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A Comparison of Upper Extremity Function between

Women with and without a History of Breast Cancer

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ABSTRACT (271 words/*with required revisions = 301*)

Background: Breast cancer treatments often result in upper extremity functional limitations in the short and long term. Current evidence makes comparisons against a baseline or contralateral limb, but does not consider changes in function associated with aging.

Objective: To compare upper extremity function between women treated for breast cancer more than 12 months in the past and women without cancer.

Design: Observational **cross-sectional** study.

Methods: Women diagnosed with breast cancer (BC) with a post-surgical treatment mean of 51 months (range 12-336 months) were compared to women without breast cancer (CTRL). Self-reported upper extremity function using the Disabilities of the Arm, Shoulder and Hand (DASH), and shoulder range of motion, strength, and muscular endurance were measured. Participants were divided into 3 groups: BC involved non-dominant (BC-ND), BC involved dominant (BC-DOM), and CTRL.

Results: A total of 59 CTRL, 23 BC-ND, and 28 BC-DOM, completed measures. Mean BC DASH scores were higher than CTRL regardless of limb on which cancer occurred (p<.01, ES=1.13). BC-ND **r**ange of motion was significantly less for flexion (p=0.006, ES=1.19) and external rotation (p=0.009, ES=1.11) compared to CTRL. Strength of external and internal rotation for BC-ND was 23-25% lower than CTRL (p=0.003, 0.001, ES=0.89, 0.92 respectively). Endurance was not significantly different between three groups (p>0.05).

Limitations: Some participants had rehabilitation which may skew results. Range of post-surgical time was broad, making it difficult to determine when function returned. Muscular endurance measures demonstrated a ceiling effect and large variance, limiting the ability to distinguish differences among participants. **These results may not be generalizable to the**

subset of women who were treated with lumpectomy, sentinel node biopsy, or chest wall radiation alone.

Conclusion: Long-term, women with BC have lower self-reported shoulder function than women without BC. Motion and strength are lower among women who have experienced cancer on the non-dominant limb.

KEY WORDS: Arm, breast neoplasms, range of motion, strength, muscular endurance

(3232 words/ *with required revisions = 3622*)

INTRODUCTION

With the five-year survival rate of breast cancer at nearly 90%, currently over 3 million women are living after a diagnosis of breast cancer.[1] Upper extremity functional deficits following surgical and radiation treatments persist beyond the first year.[2-4] Declines of upper extremity function **compared to a pre-cancer level** are self-reported in 21-35% of women treated for breast cancer (BC) up to six years following diagnosis.[5,6] **The more involved the treatment, the greater risk of upper extremity morbidity. In women surgically treated with mastectomy and axillary lymph node dissection (ALND), and who undergo axillary radiation, upper extremity deficits in function are reported at greater levels than with lumpectomy and/or sentinel node dissection surgeries.[7]** The extent of these reported deficits and whether they can be attributed to breast cancer surgery and treatment or to normal aging has not been examined adequately.

Functional performance of the upper extremity includes adequate levels of arm motion, strength, and muscular endurance. Declines in motion are reported **among women treated for breast cancer** in the long term, with one study reporting >10% decline in flexion more than 5 years following treatment for breast cancer,[8] and another study identifying that losses of ≥20° of motion were present 7 years after surgical treatment.[9] **Upper extremity** strength declines of 10-15% are reported 1-5 years after treatment **for breast cancer**.[10] Muscular endurance, the ability to sustain an activity over time, has been minimally examined among BC but conflicting results from no deficits[11] to a 20% deficit in muscular endurance are reported.[12,13] To date, studies on upper extremity functional performance in BC have primarily used self-reported measures or measured changes relative to the contralateral limb, assuming this limb is without deficit and functions similarly. Direct comparisons to an age-matched group of women without breast cancer have not been reported for long-term women with BC. Furthermore, range of motion (ROM) and strength among healthy women is dependent on limb dominance[14,15] therefore involved limb dominance should be considered when making comparisons between these groups.

