Sexual Health and Burden of Late Effects in Long-Term Breast Cancer Survivors

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Solveig Katrine Smedsland

ABBREVIATIONS

AI: Aromatase inhibitor
B: Beta coefficient
BC: Breast cancer
BCS: Breast cancer survivor
BCT: Breast conserving therapy
BMI: Body mass index
CBT: Cognitive behavioral therapy
CI: Confidence interval
CRN: Cancer Registry of Norway
DSM-V: Diagnostic and Statistical Manual of Mental Disorders, fifth edition
EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire
EORTC QLQ-BR23: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire, Breast Cancer specific module
ET: Endocrine therapy
FCR: Fear of cancer recurrence
FEC: 5-fluorouracil, epirubicin, cyclophosphamide
HER2: Human epidermal growth factor receptor 2
HR: Hormone receptor
HUNT4: The fourth Trøndelag Health Study
LE: Late effect
OR: Odds ratio
PROM: Patient-reported outcome measure
RT: Radiation therapy
SAQ: Sexual Activity Questionnaire
SAQ-D: Sexual discomfort assessed by the SAQ
SAQ-H: Sexual habit assessed by the SAQ
SAQ-P: Sexual pleasure assessed by the SAQ
SN: Sentinel node
SWEET: Survivorship Work and Sexual Health

DEFINITIONS

A **cancer survivor** is defined as an individual diagnosed with cancer from the moment of diagnosis to the end of life (1). The term *long-term survivor* is in general applied to individuals who have survived for at least 5 years after a cancer diagnosis (2).

Late effects refer to adverse effects that present months to years after end of cancer treatment, while *long-term effects* appear during treatment and continue beyond the end of treatment (2). In this PhD project, these terms are merged and referred to as late effects.

Sexual health is according to the World Health Organization defined as a state of physical, emotional, mental and social well-being in relation to sexuality (3).

Sexual activity may be defined as any activity that induces sexual arousal – solitary, between two persons, or in a group (4). In epidemiologic studies sexual activity is often defined as sexual activity with a partner (5, 6), which was the definition used in Paper I.

Sexual functioning describes how the body reacts in different stages of the sexual response cycle (7), including different aspects such as pleasure, enjoyment and discomfort. However, the European Organization for Research and Treatment of Cancer (EORTC) defines sexual functioning as to what degree an individual is sexually active and interested in sex (8). Due to different measures used to assess sexual functioning in this PhD project, the first definition was used in Paper I and the second definition in Paper II.

Sexual dysfunction is a disturbance of the sexual response, and includes lack of sexual interest and arousal, inability to achieve orgasm, and pain during intercourse. According to the Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-V), a disturbance must cause distress or interpersonal difficulties to fulfill the diagnostic criteria of a sexual dysfunction (9). In this PhD project, sexual dysfunction was defined as no sexual interest and no sexual activity in Paper III.

In this project, **sexual health impairments** is the term used to describe the different aspects of reduced sexual health in the breast cancer survivors.

THESIS SUMMARY

Breast cancer (BC) is the most prevalent cancer among women. The 5-year relative survival has surpassed 90% in most Western countries, resulting in a growing population of BC survivors (BCSs), including more than 57 000 persons in Norway. Survivorship research, including the study of long-term (> 5 years) consequences of diagnosis and treatment, has become an area of high interest. BCSs may experience a broad range of physical and mental late effects (LEs) extending into long-term survivorship, negatively affecting their quality of life and functioning. One of these possible consequences are sexual health impairments. Sexual health impairments are well documented in early BC survivorship (≤ 5 years after diagnosis), including loss of interest in sex and vaginal dryness/pain during intercourse. Treatment-induced menopause and treatment with an aromatase inhibitor are important risk factors.

At start of this PhD project, knowledge of sexual health in long-term BCSs was limited, and results were conflicting with regards to sexual health differences between BCSs and female population controls. How the other LEs may affect sexual health in long-term BCSs was also unknown. In recent years, there has been a growing awareness that BCSs may experience different LEs simultaneously, and researchers have identified symptom clusters and subgroups of BCSs with a similar burden of LEs during early survivorship. Such knowledge may enable health care providers to focus survivorship care on BCSs at risk of or with a higher symptom burden. Among long-term BCSs however, considerable gaps in knowledge existed concerning the burden of late effects.

The overall aims of this PhD project were therefore to study sexual health and total burden of LEs in long-term BCSs.

All women aged 20-65 years when diagnosed with BC stage I-III in 2011-2012 without pre- or post-malignancies were identified by the Cancer Registry of Norway and invited to the cross-sectional Survivorship Work and Sexual Health (SWEET) study. Of 2803 invited, 1355 BCSs were included after consent and completion of a multi-item questionnaire focusing on sexual health, LEs and work life.

Mean age at survey was 60 years, and eight years had passed since diagnosis. Most of the BCSs were treated for stage I-II disease (81%) with breast conserving therapy (59%), radiotherapy (80%), chemotherapy (68%) and endocrine therapy (65%). The ten most common LEs were; fear of cancer recurrence (56%), pain (47%), cognitive dysfunction (43%), sleep disturbances

(34%), chronic fatigue (32%), arm problems (32%), sexual dysfunction (28%), emotional dysfunction (28%), breast problems (23%), and neuropathy (21%).

In *Paper I*, we found that about a half (52%) of the BCSs were sexually inactive, mostly due to no interest in sex (35%) and no partner (27%). Treatment with aromatase inhibitor increased the risk of sexual inactivity and sexual discomfort. Being less sexually active at survey compared to before the BC diagnosis were more likely among BCSs treated with chemotherapy and those on current endocrine therapy. Several LEs were negatively associated with sexual health, including a poorer body image, major depression, sleep problems, breast symptoms and chronic fatigue. Physical inactivity was associated with less sexual pleasure.

Sexual health among the BCSs was compared to that in similar aged population controls in *Paper II*. The controls were 17 751 women attending the fourth survey of the population based Trøndelag Health Study (HUNT4). BCSs had lower sexual enjoyment and more sexual discomfort than controls. BCSs treated with both endocrine- and chemotherapy also had lower sexual functioning, and the lowest sexual enjoyment, and most sexual discomfort among all women assessed. Analyses were also stratified by menopausal status. BCSs who were premenopausal at diagnosis had lower sexual enjoyment, and more sexual discomfort compared to similar aged controls. No differences in sexual health were found among the postmenopausal BCSs and controls. However, after treatment with both endocrine- and chemotherapy, also those postmenopausal at diagnosis had lower sexual functioning, lower sexual enjoyment, and more sexual discomfort than similar aged controls.

Based on the presence of the ten most common LEs, three subgroups of BCSs with similar symptom burden were identified in *Paper III*. Almost half (46%) of the BCSs were assigned to a low symptom burden subgroup, characterized by low prevalence (< 15%) of all explored LEs except fear of cancer recurrence and sexual dysfunction. Thirty-seven percent of the BCSs were assigned to a medium symptom burden subgroup, characterized by high prevalence (>45%) of pain, cognitive dysfunction, chronic fatigue, sleep disturbances, emotional dysfunction and fear of cancer recurrence, and lower prevalence of arm- and breast problems, neuropathy and sexual dysfunction. The remaining 17% of the BCSs were assigned to a high symptom burden subgroup, characterized by high prevalence (>55%) of all the assessed LEs except of sexual dysfunction (36%). Younger age, combined systemic therapy, higher BMI and physical inactivity were risk factors for both medium- and high symptom burden. Chemotherapy and axillary dissection were additionally associated with high symptom burden. General functioning

was lower among BCSs in the medium- and high symptom burden subgroups compared to those in the low symptom burden subgroup. Among BCSs within working age (< 67 years) at survey (n=987), 58% were on disability pension in high symptom burden subgroup, compared to 42% and 16% in the medium- and low symptom burden subgroups respectively.

In conclusion, the results from this PhD project demonstrate that younger BCSs and BCSs treated with intensive systemic therapies are at increased risk for both sexual health impairments and a higher burden of LEs long-term. These BCSs should be offered closer and a more comprehensive survivorship care, with the ultimate goal to increase their quality of life, general functioning and work participation. Half of the long-term BCSs explored in this project experienced low symptom burden with corresponding high general functioning, further indicating that survivorship care should be focused on those who actually need it.

NORSK SAMMENDRAG

Brystkreft er den vanligste kreftformen blant kvinner. I de fleste vestlige land er 5-års relativ overlevelse over 90%, og antall brystkreftoverlevere er stadig økende og inkluderer over 57 000 personer i Norge. Forskning omhandlende mulige konsekvenser av kreftbehandling har derfor fått økende oppmerksomhet. Brystkreftoverlevere kan oppleve flere fysiske og mentale seneffekter som kan påvirke livskvalitet og generell funksjon negativt. En slik potensiell seneffekt er redusert seksuell helse. Det er dokumentert at brystkreft og brystkreftbehandling kan påvirke seksuell helse negativt de første fem årene etter diagnose. Manglende interesse for sex og tørrhet i skjede/smerter ved samleie er blant de hyppigste problemene, ofte relatert til behandlings-indusert menopause og endokrin behandling med aromatasehemmer.

Ved starten av dette doktorgradsprosjektet var kunnskap om seksuell helse hos brystkreftoverlevere lenge etter diagnose (> 5 år) begrenset. Vi visste ikke om langtids brystkreftoverlevere hadde dårligere seksuell helse enn kvinner i den generelle befolkningen. Vi manglet også kunnskap om sammenhengen mellom andre seneffekter og redusert seksuell helse i denne populasjonen. De siste årene har man i større grad erkjent at seneffekter ofte sameksisterer, og forskere har identifisert vanlige symptomklynger og undergrupper av brystkreftoverlevere med betydelig høyere byrde av seneffekter enn andre. Slik kunnskap kan brukes til å optimalisere ressursbruken i oppfølgingen av brystkreftoverlevere – med størst fokus på dem med høyere symptombyrde. Kunnskap om seneffekt-byrde hos langtids brystkreftoverlevere fantes imidlertid ikke.

De overordnede målene i dette doktorgradsprosjektet var derfor å undersøke seksuell helse og totalbyrde av seneffekter blant langtids brystkreftoverlevere.

Alle kvinner som var mellom 20 og 65 år da de ble diagnostisert med brystkreft i stadium I-III i 2011 eller 2012 ble identifisert av Kreftregisteret og invitert til å delta i en tverrsnitt studie kalt SWEET (Survivorship Work Sexual Health). Eksklusjonskriterier var tidligere eller nåværende kreft. Av totalt 2803 inviterte, var det 1355 som samtykket og svarte på et spørreskjema med fokus på seksuell helse, seneffekter og arbeidsliv.

Gjennomsnittsalder ved spørreundersøkelsen var 60 år, og det var gått åtte år siden diagnose. De fleste var behandlet for stadium I-II (81%) med brystbevarende kirurgi (59%), strålebehandling (80%), kjemoterapi (68%) og endokrin behandling (65%). De ti vanligste seneffektene var frykt for tilbakefall (56%), smerter (47%), kognitiv dysfunksjon (43%),

søvnforstyrrelser (34%), kronisk fatigue (32%), armplager (32%), seksuell dysfunksjon (28%), brystplager (23%) og nevropati (21%).

Rundt halvparten (52%) av brystkreftoverleverene var seksuelt inaktive, oftest på grunn av manglende interesse for sex (35%) og mangel på partner (27%). Behandling med aromatasehemmer økte risikoen for seksuell inaktivitet og ubehag ved sex. Mindre hyppig sex sammenlignet med før brystkreft diagnosen var mer sannsynlig hos dem som hadde fått kjemoterapi, samt hos dem som fortsatt brukte endokrin behandling. Flere seneffekter som et redusert kroppsbilde, depresjon, søvnforstyrrelser, brystplager og kronisk fatigue var assosiert med redusert seksuell helse. Fysisk inaktivitet var assosiert med lavere seksuell glede.

Seksuell helse blant brystkreftoverleverene ble sammenlignet med seksuell helse hos jevngamle populasjonskontroller. Kontrollene var 17 751 kvinner som deltok i den fjerde helseundersøkelsen i Nord-Trøndelag (HUNT4). Brystkreftoverlevere hadde lavere seksuell glede og mere seksuelt ubehag enn kontroller. Brystkreftoverlevere som var behandlet med både kjemo- og endokrin terapi hadde i tillegg lavere seksuell funksjon, samt lavest seksuell glede og mest seksuelt ubehag. Analysene ble også stratifisert etter menopausal status. Brystkreftoverlevere som var premenopausale ved diagnose hadde lavere seksuell glede og mere seksuelt ubehag en jevngamle kontroller. Det var ingen forskjell i seksuell helse mellom brystkreftoverlevere som var postmenopausale ved diagnose og kontroller. Etter behandling med kjemo- og endokrin terapi, hadde imidlertid også brystkreftoverlevere som var postmenopausale ved diagnose lavere seksuell funksjon, lavere seksuell glede og mere seksuelt ubehag sammenlignet med jevngamle kontroller.

Basert på forekomst av de ti vanligste seneffektene identifisert vi tre subgrupper av brystkreftoverlevere med lik symptombyrde. Nesten halvparten (46%) ble plassert i en subgruppe kalt «lav symptombyrde», med lav forekomst (<15%) av alle seneffekter bortsett fra frykt for tilbakefall og seksuell dysfunksjon. 37% av brystkreftoverleverene ble plassert i subgruppen «medium symptombyrde», karakterisert av høy forekomst (>45%) av smerter, kognitiv dysfunksjon, kronisk fatigue, søvnforstyrrelser, emosjonell dysfunksjon og frykt for tilbakefall, og en lavere forekomst av arm- og brystplager, nevropati og seksuell dysfunksjon. De resterende 17% ble plassert i subgruppen «høy symptombyrde», karakterisert av høy forekomst (>55%) av alle seneffekter bortsett fra seksuell dysfunksjon (36%). Ung alder, kombinert systembehandling, høyere BMI og fysisk inaktivitet var assosiert med både medium- og høy symptombyrde. I tillegg var kjemoterapi og aksilledisseksjon assosiert med høy

symptombyrde. Generell funksjon var lavere blant brystkreftoverlevere i subgruppene med medium- og høy symptombyrde sammenlignet med dem med lav symptombyrde. Blant brystkreftoverlevere i arbeidsfør alder (<67 år) ved undersøkelse (n=987), var 58% av dem med høy symptombyrde uføretrygdet, sammenlignet med 42% og 16% blant dem med henholdsvis medium- og lav symptombyrde.

Resultatene fra dette prosjektet viser at brystkreftoverlevere som er unge og/eller som har fått intensiv systemisk behandling har økt risiko for både redusert seksuell helse og høyere symptombyrde også på lang sikt. Disse brystkreftoverleverene bør derfor tilbys tettere og mere omfattende oppfølging, med mål om å bedre deres livskvalitet, generelle funksjon og arbeidslivsdeltakelse. Halvparten av brystkreftoverleverene i dette prosjektet har lav symptombyrde og høy generell funksjon, som understøtter at oppfølgingen kan fokuseres på dem som trenger det mest.

LIST OF PAPERS

Paper I:

Sexual activity and functioning in long-term breast cancer survivors; exploring associated factors in a nationwide survey

Solveig K. Smedsland, Kathrine F. Vandraas, Synne K. Bøhn, Alv A. Dahl, Cecilie E. Kiserud, Mette Brekke, Ragnhild S. Falk, Kristin V. Reinertsen

Breast Cancer Research and Treatment 2022 May, 193(1):139-149

Paper II:

Sexual health in long-term breast cancer survivors – a comparison with female population controls from the HUNT study

Solveig K Smedsland, Kathrine F. Vandraas, Ragnhild S. Falk, Julie Horn, Randi J. Reidunsdatter, Cecilie E. Kiserud, Alv A. Dahl, Mette Brekke, Kristin V. Reinertsen

Breast Cancer Research and Treatment 2023 October, 201(3): 479-488

Paper III:

Burden of late effects in a nation-wide sample of long-term breast cancer survivors

Solveig K. Smedsland, Ragnhild S. Falk, Kristin V. Reinertsen, Cecilie E. Kiserud, Mette Brekke, Synne K. Bøhn, Alv A. Dahl, Kathrine F. Vandraas

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1 BACKGROUND

1.1 Introduction

The population of breast cancer survivors (BCSs) is increasing (10), making knowledge of the long-term (> 5 years) consequences of diagnosis and treatment and survivorship care an area of high interest. BCSs may experience a broad range of physical and mental late effects (LEs) during survivorship, which may negatively affect functioning and quality of life, requiring attention during follow-up care. The most common LEs include pain, neuropathy, fatigue, sleep disturbances, arm- and breast problems, cognitive impairments, mental distress including fear of cancer recurrence and impaired sexual health (11).

Sexual health impairments are well documented in the early survivorship (12-16), but knowledge of prevalence and risk factors for impaired sexual health in long-term survivorship is limited (17-19).

LEs tend to co-occur, and studies have identified subgroups of BCSs with similar burden of LEs in early survivorship (20-24). Such knowledge may guide health care providers in how to better approach the population of BCSs, as those with higher symptom burden probably need a closer and more holistic follow-up than those not so affected. Knowledge on symptom burden among BCSs beyond the first five years of survivorship is however lacking.

In this PhD project, these topics are further explored in a nation-wide survey of long-term survivors diagnosed with early breast cancer (BC) in 2011-2012.

1.2 Breast cancer

1.2.1 Incidence, survival and prevalence

Breast cancer is the most common invasive cancer among women worldwide, with an estimate of 2.3 million new cases in 2020 (25). In Norway, BC accounts for 23% of new cancer cases among women, and 4224 women were diagnosed with BC in 2022 (10). Median age at BC diagnosis in Norway is 62 years, and 32% are younger than 55 years (26). The Cancer Registry of Norway (CRN), established in 1953, offers close to complete registrations of all new cancer cases in Norway (27). Data from the CRN show a steady increase in BC incidence, with a steeper increase in the mid-1990s, as illustrated in Figure 1 (10). This rise in incidence may be explained by increasing use of hormone replacement therapy during that time (28) and by improved diagnostics due to the Norwegian Breast Screening Program, which was introduced in 1996,

and became nationwide by 2005. This program offers screening mammography every second year to all women between 50 and 69 years.

The 5-year relative BC survival rate is also increasing and has reached 92.5% for all stages combined, due to a combination of better diagnostics and treatments (10). The BC prognosis is however closely related to the disease stage, with a 5-year relative survival of 100.7% for those with BC stage I and of 79.8% for those with stage III disease (10). Due to increased incidence and survival, the population of BCSs is increasing, counting 57 118 persons in Norway in 2022 (10).

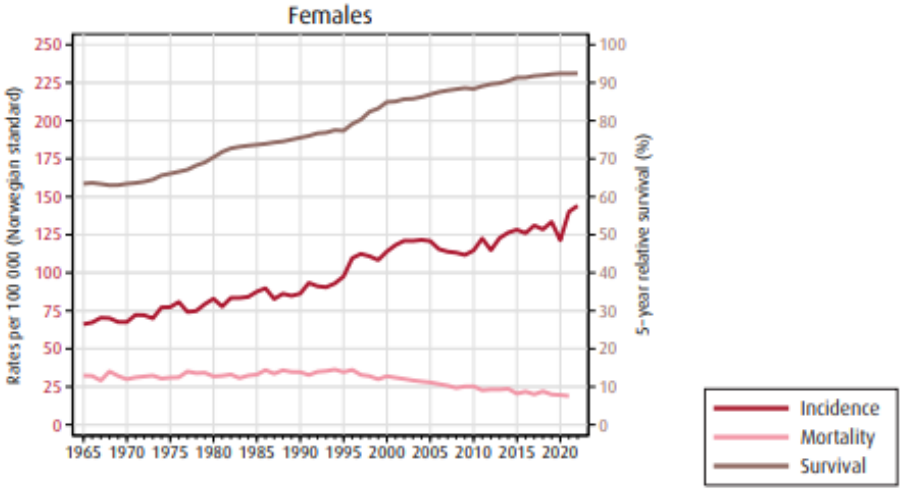


Figure 1. Trends in breast cancer incidence, mortality rates and 5-year relative survival proportions. Reprinted with permission from the Cancer Registry of Norway (10).

1.2.2 Diagnosis and staging

Triple diagnostics, including clinical examination, radiological assessment (mammography, ultrasound and/or magnetic resonance imaging) and a biopsy for pathological examination, should be performed when BC is suspected. If BC is diagnosed, staging is essential for making an optimal treatment plan and for prognosis. The TNM system classifies the cancer based on the size and extent of the primary tumor (T), nodal (N) involvement and the presence of distant metastases (M) (29, 30). Stage I-III represent loco-regional disease and is treated with curative intent, while stage IV represents metastatic disease treated with palliative intent. Histological subtype, grade, and percentage of the proliferation marker Ki67 is determined. If estrogen receptor is positive in ≥ 1% and/or progesterone receptor positive in ≥ 10% of the tumor cells, the BC is hormone receptor (HR) positive. BC with overexpression of human epidermal growth factor receptor 2 (HER2) is called HER2 positive BC. The term triple negative refers to BC that is both HR- and HER2 negative. Further, a genetic profiling test is now recommended in patients

with HR positive HER2 negative BC staged T1(≤ 2cm)/T2(> 2 ≤ 5cm)N0 or T1 with lymph node micro metastasis (31).

1.2.3 Treatment of stage I-III breast cancer in 2011-2012

Curative BC treatment is multimodal and involves surgery, and additionally radiation therapy (RT) and systemic treatments for most patients. The Norwegian Breast Cancer Group continuously updates national treatment guidelines (32). A brief overview of implementation of important curative BC treatment modalities until 2012 is presented in Figure 2.

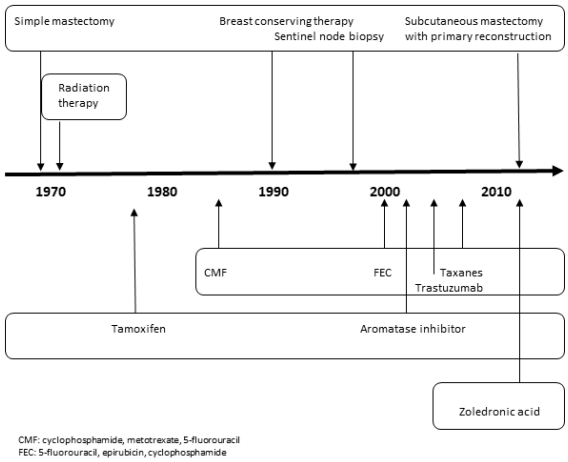


Figure 2. Timeline illustrating the approximate implementation of different curative breast cancer treatments.

The following describes curative BC treatment in Norway during 2011-2012. Present BC therapy will not be described.

There are two major types of BC surgery; mastectomy and breast conserving therapy (BCT). BCT enables tumor removal with preservation of surrounding normal breast tissue, while mastectomy implies removal of all breast tissue. In 2011-2012, BCT was preferred if the patient did not have tumors > 4 cm, multifocal tumors, widespread ductal carcinoma in situ or was unable to receive RT (33). Subcutaneous mastectomy with primary reconstruction was offered to selected patients from 2012. Axillary surgery may be performed as axillary dissection or sentinel node (SN) biopsy. Axillary dissection includes removal of all axillary level I and II lymph nodes, while only the first lymph node(s) that drains the breast lymphatics are removed with SN biopsy.

In 2011/2012, SN biopsy was performed in patients with tumors < 5 cm with clinical negative lymph nodes.

Postoperative RT was recommended after BCT, in those with positive lymph nodes, tumors > 5 cm (T3), skin or chest wall involvement (T4), and after non-radical surgery (34). The recommended fractionation was 2 Grey x 25 to the breast or chest wall, and 2 Grey x 23-24 to regional lymph nodes in those with positive lymph nodes and/or T3/T4 tumor (loco-regional RT). Patients < 40 (50) years treated with BCT were recommended an additionally boost of 2 Grey x 8 to the tumor bed to reduce the risk of local recurrence (35). After non-radical mastectomy, a total dose up to 60 Grey could be considered if massive non-radical surgery.

BCSs included in this study were treated during a time period when the use of adjuvant chemotherapy in Norway peaked, and during this period treatment guidelines were updated twice (36-38).

Systemic treatment decisions were based on tumor size, lymph node affection, grade, HR- and HER2-status and on Ki 67 (hotspot). Chemotherapy consisted of four to six cycles of 5-fluorouracil, epirubicin and cyclophosphamide (FEC60) with a higher dose of epirubicin (FEC100) in patients with HER2 positive BC. Taxanes were recommended after four cycles of FEC in high risk patients.

In the *primary 2010 guidelines*, patients with lymph nodes positive BC were recommended additional taxane treatment if estrogen receptor positive < 10%, and/or HER2 positive, and/or Ki 67 > 15%. Trastuzumab was recommended in addition to chemotherapy in all patients < 75 years with HER2 positive BC, except patients > 70 years if estrogen receptor positive ≥ 10% (36).

In the *updated September 2011 guidelines*, a Ki 67 value > 30% determined addition of taxanes also in patients ≤ 75 years with lymph node negative BC. Trastuzumab was recommended in addition to chemotherapy in all patients ≤ 75 years with HER2 positive BC (37).

In the *updated guidelines from September 2012* zoledronic acid therapy was recommended for women ≥ 55 years who were also recommended other systemic adjuvant treatment (38).

Most patients with HR positive BC were recommended endocrine therapy (ET). Premenopausal women < 55 years were recommended tamoxifen for five years. Women ≥ 55 years and postmenopausal women ≥ 50 years were recommended aromatase inhibitor (AI) for five years

or AI for two years followed by three years of tamoxifen. Extended ET for up to ten years became an option for premenopausal patients from September 2013, and was recommended from 2015 (39). For postmenopausal patients, extended ET as a treatment option for high-risk patients was included in the guidelines from 2018 (40).

1.2.4 Follow-up after breast cancer

The main aim of follow-up after BC is early detection of a loco-regional recurrence or a new BC which may be curatively treated. Other important follow-up aspects include checking the adherence of adjuvant ET and the assessment and handling of possible LEs. BCSs within working age should have their work ability evaluated in cooperation with the labor- and welfare administrations.

BCSs in Norway are recommended annual follow-up for ten years after diagnosis, where consultations are shared between the specialist health care services and the general practitioner. The annual check includes a mammography, a clinical examination and thyroid function tests for those treated with loco-regional RT (31). The guidelines for 2011/2012 recommended follow-up in the specialist health services for some subgroups of BCSs (< 35 years at diagnosis, locally advanced BC, and/or pregnancy-associated BC) during the first five years (41). Current guidelines have been somewhat expanded recommending follow-up in the specialist health services for BCSs < 40 years at diagnosis if treated with adjuvant systemic treatment, after treatment for locally advanced and pregnancy associated BC (31). Others are recommended follow-up in the specialist health care services the first, second and fifth year post diagnosis, and at their general practitioner beyond this time point. Follow-up routines should further be individualized based on stage, treatment received, recurrence risk, age, and comorbidity.

