

## Original article

## Patient-reported health problems and healthcare use after treatment for early-stage breast cancer

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## ABSTRACT

**Background:** A clear picture of treatment-related health problems following breast cancer treatment is useful in anticipating the informational and other needs of patients during follow-up. This study aimed to identify treatment-related health problems in breast cancer patients up to five years after diagnosis. Secondly, the use of care associated with these health problems was identified.

**Methods:** 876 surgically-treated female patients diagnosed between 2012 and 2016 with early-stage breast cancer were asked to complete an online survey about their current health problems and use of care. Multivariate logistic regression analyses were applied to determine the effect of patient and treatment characteristics on health problems.

**Results:** 404 patients responded (46%). The median age was 62.0 years (SD:10.9). Apart from breast surgery, patients had been treated with radiotherapy (72%), chemotherapy (49%), anti-hormonal therapy (57%), and axillary dissection (21%). Ninety-three percent experienced one or more health problems. Over 50% of respondents experienced fatigue, psychological problems, and health problems regarding the breast, and/or musculoskeletal, central nervous, and reproductive system. Treatment with chemotherapy was significantly associated ( $p < 0.05$ ) with an increased risk of health problems, respectively fatigue (OR:2.00), respiratory (OR:1.81), gastrointestinal (OR:1.87), central nervous (OR:3.40), and skin problems (OR:2.62). Use of healthcare for one or more health problems was reported by 64% of respondents.

**Discussion:** Almost all patients experienced health problems up to five years after breast cancer diagnosis, with a range of complaints that were consistently present over time. Factors associated with the development of health problems are useful for better informing patients beforehand and targeting follow-up care.

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## 1. Introduction

Breast cancer and its treatment have a major impact on psychosocial, emotional, cognitive, and physical well-being [1–3], partly due to treatment-induced effects later. Surgery (including axillary resection) is associated with lymphoedema, pain in the arm and shoulder, and movement restrictions of the arm and shoulder

[4]. Radiotherapy can lead to pneumonitis, skin changes, and pain and lymph oedema in the arm following nodal irradiation [4,5]. Chemotherapy can lead to premature menopause, neuropathy [4] and bone loss [5]. Both chemotherapy and anti-hormonal therapy were also negatively associated with cognitive decline, although the evidence is not conclusive [4,6]. Cardiotoxic effects can follow radiotherapy, chemotherapy (anthracyclines) and targeted therapies (anti-HER2 treatment and trastuzumab) [4,5,7,8]. Other common effects of breast cancer diagnosis and treatment were fatigue, insomnia, depression and cognitive dysfunction [1,4,6], and one third of patients experienced sexual problems, which were more pronounced in patients who were treated with chemotherapy [4].

All in all, the transition from treatment to 'life after cancer' is a

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difficult one, and can result in unmet needs [9]. Patients receive follow-up care to inform and counsel them about these potential physical and psychosocial late effects of the treatment and to detect these effects at an early stage [10–12]. International guidelines prescribe that follow-up visits should take place several times per year up to five years after completing treatment [10–12]. These visits are made in a hospital care setting, are often related to monitoring for recurrences of breast cancer and are done by a physician or nurse specialising in breast cancer care [10].

Although knowledge about (late) treatment-related effects is available for each treatment modality, several studies concluded that providing information to patients during follow-up could be improved: patients were often unaware of what effects to expect later and the duration of these effects, and thus felt unprepared for the post-treatment period [3,13–15]. Patients also have expressed strong unmet needs for education, information, or support related to physical impairments or activity limitations [3]. A complete overview of risks of developing health problems after each of the breast cancer treatment modalities is useful in anticipating the informational and other needs of patients during the follow-up period. The primary goal of this study was to identify treatment-related health problems in breast cancer patients up to five years after completing curative treatment. A secondary aim was to identify use of care associated with these health problems.

