Retrospective Study

High Body Mass Index Is a Potential Risk Factor for Persistent Postoperative Pain after Breast Cancer Treatment

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Background: Risk factors associated with persistent pain after breast cancer treatment are needed to develop prevention and treatment strategies to improve the quality of life for patients with breast cancer.

Objectives: To identify factors associated with persistent pain in women undergoing breast cancer treatments.

Study Design: Retrospective study.

Setting: Regional hospital in the Netherlands.

Methods: The primary outcome was pain associated with surgery at more than 6 months postoperatively and patients were stratified based on the associated visual analog" scale score they reported: reporting no pain as "no pain," pain 1 – 29 mm as "mild pain," and pain 30 – 100 mm as "moderate/severe pain." Secondary outcomes were function, symptom, and total quality of life scores. Predefined risk factors analyzed for association with outcomes included: age, smoking status, diabetes, body mass index (BMI), disease stage, surgery type, axillary lymph node dissection, reoperation, chemotherapy, radiotherapy, and hormone therapy.

Results: Of the 718 patients who were approached, 492 were included (follow-up 2.5 ± 1.8 years). Thirty-five percent of patients developed persistent pain (n = 122 "mild pain," n = 53 "moderate/severe pain'"). Age, BMI, surgery type, axillary lymph node dissection, disease stage, reoperation, chemotherapy, and radiotherapy were identified as potential risk factors in univariate ordinal regression analyses ($P < 0.10$). Age ($P < 0.01$) and BMI ($P = 0.04$) remained independently predictive in the multivariate model. BMI and age were associated with odds ratios (ORs) of 1.04 (95% confidence intervals (CI): 1.00 – 1.08) and 0.97 (95% CI: 0.95 – 0.99), respectively per point and year increase. BMI was associated with a higher symptom score (r = 0.14, $P < 0.01$), a lower level of function (r = -0.11, $P = 0.01$), and lower total quality of life scores (r = -0.13, $P < 0.01$).

Limitations: The retrospective nature of this study makes it prone to response and misclassification bias.

Conclusion: BMI and age may be risk factors for persistent postoperative pain after breast cancer treatment.

Key words: Persistent postsurgical pain, breast cancer treatment, BMI, age, chronic postoperative pain, breast cancer surgery

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Persistent pain after treatment of breast cancer is a significant clinical problem due to its effect on quality of life (1) and its general resistance to treatment (2). The incidence of persistent pain after treatment of breast cancer has been well documented in the past and has been reported to be around 20% – 30% (3,4). Recent advancements in the protocols for breast cancer management, including chemotherapy protocols, radiation therapy cycles, and surgical approaches to lymph node dissection, lumpectomy, and mastectomy seem to have lowered the incidence and severity of persistent pain after breast cancer treatment (5-9). However, moderate to severe persistent pain still affects ~15% of women (10).

There are likely multiple pathogenic mechanisms underlying persistent pain after breast cancer treatment. Among patient-related risk factors are age (11), genetic polymorphisms (12), and psychological factors such as anxiety and depression (13). Among treatment-related risk factors more extensive surgery in the axilla, radiation therapy, and chemotherapy have all been suggested as important risk factors (11,14). Recently, obesity and low-grade inflammation have also been identified as potential risk factors for persistent pain (14,15).

More data on the multiple demographic and treatment factors likely associated with persistent pain after breast cancer treatment are needed to develop prevention and treatment strategies to improve the quality of life for patients with breast cancer. In this large retrospective cohort study, we examined the prevalence and factors associated with persistent pain after breast cancer surgery and adjuvant treatments.

Methods

Study Population

We identified patients that were treated for unilateral non-metastasized breast cancer from a registry of surgical procedures. All patients were treated at a regional hospital in the Netherlands (Reiner de Graaf Gasthuis, Delft) between September 2005 and September 2008. Inclusion criteria were age 18 years or older and surgery either by lumpectomy or mastectomy for suspected breast carcinoma. Patients with a preoperatively known pain disorder were excluded. This study was conducted according to the guidelines of the Central Committee on Research Involving Human Subjects in the Netherlands (approval nr. 09 – 057) and the principles outlined in the declaration of Helsinki (16). Written informed consent was obtained from all participants.

Primary Clinical Outcome

The clinical outcome was persistent pain at long-term follow up. Patients were asked to fill out a questionnaire at least 6 months postoperatively and were asked if they have persistent pain due to their surgery. Additionally, they rated their current pain intensity on a 100 mm visual analog scale (VAS). Patients were stratified into 3 categories: patients reporting no pain related to surgery were classified as "no pain," patients reporting pain related to surgery were classified into categories based on their reported VAS score: 1 – 29 mm was considered "mild pain" and 30 – 100 mm was considered "moderate/severe pain." These cut-off scores are regularly applied in pain research (17) and recent studies on persistent pain after breast cancer surgery followed a similar approach (10,14).

Secondary Outcomes

Secondary outcomes included various quality of life scores obtained from the European Organization for Research and Treatment of Cancer quality of life questionnaire (EORTC-30) (18). We calculated function, symptom, and total quality of life scores as previously described (19). Additionally, patients were asked if they had developed lymphedema as a result of treatment.

Risk Factors Associated with Outcomes

We investigated demographic and treatment factors that have previously been reported to potentially influence persistent pain after treatment for breast cancer (11). Our predefined risk factors were age, smoking status (smoking vs. no smoking), diabetes (diabetes vs. no diabetes), body mass index (BMI), histopathological disease stage, surgery type (mastectomy vs. lumpectomy), axillary lymph node dissection (axillary lymph node dissection vs. no axillary lymph node dissection), reoperation (reoperation vs. no reoperation), chemotherapy (chemotherapy vs. no chemotherapy), radiotherapy (radiotherapy vs. no radiotherapy), and hormone therapy (hormone therapy vs. no hormone therapy).

Data Retrieval

Patient characteristics, medical history, performed intervention, and pathology reports were collected retrospectively from medical records. Height and weight for BMI calculation were extracted from the preoperative visit.

