THE IMPACT OF BREAST CANCER AND ITS TREATMENT ON ARM DYSFUNCTION AND QUALITY OF LIFE

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In dedication to my husband, Luc De Garie, and children, Sidney and Loralie (and our third to come). I was single when I started this unbelievable journey... You have changed my life for the best and you are continuing raising me up!

"Our greatest weakness lies in giving up. The most certain way to succeed is always to try just one more time."

Thomas A. Edison

"You know you have reached perfection of design not when you have nothing more to add, but when you have nothing more to take away."

Antoine de Saint-Exupéry

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List of Abbreviations

Abbreviation	Meaning
ADL	Activity of Daily Living
ALND	Axillary Lymph Node Dissection
ALT	Aqua Lymphatic Therapy
AWS	Axillary Web Syndrome
BIS	Bioelectric Impedance Spectometry
BMI	Body Mass Index
BCRL	Breast Cancer-Related Lymphedema
χ^2	Chi-square
CFI	Comparative Fit Index
ClinRO	Clinician Reported Outcome
COP	Colloidal Osmotic Pressure
CDT	Combined Decongestive Therapy
DXA	Dual Energy X-Ray Absorptiometry
EORTC	European Organization Research and Treatment of Cancer
FDA	Food and Drug Administration
FIML	Full Information Maximum Likelihood
GHP	General Health Perception
HRQOL	Health-Related Quality of Life
ICD	International Classification of Diseases
ICD-O	International Classification of Diseases for Oncology
ICF	International Classification of Functioning, Disability and Health
IPC	Intermittent Pneumatic Compression
κ_ω	Kappa (weighted)
LLLT	Low-Level Laser Therapy

MCAR	Missing Completely at Random
MLD	Manual Lymph Drainage
MLM	Maximum Likelihood estimation
ObsRO	Observer Reported Outcome
PCC	Patient-Centered Care
PRO	Patient Reported Outcome
PRT	Progressive Resistance Training
PROMIS	Patient Reported Outcomes Measurement Information System
QOL	Quality of Life
RCT	Randomized Controlled Trial
RMSEA	Root Mean Square Error of Approximation
ROM	Range of Motion
SAS	Statistical Analysis Systems
SEM	Structural Equation Modeling
SF-36	Short Form Health Survey Medical Outcomes Study
SLNB	Sentinel Lymph Node Biopsy
SRMR	Standardized Root Mean Squared Residual
SRO	Self Reported Outcome
TENS	Transcutaneous Electrical Nerve Stimulation
TLI	Tucker-Lewis Fit Index
W-C	Wilson-Cleary
WHO	World Health Organization
WHODAS	World Health Organization Disability Assessment Schedule
WHOQOL	World Health Organization Quality of Life

Abstract

After breast cancer, women experience a number of physical sequelae as a consequence of treatment, mainly concentrated in the arm such as pain, limitation in arm mobility, and breast cancer-related lymphedema (BCRL). These sequelae may be acute and/or become chronic and may lead to arm dysfunction, which can ultimately affect the quality of life (QOL). One in nine women will be diagnosed with breast cancer in their life time making breast cancer the most prevalent cancer among women worldwide.

QOL in breast cancer has been used to describe many physical, mental, emotional, and existential challenges. Inconsistent use of terminology can make it difficult to identify which aspects of QOL are being referred to and which measure best captures the constructs of interest.

The World Health Organization's International Classification of Functioning, Disability and Health (ICF) provides a common language and conceptual framework for describing the impact of a health condition on the person's capacity and performance in everyday life. The ICF distinguishes the observable signs of a health conditions from how someone feels about these, considered well-being, but this latter construct is outside of the ICF. The Wilson-Cleary (W-C) model of health-related quality of life (HRQOL) integrates aspects of the ICF with general health perception and overall QOL providing an integrated bio-psycho-social model. The combination of these two models provides an opportunity to develop a fuller understanding of QOL post-breast cancer and would guide a more integrated and person-centered approach to optimizing QOL post-breast cancer. Thus, the overall aim of this thesis is to contribute evidence towards understanding the mechanisms and determinants underlying the components of arm dysfunction and their impact on QOL in women with breast cancer.

In order to have a better understanding of arm dysfunction, the pathophysiology of lymphedema was described (Manuscript 1). BCRL affects more than one woman in five and is the most debilitating, both physically and mentally, and the feared sequelae. Also reviewed in this thesis is the evidence for the effectiveness of pharmaceutical and physical modalities on pain, shoulder mobility and/or edema (Manuscript 2). BCRL received the greatest attention in the literature and findings revealed that physical treatments to be more

effective than pharmaceuticals. However, there is a lack of high level evidence to make clear rehabilitation guidelines for arm dysfunction post-breast cancer treatment.

One of the most common measures of QOL in people with cancer is the European Organization Research and Treatment of Cancer (EORTC) QLQ-C30 and its specific module on breast cancer EORTC QLQ-BR23. These are classified as patient-reported outcomes (PROs). To identify the extent to which these PROs capture the construct of QOL, the items were linked to the ICF framework using a standardized mapping exercise (Manuscript 3). While aspects of function predominated in the core PRO, there were two items beyond functioning covering well-being; the content of the breast module PRO was entirely related to function.

PROs are the only way of capturing QOL, but function and disability can be identified using self-report and/or expert assessment. The degree to which these two sources of information on function provide comparable ratings was assessed using data from the development and testing of the ICF Core Set for Breast Cancer. Information at the item level on 245 women completing five patient/self-reported outcomes (PROs/SROs) were compared to ratings provided by health care professional completing the ICF Breast Cancer Core Set (Manuscript 4). The level of agreement was estimated with quadratic Kappa and was mostly poor to fair, suggesting that clinicians tend to underestimate symptoms, and patients underestimate physical impairments, such as edema.

Having disentangled the impact of breast cancer on function and disability, the final objective was to identify the relationships between and among these constructs and how they relate to QOL (Manuscript 5). The W-C model formed the theoretical framework for a structural equation modeling approach. The ICF informed the first three rubrics of the W-C model, and facilitated the creation of the latent variables. We found that pain had the strongest influence on all variables related to function and on perception of self. Owing to designed in missing data on QOL, the most distal outcome of the W-C model was health perception, strongly impacted by all aspects of arm dysfunction. Rehabilitation interventions have the strongest evidence for improving these outcomes and should be included early on in the continuum of care. Rehabilitation is a key component of a person-centered approach as each individual has different sequelae and needs for recovery.

Résumé

Suite à un cancer du sein, les femmes expérimentent de nombreuses séquelles physiques occasionnées par les traitements, principalement concentrées au membre supérieur, telles que la douleur, la limitation dans la mobilité du bras et le lymphoedème relié au cancer du sein (LRCS). Ces séquelles peuvent être aiguës et/ou devenir chroniques et elles peuvent mener à une dysfonction du bras qui peut ultimement affecter la qualité de vie (QV). Le cancer du sein est le plus prévalent chez les femmes à travers le monde puisqu'une femme sur neuf en sera atteinte au cours de sa vie.

Le terme QV a été utilisé en cancer du sein pour décrire de nombreux enjeux physiques, mentaux, émotionnels et existentiels. L'utilisation irrégulière de la terminologie peut rendre difficile l'identification de l'aspect de la QV qui est désigné et quelle mesure capture le plus adéquatement les concepts d'intérêt.

La Classification internationale du fonctionnement, du handicap et de la santé (CIF) de l'Organisation mondiale de la santé procure un langage commun et un cadre conceptuel décrivant l'impact que peut avoir une condition de santé sur la capacité d'une personne et sur sa performance quotidienne. La CIF distingue les signes observables d'une condition de santé de comment une personne se sent face à ceux-ci, considéré comme étant le bien-être, mais ce dernier concept est en dehors du cadre de la CIF. Le modèle de la santé relié à la qualité de vie Wilson-Cleary (W-C) incorpore des aspects de la CIF avec la perception générale de la santé et de la QV, procurant ainsi un modèle bio-psycho-social intégré. La combinaison de ces deux modèles procure une opportunité de développer une meilleure compréhension de la QV suite à un cancer du sein et guidera une approche plus intégrée et centrée sur la personne pour optimiser la QV après un cancer du sein. Ainsi, l'objectif global de cette thèse est de d'apporter des preuves afin de comprendre les mécanismes et déterminants sous-jacents à la dysfonction du bras et leur impact sur la QV chez les survivantes d'un cancer du sein.

Afin d'avoir une meilleure compréhension de la dysfonction du bras, la pathophysiologie du lymphoedème a été décrite (Manuscrit 1). Le LRCS affecte plus d'une femme sur cinq et est la séquelle la plus crainte et la plus débilitante, tant physiquement que mentalement.

Les données probantes sur l'efficacité des modalités pharmaceutiques et physiques sur la douleur, la mobilité de l'épaule et/ou l'œdème ont aussi été révisées dans le cadre de cette thèse (Manuscrit 2). C'est le LRCS qui reçoit le plus d'attention dans la littérature et les résultats révèlent que les traitements physiques sont plus efficaces que ceux pharmaceutiques. Cependant, il y a un manque de données probantes de niveau élevé permettant d'établir des lignes directrices en réadaptation pour la dysfonction du bras suite aux traitements pour un cancer du sein.

Une mesure communément utilisée pour la QV avec les gens traités pour un cancer est celle de l'Organisation européenne sur la recherche et traitement du cancer EORTC QLQ-C30 et son module spécifique pour le cancer du sein EORTC BR-23. Ces mesures sont classifiées comme étant des résultats rapportés par les patients (PRO - *Patient-Reported Outcomes*). Afin d'identifier dans quelle mesure ces PRO capturent le concept de la QV, un exercice standardisé associant le contenu des items au cadre de la CIF a été réalisé (Manuscrit 3). Alors que l'aspect de fonction prédominait dans le PRO central, il y avait deux items en dehors de la fonction et qui couvraient le bien-être; le contenu du PRO pour le module du sein était entièrement relié à la fonction.

Les PROs sont le seul moyen de capturer la QV, mais la fonction et le handicap peuvent être identifiés au moyen d'auto-évaluation et/ou d'évaluation faite par un expert. Le degré auquel ces deux sources d'information sur la fonction procurent des notes comparables a été évalué en utilisant les données qui ont servi au développement et à l'évaluation du recueil de données basé sur les catégories de la CIF pour le cancer du sein (*ICF Breast Cancer Core Set*). L'information sur 245 femmes ayant complété cinq patient/auto-évaluation (PRO/SRO – *Self-Reported Outcomes*) a été comparée au niveau des items avec l'évaluation faite par les professionnels de la santé ayant complété le *ICF Breast Cancer Core Set* (Manuscrit 4). Le niveau d'accord a été estimé à l'aide du Kappa quadratique et il était surtout de médiocre à passable, suggérant que les cliniciens tendent à sous-estimer les symptômes et que les patients sous-estiment les dysfonctions physiques, tel que l'œdème.

Après avoir démystifié l'impact du cancer du sein sur la fonction et le handicap, l'objectif final était d'identifier les relations entre et parmi ces concepts et comment ils sont reliés à la QV (Manuscrit 5). Le cadre théorique utilisé est celui du modèle W-C en utilisant une approche de modélisation par équation structurelle. La CIF a informé les trois premières rubriques du modèle W-C et a facilité la création des variables latentes. Nous avons constaté que la douleur avait la plus grande influence sur toutes les variables reliées à la fonction et à la perception de soi. En raison des données manquantes sur la QV, nous sommes uniquement parvenu à modéliser le modèle W-C jusqu'à la perception de la santé, fortement influencée par tous les aspects reliés à la dysfonction du bras. Les interventions en réadaptation détiennent les meilleures données probantes pour améliorer ces résultats et devraient être incluses très tôt dans le continuum de soins. La réadaptation est un élément-clé dans une approche centrée sur la personne, puisque chaque individu a des séquelles et des besoins différents pour récupération optimale.

Acknowledgement

"My way or the highway" is one of the first things I remember from my initial meeting with Dr. Nancy Mayo. I am so grateful that I took your way and tried to follow you on your highway of knowledge. This work would not have been possible without your invaluable guidance and support. I could probably spend the rest of my life beside you and learn a whole lot more. Stepping outside the door will show me how much I have learned during this time. I learned how to address my concerns and my PhD fears by learning that even "super heroes" are human too! You surely will be a continuous source of inspiration for me.

Even if I feel that I have been into this process forever, I feel that I don't know much about the persons in the School of Physical and Occupational Therapy, to whom I am so thankful for their financial support during my PhD studies (Richard and Edith Strauss Doctoral Fellowship in Rehabilitation, Financial aid, and Travel grant). I will always be grateful and will for sure remember the contributions that were offered. Thank you Dr. Isabelle Gélinas for giving me the opportunity of completing my PhD thesis with less financial burden.

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The beginning of this long journey would not have been possible without Dr. Anna Towers who introduced me as a research assistant to "breast cancer arm morbidity" back in 2004. You soon let me discover the wonderful field of lymphedema. You guided me and encouraged me to learn more about this unique condition. After a few years working for you, you pushed me back to school! Without your initial motivation, I would not have become the clinician-researcher I intend to become.

One year after I entered the PhD program, Dr. Sarkis Meterissian offered me a great work opportunity: developing an education/treatment service for women being diagnosed and treated for breast cancer. Over the years, we have worked to build our services and I am looking forward building the research aspect that so far has been limited. Hopefully we will be able to develop, and ultimately indicate, what should be Quebec's standard of practice from pre-surgery and along the continuum of care! Thanks for being available to answer quickly my requests!

A special thanks too to all the surgeons, nurses and medical oncologists referring patients to our service. To Dr. Ari Meguerditchian who always sees things and made me talk faster than I should sometimes! To nurses Carole Magnan and Bonnie Courte, who retired in July 2015, you have seen me growing up personally and professionally. Regardless of the experiences, we worked as a team and we always learned from each other. You helped me to build up the services now offered to the patients. Those services would not exist too without the help of the past and present therapists working with me: Katrin Schumann, Linda Henry, Sarah Khan, and Chantal Turgeon. "Ladies" you are keeping the foundations strong and I know that I can rely on you.

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Being supervised by Dr. Mayo, we have to learn that we are all part of a team and we have to gain knowledge from each other experiences. A key person with whom I started to "enjoy" statistics is Susan Scott. Thanks for helping me figure out simple to

complicated questions! Without you help and guidance, I would probably still be trying to figure out how to open a SAS database! As well as sharing knowledge, we also develop friendships. Thanks to all of you: Carolina Moriello, Sabrina Figueiredo, Alaa Arafah, Vanessa Bouchard, Stanley Hum, Kedar Mate, Sorayya Askari, Lyne Nadeau, Ala Aburub, Owis Eilayyan, and Drs. Skye Barbic, Ayse Kuspinar, Lois Finch, Shanhaz Shahrbanian, and Julio Fiore. This journey would not have been possible without you all.

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To my family... I was single when I started this long journey. It would not have been possible to achieve what I did without your help. Since my return after my second pregnancy, my husband and I have "shared custody" of the children with the grand-parents in order to reach our professional study goals. Thanks for your support and flexibility!

To my husband... I met you not long before the comprehensive examination. You stood beside me and helped me move forward since day 1. We stand and raise each other up. Thanks for being my love, my friend, my colleague, and most of all, the father of our wonderful children.

To Sidney, Loralie, and third to come... you are standing beside (or inside!) me. You changed my life for the best. You are such a bundle of joy and love. Continue raising me up!

Preface

Statement of originality

This thesis presents work carried out to understand the impact of breast cancer and its treatment on arm dysfunction and quality of life. Quality of life (QOL) is an emerging field garnering a lot of attention. To appreciate QOL in breast cancer patients, it is important to understand what needs to be measured. In order to have a better understanding of how QOL is represented, structural equation modeling (SEM) was used. The work presented in this thesis, to my knowledge, is the first application of the Wilson-Cleary (W-C) Model with SEM in a breast cancer population. Also original to this thesis is content validation of two legacy questionnaires, and agreement between clinicians' ratings (ClinRO) and patient reported outcomes (PRO). Both of these steps were vital to be able to perform SEM. This thesis contains no material published elsewhere, except where specifically referenced.

Contribution of authors

This thesis builds upon work from the validation of the ICF Breast Cancer Core Set and from original work from the doctoral candidate. The manuscripts included in this thesis are the work of Marie-Eve Letellier with extensive editing and feedback from Dr. Nancy Mayo, and support from the members of the thesis supervisory committee. All manuscripts, data analysis (when applicable), and writing were conducted by the doctoral candidate under the direct supervision and guidance of Dr. Nancy Mayo.

Mrs Diana Dawes was a co-author in the third manuscript, as she conducted the content validation of the EORTC QLQ-C30. Mrs Susan Scott was a co-author on the fifth manuscript for providing statistical guidance on SEM.

Thesis organisation and overview

The thesis consists of five manuscripts, one of which has already been published, and another in press, in recognized scientific journal. Additional chapters have been included in this thesis in order to follow the regulations of the Graduate and Postdoctoral Studies

(GPS). As requested by the GPS, an introduction and a conclusion, independent of the manuscripts have been included. Therefore, duplications are expected in this thesis.

A brief outline of the thesis is as follows:

Chapter 1 is a literature review, providing an overview on breast cancer, arm impairment, and two measurement models of health-related quality of life.

Chapter 2 presents the rationale and objectives of the thesis.

Chapter 3 consists of the first manuscript entitled 'Pathophysiology of lymphedema: Ideologies and mechanisms underlying breast cancer-related lymphedema'. The aim of this manuscript was to describe the scope and breadth of knowledge currently available regarding the pathophysiology of lymphedema and its treatment and how it informs the mechanisms and ideologies underlying breast cancer-related lymphedema treatment approaches.

Chapter 4 links manuscript 1 and 2.

Chapter 5 consists of the second manuscript entitled 'Narrative review of therapies for post-breast cancer arm morbidity'. The aim of this manuscript was to summarize, among women post-breast cancer treatment, to what extent do pharmaceutical and physical modalities impact on pain, shoulder mobility and/or edema.

Chapter 6 links manuscript 2 and 3.

Chapter 7 consists of the third manuscript entitled 'Content verification of the EORTC QLQ-C30/EORTC QLQ-BR23 with the International Classification of Functioning, Disability and Health'. The aim of this study was to estimate the extent to which the content of the EORTC QLQ-C30 and EORTC QLQ-BR23 goes beyond functioning and include global feeling of well-being. This work has been published in *Quality of Life Research*.

Chapter 8 links manuscript 3 and 4.

Chapter 9 consists of the fourth manuscript entitled 'Assessment of breast cancer disability: Agreement between expert assessment and patient reports'. The aim of this study was to estimate the extent of agreement between clinicians' (ClinRO) and patients' (PRO) ratings on disabilities associated with breast cancer. This work is in press in *Disability and Rehabilitation Journal*.

Chapter 10 links manuscript 4 and 5.

Chapter 11 consists of the fifth manuscript entitled 'Foundation of quality of life in women with breast cancer: A structural equation modeling approach'. The aim of the study was to empirically test a bio-psycho-social conceptual model of HRQOL for breast cancer survivors.

Chapter 12 is a summary of the findings and presents the lessons learned through the process of this PhD thesis.

Corresponding tables, figures, and references are presented at the end of each manuscript. Reference styles were based on each journal's requirements.

The data used for manuscripts 4 and 5 build upon the work of the validation of the ICF Breast Cancer Core Set. Ethics approval for the study was obtained from the Ethics Commission of the Faculty of Medicine of Ludwig-Maximilians Universität, project No. 269/03.

This long journey began in September 2007, during which a number of unexpected life events occurred and I am thankful to Dr. Mayo to have continuously supported me. Before starting my PhD, I was given the permission from Dr. R. Thomas to use the Montreal dataset of a research project that I was involved as a research assistant for four years and for which I had recruited 365 women and followed them every 6 months over a 2-year period. The first three years of my PhD were based on that project. After submitting the draft of my proposal, the proposed analyses were apparently too similar to what they intended to do. Therefore, in September 2010, permission to use the dataset was withdrawn. The group has since then published a paper using latent growth curve modeling:

Quinlan, E., Thomas, R., Hack, T., Kwan, W., Tatemichi, S., Towers, A., Tilley, A., Miedama, B. Secondary lymphoedema trajectories among breast cancer survivors. *Journal of lymphoedema* 2014;29:2-19.

I am still convince that both analyses could have been possible to conduct, and using only the Montreal part of the data, the group would have been able to inform the structural equation modeling model with the rest of the Canadian data. However, as permission was withdrawn, we had to search for a new dataset. Fortunately, Dr. Mayo had the permission to use the dataset originally used for the validation of the ICF Breast Cancer Core Set.

This event occurred one month before the birth of my first child, for which I took two semesters off (Fall 2010-Winter 2011). When I returned in May 2011, I started working with the new dataset.

I then had my second pregnancy, during which I was diagnosed with retinal detachment (January 2012). To this date, I had seven left eye surgeries (last occurred July 22nd 2015) (4 surgeries for retinal detachment, then cataract surgery, then fibrosis of the posterior capsule, then scar adhesion causing retinal edema).

When I came back from my second maternity leave (January 2013), a one-year time extension was granted from the McGill Graduate Studies (I had to complete my thesis by December 2015). I will be visually impaired for the rest of my life, using a monocular vision when reading/doing computer work. Headaches/ophthalmic migraine, visual fatigue and difficulty concentrating are sequelae that I experience and for which I have to reduce my pace when one of them occurs.

Another big challenge for me doing this thesis was to do it in English, as French is my mother tongue. Therefore, even if the thesis has been edited, grammar and syntax may reflect a French background!

Chapter 1: Breast cancer, an overview

Overview of breast cancer

Breast cancer is the leading cause of cancer among women worldwide[1-3]. It is known that cancer risk increases with age and, as the population is aging, the number of new cancers will continue to rise, particularly as the baby boomer generation is entering their senior years[4].

Since the late 1980s, over the last decades, early detection techniques through breast screening programs contributed to some of the rise in new breast cancer cases[4]. In Quebec, screening programs are offered every two years to women aged between 50 and 69 years old as half of the new breast cancer cases will occur within this age group (19%: under the age of 50; 30% over the age of 70)[4].

Since 1998, the mortality rate from breast cancer has declined by more than 2% per year and survival rates (5-year survival or the interval of disease-free) is now approximately 88%[4]. Screening and treatment have resulted in a mortality decrease. But the multifaceted sequelae of breast cancer do not come to an end with the termination of treatments[7-11]. With the increase survival rates, common long-term consequences of breast cancer arise, one of which is lymphedema.

Lymphedema is defined as the build up of lymph fluid, and other elements (e.g. proteins), into the interstitial space of the affected region (breast, trunk, arm and/or hand) due to an imbalance between interstitial fluid production and transport capabilities[12;13]. This is caused by a mechanical impairment of lymph drainage induced by the surgery, radiation therapy, and/or chemotherapy although there is no clear scientific evidence linking chemotherapy to lymphedema[14-17].

Breast cancer-related lymphedema (BCRL) may be acute (edema that lasts less than three months and goes away) or chronic (edema is not reversible and is present for at least three months)[18]. The onset of lymphedema is mostly within the first two years post-treatments; 29% occurring within 0-6 months, 33% 7-12 months, 31% 13-24 months, and

few cases appearing as much as 20 years post-treatment. Late occurrences maybe more frequent as the population ages[18].

The true risk factor profile for lymphedema is unknown[19;20]. Some risk factors for developing post-breast cancer lymphedema are[12;14;18]:

1) Treatment-related: surgery, radiation therapy, wound infection, seroma formation.
2) Patient-related: obesity, diabetes, hypertension.

The whole pathophysiology of BCRL is discussed in Chapter 3 (Manuscript 1).

Overview of breast cancer and its sequelae in the context of ICD and ICF

The World Health Organization (WHO) has two main international reference classifications: the International Classification of Diseases (ICD) and the International Classification of Functioning, Disability and Health (ICF)[21;22]. Used together, the classifications denote the full picture of health: the ICD captures information on mortality and morbidity and the ICF captures information on health domains at the function and impairment level[21].

The ICD and ICF classification provide a unified and standardized language for describing and classifying death, disease, health domains and health-related states[7;8;21;23-29]. In addition, the ICF provides a common framework for health outcome measurement, as illustrated in Figure 1. Within the ICF model, functioning is "an umbrella term encompassing all body functions, activities and participation" (positive) and disability serves as "an umbrella term for impairments, activity limitations or participation restrictions" (negative)[10;23;27;30].

In 2000, the WHO published the third edition of the International Classification of Diseases for Oncology (ICD-O)[21]. This classification provides a coding system specific to cancer registries[21] where breast cancer has been coded C50-C50[31]. Within the ICD, coding for post-procedural disorders is also defined[21]. One of the sequelae of breast cancer is lymphedema and it has been coded as I97.2 (post-mastectomy lymphedema)[31].

