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ORIGINAL ARTICLE – BREAST ONCOLOGY

Upper Limb Morbidity in Newly Diagnosed Individuals After Unilateral Surgery for Breast Cancer: Baseline Results from the AMBER Cohort Study

Margaret L. McNeely, MScPT, PhD[1,2], Kerry S. Courneya, PhD[3], Mona M. Al Onazi, BScPT, MSc[1], Stephanie Wharton, BSc[1], Qinggang Wang, PhD[4], Leanne Dickau, MSc[4], Jeffrey K. Vallance, PhD[5], S. Nicole Culos-Reed, PhD[6,7], Charles E. Matthews, PhD[8], Lin Yang, PhD[4,6], and Christine M. Friedenreich, PhD[4,6]

[1]Department of Physical Therapy, Faculty of Rehabilitation Medicine, University of Alberta, Edmonton, AB, Canada; [2]Supportive Care Services, Cancer Care Alberta, Edmonton, AB, Canada; [3]Faculty of Kinesiology, Sport, and Recreation, College of Health Sciences, University of Alberta, Edmonton, AB, Canada; [4]Department of Cancer Epidemiology and Prevention Research, Cancer Care Alberta, Alberta Health Services, Calgary, AB, Canada; [5]Faculty of Health Disciplines, Athabasca University, Athabasca, AB, Canada; [6]Department of Oncology, Cumming School of Medicine, University of Calgary, Calgary, AB, Canada; [7]Faculty of Kinesiology, University of Calgary, Calgary, AB, Canada; [8]Division of Cancer Epidemiology and Genetics, US National Cancer Institute, Rockville, MD

ABSTRACT

Purpose. We aimed to examine potential associations between post-surgical upper limb morbidity and demographic, medical, surgical, and health-related fitness variables in newly diagnosed individuals with breast cancer.

Methods. Participants were recruited between 2012 and 2019. Objective measures of health-related fitness, body composition, shoulder range of motion, axillary web syndrome, and lymphedema were performed within 3 months of breast cancer surgery, and prior to or at the start of adjuvant cancer treatment.

Results. Upper limb morbidity was identified in 54% of participants and was associated with poorer upper limb function and higher pain. Multivariable logistic regression analysis identified mastectomy versus breast-conserving surgery (odds ratio [OR] 3.51, 95% confidence interval [CI] 2.65–4.65), axillary lymph node dissection versus sentinel lymph node dissection (OR 2.67, 95% CI 1.73–4.10), earlier versus later time from surgery (OR 1.58, 95% CI 1.15–2.18), and younger versus older age (OR 1.01, 95% CI 1.00–1.03) as significantly associated with a higher odds of upper limb morbidity, while mastectomy (OR 1.57, 95% CI 1.10–2.25), axillary lymph node dissection (OR 2.20, 95% CI 1.34–3.60), lower muscular endurance (OR 1.10, 95% CI 1.01–1.16) and higher percentage body fat (OR 1.04, 95% CI 1.00–1.07) were significantly associated with higher odds of moderate or greater morbidity severity.

Conclusions. Upper limb morbidity is common in individuals after breast cancer surgery prior to adjuvant cancer treatment. Health-related fitness variables were associated with severity of upper limb morbidity. Findings may facilitate prospective surveillance of individuals at higher risk of developing upper limb morbidity.

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M. L. McNeely, MScPT, PhD
e-mail: mmcneely@ualberta.ca

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Breast cancer is the most common malignancy among Canadian women, with one in eight expected to develop the disease in their lifetime.[1] Breast cancer surgery frequently causes upper limb morbidity,[2] with effects reported to last more than 10 years.[3,4] Upper limb morbidity is characterized by the presence of arm/shoulder pain, arm swelling, axillary web syndrome, limited shoulder mobility, and upper limb weakness.[2,3,5,6] These symptoms are associated with poorer upper limb function and lower levels of physical activity, and can negatively impact activities of daily living, social participation, quality of life (QoL) and ability to return to work.[2,3,5,6]

Women with breast cancer are at increased risk of developing upper limb morbidity after undergoing surgery and/or radiation therapy.[7] The risk of early postoperative upper limb morbidity, prior to administration of adjuvant radiation therapy, is largely attributed to the type and extent of the breast cancer surgery, including mastectomy and axillary lymph node dissection.[5,8] Among non-surgical factors, age, lower levels of self-reported physical activity and higher body mass index (BMI) have been reported as risk factors for upper limb morbidity.[9,10] Associations between objective measures of health-related fitness, including body composition, have yet to be fully explored. Understanding the relationship between potentially modifiable health-related fitness variables may serve to guide intervention strategies to improve surgical outcomes.