Data Analysis

Demographics and clinical data for patients within our predefined subgroups of "no pain," "mild pain," and "moderate/severe pain" are presented as mean ± standard deviation, or as median and interquartile range (IQR) when not normally distributed. Association of risk factors with study outcomes followed a 2-step procedure: First, all risk factors (see above) were analyzed using univariate ordinal logistic regression. Results from these analyses are presented as odds ratios (ORs) with 95% confidence intervals (CI) as well as the corresponding *P*-value. Second, risk factors associated with study outcome in univariate models ($P < 0.10$) were included in a multivariable ordinal logistic regression model. Additional analyses were performed on the risk factors that remained independently predictive in the multivariate analysis to assess the distribution of the other risk factors among them. Logistic probability plots were generated for the independent significant predictors to aid in the interpretation of the results. These plots are helpful to determine the risk associated with a specific clinical value of a risk factor, because they display the related risk (and CI) throughout the range of possible values for the factor.

Function, symptom, and total quality of life scores showed non-normally distributed residuals, therefore the Wilcoxon rank-sum test and Spearman's correlation were used to perform univariate analysis of association between risk factors and secondary outcomes. The software package JMP, version 12 (SAS Institute Inc, Cary, NC, USA) was used for the statistical analyses. A statistical expert was consulted regarding the analyses.

A subsequent study, in the patient population that developed mild or moderate/severe pain, is currently under revision at another journal that focuses on pain medicine. That study investigated whether a neuropathic component of persistent postsurgical pain can be reliably detected using questionnaires.

Table 1. *Patient characteristics*.

	Studied Patients (n = 492)	All Screened Patients (n = 718)
Age (years ± SD)	61 ± 12	63 ± 13
Smoking, n (%)	68 (14)	
Diabetes, n (%)	47 (9)	
BMI (kg/m^2)	26 ± 5	
Mastectomy (instead of lumpectomy), n (%)	230 (46)	337 (47)
Axillary lymph node dissection, n (%)	186 (37)	263 (37)
Reoperation, n (%)	195 (39)	272 (38)
Chemotherapy, n (%)	229 (46)	300 (42)
Radiotherapy, n (%)	323 (65)	466 (65)
Hormone therapy, n (%)	264 (53)	371 (52)
Disease stage, n (%)		
0	44 (9)	61 (9)
IA	171 (36)	245 (35)
IB	16 (3)	20 (3)
IIA	118 (25)	188 (26)
IIB	71 (15)	92 (13)
IIIA	41 (9)	56 (8)
IIIB	10 (2)	19 (3)
IIIC	9 (2)	20 (3)

Students T-test and chi-squared testing were employed to compare studied patients to all screened patients, characteristics were comparable between groups ($P > 0.05$). BMI: body mass index.

Results

Seven hundred and eighteen eligible women were sent questionnaires and asked to participate. Four hundred and ninety-two patients completed the questionnaires (~69% response rate). Table 1 shows the characteristics of participating patients as well as the characteristics of all the screened patients (no significant differences). The mean duration of follow-up was 927 ± 682 days (median 850 ± IQR 789).

Primary Clinical Outcome

Out of 492, 317 patients (64%) reported no persistent pain associated with surgery and they were classified as having "no pain." One hundred twenty-two (25%) patients developed mild persistent pain and 53 (11%) developed moderate/severe persistent pain. The average clinical pain scores in the mild and moderate/severe groups were 14 ± 8 and 45 ± 13 mm VAS, respectively, at long-term follow-up (> 6 months).

Risk Factors for Primary Outcome

Preliminary univariate analyses identified 8 risk factors potentially associated with development of persistent postoperative pain. These were age ($P < 0.01$), BMI ($P = 0.06$), surgery type ($P = 0.07$), axillary lymph node dissection ($P < 0.01$), reoperation ($P = 0.01$), chemotherapy ($P < 0.01$), radiotherapy ($P = 0.03$), and histopathological disease stage ($P = 0.02$) – Table 2. None of the other predefined risk factors were associated with development of persistent post-operative pain (all $P > 0.10$). Chemotherapy treatments consisted of adriamycine and cyclofosfamide (n = 106), adriamycine and cyclofosfamide followed by a taxane (n = 52), a taxane, adriamycine, and cyclofosfamide together (n = 45), or another regimen (n = 18). The type of chemotherapy was not associated with persistent pain (chi-squared test, $P > 0.05$).

Multivariable analysis showed that age ($P < 0.01$) and BMI ($P = 0.04$) were independently and significantly associated with the development of persistent pain. The corresponding ORs and 95% CI for all risk factors in the multivariate model are reported in Table 3.

We also assessed the distribution of other risk factors throughout the range of BMI and age values (Table 4 – 7). BMI was stratified into groups < 25 kg/m^2 (normal), 25 – 30 kg/m^2 (overweight), and > 30 kg/m^2 (obese) (20). Age was categorized as ≤ 50 or > 50 (14). We found that overweight and obese patients had more diabetes than patients with a normal BMI ($P < 0.01$) and that overweight patients were slightly older than patients with a normal BMI ($P = 0.03$) (Table 4). When we compared younger (≤ 50) patients to older (> 50) patients, we found that younger patients presented with higher grade tumors, as evidenced by higher rates of IIB and IIIA tumors (Table 7). Consistently, younger women underwent more extensive treatments with higher rates of mastectomy ($P < 0.01$), axillary lymph node dissection ($P = 0.01$), reoperation ($P = 0.02$), chemotherapy ($P <$

Table 2. *Univariate analysis of putative risk factors associated with persistent post-operative pain.*