## 2. Materials and methods

Twenty hospitals in the Netherlands (8 general hospitals, 10 teaching hospitals, and 2 academic hospitals) were willing to take part by inviting patients to fill in an online survey. In each participating hospital, fifty patients were selected from the Netherlands Cancer Registry (NCR). The NCR had documented data about incidence, diagnosis, and treatment since 1989 for all cancer patients treated in Dutch hospitals [16]. Those selected for inclusion were surgically-treated female breast cancer patients, diagnosed with early stage disease (stages I to III), aged 18 and older and diagnosed between 2012 and 2016. Patients were excluded if they were undergoing treatment for recurrent disease, could not read or write Dutch, were not receiving active follow-up anymore, or if their contact information was not up to date ( $n = 124$ ). Paper questionnaires were provided on request for patients without computer access.

From September 2017 to March 2018, 876 patients were invited by letter through the patient administration systems of each participating hospital; responses were collected until May 2018. Each letter contained individual log in credentials for the PROFILES Registry ('Patient Reported Outcomes Following Initial treatment and Long-term Evaluation of Survivorship'), an online survey application developed to study the physical and psychosocial impact of cancer and its treatment from a cohort of cancer survivors [17]. On first using this application, patients set up their own password and give consent for their responses to be processed and merged with their clinical data in the NCR. The Dutch Medical Research (Human Subjects) Act does not apply for this type of study and formal approval from an ethics committee was not required. The use of NCR data in this study was approved by the NCR Privacy Review Board.

The self-administered survey (Appendix 1) consisted of three topics: 1) a predefined list of health problems experienced during the twelve months preceding the questionnaire, retrieved from Yzermans et al. [18]; 2) associated use of health care (visiting a physician or general practitioner) over the last year; 3) personal information including highest completed level of education, current treatment status, and comorbidities. Comorbidity was defined as chronic health problems that patients experienced at the time of

completing the survey, including other types of cancer, pulmonary, cardiovascular, gastrointestinal, urogenital, musculoskeletal, neurological, metabolic/coagulation, or infectious diseases. The questionnaire was tested by a panel of current and former breast cancer patients for its readability and comprehensibility.

### 2.1. Analyses

The patient-reported data from the questionnaire was linked to the clinical data in the NCR. The following analyses were performed. First, respondent characteristics (age, year of diagnosis, type of surgery, stage of disease, and type of hospital) were compared against non-respondent characteristics to assess generalisability (chi-square, level of significance  $p < 0.05$ ). Second, patient characteristics and patient-reported health problems plus health care use were presented. Health problems were categorised according to organ system, resulting in eleven categories, and presented against time since diagnosis. Thirdly, the effect of patient and treatment characteristics on the health problems experienced was tested through multivariate logistic regression analyses. A regression was formed for each category of health problems. Levels of significance of 0.10 and 0.05 were applied for univariate and multivariate regression, respectively. Factors tested in relation to reported health problems were: age at time of the survey, time since diagnosis (in years), highest completed level of education, presence of comorbidities, lateralisation of disease, type of surgical intervention (whether or not combined with radiotherapy), axillary surgery, chemotherapy (whether or not combined with targeted therapy), anti-hormonal therapy, and breast reconstruction surgery. All analyses were performed in STATA SE14.2 [19].

## 3. Results

Out of 876 invited patients, 404 completed the questionnaire (46%). Respondents were a representative sample of the invited population based on patient and treatment characteristics, with a slight underrepresentation for the youngest and oldest patients (20% for respondents versus 25% for non-respondents for age < 50; 17% for respondents versus 23% for non-respondents ages 70+;  $p = 0.010$ , results not shown). Table 1 shows all patient characteristics. The median age at the time of response was 62.0 years (range: 27.5–91.6). One (33%) or more than one (15%) comorbid diseases were present in 48% of patients. Of all patients, 59% received breast conserving therapy and 41% received a mastectomy; 21% also received axillary dissection, and 72% received treatment with radiotherapy. Adjuvant or neoadjuvant treatment with chemotherapy and anti-hormonal therapy (categories not mutually exclusive) was given to 49% and 57% respectively; chemotherapy was combined with trastuzumab in one quarter of patients treated with chemotherapy. These treatment characteristics are representative for the surgically treated breast cancer population in the Netherlands.

### 3.1. Health problems

Health problems were grouped in eleven categories based on organ system (Table 2). In total, 377 out of 404 (93%; Fig. 1) respondents experienced one or more health problems in at least one of these categories. Patients most often reported complaints in the following categories: musculoskeletal health problems (70.5%); central nervous system health problems (66.1%), in particular memory and concentration impairment (42.6%); fatigue (63.4%); reproductive system health problems (54.5%); problems related to the breast (54.0%) and psychological health problems (53.0%; Fig. 1).