Deficits in self-reported and objective measures of upper extremity function among long-term BC may be in part a result of changes seen with normal aging. Direct comparisons of upper extremity function measured by self-report, ROM, strength, and muscular endurance between BC and healthy women are important to determine whether existing deficits are due to treatment or normal aging. The purpose of this study was to compare upper extremity function of long-term BC to a population of women without breast cancer.

METHODS

Participants: A convenience sample of 59 healthy women (CTRL), 25 women with breast cancer on the non-dominant limb (BC-ND), and 29 women with breast cancer on the dominant limb (BC-DOM) **recruited via word-of-mouth, flyers, and email** agreed to participate. All participants were between 40 and 69 years. The CTRL group had no history of breast cancer, while the BC group underwent at least one of the following treatments a minimum of 12 months prior to participation: mastectomy, axillary lymph node dissection, axillary radiation. Participants were excluded with any history of shoulder, cervical, or thoracic spine pathology diagnosed by a physician within the previous six months, or any history of shoulder, cervical, or thoracic surgery **so as to not confound findings**. One participant with breast cancer was excluded after screening revealed she had undergone rotator cuff surgery on her involved side prior to the cancer diagnosis. Two other BC were excluded after clarification that the radiation received was local to the tumor site and not the axilla. The final analyses included 23 BC-ND and 28 BC-DOM.

Sample size was based *a priori* on a study examining self-reported function between women with and without breast cancer. Evaluating Disabilities of the Arm, Shoulder, and Hand (DASH) scores and flexion ROM measures between BC six months after treatment and healthy controls,[16] an estimated 14-16 participants per group was required to meet a power of 90%. The study procedures were explained to all participants, and after questions were answered, each completed consent prior to data collection. This study was approved by the Institutional Review Boards of the University of Kentucky, Lexington, Kentucky, the University of Dayton and Miami Valley Hospital, Dayton, Ohio.

<u>Procedures:</u>

On a single visit, each participant's objective upper extremity function was measured by a battery of tests: bilateral shoulder ROM and strength in three planes, and muscular endurance using the Functional Impairment Test – Hand and Neck, Shoulder, Arm (FIT-HaNSA), by one of three trained investigators.[17] Participants completed a demographic questionnaire, the International Physical Activity Questionnaire (IPAQ) and the DASH prior to completing other components of testing. Demographic variables of age and arm dominance were recorded, and height and weight were measured to determine body mass index.

<u>Patient-reported Measures:</u>

Activity level was measured by the 7-item IPAQ, which has good test-retest reliability (Spearman r = .70-.90).[18] Self-reported upper extremity function was measured by the DASH, a 30-item disability scale scored 0 to 100; lower scores denote less disability. Construct and convergent validity have been established with other shoulder functional scales, and the test-retest reliability within BC is excellent (ICC=0.97).[19-22]

Objective Clinical Measures:

Range of Motion: Bilateral active ROM of shoulder flexion, external rotation (ER), and hand behind back (HBB) were measured by taking photographs of the participant completing each motion. The HBB motion was chosen as a representation of a functional measure of internal rotation, often utilized clinically. Degrees of motion were calculated using ImageJ (National Institutes of Health, Washington DC) by the primary investigator. The ICC for intra-rater reliability of digital measurement of ROM was consistently >0.95, with a standard error of measurement <2°.

Shoulder flexion and ER measurements were taken by placing markers along the axes of motion as described by Norkin and White;[23] the marker for the HBB measure was placed at the level of the C7 spinous process.[24,25] **Shoulder flexion measurements were taken in standing; ER was taken with the participant's upper arm supported on two towels while lying supine with the arm at 90° of abduction and 90° elbow flexion.** Participants were instructed to complete the motion as far as possible, and a photograph was taken at this end range. This was repeated twice bilaterally with the mean of the two measures used for analysis.[23] The shoulder flexion angle was the intersection of two lines, one representing the shoulder and the other the thorax (Figure 1a). The shoulder ER angle was formed by a line drawn through the shaft of the ulna and a line perpendicular to the plinth (Figure 1b). To measure the HBB distance, a 10cm reference was in the same plane as the participant to provide a spatial scale of the image for accurate measurement.[26] The distance in centimeters from the C7 spinous process to the spinous process in line with the tip of the thumb was recorded (Figure 1c).[24] A lower value indicates greater motion. Inter-rater reliability of the ROM procedures was established in pilot testing of eight healthy female adults prior to data collection (ICCs = 0.90-0.99).