Risk factor	Moderate/severe persistent pain (n = 53)	Mild persistent pain (n = 122)	Pain free (n=317)	OR (95% CI)	*P*-value
Age (years ± SD)	57.8 ± 1.6	57.9 ± 9.7	62.7 ± 12.6	0.97 (0.95 – 0.98)	< 0.01
Smoking (smoking vs. no smoking), n (%)	9 (17)	14 (11)	43 (14)	1.02 (0.60 – 1.74)	0.93
Diabetes (diabetes vs. no diabetes), n (%)	8 (15)	8 (7)	29 (9)	1.12 (0.60 – 2.07)	0.72
BMI (kg/m^2)	27.3 ± 6.7	25.8 ± 4.6	25.6 ± 4.1	1.04 (1.00 – 1.08)	0.06
Surgery type (mastectomy vs. lumpectomy), n (%)	23 (43)	47 (39)	155 (49)	0.71 (0.49 – 1.03)	0.07
Axillary lymph node dissection (axillary dissection vs. no dissection), n (%)	26 (49)	56 (46)	102 (32)	1.82 (1.26 – 2.65)	< 0.01
Reoperation (reoperation vs. no reoperation), n (%)	27 (52)	54 (44)	111 (35)	1.63 (1.13 – 2.35)	0.01
Chemotherapy (chemotherapy vs. no chemotherapy), n (%)	33 (62)	66 (54)	127 (41)	1.93 (1.34 – 2.79)	< 0.01
Radiotherapy (radiotherapy vs. no radiotherapy), n (%)	37 (71)	89 (73)	194 (62)	1.57 (1.06 – 2.34)	0.03
Hormone therapy (hormone therapy vs. no hormone therapy), n (%)	27 (51)	71 (58)	163 (52)	0.88 (0.61 – 1.27)	0.50
Histopathological stage				1.13 (1.02 – 1.25)	0.02
0	30	8	6		
IA	120	37	14		
IB	10	4	2		
IIA	77	33	8		
IIB	32	27	12		
IIIA	28	7	6		
IIIB	4	1	2		
IIIC	4	3	2		

The ORs are based on changes of one year for age, 1 kg/m^2 for BMI, and one for histopathological stage.

Table 3. *Multivariate analysis of risk factors associated with persistent postoperative pain.*

Risk factor	Multivariate analysis	
	OR (95% CI)	*P*-value
Age	0.97 (0.95 – 0.99)	< 0.01
BMI	1.04 (1.00 – 1.08)	0.04
Stage	1.07 (0.90 – 1.23)	0.45
Axillary lymph node dissection	1.22 (0.74 – 2.01)	0.44
Reoperation	1.30 (0.86 – 1.96)	0.22
Chemotherapy	1.23 (0.71 – 2.14)	0.46
Surgery type	0.72 (0.41 – 1.25)	0.25
Radiotherapy	1.22 (0.68 – 2.19)	0.50

The ORs are based on changes of one year for age, 1 kg/m^2 for BMI, and one for stage. Multivariate analysis included parameters potentially associated with development of persistent postoperative pain in univariate analysis.

0.01), hormone therapy ($P < 0.01$), and a lower rate of radiotherapy ($P < 0.01$) (Table 6).

The probability plots for persistent postoperative pain based on age and BMI within the different BMI and age strata are shown in Figs. 1 and 2.

Secondary Clinical Outcomes

As in the primary analysis, a higher BMI was associated with a higher symptom score (r = 0.14, $P < 0.01$), lower functioning score (r = -0.11, $P = 0.01$), and lower total score (r = -0.13, $P < 0.01$ – Table 8). Other risk factors associated with poorer quality of life scores were diabetes, axillary lymph node dissection, histopathological disease stage, and chemotherapy. None of the other predefined risk factors were associated with quality of life scores (all $P > 0.10$). Because of the non-normal distribution of the quality of life residual scores, we were unable to assess the identified risk factors in a multivariate model.

One-hundred and eleven patients (22%) reported to suffer from lymphedema. Seventy-six (68%) of these patients underwent axillary lymph node dissection. Significantly higher rates of lymphedema were observed in patients that underwent axillary lymph node dissection vs. patients that did not have an axillary lymph node dissection (41% vs. 11%, Chi-squared test $P < 0.01$).

Table 4. *Risk factors among different BMI strata.*

Risk factor	BMI < 25 (n=252)	BMI 25 - 30 (n=155)	BMI > 30 (n=76)	*P*-value
BMI (kg/m^2), mean ± SD	22.6 ± 1.7	27.2 ± 1.3	34.3 ± 3.9	N/A
Smoking, n (%)	33 (13)	25 (16)	6 (8)	0.21
Diabetes, n (%)	7 (3)	17 (11)[a]	18 (24)[a,b]	< 0.01
Age (years), mean ± SD	60.0 ± 12.5	62.8 ± 11.3[a]	61.5 ± 11.4	0.03
Mastectomy, n (%)	119 (47)	66 (43)	33 (43)	0.68
Axillary lymph node dissection, n (%)	101 (40)	48 (32)	30 (40)	0.20
Reoperation, n (%)	105 (42)	58 (38)	27 (36)	0.54
Chemotherapy, n (%)	115 (46)	67 (44)	39 (53)	0.44
Radiotherapy, n (%)	155 (62)	107 (70)	49 (65)	0.21
Hormone therapy, n (%)	130 (52)	85 (56)	39 (52)	0.73

Comparison by Pearson Chi Squared tests and One-Way ANOVA with Tukey's HSD.
[a]Different vs. < 25.0, [b]Different vs. BMI 25 – 30
BMI = body mass index

Table 5. *Histopathological disease stage among different BMI strata.*

Risk factor	BMI 18.5 - 25 (n = 248)	BMI 25 - 30 (n = 151)	BMI >30 (n = 73)	*P*-value
Stage (overall)				0.48
0	26 (10)	13 (9)	3 (4)	N/A
IA	86 (35)	63 (42)	25 (34)	N/A
IB	11 (4)	3 (2)	2 (3)	N/A
IIA	57 (23)	40 (26)	20 (27)	N/A
IIB	41 (17)	15 (10)	13 (18)	N/A
IIIA	22 (9)	9 (6)	7 (10)	N/A
IIIB	2 (1)	3 (2)	2 (3)	N/A
IIIC	2 (1)	4 (3)	1 (1)	N/A
IV	1 (0)	1 (1)	0 (0)	N/A

Comparison by Pearson's Chi-Squared test. BMI = body mass index

Discussion

This retrospective cohort study revealed that ~36% of patients suffered from varying degrees of pain 6 months after breast cancer treatment. We identified age and BMI as independent risk factors for persistent postoperative pain development. A 1 kg/m^2 increase in BMI was associated with an OR of 1.04 (95% CI: 1.00 – 1.08). A one year increase in age was associated with an OR of 0.97 (95% CI: 0.95 – 0.99). The secondary

findings were consistent with the primary findings: a higher BMI was associated with a lower function score, higher symptom score, and a lower total quality of life score. Additionally, a significant percentage of patients were found to be suffering from lymphedema following breast cancer treatment.