1.3 Late effects

BCSs may experience a broad range of LEs (11), and below follows an overview of the most common and relevant LEs for this PhD project, excluding hypothyroidism and the more seldom, but potentially life-threatening LEs cardiovascular disease and second cancer (42-44).

1.3.1 Pain and loco-regional complaints

Pain is common in the general population, often associated with musculoskeletal and neurological diseases (45). BCSs have additional risks of pain, which may be due to a number of factors, including treatment-related loco-regional pain, chemotherapy induced neuropathy, and musculoskeletal pain caused by AI. In a Danish study of BCSs five to seven years after

treatment, more than a third of BCSs reported local pain in the breast area (46). Younger age, RT, axillary lymph node dissection and more intense post-operative pain are risk factors for persistent pain (47).

Numbness in the treated breast area may be experienced by up to 65% during the first year after treatment. It appears to remain relatively stable the first year after surgery, and present alongside with pain in roughly half of the patients (48). Risk factors for numbness are mainly the same as for pain, but mastectomy +/- reconstruction and chemotherapy are additional risk factors for numbness (48).

Lymphedema is the clinical presentation of impaired lymphatic circulation. Extensive axillary surgery is the best documented risk factor. Axillary lymph node dissection quadruple the risk of lymphedema compared to SN biopsy (49), with a prevalence estimate of 24% more than two years after axillary dissection compared to 6% more than two years after SN biopsy (50). Regional lymph node RT adds to the risk, especially after axillary dissection, with a 30% five-year cumulative incidence rate around 30 % (51, 52). Body mass index (BMI) $\geq$ 30 kg/m² at BC diagnosis is an independent risk factor (52, 53). Lymphedema onset is typically 12- 30 months after surgery, with earlier onset associated with axillary node dissection and later onset associated with regional lymph node RT (52). Lymphedema may also arise in the breast and/or chest wall after surgery and RT (54).

BC surgery and RT may also result in pain and restrictions in arm and shoulder mobility. As for other loco-regional complaints, extensive axillary surgery is the most important risk factor (50). RT of the regional lymph nodes increases the risk of reduced arm movement (55).

1.3.2 Chemotherapy induced neuropathy

Chemotherapy induced neuropathy may be dose-limiting and is a major side effect of taxane treatment. Symptoms include numbness, tingling, loss of sensation and pain and typically present with a “stocking and glove” distribution pattern. Even though symptoms often improve with time, up to 44% of taxane-treated BCSs report neuropathy at a median of six years after diagnosis (56).

1.3.3 Fatigue

Cancer-related fatigue is a distressing, persistent, subjective feeling of physical, emotional, and/or cognitive tiredness or exhaustion related to cancer or cancer treatment that is not proportional to recent activity and interferes with usual functioning (57). Chronic fatigue is by

convention defined as elevated levels of fatigue for six months or more (58). Fatigue generally improves after BC treatment cessation (59), but approximately one third of long-term BCSs will experience chronic fatigue (60, 61). Factors associated with fatigue include younger age, obesity, comorbidities and catastrophizing personality traits (62, 63). A recent review did not find consistent associations between fatigue and BC stage or treatments (62). In contrast, a meta-analysis demonstrated that higher stage and increased systemic treatment intensity are associated with severe fatigue in BCSs (64).

1.3.4 Sleep disturbances

Sleep disturbances are common in the general population. In a Norwegian population-based study using DSM-V based criteria, nine percent of women had insomnia (65). Factors associated with sleep disturbances include pain, mental distress, and hot flashes (66, 67), which are all common complaints among BCSs. One third reported insomnia seven years after BC diagnosis in a Norwegian study (68), while a recent meta-analysis estimated that the prevalence of sleep disturbances was 40% among BCSs (69).

1.3.5 Mental distress

Risks of anxiety and depression are higher among BCSs compared to women without cancer (70). The risk of mental distress is highest the first year following diagnosis, but remain elevated for up to five years after diagnosis (71). The prevalence of depression is about 10% among Norwegian females (72). The prevalence of generalized anxiety disorder has been reported to 7% among German females (73). In a systematic review of BCSs, > 30% had depression and 20-50% anxiety more than one year after diagnosis (74). Predictors of depression and anxiety among BCSs include younger age, comorbidities and less favorable tumor characteristics (74).

Fear of cancer recurrence (FCR) can be defined as the "fear, worry or concern relating to cancer returning or progressing" (75). Lower levels of FCR may be considered normal and useful after a cancer diagnosis making survivors aware of potential signs of relapse, but persistent and higher levels of fear can be debilitating. FCR is recognized as one of the most prevalent, persistent and disruptive mental problems among BCSs (76). In a Danish study 55% of BCSs reported FCR up to five years after diagnosis, (77), while in another study focusing on younger BCSs (aged 18-45 years) 70% had FCR more than a year after diagnosis (78). In addition to younger age, presence and severity of physical symptoms, other mental distress and lower quality of life are associated with FCR (79). In contrast to anxiety and depression, FCR seems to remain relative stable over time in BCSs (79, 80).

1.3.6 Cognitive dysfunction

Cognitive dysfunction, characterized by difficulties especially in memory, attention and executive function (81), is more commonly reported by BCSs compared to women with no cancer history (74). Subjective cognitive problems are more prevalent than cognitive problems objectively measured by neuropsychological tests, and prevalence rates among BCSs ranged from 21-90% in a systematic review (82, 83). No consistent association between subjective and objective measured cognitive dysfunction was found in that review, but subjective dysfunction was strongly associated with mental distress, sleep disturbances and fatigue (83, 84). Cognitive dysfunction during and after chemotherapy, commonly referred to as "chemo brain" is often mild-to-moderate with partial recovery during the first year after treatment (85). After completion of chemotherapy, 25% of BCSs experienced a decline in objective cognitive dysfunction, compared to 18% of BCSs not receiving chemotherapy (86). The development of objective cognitive dysfunction in BCSs is probably multifactorial with additionally risk factors being ET, advancing age, cognitive reserve and genetic predisposition (87, 88).

1.3.7 Body image disturbances

Body image may be affected in BCSs due to physical changes following surgery and RT such as loss/deformation of the breast, scarring, skin changes and lymphedema, but also more indirectly due to side-effects of systemic treatments, including weight gain and premature menopause (89). A meta-analysis has shown that BCSs treated with mastectomy had poorer body image compared to those treated with mastectomy with reconstruction, while there were no differences in body image among BCSs treated with BCT compared to those treated with mastectomy with reconstruction (90). BCSs with body image disturbances are up to 2.5 times more likely to experience sexual dysfunctions, pointing to the importance of addressing these topics concurrently (13).

1.3.8 Premature menopause and estrogen deprivation symptoms

Mean age at menopause is 53 years in Norway (91). Chemotherapy in premenopausal women may cause premature ovarian insufficiency and abrupt menopause. Most chemotherapy used in the treatment of early BC may be toxic to the ovaries, with cyclophosphamide having the highest risk. In addition, chemotherapy dosage, increasing age and limited ovarian reserve at treatment, are other risk factors associated with treatment-induced premature ovarian insufficiency (92). In most studies, amenorrhea is used to define ovarian insufficiency (93). After four cycles of anthracyclines and cyclophosphamide as used to treat early BC, 40-60% of women ≥ 40 years will experience permanent amenorrhea, compared to < 20% of women <

40 years. If such therapy is followed by taxanes, women have a 40-60% risk of permanent amenorrhea irrespective of age (94). Possible consequences of premature ovarian insufficiency are fertility-related problems and menopausal symptoms including hot flashes, vaginal dryness, reduced libido, weight gain and osteoporosis. These estrogen deprivation symptoms are similar to the side-effects of ET.

1.3.9 Sexual health impairments

Sexual health is an important component of quality of life and, and good sexual health is associated with mental and physical wellbeing and with relationship satisfaction (5). An individual's sexual health is influenced by multiple factors of which sexual activity and functioning are important.

In the general female population, 35-50% report to be sexually inactive (6, 95). Sexual inactivity is associated with increasing age, not living partnered, lack of interest in sex and/or partner-related factors (5, 6, 95). Sexual dysfunctions are reported by 40-50% of women in the general population (5, 6, 96). The most frequently reported problems reported by sexually active women include lack of interest in sex (34%), difficulties in reaching orgasm (16%) and uncomfortable vaginal dryness (13%) (5). Sexual dysfunctions are associated with increasing age and mental health problems (5, 6, 97). To note, sexual dysfunctions only result in distress or dissatisfaction in about 10-30% of the affected women (5, 6) .

The prevalence of sexual dysfunctions in BCSs is estimated as high as 73% in a meta-analysis (98). Impaired sexual activity and functioning after BC may be considered a LE itself, or a consequence of other LEs. A BC diagnosis may in itself negatively affect sexual health, as sexual activity often has low priority during treatment (99).

Physical changes after surgery may result in scars, changed sensibility, removal of erogenous zones, and body image disturbances. A prospective study from 2014 examined sexual health before and one year after surgery. BCSs treated with mastectomy had increased risk of sexual dysfunctions post-operatively compared to before surgery and also compared to non BC controls (100). No significant differences were found between women treated with BCT and controls, suggesting that mastectomy affects sexual health more than less invasive surgery. A major limitation of that study was that a larger proportion of those treated with mastectomy received adjuvant chemotherapy (44%) than among those treated with BCT (25%). Another study found no differences in sexual functioning between women treated with mastectomy, mastectomy with immediate reconstruction, and mastectomy with delayed reconstruction one year after surgery

(101). Neither did a recent meta-analysis demonstrate any significant group differences comparing sexual health in BCSs treated with BCT, mastectomy with-, and mastectomy without reconstruction (90). As several other studies also report inconsistent results regarding the association between surgical technique and sexual health (17, 102-104), it can at present not be concluded to what degree the different surgical techniques affect sexual health.

RT may induce skin changes, cause pain in the breast area, and is a risk factor for lymphedema in breast/chest wall and the upper limb. Few studies have explored the association between RT and sexual health in BCSs. One study focusing on quality of life in BCSs after implant reconstructive surgery, found significantly reduced sexual well-being in those treated with compared to those treated without RT (105). Another study exploring the effects of all BC treatment modalities on sexual health, found no association between RT and sexual dysfunctions (102).

It is well documented that chemotherapy induced premature menopause negatively affect sexual health (14, 106-108). Studies which have included also postmenopausal women report conflicting results on how chemotherapy affects sexual health, with most reporting no significant associations (13, 16, 102, 103). This may indicate that chemotherapy mainly affects sexual health negatively in young women through premature induced menopause.

Vaginal dryness, dyspareunia and reduced libido is reported more frequently by users of AI compared to tamoxifen (109), and the negative impact of AIs on sexual health is well documented (12, 102, 110, 111). In one study including women using AI for two years, 93% reported a sexual dysfunction and almost one fourth of the women became sexually inactive after treatment start (12). As from 2015, premenopausal women with high risk BC are recommended ovarian function suppression with goserelin in addition to AI or alternatively tamoxifen (39). This combination may aggravate hot flashes, reduced libido, vaginal dryness, dyspareunia and sleep disturbances (112, 113), suggesting that young BCSs treated with this combination are at especially high risk of experiencing sexual health impairments.

Several LEs like fatigue, depression, anxiety, and sleep disturbances may also affect sexual health negatively (14, 114-116).

1.3.10 Burden of late effects

Traditionally, LEs after BC have been identified, studied and handled independently, despite that they rarely occur in isolation (117). Exploring co-occurring symptoms has recently become

an area of active research and has diverged along two approaches (117). One approach is symptom-oriented, focusing on the identification of symptoms that seem to co-occur to form a "cluster". Pain, fatigue, and mental distress is one such troublesome symptom cluster in long-term BCSs (118). The other approach is person-centered, where subgroups of BCSs with similar burden of LEs are identified and grouped together, making it easier to identify those most burdened and most in need of symptom management. In this PhD project, the person-centered approach was used for Paper III.

1.4 Quality of Life

Quality of life is defined by the World Health Organization as "an individual`s perception of their position in life in the context of the culture and value system in which they live and in relation to their goals, expectations, standards and concerns" (119). According to individual preferences, factors that affect quality of life might vary, but they frequently include family life, health, financial security, job satisfaction and safety. Several LEs are associated with decreased quality of life among BCSs (62, 89, 120). Most studies report that BCSs experience lower quality of life compared to controls the first few years after diagnosis, but no or only small differences in overall quality of life when assessed long-term (121-125). However, several aspects of quality of life seem to be affected by a BC diagnosis also long-term, including physical-, social-, and role- functioning (123-126).

1.5 Background for this PhD project

1.5.1 Sexual health

Prior to this PhD project, knowledge on sexual health in BCSs was mostly limited to the first few years of survivorship (12-16). Studies on sexual health in long-term BCSs were few and results inconsistent, as described in the following.

Among the first studies exploring this topic, was that by Dorval et al from 1998 comparing quality of life among eight-years BCSs to similar aged controls (127). Sexual activity did not differ between BCSs and controls, but BCSs were less satisfied with their sexual life. Ganz et al found more sexual discomfort among long-term BCSs treated with chemotherapy compared to those who had received only tamoxifen or no systemic therapy (128). Another study by Broeckel et al, reported poorer sexual functioning among eight-years BCSs treated with adjuvant chemotherapy than among age-matched controls, and that vaginal dryness was related to poorer sexual functioning in BCSs (129). In one of the more recent studies, Raggio et al examined 83 BCSs seven years after diagnosis, of whom 77% reported a sexual dysfunction

(17). About a half of the BCSs reported partnered sexual activity, of whom 60% had a sexual dysfunction. Mastectomy, to be married/partnered and depressive symptoms were associated with worse sexual distress. Davis et al published data from a larger study also including population controls. (18). That study explored menopausal symptoms in 843 BCSs six years after diagnosis and no longer on ET. BCSs had significant more severe sexual symptoms compared to the controls, also when excluding BCSs treated with adjuvant chemotherapy, which had no significant impact on sexual symptoms. In contrast, Soldera et al found no significant differences in sexual activity nor sexual functioning comparing 248 BCSs at median 12.5 years after diagnosis to population controls (19). However, BCSs reported worse gynecological symptoms than controls. In that study adjuvant systemic treatments were not associated with sexual functioning, but BCSs treated with chemotherapy had worse gynecological complaints.

1.5.2 Burden of late effects

In studies using the person-centered approach, several subgroups of BCSs with similar symptom burden have been identified, typically including subgroups with low- and high symptom burden. In most studies, 10-20% of BCSs are assigned to the subgroup characterized by a high symptom burden (20-22, 24, 130, 131). The number and type of symptoms used to identify the different subgroups have varied widely among studies, and none have explored symptom burden among long-term BCSs.

In studies exploring the first five years of survivorship, a higher symptom burden is associated with younger age, lower education, not working, more advanced BC stage, chemotherapy and AI, higher BMI and comorbidity (20, 22, 131). Based on patterns of symptom severity, three subgroups of BCSs were identified in a study of 404 BCSs examined one to five years after diagnosis (130). BCSs in the low symptom burden subgroup reported lower symptom severity than controls from the general population. In that study comorbidity was the only factor associated with a higher symptom burden (130). Another study including 654 BCSs five years after diagnosis, identified two subgroups of BCSs with similar symptom burden (132). Being married/partnered, comorbidity and decreased physical activity after diagnosis were factors associated with the highest symptom burden. In a longitudinal study, Avis et al assessed symptoms in 565 BCSs within eight months after diagnosis, and four times during the next 18 months (133). The majority (70%) of the BCSs remained in the same symptom burden subgroup throughout the assessment period. The low symptom burden state was the most stable, with 88% of the BCSs remaining in this subgroup over the study period. That study also demonstrated a higher probability of transitioning to an improved state than towards a worsened state. One third

of women in the highest symptom burden subgroup moved to a lower symptom burden subgroup from baseline to end of study. Chemotherapy, being partnered, greater financial strains and lower social support were associated with higher symptom burden.

1.5.3 Summary of knowledge gaps

At start of this PhD project, knowledge concerning sexual health in long-term BCSs was limited and existing results conflicting with regards to differences in sexual health between BCSs and controls. To further explore sexual health in long-term BCSs and to compare their sexual health to that in females from the general population, there was a need for a comprehensive study including a large sample-size of long-term BCSs and a control group of similarly aged women collecting information also on sociodemographic-, health related- and lifestyle factors. Such a study would also allow analyses exploring the total symptom burden of LEs with identification of factors associated with a higher symptom burden, and assessments of how symptom burden may affect daily functioning – knowledge that was lacking among long-term BCSs. Potentially, findings from this PhD project would help shape and optimize future BC survivorship care, providing closer follow-up of BCSs suffering from sexual health challenges and a higher symptom burden. This could ultimately increase the quality of life and general functioning among long-term BCSs.

2 AIMS OF THIS PROJECT

The main aims of this PhD project were to study sexual health (Aim I) and total burden of LEs (Aim II) in a nation-wide sample of long-term BCSs.

Our assumptions were that sexual health was poorer in BCSs compared to controls, and that younger age and more intensive systemic treatment were important factors associated with impaired sexual health. Further, our assumptions were that BCSs suffering from higher symptom burden would report poorer general functioning and reduced work participation compared to those with a lower symptom burden, and that younger age and more intensive systemic treatment were important factors associated with higher symptom burden.

The specific aims were:

2.1 Paper I (Aim I)

- To describe sexual health in long-term BCSs.
- To explore factors associated with sexual inactivity and reduced sexual functioning.

2.2 Paper II (Aim I)

- To compare sexual health in long-term BCSs to that of similarly aged female controls from a population-based sample.
- To assess the impact of systemic BC treatments on sexual health.
- To examine if menopausal status at BC diagnosis influences sexual health.

2.3 Paper III (Aim II)

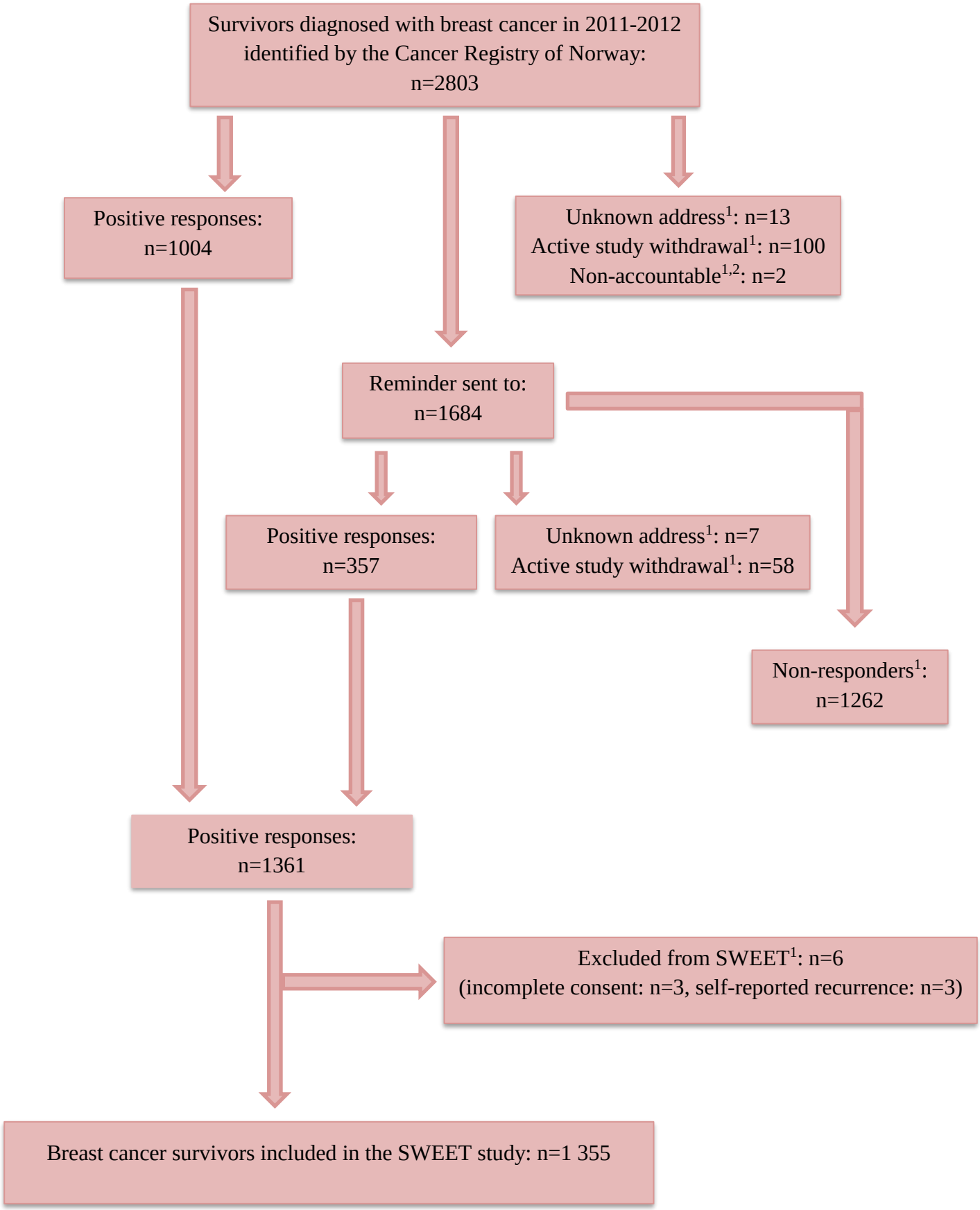
- To identify subgroups of long-term BCSs with similar total burden of LEs.
- To explore factors associated with highest symptom burden.
- To describe general functioning and the proportion of BCSs on disability pension according to subgroups of different symptom burden.

3 MATERIAL AND METHODS

3.1 Study population

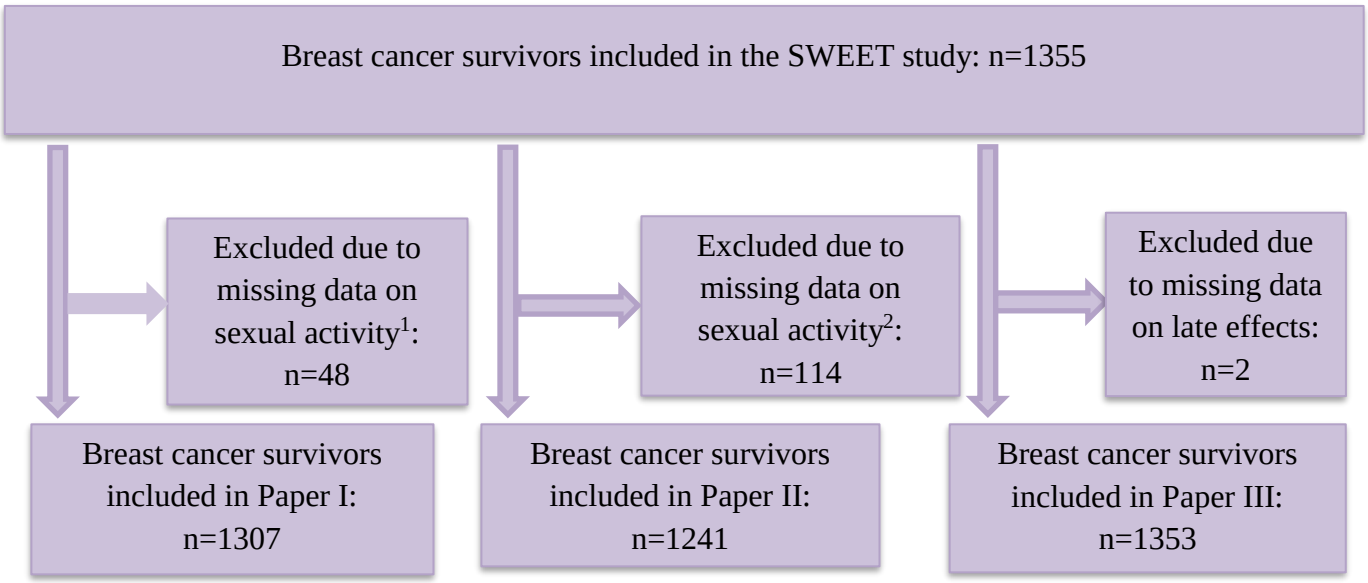
BCSs included in this thesis were participants in the **S**urvivorship **W**ork S**e**xual H**e**al**t**h (SWEET)-study. The SWEET-study was a nation-wide, cross-sectional survey exploring LEs, work life and sexual health in long-term BCSs. All women diagnosed with BC stage I-III at the age of 20-65 years in 2011 or 2012, were identified by the CRN and invited to participate. Exclusion criteria were pre- or post- malignancies except non-melanoma skin cancer and ductal carcinoma in situ. Invitations, including the questionnaire and an informed consent request, were mailed to 2803 BCSs in December 2019. One reminder was sent to non-responders (n=1684) in February 2020. In total, 1361 BCSs responded (49%). Three BCSs were excluded due to incomplete consent and three due to self-reported BC recurrence, yielding a final study population of 1355 BCSs (Figure 3). In Paper I, 48 BCSs with missing data on sexual activity were excluded, resulting in a final sample of 1307 BCSs. In Paper II, 114 BCSs were excluded due to missing data on sexual activity as defined in that paper, resulting in a final sample of 1241 BCSs. In Paper III, two BCSs were excluded due to missing data on all the explored LEs, resulting in a final sample of 1353 BCSs (Figure 4).

Figure 3: Overview of the study population



[1] Included as non-responders in attrition analysis, [2] Breast cancer survivors that returned the questionnaire, but informed consent were not obtained

Figure 4: Overview of the study populations in the different papers



[1]Assesed by the Sexual Activity Questionnaire, [2]Assessed by the EORTC QLQ-BR23

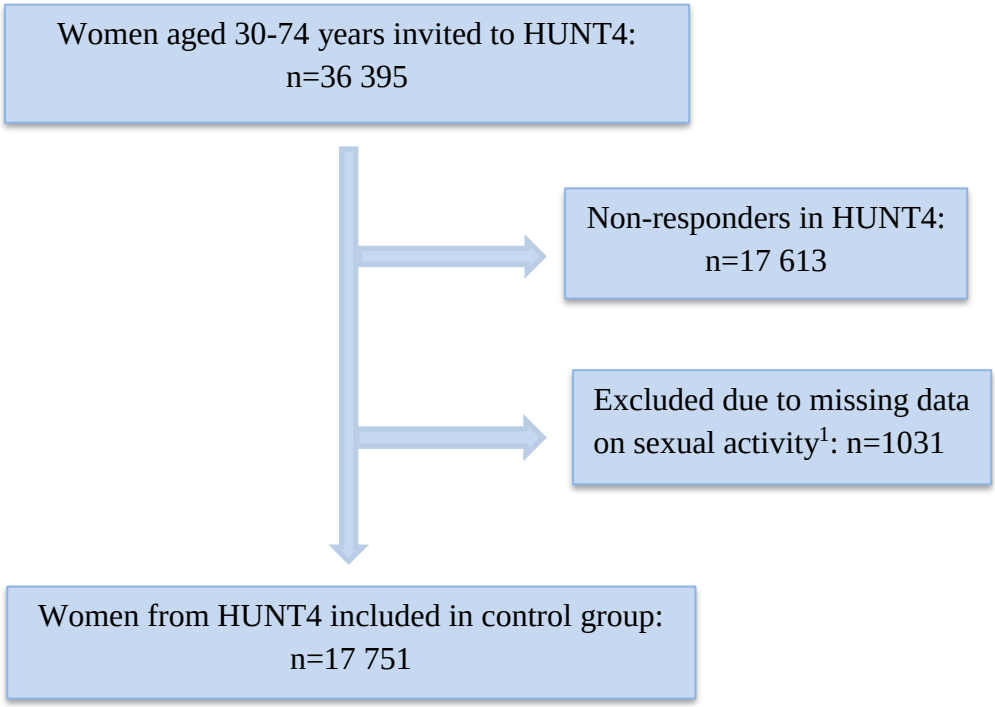
3.1.1 Attrition analysis

Information about non-responders in the SWEET-study (n=1448) was limited to age and cancer-related information obtained from the CRN. Tumor- and nodal stage, and HR status were similar in responders and non-responders. There was no significant difference in type of BC surgery. Non-responders were however significantly older (mean age 53.2 versus 51.9 years), a smaller proportion was HER2 positive (15% versus 19%) and mean value of Ki67 was lower (27% versus 31%).

