Finland and Competitive State Research Financing of the Expert Responsibility of Tampere University Hospital. The study sponsors were not involved in the study design, or the collection, analysis or interpretation of data. Nor were the sponsors involved in the writing of the manuscript or in the decision to submit it for publication. We thank study nurses Nina Puolakka and Kirsi-Marja Rintala, and secretary Outi Malkavaara for excellent patient communication and data handling.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.breast.2021.06.012.

Ethical approval

The local Ethical Committee of the Helsinki University Hospital approved the study protocol and written informed consent was obtained from all participants.

References

[1] Klein D, Mercier M, Abeilard E, et al. Long-term quality of life after breast cancer: a French registry-based controlled study. Breast Canc Res Treat 2011;129(1):125–34. https://doi.org/10.1007/s10549-011-1408-3.
[2] Doege D, Thong MS-Y, Koch-Gallenkamp L, et al. Health-related quality of life in long-term disease-free breast cancer survivors versus female population controls in Germany. Breast Canc .Res Treat. March 2019:1–12. https://doi.org/10.1007/s10549-019-05188-x.
[3] Koch L, Jansen L, Herrmann A, et al. Quality of life in long-term breast cancer survivors – a 10-year longitudinal population-based study. Acta Oncol (Madr). 2013;52(6):1119–28. https://doi.org/10.3109/0284186X.2013.774461.
[4] Schoormans D, Czene K, Hall P, Brandberg Y. The impact of co-morbidity on health-related quality of life in breast cancer survivors and controls. Acta Oncol (Madr) 2015. https://doi.org/10.3109/0284186X.2014.998277.
[5] Hsu T, Ennis M, Hood N, Graham M, Goodwin PJ. Quality of life in long-term breast cancer survivors. J Clin Oncol 2013;31(28):3540–8. https://doi.org/10.1200/JCO.2012.48.1903.
[6] Howard-Anderson J, Ganz PA, Bower JE, Stanton AL. Quality of life, fertility concerns, and behavioral health outcomes in younger breast cancer survivors: a systematic review. J Natl Cancer Inst 2012;104(5):386–405. https://doi.org/10.1093/jnci/djr541.
[7] Champion VL, Wagner LI, Monahan PO, et al. Comparison of younger and older breast cancer survivors and age-matched controls on specific and overall quality of life domains. Cancer 2014;120(15):2237–46. https://doi.org/10.1002/cncr.28737.
[8] Marschner N, Trarbach T, Rauh J, et al. Quality of life in pre-and post-menopausal patients with early breast cancer: a comprehensive analysis from the prospective MaLife project. Breast Canc Res Treat 2019;175:701–12. https://doi.org/10.1007/s10549-019-05197-w.
[9] van Leeuwen M, Husson O, Alberti P, et al. Understanding the quality of life (QOL) issues in survivors of cancer: towards the development of an EORTC QOL cancer survivorship questionnaire. Health Qual Life Outcome 2018;16(1):114. https://doi.org/10.1186/s12955-018-0920-0.
[10] Rautalin M, Färkkilä N, Sintonen H, et al. Health-related quality of life in different states of breast cancer–comparing different instruments. Acta Oncol (Madr) 2018;57(5):622–8. https://doi.org/10.1080/0284186X.2017.1400683.
[11] Roine E, Blomqvist C, Kellokumpu-Lehtinen PL, Sintonen H, Saarto T. Health-related quality of life in breast cancer patients after adjuvant treatments. Breast J 2016;22(4):473–5. https://doi.org/10.1111/tbj.12613.
[12] Penttinen HM, Saarto T, Kellokumpu-Lehtinen P, et al. Quality of life and physical performance and activity of breast cancer patients after adjuvant treatments. Psycho Oncol 2011;20(11):1211–20. https://doi.org/10.1002/pon.1837.
[13] Saarto T, Penttinen HM, Sievänen H, et al. Effectiveness of a 12-month exercise program on physical performance and quality of life of breast cancer survivors. Anticancer Res 2012;32(9):3875–84.
[14] Penttinen H, Utriainen M, Kellokumpu-Lehtinen P-L, et al. Effectiveness of a 12-month exercise intervention on physical activity and quality of life of breast cancer survivors; five-year results of the BREX-study. In Vivo 2019;33(3):881–8. https://doi.org/10.21873/invivo.11554.
[15] Roine E, Sintonen H, Kellokumpu-Lehtinen PL, et al. Health-related quality of life of breast cancer survivors attending an exercise intervention study: a five-year follow-up. *In* Vivo (Brooklyn) 2020;34(2):667–74. https://doi.org/