Strength: The strength of the shoulder flexors, internal rotators, and external rotators was measured by hand-held dynamometry (Lafayette Manual Muscle Test System, Lafayette Instruments, Lafayette, IN) using standard testing positions.[27] An inelastic 2" wide nylon strap was placed around the participant's limb and the testers' body for each motion to provide a consistent, immovable resistance for the hand-held dynamometer (Figure 2).[28-30] Each participant was instructed to generate force to a maximal level over five seconds in each direction of testing.[31,32] Two submaximal practice trials were completed prior to testing, followed by three trials with 10 seconds rest in between. The average strength in kilograms (kg) of the three trials was used for statistical analysis.[33] Strength was normalized to body weight and is presented as a percentage of body weight (kg of force/body weight in kg). Shoulder flexion was measured with the participant seated, arm elevated to 90° (Figure 2a).[27] To measure IR and ER, the participant's upper arm was supported on two towels while lying supine with the arm at 90° of abduction and 90°elbow flexion (Figures 2b, 2c).[27] In pilot testing with eight participants, the ICCs for inter-rater reliability for strength measures ranged from 0.78-0.80, and the standard error of measurement was consistently below 1.2% of body weight.

Muscular Endurance: Upper extremity muscular endurance was measured by the FIT-HaNSA sub-tests 2 and 3 following a previously established protocol for performance and termination of testing.[17] The FIT-HaNSA challenges muscular endurance by completing a series of repetitive tasks involving lifting 1kg from eye level down 25 cm, and a sustained manipulation task with nuts and bolts above the head (Figures 3a, 3b). The FIT-HaNSA demonstrates good-excellent test-retest reliability (ICC=0.79-0.97), and moderate concurrent validity (*r*=0.71-0.76) with self-reported upper extremity functional scales (Figures 3 and 4).[17,27]

Statistical Analysis

BC were divided into groups based on which side the cancer occurred: dominant (BC-DOM) or non-dominant (BC-ND). For comparison analyses, **the same limb was used for both the CTRL and BC groups:** BC-DOM was **compared to** the dominant limb of the CTRL group, whereas BC-ND was **compared to** the non-dominant limb of CTRL. For analyses which did not depend on laterality, the full BC group was compared to the CTRL group.

Descriptive statistics were calculated for all variables. Data were examined for assumptions of normality using Kolmogorov-Smirnov test. All data were normally distributed (p <0.05) except for the DASH and FIT-HaNSA scores. **Since the sample size is robust and the variance small, the DASH and FIT-HaNSA were evaluated with parametric tests, consistent with other literature in this area.[5,17]** Participant demographics of age, body mass index, activity level, **and DASH scores** were compared using a one-way analysis of variance (ANOVA). Separate multivariate analyses of variance (MANOVA) were used to analyze all ROM, strength and muscular endurance measures. Where significance was found on the **ANOVA** and MANOVA, Games-Howell *post hoc* testing determined the direction of significance based on unequal group sizes with unequal variances.[34] Significance was established *a priori* at $p \leq .05$. All data were analyzed using IBM SPSS Statistics 23 (Armonk, NY).

RESULTS

The ANOVA revealed no significant differences **in potential confounders** of age (p=0.23), body mass index (p=0.59) and activity levels (p=0.78) between the three groups. Among BC, the median duration since surgical treatment was 51 months (range 12-336); 34

(66.7%) underwent a mastectomy, 22 (43.1%) underwent ALND, and 14 (27.4%) had axillary radiation. Of these, 23 (45.1%) underwent a mastectomy alone, 5 (9.8%) had both a mastectomy and ALND, 6 (11.8%) underwent an ALND and axillary radiation, and 6 (11.8%) underwent all three procedures. **Of the 34 women who underwent a mastectomy, data on reconstruction status were available from 26 (76.4%), with 11 (42.3%) women not having reconstructive surgery, 12 (46.2%) having implant reconstruction, 2 (7.7%) having TRAM flap reconstruction, and 1 (3.4%) having latissimus reconstruction.** More than half of the participants (68.6%) who answered the question about prior therapy intervention for their shoulder did not have previous treatment. **Of those who received therapy, the majority received lymphedema treatment and education, with a small portion receiving exercise to improve motion. Enrolled participants came from a broad geographic area including 5 counties encompassing urban, suburban, and rural locales.** Participant demographics are detailed in Table 1.