Age

Younger age is commonly referred to as a predictive factor in persistent pain after breast cancer surgery. Consistent with our study, younger age has been shown to be associated with development of persistent pain after breast cancer treatment as well as higher pain intensity (11). It is unclear whether this is caused by a physiological difference in pain perception, by a difference in subjective expression, or a difference in daily physical activities (21) compared to older patients.

Table 6. *Risk factors between younger and older patients.*

Risk factor	Age ≤ 50 (n = 100)	Age > 50 (n = 392)	*P*-value
Age (years), mean ± SD	45.2 ± 4.8	65.1 ± 9.7	N/A
Smoking, n (%)	12 (12)	56 (14)	0.58
Diabetes, n (%)	5 (5.0)	41 (10.4)	0.09
BMI (kg/m^2), mean ± SD	25.6 ± 5.2	26.0 ± 4.5	0.42
Mastectomy, n (%)	59 (59)	170 (43)	< 0.01
Axillary lymph node dissection, n (%)	48 (48)	138 (35)	0.01
Reoperation, n (%)	50 (50)	145 (37)	0.02
Chemotherapy, n (%)	82 (81)	147 (37)	< 0.01
Radiotherapy, n (%)	54 (53)	269 (68)	< 0.01
Hormone therapy, n (%)	66 (65)	197 (50)	< 0.01

Comparison by unpaired T-test or Pearson's Chi-Squared test. BMI = body mass index.

Table 7. *Histopathological disease stage between different age groups.*

Risk factor	Age ≤ 50 (n = 98)	Age > 50 (n = 389)	*P*-value
Stage (overall)			< 0.01
0	4 (4)	40 (10)	0.09
IA	27 (28)	146 (38)	0.08
IB	1 (1)	16 (4)	0.24
IIA	27 (28)	93 (24)	0.54
IIB	22 (22)	51 (13)	0.03
IIIA	14 (14)	27 (7)	0.03
IIIB	0 (0)	7 (2)	0.39
IIIC	1 (1)	8 (2)	0.79
IV	2 (2)	1 (0)	0.20

Comparison by Pearson's Chi-Squared test.

BMI

In concordance with our results, 2 other large studies recently identified BMI as a potential risk factor for persistent pain. Meretoja et al (14) conducted a prospective cohort study analyzing 860 women who underwent treatment for breast cancer and, using a univariate analysis, found BMI to be potentially associated with persistent pain at 12 months after surgery. However, in a multivariate ordinal logistic regression similar to our model, BMI did not predict persistent pain. Similarly, Miaskowski et al (15) analyzed 398 patients with persistent pain at 6 months. Pain was classified as mild, moderate, or severe. Patients with severe pain had a higher BMI in comparison to the patients that were mildly affected. However, one must consider that their analysis was purely univariate.

In an earlier retrospective cohort study of 196 women undergoing breast cancer surgery by Fecho et al (22) acute pain, pain at one month, and at 6 – 12 months postoperatively was assessed. In a univariate analysis, clinically obese (BMI > 30) patients were identified as having higher levels of mean pain during the first postoperative month and a trend was described toward higher mean pain levels at 6 – 12 months postoperatively. Smith et al (23) also performed a retrospective cohort study in 511 women undergoing breast cancer surgery and assessed persistent postsurgical pain, which was defined as any pain persisting beyond 3 months postoperatively. Their univariate analysis showed a trend towards increased persistent postsurgical pain in women with higher BMI, and found women with persistent pain to be significantly heavier and taller.

Our study is the first to report a relationship in a multivariate adjusted model between higher BMI and persistent pain following breast cancer treatment. It is important to note however, that the increased risk per 1 kg/m^2 is relatively modest (~4%), in agreement with the risk reported by Meretoja et al (14).

A possible explanation for the relationship between BMI and persistent postsurgical pain may be that in patients with a high BMI axillary clearance is more challenging because of a greater amount of fatty tissue. Theoretically, this could affect the handling of the intercostobrachial nerve and thereby be subject to a potentially higher risk of pain and sensory disturbances (24). Additionally, wound infection following breast cancer surgery has been shown to be associated with a higher BMI (25). Another explanation for the relationship of BMI to persistent postsurgical pain may be that obesity is linked to persistent postsurgical pain through

Table 8. *Univariate analysis of risk factors and quality of life.*

	Function score			Symptom score			Total score		
Risk factor	**Median ± IQR**	**Median ± IQR**	***P*-value**	**Median ± IQR**	**Median ± IQR**	***P*-value**	**Median ± IQR**	**Median ± IQR**	***P*-value**
Age	N/A	N/A	0.48	N/A	N/A	0.52	N/A	N/A	0.74
Smoking vs. no smoking	88 ± 18	89 ± 20	0.80	10 ± 20	10 ± 18	0.48	86 ± 22	88 ± 19	0.73
Diabetes vs. no diabetes	80 ± 22	89 ± 22	< 0.01	18 ± 23	9 ± 18	< 0.01	80 ± 20	89 ± 19	< 0.01
BMI	N/A	N/A	< 0.01	N/A	N/A	< 0.01	N/A	N/A	< 0.01
Lumpectomy vs. mastectomy	89 ± 22	87 ± 22	0.23	10 ± 20	10 ± 18	0.41	89 ± 20	88 ± 20	0.65
Axillary lymph node dissection vs. no lymph node dissection	84 ± 22	90 ± 20	< 0.01	14 ± 18	8 ± 18	< 0.01	84 ± 21	90 ± 17	< 0.01
Reoperation vs. no reoperation	87 ± 22	89 ± 22	0.20	10 ± 18	10 ± 18	0.66	88 ± 21	89 ± 18	0.39
Chemotherapy vs. no chemotherapy	87 ± 21	91± 22	< 0.01	13 ± 18	8 ± 18	< 0.01	86 ± 19	90 ± 19	< 0.01
Radiotherapy vs. no radiotherapy	89 ± 22	89 ± 19	0.83	10 ± 20	8 ± 18	0.25	89 ± 21	88 ± 17	0.63
Hormone therapy vs. no hormone therapy	87 ± 20	89 ± 24	0.10	10 ± 18	8 ± 18	0.25	88 ± 19	90 ± 21	0.16
Histopathological disease stage	N/A	N/A	< 0.01	N/A	N/A	< 0.01	N/A	N/A	< 0.01

As function, symptom, and total quality of life scores showed non-normal distribution, the Wilcoxon rank-sum test and Spearman's correlation were used to perform univariate analysis of association between risk factors and secondary outcome. BMI = body mass index.