10.21873/invivo.11821.
[16] Penttinen H, Nikander R, Blomqvist C, Luoto R, Saarto T. Recruitment of breast cancer survivors into a 12-month supervised exercise intervention is feasible. Contemp Clin Trials 2009;30(5):457–63. https://doi.org/10.1016/j.cct.2009.04.007.
[17] Nikander R, Sievänen H, Ojala K, Oivanen T, Kellokumpu-Lehtinen PL, Saarto T. Effect of a vigorous aerobic regimen on physical performance in breast cancer patients - a randomized controlled pilot trial. Acta Oncol (Madr). 2007;46(2):181–6. https://doi.org/10.1080/02841860600833145.
[18] The 15D© health-related quality of life (HRQoL) instrument home page. http://www.15d-instrument.net/15D.
[19] Sintonen H. The 15D instrument of health-related quality of life: properties and applications. In: Annals of medicine, vol. 33. Royal Society of Medicine Press Ltd; 2001. p. 328–36. https://doi.org/10.3109/07853890109002086.
[20] Aromaa A, Koskinen S. Health and functional Capacity in Finland. Helsinki: *Baseline Results of the Health 2000 Health Examination Survey*; 2004. B12/2004.
[21] Richardson J, Iezzi A, Khan MA, Chen G, Maxwell A. Measuring the sensitivity and construct validity of 6 utility instruments in 7 disease areas. Med Decis Making 2016;36(2):147–59. https://doi.org/10.1177/0272989X15613522.
[22] Alanne S, Roine RP, Räsänen P, Vainiola T, Sintonen H. Estimating the minimum important change in the 15D scores. Qual Life Res 2015;24(3):599–606. https://doi.org/10.1007/s11136-014-0787-4.
[23] Koskinen S, Lundqvist A, Ristiluoma N. Health, functional capacity and welfare in Finland in. 2011 (in Finnish with English Abstract).; 2012. doi:Report 68/2012.
[24] Bantema-Joppe EJ, De Bock GH, Woltman-Van Iersel M, et al. The impact of age on changes in quality of life among breast cancer survivors treated with breast-conserving surgery and radiotherapy. Br J Canc 2015;112(4):636–43. https://doi.org/10.1038/bjc.2014.632.
[25] Yu J, Son WS, Lee SB, et al. Uneven recovery patterns of compromised health-related quality of life (EQ-5D-3L) domains for breast Cancer survivors: a comparative study. Health Qual Life Outcome 2018;16(1). https://doi.org/10.1186/s12955-018-0965-0.
[26] Karlsen RV, Frederiksen K, Larsen MB, et al. The impact of a breast cancer diagnosis on health-related quality of life. A prospective comparison among middle-aged to elderly women with and without breast cancer. Acta Oncol (Madr) 2016;55(6):720–7. https://doi.org/10.3109/0284186X.2015.1127415.
[27] Trentham-Dietz A, Sprague BL, Klein R, et al. Health-related quality of life before and after a breast cancer diagnosis. Breast Canc Res Treat 2008;109(2):379–87. https://doi.org/10.1007/s10549-007-9653-1.
[28] Avis NE, Levine B, Goyal N, et al. Health-related quality of life among breast cancer survivors and noncancer controls over 10 years: pink SWAN. Cancer 2020. https://doi.org/10.1002/cncr.32757.
[29] Stein KD, Syrjala KL, Andrykowski MA. Physical and psychological long-term and late effects of cancer. Cancer 2008;112(11 SUPPL):2577–92. https://doi.org/10.1002/cncr.23448.
[30] Runowicz CD, Leach CR, Henry NL, et al. American cancer society/American society of clinical oncology breast cancer survivorship care guideline. J Clin Oncol 2016;34(6):611–35. https://doi.org/10.1200/JCO.2015.64.3809.
[31] Ganz PA, Greendale GA, Petersen L, Kahn B, Bower JE. Breast cancer in younger women: reproductive and late health effects of treatment. J Clin Oncol 2003;21(22):4184–93. https://doi.org/10.1200/JCO.2003.04.196.
[32] Velikova G, Williams LJ, Willis S, et al. Quality of life after postmastectomy radiotherapy in patients with intermediate-risk breast cancer (SUPREMO): 2-year follow-up results of a randomised controlled trial. Lancet Oncol 2018;19(11):1516–29. https://doi.org/10.1016/S1470-2045(18)30515-1.
[33] Romito F, Cormio C, Giotta F, Colucci G, Mattioli V. Quality of life, fatigue and depression in Italian long-term breast cancer survivors. Support Care Canc 2012;20(11):2941–8. https://doi.org/10.1007/s00520-012-1424-9.
[34] Schover LR. Premature ovarian failure and its consequences: vasomotor symptoms, sexuality, and fertility. J Clin Oncol 2008;26(5):753–8. https://doi.org/10.1200/JCO.2007.14.1655.
[35] Partridge A, Gelber S, Gelber RD, Castiglione-Gertsch M, Goldhirsch A, Winer E. Age of menopause among women who remain premenopausal following treatment for early breast cancer: long-term results from International Breast Cancer Study Group Trials V and VI. Eur J Canc 2007;43(11):1646–53. https://doi.org/10.1016/j.ejca.2007.04.006.
[36] Rosenberg SM, Partridge AH. Premature menopause in young breast cancer: effects on quality of life and treatment interventions. J Thorac Dis 2013;5(SUPPL.1):S55–61. https://doi.org/10.3978/j.issn.2072-1439.2013.06.20.
[37] Benshushan A, Rojansky N, Chaviv M, et al. Climacteric symptoms in women undergoing risk-reducing bilateral salpingo-oophorectomy. Climacteric 2009;12(5):404–9. https://doi.org/10.1080/13697130902780846.
[38] Mar Fan HG, Houédé-Tchen N, Chemerynsky I, et al. Menopausal symptoms in women undergoing chemotherapy-induced and natural menopause: a prospective controlled study. Ann Oncol 2009;21(5):983–7. https://doi.org/10.1093/annonc/mdp394.
[39] Crandall C, Petersen L, Ganz PA, Greendale GA. Association of breast cancer and its therapy with menopause-related symptoms. Menopause 2004;11(5):519–30. https://doi.org/10.1097/01.GME.0000117061.40493.AB.