The ANOVA for the DASH resulted in statistically significantly differences between both BC groups and controls. Tukey *post hoc* testing revealed significance between BC-DOM and CTRL ($p\leq0.001$), and for BC-ND and CTRL ($p=0.008$) (Table 2). The MANOVA for ROM measures revealed statistically significant differences between BC-ND and CTRL ($p\leq0.001$). Games-Howell p*ost hoc* testing indicated that BC-ND had statistically significantly less flexion ($p=0.006$) and ER (p=0.009) motion than CTRL (Table 2). Strength was significantly less among BC-ND for shoulder internal ($p\leq0.001$) and external rotation ($p=0.003$) than for the CTRL (Table 2). FIT-HaNSA testing resulted in no statistically significant differences between groups ($p>0.05$).

DISCUSSION

This unique study directly compared DASH scores and shoulder ROM, strength, and muscular endurance between BC and healthy controls, while considering involved limb dominance. These comparisons have not been investigated among long-term BC. The results suggest that persistent deficits may be a result of breast cancer treatment and are not due to aging. Women treated for breast cancer report higher DASH scores (disability) regardless of which limb is involved. Those with cancer affecting their non-dominant limb demonstrate less upper extremity ROM and strength than a control sample of women without breast cancer. Based on these findings, clinical interventions may need to be different based on the side affected by breast cancer.

DASH scores were statistically significantly higher among BC compared to levels reported by this healthy sample, implying lower levels of overall upper extremity function. Caution should be exercised however, as this level of perceived function may not be clinically relevant when compared to DASH values among a larger population. The mean DASH score of a general population sample of 1706 adults was 10.1±14.7,[35] and among 327 women ages 18-65, the mean DASH score was 14.3±14.9.[36] That the control population in this study reported DASH scores much lower than the general population is likely due to study criteria for participation that included no current shoulder dysfunction. In comparing our results (mean score 12.0-12.3) to a general population, our sample of BC that were on average four years post-treatment reported similar levels of function. These findings indicate that BC can expect recovery of function similar to the population as a whole with adequate time. **Yet months to years after treatment, over 20% of women treated for breast cancer score greater than 20 on the DASH.[5] Given the large effect sizes of the results, the findings in this study may suggest that** the diagnosis of cancer can overlay **the** reality **of recovery** and **that** women treated for breast cancer continue to perceive that recovery is incomplete. **The** self-reported function **of the breast cancer groups** remains lower than our control population without shoulder impairment.

Nearly all ROM measures in BC were impaired by 4-12% compared to a healthy sample even four years after treatment. Only the HBB measure was not significantly diminished, yet when comparing raw numbers, the women with breast cancer on the dominate side demonstrated 3.5% less motion than the control group, while those with cancer on the non-dominant side demonstrated a 23% **less** motion. This greater loss on the non-dominant side suggests greater impact of the cancer experience on this side. The mean shoulder flexion motion among BC in this study is 12-17° less than that reported among BC within the first six months after treatment,[16] suggesting that shoulder flexion ROM loss may continue past one year. Although none of the averages of motion **are** below what is generally accepted as clinically significant level, a minimum range of 148° of shoulder flexion is documented as necessary for reaching a high shelf.[37] A secondary analysis of BC with motion less than 148° revealed that 30 of 52 (58%) BC participants did not have this level of motion available on the involved limb. The ER motion, although statistically significantly less among BC-ND, is not considered to be clinically deficient at 83° as most functional tasks can be completed with this available range. While women with breast cancer four years following treatment generally demonstrate ROM at an adequate level to complete most daily activities, these women may have difficulty completing tasks requiring what is generally accepted as full range of motion such as reaching to higher heights or participating in overhead activities. **Furthermore, the effect sizes of these results (>1) suggest that the differences seen are greater than one standard deviation from the**

mean. It is important to understand that even four years after treatment, these women demonstrate motion at levels less than their peers without breast cancer.