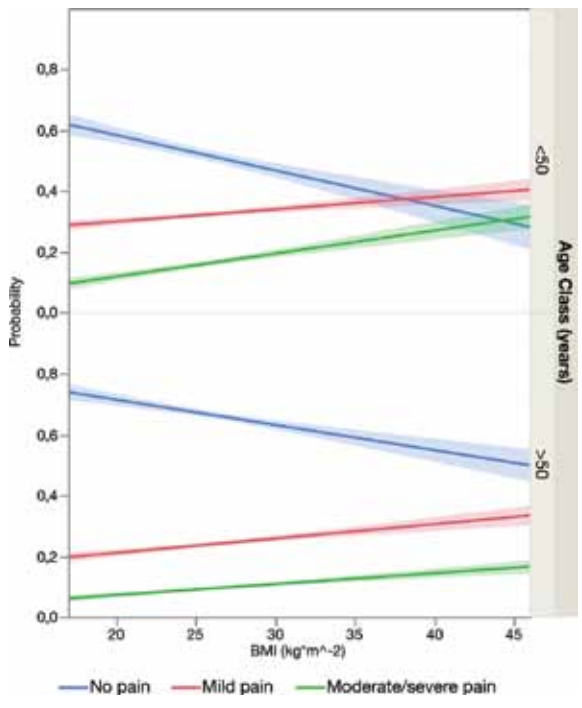

Fig. 1. *Probability of being in the different ordinal persistent postoperative pain categories at > 6 months postoperatively based on BMI ± 95% confidence interval. The relationship between BMI and probabilities of being in the different ordinal pain categories is shown for different age strata.*

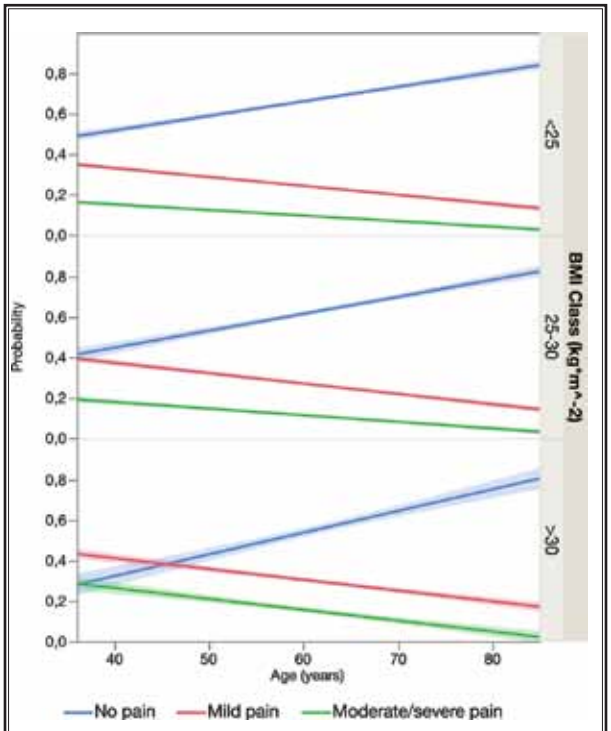

Fig. 2. *Probability of being in the different ordinal persistent postoperative pain categories at > 6 months postoperatively based on age ± 95% confidence interval. The relationship between age and probabilities of being in the different ordinal pain categories is shown for different BMI strata.*

low-grade inflammation and sensitized central pain modulation by the release of pro-inflammatory and insulin resistance-inducing substances from visceral adipose tissue. Observational studies have showed that obese people exhibited decreased pain threshold to electrical stimuli (26) as well as mechanical stimuli (27). In fibromyalgia, BMI is significantly related to the number of positive tender points (painful tender points upon palpation) as well as pain rating of the tender points (28). Experimental studies with endotoxemia, in which a small dose of lipopolysaccharide is injected into volunteers, demonstrated a possible role of inflammation in pain sensitization. In one study, intravenous lipopolysaccharide injected in healthy participants induced reduced pain thresholds after 3 hours and these reductions were associated with peak increases in serum pro-inflammatory cytokine levels (29). Similarly, another study in healthy participants found that intravenous lipopolysaccharide reduced visceral pain thresholds (measured by rectal distension) 2 hours post injection and that these reductions were correlated with IL-6 increases in blood (30).

Pathways accounting for a pain-BMI association may also be bidirectional. For example, pain may lead to decreased physical activity, depression, and subsequent obesity. Additionally, persistent pain may lead to stress and cortisol secretion that contributes to truncal obesity (31). Conversely, the metabolic derangements of obesity may predispose pain as outlined above. Obesity may also lead to psychological morbidity (32), which is an important risk factor for persistent pain after breast cancer surgery (13). These underlying relationships should be addressed in future longitudinal studies.