The primary purpose of this study was to examine the associations between upper limb morbidity after breast cancer surgery, and key demographic, medical, surgical, physical activity and health-related fitness variables. We also aimed to explore the association between upper limb morbidity and self-reported pain and disability, as well as upper body strength and endurance.

METHODS

Study Design, Participants, and Procedures

The Alberta Moving Beyond Breast Cancer Study (AMBER) is a prospective cohort study examining the role of physical activity, sedentary behavior, and health-related fitness in breast cancer treatment, recovery, and survivorship.[11,12] The present study reports the baseline data from the AMBER cohort for individuals undergoing unilateral surgery prior to or at the start of adjuvant cancer treatments. Assessments were performed at baseline (soon after diagnosis), with the goal to have participants complete all assessments within 90 days of surgery. Participants were recruited between July 2012 and July 2019 in Edmonton and Calgary, Alberta, Canada. Women with newly diagnosed breast cancer were eligible if they had histologically confirmed stage I (≥ T1c) to stage IIIc breast cancer and were 18–80 years of age, proficient in English, and not pregnant.

Ethical Considerations and Informed Consent

Ethical approval was obtained through the Health Research Ethics Board of Alberta–Cancer Committee, and each participant completed a signed consent form. We have previously described the AMBER study design and methods[12] as well as the baseline characteristics of the full cohort.[13]

Demographics

Participants self-reported sociodemographic characteristics such as age, marital status, ethnicity, education, income, employment, and comorbidities. Participants also self-reported lifestyle behaviors such as smoking, alcohol consumption, physical activity, and dietary intake using the Canadian Diet History Questionnaire-II. Clinical information about their cancer was extracted from medical charts by a trained study staff member and included date of diagnosis, disease stage, tumor grade, histology, and surgery type.

Testing Schedule

Most AMBER baseline testing occurred over 2 separate days about 1 week apart, with lymphedema and range of motion (ROM) testing, hand grip strength, body composition assessments and cardiorespiratory fitness testing taking place on Day 1. At the end of Day 1, participants were given questionnaires (including the QoL measures) and accelerometers to return the following week at Day 2 testing, which occurred 7 days following Day 1 testing and consisted of the upper and lower body muscular strength and endurance tests with about a 10-min rest between the tests (Fig. 1).

Measures

Health-related fitness assessments, performed by Clinical Exercise Physiologists using standardized testing protocols and the same equipment at both sites, have been previously published.[12] Relative to upper limb morbidity, the assessments included body composition (dual x-ray absorptiometry, body weight, height); grip strength; cardiorespiratory fitness (graded treadmill exercise test); and upper and lower body muscular strength (chest and leg press predicted one

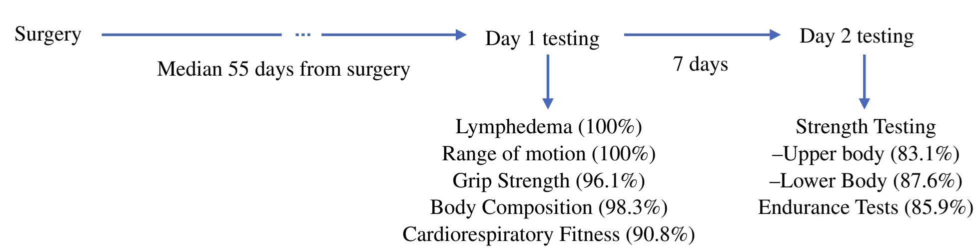

FIG. 1 AMBER testing timeline with testing completion rates. *AMBER* Alberta Moving Beyond Breast Cancer Study

repetition maximum [1-RM]) and endurance (multiple repetition maximum, based on 50% of predicted 1-RM for the chest press and 70% of predicted 1-RM for the leg press). Self-reported physical activity data were collected using the *Past Year Total Physical Activity Questionnaire*.[14] Self-reported *arm function* and *pain* were assessed using the Disabilities of the Arm, Shoulder and Hand (DASH) scale.[15]

Shoulder active and passive ROM were measured following standardized procedures using a traditional goniometer.[16,17] Each arm was measured separately for the following movements: flexion, abduction, and horizontal abduction. Active ROM was assessed with the participant sitting or standing with their back in an upright position to prevent compensation by trunk muscles. Passive shoulder flexion, abduction and horizontal abduction movements were performed in the supine position.