In the ICF, the direct classification of lymphedema is not possible: only impairment to the lymphatic vessels/nodes functions (d4352/d4353) and structures (s4200/s4201) can be characterised. As lymphedema has been coded within the ICD-10 framework, no code within the ICF is needed except to denote its cause. Therefore, lymphedema should be considered as a disease rather than impairment.

Facing breast cancer may lead to treatment-related and/or psychological sequelea and these challenges can be experienced in the short and/or long-term[32;33]. Table 1, based on the ICF model, indicates disabilities associated with breast cancer[32;34-36]. Around 43% of women are still working[6;37] and on average, it will take around 18 months post-surgery before they recover their full capacity to perform their occupation[6]. For them, work represents a necessity, as it provides income, health insurance and social interaction[6]. As disability can occur in the short and/or long term, changes in employment may also occur in the short and/or long-term and may be costly: need to change work, change in income (from changing to part-time work to changing position or retiring prematurely), increase in medication costs and health insurance and the need to pay for rehabilitation therapy[6;38;39].

The extent of arm dysfunction post-breast cancer varies; between 16 to 83% of women will experience impairments within the first year post-treatment[40-42]. The impairments will be reduced by 40-50% in the following two years. However, up to 38% of women could still experience impairment in the long term[43;44].

Even if all the physical and psychological impairments are to be integrated in a continuum of care, the interest of this thesis is on arm dysfunction and quality of life (QOL) after breast cancer treatment.

Overview of breast cancer and quality of life

Quality of life has been defined by the WHO as: “the individuals’ perception of their position in life, in the context of the cultural and value systems in which they live and in relation to their goals, expectations, standards and concerns”[45].

According to Petersen and colleagues (2008)[46], some studies have demonstrated that a diagnosis of cancer can have a favorable effect on QOL as the patient may reconsider their priorities and life goals. On the other hand, it is also suggested that a cancer survivor will show a poorer QOL compared to age-matched controls, mainly for the reason that cancer is a fearful diagnosis and treatments may be an overwhelming burden[36;46].

The primary mission of modern health care institutions should be to provide patient-centered care (PCC). The cornerstone of PCC is a focus on outcomes that people notice and care about, such as survival, function, symptoms and QOL[47]. As previously mentioned, arm dysfunction can occur at any time. Therefore, it important to consider that QOL may be affected at any time over the course of the illness, whether it is during treatment and/or for life-time post-treatment for breast[9;48;49].

Arm dysfunction after breast cancer: Definition and prevalence

Arm dysfunction after breast cancer is a term encompassing: pain, impaired range of motion (ROM), loss of strength, paresthesia, and lymphedema[9;33;40]. The mechanisms leading to the development of arm dysfunction are multi-factorial[4]:

1) Treatment-related: availability and quality of early detection, type of surgery, site of radiation therapy, chemotherapy, hormonal therapy;
2) Disease-related: stage of disease (see Table 2 for the dysfunction aspect associated with breast cancer stages), pathologic node status;
3) Patient or clinical-related: age, comorbid conditions (e.g. obesity, hypertension, diabetes), socio-economic status, lifestyle factors.

Table 3 indicates the definition and prevalence of each symptom based on the ICF model, as it procures a unified and standardized language. The gap in the literature might be explained by: 1) the fact that there is no common definition used, particularly regarding lymphedema[9;50], and 2) on the difference in the method of detection/diagnosis and the length of follow-up[44].

Factors causing arm dysfunction and lymphedema

Rietman and colleagues (2003)[51] mentioned that the aim of breast cancer treatment is to "achieve maximal locoregional control, optimal lymph node staging with minimal treatment related morbidity, good functional result, and when possible preservation of the breast". The curative care for breast cancer include: surgery, radiation therapy, and drug therapy.

Each treatment can induce impairments, with the exception of hormonal therapy as it does not trigger decreased ROM. It is important to note that each treatment may lead to acute and/or long-term side effects[11].

Causes of pain

Pain is often described by women as: burning, aching, constriction, scar sensitivity, discomfort or tenderness[52;53]. The exact cause is unclear and can be multifactorial, but the main factors contributing to pain may be: mastectomy, axillary lymph node dissection (ALND), trauma to the tissues during the surgery, dissection of the intercostobrachial nerve or intraoperative damage to axillary nerve pathways[53-55].

Pain intensity will depend on how invasive the surgery and how the woman heals and tolerates pain[56].In supplement to surgery, radiation and chemotherapy are often needed and may aggravate the sensation of pain[57;58]. The pain may be acute or may become chronic. As many as 43% of women still experience pain three years post-treatment and half were still experiencing pain after nine years[54].

The pathophysiologic mechanism of chemotherapy-related pain is unknown, however, evidence is suggesting it is a manifestation of acute neurotoxicity developing mainly within 72 hours of treatment and may be related to the type of drug received[59].

The cause of pain related to hormonal therapy is also unknown, but it was suggested that lower levels of oestrogen may play a role[60]. As many as 20% of patients will discontinue their hormonal treatment because of muscle and joint pain[57;60;61].

Causes of decreased range of motion

Musculoskeletal issues also occur with breast and/or axilla surgery[57]. Particularly with mastectomy, the woman's ability to move her upper limb freely in its complete ROM can be affected if damage to the nerves and muscles occurred during the surgery[53]. The feeling of stiffness or tightness of the arm or shoulder often goes away by three months after surgery[53]. Adherent scar tissues also limit arm movement[53]. In addition to surgery, radiation therapy may compound motor restriction as radiation may lead to more scar and fibrotic tissues[57;62;63].

Causes of loss of strength

Intraoperative damage to axillary nerve pathways can lead to a diminution in upper-extremity strength[64]. Acute brachial plexopathy, manifesting as weakness in the arm or hand, can occur during radiation treatment and may remain for a few months after completion of treatment[57]. This occurs mainly when the brachial plexus is included in the radiation field[65]. When present, women experienced weakness in their shoulder and biceps muscles[65].

The neurotoxicity produced by chemotherapy drug may also have an impact on motor neuropathy[59;66]. The neuropathy is usually mild to moderate and the severity is associated to the dose (individual and cumulative) and the schedule of administration[66]. It is also reported that Tamoxifen causes muscle weakness in 18% of the users[67].

Causes of paresthesia

During surgery, nerves may be damaged or removed. This can cause a loss of feeling or changes in sensation in the upper arm, axilla, shoulder or chest[53] and long-term symptoms of paresthesia may result[53;57]. Loss of inner upper arm sensation is often expressed by women who have had an ALND and this is caused by the transection of the intercostobrachial nerve[64].

As previously mentioned, radiation therapy can result in an acute brachial plexopathy, manifesting here as paresthesia[57], but these symptoms will usually resolve spontaneously within weeks or months[65]. The neurotoxicity of chemotherapy may also lead to sensory

neuropathy[59;66] and one of tamoxifen's side effects is paresthesia although only experienced in few women (5%)[67].

Causes of lymphedema

Breast and/or axilla surgery combined with radiation therapy may lead to the development of lymphedema[57]. Lymphatic vessels are damaged and lymph nodes are removed with the surgery; therefore, limiting the lymphatic flow[13;18]. Radiation therapy will also reduce the lymphatic flow by causing more fibrotic tissues, restraining the capacity of the lymphatic system to drain properly[13;18]. In both cases, the more invasive the treatment is, the greater the damage can be on the lymphatic system and may trigger lymphedema[18;63]. The research evidence is unclear regarding chemotherapy as a trigger of lymphedema[15-17]. However, a meta-analysis concluded that it is primarily the treatments interrupting the lymphatic flow in the axilla – such as mastectomy, the extent of axillary surgery, radiation and positive lymph nodes – that lead to the development of lymphedema[15]. For more details on BCRL, see Chapter 3 (Manuscript 1).

Treatments improving arm dysfunction and lymphedema

The actual treatments for arm dysfunction following breast cancer are: drugs and/or the use of rehabilitation therapy[55;68-72]. The greater attention in the literature is given to lymphedema, for which Chapter 3 (Manuscript 1) and Chapter 5 (Manuscript 2) grant more details. Table 3 summarizes the findings discussed below.

Treatments for pain

Chronic pain is a common consequence of cancer and its treatment[69]. Neuropathic pain may respond to drug therapy[55;68;69]. Rehabilitation therapy may also be effective in reducing pain symptoms, in particular, with manual therapy and transcutaneous electrical nerve stimulation (TENS)[68].

Treatments for decreased range of motion

Hase and colleagues (2006)[70] have investigated the efficacy of oral administration of zaltoprofen (a nonsteroidal anti-inflammatory drug which has an analgesic effect) to reduce the pain related to shoulder ROM. In their study, the improvement of ROM was greater in the group where the participant received the drug[70]. Therefore, the medication reduced the pain, but did not improve ROM. Physical therapy treatment is an appropriate solution[55;70-72]. Rehabilitation therapy will provide manual treatment and exercises in order to regain ROM[55].

Treatments for loss of strength

If the loss of strength is due to the neurotoxicity of the chemotherapy, the effects are usually temporary and should disappear after completion of treatment[66]. Pain and paresthesia can be relieved by nerve stabilizer drugs (such as Neurotin). However, this type of drug does not alleviate numbness, weakness or proprioceptive deficits[55]. Physical therapy has been proven to improve strength and should be consider as a treatment option[55;72].

Treatments for paresthesia

If paresthesia is caused by an acute brachial plexopathy following radiation therapy, the symptoms should resolve spontaneously within weeks or months[65]. As previously mentioned, paresthesia may be alleviated by a nerve stabilizer[55]. If the paresthesia is caused by an underlying problem, other than caused by surgery and/or radiation therapy, physical therapy may be helpful[55].

Treatments for lymphedema

The main ideas of Chapter 3 (Manuscript 1) and Chapter 5 (Manuscript 2) are discussed here. The hope behind medication is to have a drug that will stimulate lymph flow or remove the excess fluid present into the interstitial space. The drugs tried (benzopyrones, diuretics and selenium) are efficient to treat other medical conditions, but none have proven efficacy for lymphedema[73-75].

In rehabilitation, several therapies are offered in the management of lymphedema: manual lymph drainage (MLD), compression, skin care, exercises, intermittent pneumatic pump, and many others options (e.g. proprioceptive elastic tape, aromatherapy, acupuncture – where there is not much scientific evidence)[62;76;77]. The principle is to stimulate lymph flow progression towards the trunk and non-affected region[62;78].

Exercise is known to be effective to prevent chronic disease, such as hypertension, high cholesterol, and obesity[79]. In people suffering of lymphedema, exercise plays a major role by its physiological impact on the lymphatic system[79], and by the fact that it provides good cardiovascular health, muscle strength, functional capacity, and better QOL[80]. Originally, exercises were thought to be a potential trigger for lymphedema, especially if the person was doing repetitive and strenuous exercises[79-81]. We do know now that a slow progression is essential and this will not worsen lymphedema[79]. What is not known is the best type of exercise and the best regimen.

Combined decongestive therapy (CDT) – which include skin care, MLD, compression and exercises – is considered as the standard treatment for lymphedema[14;62]. Compression seems to be the key element: volume reduction is between 43% to 79% when combined with CDT versus 26% if MLD is used alone[62]. Compression, multi-layer bandaging and/or compression garment should be well fitted, otherwise it may aggravate lymphedema[82]. Intermittent pneumatic pump should be used with caution and should not be used as a unique therapy, but rather as a complement to CDT and/or exercises[62;78;83;84].

Arm dysfunction and quality of life: Measurement limitations

QOL and health-related quality of life (HRQOL) are concepts often used interchangeably[85;86]. Patrick and Erickson (1993)[87] defined HRQOL as the "value assigned to duration of life as modified by the impairments, functional states, perceptions and social opportunities that are influenced by disease, injury, treatment, or policy". HRQOL is not, therefore, a primary construct, but rather a constructed one operationalized using a mathematical algorithm[88].

A limitation in understanding arm dysfunction and QOL after breast cancer is that there is a variety of measurement strategies used in studies, which makes the interpretation of the results very difficult to generalize and to compare across studies. As a result, it is important to utilize available models such as the ICF[23] and the Wilson-Cleary (W-C) models[89], to guide clinicians, researchers, and patients to describe, measure, and interpret breast cancer QOL outcomes[90].

The ICF and W-C models can easily be integrated together, as both share significant characteristics, even if they have been conceived independently, as illustrated in Figure 2[91]. In addition, both are considered bio-psycho-social model[10;23;89]. The W-C model uses terms referred to "components" of HRQOL, whereas the ICF framework refers to domains of well-being, a construct similar to QOL[23;89].

The ICF model provides codes for the first three levels of the W-C model. The body structure and function of the ICF model will correspond to the biological and physiological variables and the symptom status of the W-C model. Coding of the ICF model for activity and participation can be integrated into the functional status of the W-C model. The W-C model will talk about characteristics of the individual and the environment, whereas the ICF will consider those two items as being personal and environmental factors[91].

The ICF[23] and W-C[89] models are relatively new (2001 and 1995 respectively) and are recently in research. Several studies on each model can be found, although the combination of both models is rare in the literature[91]. According to the author's knowledge, the two models have not been investigated together in breast cancer research outcomes. The ICF model has been considered with its own Breast Cancer Core Set[7]. Whereas, the W-C model has been used by Dawes et al. (2008)[9] for breast cancer lymphedema outcomes research in order to understand the relationship between impairments, disability and sub-optimal HRQOL. She reported that lymphedema was not the principal contributor to arm dysfunction, and in fact, pain was a stronger determinant of dysfunction than lymphedema. The small sample size was a limitation.

Bakas et al. (2012)[90] systematic review on HRQOL conceptual models mentioned that the W-C model was the most commonly HRQOL model used and they suggest its use, with the additional linking of the characteristics of the individual and of the environment to the biological and physical variables made by Ferrans[92]. This model is complex and difficult to analyze in its entirety. One of the reasons is because the rubrics under study are "latent", meaning that they are not directly measurable. Furthermore, this model estimates that there is a simultaneous association between latent domains, both directly and indirectly[89]. When dealing with such complex model, optimal statistical environment is required.

As the relationships between and among variables that contribute to arm dysfunction and QOL is unknown, the W-C model, which has not been tested in breast cancer, will allow establishing those relationships with a sophisticated methodological approach: structural equation modeling (SEM). SEM is a comprehensive statistical method that test and estimate the causal relationships among measured and latent variables[93-95]. This structural model represents the core of this thesis and will be described in Chapter 11 (Manuscript 5) and the hypothesized model when this whole process started is illustrated in Figure 3.

Table 1. Disabilities associated with breast cancer

Physical impairments	Psychological impairments	Activity limitations	Participation restrictions
Pain Fatigue Weakness Joint arthralgia Neuropathy Adverse effects on the cardiovascular system Osteoporosis Weight gain/ weight management	Anxiety Depression Feminine image Sleep	Use of hand/arm in everyday activities Self-care Concentrating	Mother's role Partner's role Worker's role

Table 2. Dysfunction associated with breast cancer stages

Stage	Definition[96]	Survival[4]	Dysfunction
0	*In situ*: the abnormal cells are in the lining of a milk duct or a lobule.	High	Unlikely to experience arm dysfunction as only the portion of the breast tissue with cancer is removed.
1	Tumour is 2 cm or less and the cancer has not spread outside the breast.	High	These three stages capture patients that would be likely to develop arm dysfunction as the patients will have surgery, chemotherapy and/or radiation therapy.
2	Tumour is 2 to 5 cm, or the cancer has spread to the lymph nodes, or both.	High	
3	Tumour is more than 5 cm, or cancer has spread to lymph nodes and may have spread in the surrounding tissues, like the muscle or the skin.	Good	
4	Cancer has spread to other parts of the body.	Poor	Patient unlikely to undergo surgery or radiation to the breast/axilla, which will not lead to arm morbidity.

Table 3. Arm dysfunction after breast cancer: Definition and prevalence

Dysfunction	Definition	Prevalence
Pain	Sensation of unpleasant feeling indicating potential or actual damage to some body structure. (b280)	0-68% [44;97-105]
Decrease ROM	Impairment in the functions of the range and ease of movement of more than one joint.(b7101)	0-50% [42;97-102;105]
Loss of strength	Impairment in the functions related to the force generated by the contraction of the muscles and muscle groups of one arm. (b7301)	0-43% [42;101;102]
Paresthesia	Impairment of sensory functions of sensing pressure against or on the skin. (b2702)	0-73% [97-100;102;103]
Lymphedema	Build up of lymph fluid, and other elements, into the interstitial space of the affected region due to an imbalance between interstitial fluid production and transport capabilities. (ICD-10: Post-mastectomy lymphedema I97.2)	0-86% [9;44;97-102;104;105]

Table 4. Treatments improving arm dysfunction and lymphedema

	Pain	Decrease ROM	Loss of strength	Paresthesia	Lymphedema
Pharmacological	√			√	
Rehabilitation	√	√	√	√	√
Potential for spontaneous recovery			√	√	

Figure 1. ICF Model

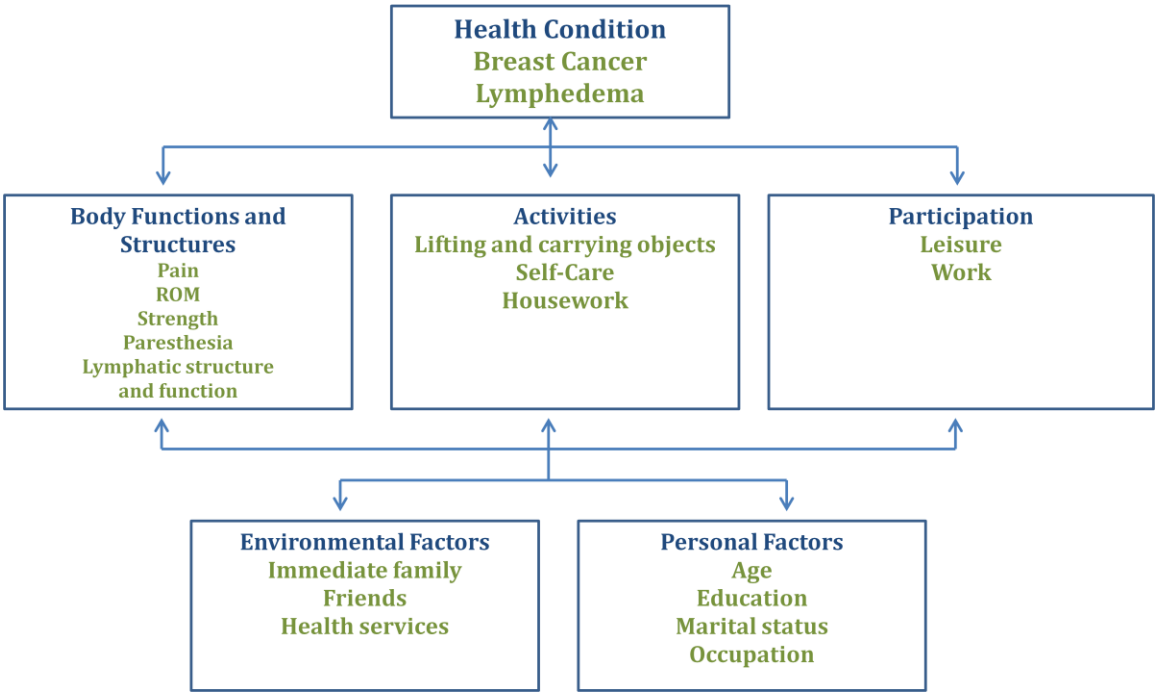


Figure 2. Combination of the ICF and Wilson-Cleary models

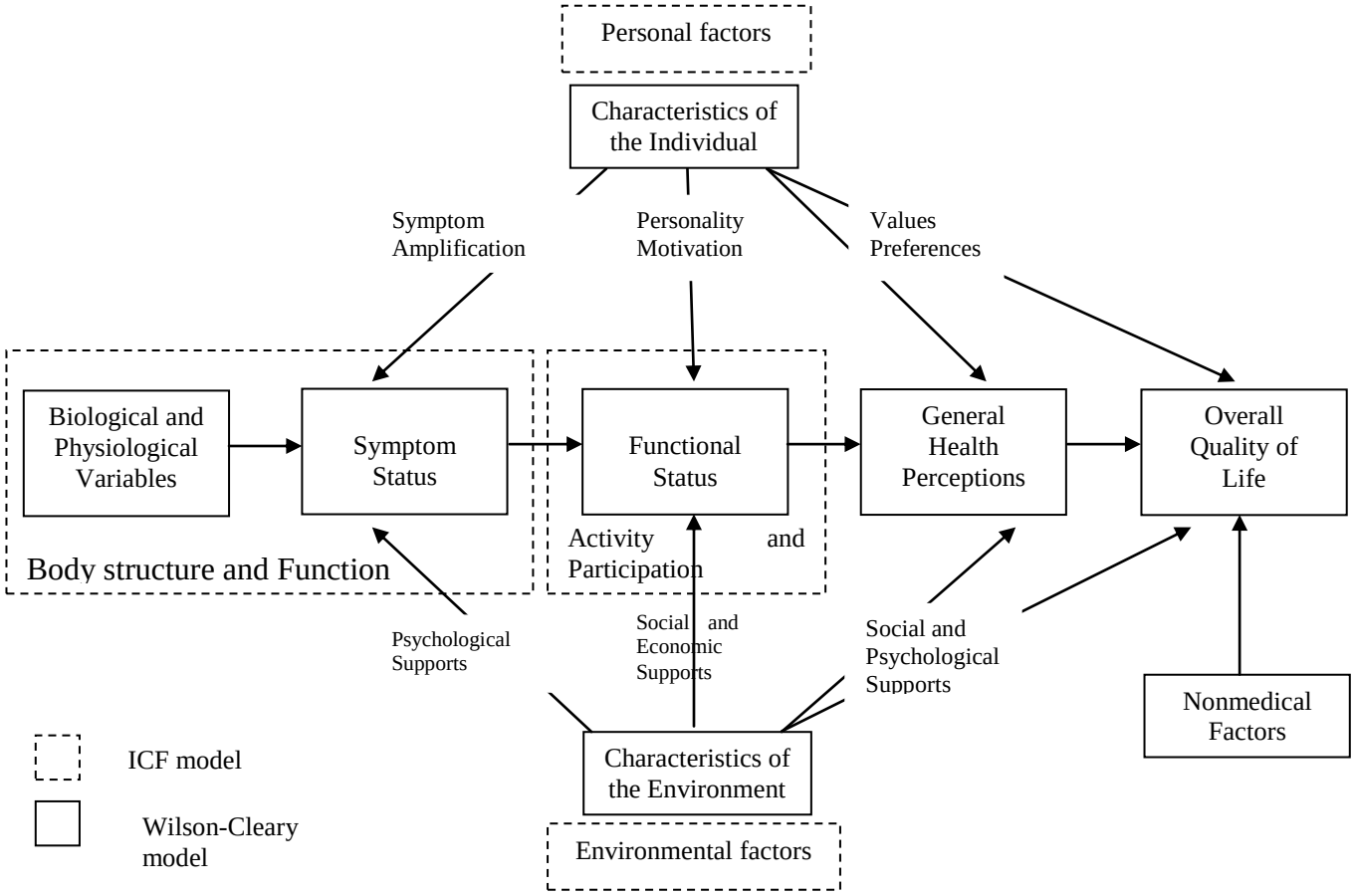
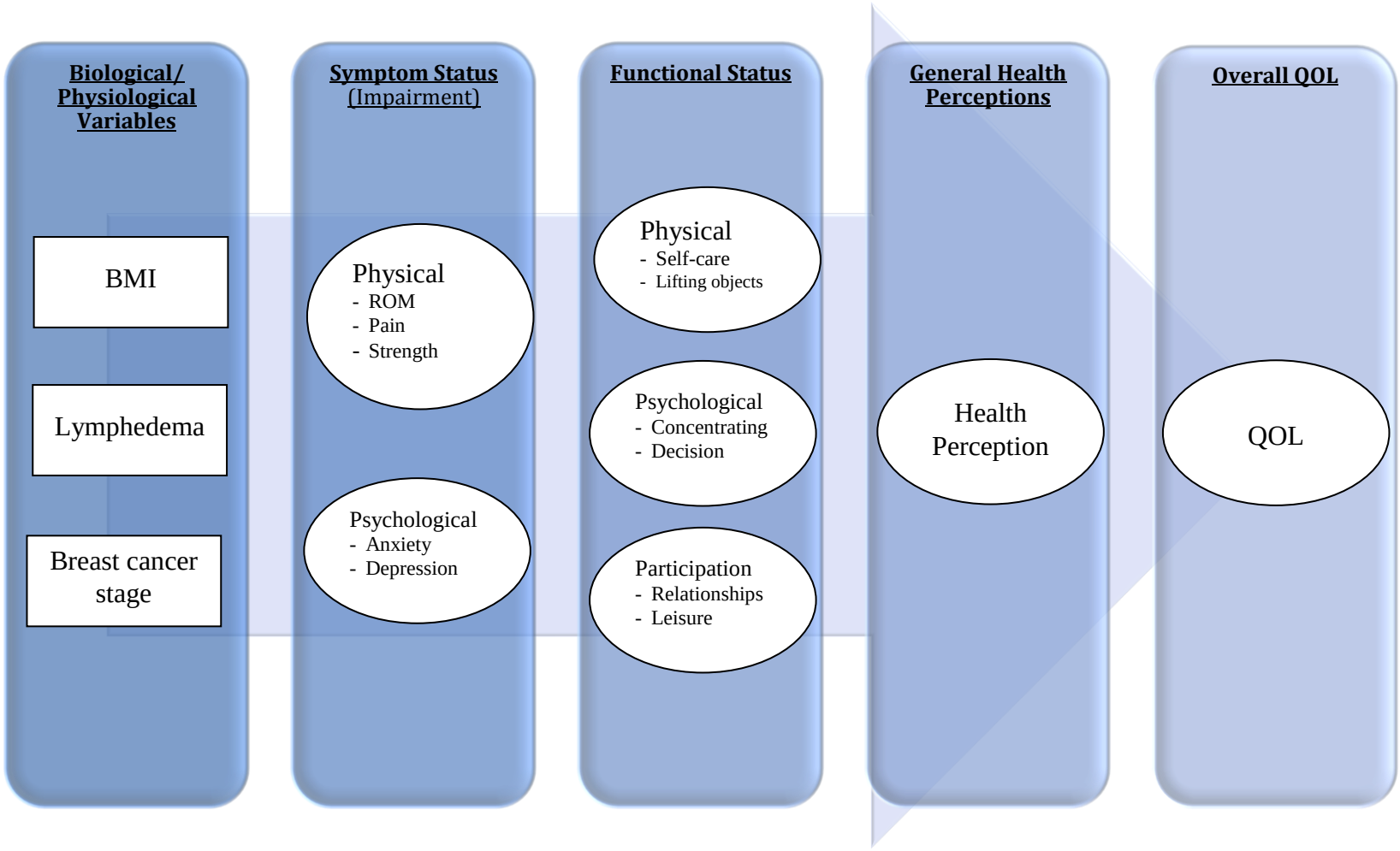


Figure 3. Hypothesized bio-psycho-social model



Chapter 2: Rationale and Objectives of the thesis

Rationale of the thesis

Cancer used to be considered an acute disease, where death was traditionally the primary outcome. These days, the effectiveness of treatment has lead to a change in how we measure breast cancer outcomes. Specifically, we need to consider cancer as a chronic disease, rather than a short illness with a binary outcome (dead or alive). This decrease in mortality and increase in disability must redefine how care is delivered.