Strength differences compared to the control group were found to affect primarily BC who had cancer on their non-dominant side. This group demonstrated strength impairments in both IR and ER that show a 26-28% deficit compared to a population of women without a history of breast cancer. Additionally, the strength values of BC in this study are more than 30% less than published reference values for a healthy population of similar aged females.[14,31] Although methodologies for measurement differed slightly (flexion resistance at the epicondyle instead of distally at the ulnar styloid process,[14] and rotation positioning at 45°[14,31] instead of 90° abduction which was used in this study), the deficits appear greater than can be explained by differing methodologies. It is possible that recovery of strength does not occur spontaneously but with use of the upper extremity, and the lack of apparent recovery seen in the BC whose involved limb is non-dominant may be due to lower levels of non-dominant limb use in daily activities. In studies of arm activity using accelerometry among healthy individuals, the non-dominant limb typically has less activity than the dominant.[38] This loss of strength occurring in the involved non-dominant limb was interesting because these strength deficits were not observed in the dominant limb, suggesting that women with breast cancer involving their non-dominant limb may need to be managed differently than women with breast cancer in their dominant limb.

Research on muscular endurance among BC is limited. Two published studies that have examined muscular endurance have used the Upper Body Strength and Endurance Test, for which psychometric data are unavailable.[39,40] Results from these studies show **less endurance in the involved limb** compared to the non-involved limb. The current study is the first study to examine the use of the FIT-HaNSA in a population of BC. Findings in this study indicate that upper extremity endurance is not impaired compared to a similar healthy population. The lack of differences found between groups may be due to the level of variance among the two groups. A large ceiling effect was observed in performing the FIT-HaNSA; 66-81% of CTRL completed the full test duration of 300 seconds and 53-76% of BC completed the full test. Examining muscular endurance with a more responsive test without a ceiling effect might provide a clearer picture of the level of muscular endurance among BC.

When examining the statistically significant deficits in light of clinical relevance in DASH scores, ROM, and involved non-dominant limb strength, most daily activities can be completed at reported levels, but it is higher level functional activities which may be compromised among this group of BC. The DASH outcome measure was designed to evaluate an overall level of disability and questions are answered based on an individual's ability to perform a task regardless of limb used.[41] This may explain why scores among BC are similar to a healthy population as not all tasks would be performed with the involved limb. Additionally, this outcome measure only asks one out of 30 questions related to reaching overhead and may not be capturing disabilities related to reaching overhead to higher levels. The limitation to higher ROM seen in nearly 60% of participants suggest that although most daily tasks can be completed, tasks which require greater motion, such as reaching high shelves or participating in overhead activities, may be difficult to perform. Certainly, clear deficits in strength are noted among women who experienced breast cancer on their non-dominant side, and this strength deficit can affect the ability to complete more demanding functional tasks that require higher levels of strength.

Study Limitations

Several limitations in this study may have impacted the results. **As the sample was limited to women with more involved cancer treatments, these results may not be generalizable to the subset of women who were treated with lumpectomy, sentinel node biopsy, or chest wall radiation alone.** Incomplete data regarding therapy intervention after surgical treatment for cancer and before data collection makes analysis of the impact of intervention difficult. It is possible that those who had interventions directed toward upper extremity functional return may have skewed the results. **Incomplete data about how many women underwent reconstructive surgery is also a limitation; the impact of reconstructive surgery on arm function cannot fully be assessed. However, with two-thirds of those who had a mastectomy reporting on reconstruction status, it appears about half of the sample who had mastectomies underwent reconstruction.** In addition, the range of time after breast cancer treatment was long (12-336 months) and may have allowed normal tissue healing to occur, thus mitigating long-term functional deficits. A longitudinal study would help differentiate at what point in time following treatment BC symptoms improve giving insight into the probable timeline for return of function. The variance associated with the FIT-HaNSA was large (>60 seconds), suggesting the measure was not sensitive enough to identify those individuals with decreased endurance. Furthermore, the significant ceiling effect does not allow for discrimination between groups.