Other Risk Factors

In addition to age and BMI, the univariate analyses identified surgery type, radiotherapy, axillary lymph node dissection, chemotherapy, reoperation, and histopathological disease stage as potential risk factors for persistent pain. This is consistent with previous studies. Lumpectomy has been shown to be associated with persistent postsurgical pain (33) and this relationship seems to be influenced by the combination of radiotherapy (34), which is the standard of care if breast conserving surgery is performed. Radiotherapy may cause persistent postsurgical pain through neuropathy and neuropathic pain (35). Axillary lymph node dissection has been found to be associated with persistent postsurgical pain in some studies (3,36), and this relationship may be mediated by nerve damage to the intercostobrachial nerve in the axilla (24). Axillary lymph node dissection is also often combined with chemotherapy, and chemotherapy is associated with persistent postsurgical pain through neurotoxicity (37), which is a side effect of many chemotherapeutic agents used in the treatment of breast cancer such as taxanes, platinum agents, and vinca alkaloids (38). Reoperation has been shown to be related to persistent postsurgical pain (39), which is likely an effect of the added risk of each individual surgery, but reoperation is often also combined with chemotherapy which may further increase the risk of persistent pain development. Histopathological disease stage may be related to persistent postsurgical pain (14) through its relationship with several of the aforementioned factors, because locally more advanced disease warrants more extensive treatments with more tissue damage and a greater need for adjuvant treatments. When we stratified patients into age groups ≤ 50 and > 50 in our study, we found that younger women had higher grade tumors, which is consistent with literature (40). As a result of this difference in disease stage younger women underwent more extensive treatments, as indicated by higher rates of mastectomy, axillary lymph node dissection, reoperation, and chemotherapy. We hypothesize that this distribution of disease stage, as well as the aforementioned interrelations between different treatment modalities, may have led to non-significant relationships of certain risk factors with persistent pain development in the multivariate model.

The remaining risk factors that we assessed (i.e., smoking, diabetes, and hormone therapy) did not show a potential association with persistent pain in the univariate analyses. We included these factors based on circumstantial evidence that they could be related to persistent pain development after breast cancer treatment. Smoking was included because it is a known risk factor for chronic pain development outside the surgical context (41) and chronic exposure to cigarette smoke may change pain perception in smokers compared with nonsmokers (42). Diabetes can cause neuropathic pain and has been shown to be associated with persistent postsurgical pain after hip and knee replacement (43). Hormone therapy consists of selective estrogen receptor modulators or aromatase inhibitors and these drugs are both known to induce musculoskeletal pain (44), which is not directly related to persistent postsurgical pain, but could have contributed to overall generalized pain.

Quality of Life

Consistent with our primary analysis, we found BMI to be associated with poorer quality of life scores after breast cancer treatment. We also found diabetes, axillary lymph node dissection, chemotherapy, and disease stage to be associated with poorer quality of life scores. Axillary lymph node dissection, chemotherapy, and disease stage have previously been reported to be associated with poorer quality of life after breast cancer treatment (36,45). Outside the surgical context, higher BMI (46) and diabetes (47) have been shown to negatively impact quality of life.

Lymphedema

In the literature lymphedema has been reported to affect between 4% and 49% of patients treated for breast cancer (11). Lymphedema is dependent on several pre-, intra-, and post-operative factors such as age, BMI, type of surgery, and adjuvant therapy. We found ~22% of patients suffer from lymphedema, which is consistent with the literature, although there are different ways of measuring this complication.

Clinical Implications

It is widely recognized that younger age is associated with a higher risk of developing persistent postsurgical pain. Although this fact may be used in preoperative risk assessments and postoperative preventative treatment plans, age itself is obviously not amenable to treatment. BMI however, may constitute a possible treatment target but the potential benefits of weight loss as a strategy for reducing or preventing persistent postsurgical pain have to be demonstrated. At present, there is limited research assessing the effects of weight loss and exercise programs on generalized pain in obesity. One investigation used a physical therapy program prior to entering a weight management program and assessed mean body pain (48). The weight management protocol included daily caloric restriction to 1,200 – 1,800 kcal/day and multimodal exercise 3 times per week. Patients receiving the intervention reported a reduction in mean body pain of 56%. Outside the pain specific literature, alternate day caloric restriction has been shown to cause clinical improvement and reduce systemic markers of inflammation and oxidative stress in obese asthmatic patients (49), which may also benefit sensitized central pain processing. Additional research should examine the effect of dietary and physical therapy programs on persistent postoperative pain conditions. This information could help clinicians determine the best strategy to manage or prevent pain in obese patients. In our specific population, female breast cancer patients undergoing cancer treatment, recommendations to restrict calories must take into consideration whether weight loss is possible during treatments such as chemotherapy. Moreover, breast cancer surgery can obviously not be postponed to allow for preoperative weight loss.

Interestingly, obesity is associated with poorer breast cancer survival, and this relationship between BMI and survival is observed both in preoperative studies and postoperative studies (> 12 months) (50). Fasting is currently being assessed as a method to ameliorate side effects of chemotherapy (51) and to improve response to chemotherapy (52) and radiotherapy (53). In this context, there has been a call for randomized clinical trials to test interventions for weight loss and maintenance on survival in women with breast cancer (50).

Methodological Considerations

Our study has some limitations that should be considered when interpreting the results. First, this was a retrospective study, and as such it is vulnerable to several types of bias. Misclassification bias may be of particular concern because the association between surgery and pain was based on patient reports. Secondly, we stratified patients into different ordinal categories according to their reported VAS scores and found the distribution skewed towards lower VAS scores. It is thus important to realize that most patients affected by the problem of persistent pain following breast cancer treatment report relatively mild pain scores and the moderate pain/severe pain group constitutes a smaller percentage of the total population of patients after breast cancer treatment who report persistent pain.

Conclusions

Younger age and higher BMI may be risk factors for persistent postoperative pain after breast cancer treatment. Higher BMI may also be associated with lower quality of life following breast cancer treatment. Taken together, BMI may be a target for preventative strategies in the context of persistent postsurgical pain.

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Author contributions: NvH, HT, and SO had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. MS, KV, NvD, and CvdP designed the study protocol. NvH managed the literature searches

and summaries of previous related work and wrote the first draft of the manuscript. HT, NvD, CvdP, SO, AD, KV, OWS, and MS provided revision for intellectual content and final approval of the manuscript.