3.2 Control group Paper II

In Paper II, participants from the SWEET-study were compared to similarly aged women participating in the fourth survey of the population based Trøndelag Health Study (HUNT4) (134). HUNT4 invited all adults aged 20 years and above living in the county of Nord-Trøndelag to an extensive health survey in 2017-2019. Participants responded to a questionnaire and were invited to a clinical examination including standardized measurements of height and weight. Those that met for the clinical examination were invited to respond to a second questionnaire including items exploring sexual health. Of 36 395 women in the same age-group as the SWEET-study participants (i.e. 30-74 years) who were invited to participate in HUNT4, 18 782 returned the second questionnaire (52%). Due to missing data on sexual activity, 1031 of these women were excluded, resulting in a control group of 17 751 participants (48%) (Figure 5).

Figure 5: Overview of the control group eligible for Paper II



[1]Assessed by the EORTC QLQ-BR23

3.3 Patient reported outcome measures

Patient reported outcome measures (PROMs) are instruments used to capture patient's self-reports on health-related outcomes (135). Outcomes measured typically include physical and mental symptoms, functioning and quality of life. As data collected by PROMs comes directly from the patients, they may provide a more comprehensive picture of the patient experience compared to assessments performed by clinicians (110). The SWEET-study included a wide range of PROMs frequently used in cancer- and survivorship research. In the following, PROMs used in this PhD project are further discussed.

3.3.1 The Sexual Activity Questionnaire

The Sexual Activity Questionnaire (SAQ) was used to assess sexual activity and functioning in Paper I, and sexual discomfort in Paper II. The SAQ was originally developed to investigate the impact of long-term tamoxifen on sexual functioning in women at high risk of developing BC (136). The questionnaire has been used in several cancer populations (19, 103, 137-139), and psychometric properties and normative data of the SAQ in a Norwegian population has been published (95).

The SAQ consists of three sections. The first section assesses whether a woman is sexually active or not. Sexually active is defined as answering yes to the item "Do you engage in sexual activity with anyone at the moment", while sexually inactive is defined as answering no to this item. In the second section, the sexually inactive tick off reasons for not being sexually active, with the predefined options; no partner at the moment, too tired, not interested in sex, physical problem that makes sexual relations difficult or uncomfortable, the corresponding problems for partner, and other reasons. The third section is completed by sexually active women only, and assesses sexual functioning during the last month through items rated on a 4-point Likert scale from 0 (not at all) to 3 (very much). Items are summed into subscales as displayed in Table 1.

Table 1: Items and subscales in the Sexual Activity Questionnaire assessing sexual functioning during the last month

Subscale	Items	Sum score (range)
Sexual pleasure (SAQ-P)	Was "having sex" an important part of your life? Did you enjoy sexual activity? Did you desire to have sex with your partner(s)? In general, did you feel satisfied after sexual activity? How often did you engage in sexual activity?[2] Were you satisfied with the frequency of sexual activity?	0-18[1]
Sexual discomfort (SAQ-D)	During sexual relations, how frequently did you notice dryness of your vagina? Did you feel pain or discomfort during penetration?	0-6[3]
Sexual tiredness	In general, were you too tired to have sex?	0-3[3]

[1]A higher score corresponds to more pleasure, [2]Scale from 0 (not at all) to 3 (five times or more), [3] A higher score corresponds to more discomfort and more tiredness.

The item, assessing sexual habit (SAQ-H), "How did the frequency of sexual activity compare with what is usual for you?" was modified to "How often are you engaged in sexual activity compared to before the BC diagnosis?" in the SWEET-study with similar response alternatives as in the original SAQ: much more, somewhat more, about the same, and less than before BC.

Primary outcomes in Paper I were the categorical variable sexual inactivity, and the continuous variables sexual pleasure (SAQ-P), sexual discomfort (SAQ-D), and sexual tiredness. As the continuous variable SAQ-H had a highly skewed distribution, it was dichotomized into "less sexual activity now compared to before BC" versus "about the same/somewhat more/much more

sexual activity compared to before BC" and used as a categorical outcome variable. In Paper II, SAQ-D served as one of the three sexual outcomes. Cronbach's alphas in the SWEET-study were 0.83 and 0.78 for SAQ-P and SAQ-D respectively, and 0.66 for SAQ-D in the HUNT4 study.

3.3.2 The European Organization for Research and Treatment of Cancer Quality of Life Questionnaires

The EORTC Quality of Life Questionnaire (EORTC QLQ-C30) is a 30-item questionnaire composed of multi-item and single item scales designed to assess the functional health, symptom burden and quality of life in cancer patients (140). The BC-specific module (EORTC QLQ-BR23) consists of 23 additional items especially relevant to BC patient (8). Items are rated from 1 (not at all) to 4 (very much) and then transformed to a 0-100 scale, were higher scores correspond to better functioning and more symptoms respectively (141). Items included in the symptom- and functioning scales used in this PhD project are listed in Table 2.

Table 2: EORTC scales used in this PhD project

	Item(s)	Paper
Symptom scales		
Pain[1,2]	Have you had pain? Did pain interfere with your daily activities?	I, III
Sleep disturbances[1,2]	Have you had troubles sleeping?	III
Arm symptoms[2,3]	Did you have any pain in your arm or shoulder? Did you have a swollen arm or hand? Was it difficult to raise your arm or to move it sideways?	III
Breast symptoms[2,3]	Have you had any pain in the area of your affected breast? Was the area of your affected breast swollen? Was the area of your affected breast oversensitive? Have you had skin problems on or in the area of your affected breast (e.g., itchy, dry, flaky)?	I, III
Sexual enjoyment[3,4,5]	To what extent was sex enjoyable for you?	II
Functioning scales		
Cognitive functioning[1,2]	Have you had difficulty in concentrating on things, like reading newspaper or watching television? Have you had difficulty remembering things?	III

Emotional functioning[1,2]	Did you feel tense? Did you worry? Did you feel irritable? Did you feel depressed?	III
Physical functioning[1]	Do you have troubles doing strenuous activities, like carrying a heavy shopping bag or a suitcase? Do you have any troubles taking a long walk? Do you have any troubles taking a short walk? Do you need to stay in bed or a chair during the day? Do you need help with eating, dressing, washing yourself or using the toilet?	III
Social functioning[1,2]	Has your physical condition or medical treatment interfered with your family life? Has your physical condition or medical treatment interfered with your social activities?	III
Role functioning[1,2]	Were you limited in doing either your work or other daily activities? Were you limited in pursuing your hobbies or other leisure activities?	III
Body image[2,3]	Have you felt physically less attractive as a result of your disease or treatment? Have you been feeling less feminine as a result of your disease or treatment? Did you find it difficult to look at yourself naked? Have you been dissatisfied with your body?	I
Sexual functioning[3,4]	To what extent were you interested in sex? To what extent were you sexually active (with or without intercourse)?	II, III

[1]EORTC QLQ C-30, [2]Time frame during last week, [3]EORTC QLQ-BR23, [4]Time frame during the past four weeks, [5]Only applicable to sexually active

In Paper I, pain, breast symptoms and body image were used as continuous variables.

In Paper II, sexually active women were defined based on a score >1 (a little, quite a bit or very much) on the item "To what extent were you sexually active (with or without intercourse)?"

Participants scoring 1 (not at all) were categorized as sexually inactive. Sexual functioning and sexual enjoyment were primary outcome variables.

In Paper III, scales were used to assess possible LEs and to describe general functioning. Established threshold values for clinical importance of the EORTC QLQ-C30 scales were used to define presence of pain (>25), sleep disturbances (>50), cognitive- (<75), and emotional dysfunction (<71) (142). A score of 3 (quite a bit) or 4 (very much) on one of the items assessing arm- and breast symptoms, defined an arm- and/or a breast problem (68). Sexual dysfunction was defined as a score of zero of the sexual function scale (i.e. answering not at all to both items). All defined LEs were used as categorical indicator variables. General functioning was measured using physical-, social, and role functioning scales. Cronbach's alphas were ≥ 0.72 for all subscales.

3.3.3 The Fatigue Questionnaire

Fatigue was assessed using the Fatigue Questionnaire, which covers fatigue symptoms during the previous month compared to when the subject last felt well (143). The questionnaire consists of seven items measuring physical- and four items measuring mental fatigue. Each item is scored from 0 (less than usual) to 3 (much more than usual), yielding a "total fatigue" score ranging from 0 to 33. Higher scores correspond to higher levels of fatigue. The item scores were dichotomized (0=0, 1=0, 2=1, 3=1) and "fatigue" defined as a dichotomized sum score ≥4 (144). "Chronic fatigue" was defined as "fatigue" with a duration of six months or longer (58). Cronbach's alpha was 0.93 for the total fatigue score.

3.3.4 The Patient Health Questionnaire-9

Depressive symptom severity during the past two weeks were assessed using the Patient Health Questionnaire-9 (145). It consists of nine items rated from 0 (not at all) to 3 (nearly every day), yielding sum scores ranging from 0 to 27. A major depression was defined as a sum score ≥ 10 (145). Cronbach's alpha was 0.85.

3.3.5 Generalized Anxiety Disorder 7-item scale

Symptoms of anxiety during the last two weeks were assessed by the General Anxiety Disorder 7-item scale, which consists of 7 items rated from 0 (not at all) to 3 (nearly every day) (146). Sum scores range from 0 to 21, and generalized anxiety disorder was defined as a sum score ≥10 (146). Cronbach's alpha was 0.87.

3.3.6 Assessment of Survivor Concerns

FCR was assessed using the Assessment of Survivor Concerns (147). This questionnaire has two subscales. We used the cancer-specific worry subscale, consisting of three items which measure worry concerning recurrence, a new cancer diagnosis and future diagnostic tests. Items are scored from 1 (not at all) to 4 (very much), yielding a sum score range from 3 to 12. After correspondence with the author of the instrument, FCR was defined as a sum score ≥ 6 or one single item score ≥ 3. Cronbach's alpha was 0.87 for the cancer-specific worry subscale.

3.3.7 Scale for Chemotherapy Induced Long-term Neurotoxicity

Neuropathy was assessed by one subscale from the Scale for Chemotherapy Induced Long-term Neurotoxicity (148). This questionnaire was originally developed for testicular cancer survivors and has three subscales: neuropathy, Raynaud`s phenomenon and ototoxicity. The neuropathy subscale consists of two items assessing pain and/or tingling in feet/toes and hands/fingers, respectively. Each item is scored from 0 (not at all) to 3 (very much), yielding a sum score range from 0 to 6. A high degree of neuropathy was defined as sum score ≥ 4. Cronbach's alpha was 0.87 for the neuropathy subscale.

3.3.8 Godin-Shepherd Leisure-Time Physical Activity Questionnaire

Physical activity was assessed using a modified version of the Godin-Shepard Leisure-Time Physical Activity Questionnaire (149). This questionnaire includes three items concerning number of times one engages in mild, moderate and strenuous leisure-time physical activity bouts during a typical week. We included additional items assessing number of minutes per bout. Physical inactivity was defined as not meeting the national public guidelines of at least 150 minutes of moderate-intensity physical activity or at least 75 minutes of high-intensity physical activity per week or an equivalent combination of moderate- and high intensity physical activity per week (150).

3.4 Other variables

3.4.1 Self-reported sociodemographic variables

Living arrangements were dichotomized into living with a partner or not. Education was dichotomized into either short (≤ 12 years) or long (>12 years) educational attainment. Work status at survey was dichotomized into being in paid work (including full-time work, part-time-work, self-employment and sick-leave) or not (disability pension, retired, job seeker, home maker and other statuses).

3.4.2 Self-reported health-related variables

Somatic comorbidities included questions concerning the presence of 14 major somatic conditions (cardiovascular-, cerebrovascular-, pulmonary- kidney-, liver-, gastro-intestinal- and rheumatic disease, hypertension, diabetes, arthrosis, muscle/joint pain, epilepsy, hypo- and hyperthyroidism). In Paper I, responses were categorized into no, 1-2 or ≥ 3 comorbid conditions. Somatic comorbidities assessed both in the HUNT4- and in the SWEET-study were cardiovascular-, cerebrovascular-, pulmonary-, kidney, thyroid-, and rheumatic disease and diabetes. In Paper II, responses were categorized into no, 1, or ≥ 2 comorbid conditions. The HUNT4 questionnaire included one additional question concerning mental comorbidities: "Have you sought health care for psychological problems". An affirmative response to this question was categorized as having mental comorbidity. In the SWEET-study, there were three questions concerning whether the BCS had sought help for anxiety, depression or other mental problems respectively. BCSs were categorized as having mental comorbidity if answering yes to at least one of these three questions. Sleep problems were defined using two questions assessing sleep during the last three months (9). Sleep problems were present if the participant reported difficulties falling asleep and/or waking up too early without going back to sleep at least three times per week. BMI was calculated from height and weight (kg/m^2), self-reported in the SWEET-study and from standardized measurements at the field stations in the HUNT4-study. Obesity was defined as BMI ≥ 30 (151).

3.4.3 Cancer-related variables

Information on age at diagnosis, BC stage, HR status, HER2 status, and surgery were obtained from the CRN. Breast surgery was dichotomized into mastectomy and BCT, and axillary surgery into axillary dissection and SN biopsy. Information on systemic treatment and RT was self-reported. RT was dichotomized into yes/no. ET was categorized into no ET, AI, tamoxifen, and unknown type. BCSs who had received both Tamoxifen and AI were included in the AI group. ET at present and chemotherapy was dichotomized (yes/no). In Paper II and III, systemic treatment were categorized into no systemic treatment, ET only, chemotherapy only and endocrine- and chemotherapy. BCSs treated with trastuzumab were assigned to the chemotherapy only (if no ET) or the endocrine- and chemotherapy group.

3.4.4 Menopausal status

As we had no information on menopausal status at BC diagnosis among the participants in the SWEET-study, age was used as a proxy for menopausal status. Premenopausal status was defined as age < 55 years, and postmenopausal status as age ≥ 55 years. This cut-off is the same

as that used for defining menopausal status in former national treatment guidelines (38). In paper II, the BCSs were stratified according to assumed menopausal status at diagnosis, and their sexual health compared to women from the HUNT4 study in the same age-group.

3.5 Statistical Analyses

3.5.1 All papers

In all three papers, categorical variables were presented as numbers and percentages, while continuous variables were presented as means with standard deviations. Missing values were presented separately. Statistical tests were performed to answer the research questions. P-values < 0.05 were considered statistically significant, and all tests were two-sided.

3.5.2 Paper I

Comparisons of sexually active and sexually inactive BCSs were performed using independent sample t-tests for continuous variables, and chi square tests for categorical variables. Logistic regression analyses were used to identify variables associated with sexual inactivity and variables associated with "less sexual activity compared to before BC" (SAQ-H dichotomized). Linear regression analyses were used to identify variables associated with SAQ-P, SAQ-D and tiredness among sexually active BCSs. Variables with p values < 0.20 in the univariate analyses were included in the multivariate model. Results were presented as beta coefficients (B) from linear regression and odds ratios (OR) from logistic regression analyses with accompanying 95% confidence intervals (CIs). The analyses were performed using IBM SPSS statistics version 26.0. Internal consistence for instruments were examined with Cronbach's alpha.

3.5.3 Paper II

Characteristics of participants in the SWEET- and the HUNT4-studies were compared using independent sample t-tests for continuous variables, and chi square tests for categorical variables. Comparison of sexual health outcomes (sexual functioning, sexual enjoyment, and SAQ-D) between BCSs (SWEET) and population controls (HUNT4) were performed using linear regression analyses. In the first model, we adjusted for sociodemographic variables (age at survey, living with a partner or not, short/long education), with additional adjustments for health-related variables (somatic co-morbidity, mental co-morbidity, BMI and sleep problems) in a second model. We only adjusted for the sociodemographic variables when exploring the effects of BC treatment on sexual health among BCSs, as the health related variables may serve as mediators of the outcomes. The analyses were further stratified by pre-/postmenopausal status at diagnosis. Results were presented as B with accompanying 95% CIs. We used a mean score

difference of ≥10% of range score to define a clinically relevant difference in the sexual outcomes between groups (152). This corresponded to ≥ 10 scale points for sexual functioning and sexual enjoyment and ≥ 0.6 scale points for SAQ-D. There were missing data for several variables, and all analyses were performed with multiple imputation procedures. As the results after imputation were similar to the complete case analyses, results with complete case analyses were presented. The analyses were performed using IBM SPSS statistics version 28.0 and STATA version 17.

3.5.4 Paper III

Latent class analysis was used to estimate subgroups of BCSs sharing similar burden of LEs. This statistical method uses multiple indicator variables to identify latent homogenous subgroups within a heterogeneous sample (153). In this paper, ten common LEs (pain, fatigue, sleep disturbances, arm problems, breast problems, neuropathy, cognitive dysfunction, emotional dysfunction, FCR and sexual dysfunction) served as categorical indicator variables. Multiple models consisting of two, three, four and five subgroups were fit to the data and evaluated. The final model was selected based on the statistical evaluation criteria Akaike Information Criteria and Bayesian Information Criteria, average posterior probability for belonging to the latent subgroups, entropy and clinical meaningfulness of subgroups (154). Multi-nominal regression analyses were performed to identify variables associated with subgroups with similar symptom burden. The average latent class posterior probabilities were used as weights to adjust for classification uncertainty. Results were presented as ORs with 95% CIs. The analyses were performed using STATA version 17. Internal consistence for instruments were examined with Cronbach's alpha.

4 ETHICAL CONSIDERATIONS

This study was approved by the Regional Committee for Medical Research Ethics (2018/2170), the Norwegian Cancer Registry and the Data Protection Officer at Oslo University Hospital. All procedures were performed in accordance with the ethical standards of the national and institutional research committee and with the 1964 Declaration of Helsinki and its later amendments (155).

All participants signed an informed consent form for study participation and permission of linkage to information in the CRN. For non-responders, pooled basic clinical information were retrieved from CRN.

Participation in SWEET did not place the participant at any direct risk or harm, however it may have reminded the BCSs of a difficult period in life and may also have created new concerns.

5 SUMMARY OF RESULTS

5.1 Characteristics of the breast cancer survivors in the SWEET-study

At survey, mean age of included BCSs was 60 years and most lived with a partner (73%). Around half (51%) had long education, and forty-one percent were in paid work. One out of four BCSs had three or more somatic comorbidities and 18% were obese. Fifty-three percent were physically inactive. Cancer-related variables and prevalence of LEs are presented in table 3.

Table 3: Characteristics of breast cancer survivors in the SWEET-study (n=1355)

Cancer-related variables	
Age at diagnosis, mean (SD)	51.9 (8.6)
Stage, n (%)	
I	606 (44.7)
II	486 (35.9)
III	108 (8.0)
Missing	*155 (11.4)*
Breast conserving therapy, n (%)	796 (58.7)
Sentinel node biopsy, n (%)	457 (63.2)
Chemotherapy, n (%)	926 (68.3)
Radiotherapy, n (%)	1087 (80.2)
Ever use of endocrine therapy (ET), n (%)	
No ET	474 (35.0)
Aromatase inhibitor[1]	423 (31.2)
Tamoxifen	385 (28.4)
Unknown type	73 (5.4)
Current use of ET, n (%)	302 (22.3)
Missing	*42 (3.1)*
Systemic treatment burden, n (%)	
No systemic treatment	245 (18.1)
ET only	172 (12.7)
Chemotherapy[2] only	226 (16.7)
Chemotherapy[2] and ET	700 (51.7)
Missing	*12 (0.9)*
Late effects, n (%)[3]	
Pain[4]	631 (46.6)
Cognitive dysfunction[4]	586 (43.3)
Chronic fatigue[5]	432 (31.9)
Sleep disturbances[4]	457 (33.8)
Emotional dysfunction[4]	373 (27.6)
Fear of cancer recurrence[6]	755 (55.8)
Arm problems[7]	428 (31.6)
Breast problems[7]	315 (23.3)
Neuropathy[8]	277 (20.5)
Sexual dysfunction[7]	380 (28.1)

[1]Included BCSs treated with both Tamoxifen and AI, [2]Including BCSs treated with trastuzumab (n=242), [3] Missing ranging from 0.4-5.9%, Defined based on [4] EORTC QLQ-C30, [5] Fatigue Questionnaire, [6] Assessment of Survivor Concerns, [7] EORTC QLQ_BR23, [8] Scale for Chemotherapy Induced Long-term Neurotoxicity.

5.2 Paper I

Fifty-two percent of the BCSs were sexually inactive. Lack of interest in sex (35%) and having no partner (27%) were the most common reasons for sexual inactivity. Treatment with AI was associated with sexual inactivity and more sexual discomfort. Chemotherapy and present ET were associated with less frequent sexual activity at survey compared to before BC diagnosis. Several LEs including a poorer body image, major depression, sleep problems, breast symptoms and chronic fatigue were negatively associated to different aspects of sexual health. Physical inactivity was associated with less sexual pleasure. Table 4 displays all significant associations in the multivariate analyses for the sexual outcomes (sexual inactivity, SAQ-P, SAQ-D, tiredness and SAQ-H).

Table 4. Variables associated with sexual health in breast cancer survivors

	Sexual inactivity		**SAQ Pleasure**		**SAQ Discomfort**		**SAQ Tiredness**		**SAQ Habit[1]**	
	OR	**95% CI**	**B**	**95% CI**	**B**	**95% CI**	**B**	**95% CI**	**OR**	**95% CI**
Age at survey (years)	1.05	1.03, 1.06	-	-	-	-	-0.02	-0.03, -0.004	-	-
Not living with partner	5.19	3.75, 6.74	1.68	0.78, 2.58	-0.87	-1.33, -0.41	-0.38	-0.59, -0.16	0.40	0.23, 0.69
Chemotherapy	-	-	-	-	-	-	-	-	1.91	1.23, 2.97
Aromatase inhibitor	1.73	1.23, 2.43	-	-	0.61	0.20, 1.01	-	-	-	-
Endocrine therapy at present	-	-	-	-	-	-	-	-	1.98	1.21, 3.25
Sleep problems	-	-	-	-	0.37	0.004, 0.02	-	-	-	-
Breast symptoms	-	-	-	-	0.01	0.003, 0.002	-	-	-	-
Body image	0.99	0.99, 0.995	-	-	-	-	-	-	0.98	0.98, 0.99
Chronic fatigue	-	-	-	-	0.43	0.05, 0.81	0.33	0.16, 0.50	-	-
Major depression	-	-	-1.04	-2.10, -0.02	-	-	-	-	-	-
Obesity	-	-	-	-	-0.63	-1.07, -0.19	-	-	-	-
Physically inactive	-	-	-0.61	-1.21, -0.02	-	-	-	-	-	-

Values close to reference are presented with three decimals. [1]Less sexual activity compared to before breast cancer diagnosis (Reference: about the same/somewhat more/much more sexual activity compared to before breast cancer diagnosis

5.3 Paper II

In total, BCSs had lower sexual enjoyment (B -13.1, 95% CI -15.0, -11.2) and more sexual discomfort (B 0.9, 95% CI 0.8, 1.0) than controls after adjusting for sociodemographic- and health-related variables. BCSs treated with both chemotherapy and ET also had lower sexual functioning (B -11.9, 95% CI -13.8, -10.1), and even lower sexual enjoyment (B -18.1, 95% CI -20.7, -15.5) and more sexual discomfort (B 1.4, 95% CI 1.3, 1.6) compared to controls. There were also clinical relevant differences in sexual enjoyment and sexual discomfort between BCSs who had received either ET or chemotherapy compared to controls.

BCSs who were premenopausal at diagnosis had lower sexual enjoyment (B -17.3, 95% CI -19.6, -14.9) and more sexual discomfort (B 1.2, 95% CI 1.0, 1.3) compared to similar aged controls. Overall, no clinical relevant differences in sexual health were found among those postmenopausal at BC diagnosis and controls. However, if treated with both chemotherapy and ET, also the BCSs who were postmenopausal at diagnosis reported lower sexual functioning (B -10.0, 95% CI -13.9, -6.2), sexual enjoyment (-12.0, 95% CI -18.2, -5.8), and more sexual discomfort (B 1.0, 95% CI 0.6, 1.4) compared to similar aged controls.

5.4 Paper III

Three subgroups of BCSs with similar burden of LEs were identified. Forty-six percent of the BCSs were assigned to the subgroup named “low symptom burden”, characterized by a low prevalence (<15%) of all the explored LEs except FCR and sexual dysfunction. Thirty-seven percent of the BCSs were assigned to the subgroup named “medium symptom burden”, characterized by a high prevalence of pain (62%), cognitive dysfunction (67%), chronic fatigue (49%), sleep disturbances (51%), emotional dysfunction (46%) and FCR (68%), and lower prevalence of arm- and breast problems (32% and 21%), sexual dysfunction (33%) and neuropathy (20%). The remaining 17% of the BCSs were assigned to the subgroup named “high symptom burden”, characterized by a high prevalence (>55%) of all the assessed LEs except of sexual dysfunction (36%). Factors associated with high symptom burden included younger age, more intensive systemic treatment, axillary dissection, higher BMI and physical inactivity. Table 5 displays all variables significantly associated with medium- and high symptom burden in the multivariate analyses.