Axillary web syndrome was determined through standard physical assessment of both active and passive ROM measurements for the movements of shoulder forward flexion and abduction.[18,19]

Arm volume was objectively measured using the Perometer (Pero-systems, Wipputal, Germany), an optoelectric limb volumeter that uses infrared technology to quantify limb volume and determine inter-limb difference. The Perometer is a valid, reliable, and sensitive method for quantifying limb volume.[20-22]

Definition of Upper Limb Dysfunction

Upper limb dysfunction was defined as the presence of one or more of the following impairments: (1) *Shoulder ROM* limitation was defined as a difference in active ROM between the affected and unaffected arm that exceeded 10° for shoulder flexion, abduction or horizontal abduction;[23] (2) *axillary web syndrome* was characterized by the presence of visible and palpable cords in the underarm, medial arm, antecubital space or forearm on the side of the breast surgery at maximal passive shoulder abduction;[18] or (3) *lymphedema* was considered present with a ≥ 200 mL volume difference between the affected and unaffected arms.[24] The number of participants presenting with one or more impairments in any of the five objectively measured upper limb outcomes (i.e. limitation in active shoulder flexion, abduction or horizontal abduction ROM, axillary web syndrome or lymphedema) were calculated (i.e. one or more impairments versus no impairments). We also calculated the number of presenting impairments, of at least mild severity, per participant (i.e. zero to five).

Severity of Upper Limb Dysfunction

Participants presenting with upper limb morbidity were then classified into categories of either mild versus moderate or greater impairment severity. The presenting impairment was considered of moderate or greater severity if any of the following criteria were met: (1) active shoulder flexion on the affected side of < 130° (threshold for functional limitation);[25,26] (2) axillary web syndrome with active shoulder abduction < 130°;[25] or (3) clinically significant lymphedema defined as > 10% difference in arm volumes between arms.[27]

Statistical Analyses

Descriptive statistics were used to present demographic, medical, surgical, and health-related fitness characteristics of the sample. Two models were created to estimate associations between descriptive variables and upper limb morbidity. For model one, a dichotomized upper limb morbidity variable was created to estimate associations between individuals with *no impairments* and those with *one or more impairments*. Model two involved the analysis of the subgroup of individuals with any presenting impairment of mild or greater severity. A dichotomized upper limb morbidity severity variable was created to compare individuals with *mild impairment* with those with impairment of *moderate or greater severity*. T-tests were performed to explore the relationship between both the prevalence and severity of upper limb morbidity and outcomes of upper body function and pain (DASH score), upper limb strength and endurance, and grip strength. We compared baseline characteristics across groups using relevant statistical tests (t-tests/analysis of variance [ANOVA] for continuous variables and the Chi-square test for categorical variables). Our multivariable analysis used a generalized logistic mixed model to control for the effect of location (Calgary/Edmonton) given the differences in the timing of upper limb assessments and other factors relative to surgery. Independent baseline characteristics associated with the dependent variable at a statistically significant level ($p < 0.05$) were entered into the final multivariable model. We handled missing data on covariates via multivariate imputations through chained equations, which includes all correlated covariates in regression models to avoid reducing the sample size.[28] All statistical tests were two-sided and the significance level was set at $p < 0.05$.

RESULTS

Of the 3673 (25%) eligible individuals with breast cancer, we recruited 1528 (42%) in the AMBER cohort study. For the present analysis, of the 1528 AMBER participants, we excluded 117 participants undergoing neoadjuvant chemotherapy, one participant not receiving cancer treatment, and 177 who had undergone bilateral surgery, resulting in a final sample of 1233 participants who had unilateral surgery. For these 1233 participants, upper limb morbidity assessments were completed a median of 55 days (interquartile range [IQR] 45–70) post-surgery.

Characteristics of the AMBER sample undergoing unilateral surgery are presented in Table 1. The mean age was 56.4 years (standard deviation [SD] 10.6), most participants were White (87.5%), diagnosed with stage I (48.5%) or II (44.4%) breast cancer, 68.8% had breast-conserving surgery, and 83.4% had a undergone a sentinel lymph node biopsy. As per standard care in our province, all participants received preoperative education and were provided with a post-surgical upper limb exercise program.