**Table 1**  
Respondent characteristics (n = 404).

	N (404)	%
<b>Patient characteristics</b>		
<b>Age at time of survey</b>		
Mean (SD, range)	62.0 (10.9, 27.5–91.6)	
<50	56	14
50–59	108	27
60–69	133	33
70+	107	26
<b>Time between diagnosis and survey</b>		
<2	83	21
2–3	92	23
3–4	85	21
4–5	89	22
>5	55	14
<b>Highest completed level of education<sup>a, b</sup></b>		
Secondary education or lower	122	30
Medium vocational training (MBO)	170	42
Higher vocational training (HBO/university)	108	27
<b>Comorbidity<sup>a, b</sup></b>		
None	188	47
One	131	33
Two or more	61	15
<b>Tumour characteristics</b>		
<b>Year of diagnosis</b>		
2012	54	13
2013	92	23
2014	86	21
2015	89	22
2016	83	21
<b>Stage</b>		
I	186	46
II	174	43
III	44	11
<b>Hormone receptor status<sup>a</sup></b>		
HR-positive	287	71
ER or PR positive	53	13
HR-negative	62	15
<b>Tumour grade<sup>a</sup></b>		
1	95	24
2	176	44
3	95	24
<b>Treatment characteristics</b>		
<b>Surgery<sup>a</sup></b>		
Breast conserving surgery	238	59
Mastectomy	160	41
<b>Local treatment modalities:</b>		
Axillary dissection	85	21
Radiotherapy	291	72
Immediate breast reconstruction	36	9
<b>Systemic treatment modalities:</b>		
Chemotherapy	196	49
- With trastuzumab	50	12
Anti-hormonal therapy	232	57
<b>Hospital characteristics</b>		
<b>Hospital type<sup>c</sup></b>		
General hospital	166	41
Teaching/academic hospital	238	59
<b>Hospital volume<sup>d</sup></b>		
Low	157	39
Medium	88	22
High	159	39

<sup>a</sup> Totals do not add up due to missing values.<sup>b</sup> Patient-reported.<sup>c</sup> Hospitals were categorised as either general, teaching, or academic hospitals.<sup>d</sup> Number of surgically treated non-metastatic breast cancer patients per year (average over 2012–2016), categorised as low (<100), medium (100–149), and high (>150) volume.

When stratified by time since diagnosis, the majority of health problems were present to the same extent over time (Table 3). Only the number of patients with fatigue (78%–56%,  $p = 0.033$ ), hair loss (34%–15%,  $p = 0.023$ ) and premature menopause (53%–35%,  $p = 0.024$ ) decreased significantly over time, whereas the number

of patients with pain and/or complaints in the back (19%–44%,  $p = 0.022$ ) and pain and/or complaints in the lower extremities (27%–51%,  $p = 0.023$ ) increased significantly over time.

### 3.2. Effect of patient and treatment characteristics on experiencing health problems

Surgical treatment with adjuvant radiotherapy was provided in 58% and 14% of patients with breast conserving surgery and amputation respectively; 25% had amputations without radiotherapy. At the time of the survey, 39% of patients were still being treated with anti-hormonal therapy, 11% had finished treatment (7% unknown ( $n = 28$ )). Chemotherapy was administered in 50% of patients, of which one quarter received additional trastuzumab.