In order to provide a conceptual framework and a common language, the use of the International Classification of Functioning, Disability and Health (ICF) and the Wilson-Cleary (W-C) model should be considered in research targeting health-related quality of life (HRQOL). The ICF will provide a rigorous coding system, whereas the Wilson-Cleary model will allow linking of the variables and their relationships. In order to inform breast cancer outcomes adequately, both models should be integrated into research to provide a comprehensive conceptual framework to guide outcome measurement and interpretation of results. A better understanding of the components of HRQOL post-treatments would lead to a more integrated and person-centered approach.

Objectives of the thesis

The overall aim of this thesis is to contribute evidence towards understanding the mechanisms and determinants underlying the components of arm dysfunction and their impact on QOL in breast cancer survivors. This thesis has three distinct components: 1) construct investigation (literature), 2) construct verification (measurement), and 3) construct impact and determinants (literature and measurement).

Construct investigation

The specific objective is:

> To summarize, in the context of rehabilitation, the scope and breadth of knowledge currently available regarding arm dysfunction after breast cancer.

This section has two proposed manuscripts:

- Manuscript 1 (Chapter 3): " **Pathophysiology of lymphedema: Ideologies and mechanisms underlying breast cancer-related lymphedema treatment**", which summarizes the scope and breadth of knowledge currently available regarding the pathophysiology of lymphedema and its treatment and how it informs the mechanisms and ideologies underlying breast cancer-related lymphedema treatment approaches.

- Manuscript 2 (Chapter 5): "**Narrative review of therapies for post-breast cancer arm morbidity**", which summarizes, for women post-acute treatment for breast cancer, the extent to which medication or physiotherapy techniques reduce pain, shoulder mobility and/or edema.

Construct verification

The specific objectives are:

> To estimate the extent to which the content of QOL measures are linked to the ICF and to estimate the extent of agreement of those measures between clinician and patient reported arm dysfunction.

This section has two proposed manuscripts:

- Manuscript 3 (Chapter 7): "**Content verification of the EORTC QLQ-C30/EORTC QLQ-BR23 with the International Classification of Functioning, Disability and Health**", which aims to estimate the extent to which the content of the EORTC QLQ-C30 and EORTC QLQ-BR23 goes beyond functioning and includes global feeling of well-being.

- Manuscript 4 (Chapter 9): "**Assessment of Breast Cancer Disability: Agreement between Expert Assessment and Patient Reports**", which aims to estimate the extent of agreement between health professionals' (ClinRO) and patients' (PRO) ratings on disabilities associated with breast cancer (impairments, activity limitations and participation restrictions).

Construct impact and determinants

Modernization of statistical methods makes them an ideal tool to help us to understand the nature of arm dysfunction after breast cancer treatment. The specific research question is:

> To empirically test a bio-psycho-social conceptual model of HRQOL for breast cancer survivors.

This construct has one manuscript:

- Manuscript 5 (Chapter 11): "**Foundation of quality of life in women with breast cancer: A structural equation modeling approach**", which aims to empirically test a bio-psycho-social conceptual model of HRQOL for breast cancer survivors.

Chapter 3: Manuscript 1

Pathophysiology of lymphedema: Ideologies and mechanisms underlying breast cancer-related lymphedema treatment

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Pathophysiology of lymphedema: Ideologies and mechanisms underlying breast cancer-related lymphedema treatment

ABSTRACT

The aim of this literature review is to summarize the scope and breadth of knowledge currently available regarding the pathophysiology of lymphedema and how it informs the mechanisms and ideologies underlying breast cancer-related lymphedema (BCRL) treatment approaches.

The lymphatic system is a system parallel to the blood system and its main role is to preserve fluid balance. Treatments for breast cancer may lead to an impaired lymphatic system which could subsequently lead to the development of lymphedema.

The most common treatment for lymphedema is combined congestive therapy, which includes manual lymphatic drainage, compression, skin care, and remedial exercises. Medical option to treat lymphedema is only via surgery, when conventional therapies have failed to reduce arm volume.

All therapies for BCRL have the same goals: reduce arm volume and maintain function. However, the greatest reduction will only be attained through the compliance of the person.

Early intervention, education, compression, weight control and exercise are key elements in the management of BCRL.

Introduction

For centuries, the lymphatic system has been studied. Ancient civilisations (350-250 BC) called it "white blood" and described chyleferous vessels without being able to distinguish the vessels from the blood system[1;2]. Despite this long history, what is known about the lymphatic system is only the tip of the iceberg. Our understanding is increasing as technologies evolve[2-4].

In normal human biology, the three main functions of the lymphatic system are to[1;5-7]: 1) preserve fluid balance, 2) absorb dietary fats (nutritional function), and 3) facilitate the immune defenses. Therefore, the lymphatic system plays a major role in our life and in the fight against diseases, such as cancer[1;3;6-9]. Worldwide, the World Health Organization (WHO) estimates 1.67 million of new breast cancer cases diagnosed in 2012[10]. Of those, more than one in five women will develop breast cancer-related lymphedema (BCRL)[11;12].

BCRL is defined as the build up of lymph fluid, and other elements (e.g. proteins), in the interstitial space of the affected region (breast, trunk, arm and/or hand) due to an imbalance between interstitial fluid production and transport capabilities[6;13-17]. Caused by a mechanical failure of the lymphatic system, it is a chronic inflammatory lymphostatic disease[13;14;18]. It can be induced by the surgery, radiation therapy, and/or chemotherapy [13;15;19-21] (evidence is unclear about whether or not chemotherapy is involved in the development of BCRL).

The aim of this literature review is to describe the scope and breadth of knowledge currently available regarding the pathophysiology of lymphedema and how it informs the mechanisms and ideologies underlying BCRL treatment approaches (e.g. drugs, alternative medicine, exercise and risk reduction strategies). This paper is structured to give an overview of the lymphatic system and its anatomy, describe its physiology and its pathophysiology, targeted to a rehabilitation audience. To conclude, the rationale behind each BCRL treatment will be described.

Overview and anatomy of the lymphatic system

The lymphatic system consists of lymphatic organs (bone marrow, thymus, spleen, lymph nodes and mucosa-associated lymphatic tissue) and lymphatic vessels[1;22]. (Only lymph nodes and lymph vessels will be discussed here.) The lymphatic vessels represent a linear network, interspersed with lymph nodes, covering the totality of the human body – with the exception of the brain, spinal cord, retina and cartilage – and are parallel to the blood system[1;22;23]. Histologically, lymph vessels are divided into initial lymphatic vessels, pre-collectors, collectors and lymphatic trunk[1;22;24].

Initial lymphatic vessels, also wrongly termed 'lymph capillaries' in the literature (they have completely different structural and functional characteristics from the capillaries of the blood vascular system[24]), are blind-ending vessels made of superposed endothelial cells and have no valves[1;4;22;24;25]. They are located within the first few millimeters of the skin, in the interstitial space and around blood capillaries[22;24;26]. Their role is to collect interstitial fluid; once the interstitial fluid enters the initial lymphatic vessels, the fluid is then called lymph. Lymph is made of: proteins, water, fat cells, white blood cells, and waste; which is similar to the composition of the interstitial fluid[22;24]. Anchoring filaments inserted on one end of the exterior surface of the overlapping endothelial cells connect with elastic and collagenous fibre of the interstitium and allow fluid collection[1;22;24;25]; this is further described in section "Physiology of the lymphatic system".

Initial lymphatic vessels are preceded by prelymphatic channels. Composed of elastic fibres rather than epithelial cells, these channels are not considered part of the lymphatic vessels[1;24;27]. Their share of the entire interstitial space is small, and accounts for only 1% of the drainage[24;27]. They are referred as "guide rails", "tissue channels", or "low resistance pathways" and function to lead the interstitial fluid to the initial lymphatic vessels[24]. They are responsible for restoring the force in the tissue[24].

Pre-collectors are sections of various lengths linking at defined areas the initial lymphatic vessels to the collectors [22;24]. They are located quite often in close contact with arterial blood vessels[24]. They can have incomplete or complete valves and they act as drains.

Because of some variation in their structure, pre-collectors have also the capacity to reabsorb some of the interstitial fluid[22;24].

Collectors are musculoendothelial tubes with complete valves, which prevent, under normal circumstances, lymph to flow back and which make the lymphatic vessels a one-way system[1;3;4;22;24]. The space between two valves is called a lymphangion and it constitutes the functional unit of the lymphatic system[3;4;22;24]. The propulsion of lymph toward the entry into the vascular system is through the collectors, and eventually the lymphatic trunk. Propulsion is mainly assured by the contraction of lymphangions, which is called lymphangionmotricity[28]. Lymphangion reflex contraction is induced by accumulation of lymph and/or because of innervations induced by the sympathetic nervous system[22;28]. At rest, lymphangiomotricity is around six to ten contraction per minute, and can increase in response to an augmentation of lymphatic load[28].

Lymphatic trunks have a structure that is similar to the collectors, with local differences[24]. They are the largest vessels and form the main parts of the transporting system[24]. The lymphatic trunks will ultimately return the lymph into the venous blood system via lymphovenous anastomoses at the right and left venous angle[22;24].

Lymph nodes are considered as secondary lymphatic organs with a multitude of functions, such as[1;22;24]: 1) biological filtration station, 2) major foundation for the recirculation of the lymphocytes, and 3) regulation of the level of proteins and water contained in the lymph. Approximately 600 to 700 lymph nodes are found in the body and they are typically embedded in adipose tissue (of these, 100 to 200 are mesenteric lymph nodes); they are dependent on size, side of the body and sex of the individual[22;24]. They usually appear in groups, or as chains of nodes, alongside the blood vessels and are interspersed in the lymph vessels system[22]. Lymph is carried to a lymph node via afferent vessels (peripheral collectors or intermodal connective branches), and from the node via efferent vessels[22]. A capsule formed by collagen fibers, elastic fibers and smooth muscle cells, covers the lymph node[22]. The lymph node is incompletely divided into compartments, where lymph and blood flow parallel to each other, allowing cellular and non-cellular elements to be exchanged between the two fluids[22].

The lymphatic system can be distinguished by three sections: 1) superficial system draining the skin and the subcutis, 2) deep system encompassing the muscles, joints, tendon sheaths and nerves, and 3) lymphatic organ system, where each organ is adapted to its structure and organ-specific features[22;24]. Perforating vessels connect the superficial and deep levels, where the lymph will mostly flow from the deep to the surface, but it may also flow in the opposite direction[22;24].

To summarize, initial lymphatic vessels cover an area, and are connected to pre-collectors leading to collectors[22]. The skin areas connected by a common collector are termed a zone. Anastomoses between zones are possible through the cutaneous lymphatic network and also through several connections between adjacent collectors[22]. When several zones are grouped from a lymph vessel bundle, they form a territory. It is the direction of the valves that determine the lymph flow within each territory[22]. In a normal condition, a few anastomotic branches allow lymph to flow superficially between two territories and this space is known as lymphatic watersheds[22]; further discussed in section "Manual lymphatic drainage". The lymph is returned to the right and left venous angle by lymph trunks which arise through the union of efferent vessels from separate lymph node groups[22].

Physiology of the lymphatic system

The main task of the lymphatic system is to carry lymph through the body, from distal to proximal, with the end point being the right – receiving one body quadrant (right arm, right part of the head, right hemi-thorax, left lower lung, and the heart) – and left venous angle – receiving the three other body quadrants[1;3;22;28]. Interstitial fluid accumulates in the interstitial space, expanding it, thus pulling the anchor filaments and opening the initial lymphatic vessels. The fluid then enters the lymphatic system as the pressure is lower[25;27;28]. As the interstitial fluid leaves the pre-lymphatic channels and enters the initial lymphatic vessels, the anchor filaments are released and close the openings[27;28]. The lymph then flows from the initial lymphatic vessels to the pre-collectors because the initial lymphatic vessel is full and the lymph pressure is higher than the tissue pressure[27].

Subsequently, intrinsic and extrinsic factors stimulate the lymphangions to propel the lymph towards the collectors and ultimately to the lymphatic trunks[3;25].

Intrinsic factors propelling the lymph are[3;25;27;28]: pacemaker activity, lymph node smooth muscle contraction, central nervous system and hormonal activity, and the functioning of Starling's hypothesis. However, lymph flow will principally depend on the extrinsic factors[3;25;27;28]: muscle and joint pump (passive and active), breathing, arterial pulsation and external pressure (e.g. massage, bandages). These extrinsic factors are important, from a rehabilitation point of view, as they are the only ones that we can have an impact on when the lymphatic system is damaged.

Of all the factors, Starling's hypothesis is probably the one that has had more attention and it is important to understand its principles in pathological situations. Based on Starling's hypothesis, transport through the capillary filters depends on four variables[15;28]: 1) capillary blood pressure, 2) interstitial tissue pressure, 3) intravascular colloidal osmotic pressure (COP) (capillaries), and 4) extravascular COP (tissue). The exchanges between these variables are mainly through the transport mechanisms of diffusion, filtration/reabsorption and pinocytosis/endocytosis. Starling stipulated that capillary blood pressure (arterial) and COP_{tissue} were responsible for filtration, whereas interstitial blood pressure and $COP_{capillaries}$ were responsible for reabsorption in a normal physiological situation. Therefore, hydrostatic (blood and tissue pressure) and oncotic (COP capillaries and tissue) pressures should be equal[27;28]. He also stipulated that approximately 90% of the interstitial fluid was reabsorbed by the venous system and the remaining 10%, mainly composed of proteins not carried by the venous system, were reabsorbed by the lymphatic system[15;28].

After being taught for more than 100 years, Starling's hypothesis has been recently challenged[29]. The revised Starling's hypothesis now stipulates that, in a standing position, 100% of fluids return to the venous system through the lymphatic system[28-30]. In addition, under normal physiological conditions, in most capillaries, there is no fluid reabsorption; net flow occurs in tissues cleared by lymphatic vessels[29].

What was also missing in Starling's hypothesis was how fluids, proteins and small molecules filter across the semi-permeable membranes[4]. It has became clear over the last decade that this is accomplished through the glycocalyx which is a matrix of glycoproteins and glycosaminoglycans present on the luminal surface of the endothelial cells and which acts as a molecular filter with varying porosity to influence the filtration rate from the capillary lumen to the interstitium[4;30]. As it is an emergent field, our understanding of the lymphatic system will increase as technologies evolve, and might lead to solving mysteries that currently confound the medical community in the fight against cancer.

Pathophysiology of the lymphatic system

An anatomically and functionally intact lymphatic system will have a transport capacity that is about 10 times greater than the lymphatic load[27]. Transport capacity represents the "volume of lymph that the lymphatic system can transport under conditions of maximum lymph production, maximum cubic capacity and full use of the lymph vessel motor system"[27p.206]. Lymphatic load – either general (related to the body as a whole) or specific (organ specific) – applies to "the substances that must leave the location where they are formed and can only do so via the lymph vessels"[27p.202]. Under normal circumstances, the transport capacity will remain the same whereas the lymphatic load could vary depending on, for example, if the person is resting or exercising[27;31]. Thus, the functional reserve, the difference between the transport capacity and the lymphatic load[27;31], may be reduced, but still remain in a normal physiological situation and balance is maintained.

To recall, the main task of the lymphatic system is to handle the lymphatic water and protein loads. Thus, if there is an increase in the lymphatic water load, compensatory mechanisms such as the safety valve mechanism, the increase in transport volume, collateral circulation, lympholymphatic and/or lymphovenous anastomoses, and the plasma protein reduction by macrophages will take place in the lymphatic system and they will all be exhausted before it fails[27;31]. If it does fail, edema will develop and one of three forms of lymphatic insufficiency (lymphatic failure) will occur: dynamic, mechanical, or combined.

In dynamic insufficiency, the lymphatic system is healthy, without anatomical or functional impairment, and the transport capacity is normal[27;31;32]. However, the lymphatic load exceeds the normal transport capacity. This is a high-volume failure where the lymph outcome is equal to transport capacity[27;31] but edema occurs because the amount of ultrafiltrate produced per unit of time surpasses the transport capacity[27]. Examples of dynamic insufficiency are[31;32]: inflammation, trauma, chronic venous insufficiency, right ventricular failure or kidney damage.

In mechanical insufficiency, there is a structural or functional impairment of the lymphatic system, which reduces the transport capacity[27;31;32]. This situation represents a low-volume failure. As the transport capacity decreases the volume of lymph flow per unit of time decreases below the level of the volume of net ultrafiltrate produced in the same period[27]. As protein accumulates in the interstitium due to the reduced transport capacity there is associated water retention which leads to edema[31]. In this situation, the lymphatic system may have a reduced, but still present, functional reserve and lymph output under resting circumstances may be normal which would explain why the person's edema is less on awakening in the morning than it is when retiring at night[27]. As an example, surgery for breast cancer with lymph node dissection damages the lymph vessels and lymph nodes, causing structural impairment[31], and uncomplicated and simple lymphedema, associated with mechanical insufficiency, can occur[27;31].

Combined insufficiency includes a restricted transport capacity of the lymphatic system (mechanical insufficiency) combined with an increase of lymphatic load (dynamic insufficiency) [27;31].

As the lymphatic system will do everything to prevent edema, mainly through the safety valve mechanism, any edema will consequently be synonymous with failure of the lymphatic system[27]. Edema could therefore be described as swelling that is caused by enhanced fluid content within the interstitium and which is visible and palpable[27]. It is only in the case of lymphedema that "edema" is used as a diagnostic term; otherwise "edema" is a symptom/sign where a diagnosis for the cause of edema should be found[27].

In addition, edema is classified from two perspectives,1) low-protein edema, and 2) high-protein edema[27], both of which can be further defined as being local or general. For example, in the case of dynamic insufficiency (high-volume failure) both low-protein (lymphatic water load elevated) and high-protein (lymphatic protein load elevated) could develop[27]. In mechanic insufficiency (low-volume failure), edema will always be high-protein as the impaired lymph vessels are unable to remove the protein molecules [27]. In combined insufficiency, edema will also, to a certain extent, be high-protein, depending on the degree of lymph vessel impairment and on whether water load or water and protein load are elevated[27].

Lymphedema, with its high-content of protein in the interstitial space, is set apart in its own category to differentiate it from all other types of edema. Still incompletely understood are the consequences of chronic lymph stasis that may be profound[7;33]: early and progressive predisposition to tissue fibrosis, central role of inflammation, and increased fat deposition as the epidermal and dermal components thicken. Further research on gene expression pathways and biomarkers will probably elucidate why those suffering from lymphedema are more prone to inflammation, fibrosis and fat deposition[33].

Pathophysiology of breast cancer-related lymphedema (BCRL)

Contrary to primary lymphedema, where an individual is born with an impaired lymphatic system[6;18], BCRL, is an acquired or secondary form of lymphedema. BCRL is the most common complication after curative treatment for breast cancer[6;11;13-15]. The real incidence of BCRL remains unknown[12;34], as there is no consensus on how to assess and clinically define it (e.g. 10% relative increase in arm volume, 2 cm difference in one or more circumferential measurements, 200 ml difference)[11;35;36]. Matters are also complicated by the use of several methods to measure lymphedema volume[12;13;37-40]. From low cost to high cost these methods include: 1) subjective assessment, 2) circumferential arm measurement by flexible measuring tape, 3) water displacement (volumeter), 4) bioelectric impedance spectroscopy (BIS), 5) dual energy x-ray absorptiometry (DXA), and 6) perometer. The simple measuring tape is the most

commonly employed measure as it easy and safe to use, with a very low cost[36;38]. The volumeter, considered the gold standard, is commonly used, however it necessitates special installation and may have hygiene issues[38;40]. On average, it is estimated that after treatment for breast cancer, approximately 20% of women will develop BCRL[11;12] with a range varying from 0%[41] [sentinel lymph node biopsy (SLNB) alone] to 94%[35] [subjective assessment after mastectomy, axillary lymph node dissection (ALND), and radiation].

After breast cancer treatment women are at lifelong risk of developing BCRL. Onset can occur immediately following surgery/radiation or many years after with most cases occurring within the first two years[11;14;35;42]. The staging of lymphedema is based on perceivable changes in the tissues and complications caused by the lymphatic stasis[6;13]. Lymphedema severity is considered mild when limb volume difference is less than 20%, moderate when between 20-40%, and severe when higher than 40%[43]. The International Society of Lymphology has established four lymphedema stages[32;43]:

Stage 0:	Subclinical state or latent stage. The patient might express symptoms such as heaviness; however, swelling is not perceivable despite impaired lymph transport. This stage may exist for months or years before edema becomes evident.
Stage I:	Spontaneously reversible. This early phase can be acute when edema lasts less than three months, or chronic when the duration of edema is longer than three months[17;31]. In both cases, the swelling subsides with limb elevation. The edema may be pitting at this stage.
Stage II:	Spontaneously irreversible. Pitting edema is present and limb elevation alone no longer reduces swelling. Late Stage II: There may or may not be pitting edema as tissue fibrosis is more evident[13].
Stage III:	Elephantiasis. The tissues are fibrotic and there is no longer pitting edema. Skin changes occur (e.g. thickening, hyperpigmentation, increased skin folds, fat deposits and warty overgrowths).

Risk factors associated with development of BCRL are[6;13;14;17;20;35;36;40;44;45]: surgery (breast and/or axilla), radiation, scar formation, axillary web syndrome (AWS), seroma formation, advanced cancer, obesity/weight gain after diagnosis, congenital predisposition, trauma in the 'at risk' arm, chronic skin disorders and inflammation,

hypertension, and taxane chemotherapy. Thus far, it is recognised that medical treatments impacting any of the four pressures (capillary blood pressure, interstitial tissue pressure, $COP_{capillaries}$ and COP_{tissue}), alterations to either extrinsic or intrinsic factors, or to lymphatic structure or to axillary lymph flow (mastectomy, axillary dissection, and radiation) may lead to development of BCRL[14;19;42]. Unfortunately, lymphatic function is likely to be impaired to some extent with all oncologic treatments for breast cancer.