Conclusion

Although long-term BC often report upper extremity functional limitations, the results of this study indicate that at an average of four years post-treatment, most women recover ROM and strength to levels similar to age-matched women without breast cancer. The important new finding focuses on which limb was involved with cancer treatment. Those women whose cancer impacted the non-dominant limb appear to demonstrate long-term deficits that their dominant involved limb counterparts do not. While the clinical relevance of these statistically significant lower ROM and strength values among women with non-dominant involvement may not seem important, these women continue to report functional deficits higher than age-matched counterparts without shoulder dysfunction. That most daily tasks can be completed with the available ROM and strength measured show some recovery of function. However, the findings in this study revealing a loss of shoulder flexion motion which can impact certain activities requiring a higher reach, and the unexpected finding that strength deficits affecting BC only who have experienced cancer in the non-dominant limb, remain a novel and important result that can impact clinical care for this subset of women with breast cancer. These findings were the most meaningful differences that require further investigation.

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Tables:

Table 1. Participant Demographics, Mean (SD)

	BCS Non-dominant (n=23)	BCS Dominant (n=28)	Control (n=58)
Age, years (range)	57 (41-67)	56 (41-69)	54 (40-68)
BMI	28.3 (6.4)	27.3 (5.9)	26.8 (5.4)
IPAQ, mets	2580 (2441)	3071 (4567)	3190 (2926)
Time since surgery, months (range)	51 (12-336)		
Surgery			
Mastectomy alone	8	15	
Mastectomy + ALND	3	2	
Mastectomy + ALND + Axillary Radiation	3	3	
ALND + Axillary Radiation	4	2	
Previous Rehabilitation (n=35)	5	11	

BMI = Body Mass Index; IPAQ = International Physical Activity Questionnaire; ALND = Axillary Lymph Node Dissection

Table 2. Outcome Measures, Mean (SD)

	BCS Non-dominant (n=23)	Control Non-dominant (n=58)	*p* value	CI	ES	BCS Dominant (n=28)	Control Dominant (n=58)	*p* value	CI	ES
DASH	12.3 (13.1)	3.3 (4.6)	*0.008**	2.20, 16.21	1.13	12.0 (11.6)	3.3 (4.6)	*≤0.001**	3.33, 14.36	1.13
Range of Motion (in degrees except as noted)										
Flexion	140 (17)	154 (9.0)	*0.006**	-13.08, -.11	1.19	146 (14)	152 (9.0)	*0.07*	-13.57, .46	0.55
External Rotation	83 (15)	94 (7.0)	*0.009**	-18.62, -1.98	1.11	90 (12)	95 (9.0)	*0.15*	-11.02, 1.17	0.50
HBB (cm)	16.6 (6.3)	13.5 (4.1)	*0.092*	-1.09, 4.13	0.64	17.6 (5.4)	17.0 (4.5)	*0.83*	-2.16, 3.50	0.12
Strength (% of body weight)										
Flexion	7.3 (3.1)	8.7 (3.1)	*0.24*	-.03, .01	0.45	8.5 (3.0)	9.2 (3.0)	*0.06*	.73, .97	0.23
External Rotation	10.3 (4.7)*	14.3 (4.4)	*0.003**	.09, .12	0.89	14.3 (5.4)	14.3 (4.2)	*0.27*	.12, .16	0.0
Internal Rotation	10.5 (3.5)*	14.2 (4.2)	*0.001**	.10, .13	0.92	12.7 (4.2)	14.3 (4.5)	*0.99*	.11, .14	0.36
Muscular Endurance (in seconds)										
FIT-HaNSA 2	237.1 (86.7)	262.7 (67.7)	*0.42*	-63.74, 19.93	0.35	246.0 (77.8)	269.7 (56.8)	*0.35*	-64.04, 17.33	0.37
FIT-HaNSA 3	257.7 (69.4)	281.1 (45.1)	*0.31*	-61.90, 15.19	0.44	269.9 (67.2)	281.1 (45.1)	*0.71*	-45.89, 23.49	0.21