Impairments are presented by the type of surgery and lymph node dissection procedure performed (Table 2). Overall, 53.9% of participants presented with at least one impairment of mild or greater severity, with the highest prevalence of impairments (84%) seen among those undergoing mastectomy and axillary lymph node dissection (Table 2). The median number of impairments per participant at baseline assessment was 1, with a range of 0–5 (Table 3). Across all breast surgical and lymph node dissection procedures, active abduction ROM (33.2%) was most limited, followed by active shoulder flexion ROM (23.2%). Axillary web syndrome was identified in 16.6% of the sample, while an arm volume difference of

TABLE 1 Baseline demographic and medical characteristics of the AMBER cohort study participants, 2012–2019 [*N* = 1233]

Demographic/medical characteristic	Variable description/category	Unilateral surgery [*N* = 1233]	
		Mean/*N*	SD/%
Age	Age at diagnosis, years (mean), SD	56.4	10.6
Charlson Comorbidity Index	Median, Q1, Q3	1	1, 2
Location	Calgary	686	55.6%
	Edmonton	547	44.4%
Race/ethnicity	White	1079	87.5%
	Asian	82	6.7%
	Asian: Indian	27	2.2%
	Black	7	0.6%
	Latin American or Hispanic	14	1.1%
	First nations	11	0.9%
	Do not know/missing	13	1.1%
Marital status	Married or common law	925	75.0%
	Divorced, separated, widowed	223	18.1%
	Single (never married)	85	6.9%
Highest level of education	High school or less	281	22.8%
	College or trade school	374	30.3%
	University undergraduate degree/nursing school	311	25.2%
	University graduate degree	233	18.9%
	Missing	34	2.8%
Income	≤ $50,000	178	14.4%
	> $50,000 to $100,000	353	28.6%
	> $100,000 to $150,000	261	21.2%
	> $150,000	320	26.0%
	Missing	121	9.8%
Body mass index category	< 18.5	10	0.8%
	18.5–24.9	449	36.4%
	25–29.9	419	34.0%
	30–39.9	319	25.9%
	> 40	36	2.9%
Breast cancer stage	I	598	48.5%
	II	547	44.4%
	III	88	7.1%
Breast cancer side	Right	613	49.7%
	Left	620	50.3%

AMBER Alberta Moving Beyond Breast Cancer Study, *SD* standard deviation

> 200 mL (threshold for lymphedema) was found in only 4%. Compared with individuals with no impairments, the presence of one or more impairments of at least mild severity was associated with poorer self-reported upper limb function (significantly lower DASH score), and more pain (Table 4).

Of the 1233 participants, 20% were found to present with impairments of moderate or greater severity (Table 3).

TABLE 2 Prevalence of upper limb impairments by surgical procedure, AMBER cohort study, 2012–2019 ($N = 1233$)

Impairment	N	Overall [$N = 1233$] (%)	Sentinel lymph node biopsy		Axillary lymph node dissection	
			BCS [$n = 763$] (%)	MRM [$n = 265$] (%)	BCS [$n = 85$] (%)	MRM [$n = 120$] (%)
Shoulder flexion	1233	286 (23.2)	91 (31.8)	103 (38.9)	27 (31.8)	65 (54.2)
Shoulder abduction	1233	409 (33.2)	152 (19.9)	137 (51.7)	44 (51.8)	76 (63.3)
Shoulder horizontal abduction	1233	161 (13.1)	50 (6.6)	66 (24.9)	8 (9.4)	37 (30.8)
Axillary web syndrome	1228	204 (16.6)	72 (9.5)	44 (21.6)	32 (37.6)	56 (47.1)
Arm volume difference	1228	50 (4.0)	23 (3.0)	10 (3.8)	4 (8.0)	13 (10.8)
Absolute > 200 mL						

AMBER Alberta Moving Beyond Breast Cancer Study, *BCS* breast-conserving surgery, *MRM* modified mastectomy

$p < 0.001$

TABLE 3 Prevalence and severity of upper limb impairments, AMBER cohort study, 2012–2019 ($N = 1233$)