Pathophysiology of BCRL in regards to surgery

Surgery is the primary treatment for breast cancer[46]. Its aim is to physically remove tissues to eliminate local growth of cancerous cells[17]. The extent of BCRL is generally related to the type of procedure for the breast (radical mastectomy versus simple mastectomy versus lumpectomy/partial mastectomy) and for the axilla (ALND versus SLNB)[14;42]. Despite improvements towards less invasive surgery resulting in less damage to the lymphatic system, BCRL still occurs[6;16;36;42].

Damage to both the circulatory and lymphatic systems occurs with surgery[14;15;42;47]. Surgery instantly affects the circulatory system as veins and arteries are cauterised to avoid bleeding. This may result in an increase in blood flow velocity, particularly with axillary dissection[15;42;47]. In addition, there is a reduction in vessel wall movement, affecting the arterial pulse, which is an extrinsic factor for lymph flow; therefore lymph flow is reduced too[47]. At a later stage, an increase in blood flow may be due to nerve damage, where the control of vasoconstriction is diminished. This will lead to an increase of the lymph load of an already impaired lymphatic system [14].

Surgery will also immediately affect the lymphatic system as all its structures (from initial lymphatic vessels up to lymph nodes, from superficial to deep levels) are damaged through the intervention[14;15;42]. As well, the fact of removing one or several lymph nodes disrupts lymph flow and reduces the transport capacity of the lymphatic vessels[14;16;42].

The immediate impact of surgery causes minor swelling in virtually all patients. For the majority, swelling resolves within the first four to six weeks[6]. The extent of damage may be greater if the surgery is performed by a resident rather than by an experienced

surgeon[18]. In the long term, scar forming tissues and/or damaged muscles may also disrupt the lymphatic transport capacity as they might have inadequate force to assist in moving the lymph[16;42].

It is therefore recognised that surgical resection of normal lymphatic structures (e.g. lymph nodes, surrounding tissues) diminishes transport capacity of the lymphatic system.

Pathophysiology of BCRL in regards to radiation therapy

Radiation is likely to be the second primary treatment for breast cancer after surgery. Breast conservation therapy, which includes partial mastectomy, SLNB and radiation, is the primary medical treatment option when possible[46]. For radiation-induced lymphedema, a series of complex processes contributes to its development. While the precise mechanisms remain unknown, radiation-induced fibrosis has been suggested as a major contributor[6;42].

During radiation treatment, the DNA of both healthy and cancerous cells within the radiation field are destroyed and surrounding tissues are also damaged [6;42]. This leads to an inflammatory response within the tissues and the lymphatic load is increased as a response[42]. However, due to the subcutis being irradiated, the density of initial lymphatic vessels is decreased, thus impacting the initial lymphatics intake[6]. Radiation also seems to disturb the formation of collateral circulation[42] which is generated by the physiological response of the lymphatic system when there is a breakdown in its structure (although lymph nodes will not regrow, enlargement of lymph vessels and/or collateral circulation is possible[27;28]). Therefore, lymph flow from the upper limb and/or the trunk is less efficient. Furthermore, if radiation is targeted to the remaining lymph nodes, these may change their composition, becoming adipose tissue, which ultimately leads to tissue fibrosis which will limit lymph filtration[14].

Damage to the tissue ceases after the end of radiation treatments and the repair process may begin[42]. In ideal situations, the damaged tissues are replaced by healthy normal cells[42]. However, like surgery, radiation may leave a permanent fibrotic scar[6;42].

Like surgery, the less invasive the intervention, the less damage to the lymphatic system; when the axillary is included in the radiation field, it doubles the risk of developing lymphedema, compared to radiation of the breast alone[12;14;34]. The damage from radiation will be localised to the treated area and may impair the lymphatic flow depending on the scarring and fibrosis of surrounding tissues/lymph structures[42]. These changes can occur in the short and/or long term, so the patient has a lifelong risk of developing BCRL[14].

Further investigations are needed. Pissas et al.[48;49] stated that irrespective of the type of surgery and/or the level of radiation received, if even one of the three lymphatic pathways is affected (delto-pectoral [Mascagni-Sappey], triceps, posterior of the scapula [Caplan-Leduc]), BCRL will occur in 100% of cases, regardless of risk reduction strategies undertaken.

Pathophysiology of BCRL in regards to chemotherapy

Whether or not chemotherapy is associated with BCRL remains unclear; two meta-analyses have different results: chemotherapy is not related to BCRL[19], or is related to it[11]. Recent studies suggest a possible correlation between taxanes and BRCL[20;21], as a common side effect is an increase of extracellular fluid, which results in fluid retention in the extremities[20].

Chemotherapy has a systemic effect on the body and aims to eradicate micrometastases that could remain[50]. It has several associated toxicities affecting different systems, such as the musculoskeletal (arthralgia, myalgia), the neurological (peripheral neurotoxicity), and in general (weight gain)[50]; all of these are either risk factors for BCRL or affect the lymphatic flow. Chemotherapy may also damage subcutaneous vessels, impacting the flow of lymph by reducing it[50].

Pathophysiology of BCRL in regards to other risk factors

Surgery, radiation and chemotherapy, the risk factors described above, are an integral part of oncologic treatment. As rehabilitation specialists, it is important to target our intervention by understanding the treatments the patient received and how they might have interrupted the lymph flow. Of the remaining risk factors, in rehabilitation, we can

intervene in the presence of axillary web syndrome (AWS, also known as 'cording') and obesity. One of our therapeutic tools is education that we can direct to reducing the risk of having a trauma in the 'at risk' arm or to providing information about skin disorders and inflammation. The remaining risk factors are linked to personal factors (seroma formation, advanced cancer, congenital predisposition, and hypertension) and will not be discussed in the scope of this review.

AWS is a surgical and/or radiation complication still not well understood, as a gold standard definition, is lacking[45]. It is variously reported as sclerified lymphatic vessels, or dilated lymphatic vessels, or fibrosis of the lymphatic vessels and venous thrombosis[51]. Trauma to the lymphatic vessels and veins, stasis and hypercoagulability might be involved in the origin of AWS[51]. It is recognised by visible and palpable cords of tissue within the axilla, and sometimes in the elbow and/or the wrist on shoulder abduction[45]. These fibrous bands may be painful and limit range of motion (ROM)[45;51]. It may occur within the first days post-surgery or even after radiation therapy[51]. Prompt referral to a rehabilitation specialist is important in order to facilitate lymph flow and regain ROM[45].

A recent study by Jammallo et al.[44] found that patients with a pre-operative body mass index (BMI) greater or equal to 30 had respectively 4.5 and 3.0 fold increased risk of developing BCRL when compared to those with a BMI below 25 and between 25 and 30. In addition, they also found that large weight fluctuation during and after the treatment for breast cancer was associated with an increased risk of BCRL. The pathophysiological changes related to obesity and BCRL indicate a decrease in lymphatic function, an impaired transport of interstitial fluid, a diminished migration of immune cells, a decreased capacity of collectors, and an abnormal lymph node architecture[6]. Furthermore, in a model with obese mice, it was shown that there was an increase in adipose deposition and fibrosis[6]. Therefore, in an obese patient just maintaining body weight during treatment (e.g. through exercise) and reducing weight at the end of treatment, will help improve and restore the lymphatic function in non-damaged lymph vessels, as lymphatic impairment in obesity is reversible[6;44].

The development of BCRL is directly linked to the consequences, physical and physiological, of the treatments for breast cancer. The more invasive the treatment, the more likely will be the risk of BCRL developing. BCRL is a chronic and debilitating condition having an impact both physical and psychological. Therapies to alleviate its burden are important in order to maintain function.

Treatment for breast cancer-related lymphedema (BCRL)

BCRL is a build up of lymph fluid, rich in protein, into the interstitial space and there is an imbalance between interstitial fluid production and transport capabilities[6;13-15]. Stage 0 and I are associated with a significantly higher risk of developing stage II or stage III BCRL[12;14;16;52]. As this is a chronic condition, early interventions are important to minimise the progression of the disease into a later irreversible stage.

As described in section "Pathophysiology of BCRL", any treatment used to cure breast cancer may lead to BCRL. Therefore, as proposed by Stout et al.[52], thorough assessments of the patient, from pre-surgery to ongoing patient dependent surveillance, provide a proper monitoring. A multi-disciplinary team of health care professionals should assess: range of motion, upper limb strength, arm volume, activity limitations and performances restrictions, fatigue, pain, function, neuropathy, weight, bone health and arthralgias, cardiovascular and pulmonary functions. In addition, the patient should learn health promoting skills and behaviors: maintenance of an adequate level of activity and function, education on ongoing detection of common treatment-related sequelae, maintenance of a healthy life style, and a tailored exercise programme.

By combining surveillance by both the patient and the multi-disciplinary team, patient function can be optimized through the course of survivorship and, early detection and treatment of any treatment-related sequelae are facilitated. It is important to address developments in the early stage. Women with BCRL (USA data) compared to women without BCRL, endure a direct medical cost of 23 167$ versus 14 887$; and higher indirect costs, such as work days lost[16].

Once BCRL has been diagnosed in its chronic condition, a few treatment options are possible. Treatments vary between non-invasive or invasive, and from being more medically oriented to more rehabilitation related. Nevertheless, all share the same aim: to reduce limb volume.

Medically oriented treatments for BCRL (overview)

Modern medicine has of course tried pharmacological and surgical approaches in attempting to cure BCRL. The rationale behind pharmacological, and nutritional supplements, is to find a cure that stimulates lymphangionmotricity or that will eliminate the excess of fluids in the interstitial space[18]. Until now, every drug tried showed interesting physiological properties able to affect permeability of lymphatic vessels[14;53]. However, they all failed to show efficacy to treat BCRL[36;53-58]. Only a brief overview of these two approaches will be provided, as the scope of this review is more rehabilitation oriented.

Pharmacological: Benzopyrones (couramin)

This drug was primarily use to treat vascular problem[54]. It was tried with lymphedema patients as it had the properties of reducing vascular permeability and also the quantity of fluid going into the subcutaneous tissues[32;54]. The reasoning behind the use of benzopyrones was[36;53;54;57]:

1) As they reduce fluid filtration in the interstitial space, pain and discomfort in the lymphedematous limb should reduce;
2) Macrophage activity is improved, which stimulates protein lysis, thus limiting build-up of fibrotic tissues in the lymphedematous limb;
3) COP is reduced, which in turn reduces lymph capacity and the macrophage activity limiting extracellular proteins;
4) The drug would affect every part of the microcirculation.

Despite its interesting properties, it has been shown that benzopyrones in fact limit filtration rather than stimulating it in the case of lymphedema[54]. Scientific evidence[36;53;54;57] lead to the conclusion that the use of benzopyrones is not indicated, and they are not approved now in the USA[36], in the treatment of lymphedema.

Pharmacological: Diuretics

Diuretics are quite often used for the treatment of hypertension and edema[18;53] as they remove fluids in the subcutaneous tissues via venous circulation[18]. Removing water in a lymphedematous limb, however, leads to an increase of protein concentration in the interstitial space, which is already increased when lymphedema is present[53]. This would promote fibrosclerosis processes[53]. Diuretics have also been shown to slow down lymph transport[18]. Therefore, diuretics should be used only when a comorbid condition (e.g. congestive heart failure, arterial hypertension) requires its use; otherwise, their use should be contra-indicated in the treatment of BCRL[18;32;53].

Nutritional supplement: Selenium

Selenium is an essential trace element for the body and has antioxidant properties[36]. It is use to counterbalance toxics effects of chemotherapy and radiation therapy[56]. In a lymphedematous limb, increased interstitial pressure reduces the tissue intake in oxygen, leading to fibrosis of small lymphatic vessels[56]. The idea behind selenium use is that it would improve stasis in sparsely perfuse edematous tissues, and would consequently be effective in treating lymphedema[56]. However, the real mechanism on the lymphatic system remains unknown[56]. It was concluded from two systematic reviews that there is not sufficient evidence to support the use of selenium in the treatment of lymphedema[55;56].

Surgeries for BCRL

Currently two types of surgical procedures are offered[18;40;59]: 1) Debulking operation, or liposuction, and 2) microsurgical reconstruction or tissue transfer. This will quite often depend on the surgeon's specialty/country (e.g. Dr. Brorson, Sweden, suction-assisted lipectomy[60], Dr. Campisi, Italy, microsurgical anastomosis[18]). Actually, there is no absolute indication for any type of surgery in the treatment of lymphedema, and only carefully well-selected patients may benefit from it[18;53;59].

Surgery should be offered only in the eventuality that conventional therapy, described in section "Rehabilitation oriented treatments for BCRL", fails to reduce arm volume and/or the person is not satisfied with the outcome of the conventional therapy[12;18;40;59].

However, the patient should be aware that the outcomes of the surgery might not be good, and that they will need to comply with lifelong compression (almost 24/7)[12;18;40;53;59]. In addition, in the case of lymph node graft, lymphedema could also occur at the donor site, and there might be no improvements in the lymphedematous limb[18;53].

It should also be kept in mind, as mentioned by Browse et al., that "the ideal surgical treatment of lymphedema would return the ... limb to a normal size with minimal scarring and near-perfect cosmetic result. This is at present unachievable"[18]. Therefore, a person suffering from BCRL should always first seek rehabilitation interventions for treatment of their condition, once the etiology of lymphedema has ruled out recurrence of cancer, or thrombosis[18].

Rehabilitation oriented treatments for BCRL

As described above, pharmacological and surgical procedures should not be the primary intervention for lymphedema treatment in an industrialised country. Many alternative rehabilitation approaches have been used in the treatment of lymphedema, such as[12;18;53;61]: combined decongestive therapy (CDT), intermittent pneumatic compression (IPC), exercises, acupuncture, neuroproprioceptive taping, low-level laser therapy, hyperbaric oxygen therapy, and aromatherapy. Only CDT, IPC and exercise will be addressed here as they are supported by the most scientific evidence and are the most commonly used forms of therapy.

Combined decongestive therapy (CDT)

Combined decongestive therapy (CDT), is the most common therapy treating BCRL[16;17;40;59]. CDT is composed of[14;16-18;40;62]: 1) manual lymphatic drainage (MLD), 2) compression, 3) skin care, and 4) remedial exercises. It consists of two phases[16-18;32;40;59;62]:

Phase 1 – "intensive" phase –

- Goal: achieve a 30-40% lymphedema-volume reduction;
- Duration: usually from one to four weeks, depending on the severity and the stage of BCRL;

- Components: all four performed daily, except MLD which is not usually performed over the weekend;
- Compression: multi-layer bandages worn almost 24/7 for the duration of the therapy and removed only for daily hygiene and when MLD is performed.

Phase 2 – "maintenance" phase –

- Goal: maintain the volume reduction obtained in phase 1;
- Duration: lifelong (sometimes phase 1 may need to be repeated);
- Component: all performed daily, except MLD that is done when necessary by a therapist and/or modified for daily self-lymphatic drainage;
- Compression: compression garment (sleeve with or without glove) worn daily during the day. Night compression should also ideally be applied two/three times a week, either with multi-layer bandages or a night compression garment.

To treat BCRL, a multi-factorial approach will provide the best volume reduction, where each component has its own rationale of use but not the same importance[62]. The success of the therapy depends partially on the therapist's experience, and foremost on the patient's compliance to therapy.

Manual lymph drainage (MLD)

First introduced in 1936 by Vodder, MLD is a gentle, low pressure, specialised manual therapy based on the anatomy of the lymphatic system[16;40;63;64]. Although MLD has been shown to reduce lymphatic swelling[16;18;63;64], its use within CDT is controversial, and there is a tendency to favor compression[61;65]. In addition the false myth that MLD would promote metastases might have played a role; however, molecular biology has shown that "formation of metastases is an active process, initiated and controlled by the cancer cells themselves"[18p.275].

The idea behind the use of MLD is that through specific pressure and techniques, it will act on different mechanisms, such as collateral connections, lymphangiomotricity, and protein reabsorption. Consequently, lymph flow will be stimulated, interstitial fluid decreased and fibrotic tissues softened[16].

Pressure

- Initial lymphatic vessels are found within the first few millimeters of the skin. This type of massage (MLD) uses a light pressure targeting the opening and closing of those vessels through the action of the anchor fillaments[18;26;63;64].

- If stronger pressure is applied, it can damage initial lymphatic vessels that are already fragile, and it will compromise lymph formation, as the interstitial fluid will not be collected[26].

Technique

- Different techniques (e.g. pump, scoop, stationary circle, effleurage – depending on the certification of the specialized therapist) are performed at a slow rhythm directly on the skin, to stretch the skin in the direction of lymph flow [18;53;62].
- It has been demonstrated with lymphoscintigraphy that MLD performed on healthy regions, through the stimulation of the lymphatic anastomoses and watershed, is able to suction the high-protein fluid of the congested area into the healthy region[18]. Most techniques will therefore be performed on the healthy side first, then on the proximal-distal-proximal affected areas, and finally again on the trunk and healthy side[18;26].

Stimulation of collateral connection

- Usually, lymph flow within one section is delimited by lymphatic watersheds with only a few collateral connections[22].
- When MLD is applied properly, it creates anastomoses crossing the watershed[14;26;64].
- Consequently, lymph flow is improved and fluids are moved away from the lymphedematous area to a healthy one[64].

Improvement of lymphangiomotricity

- At rest, lymphangiomotricity is six to ten contractions per minute[28]. During MLD, it increases threefold to 25 to 30 contractions per minute[28;64]. Consequently, lymph transport capacity is largely improved.

Improvement of protein reabsorption

- MLD increases macrophage activity, which improves degradation of interstitial proteins, consequently reducing lymphatic load[53;64].

In the case of BCRL, MLD should never be used as a standalone procedure[62]; its full potential in volume reduction is reached when it is combined with compression[16;62].

Compression

Compression in the centerpiece of CDT, and if only one of the four components can be employed, this is the one to favor[62]. Two types of compression are commonly used with BCRL[16;18;53]: 1) multi-layer short-stretch bandaging, 2) compression garment (sleeve with or without a glove). The first is used during the intensive phase of CDT and the second is

used during the maintenance phase or in lymphedema stage 0 and I[18;62], where CDT is not suggested[18].

Multi-layer short-stretch bandaging[16;18;53;62]

- Goal: achieve a significant arm volume reduction;
- Worn 24/7, applied from proximal to distal;
- Stockinette protects the skin of the whole arm;
- Gauze wraps the fingers;
- Soft cotton and/or high density foam shape the limb;
- Short-stretch bandages apply compression (two to four layers are requested for the full arm).

Compression garment[32;53;62;66;67]

- Goal: stabilize arm volume after the intensive phase or serve as a prophylactic measure;
- Worn daily during the day, sometimes a night garment may be appropriate;
- Readymade (if the limb has a regular shape and fits the manufacturer's chart) or custom-made;
- Circular knit: used with lymphedema stage 0 or I;
- Flat knit: stronger material, ideally should be custom-made. (Best choice: custom-made flat knit compression garment, in BCRL stage II and III.)

Both types of compression will ideally deliver a higher distal pressure than proximal, as, following Laplace's law, the radium of the wrist is smaller than the upper arm [13;67]. Thus lymph flow will be moved from distal to proximal, and backflow of lymph will be limited. Compression is based on two ideas:

1) Apply a low resting pressure: when the limb is resting, compression is constant on the skin, stimulating lymph flow[13;16;62];

2) Produce a high movement pressure: when the muscles contract, expand and then release, internal limb pressure increases and is applied against the resistance induced by the compression[16;62]. This temporally increases the limb tissue pressure. This brief amplification compress the lymphatic vessels and as the collectors are large and have valves, lymph is pumped passively without the vessels having to contract[16].

Therefore, whether at rest or in movement, when compression is applied to a lymphedematous limb, lymph will always be moved from distal to proximal and will be directed toward the trunk. Similar to MLD, compression activates several mechanisms.

Increase of interstitial pressure and improvement of tissue fluid exchange

- The exchange between the venous system and the interstice is improved, preventing interstitial fluid from accumulating. The transport capacity can than carry the lymph load and there is no increase of edema[16;53].

Decrease of tissue fibrosis

- Proteins tend to accumulate in the interstitial space when fibrosis is present, thus limiting lymph filtration[14]. When compression is applied, the application of tension breaks down protein organization, and facilitates lymph flow[14].

Prevent fluids back flow

- The fact that the compression is higher distally than proximally leads to the evacuation of lymph and prevents its return[16].

Improve muscular pump

- When BCRL is present, skin is lacking in elasticity and cannot play its natural compressive role on muscles and tissues[14]. Compression applies an external force, therefore muscles can now compress against something and play their role as an extrinsic factor promoting lymph flow[16].

Importantly, MLD is generally well tolerated by patients, as this is a non-invasive and gentle therapy. Conversely, compression is quite often more problematic to tolerate as it limits the person in their daily activities and can provoke questions from "curious" outsiders. How compression is applied will therefore depend on the person's tolerance and willingness to comply with the therapy[53]. In addition, both, multi-layer bandaging and compression garments should always be well adapted to the person's comfort and limb shape, as inadequate compression can be harmful, and could create pressure necrosis, leading to a more severe BCRL[18;32;53].

Skin care

Intact skin acts as a natural barrier against viruses and bacterias[13]. Skin problems are commonly associated with BCRL as the skin is stretched, which increases the risk of skin injury and skin infection[13;16;40]. Fungal and bacterial infections can develop more easily as the swelling may produce deep skin folds[13]. Any skin complication should be addressed and treated in order to optimise the skin condition, maintain skin integrity and minimise the risks of developing an erysipelas (cellulitis)[13;16;62].

Cellulitis is an acute bacterial (mostly streptococci) infection of the skin and subcutaneous tissues that tends to recur[13]. Those with BCRL are at higher risk of developing a cellulitis, as the high content of protein in the lymphatic fluid may serve as a medium where bacteria may prosper. An episode of cellulitis may trigger lymphedema and vice versa.

For these reasons, meticulous skin and nail care is mandatory[32;62]. A person with BCRL is instructed to carry out continuous skin care in both intensive and maintenance phases of CDT[18]. Such care includes[13;16;17;40;62]: good skin hygiene (wash daily with a natural or pH neutral soap), avoiding dry skin (use emollient, hydrating cream), avoiding cutting cuticles, applying sunscreen and insect repellent lotion when required, avoiding cutaneous abrasions, and protecting the skin during daily activities (e.g. wearing gloves for washing the dishes).

During the intensive phase, it is the therapist's responsibility to assure skin care, such as applying moisturising cream before applying the multi-layer bandages and looking for any hidden skin injury. During the maintenance phase, patients are instructed to carry out the necessary skin care. If they experience any signs and symptoms of skin infection, immediate medical attention should be sought[13].

Remedial exercises

Of the four components of CDT, remedial exercises receive the least attention, but are as important as the others[62]. Remedial exercises should not be interchanged with general activity and exercises (described in section "Exercises"), which patients are encouraged to perform regularly[62]. The rationale behind remedial exercise is that lymph resorption into the remaining functional lymph vessels will be facilitated by the activity of the muscles and joints (extrinsic factors). When remedial exercises are performed in the intensive phase, the compression of the multi-layer bandages allows the muscles to contract against resistance, which will enhance lymphatic and venous return as the "muscle pump" will be more effective[16]. Examples of remedial exercises are[62]: abdominal breathing, postural exercises, joint circles (neck, shoulder, elbow, wrist); and Casley-Smith remedial exercises[26].

CDT, as described above, is currently the primary treatment for BCRL. Many well recognised lymphedema advocate organisations (e.g. International Society of Lymphology, National Lymphedema Network, American and Canadian Lymphedema Frameworks) recognise CDT as the therapy of choice[16].

Intermittent Pneumatic Compression (IPC)

Since the 1950's, IPC has been used in the treatment of BCRL[68;69]. This well-known method, just like CDT, has not yet attained the criteria of "evidence-based medicine"[18;69]. Contrary to MLD, IPC is not specifically design to follow the anatomy, the physiology, and the pathophysiology of the lymphatic system[18].

The idea behind IPC is to mimic lymph flow distally to proximally, and stimulate lymph to flow back to the trunk area[69;70]. Compression induced by the IPC empties initial lymphatic vessels, which facilitates the entry of fluids from the interstitial space into those vessels[70].

IPC seems promising in treating BCRL. However, the mechanisms impacting BCRL are diverse and optimal frequency and duration of IPC therapy remain unclear[59]:

Mechanisms in favor of IPC efficacy

- Mimic the muscles' pumping action[59;68];
- Stimulate the lymph of the upper limb to flow toward the trunk[59;70];
- Decrease initial lymphatic vessels filtration, which decreases lymph formation[13;59].