Treatment modalities that were significantly associated with reported health problems based on the multivariate analyses are shown in Table 4. Surgery with adjuvant radiotherapy treatment and axillary dissection were significantly associated with a higher risk of problems in the breast area (breast conserving surgery: OR:3.16,  $p < 0.001$ ; amputation: OR:2.25,  $p = 0.032$ ; axillary dissection: OR:2.84,  $p = 0.001$ ). Immediate breast reconstruction was associated with musculoskeletal health problems (OR:4.44,  $p = 0.022$ ). Treatment with chemotherapy was significantly associated with an increased risk for fatigue (OR: 2.00,  $p = 0.020$ , with trastuzumab OR: 2.40,  $p = 0.031$ ), respiratory health problems (OR:1.81,  $p = 0.029$ ; with trastuzumab OR:2.74,  $p = 0.005$ ), gastrointestinal health problems (OR:1.87,  $p = 0.011$ ; with trastuzumab OR:2.06,  $p = 0.035$ ), central nervous system health problems (OR:3.40,  $p < 0.001$ ; with trastuzumab OR:2.51,  $p = 0.029$ ), and skin health problems (OR:2.62,  $p < 0.001$ ; with trastuzumab OR:2.51,  $p = 0.029$ ). Currently receiving anti-hormonal therapy was significantly associated with an increased risk of fatigue (OR:1.73,  $p = 0.040$ ), and reproductive system health problems (OR:1.91,  $p = 0.019$ ). Completed administration of anti-hormonal therapy was significantly associated with a reduction in central nervous system health problems (OR:0.42,  $p = 0.028$ ).

Supplementary Table 1 shows factors that were significant in univariate and multivariate testing. The area under the ROC curve for all eleven regression models ranged between 0.6438 (for skin problems) and 0.7791 (for reproductive system health problems).

### 3.3. Use of care

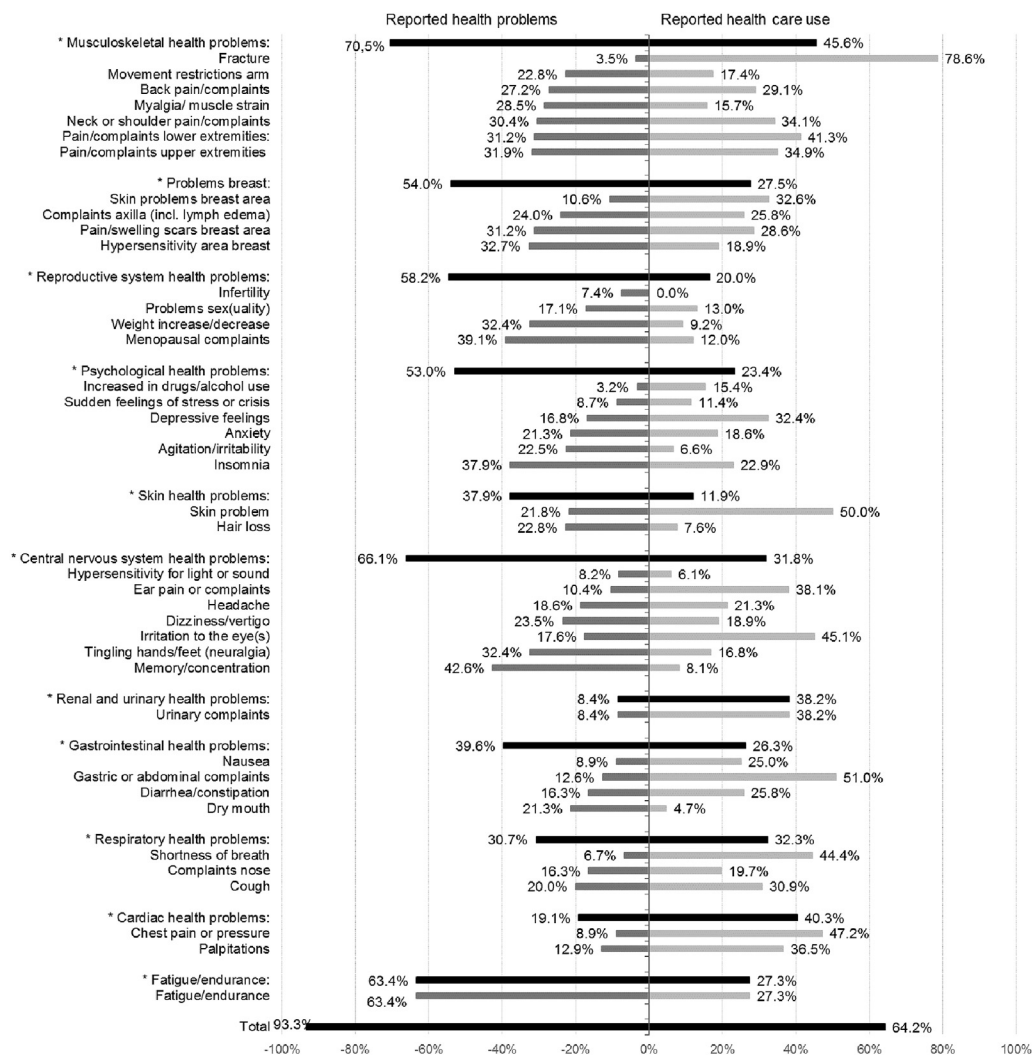
Of the 93% percent of respondents who experienced health problems, 64% used care for at least one of those problems (Fig. 1). Patients most often visited their physician for fractures (78.6%), gastric/abdominal complaints (51.0%), and skin problems (50.0%), and least often for infertility (0.0%), dry mouth (4.7%), and hypersensitivity to light or sound (6.1%). The most commonly reported health problems such as fatigue (63.4%), memory/concentration problems (42.6%), and menopausal complaints (39.1%) were not necessarily the ones for which the most use of care was reported (27.3%, 8.1%, and 12.0% respectively).