	Overall [$n = 1233$] (%)	Sentinel lymph node biopsy		Axillary lymph node dissection	
		BCS [$n = 763$] (%)	MRM [$n = 265$] (%)	BCS [$n = 85$] (%)	MRM [$n = 120$] (%)
No. of presenting impairments of at least mild severity per participant					
No impairment	569 (46.1)	456 (59.8)	74 (27.9)	20 (23.5)	19 (15.8)
1	355 (28.8)	216 (28.3)	80 (30.2)	32 (37.6)	27 (22.5)
2	173 (14.0)	69 (9.0)	58 (21.9)	17 (20.0)	29 (24.2)
3	95 (7.7)	21 (2.8)	43 (16.2)	12 (14.1)	19 (15.8)
4	38 (3.1)	1 (0.1)	10 (3.8)	4 (4.7)	23 (19.2)
5	3 (0.2)	0 (0)	0 (0)	0 (0)	3 (2.5)
Overall prevalence of mild or greater severity of impairment					
No. of participants	664 (53.9)	307 (40.2)	191 (72.1)	65 (76.5)	101 (84.2)
Overall prevalence of moderate or greater severity of impairment[a]					
No. of participants	247 (20.0)	97 (12.7)	72 (27.2)	25 (29.4)	53 (44.2)

[a]Moderate or higher severity defined as one of the following: (1) active shoulder flexion < 130°; (2) axillary web syndrome + active shoulder abduction < 130; or (3) lymphedema > 10% difference between arms; $p < 0.001$ between subgroups

TABLE 4 Prevalence and severity of upper limb symptoms and function, AMBER cohort study, 2012–2019 ($N = 1233$)

Functional and symptom outcome	Prevalence of impairment			Severity of impairment		
	No impairments	One or more impairments	p-Value	Mild morbidity [$n = 417$]	Moderate morbidity [$n = 247$]	p-Value
DASH score[a]	7.7 (9.2)	12.6 (11.9)	**< 0.001**	10.6 (10.7)	15.4 (13.0)	**< 0.001**
Upper limb pain	1.5 (0.72)	1.7 (0.85)	**< 0.001**	1.7 (0.81)	1.9 (0.89)	**< 0.002**
Upper body strength [1-RM, kg]	36.0 (9.6)	35 (10.4)	0.08	35.6 (10.6)	34.0 (9.9)	0.06
Upper body endurance [reps × 50% 1-RM]	485 (202)	468 (224)	0.17	491 (221)	426 (224)	**< 0.001**
Affected side grip strength [kg]	27.3 (6.3)	27.3 (6.6)	0.46	27.4 (6.5)	27.0 (6.8)	0.44

Bold values indicate significant findings

DASH Disabilities of the arm, shoulder and hand, *1-RM* 1 repetition maximum, *reps* repetitions

[a]Higher scores = worse function

Similarly, these individuals were found to have poorer DASH score, more pain, and worse upper body endurance when compared with individuals with impairments of mild severity (Table 4).

Adjusted Multivariable Associations

In model 1, study participants undergoing mastectomy had 3.51 times higher odds (odds ratio [OR] 3.51, 95% confidence interval [CI] 2.65–4.65) of upper limb morbidity when compared with breast-conserving surgery, and those undergoing axillary lymph node dissection had 2.67 times higher odds (OR 2.67, 95% CI 1.73–4.10) when compared with sentinel lymph node biopsy. Findings also indicated that younger age was associated with higher odds of upper limb morbidity, as was earlier time from surgery (electronic supplementary material [ESM] Table 5). In model 2, study participants who had a mastectomy had 1.57 times higher odds (OR 1.57, 95% CI 1.10–2.25) of upper limb morbidity of moderate or greater severity compared with those who did not have this surgery. Likewise, participants undergoing axillary lymph node dissection had 2.2 times higher odds (OR 2.20, 95% CI 1.34–3.60) of moderate or greater morbidity severity when compared with participants undergoing sentinel lymph node biopsy. We found that higher percentage body fat and poorer lower body muscular endurance were associated with greater severity of upper limb morbidity (ESM Table 6).

DISCUSSION

In our prospective cohort of 1233 newly diagnosed individuals with breast cancer after unilateral surgery, one in two participants presented with upper limb morbidity and one in five experienced morbidity of moderate or greater severity. Consistent with prior reports, we found that mastectomy and axillary lymph node dissection were associated with both higher prevalence and severity of upper limb morbidity.[5,29,30] Although the majority of AMBER participants had undergone a sentinel lymph node biopsy (83%) versus axillary lymph node dissection (17%), upper limb morbidity was common, albeit to a significantly lesser extent after breast-conserving surgery and sentinel lymph node biopsy (40%) than after mastectomy and axillary lymph node dissection (84%).[10] Our findings align with previous studies reporting prevalence rates after surgery in the range of 10–64% and greater severity reported among 15–28% of participants.[10,29,31] Earlier time from surgery was associated with higher odds of presenting with impairment but was not associated with severity of impairment. This finding is consistent with the literature, suggesting that over time, the prevalence of upper limb symptoms is reduced.[5,10] Participants with morbidity of moderate or greater severity were also found to have a mean DASH score > 15 points, a score that indicates mild or greater difficulty with at least 50% of upper limb activities.[10]