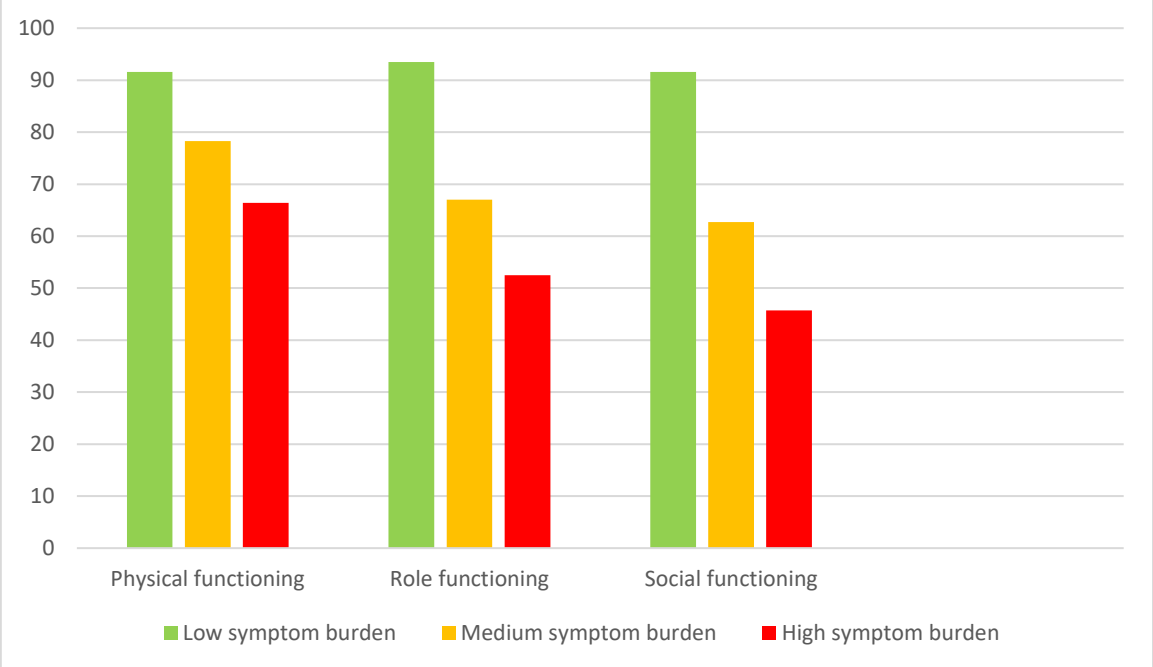
Table 5. Variables associated with medium- and high symptom burden in breast cancer survivors[1]

	Medium symptom burden		High symptom burden	
	OR	**95% CI**	**OR**	**95% CI**
Age at survey (years)	0.97	0.96, 0.99	0.96	0.94, 0.98
Short education	-	-	1.54	1.15, 2.07
Axillary dissection	-	-	1.58	1.15, 2.16
Chemotherapy only	-	-	1.72	1.02, 2.87
Chemo- and endocrine therapy	1.75	1.25, 2.44	1.68	1.08, 2.63
Body mass index, kg/m^2	1.03	1.01, 1.06	1.07	1.04, 1.10
Physical inactivity	1.31	1.04, 1.65	1.74	1.28, 2.37

[1]Low symptom burden subgroup as reference

Mean general functioning scores in the different subgroups are presented in figure 6. The percentage of BCSs within working age (<67 years) at survey (n=987) that held disability pension was 58% in high symptom burden subgroup, compared to 42% and 16% in medium- and low symptom burden subgroup respectively.

Figure 6. Mean values for functioning scales[1] in the three subgroups of symptom burden



[1]EORTC QLQ C-30, scale 0-100, a higher score corresponds to better functioning

6 DISCUSSION OF MAIN FINDINGS

6.1 Sexual health in long-term breast cancer survivors: general aspects

Approximately half of the BCSs did not have partnered sex eight years after BC-diagnosis, a finding in line with results from other studies exploring sexual inactivity in long-term BCSs (17, 19). Similar to what has been reported among BCSs three years after diagnosis, lack of interest was the most common reason for sexual inactivity (103). In the general female population, lack of partner is the most common self-reported reason for sexual inactivity (6, 95), indicating that sexual interest may be affected by BC and its treatment.

Even though we found lower sexual enjoyment and more sexual discomfort among BCSs compared to similarly aged controls, there was no clinically relevant difference in sexual functioning between those groups in the adjusted analyses. As the measure used to define sexual functioning includes assessment also of sexual activity, our findings support results in the study by Dorval et al, showing no difference in sexual activity, but less satisfaction with sexual life among eight-years BCSs compared to controls (127). Neither did Soldera et al find any differences in sexual activity between long-term BCSs and controls (19). However, in contrast to our results, Soldera et al reported no differences in sexual pleasure or sexual discomfort between BCSs and controls. This discrepancy could partly be explained by the higher proportion of BCSs in the SWEET-study treated with ET and chemotherapy (54%) compared to in the study by Soldera et al (10%), as we found such therapy to be associated with both less sexual enjoyment and more sexual discomfort.

Three other studies focusing on sexual health among long-term BCSs have been published since the SWEET-study was initiated, demonstrating results in line with our findings. A large, register-based cohort study by Chang et al compared sexual health in ~20 000 BCSs to that in ~93 000 aged-matched female controls (156). BCSs were grouped after time since diagnosis. All BCSs, including the subgroup of long-term BCSs, had higher risks of sexual dysfunctions compared to controls, of which vaginal dryness was the most frequent. In another large cohort study, ~2700 long-term BCSs had less sexual interest, more pain during intercourse and were more dissatisfied with their sex life than the ~99 000 controls (157). A recent Norwegian longitudinal study examined sexual health in BCSs during the first year after BC surgery and with another assessment 7-12 years thereafter using the same measure as used in the SWEET-study. At long-term follow-up, the ~250 BCSs reported similar scores of sexual functioning and sexual enjoyment as the BCSs included in the SWEET-study (158).

In sum, our findings are in line with results in previous and recent studies, showing that long-term BCSs have less sexual satisfaction- and enjoyment, and more sexual discomfort than similarly aged controls. However, sexual activity seems to be less affected in long-term BCSs. It might be that BCSs maintain some degree of sexual activity, despite their sexual impairments, as a way to express and maintain intimate partnerships (97).

6.2 Sexual health and late effects

A poorer body image was associated with sexual inactivity and with reduced sexual activity at survey compared to pre-BC diagnosis. Sleep disturbances, breast symptoms and chronic fatigue were related to more sexual discomfort, while major depression was related to less sexual pleasure. Similar associations between LEs and sexual health outcomes have been shown in studies exploring earlier phases of BC survivorship (15, 114-116, 139, 159), but have not previously been studied in long-term BCSs.

Sexual dysfunction was one of the ten LEs used to identify subgroups of BCSs sharing similar symptom burden in Paper III. We observed only slight differences in prevalence between the subgroups (ranging from 25-36%). This may be because of the applied definition of sexual dysfunction, which was no interest in sex and no sexual activity. As previously discussed, other aspects of sexual health seems more affected in long-term BCSs than sexual activity, including sexual enjoyment and discomfort, probably making the measure used in Paper III less appropriate to capture all relevant aspects of sexual health among long-term BCSs.

6.3 Burden of late effects in long-term breast cancer survivors: general aspects

More than a half of the BCSs in this study suffered from a high- or medium symptom burden. Compared to BCSs with a low symptom burden, these BCSs had lower general functioning. Mean general functioning scores among BCSs with high- or medium symptom burden ranged from 46-78, considerably lower than reported European and Norwegian normative scores ranging from 82-89 (160-162). Such figures suggest that these long-term BCSs struggle with daily life activities, probably hampering their ability to work and participate in leisure time activities, family- and social life. Supporting this statement are our findings that the proportion of BCSs within working age holding disability pension was 58%, 42 % and 16 % in the high-, medium-, and low symptom burdened subgroups respectively. In another SWEET-sub study, examining BCSs within working age at survey, 8 % of the BCSs held disability pension at diagnosis, while 34 % received disability pension at survey (163). Among BCSs who had reduced their work status since diagnosis, 64% reported that LEs were the main or partial reason.

On the other hand general functioning scores were ≥ 92 among BCSs with low symptom burden, i.e. higher than reported normative data (160-162). Further, the proportion holding disability pension in this subgroup was somewhat lower (16%) than reported statistics on Norwegian women aged 55-59 years in 2019 (19%) (164). Even though examining BCSs in early BC survivorship, the study by de Ligt et al supports our findings that a subgroup of BCSs is doing very well (130). That study showed that a third of the BCSs had low symptom burden the first five years after diagnosis, and lower symptom severity than the general population. It might be that general functioning in these low-burdened subgroups is not affected by a BC diagnosis and treatment. Another explanation may be posttraumatic growth, i.e. a positive change that occurs as a result of a stressful experience like cancer (165). Posttraumatic growth may manifest in a variety of ways, including an increased appreciation for life in general, more meaningful interpersonal relationships and changed priorities. Post-traumatic growth may in turn lead to a response-shift, i.e. PROMs reflect better outcomes over time not because the patient is doing better but because the patient has adapted, psychologically, to match new life circumstances (166).

6.4 Younger age as a risk factor for sexual health challenges and higher burden of late effects

Sexual inactivity and reduced sexual functioning are associated with increasing age in the general female population (5, 6). This decline corresponds with the transition from pre- to post-menopausal status, however several other factors like comorbidity, medications and partner factors may also contribute (97). We found sexual inactivity associated with increasing age also in BCSs. The sexual inactivity prevalence rate was 54% among the BCSs aged 56-69 years at survey, similar to the prior reported rate of 52% in a similarly aged normative sample (95). However, among those aged 35-44 years, the sexual inactivity prevalence rate was twice as high among BCSs (33%) as that reported in the normative sample (16%), indicating that sexual health also long-term is more affected by a BC diagnosis at premenopausal compared to at postmenopausal age. The impact of menopausal status was further explored in Paper II, in which sexual health among the BCSs were compared to that of similar aged female population controls from the HUNT4 study. The BCSs who were premenopausal at diagnosis had clinically relevant lower sexual enjoyment and more sexual discomfort than similarly aged controls, while no such differences were found between BCSs and controls in the postmenopausal group. The association between premenopausal age and sexual health impairments was also demonstrated in another comparative study examining BCSs three to eight years after diagnosis and age-

matched controls (167). Further, the recent study by Chang et al reported a higher risk of sexual dysfunctions in BCSs compared to controls, with the highest risk observed among BCSs <50 years at diagnosis (156).

We found that younger age was also associated with a higher symptom burden. This result corresponds to findings in several studies assessing symptom burden during the first years of survivorship (20, 22, 168). Younger age is an established risk factor for several of the LEs included as indicator variables in our study, such as pain, emotional dysfunction, FCR and sexual dysfunction (47, 70, 79, 167). Treatment-induced premature menopause, limited coping resources concerning serious illness and greater demands in the areas of work and parenting, may explain why younger BCSs struggle more and report more symptoms than older BCSs. Further, older BCSs may underreport symptoms and instead attribute them to normal aging.

Younger BCSs may be in "double trouble" for sexual health impairments and higher symptom burden, as they are more often diagnosed with more aggressive disease and hence receive more intensive BC treatment – another major risk factor discussed in the following.

6.5 Systemic treatment burden as a risk factor for sexual health challenges and higher burden of late effects

In Paper I, treatment with AI was associated with sexual inactivity and sexual discomfort in BCSs. Vaginal dryness, dyspareunia and reduced libido are well-documented side effects during AI treatment (110, 169). However, in the SWEET-study, only one in five of BCSs reporting AI treatment were still on ET at survey, implying that AI negatively affects sexual health also after treatment cessation. This theory is supported by findings from the Intergroup Exemestane Study, in which BCSs up to 2-3 years post-treatment reported reduced libido, vaginal dryness and discomfort at intercourse at the same level as when they were on active treatment (170). In Paper II, all sexual health outcomes were poorer among BCSs treated with both endocrine- and chemotherapy compared to the controls irrespective of age. BCSs treated with either ET or chemotherapy had less sexual enjoyment and more sexual discomfort than controls. Contrary to these results, Soldera et al found no differences in sexual health between BCSs and controls, neither in total nor when stratifying by systemic treatment burden (19). This discrepancy may partly be explained by the different aspects of sexual health explored in these two studies as Soldera et al did not define "gynecological symptoms" including vaginal dryness and pain with intercourse as a sexual outcome. However, BCSs treated with chemotherapy reported worse gynecological symptoms than controls also in the study by Soldera et al. Further, AIs were not

in use when BCSs in that study was treated (1989-1996). Supporting our finding that chemotherapy negatively affects sexual health long-term is the study by Ganz et al in which BCSs treated with chemotherapy reported more sexual discomfort six years after diagnosis compared to those not receiving such therapy (128).

Combined treatment with chemotherapy and ET was associated with medium- and high symptom burden. Chemotherapy was also associated with a medium symptom burden, while no association was found between ET only and symptom burden. Systemic treatments are associated with several of the LEs explored including fatigue, pain, neuropathy, and cognitive dysfunction (56, 64, 86, 171).

6.6 Physical activity and late effects

A beneficial effect of physical activity on several LEs, including fatigue, sleep disturbances, depression and cognitive dysfunction is well documented (172-175). In Paper I, physical inactivity was associated with less sexual pleasure. This result corresponds to findings from a study exploring BCSs about five years after diagnosis, reporting that physical activity lower the risk of hypoactive sexual desire disorder (176). In a small pilot study (n=55) including BCSs on average 3 years after diagnosis, BCSs randomized to multimodal life style intervention including physical activity, reported a reduction in both menopausal symptoms and sexual dysfunction compared to a control group offered standard care (177).

Physical inactivity was associated with high symptom burden in paper III. In line with this finding, a study of five-years BCSs reported an association between decreased physical activity compared to pre-diagnosis and a higher symptom burden (132).

7 METHODOLOGICAL CONSIDERATIONS

7.1 Cross-sectional design

The SWEET-study had a cross-sectional design, i.e. an observational study collecting all information at one time point. A cross-sectional design is appropriate for determining the prevalence of variables and exploring associations between variables (178). The cross-sectional design allowed exploration of sexual health and the total burden of LEs, as well as a range of factors associated with these outcomes, which were the main aims for this project. Comparisons with population-controls made it possible to assess differences in sexual health outcomes between BCSs and similarly aged women in the general population.

A cross-sectional design does however have obvious limitations. We had no baseline data, thus both sexual health challenges and complaints classified as LEs may have been present before the BC diagnosis. Further, the cross-sectional design do not allow for causal conclusions. We found several factors associated with impaired sexual health and higher symptom burden, but cannot conclude on the directionality between these relations. As an example, we found an association between poorer body image and sexual inactivity in Paper I. However, we cannot judge whether a poorer body image may cause sexual inactivity or if sexual inactivity may cause a poorer body image.

7.2 Internal validity

Internal validity examines whether the design of the study, the conduct and analyses answer the research questions without bias (178). Bias refers to any systematic error in a study causing distorted results and an incorrect estimate of the truth (179). In the following, possible selection-, information- and confounding bias in the SWEET-study are discussed.

7.2.1 Selection bias

Selection bias concerns the examined sample's representativeness for the overall population intended to be studied (178). BCSs in this study were identified from the CRN, which have close-to complete registration of all new cancer cases in Norway (27). Thus, the population invited to participate in the SWEET-study was representative for all women between 20-65 years diagnosed with BC in 2011-2012 in Norway, who were still alive, and without relapse or other cancers. The control group in Paper II were similar aged women from the HUNT4 survey. The HUNT4 participants are considered fairly representative for the general population in Norway, except for the lack of representation from large cities and immigrant population (134).

Non-response bias is a type of selection bias that may occur when the characteristics of the responders differ from that of the non-responders (179). The response rate in the SWEET-study was 49 %, which is considered acceptable, both compared to other surveys of Norwegian long-term cancer survivors (180, 181) and to surveys on sexual health among BCSs in general (103, 111). In the attrition analysis, responders were somewhat younger, a higher proportion were HER2 positive, and mean Ki67 was higher, which could have resulted in responders being more heavily treated than non-responders. The questionnaire used in both the SWEET- and HUNT4-studies were in Norwegian, which could have resulted in underrepresentation of ethnic minorities. In general, lower education and ethnic minority background are typically underrepresented among responders, and those with better health overrepresented (182, 183). We had no further information of this among non-responders, however studies suggest that such differences do not necessarily translate into biased outcomes in surveys (184). The response rate in the control group from HUNT4 was 52%, with low concerns of non-response bias (134).

7.2.2 Information bias

Information bias occurs when the variables are measured, collected or interpreted inaccurately (179).

7.2.2.1 Self-reporting bias

The SWEET-study was primarily based on self-reported data. Examples of self-reporting bias include recall bias and social desirability bias (185). Information on systemic BC treatment and RT was self-reported, with the potential of recall bias. In general, studies report a high degree of agreement between self-reported treatment and the actual given medical treatments (186, 187), suggesting a low risk of recall-bias regarding this information in the SWEET-study. Surveys of sensitive topics including sexual health, are at risk of social desirability bias (188), which refers to the tendency of a research subject to give socially desirable responses instead of choosing responses that reflect their true experience (189). Data in both the SWEET- and the HUNT4-study were self-reported and the questionnaires were confidential, which likely reduced the risk of social desirability bias substantially.

7.2.2.2 Measurement error bias

To draw valid research conclusions in studies based on self-reported data, the measures used must have good psychometric properties, i.e. reliability and validity. Reliability refers to the consistency of a measure, including consistency over time (test-retest reliability) and across items (internal consistency) (190). Several of the PROMs used in the SWEET-study have shown

acceptable test-retest reliability (136, 191). Internal consistencies measured by Cronbach's alpha ranged from 0.72-0.93 across the measures used in the SWEET-study, meeting the recommendations that Cronbach's alpha should be above 0.70 (192). Validity refers to the extent to which the scores from a measure represents the variable they are intended for. Content validity refers to what degree the measure includes the most relevant and important aspects of the construct of interest, while construct validity refers to what degree the scores of a measure relate to other measures (193).

In Paper I, the construct "sexually active" was defined based on responses to the item "Do you engage in sexual activity with partner". This item was somewhat modified from the original item in the SAQ which is "Do you engage in sexually activity with anyone at the moment". This difference in wording may have resulted in a smaller proportion being defined as "sexually active" in the SWEET-study than in other studies using the SAQ, as sexual activity may be interpreted as requiring a steady partner. Further, the construct "sexually active" in the SAQ has a narrow definition of sexual activity, excluding masturbation.

In Paper III, the construct "sexual dysfunction" was defined based on responses to items concerning sexual activity and interest. Items assessing sexual pleasure, enjoyment and discomfort are also relevant to the construct sexual dysfunction, but were not included as these domains were applicable only to sexually active BCSs. Thus, there were weaknesses in the content validity of this measure as further discussed in the section about sexual health and LEs above.

Sexual inactivity and sexual dysfunctions do not necessarily cause distress to the individual and/or eventual partner, a criteria required for a DSM-V clinical diagnosis of sexual dysfunction. We did not have such information, which may be a weakness of the construct validity of the sexual outcome measures used in this project.

We had no information of menopausal status at diagnosis in SWEET, and used age $<55/\geq55$ years as a proxy. This could be a source of measurement bias, as some postmenopausal women may have been classified as premenopausal, and to a lesser degree the other way. If so, this possible bias actually strengthens our finding of premenopausal age at BC diagnosis as a major risk factor of impaired sexual health.

Several LEs used as explanatory variables in paper I and all LEs used as indicator variables in Paper III were continuous variables that were dichotomized. By dichotomizing, information is

lost, and the statistical power to detect a relation between the variable and the outcome is reduced (194). The main advantage of dichotomization is that it makes presentation and interpretation of results easier, which was the reason why this approach was chosen for several variables in Paper I. For using latent class analyses in Paper III, the indicator variables had to be categorical. Our results could be biased by the cut-off selected for dichotomization. Established threshold values for clinically importance were used as cut-offs for defining LEs when available (142), while for other variables cut-offs from scale manuals were applied, thus minimizing the risk of measurement bias as much as possible. The cut-off score for FCR was defined in collaboration with the developer of the Assessment of Survivor Concerns instrument. This cut-off had not been used before and was therefore not validated, and could be a source of measurement bias. One might imagine that when directly asked about their FCR, the majority of BCSs will report some degree of fear, and thus overestimating the prevalence of clinical relevant FCR.

7.2.2.3 Missing data bias

Missing data may lead to different results than those that would have been obtained from a complete dataset if deviating from the non-missing. In the SWEET-study, items concerning sexual health and physical activity had the highest proportion of missing data, ranging from 2-8%. Several PROMs have established and recommended strategies for handling of missing data. Mean imputation is a method in which the mean of the observed values for each variable is computed and the missing values for that variable are imputed by this mean (195). This method was used when at least 50% of the items had been completed for the EORTC scales, the Generalized Anxiety Disorder 7-item scale and within each subscale of the Fatigue Questionnaire. For the Patient Health Questionnaire 9, mean imputation procedure was performed if no more than two items were missing.

In Paper II, multiple imputation procedure was performed. Using this procedure, missing values were generated as plausible values derived from distributions of and relationships among observed variables in the dataset (196). This procedure was repeated 20 times, and the results from all imputed data sets were combined. These analyses yielded similar results as complete case analyses, indicating just minor missing data bias.

We used different measures for defining sexual (in) activity in Paper I and II, with more missing data for the item used in Paper II. This may be due to sexual activity being assessed during a time frame of four weeks in the item in Paper II, while there was no time frame for the item used

to define sexual activity in Paper I. The probability of missing data bias in paper II was thus some higher than in paper I.

7.2.3 Confounding bias

A variable is a confounder if it is: 1) associated with the explanatory variable, 2) associated with the outcome being investigated, and 3) not in the causal pathway between the explanatory variable and the outcome (179). Confounding could result in a distortion of the association between the variables. A way of controlling for confounding is multivariable regression analysis, where the effect of a variable of interest can be examined with confounding variables held statistically constant. Multivariable regression analyses were used in this project to reduce the risk of this kind of bias. As an example the variables age and somatic co-morbidities were included in the multivariable regression models in Paper I and II as both could be related to the sexual outcomes and potentially to each other. To note, as sexual health and LEs are complex constructs, unidentified confounders are likely to be present.

7.3 External validity

External validity examines whether the study findings may be generalized to other contexts (178). Internal validity is a prerequisite for external validity. For the current project this means to what degree our results may be generalized to other long-term BCSs. The population-based nationwide inclusion represents a major strength for generalizability. However, our study was restricted to women who were 20-65 at BC diagnosis, free from pre- or post- malignancies at survey, and able to respond to the questionnaire written in Norwegian. Thus, our results cannot be generalized to BCSs diagnosed at older age, to BCSs with metastatic disease, nor to those not understanding Norwegian. BCSs in this study were treated in a time period where the guidelines recommended adjuvant chemotherapy to a higher proportion of BC patients (36-38) compared to present guidelines (31). Consequently, the examined population of BCSs may have more sexual health challenges and LEs than the BCSs treated today will experience in the future. On the other hand, ovarian function suppression was not used when BCSs in this study was treated, which obviously will affect sexual health and add to symptom burden in younger BCSs (112, 113). Further, immunotherapy (197) and chemotherapy after preoperative chemotherapy (198) have been introduced for subgroups of BC patients with scarce knowledge of the LEs of this additional treatments. Despite these limitations, we believe our results still generalizable to other long-term BCSs undergoing therapy as in the SWEET-study, and also to long-term BCSs in other countries offering similar BC therapy. In the HUNT4-study, the ethnically

homogeneous population limits the generalizability to people of non-European ancestry (134), a limitation that also may be relevant for the SWEET-study.

7.4 Sample size calculations and statistical assumptions

A type I error occurs when a true null hypothesis is falsely rejected (199). This type of error can be minimized by selecting an appropriate significance level. A generally accepted level is $p < 0.05$, as used in this study.

A type II error occurs when a false null hypothesis is not rejected (199). The risk of a type II error is related to the power of the study, and is reduced by increasing sample size. The power calculation performed before the SWEET-study concluded that a sample size >1000 was appropriate for the statistical comparisons of two or three groups. In the different sub-studies, both logistic and linear regression analyses were performed. For logistic regression the sample size should be ≥10 per explanatory variable, and for linear regression the sample size should be ≥ (50 + 8 x number of explanatory variables) (200, 201). The SWEET-study did not have enough power for some subgroup analyses in Paper II. Three subgroups were considered too small to compare sexual health stratified by menopausal status between population controls and BCSs according to systemic treatment burden (premenopausal BCSs with no systemic treatment [N=81], premenopausal women with ET only [N=31] and postmenopausal women with chemotherapy only [N=61]). To avoid type II errors, results from these subgroups were not presented.

The choice of research method should be appropriate to the research question of interest. In all three papers, there were independence between observations in the compared groups, essential for the use of independent t-test, chi-square tests and regression analysis. When using independent t-tests, as in paper I and II, the data should be approximately normally distributed (199). Some of the variables, as e.g. the EORTC scores, were not perfectly normally distributed, but because of the large sample size, we used t-test and not non-parametric tests (202). When using chi-square tests, as in paper I and II, the expected number in each cell should not be fewer than five (199), a prerequisite fulfilled in the SWEET-study.

In regression models, there should be no muliticollinearity, i.e. no strong linear relationship between two or more independent variables (203). Muliticollinearity was assessed by variance inflation factor (VIF). Due to multicollinearity, the variables age at diagnosis and living with children <18 years were omitted in paper I and current ET and RT in paper III. For other variables, multicollinearity was not considered a problem as VIF was below 3.

In regression analysis, including continuous independent variables, an assumption if linearity is assumed. In the logistic regression analyses in paper I and III, the independent variables should be linearly related to the logit of the outcome (204). In the linear regression analyses in paper I and II, there should be a linear relationship between independent variables and dependent variables, i.e. the residuals should be normally distributed, and the residuals should have constant variance (homoscedasticity). These assumptions were fulfilled in the SWEET-study.

Latent class analysis relies on the assumption that homogenous sub-populations exist within the data. For using latent class analysis in paper III, the indicator variables should be categorical and the indicator variables not correlated. These assumptions were fulfilled in the SWEET-study.

8 CONCLUSION AND CLINICAL IMPLICATIONS

8.1 Conclusion

BCSs experienced several sexual health impairments long-term. Sexually active BCSs reported less sexual enjoyment and more sexual discomfort compared to similar aged female controls. Despite these challenges, the proportion remaining sexually active seemed similar to that of controls. Several common LEs were associated with sexual health impairments, including a poorer body image, chronic fatigue, breast problems, sleep problems and depression.

More than half of the BCSs experienced a medium- or high total burden of LEs more than eight years after BC, and reported lower general functioning compared to BCSs with a low symptom burden. Among BCSs within working age with a medium- or high symptom burden, 42% and 58% held disability pension respectively, compared to 16% among BCSs with low symptom burden.

Younger age and more intensive systemic BC treatments were significant risk factors of both sexual health impairments and a higher total burden of LEs in long-term BCSs.

Physical inactivity was associated not only with a higher symptom burden, but also with reduced sexual pleasure.