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References

1. Caffo O, Amichetti M, Ferro A, Lucenti A, Valduga F, Galligioni E. Pain and quality of life after surgery for breast cancer. *Breast Cancer Res Treat* 2003; 80:39-48.
2. Turk DC, Wilson HD, Cahana A. Treatment of chronic non-cancer pain. *Lancet* 2011; 377:2226-2235.
3. Gartner R, Jensen MB, Nielsen J, Ewertz M, Kroman N, Kehlet H. Prevalence of and factors associated with persistent pain following breast cancer surgery. *JAMA* 2009; 302:1985-1992.
4. Kehlet H, Jensen TS, Woolf CJ. Persistent postsurgical pain: Risk factors and prevention. *Lancet* 2006; 367:1618-1625.
5. Cardoso F, Costa A, Senkus E, Aapro M, Andre F, Barrios CH, Bergh J, Bhattacharyya G, Biganzoli L, Cardoso MJ, Carey L, Corneliussen-James D, Curigliano G, Dieras V, El Saghir N, Eniu A, Fallowfield L, Fenech D, Francis P, Gelmon K, Gennari A, Harbeck N, Hudis C, Kaufman B, Krop I, Mayer M, Meijer H, Mertz S, Ohno S, Pagani O, Papadopoulos E, Peccatori F, Pernault-Llorca F, Piccart MJ, Pierga JY, Rugo H, Shockney L, Sledge G, Swain S, Thomssen C, Tutt A, Vorobiof D, Xu B, Norton L, Winer E. 3rd ESO-ESMO international consensus guidelines for advanced breast cancer (ABC 3). *Ann Oncol* 2017; 28:16-33.
6. Senkus E, Kyriakides S, Ohno S, Penault-Llorca F, Poortmans P, Rutgers E, Zackrisson S, Cardoso F. Primary breast cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2015; 26:v8-v30.
7. Mascaro A, Farina M, Gigli R, Vitelli CE, Fortunato L. Recent advances in the surgical care of breast cancer patients. *World J Surg Oncol* 2010; 8:5.
8. Hassan MS, Ansari J, Spooner D, Hussain SA. Chemotherapy for breast cancer (Review). *Oncol Rep* 2010; 24:1121-1131.
9. Currey AD, Bergom C, Kelly TR, Wilson JF. Reducing the human burden of breast cancer: Advanced radiation therapy yields improved treatment outcomes. *Breast J* 2015; 21:610-620.
10. Andersen KG, Duriaud HM, Jensen HE, Kroman N, Kehlet H. Predictive factors for the development of persistent pain after breast cancer surgery. *Pain* 2015; 156:2413-2422.
11. Andersen KG, Kehlet H. Persistent pain after breast cancer treatment: A critical review of risk factors and strategies for prevention. *J Pain* 2011; 12:725-746.
12. Langford DJ, Paul SM, West CM, Dunn LB, Levine JD, Kober KM, Dodd MJ, Miaskowski C, Aouizerat BE. Variations in potassium channel genes are associated with distinct trajectories of persistent breast pain after breast cancer surgery. *Pain* 2015; 156:371-380.
13. Bruce J, Thornton AJ, Powell R, Johnston M, Wells M, Heys SD, Thompson AM, Cairns Smith W, Chambers WA, Scott NW. Psychological, surgical, and sociodemographic predictors of pain outcomes after breast cancer surgery: A population-based cohort study. *Pain* 2014; 155:232-243.
14. Meretoja TJ, Leidenius MH, Tasmuth T, Sipila R, Kalso E. Pain at 12 months after surgery for breast cancer. *JAMA* 2014; 311:90-92.
15. Miaskowski C, Cooper B, Paul SM, West C, Langford D, Levine JD, Abrams G, Hamolsky D, Dunn L, Dodd M, Neuhaus J, Baggott C, Dhruva A, Schmidt B, Cataldo J, Merriman J, Aouizerat BE. Identification of patient subgroups and risk factors for persistent breast pain following breast cancer surgery. *J Pain* 2012; 13:1172-1187.
16. World Medical Association Declaration of Helsinki: Ethical principles for medical research involving human subjects. *JAMA* 2000; 284:3043-3045.
17. Collins SL, Moore RA, McQuay HJ. The visual analogue pain intensity scale: What is moderate pain in millimetres? *Pain* 1997; 72:95-97.
18. Groenvold M, Klee MC, Sprangers MA, Aaronson NK. Validation of the EORTC QLQ-C30 quality of life questionnaire through combined qualitative and quantitative assessment of patient-observer agreement. *J Clin Epidemiol* 1997; 50:441-450.
19. Hinz A, Einenkel J, Briest S, Stolzenburg JU, Papsdorf K, Singer S. Is it useful to calculate sum scores of the quality of life questionnaire EORTC QLQ-C30? *Eur J Cancer Care (Engl)* 2012; 21:677-683.
20. NIH – National Heart, Lung, and Blood Institute, Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults: The Evidence Report, Washington, DC, 1998.
21. Ip HY, Abrishami A, Peng PW, Wong J, Chung F. Predictors of postoperative pain and analgesic consumption: A qualitative systematic review. *Anesthesiology* 2009; 111:657-677.
22. Fecho K, Miller NR, Merritt SA, Klauber-Demore N, Hultman CS, Blau WS. Acute and persistent postoperative pain after breast surgery. *Pain Med* 2009; 10:708-715.
23. Smith WC, Bourne D, Squair J, Phillips DO, Chambers WA. A retrospective cohort study of post mastectomy pain syndrome. *Pain* 1999; 83:91-95.
24. Taylor KO. Morbidity associated with axillary surgery for breast cancer. *ANZ J Surg* 2004; 74:314-317.
25. de Blacam C, Ogunleye AA, Momoh AO, Colakoglu S, Tobias AM, Sharma R, Houlihan MJ, Lee BT. High body mass index and smoking predict morbidity in breast cancer surgery: A multivariate analysis of 26,988 patients from the national surgical quality improvement program database. *Ann Surg* 2012; 255:551-555.
26. Pradalier A, Willer JC, Boureau F, Dry J. Relationship between pain and obesity: An electrophysiological study. *Physiol Behav* 1981; 27:961-964.
27. McKendall MJ, Haier RJ. Pain sensitivity and obesity. *Psychiatry Res* 1983; 8:119-125.
28. Neumann L, Lerner E, Glazer Y, Bolotin A, Shefer A, Buskila D. A cross-sectional

study of the relationship between body mass index and clinical characteristics, tenderness measures, quality of life, and physical functioning in fibromyalgia patients. *Clin Rheumatol* 2008; 27:1543-1547.