**Significant at alpha ≤0.05*

CI = confidence interval; DASH = Disabilities of the Arm, Shoulder, Hand; ES = effect size; FIT-HaNSA = Functional Impairment Test-Hand and Neck, Shoulder, Arm; HBB = hand behind back

Figure Legend:

Fig 1a Flexion ROM

Arc of motion generated for illustrative purposes only by Kinovea.org

Fig 1b External Rotation ROM

Arc of motion generated for illustrative purposes only by Kinovea.org

Fig 1c Hand Behind Back Motion

Fig 2a Flexion Strength

Fig 2b Internal Rotation Strength

Fig 2c External Rotation Strength

Fig 3a FIT-HaNSA sub-test 2

Fig 3b FIT-HaNSA sub-test 3

Figure 1a

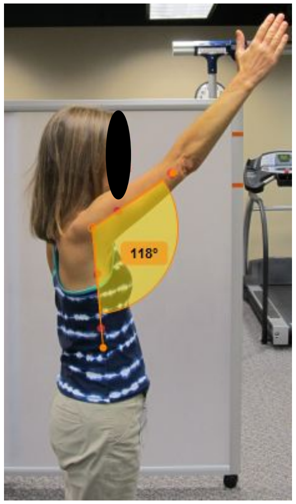


Figure 1b

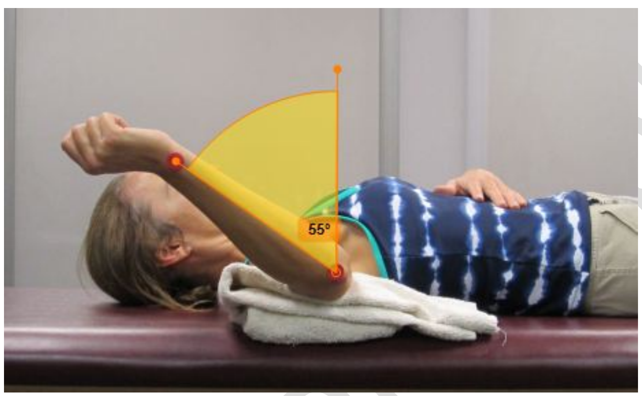


Figure 1c

Figure 2a

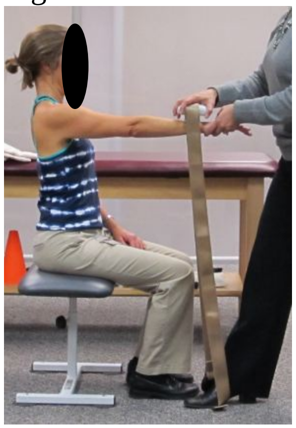


Figure 2b

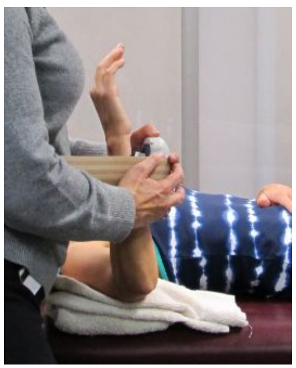


Figure 2c

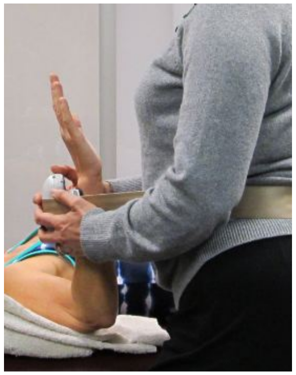
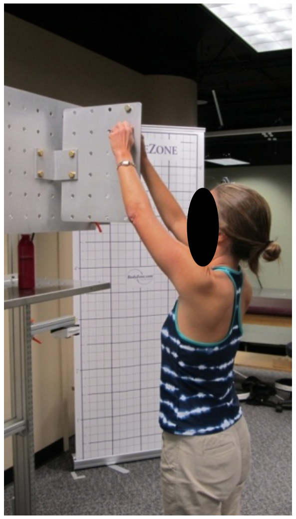


Figure 3a

Figure 3b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