Mechanisms against IPC efficacy

- Lymph vessel damage can occur if the applied pressure is too high (also the case if the pressure applied is too strong with MLD) which will further decrease lymph flow in an already impaired lymphedematous limb[59;68];
- IPC pushes the interstitial fluid out of the lymphedematous limb, which removes only the water and leaves behind the proteins in the interstitial space, causing development of more scarring and fibrotic tissues[18;53];
- Fluids of the upper limb are pushed into the torso quadrants that share the same drainage territory which could lead to a palpable fibrosclerotic wall as protein-rich fluid backs up in the torso quadrants[18].

Currently, newer devices are composed of multiple chambers with sequential compression with gradient options[59;68;69]. The recent advancement in IPC now allows the devices to mimic MLD techniques and promote fluid clearance from the proximal trunk

and extremity[59;69]. It was argued, with prior devices, that IPC was causing the development of a fibrotic band in the upper limb; this problem should be solved as newer devices included truncal and proximal chambers[69]. IPC is now accepted as an adjunct treatment of CDT, when used under the supervision of a medical team and/or certified lymphedema therapist, and accompanied by compression and/or other components of CDT[13;40;59;68;69].

Exercises

Until the late 1990's, women were encouraged not to perform any type of physical activity or exercise as it might exacerbate or trigger lymphedema[17;71;72]. Exercise is an important component in prevention of chronic diseases such as cancer, hypertension, or obesity[59;71]. For people suffering with BCRL, the physiological responses of the body to exercise play a major role on the lymphatic system and stimulate extrinsic factors of lymphangiomotricity[25]. The ideas behind the performance of different type of exercises are:

Stretching[13;72]

- Goal: maintain or improve range of motion and flexibility;
- Principle: reduce fibrotic tissues and improve lymph flow.

Aerobic[13;17;71]

- Goal: maintain or improve cardio vascular health;
- Principle: muscular contractions arouse lymph flow and the increased breathing activity enhances diaphragm movement increasing lymphangiomotricity of the thoracic duct.

Resistance[13;40;72]

- Goal: maintain or improve muscular strength;
- Principle: vascular and lymphatic flows are increased by muscle contractions, which reduce lymph stasis and improve protein resorption.

During exercise the physiology of the lymphatic system ensures that fluids and proteins are returned to the venous system[25]. The following mechanisms act on the lymphatic system during exercise:

Lymph flow[13;17;72]:

- Increased with exercise, which facilitate protein absorption and reduce fluids into the interstitial space.

Lymphangiomotricity[25]

- Doubled during exercise: the contraction frequency is 15 to 18 contractions per minute.

Intrathoracic pressure[13;17;25;71]

- Varies with breathing: inhaling reduces it and exhaling increases it, which stimulates the contraction of the lymphatic duct and therefore helps to increase lymph clearance.

Extrinsic factors[3;25]

- Stimulated, which in return create a pumping action and increase lymph flow.

The type of exercise can vary from quite gentle exercise (e.g. yoga, Pilates, Qi Gong) to strenuous activity (e.g. aerobics, dragon boat paddling)[71]. In addition, since the early 2000s, specific exercises based on the physiology of the lymphatic system and on the pathophysiology of lymphedema have been designed and need to be further investigated (the Lebed Method[73;74] (2002) – therapeutic exercise programme based on movement and dance – and the Tidhar method[75-77] (2004) – therapeutic exercises performed in water use the physical properties of water to stimulate lymph flow and reduce lymphedema).

In rehabilitation, exercise is a common form of therapy. In the case of BCRL, it is important to guide the patient toward a progressive program well adapted to the person's physical and cognitive capacities[17;40;71]. Performing different types of exercise provide many benefits, such as improving flexibility, reducing fatigue, increasing strength, improving body image and quality of life, improving body composition, and decreasing anxiety[71]. The worse enemy of BCRL is inactivity. Remedial exercises should be performed as part of CDT, and any other type of exercise should be performed on a regular basis, both to maintain activities of daily living and maintain optimal body function (cardiovascular, muscular and lymphatic).

Conclusion

With emerging technologies, knowledge regarding the lymphatic system's anatomy, physiology and pathophysiology will grow and will hopefully bring additional illumination to our understanding of BCRL.

The scope and breadth of knowledge currently available regarding the pathophysiology of lymphedema and how it informs the mechanisms and ideologies underlying BCRL treatment approaches have been explained here for CDT, IPC, and exercise. However, this is only the tip of the iceberg as many other complementary medicine approaches are being used and require more investigation (e.g. neuroproprioceptive tape, acupuncture) and may become stand alone treatments or adjunctive to CDT. Treatment of many other types of cancer (e.g. melanoma, prostate, gynecological, head and neck) also leave patients susceptible to the risk of developing lymphedema and requiring greater research and treatment options.

Patients treated for breast cancer are at risk for life of developing BCRL. This chronic and debilitating condition is quite often perceived as far worse than the oncologic treatment for breast cancer itself. It is a constant reminder of the disease; it affects body image, physical function, and many other health-related topics affecting the women's quality of life which have not been addressed here.

Rehabilitation interventions are up to now the first treatment option, with CDT as the primary choice. No medication so far has proven its efficacy in treating BCRL, and surgeries for BCRL should be performed only on well-selected patients where conventional therapies have failed. At the moment, there is no curative therapy available. Weight control, close monitoring and education throughout the continuum of care will allow early intervention that will reduce the burden of BCRL. Treatment should focus on symptom management and preservation of function through CDT, combined or not with IPC, and a tailored exercise programme. The success of the therapy depends on both the therapist's experience, but foremost, on the patient's compliance.

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Chapter 4: Integration of Manuscripts 1 and 2

Research questions of Manuscripts 1 and 2

Manuscript 1:

To summarize the scope and breadth of knowledge currently available regarding the pathophysiology of lymphedema and its treatment and how it informs the mechanisms and ideologies underlying breast cancer-related lymphedema treatment approaches.

Manuscript 2:

To estimate, for women post-acute treatment for breast cancer, the extent to which medication or physiotherapy techniques reduce pain, shoulder impairment and/or edema.

Integration of Manuscripts 1 and 2

Both manuscripts fall under "construct investigation" part of this thesis. The aim was to summarize, in the context of rehabilitation, the scope and breadth of knowledge currently available regarding arm dysfunction after breast cancer.

The first manuscript is a review of the literature providing a better understanding of the lymphatic system, its physiology and pathophysiology related to breast cancer. The therapies for breast-cancer related lymphedema (BCRL) are exposed; however, they are not critically commented upon.

The second manuscript is a narrative review of the literature building on the knowledge obtained in Manuscript 1 regarding the pathophysiology of lymphedema, and comments its therapies. In addition, not only BCRL is reported, but also other common arm dysfunctions are reported with their treatments.

Chapter 5: Manuscript 2

Narrative review of therapies for post-breast cancer arm dysfunction

This chapter is presented as Manuscript 2. The original work *"Systematic review of therapies for post-breast cancer arm morbidity"* was done in terms of the comprehensive examination, submitted July 6th 2009 and successfully passed. It is presented here as a narrative review. The first part of this chapter is the original document (formatted to fulfill thesis requirements), and the second part constitutes of an addendum reporting on the literature from July 2009 to November 2015.

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Narrative review of therapies for post-breast cancer arm dysfunction

Abstract

Objective: Breast cancer survivors may experience arm dysfunction, manifested by pain, reduced range of motion (ROM), and breast cancer-related lymphedema (BCRL). The aim of this narrative review is to estimate, for women post-acute treatment for breast cancer, the extent to which medication or physiotherapy techniques reduce pain, shoulder impairment and/or edema.

Search strategy: We searched the Specialised Register of the Cochrane Breast Cancer group, MEDLINE, EMBASE, CINAHL, PEDro, and hand search reference lists, until November 2015.

Results: A total of 44 randomized controlled trials (RCTs) met the inclusion criteria and 30 reviews are discussed. Only one study addressed medication and ROM. The use of drugs in the management of BRCL is inconclusive. The greatest attention is given to BCRL with 28 RCTs and 15 reviews. Exercises are used for the treatment and management of pain, ROM, and BCRL. Manual lymph drainage (MLD), combined decongestive therapy (CDT), and intermittent pneumatic compression (IPC) are commonly used to reduce BCRL.

Conclusion: There is a lack of high quality evidence-based research. No guidelines define what the best regimen is for therapy and/or exercise for arm dysfunction. Therapeutic exercises seem promising in reducing the symptoms of pain and in improving ROM. All type of exercise (low to high intensity) performed progressively are indicated for women with or without BCRL. The use of MLD remains uncertain, indicating some benefits when used in combination with other modality, such as in CDT. IPC have shown arm volume reduction and could be used as a home-based therapy. CDT, which involves MLD, compression bandages, skin care, and exercise, is considered the standard of care for BCRL.

Comprehensive examination document (Part 1)

Note from the author: This paper is entitled "Systematic review of therapies for post-breast cancer arm morbidity". In this document, most of the methodology and rigorous application of a systematic review protocol will be applied. However, only one author (M-E Letellier) will have reviewed the articles. Therefore, the literature will be reviewed in a systematic manner, but it cannot be stated that this essay is a "systematic review" per se.

Introduction

Breast cancer is the leading cause of cancer among women worldwide[6, 7, 48]. Actually, in Canada, survival rate – 5-year survival or the interval of disease-free – is approximately 87% [37]. Regardless of the fact that mortality rate is now decreasing, more and more evidence is going toward the fact that multifaceted sequelae of breast cancer do not necessarily come to an end with the termination of treatments[1, 6, 8, 12, 16, 25].

Gratefully, surgical techniques have improved over the last decades. This leads women to have less invasive surgery: partial mastectomy versus radical or modified radical mastectomy, and sentinel lymph node biopsy (SLNB) versus axillary lymph node dissection (ALND). So far, SLNB technique has shown great results in decreasing arm symptoms following breast cancer surgery, as indicated in Table 1[12, 13, 18, 29, 31, 33, 44].

Regardless of the fact that the surgery techniques have improved, women are still experiencing arm dysfunction and/or can see their quality of life (QOL) affected. Montazeri (2008)[85] did a bibliographic review regarding health-related quality of life (HRQOL) in breast cancer patients. He reviewed 477 English papers written between 1974 and 2007. He reports that for women, having breast cancer has a significant impact on body image, body function, and sexual functioning. Breast cancer has also an impact on the psychological aspect of the woman's life: anxiety, depression, feminine image, mother's role, and worker's role. The literature also states that between 30% and 80% will develop a form of upper extremity limitation at one point following treatment for breast cancer: functional problems (restricted range of motion (ROM), loss of strength, shoulder stiffness, paresthesia), pain, and lymphedema (also spelled lymphoedema)[5, 14, 15, 17, 21, 28, 41, 45, 46].

Arm dysfunction involves pain, restricted ROM, loss of strength, and lymphedema. If the first three components tend to appear in the early stage post-surgery[18, 19, 30, 46], lymphedema will occur in 93% of the cases within the first two years post-treatment[47]. The literature also reports the onset of lymphedema up to 20 years following treatments[32, 39, 42]. Lymphedema following breast cancer can be defined as a build up of lymph fluid into the interstitial space of the affected region (e.g. breast, trunk, and/or arm) caused by mechanical impairment of lymph drainage induced by the surgery and/or radiation therapy[25, 47].

As previously mentioned, both SLNB and ALND can cause arm dysfunction. However, patients having SLNB compared to ALND tend to have better outcomes and have less impact on their upper body function, as indicated in Table 1[13, 19, 23, 30, 31, 33]. Over time, every woman is getting better and see an improvement of their arm function[33, 38]. Arm symptoms are common in the first year following breast cancer treatment; 16% to 83% of the breast cancer patients will experience a form of dysfunction within that period[11, 15, 20, 25]. The symptoms will be reduced by 40% to 50% in the two following years[30]. However, up to 38% of the women could still experience arm dysfunction in the long-term[15]. Therefore, when investigating arm dysfunction after breast cancer treatment, women should be followed for at least two years after the completion of the last treatment[25].

Women of all ages can be afflicted by breast cancer. This disease occur primarily between the ages of 50 to 69 years old (52%); 28% of the cases women are 69 years old and older, and women under 50 years old represent 20% of the diagnosed population[37]. This means that women can be at different stages in their lives and consequences of arm dysfunction can be more or less affecting their HRQOL (e.g. having your children at home or being retired)[85]. Therefore, there is an urgent need to assess and treat arm dysfunction symptoms post-breast cancer treatment.

The aim of this narrative review is to estimate, for women post-acute treatment for breast cancer, the extent to which medication or physiotherapy techniques reduce pain, shoulder impairment and/or edema. Where post-acute treatment is define as being more than three

months post-treatment for breast cancer (surgery, chemotherapy and/or radiation therapy).

The Cochrane Breast Cancer Group has several systematic reviews (69) related to breast cancer. Of interest, only six papers are related to rehabilitation: four are on prevention and management of lymphedema, and two are on post-operation care: exercises during treatment[34] and the other one is on the benefits of exercises on arm dysfunction[35]. Of those related to lymphedema, two are about drug efficacy (Badger 2003[3] & Badger 2004[4]), one is concerning physical therapies (Preston[40]), and the last one is at the stage of protocol (Howell[22]). Both reviews conducted by Badger and colleagues (2003 & 2004)[3, 4] have not been able to conclude about the effectiveness of drugs intervention in the treatment of lymphedema. The main interest of this review is to look at arm dysfunction post-treatment. Therefore, Markes et al. (2006) review[34] has not been considered, as it looks at the effect of exercise during adjuvant treatment. Like the other ones, the review conducted by Preston and colleagues (2004)[40] has not been able to conclude about the effect of physical treatment as there is a lack of randomized controlled trial (RCT) in rehabilitation area post-breast cancer treatment. Robb and colleagues (2008)[43] have proposed to the Cochrane Library a systematic review about transcutaneous nerve stimulation (TENS) for cancer pain in adults. They resumed their article by stating that also in this field there is a lack of proper RCT and that no conclusion can be drawn from their findings regarding the use of TENS with person who has cancer pain. Table 2 summarizes the findings.

Other systematic reviews have also been performed and are cited in the Cochrane Library. However, those articles have not applied the Cochrane protocol for systematic review. Of the 148 reviews quoted, only four were of interest. Kligman and colleagues (2004)[27] and Megens and colleagues (1998)[36] are both looking at therapies for lymphedema following breast cancer. Both concluded that there are some evidences of lymphedema treatment efficacy; however, those evidences should be taken cautiously, as there is a lack of proper and rigorous RCTs that really assess their efficiency. Cheema and colleagues (2008)[9] have proposed a review regarding progressive resistance training (PRT) following breast cancer treatment. So far, PRT seems to be a program that women

can take part in, although, more evidences from robust RCTs are required. Rietman and colleagues (2003)[42] have proposed a paper concerning late dysfunction and its impact on activities of daily living (ADL) and QOL. They have found a significant relationship between late dysfunction and ADL and QOL: when dysfunction is present, ADL are reported as being restricted and consequently QOL is poorer. However, the strength of the relationship is low. Table 3 summarizes the reviews.

The actual settings to treat arm dysfunction following breast cancer are: drugs, intermittent pneumatic Compression (IPC), exercises, compression, physiotherapy, and combined decongestive therapy (CDT). CDT is used in lymphedema cares and combines four elements: 1) skin care, 2) manual lymph drainage (MLD), 3) bandages/compression, and 4) exercises[2, 10, 26, 47].

Most of the reviews done on rehabilitation post-breast cancer treatment are mainly on lymphedema (6/10). In this review, pain, shoulder impairment and edema are targeted with the implication of medical or physiotherapy intervention. If lymphedema has had more attention, the other two areas also need to be investigated.

Objectives

The primary objectives are:

1) To assess the effect of drugs on: pain, shoulder impairment and/or edema.
2) To appraise the effect of physiotherapy techniques on: pain, shoulder impairment and/or edema.

The hypotheses are:

1) Drugs will reduce pain related to breast cancer treatment.
2) Drugs will improve shoulder impairment.
3) Drugs will reduce edema.
4) Physiotherapy techniques will reduce pain.
5) Physiotherapy techniques will improve shoulder impairment.
6) Physiotherapy techniques will reduce edema.

Criteria for considering studies for this review

Types of studies

Only RCTs were included in this review. Usually – when doing a proper systematic review – when information on the randomization procedure is missing, the author given as "the correspondent for the article" is contacted in order to obtain more details. In this case, it needs to be acknowledged that corresponding authors were not reached.

Types of participants

To be eligible for this review, studies had to recruit adult women: greater than 18 years of age with a diagnostic of breast cancer. Only unilateral breast cancer is considered, as it provided a control arm to assess arm dysfunction, such as ROM, loss of strength and lymphedema. Participants had to be post-acute treatment; they can have been recruited during the treatment phase (surgery, chemotherapy, and/or radiation therapy), but results should report long-term follow-up (at least six months post any intervention). In the case of edema intervention, lymphedema needs to be clinically detectable (either with a tape measure, a volumeter, or a perometer). As the definition of lymphedema varies along the literature[12, 28], the swollen limb needs to be described as at least 10% greater than the contra-lateral arm, have a 2-cm difference at a landmark point, or a volume difference of 200 ml.

Types of interventions

The following interventions have been considered for this review:

1) Drugs compared to placebo: for pain, for shoulder impairment, or for edema.
2) Drugs compared to "conventional drug": for pain, for shoulder impairment, or for edema.
3) Drugs compared to no intervention: for pain, for shoulder impairment, or for edema.
4) Physiotherapy techniques versus conventional treatment: for pain, for shoulder impairment, or for edema.

5) Physiotherapy techniques versus no intervention: for pain, for shoulder impairment, or for edema.
6) Multi-layer bandaging compared to hosiery.
7) Multi-layer bandaging or hosiery versus exercise / no treatment / MLD / IPC
8) MLD or CDT versus physiotherapy / exercises / IPC / no treatment
9) Exercise compared to no treatment
10) IPC versus exercises / no treatment

Types of outcome measures

The primary outcomes of this review are:

1) Measurement of: pain, ROM, muscular strength/endurance, lymphedema (volume measurement by measuring tape, water displacement and/or perometer).

The secondary outcomes are:

1) Impact on QOL and/or on participant's mobility.
2) Reduction of symptoms.

Search strategy

In order to perform the search, the following databases have been considered:

1) Cochrane Library (1993 to June 2009)
2) Cochrane Breast Cancer Specialized Register (1996 to June 2009)
3) Medline (Pubmed) (1950 to June 2009)
4) Embase (1980 to June 2009)
5) CINAHL (1937 to June 2009)
6) PEDRO (1999 to June 2009)
7) CANCERLIT (1937 to June 2009)

Grey literature has been looked at with Google Scholar. The search has been conducted with the combination of key words and Medical Sub-Heading (MeSH) terms under three concepts: 1) Population (breast cancer), 2) Intervention (medication or physiotherapy techniques), and 3) Outcome (reduction of: pain, shoulder impairment and/or

lymphedema). Table 4 describes the key words and MeSH terms and Table 5 gives an example of the search strategy performed in Medline.

Limit has been put to the search:

1) Only English and French articles were reviewed.

In order to make sure that the search strategy was appropriate and no key concepts and/or terms were missing, Mrs. Jill Boruff, MLIS, Liaison Librarian at the Life Sciences Library at McGill University, was consulted. However, she only revised the search strategy and gave advices on how to perform adequately the search in the different databases. Otherwise, all the searches were performed by the author of this paper (M-E Letellier).

Methods

Eligibility criteria

The proper way to assess eligibility criteria in a systematic review is to have two reviewers that blindly assess the articles according to an inclusion/exclusion criteria list already pre-established. When there are disagreements between the reviewers, a third one is involved to resolve the discrepancies. Inclusion and exclusion criteria of the studies retain for this review are stated in Table 6.

Data extraction

Like for assessment of eligibility, usually data extraction is done blindly by two reviewers and disagreement is resolved by a third reviewer. As only one reviewer have extracted the data, it is not possible to measure inter-rater reliability.

Wherever possible, the following data were extracted from each study:

1) Details of participants, including: demographic characteristics, source of recruitment (type randomization), affected side, duration of arm dysfunction (pain, reduce ROM, loss of strength, lymphedema), and number of participants allocated in each group and the number lost to follow-up with the reasons why.

2) Details on medical information: type of surgery, type of axillary dissection, number of lymph nodes involves, and cancer stage.
3) Details of the experimental and control intervention: length of the intervention, homogeneity of both groups at the beginning.
4) Methods of assessment of arm dysfunction.

Assessment of study quality

Study quality is also usually assessed by two reviewers in a blind manner and disagreement is resolved by a third reviewer. Having two reviewers allow to measure inter-rater reliability, but it will not be measured here, as there is only one reviewer.

Quality of studies has been assessed with the Jadad Scale[24]. This scale has a score ranging from 0 to 5, and high quality is considered as a score of 3 and above; see Figure 1 to have an overview of this scale. This scale is quite simple, fast, and easy to administer. The number of RCT available regarding medication or physiotherapy techniques reducing pain, shoulder impairment and/or oedema is quite small. Therefore, the quality of the studies will be taken into consideration, but even low quality studies will be kept. Also, the previous systematic reviews done have mentioned that there is a lack RCT in this domain[3, 3, 9, 27, 36, 40, 42], which emphasis the fact that all RCT should be included.

Analysis

As it will be discussed in Results, none of the studies included in this review compared the same intervention. Therefore, it is not possible to combine the data; neither analysis nor meta-analysis was possible to perform in this review. As no studies are comparing the same interventions, the results of each study will be discussed in a text form.

The quality of each paper has been assessed by the Jadad scale[24]. Only one article (Sandel[60]) has obtained a high quality score. Therefore, all studies have been included regardless of their quality. This means that caution regarding the conclusion drawn should be taken into consideration.

Results

Description of studies

The results of the searches performed identified 362 articles. After reading titles and abstracts and removing duplicates, 52 papers were looked more in details. Of these, only 17 were found to meet the inclusion/exclusion criteria. Figure 2 gives the flow diagram of the searches and the articles kept.

The following article has been cited by many authors and was of interest for this review; however, it was not possible to have access to the entire paper (only abstract was obtained). Their conclusion was that MLD and sequential pneumatic compression each significantly decreased arm volume, but there was not a significant difference detected between the two methods. Therefore, it has not been taken into consideration.

> Johansson, K., Lie, E., Ekdahl, C., Lindfeldt, J. A randomized study comparing manual lymph drainage with sequential pneumatic compression for treatment of postoperative arm lymphedema. Lymphology 1998; 31: 2, 56-64.

According to the Jadad scale, of the 17 articles, only one can be considered as good quality: Sandel [60] 4/5. The other ones are distributed as follow: 0/5 – 7 articles; 1/5 – 4 articles; 2/5 – 5 articles. Table 7 describes the 17 articles kept for this review. Retained articles can be divided into two main categories:

1) Intervention without lymphedema
    a. Drug: Hase[54]
    b. Exercise: Mustian[59], Sandel[60], Sprod[62]
    c. Physiotherapy: Lauridsen[56]
2) Intervention with lymphedema
    a. Exercise: Ahmed[49], McKenzie[57]
    b. Physiotherapy
        i. MLD/CDT: Andersen[50], Didem[52], Jahr[55], McNeely[58], Sitzia[61], Williams[65]
        ii. IPC: Dini[53], Szuba[63], Wilburn[64]
        iii. Program: Cho[51]

Like the previous review performed, the vast majority of studies are regarding lymphedema. Very few information is available regarding drug therapy intervention for pain, shoulder impairment, or lymphedema.

Of the excluded studies, 12 were related to exercise intervention without lymphedema, two were concerning physiotherapy techniques without lymphedema, and three were about physiotherapy techniques for participants with lymphedema. The reasons for excluding those RCTs were: not assessing arm dysfunction[67, 73, 74, 75, 76, 77, 78, 81], intervention given during treatment[69, 70, 72], reporting the incidence of lymphedema[68, 71, 82], reporting the incidence of seroma formation[80], reporting the protocol[79], and assessing men and women for upper and lower limb lymphedema[66]. Table 8 expresses those 17 excluded articles.

Risk of bias in included studies

All studies included were RCTs, which reduce the risk for selection bias. Furthermore, all studies reported that intervention and control groups were the same at baseline. In some cases, the procedure for the randomization is not mentioned (10/17)[50, 51, 54, 55, 56, 57, 61, 62, 63, 64, 65]. The other ones were randomized by: block (2)[49, 55], card and envelope (1)[52], phone (1)[53], computer-generated (2)[58, 60], and flip coin (1)[59].

As most participants are aware of intervention that they are taking part, most of the studies (11/17) were not blinded to either participant or staff [50, 51, 53, 55, 56, 57, 59, 61, 62, 63, 65]. Although, in five studies staff were blinded to participant allocation [49, 54, 58, 60, 64], and in only one study the participant was blind[52].