29. Wegner A, Elsenbruch S, Maluck J, Grigoleit JS, Engler H, Jager M, Spreitzer I, Schedlowski M, Benson S. Inflammation-induced hyperalgesia: Effects of timing, dosage, and negative affect on somatic pain sensitivity in human experimental endotoxemia. *Brain Behav Immun* 2014; 41:46-54.
30. Benson S, Kattoor J, Wegner A, Hammes F, Reidick D, Grigoleit JS, Engler H, Oberbeck R, Schedlowski M, Elsenbruch S. Acute experimental endotoxemia induces visceral hypersensitivity and altered pain evaluation in healthy humans. *Pain* 2012; 153:794-799.
31. Hannibal KE, Bishop MD. Chronic stress, cortisol dysfunction, and pain: A psychoneuroendocrine rationale for stress management in pain rehabilitation. *Phys Ther* 2014; 94:1816-1825.
32. Karasu SR. Of mind and matter: Psychological dimensions in obesity. *Am J Psychother* 2012; 66:111-128.
33. Karki A, Simonen R, Malkia E, Selfe J. Impairments, activity limitations and participation restrictions 6 and 12 months after breast cancer operation. *J Rehabil Med* 2005; 37:180-188.
34. Tasmuth T, Kataja M, Blomqvist C, von Smitten K, Kalso E. Treatment-related factors predisposing to chronic pain in patients with breast cancer: A multivariate approach. *Acta Oncol* 1997; 36:625-630.
35. Cross NE, Glantz MJ. Neurologic complications of radiation therapy. *Neurol Clin* 2003; 21:249-277.
36. Steegers MA, Wolters B, Evers AW, Strobbe L, Wilder-Smith OH. Effect of axillary lymph node dissection on prevalence and intensity of chronic and phantom pain after breast cancer surgery. *J Pain* 2008; 9:813-822.
37. Jung BF, Herrmann D, Griggs J, Oaklander AL, Dworkin RH. Neuropathic pain associated with non-surgical treatment of breast cancer. *Pain* 2005; 118:10-14.
38. Windebank AJ, Grisold W. Chemotherapy-induced neuropathy. *J Peripher Nerv Syst* 2008; 13:27-46.
39. Vilholm OJ, Cold S, Rasmussen L, Sindrup SH. The postmastectomy pain syndrome: An epidemiological study on the prevalence of chronic pain after surgery for breast cancer. *Br J Cancer* 2008; 99:604-610.
40. Assi HA, Khoury KE, Dbouk H, Khalil LE, Mouhieddine TH, El Saghir NS. Epidemiology and prognosis of breast cancer in young women. *J Thorac Dis* 2013; 5:S2-S8.
41. Leboeuf-Yde C. Smoking and low back pain. A systematic literature review of 41 journal articles reporting 47 epidemiologic studies. *Spine (Phila Pa 1976)* 1999; 24:1463-1470.
42. Shi Y, Weingarten TN, Mantilla CB, Hooten WM, Warner DO. Smoking and pain: Pathophysiology and clinical implications. *Anesthesiology* 2010; 113:977-992.
43. Rajamaki TJ, Jamsen E, Puolakka PA, Nevalainen PI, Moilanen T. Diabetes is associated with persistent pain after hip and knee replacement. *Acta Orthop* 2015; 86:586-593.
44. Niravath P. Aromatase inhibitor-induced arthralgia: A review. *Ann Oncol* 2013; 24:1443-1449.
45. Hong-Li C, Xiao-Chun W, Jiang-Bin W, Jing-Bo Z, Yao W. Quality of life in patients with breast cancer and their rehabilitation needs. *Pak J Med Sci* 2014; 30:126-130.
46. Ul-Haq Z, Mackay DF, Fenwick E, Pell JP. Meta-analysis of the association between body mass index and health-related quality of life among children and adolescents, assessed using the pediatric quality of life inventory index. *J Pediatr* 2013; 162:280-286.e281.
47. Rubin RR, Peyrot M. Quality of life and diabetes. *Diabetes Metab Res Rev* 1999; 15:205-218.
48. Snow R, Ruane J, LaLonde M, Shaffer L, Kim B, Graffagnino C, Falko J, Spencer K, Caulin-Glaser T. Randomized trial assessing the impact of a musculoskeletal intervention for pain before participating in a weight management program. *J Cardiopulm Rehabil Prev* 2010; 30:173-180.
49. Johnson JB, Summer W, Cutler RG, Martin B, Hyun DH, Dixit VD, Pearson M, Nassar M, Telljohann R, Maudsley S, Carlson O, John S, Laub DR, Mattson MP. Alternate day calorie restriction improves clinical findings and reduces markers of oxidative stress and inflammation in overweight adults with moderate asthma. *Free Radic Biol Med* 2007; 42:665-674.
50. Chan DS, Vieira AR, Aune D, Bandera EV, Greenwood DC, McTiernan A, Navarro Rosenblatt D, Thune I, Vieira R, Norat T. Body mass index and survival in women with breast cancer-systematic literature review and meta-analysis of 82 follow-up studies. *Ann Oncol* 2014; 25:1901-1914.
51. Safdie FM, Dorff T, Quinn D, Fontana L, Wei M, Lee C, Cohen P, Longo VD. Fasting and cancer treatment in humans: A case series report. *Aging (Albany NY)* 2009; 1:988-1007.
52. Lee C, Raffaghello L, Brandhorst S, Safdie FM, Bianchi G, Martin-Montalvo A, Pistoia V, Wei M, Hwang S, Merlino A, Emionite L, de Cabo R, Longo VD. Fasting cycles retard growth of tumors and sensitize a range of cancer cell types to chemotherapy. *Sci Transl Med* 2012; 4:124ra127.
53. Safdie F, Brandhorst S, Wei M, Wang W, Lee C, Hwang S, Conti PS, Chen TC, Longo VD. Fasting enhances the response of glioma to chemo- and radiotherapy. *PLoS One* 2012; 7:e44603