8.2 Sexual health in survivorship care

Even though a considerable subgroup of long-term BCSs suffer from sexual health impairments, such issues often remain unaddressed during follow-up care (205). One study reported that among BCSs with sexual problems, less than a half had any communication with health care professionals regarding sexual health during their follow-up visits (206). Health-care professionals report several reasons for not focusing on sexual health in follow-up care; differences in age and gender between BCSs and the health care provider, the belief that this topic is not relevant to older BCSs and to BCSs in later survivorship, lack of knowledge, lack of available treatment, and time constraints (207). On the other side, BCSs clearly want health care providers to initiate talk about and to address this topic (208). The survivorship guidelines issued by the American Cancer Society/ American Society of Clinical Oncology recommend health care professionals to address sexual health in follow-up care (209). Based on these recommendations and further supported by our findings, all the involved health care providers should screen for sexual impairments during follow-up visits, with special attention to younger BCSs, those treated with both chemotherapy and ET, and BCSs treated with an AI.

Several treatment options for sexual health impairments are available (209-212). Vaginal dryness and dyspareunia should be treated with non-hormonal vaginal lubricants (213). Temporary low-dose vaginal estrogen therapy can be considered when non-hormonal alternatives are inefficient, but not in BCSs on AI treatment (31). The replacement of AI with tamoxifen may also be discussed. Studies have shown beneficial effects of cognitive behavioral therapy (CBT) for sexual dysfunctions (214-216). If available, BCSs with sexual dysfunctions should be referred to health care providers with such competence. Also, referral to personnel with competence in sexual rehabilitation should be considered. Vaginal laser therapy has shown promising results alleviating vaginal symptoms, but randomized trials and long-term results are lacking (217, 218).

8.3 Personalized breast cancer survivorship care

Findings from this project point to a need for personalized survivorship care, tailored to the individual BCS. BCSs experiencing a medium- and high symptom burden should be prioritized for closer follow-up and assessed for specialized interdisciplinary rehabilitation services.

Ideally, BCSs with or at risk of higher symptom burden should be identified early in the survivorship trajectory. Results from longitudinal studies from the first three years of survivorship, indicate that the majority of BCSs remain within the same symptom burden subgroup over time (133, 168). One might therefore anticipate that the BCSs identified in the medium- and high symptom burden subgroups in our study, also struggled during early survivorship. Younger age and higher systemic treatment burden are important risk factors for experiencing higher symptom burdens also in studies addressing the first part of survivorship (20, 22, 131, 133). It is therefore reasonably to conclude that premenopausal women receiving adjuvant systemic BC treatment are at high risk of developing LEs, and should be offered closer follow-up than postmenopausal BCSs receiving no systemic BC treatments. As we observed that risk factors for sexual health impairments and experiencing a high symptom burden were similar, such a conclusion is also relevant with regards to follow-up of sexual health.

A personalized strategy for follow-up of BCSs is already implemented in several survivorship guidelines (31, 209). The American guidelines recommend individualized follow-up based on age, the specific BC diagnosis and treatment received (209). In the Norwegian guidelines, it is emphasized that follow-up should be customized based on individual needs and age (31). Another personalized strategy is the "Cancer pathway – home" launched by the Norwegian Directorate of Health in 2022 (219). Anyone diagnosed with cancer will be offered inclusion,

and the intention is to identify complaints and problems needing further action during cancer therapy and follow-up, aiming to ensure a predictable transition from hospital to primary care based on individual needs. A recommended screening tool is the Distress Thermometer (220), which measures distress on a 0 to 10 scale and identifies sources of distress from a comprehensive problem list. This pathway has recently been implemented in some Norwegian hospitals, and stands out as an excellent measure for assessment of total symptom burden and personalized survivorship care and rehabilitation.

Limited resources is a key challenge in patient care. A necessary implication of this is that health care resources have to be allocated to those most in need, re-locating them from other subgroups. The findings from this project suggest that BCSs with low symptom burden could be offered a more simplified follow-up. Annual mammography will be a minimum, but the following personal consultation with a doctor could be adjusted to a less resource demanding setting. Several alternatives exist; consultations by a nurse, in groups, and/or by telephone/virtual (221-223). The COVID-19 pandemic clearly demonstrated that there is a potential for increased use of audiovisual aids during consultations, which may save time and resources. BCSs diagnosed $\geq$ 55 years receiving no systemic treatment are a subgroup of survivors with a low risk of a high symptom burden and also a low risk of relapse, where follow-up could be limited to annual mammography and a less resource demanding consultation.

8.4 Physical activity in breast cancer survivorship care

The World Health Organization's guidelines on physical activity, also implemented in Norwegian public guidelines and the current American guidelines for cancer survivors, recommend engagement in regular physical activity including 150-300 minutes of moderate or 75-150 minutes of vigorous physical activity per week (150, 224, 225). Muscle-strengthening activities two or more days per week are additionally recommended.

Despite the beneficial effects of physical activity on several LEs, overall- and even BC-specific survival in BCSs (174, 226-230), approximately two-thirds of BCSs do not meet the physical activity recommendations (231). In the SWEET-study, more than a half of the BCSs were physically inactive, which we found associated with higher symptom burden. Increasing physical activity among BCSs may thus be a key intervention to alleviate total burden of LEs. Several efficacious strategies have been identified for increasing physical activity among cancer survivors, ranging from brief physical activity screening, patient education and self-monitoring, to more intensive lifestyle counseling (231). However, a study from 2018, showed that only

about half of oncologists and breast surgeons routinely advise BCSs to engage in physical activity during follow-up care visits (231), which is a simple approach for getting more BCSs to meet the recommendations (232).

Physical activity is an important component of rehabilitation. For BCSs with low symptom burden not meeting the physical activity recommendations, participation in low threshold services in primary care such as Healthy Life Centers and/or support from AKTIV instructors who have special competence in physical activity after cancer treatment, may increase their physical activity. BCSs with higher symptom burdens may benefit from more specialized and interdisciplinary rehabilitation facilities.

8.5 Clinical implications summed up and future perspectives

This PhD project has clearly demonstrated that one subgroup of BCSs stands out with a high risk of both sexual health challenges and higher burden of LEs affecting their general functioning; younger BCSs who have received systemic treatments. These BCSs should be prioritized for closer and comprehensive survivorship care, with the ultimate goal to increase their functioning and work participation.

This project was a part of the SWEET-study, from which eight papers have been published during 2019-2023 (163, 233-239). Findings from the SWEET-study have resulted in new knowledge and increased awareness of LEs among long-term BCSs, valuable for survivors and health care professionals. Together with collaborators, researchers from the SWEET-study have published a scoping review in The Journal of The Norwegian Medical Association on the clinical presentation and handling of the most common LEs after BC in Norway (240), in which sexual health and estrogen deprivation symptoms were discussed. That paper also described the co-existence of several LEs and underscored the importance of a holistic rehabilitation that should be adjusted according to severity and burden of LEs. This is one step towards increased clinical awareness of these issues during follow-up care for doctors in general, and especially for the general practitioners who are expected to be the most important health care provider for the majority of BCSs.

How to best approach BCSs suffering from a higher symptom burden and increase their general functioning remains to be addressed. All clinicians working with this population should be aware of co-occuring LEs, educate and involve BCSs in identifying such symptoms and aggravating/alleviating factors, and coordinate treatment strategies that are likely beneficial (241). Few studies have tested intervention strategies managing co-occuring symptoms, but

encouraging evidence exist for educational intervention, physical exercise, mindfulness-based stress reduction and CBT (242-244). An ongoing Norwegian randomized controlled trial recruiting BCSs about seven months after diagnosis aims to investigate if web-based interventions with either CBT or mindfulness-based stress management reduces LEs and improves quality of life and work-related outcomes compared to a control group offered usual care (245). Interdisciplinary holistic interventions including lifestyle interventions, educational programs and different types of CBT are likely the most effective treatments for BCSs suffering from a higher symptom burden, but no prior study has explored if such a holistic intervention is beneficial in BCSs. Another Norwegian randomized trial is examining the effect of such complex interventions on chronic fatigue in lymphoma survivors (246). If this study proves effective, BCSs need to be explored specifically in upcoming studies, including also other LEs than fatigue. Further, evidence of the long-term effectiveness of such interventions is generally lacking and future studies with extended follow-up assessments of outcomes should be undertaken.

As discussed, BCSs with high symptom burden long-term are most likely the same as those struggling during the first five years after diagnosis. This subgroup should therefore be identified early in survivorship and prioritized for closer follow-up and rehabilitation. Individualized follow-up is already recommended in the Norwegian guidelines, and the recently launched "Cancer pathway-home" may help guiding BCSs to the right level of follow-up and rehabilitation based on their individual needs. Also using the Distress Thermometer, a Swedish trial is testing whether screening-based identification of rehabilitation needs and individualized rehabilitation after primary BC treatment is effective in reducing distress (247). Distressed BCSs are randomized to intervention or standard follow-up, while those not distressed will receive standard follow-up. In Norway, the project CaReScreen aims to develop a digital clinical decision tool to identify cancer patients at high risk of functional impairments and facilitate referral and triage to the most efficient rehabilitation level (248). Further studies are needed in order to evaluate if such individualized strategies will help.

In later years, there has been a trend towards less intensive systemic BC treatment due to genetic profiling of tumor tissue (249). There is however no reason to believe that the risk of LEs among BCSs are lower today compared to in 2011/2012. New treatments have been introduced for several subgroups with high risk BC, including more intense and extended ET. The potential LEs following adjuvant systemic therapies such as goserelin for premenopausal women, immunotherapy for triple negative BC and post neo-adjuvant chemotherapy for BCSs with

residual disease, are scarcely known. The continuous evolvement of BC treatment strategies must also result in further research concerning the risk of LEs in this population.

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EPIDEMIOLOGY

Sexual activity and functioning in long-term breast cancer survivors; exploring associated factors in a nationwide survey

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Abstract

Purpose Sexual health is a key quality of life issue. Knowledge concerning sexual health in long-term breast cancer survivors (BCSs) is limited. Within a nationwide sample, we aimed to assess the prevalence of sexual inactivity and to explore factors associated with sexual inactivity and reduced sexual functioning among long-term BCSs.

Methods Long-term BCSs aged 20–65 years when diagnosed with early-stage breast cancer in 2011–2012 were identified by the Cancer Registry of Norway in 2019 ($n=2803$) and invited to participate in a nationwide survey. Sexual health was measured using the multidimensional Sexual Activity Questionnaire. Factors associated with sexual inactivity and reduced sexual functioning were explored using multivariable logistic- and linear regression analyses with adjustments for relevant sociodemographic, health-, and cancer-related variables.

Results The final sample consisted of 1307 BCSs with a mean age of 52 years at diagnosis. Fifty-two percent of the BCSs were sexually inactive. Lack of interest was the most common reason for sexual inactivity. Treatment with aromatase inhibitor (OR 1.73, 95% CI 1.23, 2.43) and poor body image (OR 0.99, 95% CI 0.99, 0.995) were associated with sexual inactivity. Among sexually active BCSs, depression (B − 1.04, 95% CI − 2.10, − 0.02) and physical inactivity (B − 0.61, 95% CI − 1.21, − 0.02) were inversely related to sexual pleasure. Treatment with aromatase inhibitor (B 0.61, 95% CI 0.20, 1.01), sleep problems (B 0.37, 95% CI 0.04, 0.70), breast symptoms (B 0.01, 95% CI 0.003, 0.02), and chronic fatigue (B 0.43, 95% CI 0.05, 0.81) were associated with sexual discomfort. Chemotherapy (OR 1.91, 95% CI 1.23, 2.97), current endocrine treatment (OR 1.98, 95% CI 1.21, 3.25), and poor body image (OR 0.98, 95% CI 0.98, 0.99) were associated with less sexual activity at present compared to before breast cancer.

Conclusion Treatment with aromatase inhibitor seems to affect sexual health even beyond discontinuation. Several common late effects were associated with sexual inactivity and reduced sexual functioning. To identify BCSs at risk of sexual dysfunction, special attention should be paid to patients treated with aromatase inhibitor or suffering from these late effects.

Keywords Sexual function · Breast cancer survivorship · Late effects · Aromatase inhibitor

Introduction

Due to advances in diagnostics and treatment, the five-year relative survival rate for early-stage breast cancer (BC) has surpassed 90% in the Western world [1, 2]. The number of long-term breast cancer survivors (BCSs) (i.e., more than five years since diagnosis) is steadily increasing, and research concerning different aspects of survivorship care is of considerable interest.

Sexual health, defined as a state of physical, emotional, mental, and social well-being in relation to sexuality [3], is an important aspect of quality of life [4, 5]. Female sexual dysfunction includes lack of sexual interest and arousal,

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inability to achieve orgasm, and pain during intercourse [6]. Reasons for sexual dysfunction are multifactorial, including biological, psychological, interpersonal, and sociocultural factors [7].

In the general female population the prevalence of sexual dysfunction is estimated at 40–50% based on a consensus statement [8]. BCSs face challenges related to BC treatment and to late effects of different treatment modalities that may further negatively affect their sexual health. BC treatment is often intensive, including combinations of surgery, radiotherapy, and systemic therapies. Surgery and radiotherapy may result in physical changes such as loss of erogenous zones or scarring and in psychological challenges, such as altered body image [9, 10]. Chemotherapy-induced premature menopause or estrogen deprivation therapy may affect sexual health both directly through the effects on genital tissues and indirectly as troublesome vasomotor symptoms and sleep problems [11]. In the post-treatment phase, many BCSs struggle with late effects, such as chronic fatigue (CF) and persistent mental distress [12], which also may affect their sexual health in a negative way. Combined, BCSs represent a particularly vulnerable group with regards to impaired sexual health.

Sexual dysfunction is frequently reported among BCSs with prevalence of 73% in a recent meta-analysis [13]. Prevalence estimates differ, however, widely across studies from 27% [14] to 93% [15], primarily reflecting methodological differences. Most studies focus on sexual health during the first few years after BC diagnosis [15–19] and therefore research-based knowledge concerning sexual health among long-term BCSs is limited [20–24]. Furthermore, how different BC treatments (surgery, chemotherapy, and endocrine therapy) contribute to sexual dysfunction at long term is still unclear [5, 24–28].

In order to improve the quality of survivorship care in long-term BCSs, these knowledge gaps need to be addressed. An important step in that direction is to identify factors associated with poor sexual health, as such information may aid clinicians dealing with this growing survivor population.

The aim of this study was twofold; firstly, to describe different aspects of sexual health in a nationwide sample of long-term BCSs by assessing the prevalence and reasons for sexual inactivity and secondly, to explore factors associated with sexual inactivity and reduced sexual functioning.

Materials and methods

Study population

This study is part of the SWEET study (**s**urvivorship **w**ork-**s**exual h**e**al**t**h-study), a cross-sectional questionnaire study examining work life and sexual health among Norwegian long-term BCSs. All women diagnosed with BC stage I–III in 2011 or 2012 at the age of 20–65 years were identified by the Cancer Registry of Norway (CRN). CRN is based on mandatory reporting and has, as from when it was established in 1951, close to complete registration of all new cancer cases in Norway [29]. To be included in the study, women had to be free of pre- or post-malignancies (except non-melanoma skin cancer and ductal carcinoma in situ). Invitation was mailed to 2803 BCSs during December 2019. One reminder was sent to non-responders ($n = 1684$) in February 2020.

Primary outcomes

The Sexual Activity Questionnaire (SAQ) [30] was used to assess the prevalence of sexual inactivity, reasons for sexual inactivity, and different aspects of sexual functioning among the sexually active BCSs. The SAQ is reported to have good psychometric properties in the general population [31] and has been used in several BC-specific settings [5, 20, 23, 32].

The first part of the SAQ assesses whether women are sexually active. Sexually active is defined as being sexually engaged with a partner. In the second part eight reasons for eventual sexual inactivity are listed, and the sexually inactive women tick the reasons that apply to them. The third part measures sexual functioning (SAQ-F) during the last month among sexually active women across four subscales: pleasure (SAQ-P), discomfort (SAQ-D), habit (SAQ-H), and tiredness. SAQ-H was modified from "How did the frequency of sexual activity compare with what is usual for you?" to "How often are you engaged in sexual activity compared to before the BC diagnosis?" Responses to the SAQ-F items are scored on a 4-point scale ranging from 0 to 3 and summarized within each subscale. A higher sum score indicates greater pleasure, more discomfort, more sexual activity, and more tiredness. The SAQ-P consists of six items with sum score ranging from 0 to 18. The SAQ-D consists of two items with sum score ranging from 0 to 6. The SAQ-H and tiredness-scale consist of one item each with sum score from 0 to 3. Cronbach's alpha for SAQ-F was 0.81.

Explanatory variables

Socio-demographic information was self-reported and included age at survey, living with a partner or not, living with children < 18 years or not, educational level (≤ 12 years/ > 12 years), and paid work status (full-time work, part-time work, self-employment, and workers on sick leave) versus not (disability pension, retirement) at survey.

Cancer-related variables (BC stage, hormone receptor-, and human epidermal growth factor receptor 2 (HER2) status), age at diagnosis, and type of surgery were obtained from the CRN. Information on chemotherapy, radiation

therapy, and endocrine therapy (tamoxifen, aromatase inhibitor (AI)) was based on self-report.

The presence of self-reported somatic comorbidity included 17 questions on major somatic conditions (cardiovascular, pulmonary, thyroid, kidney, gastro-intestinal-, or rheumatic disease, diabetes, arthrosis, muscle/joint pain, and epilepsy). Affirmative responses were categorized into no comorbid condition, 1–2 or ≥ 3 comorbid conditions.

Sleep problems were defined as more than three episodes per week of difficulty falling asleep and/or waking up too early without going back to sleep for the past three months [33].

Pain was assessed using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC-QLQ C30 version 3) [34], while breast symptoms and body image (BI) were assessed by the EORTC-QLQ breast cancer-specific module—BR23 [35]. Items are rated from 1 (not at all) to 4 (very much) and then transformed to 0–100 scales according to manuals. Higher scores correspond to more pain, more breast symptoms, and better BI.

The Fatigue Questionnaire (FQ) [36] measures fatigue symptoms during the past month through eleven items; seven on physical and four on mental fatigue. Responses are rated from 0 (less than usual) to 3 (much more than usual) and summarized, yielding sum scores from 0 to 33. A higher score indicates more fatigue. Cases with CF were identified by a dichotomized score for each response alternative, resulting in sum scores from 0 to 11. CF was defined as a sum score ≥ 4 with duration six months or more [37]. Cronbach's alpha was 0.93 for total fatigue.

Height and weight were self-reported. Obesity was defined as body mass index (BMI) ≥ 30 kg/m^2 [38].

"Physically inactive" was defined as not meeting the public guidelines of ≥ 150 min moderate-intensity physical activity or ≥ 75 min of high-intensity physical activity per week or an equivalent combination of moderate- and high-intensity physical activity per week [39], using a modified version of the Godin Leisure Time Questionnaire [40].

Anxiety was assessed by the General Anxiety Disorder 7-item scale (GAD-7) covering the last two weeks. All items are rated from 0 (not at all) to 3 (nearly every day) resulting in sum scores from 0 to 21. The presence of generalized anxiety disorder was defined as a sum score ≥ 10 [41]. Cronbach's alpha was 0.87.

Depression was measured by The Patient Health Questionnaire-9 (PHQ-9) assessing symptom severity during the past two weeks by nine items rated from 0 (not at all) to 3 (nearly every day) resulting in sum scores from 0 to 27. Major depressive episode was defined as a sum score ≥ 10 [42]. Cronbach's alpha was 0.85.

Statistical analysis

Missing data were handled according to the respective manuals. When at least 50% of the items had been completed, mean imputation procedures were performed for the EORTC-QLQ C 30 and BR 23, the GAD-7, and within each subscale for the FQ. For the PHQ-9 mean imputation procedure was performed if no more than two items were missing. For the subscales of the SAQ-F, responders with missing items were excluded from the analyses.

Descriptive statistics are presented as frequencies and proportions for categorical data, and as mean and standard deviation (SD) for continuous data. Comparisons of sexually active and inactive BCSs were performed by independent sample t-tests and chi square tests as appropriate.

Factors associated with sexual inactivity were identified using logistic regression analyses, while factors associated with SAQ-P, SAQ-D, and tiredness were identified using linear regression analyses.

Due to a highly skewed distribution of SAQ-H, this variable was dichotomized into "less sexual activity now compared to before BC" versus "same/some more/much more sexual activity compared to before BC" and analyzed using logistic regression analyses.

Both univariate and multivariable regression analyses were performed. Variables with p value < 0.20 in the univariate analyses were included in the multivariable models. Age at diagnosis and living with children under 18 years were omitted due to high correlations with age at survey, but otherwise no multicollinearity was observed. Due to the large sample size, no backward elimination was performed to avoid exclusion of important factors associated with sexual health. The assumption of linearity was fulfilled for all the continuous variables.

Results were presented as beta coefficients (B) for linear regression and odds ratio (OR) for logistic regression analyses with accompanying 95% confidence intervals (CI). p values < 0.05 were considered statistically significant.

To explore potential selection bias of our sample, we compared registry information of responders versus non-responders.

All analyses were performed using IBM SPSS statistics version 26.0 (Armonk, NY).

Results

Patient characteristics

Of the 2803 BCSs invited, 1361 returned the questionnaire (49%). We excluded six BCSs with either incomplete consent or self-reported BC recurrence, in addition to 48 BCSs

with incomplete information on sexual activity, resulting in a final sample of 1307 women.

Mean age at diagnosis was 51.7 (SD 8.6) years and 59.7 (SD 8.7) years at survey. Most participants lived with a partner (74%) and had been treated for BC stage I or II (81%) with breast-conserving therapy (59%), radiotherapy (80%), endocrine therapy (65%), and chemotherapy (69%). Twenty-three percent reported current use of endocrine therapy (Table 1).

The sexually inactive BCSs

About half (52%) of the BCSs were sexually inactive. Prevalence rate was highest among the oldest BCSs, ranging from 32% among those aged 30–39 years, 56% among those aged 60–69 years, and 67% in the oldest age group (70–74 years). Older age (OR 1.05, 95% CI 1.02, 1.07), living without a partner (OR 5.19, 95% CI 3.75, 7.19), and treatment with AI (OR 1.73, 95% CI 1.23, 2.43) were positively associated with sexual inactivity in multivariable analyses. Better BI was negatively associated with sexual inactivity (OR 0.99, 95% CI 0.99, 0.995) (Table 2).

The most common reasons for sexual inactivity were lack of interest (35%), lack of partner (27%), being too tired (19%), and having a physical problem (18%). Partner issues were reported by 25% (Fig. 1).

Sexual functioning among the sexually active BCSs (i.e., sexually engaged with a partner)

Among sexually active BCSs, 555 (89%) lived with a partner, while 72(11%) did not.

Mean SAQ-P score was 10.8 (SD = 3.7). Living without a partner was positively associated with sexual pleasure (B 1.68, 95% CI 0.78, 2.58), while physical inactivity (B − 0.61, 95% CI − 1.21, − 0.02) and depression (B − 1.04, 95% CI − 2.10, − 0.02) were negatively associated with sexual pleasure in multivariable analyses (Table 3).

Mean SAQ-D score was 2.2 (SD = 1.9). Treatment with AI (B 0.61, 95% CI 0.20, 1.01), sleep problems (B 0.37, 95% CI 0.04, 0.70), breast symptoms (B 0.01, 95% CI 0.003, 0.02), and CF (B 0.43, 95% CI 0.05, 0.81) were positively associated with sexual discomfort, while living without a partner (B − 0.87, 95% CI − 1.33, − 0.41) and obesity (B − 0.63, 95% CI − 1.07, − 0.19) were negatively associated with discomfort in multivariable analyses (Table 3).

Mean tiredness score was 1.2 (SD = 0.9). CF (B 0.33, 95% CI 0.16, 0.50) was positively associated with tiredness related to sex, while older age (B − 0.02, 95% CI − 0.03, − 0.004) and living without a partner (B − 0.38, 95% CI − 0.59, − 0.16) were negatively associated with tiredness in multivariable analyses (Table 3).

Fifty-four percent of the sexually active BCSs reported lower frequency of sexual activity at survey compared to before BC. Chemotherapy (OR 1.91, 95% CI 1.23, 2.97) and current endocrine therapy (OR 1.98, 95% CI 1.21, 3.25) were positively associated with less sexual activity, while living without a partner (OR 0.40, 95% CI 0.23, 0.69) and a better BI (OR 0.98, 95% CI 0.98, 0.99) were negatively associated with less sexual activity after BC in multivariable analyses (Table 3).

As shown in Table 3, explained variance in the models varied from 0.059 to 0.158.

Attrition analysis

Information about non-responders ($n = 1448$) was limited to cancer-related information obtained from the CRN. Responders yielded similar results as non-responders for all variables except for age at diagnosis (51.7 years versus 53.2 years, $p < 0.001$), HER2 positivity (20% versus 15%, $p < 0.001$), and mean value of the proliferation marker Ki67 (31 versus 27, $p < 0.001$).

Discussion

Approximately half of the BCSs were sexually inactive eight years after diagnosis, with highest prevalence among the oldest. Lack of interest was the most common reason for sexual inactivity. AI therapy was the most important treatment modality negatively affecting sexual health. Several individual and potential modifiable factors such as a poor BI, CF, depression, sleep problems, breast symptoms, and physical inactivity were associated with different aspects of sexual functioning.

As stated, studies concerning sexual activity and functioning in long-term BCSs are few. Only two other studies report prevalence rates of sexual inactivity and these rates are in line with our findings [21, 23]. Lack of interest was the most common reported reason for sexual inactivity both in our study and in another study using the SAQ among BCSs three years after diagnosis [5].