## 4. Discussion

In this study, which uses a survey from 404 women previously treated for early-stage breast cancer, 93% of respondents experienced one or more health problems during the five-year period after diagnosis. The most frequently reported categories of health problem (by >50% of respondents) were: musculoskeletal or related to the nervous system, fatigue, reproductive system, breast area, and psychological health. The majority of health problems were reported consistently over time. The present study found that treatment with chemotherapy and anti-hormonal therapy in

**Table 2**  
Health problems categorised by organ system.

Category	Health problems
Fatigue/stamina	Fatigue/stamina.
Cardiac	Palpitations, chest pain or tightness.
Respiratory	Cough, complaints in the nose, shortness of breath.
Gastrointestinal	Dry mouth, diarrhoea/constipation, gastric or abdominal complaints, nausea.
Renal and urinary	Urinary complaints,
Central nervous system	Memory/concentration, tingling hands/feet (neuralgia), irritation of the eyes, dizziness/vertigo, headache, earache or ear complaints, hypersensitivity to light or sound.
Skin	Hair loss, skin problems.
Psychological	Insomnia, agitation/irritability, anxiety, depressive feelings, sudden feelings of stress or crisis, increased use of drugs/alcohol.
Reproductive system	Menopausal complaints, weight increase/decrease, problems with sex or sexuality, infertility.
Breast	Hypersensitivity in the area breast, pain/swelling scars in the breast area, axillary complaints (including lymphoedema), skin problems in the breast area.
Musculoskeletal	Pain/complaints in the upper extremities, pain/complaints in the lower extremities, neck or shoulder pain/complaints, myalgia/muscle strain, back pain/complaints, movement restrictions in the arm, fractures.



**Fig. 1.** Patient-reported health problems and use of care.

particular were associated with a range of health problems. A secondary aim of this study was to identify use of care for the health problems reported. The three most commonly reported health problems for which care was used were fractures, gastric/abdominal complaints, and skin problems. Care was used least for infertility, dry mouth, and hypersensitivity to light or sound.

The results of the present study fit with the literature about treatment-induced effects in breast cancer patients. In multivariate regression analyses, treatment with chemotherapy and anti-hormonal therapy in particular were associated with an increase in several health problems. The literature has already described a wide range of complaints resulting from chemotherapy, including