To our knowledge this study is the first to evaluate upper limb morbidity in the context of objectively collected measures of health-related fitness. Prior research suggests that lower levels of physical activity are associated with higher rates of impaired arm mobility and lymphedema.[32,33] With the AMBER cohort study, we did not find a statistically significant association between self-reported measures of physical activity and upper limb morbidity. While these findings appear in contrast, studies supporting a protective effect of physical activity have largely involved physical activity through the cancer treatment and survivorship time period.[32,33] Our results did show that poorer health-related fitness components including cardiorespiratory fitness (i.e. VO_{2peak}), lower body muscular strength and endurance, and higher percentage body fat were associated with a greater severity, but not prevalence, of upper limb morbidity. A unique finding of the multivariable analysis was that poorer lower body muscular endurance remained independently associated with greater severity of upper limb morbidity. Muscular endurance is the ability of the body to withstand physical work for an extended period of time and is necessary for many sports, leisure activities and repetitive work activities.[34] Loss of muscle quantity and quality have been associated with poorer surgical outcomes in other cancer groups.[35-37] Suboptimal body composition prior to breast cancer treatment has been associated with poor physical function, a higher number of adverse events, and an increased risk of late-onset lymphedema.[38-40]

Patient-related risk factors revealed in our study were arm dominance and age. Our findings are consistent with other studies, suggesting an increased likelihood of morbidity on the non-dominant side in the early post-surgical period.[41,42] Moreover, we found that younger age was associated with higher odds of upper limb morbidity. This finding aligns with previous research reporting that younger individuals are more likely to experience upper limb symptoms than older individuals,[29,43] but is in contrast with research suggesting more long-term morbidity in older individuals.[44,45]

A notable finding was the low rate of lymphedema seen among AMBER participants early in the post-surgical period. An arm volume difference of > 200 mL between affected and unaffected limbs was observed in only 4% of AMBER participants, and only 1% of participants presented with a > 10% inter-limb difference (threshold for clinically significant lymphedema).[27] This finding may reflect our sample's less invasive surgical procedures and the timing of the assessment prior to undergoing adjuvant cancer therapy. While higher rates of lymphedema are seen with self-reported questionnaires when compared with objective measures of arm volume,[5] our findings align with recent data showing lower rates (2%) following sentinel lymph node biopsy in clinically node-negative patients.[46] Given the increased risk of lymphedema over the first 3 years after cancer treatment, we anticipate that lymphedema rates will increase in the AMBER study participants over time.[10]

Early identification and treatment of upper limb morbidity may lessen the impact on symptoms and function over time.[47] Currently, physical therapy is initiated once impairments are identified following cancer treatment.[48] Given our findings related to modifiable health-related fitness variables, further research is warranted examining the benefits of exercise and nutrition-focused interventions delivered in the perioperative period. Surgical prehabilitation includes interventions that are administered between the time of diagnosis and prior to the planned surgery, with the aim to enhance recovery over both the short- and long-term.[48] Moreover, prospective surveillance involves a preoperative baseline assessment to establish performance status, inform risk stratification, and allow for an appropriate rehabilitation strategy before and following the surgery.[49,50] Our findings may facilitate identification of individuals at higher risk of developing upper limb morbidity and reduce the need for intensive rehabilitation and its associated costs.[47,49-52]

Strengths of our study include the large sample size, the collection of post-surgical data prior to or at the start of adjuvant cancer treatments, the comprehensive and gold-standard assessments of health-related fitness, and the high completion rates (99.6%) for measures of upper limb morbidity. The primary limitation of our study was the lack of preoperative measurements that would have allowed us to establish more sensitive cut points for upper limb morbidity. Further limitations include the cross-sectional design and a younger, predominantly White, and relatively healthier breast cancer sample. Future analyses of the AMBER cohort objective and self-report data at 1- and 3-year follow-ups, as well as self-report data at the 5-year follow-up, will allow us to examine findings related to the natural progression of upper limb morbidity over time.

CONCLUSIONS

We found that upper limb morbidity is common after breast cancer surgery and is associated with poorer self-reported upper limb function and more pain. Poorer lower body muscular endurance and higher percentage body fat were significantly associated with greater severity of upper limb morbidity. These findings may be used to inform prospective surveillance programming with the goal of improving early post-surgical upper limb outcomes.

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