Of all the studies, only one has no withdrawal and loss to follow-up as the study was conducted once and tested pre and post-physiotherapy intervention[54]. All 16 studies acknowledge and give the reasons for withdrawing and lost to follow-up[48, 49, 50, 51, 52, 53, 55, 56, 57, 58, 59, 60, 61, 2, 63, 64, 65]. Of these, only two studies mentioned that they have use intention to treat analysis[50, 60], which reduce the risk of bias.

Effects of intervention

Drugs and pain

None of the articles found was related to pain and the use of drugs. Chronic pain is a common consequence of cancer and its treatment[83]. As noticed while performing the search, this complication is quite often under-reported, under-diagnosed, and under-treated. Levy and colleagues (2008)[83] described three different types of pain that can be induced by cancer treatment: 1) somatic pain, 2) visceral pain, and 3) neuropathic pain. Of these, neuropathic pain is the most common and it is usually treated with opioid analgesia[83].

Drugs and shoulder impairment

Of the articles found, only one study found targeted the intervention of drugs and ROM. Hase and colleagues (2006)[54] have investigated the efficacy of oral administration of zaltoprofen – a nonsteroidal anti-inflammatory drug which has an analgesic effect on shoulder ROM. Forty participants were randomized to taking (n = 20) or not (n = 20) a zaltoprofen tablet before a single session of physiotherapy. They have concluded that the drug may enhance the effect of physiotherapy on ROM, as shoulder flexion, abduction and external rotation significantly improved. ROM improved in both the intervention group and the control group; however it was superior in the intervention group.

Drugs and edema

No study investigated this intervention.

Physiotherapy and pain

In the study proposed by Hase and colleagues (2006)[54] pain was assess subjectively as a secondary outcome. Of the forty participants, there were no differences in pain scores between the intervention group (zaltoprofen) and the control group, except for two participants that were in the control group that complained about the pain that has increased following the single physiotherapy session.

Jahr and colleagues (2008)[55] have use MLD and low-frequency electrostatic fields (deep oscillation) (n = 11) versus MLD alone (n = 11) and have subjectively assess pain with a visual analogue scale. Participants were involved for four weeks: 12 sessions of MLD and deep oscillation versus once or twice per week 30-45 minutes of MLD alone. Pain was significantly reduced over time in favor of the experimental group ($p = 0.048$ vs $p = 1$). This has lead to the conclusion that deep oscillation, combined to MLD, significantly reduces pain symptoms.

Physiotherapy and shoulder impairment

In their study, Cho and collaborators (2006)[51] wanted to assess the efficacy of a comprehensive group rehabilitation. The comprehensive group rehabilitation consists of: psychology-based education, exercises, and peer support group activity, meeting three times per week for ten weeks. This group (n = 34) had been compared to a control group (n = 31) who received the intervention at the end of the trial. Their outcome of interest for this review was ROM, for which they have concluded that their program promote the recovery of ROM.

Didem and collaborators (2005)[52] have also targeted ROM by comparing two different physiotherapy methods: CDT versus standard physiotherapy (bandages, elevation, head-neck and shoulder exercises). Twenty-seven participants received CDT and 26 had standard physiotherapy. Both groups were treated once a day, three times per week, for four weeks. No conclusion can be drawn for those two therapies, as both group obtained a significant increased in ROM.

In addition to pain, Jahr and colleagues (2008)[55] have also looked at ROM. The group who did received MLD, but not deep oscillation, remained unchanged regarding shoulder mobility. This also favors deep oscillation to alleviate ROM function.

Lauridsen and colleagues (2002)[56] have assessed both muscle strength and ROM. A total of 59 participants were randomized into four cohorts: A and C, and B and D. The cohorts were divided according to the type of surgery (mastectomy or lumpectomy). Therefore, both types of surgery were represented in the group A and C (warm swimming and

training on the floor) and B and D (individual treatment with a physiotherapist). Both groups had once a week intervention, for ten weeks. They have concluded that physiotherapy can improve strength and ROM and can also decrease the presence and severity of late symptoms following treatment for breast cancer.

Mustian's (2006) [59] study has used Tai Chi Chuan as intervention (n = 17) compared to a psychology support group (n = 14) in order to assess the effectiveness and appropriateness of this exercise with a breast cancer population. Muscular strength and ROM were both evaluated. Both groups were involved in their activity three times per week, for 12 weeks. With their pilot study, they have proven that Tai Chi Chuan was a same form of exercise that can have a significant improvement on muscular strength and flexibility.

With dance exercise, Sandel and colleagues (2005)[60], 19 participants took part in this type of exercise for 12 weeks: twice a week for the first six weeks, and once a week for the other six weeks. Nineteen more participants' crossover at the end of the trial, as the control group was a waiting list. Authors have not found any difference in the group order and both groups have seen their ROM significantly increased after the intervention ($p = 0.03$).

A third type of exercise has been investigated by Sprod and collaborators (2005)[62]: walking poles. Two small groups of eight participants each have performed a 20-minute aerobic walk (with or without poles), twice a week for eight weeks. Muscular endurance was assessed and has shown to improve when using poles compare to not using them. However, ROM has not improved in either group.

Physiotherapy and edema

Exercises

Ahmed and her team (2006)[49] proposed a weight training intervention and have assessed arm volume changes over a six-month period. Participants were involved in twice-a-week of resistance and stretching exercises (n = 42) compared to nonintervention (n = 43). Of

these participants, 13 women already had lymphedema. At the end of the trial, the training program did not increase the incidence of lymphedema, nor the arm volume.

With their pilot study, McKenzie and Kalda (2003)[57] have looked at the effect of a progressive upper-body exercise program with women already having lymphedema. Seven women were allocated to an 8-week upper-body exercise program (resistance training and aerobic exercise) versus a control group. In both groups, a compression sleeve had to be worn daily. Women who have taken part in the progressive program have not seen a change in their arm volume, meaning that this type of exercise will not exacerbate their lymphedema.

With her dance exercise study, Sandel[60] have also shown that this type of exercise have not change arm circumferences.

Manual Lymph Drainage / Combined Decongestive Therapy

In the study done by Andersen and colleagues (2002)[50] the standard care (n = 22) were compared to the standard care supplement with MLD. For them, standard cares were: custom made sleeve and glove, educational information, instruction on physical exercises, education in skin care, and safety and precaution. The group who received MLD had eight treatments over a two-week period. This study has failed to show the efficacy of MLD in treatment for lymphedema when standard cares are also provided.

Like previously mentioned, Didem[52] compared CDT versus standard physiotherapy (bandages, elevation, head-neck and shoulder exercises in 53 women with unilateral lymphedema. Regarding limb volume, both groups have obtained a significant reduction; although, the reduction was more important in the CDT group.

As in the previous outcome, Jahr[55] have found that deep oscillation, when supplement with MLD, also provide a greater reduction in arm swelling compared to MLD alone.

McNeely and collaborators (2004)[58] studied the application of MLD and bandages (n = 25) versus bandages alone (n = 25) in women suffering of unilateral arm lymphedema. Participants received MLD 45 minutes daily, and bandages were applied daily too (both

groups), for four weeks. They found that bandages were a key element in lymphedema treatment, as with or without MLD it is effective to reduce limb volume.

Sitzia and collaborators (2002)[61] investigated MLD (n = 15) versus Simple Lymphatic Drainage (SLD) (n = 13). Both groups received the intervention daily for a 2-week period. MLD was performed for 40-80 minutes and SLD for 20 minutes, followed with bandages and exercises for both. The data were not statistically conclusive, but they favor MLD to SLD in reducing limb volume.

Williams and colleagues (2005)[65] have done a crossover study comparing MLD followed by SLD versus SLD followed by MLD. The first group (n = 15) received three weeks of daily MLD for 45 minutes, followed by a 6-week non treatment period, and followed by three weeks of daily SLD for 20 minutes. The second group (n = 16) received the opposite treatment regiment. The findings have shown that MLD significantly reduces excess arm volume.

Intermittent pneumatic compression

Eighty women having unilateral arm lymphedema were randomized to IPC (n = 40) versus no treatment (n = 40) into Dini and collaborators' (1998)[53] study. Women who had the pump therapy had two cycles of two weeks, separated by 5-week interval, five 2-hour sessions per week. They concluded that IPC has a limited clinical role in the treatment of upper limb lymphedema.

Szuba and colleagues (2002)[63] have published two studies in the same paper. The first study looked at women newly diagnosed with lymphedema and they have investigated MLD combined with IPC for 30 minutes and bandages (n = 23) versus CDT (n = 11), performed daily for 10 days. In the second study, women (n = 27) were in their maintenance phase of lymphedema and they were allocated to maintenance (daily, self-administer, SLD) compared to maintenance supplemented with an hour of daily IPC for one month (no information is provided regarding the distribution of participants in each group). They found that in both studies participants who used the IPC had a greater volume reduction.

Wilburn and collaborators (2006)[64] compared the use of IPC with standard treatment and crossover intervention. Participants had a 7-day washout period, days 7-21 IPC or standard care, days 21-28 washout period, and days 28-42 IPC or standard care. Five women were randomized in each group. They found that the use of the IPC may provide a better maintenance control than self-administered massage when lymphedema is present.

Discussion

For the cancer-related pain aspect, as Levy and colleagues (2008)[83] mentioned, the problem has been underreported and does not seem to be clearly understood from both the medical aspect (with drugs) and the rehabilitation aspect (only two studies had pain as an outcome). Pain is present in 30% to 40% of all cancer patients[83], which should flag the importance of being integrated into comprehensive cancer care in order to improve the patient's QOL. Pain is really hard to work with: it is sometimes complicated to qualify and to quantify it. Nevertheless, rigorous methodological RCTs should be conducted on both the medical and the rehabilitation aspect in order to have a better understanding of pain and what will be the most effective in treating it.

Shoulder impairment has obtained a little bit more interest than pain in the articles found for this review. However, findings should been taken cautiously. Only one study indicates that drug (zaltoprofen) might be effective in the alleviation of ROM after a single physiotherapy session. Therefore, other RCTs should be done with a greater sample size, with rehabilitation intervention described and patients should be followed over time. When looking at the physiotherapy intervention for shoulder impairment, it goes all around the places and none of the studies has investigated the same thing. Consequently, it is hard to conclude about the effectiveness of physiotherapy intervention. We can assume that physiotherapy is efficient to treat ROM impairment and/or muscular strength/endurance reduction; however, we cannot define which regimen is more efficient in relieving these outcomes.

Most of breast cancer arm dysfunction outcomes are toward lymphedema and its treatment/management. Since both Badger and colleagues' reviews[3, 4] in 2003 and 2004,

to my knowledge, no RCT have been done regarding the use of drugs in the treatment/management of lymphedema. Furthermore, Badger's 2003[3] investigated on the use of Benzo-pyrones (coumarin) to reduce and controlling lymphedema of the limb. Since this review, the sale of this drug has been suspended in Australia, Belgium, Canada, and France[84]. So far, the use of drugs in the management and treatment of lymphedema has not proven its efficacy.

Originally, exercises were tough to be a potential trigger for lymphedema, especially if the person was doing repetitive and strenuous exercises[49, 57, 60, 84]. The five articles found on this topic[49, 57, 59, 60, 62] indicate that exercises did not make lymphedema worse, when this was tested as an outcome[49, 57, 60]. Only two papers compared approximately the same thing[49, 57]: progressive resistance training (PRT). However the intervention was not the same: 6 months twice weekly[49] versus 8 weeks[57] (no mention regarding the number of times per week), and resistance and stretching exercises are not described, so it is not possible to know if they have evaluate the same exercises. These two references were included into Cheema's systematic review[9], from which the authors have concluded that robustly designed RCTs regarding PRT throughout different phases of breast cancer are necessary in order to establish its efficacy. The other RCTs given in reference in Cheema's review[72, 75, 76] were not included in this review, because the intervention was given during treatment phase.

Exercise is known to be effective to prevent chronic disease, such as hypertension, high cholesterol, and obesity[49]. In people suffering of lymphedema, exercise plays a major role by its physiological impact on the lymphatic system[49], and by the fact that it provides good cardiovascular health, muscle strength, functional capacity, and better QOL[57, 59, 60]. What is not known is: the best type of exercise and the best regimen (frequency, intensity, time of training, number of sets and repetitions). Tai Chi Chuan[59], dance[60] and walking poles[62] have shown great promises for breast cancer patient, but all these interventions need to be replicated with a greater sample size and women followed over time.

Remedial exercises are an integral part of CDT. However, none of the intervention that has use CDT describes the remedial exercises that are given to the participants[52, 63]. It is

not possible to know what was performed and if remedial exercises have really an impact in this type of therapy.

Actually, it is CDT that is recognized as the traditional approach to treat lymphedema[40, 52, 63]. However, none of the four components (skin care, MLD, bandages/compression, and exercises) has shown its individual efficacy[58, 84]. Regarding the studies that have use MLD/CDT, none of them have compared the same intervention or even the duration of the therapy (ranging from 10 days to nine weeks)[50, 52, 55, 58, 65]. Some studies have concluded that MLD showed a lack of effect in volume reduction[50, 58], while others said that it did have an effect on lymphedema reduction[52, 61, 65]. This leads to state again that robust RCTs are required to find what the best approach is, because CDT is quite expensive and time consuming for both the patient and the therapist.

An approach commonly used in hospital settings is the utilization of IPC. Both Dini[53] and Wilburn[64] have tested the IPC compared to either no treatment or standard treatment respectively. Szuba[63] combined IPC with MLD and bandages. Again, none of the three studies used the same duration: two cycles of two weeks[53], daily for 10 days[63], and daily for 14 days, but at least they all had the same outcome: volume reduction. As the literature mention[47, 84], and as proposed by Szuba and collaborators[63], the use of IPC should not be consider as the only therapy, because the pump assists the reabsorption of water in the arm, however the protein are left behind, which may accelerate the creation of fibrotic tissues and worsen the lymphedema.

One avenue that might be interesting to apply, and which has not been taken into consideration in this review, is the use of delayed versus immediate exercises following breast cancer surgery. Shamley and colleagues (2005)[86] did a systematic review and concluded that delayed exercises reduced the seroma formation. Other RCTs excluded from this review also suggest that delayed exercises might reduce the risk of developing lymphedema/arm dysfunction[68, 69, 70, 82]. The objectives of this review were to assess the effect of drugs and physiotherapy techniques on pain, shoulder impairment and/or edema. Unfortunately, the area is still gray, as no clear evidences are provided with either drugs or rehabilitation regarding arm dysfunction following breast cancer treatment.

Conclusion

From the 17 studies included in this review, it is difficult to draw clear conclusion about the effectiveness of drugs or physiotherapy techniques when dealing with arm dysfunction following breast cancer, because:

1) The quality of every studies, except one[60], is below the mark consider as being good (3 and above on the Jadad scale[24]);
2) Every study had a small sample size;
3) None of the intervention compared the same outcome;
4) Length of intervention was also not the same.

Within this field, it is complicated to achieve really high quality study, as the participant is initially unblinded as to intervention that she is receiving. However, in order to increase the quality, a minimum is that assessors be blinded to allocation.

There is a definite need to have robust RCTs conducted regarding arm dysfunction. This future research on arm dysfunction should consider:

1) RCT design;
2) Large sample size;
3) Follow-up, as arm dysfunction can occur in the long term and can be very debilitating, and there is a need to know the long effects of the therapy;
4) Detailed description of intervention, such as the time spent doing MLD, type of bandages applied, remedial exercises given and their regimen to assure consistency of treatment (TIDieR guidelines – Template for Intervention Description and Replication – www.equator-network.org).

Presently, there is a lack of high quality evidence-based research available to answer this research question. There is a clear need for higher quality studies to be conducted in this area. This will contribute valuable information for rehabilitation specialists to provide optimal care for individuals who seek services for arm dysfunction post-breast cancer treatment.

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Table 1. Dysfunction aspects: SLNB versus ALND.

Dysfunction aspects	**SLNB**	**ALND**
Paresthesia	22%	70%
Decreased range of motion	12-15%	22-29%
Lymphedema	0-16.8%	7.1-56%
Pain	20%	40%

Table 2. Systematic reviews – Cochrane Breast Cancer Group

Main Author	Year	Objective of the review	Authors' conclusion
Badger[3]	2003	*To assess the effectiveness of benzopyrones compared to placebo in the management of lymphoedema.*	*It is not possible to draw conclusions about the effectiveness of Benzopyrones in the management of lymphoedema from the current available trials.*
Badger [4]	2004	*To determine whether antibiotic/anti-inflammatory drugs given prophylactically reduce the number and severity of infective/ inflammatory episodes in patients with lymphoedema*	*The effectiveness of selenium in preventing infective/ inflammatory episodes in lymphoedema remains inconclusive in the absence of properly conducted randomized-controlled trials.*
Howell[22]	2002	*To assess the effects of complete decongestive physiotherapy or manual lymphatic drainage alone on the primary outcome of arm volume reduction or the secondary outcomes of chest wall volume reduction, functional improvement, and pain reduction for women with secondary lymphedema as a result of treatment of breast cancer.*	No conclusion, this article is the protocol of the review
McNeely[35]	2005	*The purpose of this systematic review is to examine the evidence from randomized controlled trials on the benefit of therapeutic exercise interventions in preventing and/or minimizing upper limb morbidity due to breast cancer treatment.*	No conclusion, this article is the protocol of the review
Preston[40]	2004	*To assess the effect of physical treatment programmes on: volume, shape, condition and long-term control of oedema in lymphoedematous limbs; psycho-social benefits.*	*All three trials have their limitations and have yet to be replicated, so their results must be viewed with caution. There is a clear need for well-designed, randomised trials of the whole range of physical therapies if the best approach to managing lymphoedema is to be determined.*
Robb[43]	2008	*The aim of this systematic review was to determine the effectiveness of TENS for cancer-related pain in adults.*	*The results of this systematic review are inconclusive due to a lack of suitable RCTs. Large multi-centre RCTs are required to assess the value of TENS in the management of cancer-related pain in adults.*

Table 3. Systematic reviews – Others

Main Author	Year	Objective of the review	Authors' conclusion
Cheema[9]	2008	*(1) To systematically review studies that have prescribed progressive resistance training (PRT) after breast cancer surgery, (2) to summarize the efficacy of PRT in this cohort, and (3) to delineate areas for future investigations*	*Robustly designed RCTs prescribing targeted PRT regimens throughout various phases of breast cancer treatment are warranted. RCTs with thorough, standardized reporting of interventions and adverse events are required to establish the efficacy of this intervention for the post-treatment management of breast cancer patients and survivors as a means to improve health status and quality of life*
Kligman[27]	2004	*To provide an evidence summary report on the question: What are the treatment options for women with lymphedema following treatment for breast cancer?*	*There is some evidence to suggest that compression therapy and manual lymphatic drainage may improve established lymphedema, but further studies are needed. Compression garments should be worn from morning to night and be removed at bedtime. Patients should be advised that lymphedema is a lifelong condition and that compression garments must be worn on a daily basis. Patients can expect stabilization and/or modest improvement of edema with the use of the garment in the prescribed fashion. (2) There is no current evidence to support the use of medical therapies, including diuretics. (3) Additional efforts to define relevant clinical outcomes for the assessment of patients with lymphedema would be valuable. (4) These opinions are appropriate for patients with more than mild lymphedema, where the signs and symptoms are considered significant from the patients' perspective.*
Megens[36]	1998	*To analyze the research literature that has examined the effectiveness of physical therapy in the management of lymphedema following treatment for breast cancer.*	*Caution must be exercised when considering these recommendations because none of them are supported by numerous, definitive studies. More rigorous research, incorporating blind assessment of outcomes and random assignment of subjects to groups, will enhance clarification of these tentative recommendations.*
Rietman[42]	2003	*Relationship of this late morbidity with activities of daily life (ADL) and quality of life (QOL) is infrequently described and the strength of this relationship is not clear*	*Few studies investigated the relationship between late morbidity of the upper limb after treatment of early breast cancer and ADL/QOL. Significant relationship between late morbidity and restrictions of daily activities and poorer QOL was reported, however, the strength of this relationship was rather low.*

Table 4. Key words and MeSh terms

Concept 1: Population → Breast cancer
Breast cancer / breast neoplasms / survivor*
Concept 2: Intervention → Medication or physiotherapy techniques
Medication / drug / pharmaceutical preparations
Physiotherapy / physical therapy modalities / exercise therapy / rehabilitation
Manual lymph drainage / combined decongestive therapy, complete decongestive physiotherapy, complete physical therapy, complex lymphatic therapy / massage
Pneumatic compression / intermittent pneumatic compression devices / intermittent pneumatic pump / pneumatic compression hose
Hosiery / bandages / multi layer bandages / compression sleeve / compression garment
Exercise / exercise movement techniques / stretching
Concept 3: Outcome → Reduction of: pain, shoulder impairment and/or lymphedema
Pain
Shoulder impairment / shoulder limitation / shoulder mobility / range of motion, articula articular range of motion
Edema / oedema / lymph$edema

Table 5. Example of the search strategy
Database: Ovid MEDLINE(R) <1950 to June Week 2 2009> Search Strategy:

#	Search	Results
1	breast cancer.mp. or Breast Neoplasms/	180190
2	breast neoplam*.mp.	1
3	1 or 2	180190
4	survivor*.mp. or Survivors/	46979
5	4 and 3	1984
6	medication.mp.	101422
7	drug.mp. or Pharmaceutical Preparations/	1389632
8	drug therapy.fs.	1319985
9	8 or 6 or 7	2320508
10	Exercise Therapy/ or Physical Therapy Modalities/ or physiotherapy.mp.	41837
11	rehabilitation.mp. or Rehabilitation/	84371
12	11 or 10	117954
13	manual lymph drainage.mp.	84
14	combined decongestive therapy.mp.	2
15	complete decongestive physiotherapy.mp.	12
16	complete physical therapy.mp.	4
17	complex lymphatic therapy.mp.	0
18	Massage/ or massage.mp.	8509
19	18 or 16 or 13 or 17 or 15 or 14	8585
20	Intermittent Pneumatic Compression Devices/ or pneumatic compression.mp.	723
21	intermittent pneumatic pump.mp.	0
22	pneumatic compression hose.mp.	2
23	22 or 21 or 20	723
24	hosiery.mp.	145
25	Bandages/ or bandages.mp.	12692
26	multi layer bandages.mp.	2
27	compression sleeve.mp.	12
28	compression garment.mp.	33
29	27 or 25 or 28 or 24 or 26	12788
30	exercise.mp. or Exercise/ or Exercise Movement Techniques/	168231
31	stretching.mp.	10137
32	30 or 31	177533
33	32 or 23 or 19 or 9 or 29 or 12	2581853
34	pain.mp. or Pain/	328175
35	shoulder impairment.mp. or "Range of Motion, Articular"/	21004
36	shoulder limitation.mp.	4
37	shoulder mobility.mp.	108
38	articular range of motion.mp.	4
39	38 or 35 or 36 or 37	21077
40	edema.mp. or Edema/	89765
41	oedema.mp.	16049
42	lymph$edema.mp. or Lymphedema/	6358
43	42 or 40 or 41	104611
44	39 or 34 or 43	440961
45	33 and 44 and 5	51

Table 6. Inclusion and exclusion criteria

Inclusion	Exclusion
RCT Women aged over 18 years old Unilateral breast cancer Participants are post-acute treatment Intervention: see *Type of interventions*	Language other than English or French No component of arm morbidity assess Intervention given during treatment phase No definition of lymphedema given

Table 7. Details of included trials

Study ID	Randomization	Intervention	Outcome	Conclusion	Quality
Ahmed[49]	Blocked randomization	Weight training intervention vs Control N = 42 vs 43 1st 3 months training groups (3-6), 3-6 months in pairs, resistance: 3 sets 8-10 repetitions, stretching, 60 minutes, 2x week	Arm circumferences	Training program over 6 months did not increase incidence, arm-circumference measurement differences, or symptoms of lymphedema	1/5
Andersen[50]	No mention on the procedure	Standard therapy vs Standard therapy and MLD and self-massage Standard therapy: compression sleeve, educational information, exercises, skin care, and safety precaution N = 22 vs 20 MLD given 8 times in 2 weeks, daily self-massage	Change in arm volume Patient-reported symptoms HRQOL	Study showed a lack of effect of MLD and a supplement to standard therapy, as both groups obtained a significant reduction in limb volume, a decrease in discomfort and an increased joint mobility	1/5 6/10*
Cho[51]	No mention on the procedure	Experimental vs Control N = 34 vs 31 3x week for 10 weeks, psychology-based education, exercise, and peer support group activity (Control had the intervention at the end of the trial)	ROM Psychological adjustement QOL	Rehabilitation program promote the recovery of ROM, alleviate physical symptoms, improve psychological adjustment and QOL	0/5 4/10*