**Table 3**  
Patient-reported health problems presented per year of diagnosis.

Health problems	Time since diagnosis (in years)										Total (n = 404)	%	
	<2		2 < 3		3 < 4		4 < 5		5 ≥				P*
	(n = 83)		(n = 92)		(n = 85)		(n = 89)		(n = 55)				
n	%	n	%	n	%	n	%	n	%				
Patient reported at least 1 health problem											377	93.3	
Fatigue/stamina	62	78	60	69	53	62	52	59	29	56	<b>0.033</b>	256	63.4
Cardiac													
Palpitations	12	15	13	15	14	16	7	8	6	12	0.470	77	19.1
Chest pain/tightness	8	10	13	15	5	6	7	7	4	8	0.250		
Respiratory													
Shortness of breath	8	10	5	6	7	8	5	6	2	4	0.593	124	30.7
complaints nose	10	13	16	18	16	19	14	16	10	19	0.828		
Cough	11	14	19	22	18	21	21	24	12	23	0.591		
Gastro-intestinal													
Stomach/abdomen complaints	10	13	12	14	7	8	13	15	9	17	0.585	160	39.6
Dry mouth	20	25	23	26	18	21	15	17	10	19	0.540		
Nausea	11	14	4	5	8	9	9	10	4	8	0.320		
Diarrhoea/constipation	15	19	11	13	16	19	17	20	7	13	0.643		
Renal and urinary													
Urinary complaints	8	10	8	9	8	9	6	7	4	8	0.943	34	8.4
Central nervous system													
Memory/concentration	40	51	39	45	37	44	37	42	19	36	0.513	267	66.1
Irritation to the eye(s)	14	18	15	17	15	18	18	20	9	17	0.982		
Dizziness	21	27	24	28	23	27	16	18	11	21	0.508		
Head ache	17	22	20	23	15	18	12	14	11	21	0.539		
Ear pain or complaints	9	12	6	7	9	11	8	9	10	19	0.236		
Tingling hands/feet	24	31	31	36	35	41	26	30	15	28	0.413		
Hypersensitive for light	3	4	10	11	8	9	5	6	7	13	0.215		
Skin													
Skin problems	19	24	22	25	19	22	15	17	13	25	0.712	153	37.9
Hair loss	27	34	13	14	20	24	24	27	8	15	<b>0.023</b>		
Psychological													
Anxiety	17	22	23	26	21	25	14	16	11	21	0.507	214	53.0
Depressive feelings	12	15	15	17	18	21	14	16	9	17	0.877		
Sudden feelings of stress or crisis	6	8	5	6	8	9	10	11	6	11	0.687		
agitation/irritability	14	18	22	25	23	27	19	22	13	25	0.680		
Insomnia	28	36	38	44	35	41	34	39	18	34	0.763		
Increase drugs/alcohol use	2	3	4	5	3	4	2	2	2	4	0.921		
Reproductive system													
Problems with sex or sexuality	17	22	10	11	18	21	11	13	13	25	0.128	220	54.5
Menopausal complaints	42	53	37	43	35	41	25	28	19	36	<b>0.024</b>		
Weight increase/decrease	33	42	32	37	31	36	21	24	14	26	0.090		
Infertility	5	6	7	8	10	12	4	5	4	8	0.485		
Breast													
Pain/swelling scars	28	35	28	32	23	27	28	32	19	36	0.783	218	54.0
Hypersensitive breast area	25	32	28	32	32	38	27	31	20	38	0.813		
Complaints axilla (incl. lymphoedema)	21	27	26	30	21	25	13	15	16	30	0.140		
Skin problems breast area	9	11	10	11	8	9	11	13	5	9	0.964		
Musculo-skeletal													
Neck or shoulder pain/complaints	25	32	28	32	28	33	19	22	23	44	0.091	285	70.5
Back pain/complaints	15	19	22	25	28	33	22	25	23	44	<b>0.022</b>		
Pain/complaints upper extremities	27	35	27	31	33	39	24	27	18	35	0.573		
Fractures	0	0	4	5	6	7	4	5	0	0	0.080		
Pain/complaints lower extremities	21	27	26	30	29	34	23	26	27	51	<b>0.023</b>		
Myalgia/muscle strain	28	36	23	26	23	27	24	27	17	32	0.635		
Movement restrictions arm	24	30	19	22	21	25	14	16	14	26	0.253		

\* Chi-squared tested (level of significance: 0.05).

premature menopause, pneumonitis, bone loss, and skin changes, cardiotoxic effects, neuropathy, and cognitive decline [4–6]. The present study found a positive association between receiving anti-hormonal therapy and reproductive system health problems. Literature states that anti-hormonal treatment may lead to vasomotor symptoms, sexual dysfunction, and infertility [4]. In total, 17% of our respondents reported problems with sexuality. The actual proportion of patients with sexuality problems may be higher, as patients may feel uncomfortable reporting these problems [20]. Furthermore, the negative effects of autologous breast reconstruction on arm symptoms, and breast conserving therapy (with additional radiotherapy) on breast symptoms have already been described in the literature [21]. The present study found an association between breast reconstruction and musculoskeletal problems (including arm symptoms), and between radiotherapy treatment and health problems in the breast (including skin problems). However, in the utilised database, only data about immediate breast reconstruction was available in the database used, whereas patients treated with radiotherapy may have received delayed breast reconstruction to avoid these effects [22].