Reported prevalence rates of sexual inactivity in the general population are higher in older than younger age groups [43]. Normative data for the SAQ from a random sample of Norwegian women showed that 52% in the age group 56–69 years were sexually inactive [31]. In our study, the prevalence rate of sexually inactive BCSs in this age group was quite similar (54%). However, among those aged 35–44 years, the proportion of sexually inactive women was considerably higher among the BCSs in our study (33%) compared to the normative sample (16%). This finding is supported by another study of long-term BCSs where pre/peri-menopausal BCSs were less likely to be sexually active

Table 1 Characteristics of the total sample and the subgroups of sexually active and inactive breast cancer survivors

Variables	Total sample $n=1307$	Sexually active $n=627$	Sexually inactive $n=680$	p value
Socio-demographic variables				
Age at diagnosis (years), mean (SD)	51.7 (8.6)	50.0 (8.7)	53.3 (8.2)	**< 0.001**
Age at survey (years), mean (SD)	59.7 (8.7)	58.0 (8.8)	61.3 (8.3)	**< 0.001**
Living with spouse/partner, *n* (%)	966 (74)	555 (89)	411 (60)	**< 0.001**
Living with children < 18 years, *n* (%)	199 (15)	118 (19)	81 (12)	**0.001**
Education > 12 years, *n* (%)	671 (52)	354 (57)	317 (47)	**0.001**
Paid work at survey, *n* (%)	545 (43)	308 (50)	237 (36)	**< 0.001**
Cancer-related variables				
Stage[a]				0.92
I, *n* (%)	583 (45)	282 (45)	301 (44)	
II, *n* (%)	470 (36)	228 (36)	242 (36)	
III, *n* (%)	105 (8)	49 (8)	56 (8)	
Missing	*149*	*68*	*81*	
Hormone receptor positive, *n* (%)	1111 (85)	523 (84)	588 (87)	0.12
HER-2[b] positive, *n* (%)	241 (18)	117 (19)	124 (18)	0.98
Triple negative, *n* (%)	112 (9)	60 (10)	52 (8)	0.22
Surgery				0.62
Mastectomy, *n* (%)	537 (41)	262 (42)	275 (40)	
Breast-conserving therapy, *n* (%)	770 (59)	365 (58)	405 (60)	
Chemotherapy, *n* (%)	895 (69)	429 (68)	466 (69)	0.97
Radiotherapy, *n* (%)	1047 (80)	504 (80)	543 (80)	0.81
Endocrine treatment (ET)				**< 0.001**
No ET, *n* (%)	456 (35)	227 (36)	229 (34)	
Aromatase inhibitor, *n* (%)	404 (31)	159 (25)	245 (36)	
Tamoxifen, *n* (%)	378 (29)	214 (34)	164 (24)	
Unknown type, *n* (%)	69 (5)	27 (4)	42(6)	
ET at present, *n* (%)	295 (23)	157 (25)	138 (20)	**0.04**
Health variables				
Somatic comorbidity				**< 0.001**
No condition, *n* (%)	281 (22)	166 (27)	115 (17)	
1–2 condition(s), *n* (%)	706 (54)	344 (55)	362 (54)	
≥ 3 conditions, *n* (%)	313 (24)	114 (18)	199 (29)	
Missing	*7*	*3*	*4*	
Sleep problems, *n* (%)	571 (44)	243 (39)	328 (49)	**< 0.001**
Pain[c], mean (SD)	28.0 (29.3)	24.4 (27.8)	31.4 (30.2)	**< 0.001**
Breast symptoms[c], mean (SD)	16.0 (19.0)	14.3 (17.6)	17.5 (20.0)	**0.002**
Body image[c], mean (SD)	75.8 (26.2)	79.0 (24.7)	72.9 (27.2)	**< 0.001**
Chronic fatigue, *n* (%)	420 (33)	177 (29)	243 (37)	**0.002**
Obesity[d], *n* (%)	234 (18)	91 (15)	143 (22)	**0.001**
Physically inactive, *n* (%)	693 (53)	307 (49)	386 (57)	**< 0.001**
Anxiety disorder, *n* (%)	94 (7)	35 (6)	59 (9)	**0.03**
Major depression, *n* (%)	238 (19)	87 (14)	151 (23)	**< 0.001**

Bold statistically significant ($p < 0.05$)

SD standard deviation

[a]Based on TNM

[b]HER-2 = human epidermal growth factor receptor 2

[c]Scale 0–100 (a higher score corresponds to more pain and breast symptoms and a better body image)

[d]Body mass index ≥ 30 kg/m^2

Table 2 Factors associated with sexual inactivity in breast cancer survivors (sexual activity as reference)

Variables	Bivariate analysis		Multivariable analysis		
	OR	95% CI	OR	95% CI	*p* value
Age at survey (years)	**1.05**	**1.03, 1.06**	**1.05**	**1.02, 1.07**	**< 0.001**
Not living with partner	**5.05**	**3.78, 6.74**	**5.19**	**3.75, 7.19**	**< 0.001**
Education ≤ 12 years	**1.47**	**1.18, 1.83**	1.08	0.83, 1.41	0.56
No paid work at survey	**1.81**	**1.45, 2.27**	0.93	0.68, 1.26	0.62
Mastectomy (BCT = ref)	0.95	0.76, 1.18	–	–	–
Chemotherapy	1.01	0.80, 1.27	–	–	–
Radiotherapy	0.97	0.74, 1.27	–	–	–
Endocrine treatment (ET)					
No ET (ref)	–	–	–	–	–
Aromatase inhibitor	**1.53**	**1.17, 2.00**	**1.73**	**1.23, 2.43**	**0.002**
Tamoxifen	0.76	0.58, 1.00	1.03	0.71, 1.51	0.87
Unknown type	1.54	0.92, 2.59	1.24	0.66, 2.33	0.50
ET at present	**0.76**	**0.59, 0.99**	1.09	0.76, 1.56	0.64
Somatic comorbidity					
No disease (ref)	–	–	–	–	–
1–2 comorbid disease(s)	**1.52**	**1.15, 2.01**	1.22	0.88, 1.71	0.24
≥ 3 comorbid diseases	**2.52**	**1.81, 3.51**	1.29	0.83, 2.00	0.26
Sleep problems	**1.49**	**1.20, 1.86**	1.15	0.87, 1.52	0.32
Pain[a]	**1.01**	**1.01, 1.01**	1.00	1.00, 1.01	0.74
Breast symptoms[a]	**1.01**	**1.00, 1.02**	1.00	1.00, 1.01	0.46
Body image[a]	**0.99**	**0.99, 0.995**	**0.99**	**0.99, 0.995**	**0.003**
Chronic fatigue	**1.44**	**1.14, 1.82**	1.30	0.95, 1.79	0.10
Obesity	**1.60**	**1.20, 2.13**	1.30	0.91, 1.85	0.15
Physically inactive	**1.58**	**1.26, 1.98**	1.21	0.93, 1.58	0.16
Anxiety disorder	**1.62**	**1.05, 2.50**	1.13	0.65, 1.99	0.66
Major depression	**1.82**	**1.36, 2.43**	1.20	0.79, 1.83	0.39

Bold statistically significant ($p < 0.05$)

OR odds ratio, *CI* confidence interval, *BCT* breast-conserving therapy

[a]Scale 0–100 (a higher score corresponds to more pain and breast symptoms and a better body image).

compared to corresponding controls, while no significant difference in sexual activity was observed between the postmenopausal groups [23]. Reasons for sexual inactivity were different in the Norwegian normative sample compared to in our study. In the normative sample the most common reason for sexual inactivity was lack of partner (48%), while only 19% reported that sexual inactivity was due to lack of interest [31].

AI therapy was associated with both sexual inactivity and more sexual discomfort in our study. Vaginal dryness, dyspareunia, and reduced libido are common adverse effects during AI treatment [44, 45] and in the first years after discontinuation [46]. Knowledge concerning sexual activity and functioning in long-term BCSs after discontinuation of adjuvant AI is missing. In our study, 78% of the BCSs treated with AI had discontinued the treatment. Thus our results are relevant for what happens after the adjuvant treatment period. Soldera et al., exploring sexual health in BCSs 12.5 years after diagnosis, found no significant differences in sexual activity according to former receipt of adjuvant endocrine treatment [23]. In that study the participants had used tamoxifen, which to a lesser extent cause vaginal dryness and dyspareunia compared to AI [44]. Davis et al. compared post-menopausal symptoms in long-term BCSs with controls and found worse sexual functioning in BCSs [22]. As BCSs treated with chemotherapy and still on endocrine treatment were excluded in that sub-analysis, the authors concluded that severe menopausal symptoms may persist even after cessation of endocrine treatment. Our findings support this viewpoint.

In our study, chemotherapy and current use of endocrine therapy were associated with less sexual activity eight years after diagnosis compared to before BC diagnosis. A larger proportion of BCSs < 55 years compared to BCSs ≥ 55 years at diagnosis received adjuvant chemotherapy in the present study, indicating that chemotherapy-induced premature menopause may be a possible explanation. BCSs still on adjuvant endocrine treatment are younger, adding to our findings that the youngest BCSs are especially vulnerable to sexual challenges after BC.

A poorer BI was associated with sexual inactivity and reduced sexual activity compared to before BC, which is well known from previous studies [18, 47, 48]. Depression was associated with lower sexual pleasure. In the general population there is a known bidirectional relation between depression and sexual dysfunction [49] and former studies of BCSs have showed an association with depression and lower sexual interest and desire [25, 32]. As expected, CF was associated with sexual tiredness. CF was also associated with more sexual discomfort, as were sleep problems and breast symptoms. We have found only one prior study reporting a relation between sexual dysfunction and fatigue in BCSs, and this study examined young BCSs one year after diagnosis [17]. Another study examining BCSs on average three years after diagnosis showed a relation between sleep problems and sexual discomfort, but not between fatigue and sexual functioning [50].

Physical inactivity was associated with lower sexual pleasure. A recent review stated that physical activity improves menopausal symptoms in the general female population, and indirectly physical activity may improve sexual

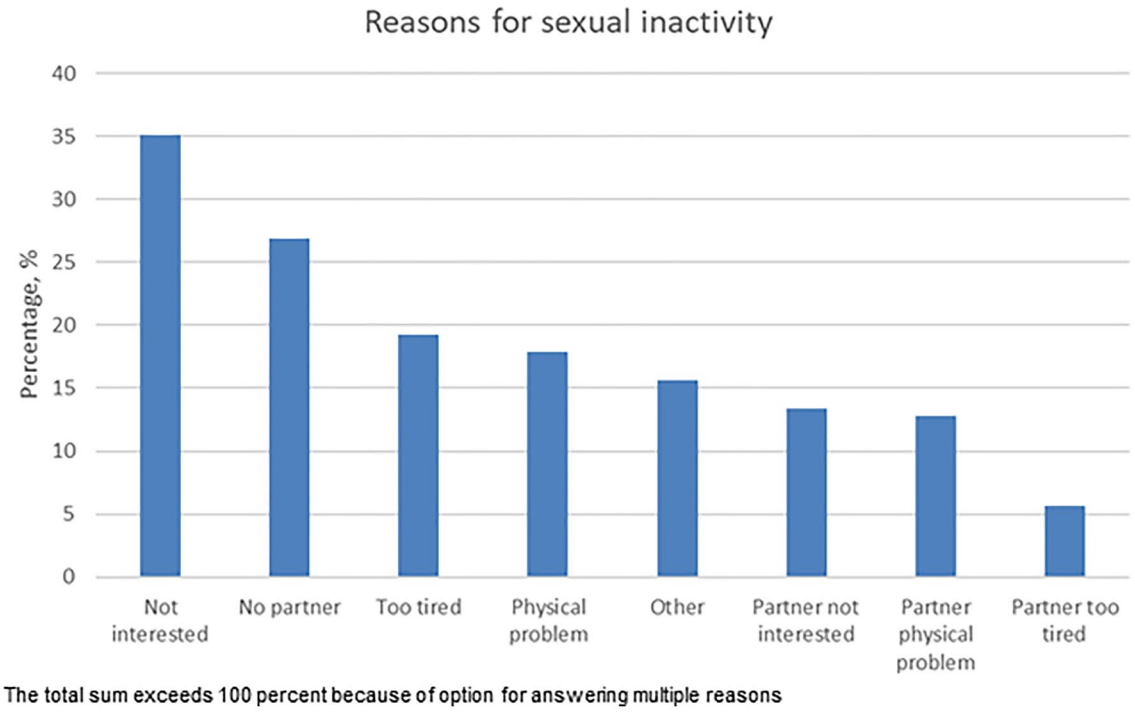

Fig. 1 Reasons for being sexually inactive in sexually inactive breast cancer survivors

functioning [51]. Results from a pilot study randomizing BCSs with menopausal symptoms to a lifestyle program including physical activity or standard care support this statement, demonstrating clinically significant reduction in both menopausal symptoms and sexual dysfunction in the intervention group [52]. Another study, exploring the associations of BMI, physical activity, and sexual dysfunction in BCSs, found that regular physical activity was associated with better sexual desire [53]. Further, physical activity may alleviate symptoms of depression [54], fatigue [55], and sleep problems [56], with the potential of indirectly improving sexual functioning.

Obesity was somewhat surprisingly associated with less sexual discomfort. This relation has been shown in one former study of BCSs [57]. Theoretically this finding may be explained by increased levels of circulating estrogen due to excessive aromatization activity in the adipose tissue [58]. Even though this theory was not verified in the above-mentioned study [57], it will be interesting to explore further in upcoming studies.

Living without a partner was as expected associated with sexual inactivity. More surprisingly, the sexually active women not living with a partner reported better sexual functioning across all domains than those living partnered. Similar associations have been shown in a study of BCSs four years after diagnosis. In that study, BCSs who had a partner they did not live with, had fewer problems related to desire, excitement, and lubrication compared to those living with a partner [26]. Further, a study of midlife women in the general population found that being partnered was associated with hypoactive sexual desire dysfunction.[59]. As only 72 of the sexually active BCSs in our study lived without a partner, these findings were not further explored.

Strengths and limitations

This study is based on a nationwide sample of all Norwegian BCSs diagnosed in 2011 or 2012 registered in the CRN. The response rate was 49%, which is considered acceptable and comparable to other large-scale surveys on long-term survivors in Norway [60, 61] and cross-sectional studies on sexual health [5, 28]. Questionnaires with established psychometric properties were used. This is the first study to explore sexual health in long-term BCSs treated with modern BC therapies separating between different endocrine treatments. Few other studies have included both sociodemographic, treatment related, somatic-, and mental health-related variables to explore sexual outcomes in this population.

There are several limitations that need to be considered. Cross-sectional design precludes conclusions on causality. Furthermore, the study did not include a control group. Some findings are compared to normative Norwegian data, but comparisons with a matched control group from same time period would have strengthened the study. Lack of information on menopausal status is a limitation, as menopausal status obviously affect sexual

Table 3 Factors associated with sexual functioning (SAQ-F) subscales in sexually active breast cancer survivors

Variables	Pleasure (SAQ-P)[a] Linear regression		Discomfort (SAQ-D)[b] Linear regression		Tiredness[c] Linear regression		Habit (SAQ-H)[d,e] Logistic regression	
	B	95% CI	B	95% CI	B	95% CI	OR	95% CI
Age at survey (years)	–	–	–	–	**− 0.02**	**− 0.03, − 0.004**	1.00	0.97, 1.03
Not living with partner	**1.68**	**0.78, 2.58**	**− 0.87**	**− 1.33, − 0.41**	**− 0.38**	**− 0.59, − 0.16**	**0.40**	**0.23, 0.69**
Education ≤ 12 years	–	–	–	–	–	–	–	–
No paid work at survey	–	–	–	–	–	–	–	–
Mastectomy (BCT = ref)	− 0.04	− 0.78, 0.71	0.20	− 1.18, 0.59	0.04	− 0.14, 0.22	1.10	0.74, 1.62
Chemotherapy	− 0.33	− 1.05, 0.40	0.19	− 0.18, 0.57	0.13	− 0.05, 0.31	**1.91**	**1.23, 2.97**
Radiotherapy	0.69	− 0.18, 1.55	− 0.28	− 0.72, 0.17	− 0.05	− 0.25, 0.15	–	–
Endocrine treatment (ET)								
No ET (ref)	–		–		–		–	
Aromatase inhibitor	− 0.63	− 1.42, 0.16	**0.61**	**0.20, 1.01**	0.11	− 0.08, 0.31	1.01	0.62, 1.64
Tamoxifen	0.06	− 0.78, 0.89	0.07	− 0.36, 0.50	0.05	− 0.15, 0.24	0.65	0.40, 1.08
Unknown type	0.74	− 0.76, 2.23	− 0.30	− 1.08, 0.48	− 0.04	− 0.40, 0.31	0.96	0.39, 2.37
ET at present	− 0.38	− 1.19, 0.43	0.28	− 0.13, 0.69	− 0.01	− 0.19, 0.18	**1.98**	**1.21, 3.25**
Somatic comorbidity								
No disease (ref)	–	–	–		–		–	
1–2 comorbid disease(s)	–	–	0.08	− 0.29, 0.45	0.08	− 0.09, 0.24	0.85	0.56, 1.29
≥ 3 comorbid diseases	–	–	0.35	− 0.18, 0.88	0.01	− 0.23, 0.25	1.49	0.80, 2.78
Sleep problems	− 0.33	− 0.97, 0.32	**0.37**	**0.04, 0.70**	0.04	− 0.12, 0.19	1.02	0.69, 1.50
Pain[f]	0.003	− 0.01, 0.02	0.003	− 0.004, 0.01	0.003	0.000, 0.006	1.00	0.99, 1.01
Breast symptoms[f]	–	–	**0.01**	**0.003, 0.02**	− 0.001	− 0.006, 0.003	1.00	0.99, 1.01
Body image[f]	0.001	− 0.01, 0.02	− 0.01	− 0.01, 0.003	− 0.002	− 0.005, 0.001	**0.98**	**0.98, 0.99**
Chronic fatigue	− 0.56	− 1.30, 0.17	**0.43**	**0.05, 0.81**	**0.33**	**0.16, 0.50**	1.54	0.99, 2.40
Obesity	–	–	**− 0.63**	**− 1.07, − 0.19**	–	–	–	–
Physically inactive	**− 0.61**	**− 1.21, − 0.02**	–	–	–	–	–	–
Anxiety disorder	− 0.34	− 1.70, 1.03	0.26	− 0.46, 0.97	0.18	− 0.14, 0.51	0.87	0.36, 2.12
Major depression	**− 1.04**	**− 2.10, − 0.02**	− 0.44	− 0.97, 0.09	0.21	− 0.03, 0.45	1.01	0.53, 1.93

Results from multivariable analyses adjusted for all variables listed. Statistically significant ($p < 0.05$) associations are indicated in bold

B beta coefficient, *CI* confidence interval, *OR* odds ratio, *BCT* breast-conserving therapy

[a]Adjusted R^2 0.059

[b]Adjusted R^2 0.125

[c]Adjusted R^2 0.158

[d]Nagelkerke R^2 0.174

[e]SAQ-H dichotomized into less vs same/more (reference) sexual activity after breast cancer diagnosis

[f]Scale 0–100 (a higher score corresponds to more pain and breast symptoms and a better body image)

functioning. On the other hand, adjustments for menopausal status may have disguised the effect of chemotherapy-induced menopause and endocrine deprivation therapy in premenopausal BCSs. Sexual activity and function were measured with the SAQ which has a rather narrow definition of sexually activity restricted to partnered sex and do not capture all elements of sexual activities. We cannot rule out that selection bias exists as we only had access to cancer-related variables for the non-responders. Given that a larger proportion of responders were HER2 positive and the mean Ki67 was higher, a higher proportion of responders may have received chemotherapy. Many variables in this study were based on patient-reported outcome measures, with the inherent risk of recall bias. Additionally, questionnaires concerning sexual health issues have a special risk of reporting bias [62]. BCSs > 65 years at diagnosis and BCSs with relapse or metastatic disease were not invited in the study. Thus, the results cannot automatically be generalized to the oldest BCSs or to BCSs with advanced disease.

Regression analyses showed a lower degree of explained variance for sexual pleasure compared to the other domains of sexual functioning. This could partly be due to the simplified model (where all variables were assumed to be independent), but could also indicate that other factors not included in the model may be important. Unfortunately, we had no information about the length, quality, and satisfaction of couple relationships or any sexual problems experienced by the partner, which are important predictors of sexual health in BCSs [14, 25, 32, 50, 63].

Conclusion

Addressing sexual health issues should be a part of the standard follow-up of BCSs, even several years after treatment cessation. Specific attention should be paid to younger BCSs and those treated with AI. BCSs with gynecological symptoms should be offered treatment, and if using adjuvant AI, a switch to tamoxifen may be discussed. A poor body image, physical inactivity, depression, sleep problems, breast symptoms, and chronic fatigue should be assessed and handled as factors that may improve sexual health.

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Availability of data All data are available at the National Advisory Unit for Late Effects after Cancer Treatment, Department of Oncology, Oslo University Hospital, the Radium Hospital, Oslo, Norway.

Declarations

Conflict of interest The authors declare no conflict of interest.

Ethical approval This study was approved by the Regional Committee for Medical Research Ethics (2018/2170), the Norwegian Cancer Registry, and the Data Protection Officer at Oslo University Hospital. All procedures were performed in accordance with the ethical standards of the national and institutional research committee and with the 1964 Declaration of Helsinki and its later amendments.

Informed consent Informed consent was obtained from all participants included in the study.

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EPIDEMIOLOGY

Sexual health in long-term breast cancer survivors: a comparison with female population controls from the HUNT study

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Abstract

Purpose Sexual health is an important aspect of quality of life. Knowledge concerning sexual health in long-term breast cancer survivors (BCSs) is limited. This study compared sexual health in BCSs 8 years after diagnosis with similarly aged controls and examined the impact of menopausal status at diagnosis and systemic breast cancer treatments on sexual health.

Methods Women aged 20–65 years when diagnosed with stage I–III breast cancer in 2011–2012 were identified by the Cancer Registry of Norway ($n = 2803$) and invited to participate in a nationwide survey. Controls were women from the Trøndelag Health Study (HUNT4). Sexual functioning and sexual enjoyment were measured by the EORTC QLQ-BR23 subscales scored from 0 to 100, and sexual discomfort by the Sexual Activity Questionnaire scored from 0 to 6. Linear regression analyses with adjustments for sociodemographic and health-related variables were performed to compare groups. Differences of ≥ 10% of range score were considered clinically significant.

Results The study samples consisted of 1241 BCSs and 17,751 controls. Sexual enjoyment was poorer (B − 13.1, 95%CI − 15.0, − 11.2) and discomfort higher (B 0.9, 95%CI 0.8, 1.0) among BCSs compared to controls, and larger differences were evident between premenopausal BCSs and controls (B − 17.3, 95%CI − 19.6, − 14.9 and B 1.2, 95%CI 1.0, 1.3, respectively). BCSs treated with both endocrine- and chemotherapy had lower sexual functioning (B − 11.9, 95%CI − 13.8, − 10.1), poorer sexual enjoyment (B − 18.1, 95%CI − 20.7, − 15.5), and more sexual discomfort (B 1.4, 95% 1.3, 1.6) than controls.

Conclusion Sexual health impairments are more common in BCSs 8 years after diagnosis compared to similar aged population controls. During follow-up, attention to such impairments, especially among women diagnosed at premenopausal age and treated with heavy systemic treatment, is warranted.

Keywords Breast cancer survivors · Sexual health · Sexual functioning · Sexual enjoyment · Sexual discomfort

Introduction

Breast cancer (BC) is the most frequent female cancer globally with an estimated 2.3 million new cases in 2020 [1]. The 5-year relative survival is steadily increasing and

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has surpassed 90 percent in several western countries [2, 3]. Consequently, the population of BC survivors (BCSs) is growing, making their quality of life a key outcome measure besides to survival [4, 5].

Sexual health, defined as a state of physical, emotional, mental and social well-being related to sexuality [6], is an important aspect of quality of life [7, 8]. Treatment for stage I–III BC is often intense including combinations of surgery, radiotherapy, and adjuvant systemic therapies (endocrine therapy, chemotherapy, and targeted therapy), which may have a negative impact on sexual health [8–10]. Studies have focused on various aspects of sexual health, like sexual activity, interest, enjoyment and discomfort, and reported that sexual health impairments are prevalent among BCSs both during treatment and during the first years after diagnosis [11–15]. However, it remains unclear if these sexual health impairments persist long-term (> 5 years after diagnosis), as data from this part of survivorship are scarce and results conflicting [16–19]. A recent study from our research group found that adjuvant treatment with aromatase inhibitors, extended endocrine treatment and adjuvant chemotherapy were associated with sexual health impairments also in long-term BCSs [20]. As in several prior studies, a limitation with our study was the lack of a general population control sample.

In the general population, increasing age is associated with reduced sexual activity and increasing sexual complaints [21, 22]. In BC populations, also women at a younger age seem to be at high-risk of sexual health impairments [23, 24]. This may be due to troublesome estrogen deprivation symptoms caused by systemic adjuvant BC therapies. Several studies report that younger BCSs with chemotherapy-induced premature menopause are at special risk of such impairments the first years after diagnosis [13, 25]. Endocrine therapies also demonstrate a clear negative effect on sexual health the first 5 years after diagnosis [8, 11, 26, 27]. For most BC patients, the recommended duration of endocrine therapy is 5 years, but extended therapy for up to 10 years is an option for high-risk patients [28]. Consequently, a subgroup of patients may struggle with estrogen deprivation symptoms and sexual health impairments during the first decade after their BC diagnosis. This subgroup includes women of childbearing age where unimpaired sexual health may be especially important.

Given the scarce and inconclusive evidence of sexual health in long-term BCSs, there is a need for large-scale studies comparing sexual health among long-term BCSs to that of similarly aged population controls.

The aims of the present study were: (1) to compare sexual health among long-term BCSs to that of similarly aged female controls from a population-based sample, (2) to assess the impact of systemic BC treatments on sexual health, and (3) to examine if menopausal status at BC diagnosis influences sexual health.

Material and method

Breast cancer survivors

This study is part of the **S**urvivorship-**w**ork-s**e**xual-he**a**l**t**h (SWEET) study, a cross-sectional survey examining work life and sexual health among Norwegian long-term BCSs. All women diagnosed with BC stage I–III in 2011 or 2012 at the age of 20–65 years were identified by the Cancer Registry of Norway (CRN). CRN is based on mandatory reporting, and has close- to complete registration of all cancer cases in Norway [29]. To be included in SWEET, women had to be free of pre- or post- malignancies (except non-melanoma skin cancer and ductal carcinoma in situ). Invitation was mailed to 2803 BCSs in December 2019 and one reminder was sent to non-responders ($n = 1684$) in February 2020. The questionnaire was returned by 1361 BCSs (49% response rate). We excluded BCSs with either missing consent or self-reported BC recurrence ($n = 6$) and BCSs with missing data on sexual activity ($n = 114$), resulting in a final sample of 1241 BCSs. Characteristics of non-responders and attrition analysis of SWEET have previously been reported [20]. BCSs with missing data on sexual activity were older, fewer lived with a partner, and they had shorter education compared to the included BCSs (data not shown).

Population controls

SWEET participants were compared to similarly aged women participating in the fourth survey of the population-based Trøndelag Health Study (HUNT4) [30]. HUNT4 invited all adults in the Nord-Trøndelag region aged 20 years and above to an extensive health assessment during 2017–2019. Participants responded to questionnaires and attended clinical examinations. In total, 18,782 women in the age group relevant for this study (30–74 years) participated (52% of those invited). Due to missing data on sexual activity, 1031 women were excluded, resulting in a control group of 17,751 women. Controls with missing data on sexual activity were older, fewer lived with a partner, had shorter education, more somatic co-morbidity and less mental co-morbidity compared to the included controls (data not shown).

Sexual health measures in SWEET and HUNT4

The sexual health outcomes explored in this study were sexual functioning, sexual enjoyment, and sexual discomfort.

The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire BC-specific module (EORTC-BR23) [31] includes three items exploring sexual health during the past 4 weeks. Two items concerning sexual interest and activity assess sexual functioning, and one item assesses sexual enjoyment among those who are sexually active. Responses were rated from 1 (not at all) to 4 (very much) and transformed to a 0–100 scale according to the scoring manual [32]. Higher scores indicate better sexual functioning and sexual enjoyment. Sexually active women were defined as being sexually active (with or without intercourse) during the past 4 weeks.