*Score given in the PEDro database

Table 7. Details on included trials (continued)

Study ID	Randomization	Intervention	Outcome	Conclusion	Quality
Didem[52]	Card in unmarked envelopes	CDP (MLD, compression bandages, remedial exercises and skin care) vs Standard physiotherapy (bandages, elevation, head-neck and shoulder exercises) N = 27 vs 26 1x day, 3x week for 4 weeks	Arm volume and circumferences ROM	Both group obtained a significant reduction in limb volume, decrease in discomfort and an increased joint mobility. Reduction of edema was found to be better in the CDP group.	2/5 6/10*
Dini[53]	Phone call to Clinical Epidemiology Office	No treatment vs Pump N = 40 vs 40 2 cycles of 2 weeks, separated by 5-week interval, 5 2-hour session/week, pressure 60 mmHg	Reduction of lymphedema	No clear evidence in the treatment of lymphedema	2/5
Hase[54]	No mention on the procedure	Zaltoprofen vs No treatment N = 20 vs 20 1 day intervention, tablet given before the trial	ROM	Zaltoprofen taken orally before ROM exercises may enhance the effects of physiotherapy	2/5 6/10*
Jahr[55]	Block randomization	MLD + deep oscillation vs MLD N = 11 vs 11 4-week course of 12 session of MLD + deep oscillation, after 8 weeks MLD alone / 1-2 session week 30-45 minutes MLD	Swelling Pain ROM	Greater reduction in pain and in swelling, and improvement of ROM in the intervention group	1/5
Lauridsen[56]	No mention on the procedure	Cohorts A and C: warm swimming bath and training on the floor vs Cohorts B and D (treatment group): individual treatment of physiotherapy N = 55 (do not know the allocation in each group) 1x week for 10 weeks	Circumferences Mobility Strength Muscle tone Traction Abnormal tension Sensitivity	Physiotherapy improved strength, movement and muscle tone, and reduce the presence and severity of late symptoms	0/5

* Score given in the PEDro database

Table 7. Details on included trials (continued)

Study ID	Randomization	Intervention	Outcome	Conclusion	Quality
McKenzie[57]	No mention on the procedure	Exercise vs Control N = 7 vs 7 8-week exercise program, fitted compression sleeve worn daily, resistance training, stretching, 2x 10 repetitions	Arm volume and circumference QOL	Progressive and controlled upper-body exercise program does not significantly affect the volume of the arm	0/5 2/10*
McNeely[58]	Computer-generated code	MLD + bandages vs Bandages N = 25 vs 25 45 minutes daily MLD, bandages applied in "eight shape"	Arm volume	Bandages, with or without MLD, is an effective intervention in reducing arm lymphedema volume	2/5 6/10*
Mustian[59]	Flip coin	Tai Chi Chuan vs Psychology support N = 17 vs 14 12- week program, 3x week 60 minutes	Aerobic capacity Muscular strength Flexibility Body composition	Tai Chi Chuan may be effective in improving functional capacity	2/5 5/10*
Sandel[60]	Computer-generated	Dance vs Wait list (crossover) N = 19 vs 19 12 weeks, 2x week 1st 6 weeks, 1x week other 6 weeks	Shoulder ROM and circumferences QOL	No significant difference effect of the order or training. Dance movement program that addressed the physical and emotional needs of women improved ROM, QOL. Circumferences remained the same.	4/5 8/10*
Sitzia[61]	No mention on the procedure	MLD vs SLD N = 15 vs 13 MLD: 40-80 minutes, SLD: 20 minutes, both followed with bandages and exercises Daily for 2 weeks	Volume change	MLD lost 1/3 of their initial limb volume; SLD lost ¼. Results suggest that MLD is more effective than SLD	2/5

* Score given in the PEDro database

Table 7. Details on included trials (continued)

Study ID	Randomization	Intervention	Outcome	Conclusion	Quality
Sprod[62]	No mention on the procedure	Walking poles vs Control N = 8 vs 8 20 minutes aerobic (with or without poles) 2x week for 8 weeks	Muscular endurance ROM	No changes in ROM. Using walking poles is more beneficial than performing cardiorespiratory exercise and resistance training alone	0/5 3/10*
Szuba[63]	No mention on the procedure	Study 1: Tx: MLD + pump 30 minutes + bandages vs Control: DLT (MLD, bandages, exercise) / after completion: sleeve / daily for 10 days N = 12 vs 11 Study 2: Maintenance (daily, self-administer, manual lymphatic massage, compression) vs maintenance + 1 hour pump daily N = 27 (no information regarding the distribution)	Volume reduction	Pump, when use in adjunction to other elements of CDT provides an enhancement of the therapeutic response	0/5
Wilburn[64]	No mention on the procedure	Flexitouch vs Standard treatment N = 5 vs 5 Flexitouch 1 hour daily for 14 days, crossover after 1-week period washout	Volume reduction	Use of the Flexitouch (pump) suggests that it may provide better maintenance control of lymphedema	1/5 4/10*
Williams[65]	No mention on the procedure	A: MLD-SLD vs B: SLD-MLD N = 15 vs 16 Group A received 3 weeks of daily 45 minutes MLD followed by a 6- week non-treatment period. This was followed by 3 weeks of daily 20 minutes SLD. Group B received 3 weeks of SLD, followed by a 6-week non-treatment period and then 3 weeks of MLD Both groups fitted with a sleeve	Volume reduction QOL	MLD provide a statistically significant reduction in limb volume and improve several QOL parameters and symptoms associated with lymphedema	0/5 3/10*

* Score given in the PEDro database

Table 8. Details of excluded trials

Study ID	Randomization	Intervention	Outcome	Reason of exclusion	Quality
Badger[66]	Allocated randomly by telephone	Multilayer bandaging + hosiery vs Hosiery alone N = 34 vs 49 18-day course of multilayer bandages, worn hosiery for the rest of the trial (24 weeks) / hosiery worn for 24 weeks	% reduction in limb volume	Upper and lower limb are assessed, and it targeted men and women	2/5
Basen-Engquist[67]	minimization	Life style intervention vs Standard care control N = 35 vs 25 90 minutes group meeting 1x week for 16 weeks, and every other week for 8 weeks (21 sessions total)	Physical performance QOL Physical activity	Does not assess arm morbidity	2/5
Bendz[68]	No mention on the procedure	Early vs Delayed shoulder exercise N = 101 vs 104	ROM Hand strength Arm volume	Does not deal with arm morbidity treatment, look at the incidence of lymphedema	0/5
Beurskens[69]	Computer-generated random list	Physiotherapy (exercise) vs Control N = 15 vs 15 Physio: 2 weeks post-op, guidelines for exercises, 9 treatments, once or twice 1st 3 weeks Control: leaflet flyer with advice and exercises for arm/shoulder 1st week, no further contact with a physiotherapist	Shoulder function Pain QOL	Physiotherapy intervention given immediately post-op	1/5
Box[70]	No mention on the procedure	Physiotherapy management care plan vs Exercise instruction booklet N = 33 vs 32	ROM Physical functioning	Intervention given immediately after surgery	0/5

Table 8. Details on excluded trials (continued)

Study ID	Randomization	Intervention	Outcome	Reason of exclusion	Quality
Box[71]	No mention on the procedure	Treatment vs Control N = 65	Arm volume and circumferences	This study compare the incidence of lymphedema in the long term having providing physiotherapy post-op	0/5
Courneya[72]	Stratified by center and chemotherapy proptocol by computer-generated program	Usual care vs Supervised resistance exercise N = 82 vs 78 During the time of their chemotherapy	QOL Fatigue Psychosocial functioning Physical fitness Body composition Chemotherapy completion rate Lymphedema	Intervention provided during chemotherapy treatment	1/5
Daley[73]	Stratified random permuted blocks	Supervised aerobic exercise therapy vs exercise-placebo or usual care N = 34 vs 36 vs 38 Exercise: 3x week for 8 weeks	QOL Depression Exercise behaviour Aerobic fitness	Does not assess arm morbidity	1/5
Fleissig[74]	No mention on the procedure	SLNB vs ALND N = 424 vs 405	FACT-B+4	No intervention regarding arm morbidity is given	1/5
Herrero[75]	No mention on the procedure	Training vs Control group N = 10 vs 10 8-week exercise program: 3x week 90 minutes of resistance exercises and aerobic training	Cardiorespiratory fitness Strength endurance Muscle capacity Body composition QOL	Does not assess arm morbidity	0/5
Nieman[76]	No mention on the procedure	Exercise vs Nonexercise N = 16 (no information regarding the distribution) 60 minutes weight training and aerobic activity, 3x week for 8 weeks	Natural killer cell cytotoxic activity	Does not assess arm morbidity	0/5

Table 8. Details on excluded trials (continued)

Study ID	Randomization	Intervention	Outcome	Reason of exclusion	Quality
Ohira[77]	Block randomization	Treatment vs control N = 43 vs 43 2x week for 13 weeks training in groups, training on their own for another 13 weeks	QOL Depression	Does not assess arm morbidity	1/5
Schmitz[78]	Blocked randomization	Immediate vs Delayed exercise N = 42 vs 43 2x week weight training intervention	Body size Biomarkers	Does not assess arm morbidity	1/5
Schmitz[79]	Minimization	Exercise intervention vs Nonexercise control	Physiologic capacity of the arm Arm volume	The study is reporting only details regarding study design, statistical design, and protocol of the PAL trial	2/5
Schultz[80]	Randomized according to even or uneven day of birth	Early vs Delayed physiotherapy N = 89 vs 74	Seroma formation	Intervention given after the surgery and looking at seroma formation	0/5
Segal[81]	Random numbers table	Usual care vs Self-directed exercise or supervised exercise N = 41 vs 40 vs 42	QOL Aerobic capacity Body weight	Does not assess arm morbidity	1/5
Todd[82]	Random number table and sealed envelope method	Early exercise vs Delayed N = 58 vs 58 Arm exercises and shoulder movement restricted to below shoulder level for the 1st 7 days. Controls started exercise program that incorporated exercises above shoulder level within 48 hours	Incidence of lymphedema	Reporting the incidence of lymphedema	2/5

Figure 1. Jadad scale for quality of trials

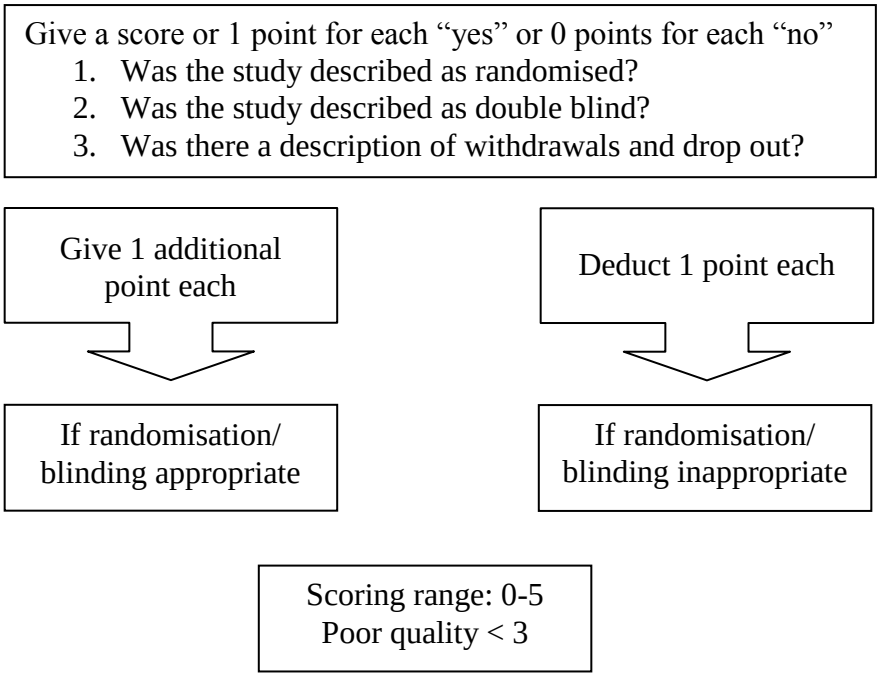
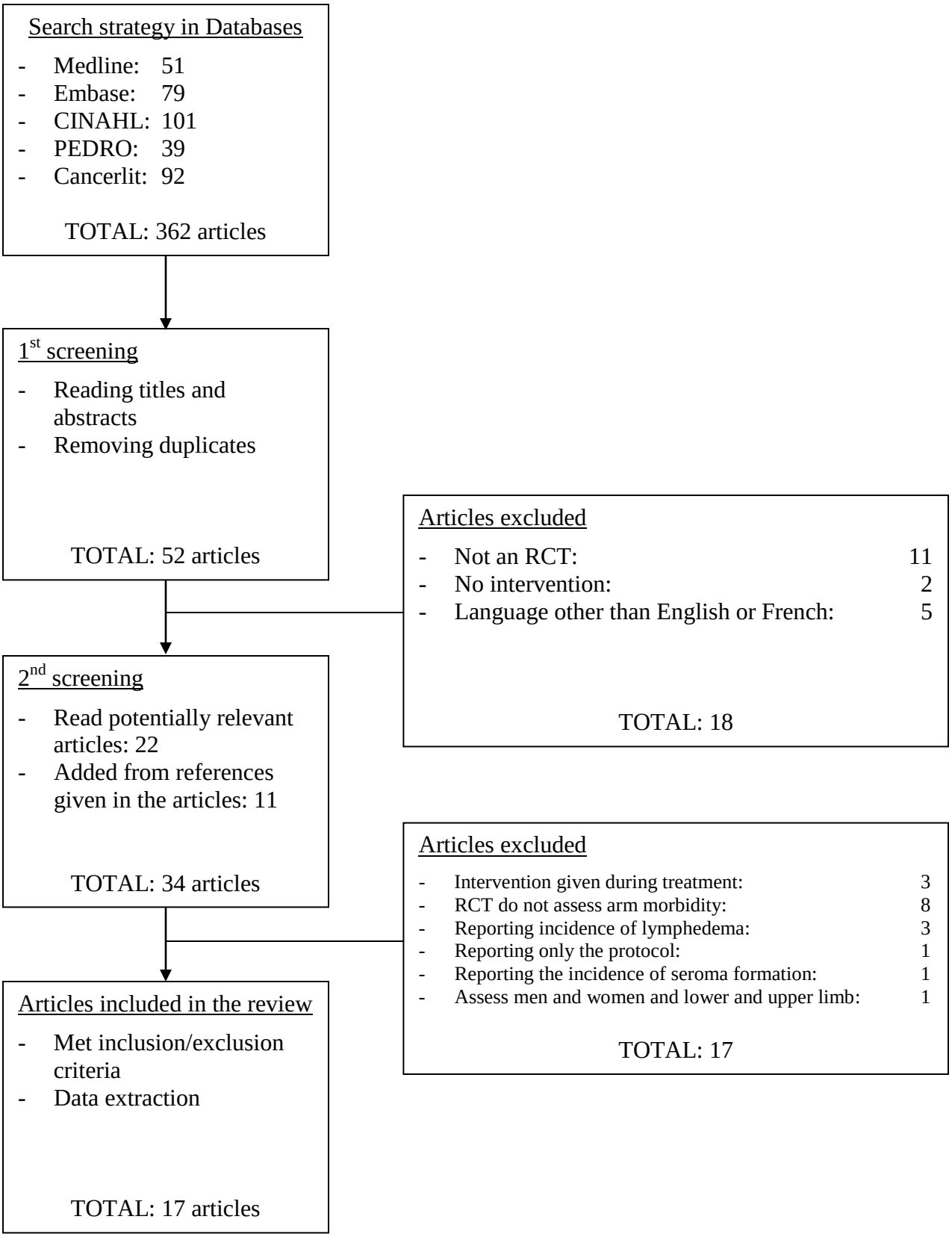


Figure 2. Flow chart



Narrative review of therapies for post-breast cancer arm dysfunction: Update of the literature from 2009-2015 (Part 2)

Introduction

The objective of this narrative review was to update the original search (- June 2009) and include June 2009 to November 2015. The aim remains to estimate, for women post-acute treatment for breast cancer, the extent to which medication or physiotherapy techniques reduce pain, shoulder impairment and/or edema. To update the review, the initial search strategies were repeated.

Among the arm dysfunctions occurring after breast cancer treatment, the greatest attention continues to be focused on lymphedema. The latest evidence suggests that more than one in five women will develop breast cancer-related lymphedema (BCRL) in their life time[87]. In addition, decreased range of motion (ROM) will impact between 2 to 51% of women[88]; 10 to 50% will also see their activity of daily living (ADL), work, and/or leisure be reduced as a consequence of breast cancer treatment[89].

Arm dysfunction, including pain, decreased ROM, decreased strength, and BCRL, may greatly impact quality of life (QOL)[90;91]. Another aspect not addressed here is the depression and/or anxiety following the diagnosis, which affect up to 50% of women[92]. This will influence QOL, also prevent women from engaging in rehabilitation/exercise to regain function.

Results

Description of studies (2009-2015)

The field of breast cancer is a growing area of research. As an example, the first search originally yielded 51 articles in Medline (see Table 5), whereas the literature from 2009 to 2015 revealed 133 articles (see Table 9). In six years, the number of articles found using the same search strategy has more than doubled, making it harder to remain up-to-date.

The initial search included 17 randomised controlled trials (RCTs) (see Figure 2) and 10 systematic reviews. The primary findings were that no clear conclusions can be drawn about the effectiveness of drugs or physiotherapy techniques when dealing with arm dysfunction. Figure 3 illustrates the updated flow chart, where 47 articles will be discussed, including 20 reviews and 27 RCTs.

Table 10 summarizes the findings of the 20 more recent reviews. Most of the reviews (14/20) were systematic reviews[87;88;90;93-103], three were narrative reviews[92;104;105], one a clinical review[91], and two were reviews of systematic reviews[89;106]. The main outcomes addressed were: lymphedema treatment[87;91;93-95;98;100;101;104;106], exercises[92;97;103;105], ROM[88-90;99], and pain[90;96;102]. Table 11 summarizes the three excluded reviews that did not report any of the targeted outcomes[107-109], and the two reporting on surgical treatment of lymphedema[110;111].

Table 12 reviews the 27 RCTs, where 16 articles report on lymphedema treatments[112-127], 10 on exercise[128-135], two on pain[136;137], and one on ROM[138]. According to the scoring of the Jadad scale[24], only six studies are considered of good quality[114;115;129;130;137;139]. Table 13 describes the seven excluded RCTs, where three did not assess arm dysfunction[140-142], and 4 were immediately post-surgery (during the intensive phase of treatment)[139;143-145].

All studies provided similar baseline information for both the intervention group and the control group, which reduces the risk of selection bias. None of the studies had participants blinded to the intervention, but for most of them the assessors were.

Effects of intervention

Drugs and pain, shoulder impairment, and edema (2009-2015)

None of the interventions included involved drugs as a treatment modality for pain, shoulder impairment, or edema.

Physiotherapy and pain (2009-2015)

Three systematic reviews[90;96;102] and two RCTs[136;137] addressed pain as one of the outcomes. The systematic reviews conducted by De Groef et al. (2015)[90] and by Tatham

et al. (2013)[102] searched for exercise as a modality to alleviate pain, whereas the one conducted by Hurlow et al. (2012)[96] searched for transcutaneous electrical nerve stimulation (TENS).

The systematic review of De Groef et al. (2015)[90] which examined 18 RCTs with 2389 participants in the post-operative phase is discussed here as early onset of pain might persist through the continuum of care and become chronic. Their findings suggest that exercise (e.g. stretching, active exercise) is beneficial to reduce post-operative pain.

In Tatham's et al. (2013)[102] systematic review, six studies with 464 participants met their inclusion criteria. Their findings suggest that shoulder pain may be alleviated with therapeutic exercise. Hurlow's et al. (2012)[96] results (3 RCTs, 88 participants) are inconclusive regarding the use of TENS to alleviate cancer-related pain, as there is a lack of suitable RCTs.

Cantarero-Villaneuva et al. (2012)[136] investigated 66 participants randomly allocated to water-exercise versus usual care to address cervical and shoulder pain. The control group received healthy lifestyle recommendations from the oncologist. They concluded that only the intervention group (low-intensity exercises in a warm pool) experienced significantly less pain after the 8-week intervention program.

Fernández-Lao et al. (2012)[137] (43 participants) compared the CUIDATE program (multidimensional physical therapy – stretching, endurance exercises, relaxation, massage – given for 8 weeks) versus usual care (recommendations on healthy lifestyle given by the oncologist). Neck, shoulder, and axillary pain were reduced only in the intervention group, suggesting benefits of their program.

Physiotherapy and shoulder impairment (2009-2015)

Of the four systematic reviews targeting shoulder impairment (ROM), three report on exercises performed post-operatively[88-90], and one on exercise at different stages of treatment[99]. Only one pilot RCT had ROM as the main outcome[138]. As for pain, early onset of ROM issues can persist and become chronic. Therefore, addressing both pain

and ROM in the early stage might be beneficial and this is why the systematic reviews are discussed.

The systematic review conducted by Chan et al. (2010)[88] included 6 RCTs with a total of 429 participants. They report on the effectiveness of exercise programmes performed post-operatively for targeting both ROM and the incidence of lymphedema. Their findings suggest that for ROM early introduction of exercise is beneficial and that it subsequently does not affect the incidence of post-operative lymphedema.

In addition to pain, De Groef et al. (2015)[90] also addressed the role of early initiated exercise for recovery of shoulder ROM. Their results are mixed regarding the timing of exercise: early introduction of exercise is beneficial to recover ROM after surgery; however delaying exercise might help in avoiding prolonged wound healing.

Loh and Musa (2015)[89] conducted a review of systematic reviews, which included seven reviews (two of which are included in this review[88;99], the others are not pertinent). They concluded that impaired ROM following breast cancer surgery can be improved with rehabilitation exercises.

McNeely et al. (2010)[99] reported on 24 RCTs, involving 2132 participants at different stages of their treatment (post-surgery, during adjuvant treatment, and following cancer treatment). At every stage, exercise resulted in a significant and clinically meaningful improvement in shoulder ROM. They recommended that exercise could start early and progressive post-operatively. Careful attention should be paid as wound drainage volume and duration might increase if exercises are performed too soon or incorrectly.

Lee et al. (2010)[138] conducted a pilot RCT with 32 women investigating scapular exercise versus general exercise and compared to an historical control group (n = 18). ROM was addressed as a main outcome. They found a trend toward significantly improved ROM with no difference between the two exercise groups. As a secondary outcome, they addressed pain, where only the scapula exercise intervention group significantly improved.

Shoulder impairment was also addressed by Pan et al. (2014)[103]. They published a systematic review on upper limb function using Tai Chi Chuan exercise. They included nine RCTs for a total of 322 participants. They found that Tai Chi Chuan had positive, but moderate benefits, on upper limb function mobility in the short term.

Physiotherapy and edema (2009-2015)

Exercises

Four types of exercise can be categorized regarding exercise and lymphedema, varying from low to high intensity: relaxation exercise[132;133] (e.g. tai chi, yoga), aerobics and resistance exercise[92], water exercise[130;131;134], and resistance exercise[97;105;128;129;135] (e.g. weight lifting, dragon boat paddling).

Management of BCRL was addressed using yoga by Loudon et al. (2014)[132] in a pilot RCT where 28 participants were randomised to a yoga intervention versus a usual care wait list. After an 8-week weekly intervention, they found that yoga did not exacerbate BCRL and it also improved tissue indurations and QOL.

In another pilot study McClure et al. (2010)[133] randomised 32 women to an exercise and relaxation group or a usual care group to investigate whether an exercise program achieved synergistic improvements in physical and emotional symptoms related to BCRL. They found in their intervention group that BCRL decreased, and that ROM, mood and QOL also all improved.

In their narrative review, Dieli-Conwright and Orozco (2015)[92] discussed the benefits of both aerobic and resistance exercise after breast cancer treatments. It is known that exercise plays a major role in improving cardiopulmonary function, muscular strength, and endurance, as well as stimulating emotional well-being. Their findings suggest that every woman should participate in a form of exercise after breast cancer treatment because of benefits to both physical and emotional well-being. Exercise also favors lymphedema management and helps maintain bone mineral density.

Of the three included studies regarding the management of BCRL with water exercise, two are based on the aqua lymphatic therapy (ALT) program[131;134] developed by Dorit Tidhar[146]. This program is based on the anatomic principles of the lymphatic system and it uses the properties of water to increase the therapeutic effect of the exercise routine. In the pilot randomised study (n = 25) published by Letellier et al. (2014)[131], ALT did not worsen BCRL and they suggest that ALT may serve as a safe treatment alternative. Those findings are similar to those previously reported by Tidhar and Katz-Leurer (2010)(n = 48)[134]. They reported that an immediate volume reduction was obtained with ALT, but no long-term effects were noted.