Almost all health problems were reported consistently over the time since diagnosis (except for fatigue, hair loss and menopausal complaints), suggesting the majority of problems remained present over time. This was confirmed in a cohort study by Van Leeuwen et al. [2]. The decrease in menopausal complaints may follow from decreasing therapy adherence to anti-hormonal treatment [23]; Hershman et al. [24] stated that 18% of patients are non-compliant in the first two years. This underlines the need for longitudinal studies to gain an understanding of the possible ongoing cancer-related late effects, that may not have the same development over time in patients. This is important, because persistent symptoms or side-effects have been associated with distress and poor quality of life for breast cancer survivors and cancer survivors in general [9,13]. This negative effect of continuing symptoms on the quality of life is important regarding the use of care that was evaluated in the present study, which also sheds light on the share of health problems that is presented to the physician: almost all breast cancer patients experienced health problems, but only half of the respondents reported the use of care for one or more of these. Lubberding et al. [15] described how post-treatment symptoms

**Table 4**  
The effect of treatment factors on patient-reported health problems.

Treatment modality <sup>x</sup>	Surgical treatment and radiotherapy			Axillary dissection		Breast reconstruction		Anti-hormonal therapy			Chemotherapy		
	BCS incl. radiotherapy <sup>x</sup>	AMP excl. radiotherapy	AMP incl. radiotherapy					Not applied <sup>x</sup>	ongoing <sup>x</sup>	completed <sup>x</sup>	Not applied	Applied	Applied + Trastuzumab
Group size (%)	233 (58)	102 (25)	58 (14)	319 (79)	85 (21)	368 (91)	36 (9)	172 (43)	159 (39)	45 (11)	208 (51)	146 (36)	50 (12)
Health problems <sup>†</sup> :													
Fatigue/stamina	-	ref	-	ref	-	ref	-	ref	1.01	1.73* (0.03-2.91)	ref	2.00* (1.12-3.57)	2.40* (1.09-5.31)
Cardiac	-	ref	-	ref	-	ref	-	ref	-	-	ref	-	-
Respiratory	-	ref	-	ref	-	ref	-	ref	-	-	ref	1.81* (1.06-3.08)	2.74* (1.36-5.54)
Gastrointestinal	-	ref	-	ref	-	ref	-	ref	-	-	ref	1.87* (1.15-3.01)	2.06* (1.05-4.04)
Renal and urinary	-	ref	-	ref	-	ref	-	ref	-	-	ref	-	-
Central nervous system	-	ref	-	ref	-	ref	-	ref	0.42* (0.19-0.91)	1.20	ref	3.40* (1.80-6.42)	2.51* (1.10-5.74)
Skin	-	ref	-	ref	-	ref	-	ref	-	-	ref	2.62* (1.59-4.34)	2.13* (1.09-4.21)
Psychological	-	ref	-	ref	1.66	ref	1.21	ref	-	-	ref	1.66	1.21
Reproductive system	-	ref	-	ref	1.13	ref	-	ref	0.60	1.91* (1.11-3.27)	ref	1.73	2.07
Breast	3.16* (1.75-5.69)	ref	2.25* (1.07-4.72)	ref	2.84* (1.52-5.30)	ref	0.87	ref	-	-	ref	-	-
Musculoskeletal	-	ref	-	ref	1.66	ref	4.44* (1.24-15.85)	ref	0.77	1.49	ref	1.49	0.96

BCS: breast conserving surgery; AMP: amputation

Factors that were significant in univariate testing (p<0.10) were included in multivariate testing. Cells are empty when factors were not significant in univariate testing and thus not included in multivariate testing. Reference categories were patients treated without the specified treatment modalities.  
Corrected for age at time of the survey, years since diagnosis, highest completed level of education, presence of comorbidities, and lateralisation of disease.