Sexually active women also responded to two items from The Sexual Activity Questionnaire [33], assessing sexual discomfort during the past 4 weeks. Responses were rated from 0 (not at all) to 3 (very much) and summarized, yielding a sum score ranging from 0 to 6, where a higher score correspond to more sexual discomfort.

Covariates

Both in SWEET and HUNT4 sociodemographic information included age at survey, self-reported living arrangements (partner or not) and length of education ($\leq$ 12 years/ > 12 years).

Somatic comorbidities included a self-reported history of heart-, pulmonary-, thyroid-, kidney-, or rheumatic disease, cerebral stroke and/or diabetes, and were categorized into three; no comorbid condition, 1 or $\geq$ 2 comorbid conditions.

Mental co-morbidity was assessed by one question regarding help seeking for mental health problems (Yes/No).

Sleep problems were present when participants reported more than three episodes per week of difficulty falling asleep and/or waking up too early without going back to sleep (Yes/No). Recall time was the past 3 months [34].

Body mass index (BMI) was calculated from height and weight, self-reported in SWEET and from standardized measurements at the field stations in HUNT4.

Menopausal status

As information on menopausal status at diagnosis was unavailable in SWEET, we used age as a proxy. The estimated mean age of menopause in Norwegian women is 52.7 years [35]. In order to avoid misclassification of premenopausal women, postmenopausal status was defined as being $\geq$ 55 years.

Cancer-related information

In SWEET, age at diagnosis, BC stage, and surgical treatment were retrieved from the CRN. Information on adjuvant radiotherapy and on systemic adjuvant therapies was self-reported. Systemic treatment was categorized into no systemic treatment, endocrine therapy only, chemotherapy only, and endocrine- and chemotherapy.

Information on prior or present cancer among participants in HUNT4 was self-reported.

Statistical analysis

Descriptive statistics are presented as frequencies and proportions for categorical data, where missing data are given as a separate category. Continuous data are presented with mean and standard deviation.

The three outcome variables sexual functioning, sexual enjoyment and sexual discomfort, were compared between BCSs and controls using linear regression analyses. Two models were performed, the first with adjustments for the sociodemographic variables (age at survey, living with partner or not, education), and the second with additional adjustments for the health-related variables (somatic co-morbidity, mental co-morbidity, BMI and sleep problems). Further, the analyses were stratified by age to study the impact of pre-/postmenopausal age at diagnosis. When exploring the impact of systemic BC therapies on the sexual outcome variables, we only adjusted for the sociodemographic variables, as the health-related covariates may be considered as mediators. Results are presented as beta coefficients (B) with 95% confidence intervals (CI).

A clinically significant difference between the groups was defined as a mean score difference of $\geq$ 10% of range scores [36, 37], i.e., $\geq$ 10 scale points for sexual functioning and enjoyment and $\geq$ 0.6 for sexual discomfort.

Due to missing data in several of the covariates included in the analyses, multiple imputations procedures were performed. These analyses yielded similar results compared to the main results, and were therefore not presented.

Analyses were performed using IBM SPSS statistics version 28.0 (Armonk, NY) and Stata version 17 (StataCorp LLC, College Station, TX).

Results

Characteristics of BCSs and controls

Mean age of BCSs was 59 years at survey, and 8 years had passed since diagnosis. Most BCSs had been treated for BC stage I or II (80%) with breast conserving therapy (58%), radiotherapy (80%) and/or systemic treatment with both chemo- and endocrine therapy (54%). Sixty-two percent were premenopausal when diagnosed with BC. BCSs premenopausal at diagnosis had more advanced disease and higher treatment burden compared to BCSs who were postmenopausal at diagnosis (p-values < 0.001).

Table 1 Characteristics of breast cancer survivors (SWEET) and population controls (HUNT4)

	SWEET ($n=1241$)			HUNT4 ($n=17,751$)	p-value
Sociodemographic variables					
Age at survey, mean (SD)	59.4 (8.6)			53.9 (12.0)	< 0.001
Living with a partner, *n* (%)	931 (75.0)			14,121 (79.6)	< 0.001
Education > 12 years, *n* (%)	658 (53.0)			8406 (47.4)	< 0.001
Missing	*11 (0.9)*			*56 (0.3)*	*
Health variables					
Somatic co-morbidity[a], *n* (%)					0.29
No condition	753 (60.7)			10,730 (60.4)	
1 condition	330 (26.6)			4284 (24.1)	
≥ 2 or more conditions	101 (8.1)			1286 (7.2)	
Missing	*57 (4.6)*			1451 (8.2)	
Mental co-morbidity, *n* (%)	352 (28.4)			3775 (21.3)	< 0.001
Missing	*25 (2.0)*			*550 (3.1)*	
Body mass index, (kg/m^2), mean (SD)	26.2 (4.4)			27.2 (5.0)	< 0.001
Missing, n (%)	*18 (1.5)*			68 (0.4)	
Sleep problems, *n* (%)	547 (44.1)			3830 (21.6)	< 0.001
Missing	*15 (1.2)*			*482 (2.7)*	
Cancer-related variables	In total ($n=1241$)	Premenopausal at diagnosis[b] ($n=769$)	Postmenopausal at diagnosis[c] ($n=472$)		
Age at diagnosis, mean (SD)	51.4 (8.6)	46.1 (6.3)	60.0 (3.1)	–	–
Time since diagnosis, mean (SD)	8.0 (0.7)	8.0 (0.7)	8.1 (0.7)	–	–
Stage, *n* (%)					
I	541 (43.6)	276 (35.9)	265 (56.1)	–	–
II	450 (36.3)	309 (40.2)	141 (29.9)	–	–
III	103 (8.3)	69 (9.0)	34 (7.2)	–	–
Missing	*147 (11.8)*	*115 (15.0)*	*32 (6.8)*		
Breast conserving surgery, *n* (%)	718 (57.9)	381 (49.5)	337 (71.4)	–	–
Chemotherapy, *n* (%)	867 (69.9)	653 (84.9)	214 (45.3)	–	–
Radiotherapy, *n* (%)	994 (80.1)	601 (78.2)	393 (83.3)	–	–
Ever use of endocrine therapy (ET), *n* (%)	827 (66.7)	549 (71.4)	278 (58.9)	–	–
Current use of ET, *n* (%)	289 (23.3)	264 (34.3)	25 (5.3)	–	–
Missing	*34 (2.7)*	*11 (1.4)*	*23 (4.9)*		
Systemic treatment burden, n (%)					
No systemic treatment	211 (17.0)	81 (10.5)	130 (27.5)	–	–
ET only	153 (12.3)	31 (4.0)	122 (25.8)	–	–
Chemotherapy[d] only	200 (16.1)	139 (18.1)	61 (13.0)	–	–
Chemotherapy[d] and ET	667 (53.8)	514 (66.8)	153 (32.4)	–	–
Missing	*10 (0.8)*	*4 (0.5)*	*6 (1.3)*		

[a]Heart, pulmonary, thyroid, kidney, rheumatic disease, cerebral stroke, diabetes,

[b]Breast cancer survivors < 55 years at diagnosis,

[c]Breast cancer survivors ≥ 55 years at diagnosis,

[d]Including breast cancer survivors treated with trastuzumab

SD standard deviation

Statistically significant: $p < 0.05$

The controls were younger (mean age of 54 years) than the BCSs, and 7% reported prior or present cancer. BCSs and controls had similar prevalence of somatic co-morbidity, but BCSs had more mental co-morbidity, more sleep problems and lower BMI compared to controls (all p-values < 0.001). (Table 1).

Comparison of sexual health between all BCSs and controls

All sexual health outcomes were poorer among BCSs than among controls (unadjusted mean scores for sexual functioning (27.2 vs 38.9), sexual enjoyment (63.1 vs 79.0) and sexual discomfort (2.4 vs 1.2) (Fig. 1).

When adjusting for sociodemographic variables, the BCSs had clinically significant lower sexual enjoyment (B − 14.4, 95%CI − 16.4, − 12.5) and more discomfort (B 1.0, 95%CI 0.9, 1.1) than controls. These differences slightly decreased, but remained clinically significant when additionally adjusting for health-related variables. However, for sexual functioning we found no clinically significant difference between BCSs and controls in the adjusted analyses (Table 2).

The complete linear regression model with estimates is shown in Supplementary Table 1.

Comparisons of sexual health between BCSs according to systemic treatment burden and controls

BCSs treated with both endocrine- and chemotherapy had clinically significant lower sexual functioning (B − 11.9, 95%CI − 13.8, − 10.1), lower sexual enjoyment (B − 18.1, 95% − 20.7, − 15.5), and more sexual discomfort (B 1.4, 95%CI 1.3, 1.6) compared to controls. These differences were smaller when comparing BCSs treated with endocrine- or chemotherapy only with controls, and were not clinically significant for sexual functioning. There were no clinically significant differences in any sexual health outcomes when comparing BCSs treated without systemic therapies and controls (Table 3).

Stratified analyses according to age at diagnosis

The differences in unadjusted sexual health outcomes between BCSs and controls were most pronounced in the premenopausal group (Fig. 1).

BCSs who were premenopausal at diagnosis, had clinically significant lower sexual functioning (B − 11.0, 95%CI − 12.8, − 9.2), lower enjoyment (B − 18.9, 95%CI − 21.2, − 16.6) and more discomfort (B 1.3, 95%CI 1.2, 1.4) compared to similar aged controls after adjusting for sociodemographic variables. When additionally adjusting for health-related variables, sexual enjoyment and discomfort

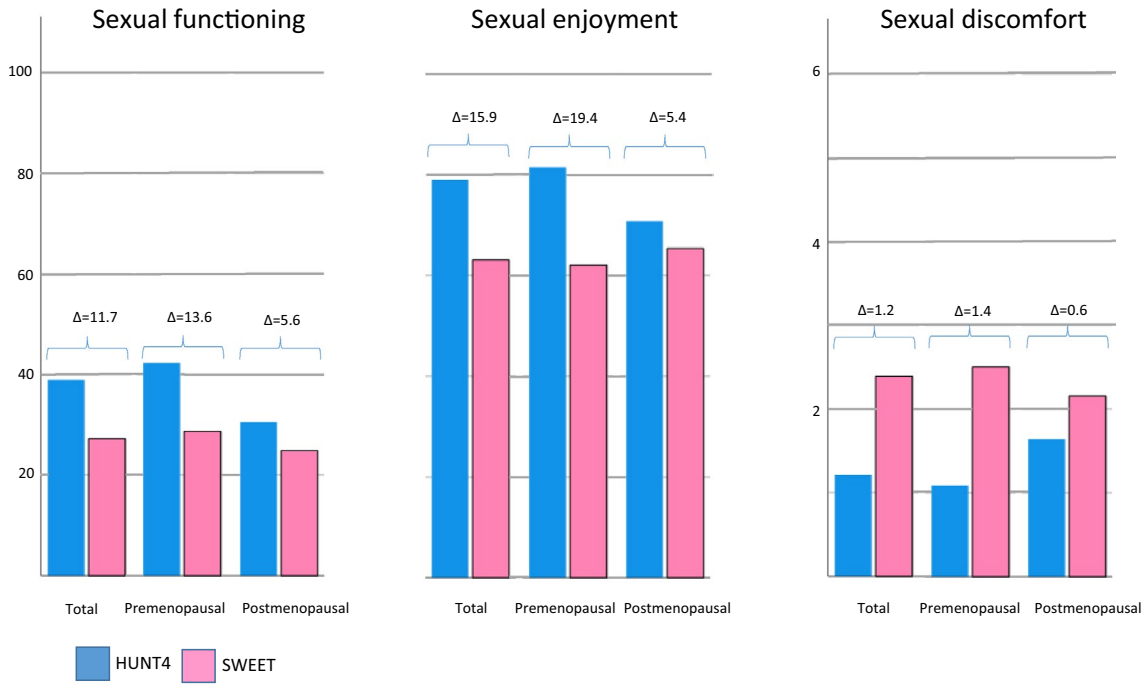

Fig. 1 Sexual health in long-term breast cancer survivors (SWEET) and population controls (HUNT4)

Table 2 Comparison of sexual health between breast cancer survivors (SWEET) and population controls (HUNT4) in total samples and separated by menopausal status

	Sexual functioning[a]		Sexual enjoyment[b]		Sexual discomfort[c]	
	Beta	95% CI	Beta	95% CI	Beta	95% CI
All age groups						
HUNT4	Ref	–	Ref	–	Ref	–
SWEET[d]	− 8.7	− 10.1, − 7.3	**− 14.4**	**− 16.4, − 12.5**	**1.0**	**0.9, 1.1**
HUNT	Ref	–	Ref	–	Ref	–
SWEET[e]	− 7.7	− 9.1, − 6.3	**− 13.1**	**− 15.0, − 11.2**	**0.9**	**0.8, 1.0**
Premenopausal status[f]						
HUNT4	Ref	–	Ref	–	Ref	–
SWEET[−d]	**− 11.0**	**− 12.8, − 9.2**	**− 18.9**	**− 21.2, − 16.6**	**1.3**	**1.2, 1.4**
HUNT4	Ref	–	Ref	–	Ref	–
SWEET[e]	− 9.7	− 11.5, − 7.9	**− 17.3**	**− 19.6, − 14.9**	**1.2**	**1.0, 1.3**
Postmenopausal status[g]						
HUNT4	Ref	–	Ref	–	Ref	–
SWEET[d]	− 5.3	− 7.6, − 2.9	− 5.7	− 9.3, − 2.2	0.4	0.2, 0.7
HUNT4	Ref	–	Ref	–	Ref	–
SWEET[e]	− 5.0	− 7.4, − 2.7	− 5.1	− 8.6, − 1.5	0.4	0.1, 0.6

Linear regression with sexual health measures as outcome variables

[a]Scale 0–100 (EORTC-BR23)

[b]Scale 0–100 (EORTC-BR23) among sexually active women

[c]Scale 0–6 (Sexual Activity Questionnaire) among sexually active women

[d]Adjusted for age at survey, living with a partner or not, education > / ≤ 12 years

[e]Adjusted for age at survey, living with a partner or not, education > / ≤ 12 years, somatic co-morbidity (no, 1, ≥ 2), mental co-morbidity (yes/no), body mass index, sleep problems (yes/no)

[f]Breast cancer survivors (BCSs) premenopausal at diagnosis (< 55 years) and similar aged controls

[g]BCSs postmenopausal at diagnosis (≥ 55 years) and similar aged controls

CI confidence interval

Bold: Clinically significant findings

remained significantly worse among BCSs than among controls. There were no clinically significant differences in any of the sexual health outcomes when comparing BCSs diagnosed at postmenopausal age with similar aged controls (Table 2).

Separating BCSs treated with both endocrine- and chemotherapy in being pre-and postmenopausal at diagnosis, all sexual health outcomes were poorer among BCSs compared to controls. The differences observed were most pronounced in the premenopausal group (Table 3).

Discussion

Eight years after diagnosis, BCSs had lower sexual enjoyment and more sexual discomfort compared to similarly aged controls. Sexual health impairments were most pronounced in BCSs who were premenopausal at diagnosis, and in BCSs with heavy systemic treatment burden.

Comparisons between BCSs and similar aged population controls are crucial to differentiate age-related changes in sexual health from those associated with BC diagnosis and treatment. However, only few such comparative studies have been performed. Dorval et al. [19] and Soldera et al. [18] reported no differences in sexual activity between long-term BCSs and controls. Their results partly correspond to our finding of no difference in sexual functioning between BCSs and controls in the adjusted analyses. In line with our results showing poorer sexual enjoyment and more sexual discomfort among BCSs than controls, Dorval et al. [19] reported that sexually active BCSs were less satisfied with their sexual life compared to controls. In a recent Finnish study assessing health-related quality of life up to 10 years after BC treatment, BCSs reported more sexual problems than controls [38]. On the other hand, Soldera et al. [18] found no differences in sexual pleasure and sexual discomfort in sexually active BCSs compared to controls 12 years after diagnosis. This discrepancy between the Soldera et al. study and our study may be due to differences in treatment burden among BCSs, as only 66% of the BCSs in their study had received systemic adjuvant treatment including only 10% with the combination of endocrine- and chemotherapy, while the corresponding numbers in our study were 82 and

Table 3 Comparison of sexual health between breast cancer survivors (SWEET) according to systemic treatment burden and population controls (HUNT4) in total samples and separated by menopausal status

	Sexual functioning[a]		Sexual enjoyment[b]		Sexual discomfort[c]	
	Beta	95% CI	Beta	95% CI	Beta	95% CI
All age groups						
HUNT4	Ref	–	Ref	–	Ref	–
SWEET – no systemic treatment	– 2.9	– 5.9, 0.7	– 6.4	– 10.9, – 1.8	0.3	0.04, 0.6
SWEET – ET only	– 5.8	– 9.6, – 1.9	**– 11.0**	**– 16.2, – 5.7**	**0.7**	**0.4, 1.0**
SWEET – chemo[d] only	– 8.2	– 11.6, – 4.9	**– 12.6**	**–17.0, –8.2**	**0.8**	**0.5, 1.0**
SWEET – chemo[d] + ET	**– 11.9**	**– 13.8, – 10.1**	**– 18.1**	**– 20.7, – 15.5**	**1.4**	**1.3, 1.6**
Premenopausal status[e]						
HUNT4	Ref	–	Ref	–	Ref	–
SWEET – no systemic treatment	–	–	–	–	–	–
SWEET – ET only	–	–	–	–	–	–
SWEET – chemo[d] only	– 9.0	– 13.0, – 5.0	**– 15.8**	**– 20.8, – 10.8**	**0.9**	**0.6, 1.2**
SWEET – chemo[d] + ET	**– 13.1**	**– 15.2, – 11.0**	**– 20.3**	**– 23.1, – 17.5**	**1.5**	**1.4, 1.7**
Postmenopausal status[f]						
HUNT4	Ref	–	Ref	–	Ref	–
SWEET – no systemic treatment	– 0.3	– 4.6, 3.9	0.8	– 5.5, 7.1	– 0.1	– 0.5, 0.3
SWEET – ET only	– 6.3	– 10.6, – 2.0	– 9.4	– 15.7, – 3.0	**0.6**	**0.2, 1.0**
SWEET – chemo[d] only	–	–	–	–	–	–
SWEET – chemo[d] + ET	**– 10.0**	**– 13.9, – 6.2**	**– 12.0**	**– 18.2, – 5.8**	**1.0**	**0.6, 1.4**

Linear regression with sexual health measures as outcome variables. Adjusted for age at survey, living with a partner or not, education > / ≤ 12 years

[a]Scale 0–100 (EORTC-BR23)

[b]Scale 0–100 (EORTC-BR23) among sexually active women

[c]Scale 0–6 (Sexual Activity Questionnaire) among sexually active women

[d]Including BCSs treated with trastuzumab

[e]Breast cancer survivors (BCSs) premenopausal at diagnosis (< 55 years) compared to similar aged controls

[f]BCSs postmenopausal at diagnosis (≥ 55 years) compared to similar aged controls

CI confidence interval, *ET* endocrine therapy

Italics: Treatment groups with too small *n* to present valid statistical analyses

Bold: Clinically significant findings

54%. Also in Soldera's study, BCSs treated with adjuvant therapy, and especially with chemotherapy, reported worse gynecological symptoms than controls. Another study by Ganz et al. [16], reported more sexual discomfort among 6 years BCSs treated with adjuvant chemotherapy compared to those who had received tamoxifen only or no systemic therapy. To note, the studies by Soldera et al. and Ganz et al. were both conducted before the introduction of aromatase inhibitors and before extended endocrine therapy became a recommended treatment option for high-risk patients, and were thus not able to explore the impact of these treatment options as done in our study.

The present study shows a significant association between premenopausal age at diagnosis and long-term sexual health impairments in BCSs. Our findings are in line with results from another comparative study examining BCSs 3–8 years after diagnosis [23], reporting poorer sexual health in BCSs at young age (≤ 45 years) compared to both age-matched controls and BCSs who were older (≥ 55 years) at diagnosis. In our study, younger compared to older BCSs were generally diagnosed with more advanced BC, and received more intensive treatments including extended endocrine treatment.

We found no differences in sexual health between BCSs who had not received systemic adjuvant treatment and controls. The majority of these BCSs were postmenopausal at diagnosis. However, BCSs diagnosed at postmenopausal age and treated with endocrine- and chemotherapy, reported poorer sexual health than controls. David et al. [17] found worse sexual symptoms also among postmenopausal long-term BCSs not treated with chemotherapy and no longer on adjuvant endocrine therapy than among controls. The majority of these BCSs

had, however, been previously treated with adjuvant endocrine therapy, supporting our finding of more sexual discomfort in postmenopausal BCSs treated with adjuvant endocrine therapy.

Thus, findings support that even though sexual activity seems not significantly affected in BCSs, systemic BC treatments have great negative impact on other aspects of sexual health among long-term BCSs, including satisfaction, enjoyment and discomfort, and mostly so in the most heavily treated.

Strengths and limitations

At present, this is the largest study comparing sexual health in long-term BCSs with population controls. No prior study has presented data on sexual health among BCSs receiving extended endocrine treatment. The BCSs were included nationwide, and the controls were considered fairly representative for Norwegian females except for the lack of large cities and immigrant populations [30]. We could have wished for a higher response rate in SWEET, however, based on comparable studies we consider it acceptable [39, 40]. Questionnaires with established psychometric properties were used. We are not aware of other studies reporting mean scores for the domains sexual functioning and sexual enjoyment of EORTC BR23 from population-based samples. Even though this is a BC-specific questionnaire, the sexual items are relevant in the general female population.

Some methodological aspects should be considered. We chose not to exclude controls with prior and/or present cancer as this in our opinion best reflected the general population. The sexual health differences between BCSs and controls may have been even larger if women with cancer had been excluded. The group defined as premenopausal in our study probably includes some postmenopausal women, while the opposite is less likely. These aspects strengthen the finding of poorer sexual health in women diagnosed with BC at premenopausal age compared to controls.

We defined a mean score difference of $\geq 10\%$ between groups as a clinically significant difference. Even smaller differences of 5–10% may have some clinical relevance [37], which if used would have resulted in clinically significant differences between groups for more outcomes in the analyses. BCSs in this study were treated in a period where the use of adjuvant chemotherapy peaked. Because few premenopausal BCSs were treated without systemic therapies or with endocrine therapy only, no comparative results from these treatments groups could be presented. Treatment with ovarian suppression, in addition to tamoxifen or aromatase inhibitor in premenopausal women with high-risk BC, was not standard of care in 2011 or 2012. Such treatment, which is given today [41], is associated with further reduction in sexual health [42]. BCSs > 65 years at diagnosis and BCSs with relapse or metastatic disease were not invited in the study. Thus, our results cannot be generalized to all age groups or BCSs with advanced disease.

Conclusion

BCSs experienced more sexual health impairments 8 years after diagnosis compared to similar aged population controls. At particular high-risk of sexual health impairments are BCSs diagnosed at premenopausal age and those treated with intensive systemic adjuvant treatments. This knowledge is important, not only for BCSs, but also for the health care providers. During follow-up, attention to sexual health impairments, especially among BCSs with these risk factors, should be provided and handled according to relevant recommendations [43, 44].

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s10549-023-07021-y.

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Author contributions All authors contributed to the conception and design of this study. Data collection was performed by KVR and KF. Data preparation was performed by KVR, KFV and SKS. SKS and RSF: performed the analyses. The first version of the manuscript was written by SKS. All authors discussed the analyses and results, and commented on that version. All authors read and approved the final manuscript.

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Data availability Data from SWEET is available at the National Advisory Unit for Late Effects after Cancer Treatment, Department of Oncology, Oslo University Hospital, the Radium Hospital, Oslo, Norway. Data from the HUNT study used in research projects is available upon reasonable request to the HUNT data access committee (hunt@medisin.ntnu.no).

Declarations

Competing interests The authors declare no conflict of interest.

Ethical approval This study was approved by the Regional Committee for Medical Research Ethics (2018/2170), the Norwegian Cancer Registry and the Data Protection Officer at Oslo University Hospital. All procedures were performed in accordance with the ethical standards of the national and institutional research committee and with the 1964 Declaration of Helsinki and its later amendments.

Informed consent Informed consent was obtained from all participants included in the study.

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ORIGINAL ARTICLE

Burden of late effects in a nationwide sample of long-term breast cancer survivors

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Abstract

Background: Long-term breast cancer survivors (BCSs) may experience several late effects (LEs) simultaneously. This study aimed to identify subgroups of 8-year BCSs with higher burden of LEs who could benefit from closer survivorship care, explore variables associated with higher symptom burden, and describe how symptom burden may affect general functioning.

Methods: All Norwegian women aged 20 to 65 years when diagnosed with stage I-III breast cancer in 2011 and 2012 were invited (n = 2803). The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire/BR23, the Fatigue Questionnaire, Assessment of Survivor Concerns, and Scale for Chemotherapy Induced Long-term Neurotoxicity were used to assess 10 common LEs and general functioning. Using latent class analysis, subgroups of BCSs with similar burden of LEs were identified. Multinominal regression analysis were performed to examine variables associated with higher symptom burden.

Results: The final sample consisted of 1353 BCSs; 46% had low, 37% medium, and 17% high symptom burden. Younger age, short education, axillary dissection, higher systemic treatment burden, higher body mass index, and physical inactivity were associated with higher symptom burden. General functioning scores were lower, and the proportion on disability pension were higher among BCSs in the two most burdened subgroups compared with those in the low burden subgroup.

Conclusion: More than half of long-term BCSs suffered from medium or high symptom burden and experienced impaired general functioning compared with BCS with low symptom burden. Younger age and systemic treatment were important risk factors for higher symptom burden. BCSs at risk of higher symptom burdens should be identified and offered closer and extended survivorship care.

KEYWORDS
breast cancer, late effects, latent class analysis, long-term effects, survivorship

INTRODUCTION

Breast cancer (BC) survival is increasing, with an overall 5-year relative survival rate surpassing 90% in several Western countries.[1,2] Consequently, the population of long-term (i.e., >5 years after diagnosis) BC survivors (BCSs) is growing. BCSs may experience a broad range of physical and mental adverse effects during survivorship. Long-term effects refer to adverse effects that appear during treatment and continue beyond treatment completion, whereas late effects are adverse effects that first appear after treatment cessation.[3] In this study, these terms are merged and referred to as late effects (LEs). Pain, fatigue, sleep disturbances, arm and breast problems, neuropathy, cognitive dysfunction, and emotional dysfunction including fear of cancer recurrence, are the most prevalent LEs.[4] Sexual dysfunction is also frequently reported by BCSs.[5] Most LEs are associated with lower daily functioning.[6] Traditionally, LEs have been studied and managed separately. However, LEs tend to co-occur and have the potential to exacerbate one another.[7] In recent years, the study of total symptom burden in BCSs has received increasing attention.[8] Studies report that up to 20% of BCSs suffer from a high burden of LEs during treatment and the first 5 years after diagnosis,[9–13] negatively affecting their daily functioning and quality of life.[7] Knowledge concerning burden of LEs beyond the first 5 years of BC survivorship and its potential consequences on general functioning, including work participation, is lacking. Identification of BCSs with higher burden of LEs is important to improve follow-up care, and aims to increase quality of life, function levels, and work participation. Such knowledge may also result in more holistic clinical strategies for symptom management, rather than focusing on one LE at a time.