\* significant in multivariate testing (level of significance in multivariate testing: 0.05). 95% confidence interval between brackets.  
† See Table 2 for the health problems identified per category  
x Totals do not add up due to missing values.

often remain unknown to health care providers, for both social (not wanting to bother people in their surroundings) and practical reasons (short consultation time, not having a follow-up appointment when symptoms emerged, not knowing who to contact in the event of symptoms). However, they noted as well that a complete overview of the patient's health status was missing, resulting in a lack of coordination of care and suboptimal referral to supporting care services. However, a complete overview of health status should be the foundation of follow-up for later effects of breast cancer treatment. During consultations, this overview could be obtained by administering and discussing of patient-reported outcome measures that consist of symptom-specific measurement scales addressing both physical and psychosocial topics [25,26], or by symptom checklists [27,28]. Long-term regular assessment of these measures during follow-up means that health problems that persist become a burden later are detected as well.

Discrepancies with the literature were found as well. No treatment factors were associated with the risk of cardiac health problems, even though the risk of cardiovascular disease is increased by 30% in cancer survivors and was significantly associated with radiotherapy and systemic treatment [7,8,29]. The increased risks for coronary events starts within the five years after radiotherapy, but may continue for up to 20–30 years [8,29]. Effects that develop over a period of time longer than five years, may therefore have been missed in the present study. Furthermore, no significant association between chemotherapy and reproductive system health problems was found, whereas literature reports infertility in more than half of patients younger than 40 [4]. However, only 4% of respondents (n = 16) were younger than 40, possibly reducing the

power to detect this effect.

Some notes are needed when interpreting the results of this study. The application of patient-reported surveys is related to forms of bias, including recall bias and response bias. Recall bias might lead to underestimation of complaints, as patients may not recall all the health problems they experienced. Response bias may lead to underestimation or overestimation, as patients with poorer health may either feel more urgency or feel too sick to participate. Underestimation of health problems may have occurred, as 79% of patients with fractures reported use of the healthcare system, where this would be expected to be 100%. The interpretation of our results could be improved by comparing them against health problems in the general population, to better understand which health problems are more prevalent in breast cancer patients. This step will be undertaken in our further research. Most breast cancer patients (76%) in a study by Hagen et al. [30] reported health complaints equally as often as the controls, however, health problems such as leg pain, interrupted sleep, hot flushes, tiredness, dizziness, and diarrhoea were reported significantly more by patients than controls. Lastly, interaction between treatment modalities that were associated with the health problems reported were tested, but no interactions were found. Friese et al. [31] found that receiving combined chemotherapy and radiation therapy was associated with a greater severity of toxicity reported.

#### 4.1. Implications for practice

Breast cancer is the most commonly diagnosed cancer in women worldwide, estimated at 2.1 million new diagnoses in 2018

[32]. Breast cancer patients in North America and Europe have a five-year survival of over 80% [33]. The extrapolation of the health problems found in the present study to this enormous group of surviving patients endorses the importance of proper follow-up care. The factors associated with the health problems found in this study could be used in multiple ways. First, they could be helpful in recognising current symptoms in relation to previous cancer treatment [9]. This could also be important for general practitioners, who might be consulted by patients about health issues induced by breast cancer treatment long after follow-up is completed [9]. Secondly, it would be applicable in a prospective model of monitoring, to promote monitoring and healthy behaviours, to provide education about health problems and early identification of them, and to introduce rehabilitation when limitations are identified [34]. Thirdly, information about health problems after breast cancer treatment focus more on specific target groups, ranging from patients with low to high burdens of symptoms in terms of pain, psychological complaints and fatigue, and burdens due to other complaints [35]. Patient-reported outcome measures (PROMS), for instance the standard set suggested by the International Consortium for Health Outcomes Measurement (ICHOM) Initiative, can be used to monitor health problems and quality of life [36].

## 5. Conclusion

Almost all patients treated for early-stage breast cancer experienced health problems up to five years after diagnosis. The most frequent categories of health problems (>50%) were related to the musculoskeletal system, nervous system, fatigue, reproductive system, breast area, and psychological health. Treatment with chemotherapy and anti-hormonal therapy in particular were associated with health problems being reported. Factors associated with the development of health problems are useful for informing patients better beforehand and for targeting follow-up care.

## Conflicts of interest

None.

## Ethical approval

The Medical Research (Human Subjects) Act does not apply for this type of study and formal approval from an ethics committee was not required.

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.breast.2019.03.010>.

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