Based on data from a nationwide survey of BCSs examined 8 years after diagnosis, the aims of the present study were therefore to identify subgroups of BCSs with higher total burden of LEs who could potentially benefit from closer and extended survivorship care, explore factors associated with increasing symptom burden, and describe general functioning including work participation across different symptom burdens.

METHODS

Study population

This study is a part of the Survivorship-Work-Sexual Health study, a nationwide, cross-sectional survey exploring LEs, work life, and sexual health in long-term BCSs. The sampling procedure has been described previously.[14] In short, all women diagnosed with BC stage I-III in 2011 and 2012 at the age of 20 to 65 years were identified by the Cancer Registry of Norway.[15] To be included, women had to be free of pre- and postmalignancies (except nonmelanoma skin cancer and ductal carcinoma in situ). Among the 2803 BCSs invited to participate in 2019, 1361 (49%) responded. BCSs with either missing consent or self-reported BC recurrence ($n = 6$), and with missing data on all LEs of interest ($n = 2$) were excluded, resulting in a final sample of 1353 BCSs.

Late effects

The most prevalent LEs among BCSs served as indicator variables for the statistical identification of subgroups of BCSs with similar symptom burden. These were pain, fatigue, sleep disturbances, arm problems, breast problems, neuropathy, cognitive dysfunction, emotional dysfunction, fear of cancer recurrence, and sexual dysfunction. Emotional dysfunction covers symptoms of generalized anxiety and depression,[16] whereas fear of cancer recurrence measures cancer-specific fear, worry, and concern.[17]

Pain, sleep disturbances, and cognitive and emotional function were assessed using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire version 3 (EORTC QLQ-C30).[16] Items were rated from 1 (not at all) to 4 (very much) and then transformed to 0 to 100 scales according to the manual.[18] Established threshold values were applied to identify clinically relevant LEs.[19] Cronbach alpha was 0.87, 0.72, and 0.85 for pain, cognitive, and emotional function, respectively. Arm and breast symptoms were assessed using the EORTC BC-specific module (EORTC QLQ-BR23).[20] Items were rated as in the EORTC QLQ-C30, and BCSs reporting 3 (quite a bit) or 4 (very much) to at least one of the items within each subscale were defined as having arm and/or breast problems. Cronbach alpha was 0.79 for arm and 0.77 for breast symptoms. Sexual function was measured using two items from the EORTC QLQ-BR23, and sexual dysfunction defined when the transformed score was zero (i.e., no sexual interest and no sexual activity). Cronbach alpha was 0.85.

The Fatigue Questionnaire[21] measures symptoms of fatigue over the past month through 11 items; seven concern physical and four mental fatigue. Responses were rated from 0 (better than usual) to 3 (much worse than usual). BCSs scoring 2 or 3 in at least 4 of the 11 items were categorized as having fatigue.[22] Chronic fatigue was defined as having fatigue with duration 6 months or more. Cronbach alpha was 0.93.

Fear of cancer recurrence was assessed using the cancer-specific subscale of the Assessment of Survivor Concerns.[17] The three items were rated from 1 (not at all) to 4 (very much), yielding a sum score from 3 to 12. BCSs with a sum score ≥6, or a single score on one of the items ≥3, were categorized as having fear of cancer recurrence. These thresholds were set after personal correspondence with the author of the instrument. Cronbach alpha was 0.87.

Neuropathy was assessed using two items from the Scale for Chemotherapy Induced Long-term Neurotoxicity.[23] Presence of peripheral sensory neuropathy in hands or feet, respectively, were rated from 0 (not at all) to 3 (very much), providing a sum score from 0 to 6. The sum score was dichotomized into high (≥4) and low (≤3) degree of neuropathy, in which high degree was defined as an LE. Cronbach alpha was 0.77.

Self-reported sociodemographic and lifestyle variables

Sociodemographic variables included living arrangements (partnered or not), length of education (short [≤12 years] and long [>12 years]), and information on work status including disability pension. Body mass index (BMI) was calculated from height and weight (kg/m^2). "Physically active" was defined as meeting the public guidelines ≥150 minutes moderate-intensity or ≥75 minutes of high-intensity physical activity per week, or an equivalent combination of moderate and high intensity physical activity per week.[24]

Cancer-related variables

Information on age at diagnosis and surgical treatment were provided from the Cancer Registry of Norway. Information on adjuvant radiotherapy and systemic treatment were self-reported. Systemic treatment was categorized into no systemic treatment, endocrine therapy only, chemotherapy only, and chemotherapy and endocrine therapy. BCSs treated with trastuzumab (n = 230) were categorized either to the chemotherapy only or to the chemotherapy and endocrine therapy group.

Measures of general function

General function was assessed using three separate scales (physical, role, and social functioning) from the EORTC QLQ C-30.[16] These scales cover activities of daily life including the ability to work and participate in leisure time activities, family, and social life. Items were scored and transformed as previously described for the EORTC questionnaires, yielding scales from 0 to 100 where increasing scores represent better functioning.

Statistics

Descriptive statistics were presented as frequencies and proportions for categorical data, and as means with standard deviations and range for continuous data. Missing data were presented separately.

Latent class analysis (LCA) was used to estimate classes (in the following referred to as subgroups) of BCSs sharing similar symptom burden. LCA assumes that there is a latent nominal variable categorizing survivors into subgroups based on responses to categorical indicator variables.[25] The indicator variables in this study were the 10 defined LEs. LCA handles missing data in the indicator variables when estimating the latent subgroups.[26] LCA including two, three, four, and five subgroups were evaluated. Statistical fit indices were used to evaluate model fit and to determine the final number of subgroups. The model that fit the data best was selected based on Bayesian Information Criterion, Akaike Information Criterion, average latent class posterior probability, entropy, and clinical relevance of the subgroups.[26]

To assess the association between sociodemographic, cancer, and lifestyle variables and subgroups with a similar symptom burden, we used a three-step approach[26] combined with multinominal logistic regression analysis. The LCA, as described previously, was the first step. The second step consisted of assigning subgroup membership to each participant. Posterior probabilities of belonging to each subgroup were calculated for each participant. We used the proportional assignment methods (i.e., each participant was replicated several times in the data set and assigned to each of the subgroups with its related posterior probabilities).[27] In the third step, we explored the association between sociodemographic, cancer, and lifestyle variables with the subgroup membership from step 2 using multinominal regression analysis. To take the uncertainty of classification into account, the posterior probabilities from step 2 were used as weights. Variables included in the model were age at survey, living arrangements, education, surgical treatment, systemic treatment burden, BMI, and physical activity. Current endocrine therapy and radiotherapy were omitted because of multicollinearity with the included variables. Only participants with complete information for all variables were included in step 3. Results were presented as odds ratio with 95% CIs.

For the graphical presentation of subgroups with similar symptom burden, participants needed to belong to a unique subgroup. Thus, the modal assignment method was used (i.e., each participant was assigned to the subgroup with the highest posterior probability computed in step 2).[27]

All analyses were performed using Stata version 17 (StataCorp LLC, College Station, Texas). We used two-sided tests and a 5% statistical significance level.

RESULTS

Characteristics of study sample

Mean age at survey was 60 years and 8 years had passed since diagnosis. Most BCSs were treated with breast-conserving therapy (59%), sentinel node biopsy (63%), and radiotherapy (80%). More than half had received both chemotherapy and endocrine therapy. The included LEs were reported by more than 20% of BCSs, with fear of cancer recurrence (56%), pain (47%), cognitive dysfunction (43%), sleep disturbances (34%), arm problems (32%), and fatigue (32%) as the most prevalent (Table 1).

Subgroups of BCSs with similar burden of late effects

Based on the best compromise of the evaluation criteria, the model with three subgroups was chosen (Table S1). The subgroups were named according to total burden of LEs (Figure 1). The subgroup "low symptom burden" was characterized by low prevalence (<15%) of all LEs except for fear of cancer recurrence and sexual dysfunction. The

TABLE 1 Characteristics of long-term breast cancer survivors (n = 1353).

	Mean (SD) [range]/*n* (%)	Missing, *n* (%)
Sociodemographic variables		
Age at survey (years)	59.9 (8.7) [30.0–74.0]	0
Living with a partner	994 (73.5)	0
Long education (>12 years)	690 (51.0)	16 (1.2)
Cancer-related variables		
Time since diagnosis (years)	8.0 (0.7) [7.0–9.0]	0
Surgery breast		0
Breast conserving therapy	795 (58.8)	
Mastectomy	558 (41.2)	
Surgery axillae		0
Sentinel node biopsy	856 (63.3)	
Axillary dissection	497 (36.7)	
Radiotherapy	1086 (80.3)	0
Current use of endocrine therapy (ET)	302 (22.3)	42 (3.1)
Systemic treatment burden		12 (0.9)
No systemic treatment	243 (18.0)	
ET only	172 (12.7)	
Chemotherapy[a] only	226 (16.7)	
Chemotherapy[a] and ET	700 (51.8)	
Lifestyle variables		
Body mass index (kg/m^2)	26.2 (4.4) [16.5–48.4]	23 (1.7)
Physically active[b]	532 (39.3)	106 (7.8)
Late effects		
Pain[c]	631 (46.6)	5 (0.4)
Cognitive dysfunction[c]	586 (43.3)	5 (0.4)
Chronic fatigue[d]	432 (31.9)	23 (1.7)
Sleep disturbances[c]	457 (33.8)	11 (0.8)
Emotional dysfunction[c]	373 (27.6)	5 (0.4)
Fear of cancer recurrence[e]	755 (55.8)	24 (1.8)
Arm problems[c]	428 (31.6)	31 (2.3)
Breast problems[c]	315 (23.3)	54 (4.0)
Neuropathy[f]	277 (20.5)	35 (2.6)
Sexual dysfunction[c]	380 (28.1)	80 (5.9)

Abbreviation: SD, standard deviation.

[a]Including BCSs treated with chemotherapy and trastuzumab (n = 230).

[b]Meeting the public guidelines for physical activity.

[c]EORTC QLQ-C30/BR23.

[d]Fatigue Questionnaire.

[e]Assessment of Survivors Concern.

[f]Two items from Scale for Chemotherapy-induced Long-term Neurotoxicity.

"medium symptom burden" subgroup was characterized by a high prevalence of pain (62%), cognitive dysfunction (67%), chronic fatigue (49%), sleep disturbances (51%), emotional dysfunction (46%), and fear of cancer recurrence (68%), and a lower prevalence of arm and breast problems (32% and 21%) and neuropathy (20%). The "high symptom burden" subgroup had a high prevalence of all 10 LEs,

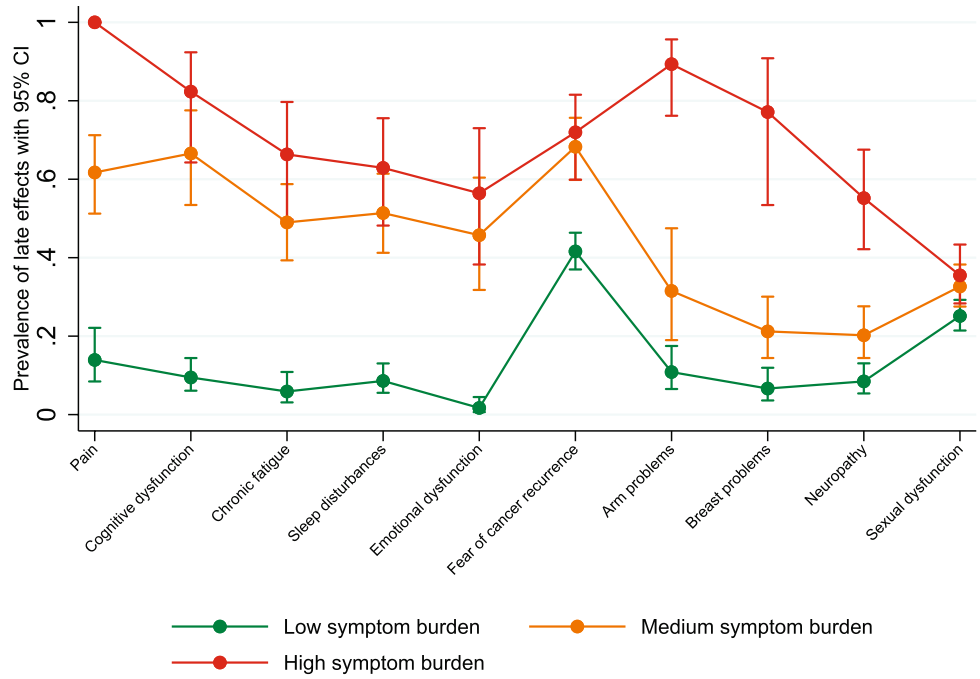

FIGURE 1 Model with three subgroups of breast cancer survivors with similar symptom burden (n = 1353). The actual numbers are given in Table S2.

ranging from 36% (sexual dysfunction) to 100% (pain). Fear of cancer recurrence was prevalent in all subgroups (>40%), although significantly lower among BCSs in the subgroup with low compared with the subgroups with medium and high symptom burden. Sexual dysfunction had a prevalence ranging from 25% to 36%, with no significant difference across subgroups (Table S2). The model estimated that 46% of the BCSs belonged to the subgroup with low, 37% to the subgroup with medium, and 17% to the subgroup with high symptom burden (Table 2).

Variables associated with higher burden of late effects

The low symptom burden subgroup was used as reference in the multinominal logistic regression analyses (Table 3). Younger age, chemotherapy and endocrine therapy, higher BMI, and physical inactivity were associated with both medium and high symptom burden. Short education, axillary dissection, and adjuvant chemotherapy were additionally associated with high symptom burden. For variables included in the multinominal regression analyses, the subgroup distribution within each category is presented in Table S3.

General function and work status in subgroups with similar burden of late effects

Mean physical functioning score in the low, medium, and high symptom burden subgroups respectively was 92, 78, and 66, whereas the corresponding scores were 94, 67, and 53 for role functioning and 92, 63, and 46 for social functioning (Figure 2A). In a subanalysis of BCSs within working age (<67 years) at survey (n = 987), 58% of BCSs assigned to high symptom burden subgroup held disability pension. In the low and medium symptom burden subgroups, the proportion of BCSs on disability pension was 16% and 42%, respectively (Figure 2B).

DISCUSSION

In the present study exploring total burden of LEs 8 years after early-stage BC, more than half of BCSs reported medium or high symptom burden. Both sociodemographic, cancer-related, and lifestyle variables were associated with higher levels of symptom burden. BCSs with higher symptom burden had poorer general functioning and a larger proportion held disability pension compared with BCSs with low symptom burden.

Our finding, that almost one in five BCSs experienced a high symptom burden, was in line with results from studies focusing on the first 5 years of survivorship,[9–12] indicating that the overall prevalence of high symptom burden may not decrease with time since diagnosis.

BCSs with medium and high symptom burden had lower general functioning and higher proportions received disability pension compared with BCSs with low symptom burden. General functioning in the two most burdened groups was also lower than reported in European and Norwegian female normative data.[28,29] Furthermore, functioning scores among BCSs in the high burden subgroup were

TABLE 2 Characteristics of breast cancer survivors by subgroups of symptom burden (n = 1353).

	Low symptom burden n = 624 (46%)	Medium symptom burden n = 501 (37%)	High symptom burden n = 228 (17%)
Age at survey (years), mean (SD)	61.2 (8.5)	59.2 (8.7)	57.8 (8.5)
Living with a partner, n (%)	462 (74.0)	367 (73.3)	165 (72.4)
Long education (>12 years), n (%)	334 (53.5)	253 (50.5)	103 (45.2)
Mastectomy, n (%)	241 (38.6)	206 (41.1)	111 (48.7)
Axillary dissection, n (%)	196 (31.4)	189 (37.7)	112 (49.1)
Radiotherapy, n (%)	504 (80.8)	394 (78.6)	188 (82.5)
Current use of endocrine therapy (ET), n (%)	117 (18.8)	127 (25.3)	58 (25.4)
Systemic treatment burden, n (%)			
No systemic treatment	140 (22.4)	77 (15.4)	26 (11.4)
ET only	101 (16.2)	55 (11.0)	16 (7.0)
Chemotherapy[a] only	103 (16.5)	70 (14.0)	53 (23.2)
Chemotherapy[a] and ET	272 (43.6)	296 (59.1)	132 (57.9)
Body mass index (kg/m^2), mean (SD)	25.7 (4.0)	26.5 (4.7)	27.2 (4.5)
Physically active[b], n (%)	274 (43.9)	189 (37.7)	69 (30.3)

Abbreviation: SD, standard deviation.

[a]Including breast cancer survivors treated with chemotherapy and trastuzumab (n = 230).

[b]Meeting the public guidelines for physical activity.

TABLE 3 Results from multi-nominal regression analysis of subgroups of symptom burden among breast cancer survivors (n = 1304)[a].

	Medium symptom burden		High symptom burden	
	OR	95% CI	OR	95% CI
Age at survey (years)	**0.97**	**0.96, 0.99**	**0.96**	**0.94, 0.98**
Living without a partner	1.05	0.82, 1.36	1.14	0.83, 1.56
Short education (≤12 years)	1.25	0.99, 1.58	**1.54**	**1.15, 2.07**
Mastectomy	0.98	0.77, 1.25	1.08	0.79, 1.48
Axillary dissection	1.10	0.85, 1.42	**1.58**	**1.15, 2.16**
Systemic treatment burden				
No systemic treatment	Ref	-	Ref	-
Endocrine therapy (ET) only	1.09	0.74, 1.62	0.87	0.49, 1.56
Chemotherapy[b] only	1.14	0.76, 1.71	**1.72**	**1.02, 2.87**
Chemotherapy[b] and ET	**1.75**	**1.25, 2.44**	**1.68**	**1.08, 2.63**
Body mass index, kg/m^2	**1.03**	**1.01, 1.06**	**1.07**	**1.04, 1.10**
Physically inactive[c]	**1.31**	**1.04, 1.65**	**1.74**	**1.28, 2.37**

Note: Significant associations in **bold**.

Abbreviations: CI, Confidence interval; OR, Adjusted odds ratio.

[a]Subgroup "low symptom burden" was used as reference.

[b]Including breast cancer survivors treated with chemotherapy and trastuzumab (n = 230).

[c]Physical activity was categorized as active (meeting public guidelines for physical activity, reference group), inactive (not meeting the public guidelines for physical activity) and missing (information not available for 106 women, omitted in table).

lower than the established threshold values indicating functional impairments and lower for physical functioning also in the medium burden subgroup.[19]

Our findings that younger age and high systemic treatment burden were associated with a higher symptom burden were in line with other previous results.[9,10,30] In contrast, De Ligt et al. found no association between younger age and higher symptom burden in BCSs 1 to 5 years after diagnosis, which may be due to underrepresentation of younger and older BCSs in that study.[11] Younger age and systemic treatment burden have also been associated with several of the LEs when studied separately, including pain, depression, fatigue, sleep disturbances, fear of cancer recurrence, and sexual dysfunction.[31–36] Treatment-induced premature menopause, limited coping skills concerning serious illness, and a higher expectation of maintaining family and work life participation may explain why younger BCSs report a higher symptom burden compared with older ones. Younger BCSs are also often diagnosed with more aggressive BC and receive more intensive systemic treatments, which may further reinforce the finding that young age is an important risk factor for higher symptom burden.

Axillary dissection was associated with being in the high but not in the medium symptom burden subgroup. The main differences between these subgroups were a higher prevalence of pain, neuropathy, and arm and breast problems among BCSs in the high compared with those in the medium symptom burden subgroup. Axillary dissection is a significant risk factor for lymphedema[37] and persistent pain after BC surgery,[31] which may partly explain this finding. No association was found between axillary surgery and symptom burden in the study by de Ligt et al.,[11] but arm and breast problems were not included as indicator variables in that study. Our

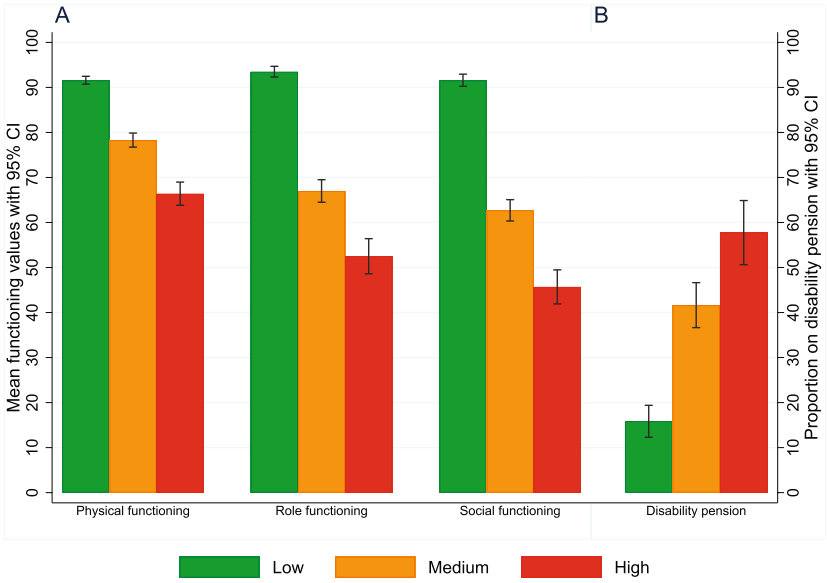

FIGURE 2 (A) Mean values of EORTC functioning scales.[a] (B) Percentage of BCSs on disability pension[b] in the three subgroups of symptom burden. [a]Scale 0–100; a higher score corresponds to higher functioning. [b]Subanalysis of BCSs within working age at survey ($n = 986$). BCS indicates breast cancer survivor; EORTC, European Organization for Research and Treatment.

finding emphasizes the importance of deescalating axillary surgery when possible to spare BCSs for considerable long-term morbidity.

Higher BMI and physical inactivity were associated with higher symptom burden. Delrieu et al. found an association between decreased physical activity compared with prediagnosis and higher symptom burden, but no association between BMI and symptom burden in 5-year BCSs.[38] The association between higher BMI and high symptom burden is however reported in another study of BCSs 1-5 years after diagnosis.[13] Higher BMI has also been associated with several of the LEs studied separately including pain, fatigue, and arm problems,[36,37,39] as has physical inactivity with fatigue.[39]

Fear of cancer recurrence is increasingly recognized as a common problem and one of the most prevalent areas of unmet supportive care needs among cancer survivors.[33] In this study, fear of cancer recurrence was prevalent across all subgroups. Similar prevalence have been reported in a study of Danish BCSs during the first 5 years of survivorship,[40] and even higher prevalence in a study of younger BCSs at least 1 year after diagnosis.[41]

BCSs with low symptom burden had better general functioning scores compared with normative data,[28,29] and the functioning scores were higher than established threshold values for functional impairments.[19] These findings imply that almost half of long-term BCSs experience high general functioning.

Strengths and limitations

This is the first study exploring symptom burden in BCSs more than 5 years after diagnosis. A large sample size, nationwide inclusion of BCSs, and the broad spectrum of LEs included in the LCA represent major strengths of this study. Validated questionnaires with good psychometric properties were used when available. A response rate of 49% is considered acceptable and is comparable to other surveys of long-term cancer survivors.[42,43] Results from an attrition analysis for the Survivorship-Work-Sexual-Health study have been reported previously, demonstrating that responders were somewhat younger and had more aggressive tumor characteristics compared with non-responders.[14] Thus, we cannot exclude the presence of some selection bias, resulting in an overestimation of symptom burden. Another limitation is that all the complaints explored as LEs, except of fear of cancer recurrence, may be complaints present before the BC without association to the diagnosis or treatment. Furthermore, cutoffs for defining the LEs assessed by EORTC QLQ-BR23 and Assessment of Survivor Concerns were not validated. The high prevalence of fear of cancer recurrence may be caused by the threshold being set too low. Finally, the cross-sectional design does not allow for causal inference.

Clinical implications

The findings of the present study imply that there are subgroups of BCSs who may benefit from closer survivorship care also beyond the first 5 years. Identifying BCSs at risk for or with persistent higher symptom burden represents the first step of such a strategy. As in our study, younger age and high systemic treatment burden are reported as risk factors for high symptom burden also in most studies exploring earlier survivorship. A reasonable interpretation of these findings is that premenopausal BCSs receiving systemic adjuvant treatment have a higher risk for debilitating LEs and should be offered closer follow-up than most postmenopausal BCSs treated without systemic adjuvant treatment. Such a strategy would allocate the health resources where they are most needed and is in line with

several national guidelines recommending individualized follow-up strategies based on age, diagnosis, and treatment.[44,45] Follow-up in general practice is easily adjusted to a more individualized survivorship care. Ultimately, this may lead to better general functioning and higher work participation in long-term BCSs.

Our findings support that healthy lifestyle should be encouraged both during adjuvant treatment and in follow-up. Physical activity may have beneficial effects on fatigue,[46] pain,[47] cognitive dysfunction,[48] and depressive symptoms.[49] Additionally, a recent meta-analysis has shown an association between higher physical activity and reduced BC-specific and overall mortality.[50] Lifestyle recommendations are already incorporated as a part of follow-up by several national survivor guidelines.[44,51]

Finally, fear of cancer recurrence is a highly prevalent LE independent of total symptom burden, and inquiry as to whether patients experience fear of cancer recurrence should be a part of standardized follow-up for all BCSs.

CONCLUSION

In this nationwide sample of BCSs, approximately half had medium or high symptom burden 8 years after diagnosis. Younger age, short education, axillary dissection, higher systemic treatment burden, higher BMI, and physical inactivity were associated with higher symptom burden. General functioning and work participation seems reduced among these survivors. This study underlines the importance of tailored survivorship care, as opposed to one-size-fits-all approach.

AUTHOR CONTRIBUTIONS

All authors: Conceptualization. **Solveig K. Smedsland**: Data curation, formal analysis, and writing – original draft. **Ragnhild S. Falk**: Formal analysis and writing –review and editing. **Kristin V. Reinertsen**: Funding acquisition, investigation, project administration, data curation, and writing –review and editing. **Cecilie E. Kiserud**: Funding acquisition and writing–review and editing. **Mette Brekke**: Writing – review and editing. **Synne H. Bøhn**: Data curation and writing – review and editing. **Alv A. Dahl**: Funding acquisition and writing – review and editing. **Kathrine F. Vandraas**: Investigation, project administration, data curation, and writing – review and editing.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

All data are available at the National Advisory Unit for Late Effects after Cancer Treatment, Department of Oncology, Oslo University Hospital, Oslo, Norway.

PATIENT CONSENT STATEMENT

Informed consent was obtained from all participants included in the study.

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Additional supporting information can be found online in the Supporting Information section at the end of this article.

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