Johansson et al. (2013)[130] have used water-based exercise, combining exercise and massage in the water. In their pilot RCT involving 29 participants, they found that water-based exercises were safe and that shoulder ROM improved.

Once feared and proscribed, resistance exercises are now welcomed in post-breast cancer exercise regimens[105]. Harris (2012)[105] published a narrative review on women at risk and living with lymphedema who became involved in dragon boat racing. She proposed that dragon boat paddling is safe and that it does not worsen or create lymphedema when it is performed properly and progressively.

Kwan et al. (2011)[97] also reported in a systematic review that resistance exercise, (weight lifting) did not exacerbate or cause lymphedema. They also included aerobic exercises and report the same findings. They mentioned that progression and proper supervision should be observed.

Brown et al. (2012)[128] compared 295 women either doing progressive weightlifting or having standard care (no description of standard care). While weightlifting exercise was efficacious, musculoskeletal injuries did occur in women with or at risk of BCRL. Their recommendations are to perform the exercises progressively and be monitored by a well-trained rehabilitation therapist.

Cormie et al. (2013)[129] randomised 62 women to either high-load resistance, low-load resistance, or usual care (no description of standard care was). They found that both high-

and low-load resistance were safe to perform in women with BCRL. They also reported that high-load resistance did not increase BCRL or symptom severity.

Schmitz et al. (2010)[135] compared 147 women who were one year post-surgery and at risk of BCRL. They were randomised to either weight lifting exercise or no exercise and were followed for a period of one year. They found that in the group performing progressive weight lifting exercises, arm swelling was less likely to occur then in the no exercise group.

Manual lymph drainage (MLD)

Three systematic reviews investigated the efficacy of manual lymph drainage (MLD) in the treatment of BCRL[87;95;101] and two RCTs[112;115]. The systematic reviews reached different conclusions while the two RCTs have similar findings. Most of the RCTs included in the systematic reviews were either discussed in the initial review or here[50;52;58;61;65;115;145].

Ezzo et al. (2015)[87] addressed the efficacy and safety of MLD in treating BCRL. They reviewed six RCTs. They concluded that MLD is safe, well tolerated and may offer additional benefit when it is combined with compression bandaging. MLD is also beneficial in reducing symptoms of pain and heaviness, but results were contradictory for ROM and inconclusive for QOL.

Huang et al. (2013)[95] investigated if MLD could prevent or manage BCRL. Their review included 10 RCTs with 566 participants. Their findings suggest that the use of MLD, in addition to compression and exercise therapy, is unlikely to produce a significant reduction in BCRL.

Stuiver et al. (2015)[101] reviewed conservative interventions in the prevention of BCRL. Of the 10 RCTs included, four addressed the use of MLD. They concluded that no firm conclusion can be drawn on the effectiveness of interventions containing MLD.

Bergmann et al. (2014)[112] randomized 57 participants into two groups, where both groups received bandages, skin care and remedial exercises, and the intervention group was

supplemented with MLD. They found that both groups were able to reduce BCRL, pain intensity, and improved ROM. However, MLD did not significantly increase the reduction of volume excess.

Devoogdt's et al. (2011)[115] RCT is reported in Huang (2013)[95] and Stuiver (2015)[101] systematic reviews. Devoogdt et al. (2011)[115] randomized 160 participants, both receiving guidelines and exercise therapy, and where the intervention group also received MLD. No participants had BCRL. They concluded that the addition of MLD to guidelines and exercise therapy did not reduce the risk of developing BCRL.

Combined decongestive therapy (CDT)

Combined decongestive therapy (CDT) is the recognized standard of treatment for BCRL. It includes MLD, bandages, skin care and remedial exercises. As described above for MLD, the four individual components have not proved their individual efficacy. The two systematic reviews performed by Devoogdt et al. (2010)[93] and Lasinski et al. (2012)[98], which respectively included 15 studies (656 participants) and 43 studies (1673 participants), concluded that CDT is effective in reducing BCRL. Lasinski et al. (2012)[98] also reported that CDT improves overall QOL and that continuous use of compression is required to maintain volume reduction.

Buragadda et al. (2015)[113] randomized 60 women with BCRL into either CDT combined with a home program or conventional therapy (MLD, low elastic compression, shoulder mobilization, and deep breathing). They found that both groups improved on all outcomes and in the CDT group combined with a home exercise program recovery was quicker.

Dayes et al. (2013)[114] compared CDT with compression garment alone in 103 participants. Both groups obtained similar arm volume reduction and no differences were found in QOL and arm function. They concluded that they were unable to demonstrate the benefit of CDT versus a more conservative and less time consuming approach.

King et al. (2012)[120] did a pilot study where 21 women with mild to moderate BCRL were randomized to CDT using conventional bandages or CDT using compression

garment. Both groups obtained an arm volume reduction, which was more significant in the bandages group. However, during the time of the intervention, the bandages group had worse upper extremity functional status, being more limited than the compression garment group in performing tasks of daily living.

Pekyvaş et al. (2014)[122] conducted a three-arm pilot study of 45 women with BCRL. Each group received CDT: conventional treatment, with Kinesio Tape®, or with Kinesio Tape® and without bandages. All 3 groups obtained a significant arm volume reduction and participants improved their QOL. Long term effects were observed only in the CDT group combined with Kinesio Tape®.

Intermittent pneumatic compression (IPC)

Intermittent pneumatic compression (IPC) is used in hospital-based or home-based treatment. In their systematic review, Feldman et al. (2012)[94] reviewed 13 articles on different types of IPC. IPC has now evolved and multi-chamber segmented and advanced compression systems are now used. Their findings suggest that IPC devices can be used as an adjunct treatment for BCRL as they are well tolerated with low-to-moderate pressure.

Shao et al. (2014)[100] reviewed seven RCTs (287 participants), and report on the use of IPC in the management of BCRL. They concluded that IPC do procure a significant alleviation of edema and subjective symptoms, as does CDT, with no method being superior to the other. Their review failed to demonstrate the effectiveness of the addition of IPC in the routine management of BCRL, indicating that IPC could be used in the reduction phase of treatment, but not necessarily in the maintenance phase.

Fife et al. (2012)[116] randomized 36 women to advanced IPC or standard IPC, where the advanced IPC had more programming functions and included the thorax; standard IPC only includes the upper limb and has fewer programming functions. They found that for home maintenance, the advanced IPC provides better reduction of arm circumferences and local tissue water than the standard IPC.

Ridner et al. (2012)[123] compared 42 women with BCRL receiving either IPC including truncal, chest, and arm area or IPC including only the arm. Both group had a significant reduction of symptoms. No change in arm circumferences was observed in either group. They concluded that IPC, whether involving the truncal and chest area or not, might be beneficial for BCRL.

Multi-modalities

As described above, exercises, MLD, CDT and IPC have been used as a "single modality" in the treatment of BCRL. However, some evidence combines those single modalities into a "multi-modality" treatment. No standard of therapy was established in the single modalities and none of the multi-modality reviews and RCTs discussed here has investigated the same approach.

Chang et al. (2013)[104] performed a narrative review of exercise, surgical treatment and IPC as a risk reduction or management strategy for BCRL. They report that, as a complement to CDT, exercise and IPC are safe and effective therapies. Cheifetz and Haley (2010)[91] report on almost the same outcomes, but discussed physiotherapy treatment instead of IPC. They had the same findings as Chang et al.(2013)[104], and they stated that exercise should be performed progressively.

Finanne et al. (2015)[106] reviewed 21 systematic reviews and aimed to provide evidence for BCRL treatment effect. They reported that single modalities (e.g. compression garment, IPC, MLD) reduce lymphedema volume, and that they are more effective when they are combined into a treatment program (e.g. CDT). Most importantly, they concluded that large, well-designed RCTs are required to evaluate and compare adequately all treatment modalities.

Gurdal et al. (2012)[117] compared 30 women randomized to either CDT or IPC combined with simple lymphatic drainage (a simpler form of MLD that participants learn to do themselves). They found that both modalities were effective and well tolerated by the participants. IPC combined with simple lymphatic drainage has the advantage that it can be performed at home at any convenient time.

Haghighat et al. (2010)[118] compared CDT, with or without IPC, in 112 women having BCRL. The four components of CDT were performed in both groups, and the IPC group also had 30 minutes IPC. Both groups obtained significant arm volume reduction; however the CDT alone provided better results. Uzkeser et al. (2015)[127] conducted a similar study with 31 participants. Their CDT combined with IPC group received 45 minutes of IPC. Their findings were also significant in arm volume reduction, with no between group differences. They also concluded that the addition of IPC did not contribute in the reduction of BCRL.

In their study, Kim et al. (2010)[119] randomized 40 participants to receive CDT alone or combined with resistance exercise. They found that BCRL reduced and that QOL improved in both groups. A more significant change was observed in the CDT group combined with resistance exercise.

Other modalities

Other modalities aiming at reducing BCRL have emerged over the years, such as low-level laser therapy (LLLT), acupuncture and kinesiology taping. LLLT has been investigated in pilot RCTs by Lau et al. (2009)[121] and by Ridner et al. (2013)[124]. Both concluded that LLLT was effective in reducing BCRL and it may serve as an alternative treatment modality. Acupuncture, as proposed in a pilot RCT by Smith et al. (2014)[125], is acceptable in women with BCRL and may help in stabilizing symptoms related to breast cancer treatments.

Kinesio Tape® was described above and was used in combination with CDT[122]. It was found to be beneficial. Smykla et al. (2013)[126] used a similar approach, where all 65 participants received skin care, IPC, and MLD combined with kinesiology taping, quasi kinesiology taping or bandages. They found that the 3 groups obtained a significant arm volume reduction, and that it was greater in the bandages group. They concluded that kinesiology taping could not replace bandages in BCRL treatment.

Discussion

All studies were rehabilitation oriented. None of the studies included in this updated review used drugs to alleviate pain, shoulder impairment, or edema. Compared to the findings of the earlier reviews, for cancer-related pain, patients still tend to underestimate their symptoms and health care professionals tend to neglect them[147]. From two systematic reviews[90;102] and two RCTs[136;137], therapeutic exercise seems promising in reducing the symptoms of pain. Nevertheless, larger methodological RCTs should be conducted to have a better understanding of cancer-related pain and be able to draw clear conclusions.

Most of the information regarding shoulder impairment in this review is provided by systematic reviews involving the acute post-surgery phase of treatment. There are still debates about whether or not exercises should start in the early stage (e.g. one day post-surgery) or be delayed (e.g. one week post-surgery or after drain removal). This update indicates that rehabilitation exercises are beneficial in addressing ROM issues; however, the best regimen still needs to be defined.

A variety of types of exercise varying from low to high intensity are now used either to reduce the risk of developing BCRL or to treat/maintain it. Similar to the original findings, updating the literature did not provide any new information regarding what is the best exercise regimen and what is/are the best type(s) of exercise to perform in women at risk of or living with BCRL. However, women should be encouraged to perform any type of exercise that they enjoy and it should be adapted and tailored to their new reality, and they need to do it progressively.

The use of MLD remains uncertain as a BCRL risk reduction strategy or for its management. When combined with other modalities, it may be beneficial. None of the RCTs alone or included in the systematic reviews investigated the same MLD intervention, making it difficult to draw firm conclusions. Patients with mild-to-moderate BCRL might be the ones who would benefit more from MLD therapy. MLD is less likely to be a “stand alone” therapy, and only robust methodological RCTs will show whether it has real efficacy or not.

The evidence is more in favor of the use of CDT in the treatment of BCRL. Even if results indicate some benefits of using CDT, none of the reviews and RCTs investigated the same modality of therapy. Thus, recommendation regarding the frequency and length of therapy still need to be addressed through robust methodological RCTs.

New IPC devices that include the truncal/chest area and that offer more programming possibilities could be used as a home-based therapy modality. IPC should be combined with other forms of therapy to obtain the greatest arm volume reduction. Guidelines on the frequency of use, treatment sequences and pressure should be developed through robust methodological RCTs. Newer modalities, such as LLLT and kinesiology taping, might be beneficial, but need further study.

This narrative review discussed arm dysfunction, including pain, ROM impairment, and BCRL, in the post-acute phase of cancer treatment. Arm dysfunction needs to be addressed early on in the continuum of care, before it becomes a chronic condition.

In the original review, we concluded that there was a lack of high quality evidence-based research, and this remains true with this update. In addition, all reviews included here also had the same conclusion. Even if CDT is considered the standard of care for BCRL, the greatest results will be obtained through defining what the best therapy is for each individual, as the person needs to comply and adhere to the therapy in order to obtain significant results. Even if guidelines define what the best regimen is for therapy and/or exercise for arm dysfunction, it might not ever be possible to have a “one size fits all” program.

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Table 9. Example of the search strategy (2009-2015)
Database: Ovid MEDLINE(R) <June Week 3 2009 to November Week 2 2015>

#	Search	Results
1	breast cancer.mp. or Breast Neoplasms/	210748
2	breast neoplam*.mp.	2
3	1 or 2	210748
4	survivor*.mp. or Survivors/	4819
5	4 and 3	61436
6	medication.mp.	139925
7	drug.mp. or Pharmaceutical Preparations/	1320914
8	drug therapy.fs.	9908
9	8 or 6 or 7	1412098
10	Exercise Therapy/ or Physical Therapy Modalities/ or physiotherapy.mp.	40164
11	rehabilitation.mp. or Rehabilitation/	87251
12	11 or 10	117790
13	manual lymph drainage.mp.	106
14	combined decongestive therapy.mp.	8
15	complete decongestive physiotherapy.mp.	19
16	complete physical therapy.mp.	2
17	complex lymphatic therapy.mp.	0
18	Massage/ or massage.mp.	7140
19	18 or 16 or 13 or 17 or 15 or 14	7243
20	Intermittent Pneumatic Compression Devices/ or pneumatic compression.mp.	989
21	intermittent pneumatic pump.mp.	1
22	pneumatic compression hose.mp.	1
23	22 or 21 or 20	989
24	hosiery.mp.	158
25	Bandages/ or bandages.mp.	9671
26	multi layer bandages.mp.	3
27	compression sleeve.mp.	23
28	compression garment.mp.	79
29	27 or 25 or 28 or 24 or 26	9820
30	exercise.mp. or Exercise/ or Exercise Movement Techniques/	182015
31	stretching.mp.	17367
32	30 or 31	197734
33	32 or 23 or 19 or 9 or 29 or 12	1698558
34	pain.mp. or Pain/	406508
35	shoulder impairment.mp. or "Range of Motion, Articular"/	24
36	shoulder limitation.mp.	33356
37	shoulder mobility.mp.	169
38	articular range of motion.mp.	22
39	38 or 35 or 36 or 37	33489
40	edema.mp. or Edema/	74023
41	oedema.mp.	14317
42	lymph$edema.mp. or Lymphedema/	5391
43	42 or 40 or 41	88026
44	39 or 34 or 43	508791
45	33 and 44 and 5	173
46	Year limitation June week 3 2009 to November Week 2 2015	133

Table 10. Reviews included (2009-2015)

Main author (year)	Type of review	# articles included	N (range)	Years studies included	Conclusion
Chan (2010)[88]	Systematic	6 RCTs	429 (27-205)	2000 – 2009	Early onset of training does not affect the incidence of post-operative lymphedema, and is a valuable method in avoiding deterioration in ROM.
Chang (2013)[104]	Narrative	N/A	N/A	2004 – 2010	In complement to CDT, exercise and IPC are safe and effective therapies. Surgical treatments for lymphedema require life-long compression therapy and are beneficial in carefully selected patients.
Cheifetz (2010)[91]	Clinical	21	N/A	2005 – 2009	CDT, physiotherapy and exercise are safe and beneficial treatments for the management of BCRL. Resistive exercises are beneficial and safe when they are performed progressively.
De Groef (2015)[90]	Systematic	18 RCTs	2389 (30-344)	Until 10-2012	Physiotherapy (passive mobilization, exercise, and manual stretching) is effective in improving shoulder ROM post-breast cancer surgery. Exercises are also beneficial to reduce post-operative pain. There is still a debate regarding whether the exercise should start early for shoulder ROM recovery or should be delayed to avoid prolonged wound healing.
Devoogdt (2010)[93]	Systematic	15	656 (14-80)	1980 – 2005	CDT is effective in reducing BCRL. The effectiveness of its different components needs to be further assessed individually with high-quality studies. The long-term effects of IPC need to be proven.
Dieli-Conwright (2015)[92]	Narrative	31	N/A	N/A	Participating in exercise after cancer-related treatments provides beneficial effects on physical and emotional well-being. It also favors lymphedema management and maintains bone mineral density.
Ezzo (2015)[87]	Systematic	6 RCTs	N/A	Until 05- 2013	MLD is safe, well tolerated and may offer additional benefit when combined with compression bandaging to reduce BCRL. MLD findings were contradictory for ROM and inconclusive for QOL. MLD helped to reduce symptoms of pain and heaviness.
Feldman (2012)[94]	Systematic	13	N/A	2004 – 2011	In low to moderate pressure IPC devices are well-tolerated and could be used as an adjunct treatment for BCRL
Finnane (2015)[106]	Review of reviews	21 Reviews	N/A	1998 – 2014	Compression garments, IPC and MLD are reported to reduce lymphedema volume, and are more effective when a combined treatment program, such as CDT, is performed.
Harris (2012)[105]	Narrative	N/A	N/A	N/A	Resistance exercise performed adequately and progressively, such as dragon boat paddling, is safe for breast cancer survivors and does not worsen lymphedema.

Table 10. Reviews included (2009-2015) (continued)

Main author (year)	Type of review	# articles included	N (range)	Years studies included	Conclusion
Huang (2013)[95]	Systematic	10 RCTs	566 (24-158)	Until 12-2012	The addition of MLD to compression and exercise therapy for BCRL is unlikely to produce a significant reduction in arm volume.
Hurlow (2012)[96]	Systematic	3 RCTs	88	2008 – 2011	The use of transcutaneous electrical nerve stimulation (TENS) for cancer-related pain is inconclusive.
Kwan (2011)[97]	Systematic	19	N/A	2004 – 2010	Resistance exercise does not exacerbate or cause lymphedema. Exercise should be performed progressively and with proper supervision throughout the continuum of care of cancer treatments.
Lasinski (2012)[98]	Systematic	43	1673 (29-537)	2004 – 2011	CDT is effective in all lymphedema stages and improves overall QOL. Continuous use of compression is required after CDT to maintain volume reduction.
Loh (2015)[89]	Review of systematic reviews	7 reviews	N/A	2009 – 2014	Physical impairment (e.g. shoulder ROM and lymphedema) post-breast cancer surgery is improved with rehabilitation exercise. Results were inconclusive regarding methods to improve psychosocial, cognitive and occupational outcomes.
McNeely (2010)[99]	Systematic	24 RCTs	2132	Until 08-2008	Shoulder ROM can be improved with exercise. Exercise can start early post-operative, however wound drainage volume and duration might increase, suggesting carefully introduction or delay to 1 week post-surgery.
Pan (2014)[103]	Systematic	9 RCTs	322 (19-73)	Until 11-2014	Tai Chi Chuan has positive but moderate benefits in upper limb functional mobility in the short term.
Shao (2014)[100]	Systematic	7 RCTs	287 (23-112)	1990 - 2013	Both CDT and IPC lead to a significant alleviation of edema and subjective symptoms; no method is superior to the other, and IPC added to the routine management of BCRL failed to demonstrate its effectiveness.
Stuiver (2015)[101]	Systematic	10 RCTs	1205	Until 05-2013	No firm conclusion about the effectiveness of interventions containing MLD can be drawn. Starting shoulder-mobilising exercises early after surgery compared to a delayed start does not lead to a greater incidence of lymphedema, and favors a better ROM. Progressive and monitored resistance exercise does not increase the risk of developing lymphedema.
Tatham (2013)[102]	Systematic	6	464 (8-257)	Until 04-2011	Shoulder pain may be alleviated with therapeutic exercise.

Table 11. Reviews excluded (2009-2015)

Main author (year)	Type of review	# articles included	N (range)	Years studies included	Conclusion	Reason for exclusion
Bradt (2015)[107]	Systematic	3 RCTs	207	Until 07-2014	No conclusion regarding depression, stress, anxiety, fatigue and body image can be drawn for persons participating in dance/movement therapy	Not reporting on outcomes.
Cormier (2012)[110]	Systematic	20	1206 (9-732)	2004 – 2010	In well selected patients, different types of surgeries are beneficial and reduced lymphedema. Daily use of compression garments is required after all surgeries.	Surgical management of BCRL.
Khan (2012)[108]	Systematic	2 RCTs	262	Until 12-2011	Functional ability, psychosocial adjustment and participation in social activities might be improved through multidisciplinary rehabilitation.	Not reporting on outcomes.
Lopez Penha (2013)[111]	Systematic	10	248 (6-127)	2000 – 2012	Only positive findings with no complications regarding microsurgical techniques for BCRL are reported in small sample size studies.	Surgical management of BCRL.
Ridner (2012)[109]	Systematic	16 RCTs	3494	2004 – 2011	Lymphedema requires a lifetime management; however there is little evidence on appropriate self-management methods.	Not reporting on outcomes.

Table 12. Details of included trials (2009-2015)

Study ID	Randomization	Intervention	Outcome	Conclusion	Quality
Bergmann (2014)[112]	No mention on the procedure	MLD vs no MLD N = 28 vs 29 Both groups: bandages, skin care and remedial exercises, 3x/wk, when plateau reached, bandaging changed to compression garment	Arm volume ROM	Both groups were able to reduce volume excess and pain intensity, and improve ROM. MLD did not significantly increase the reduction of volume excess.	0/5 5/10*
Brown (2012)[128]	Computer software	Progressive weightlifting vs Standard care N = 147 vs 148 Both groups had persons with and at risk of BCRL Program: 2x/wk	Strength Physical activity ROM Arm volume Musculoskeletal injury	Musculoskeletal injuries occur in women with or at risk of BCRL when performing weightlifting exercises. Progressive and monitored exercises should be performed under the guidance of a well-trained rehabilitation therapist.	2/5 4/10*
Buragadda (2015)[113]	No mention on the procedure	CDT vs Conventional therapy N = 30 vs 30 CDT: MLD, compression garment, remedial exercise, home program Conventional: MLD, low elastic compression, shoulder mobilization, deep breathing exercise Both groups: 5x/wk for 6 weeks	Arm volume Arm disability Pain	Home exercise program, combined to CDT, hastens recovery. Both groups improved in all outcomes.	1/5
Cantarero-Villaneuva (2012)[136]	Computer-generated numbers	Water exercise vs Usual Care N = 33 vs 33 Water: 3x/wk for 8 weeks	Pain Pressure pain threshold	Only the water exercise group experienced significantly less pain.	2/5 7/10*

*PEDro score given in the database

Table 12. Details on included trials (2009-2015) (continued)

Study ID	Randomization	Intervention	Outcome	Conclusion	Quality
Cormie (2013)[129]	Computer program	High-load resistance vs low-load resistance vs Usual care N = 22 vs 21 vs 19 High/Low-load: 2x/wk for 3 months	Arm volume Symptom severity Physical function QOL	High-load resistance exercise did not increase BCRL or symptom severity. Both high- and low-load resistance may be safe for women with BCRL.	4/5 7/10*
Dayes (2013)[114]	Computer program	CDT vs Compression garment N = 56 vs 39 CDT: MLD + bandages, after 4 weeks fitted for compression garment Compression garment: 30-40 mmHg sleeve + glove, 12 hrs/day Both groups: skin care, exercise	Change of excess arm volume QOL Arm function	CDT and compression garment obtained similar arm volume reduction. No differences were found in secondary outcomes (QOL, arm function).	4/5 8/10*
Devoogdt (2011)[115]	Permuted block	MLD vs No MLD N = 75 vs 79 Both groups: guidelines and exercise therapy	Arm volume HRQOL	The addition of MLD to guidelines and exercise therapy did not reduce the risk of developing BCRL.	4/5 8/10*
Fernandez-Lao (2012)[137]	Computer-generated numbers	CUIDATE vs Control N = 22 vs 21 CUIDATE: multidimensional physical therapy for 8 weeks	Pain Pressure pain threshold	Multidimensional physical therapy intervention (stretching and endurance exercises, relaxation, and massage) induced changes in nociceptive processing and reduced neck/shoulder/ axillary pain compared to usual care.	4/5 8/10*

*PEDro score given in the database

Table 12. Details on included trials (2009-2015) (continued)

Study ID	Randomization	Intervention	Outcome	Conclusion	Quality
Fife (2012)[116]	No mention on the procedure	APCD vs SPCD N = 18 vs 18 APCD: Flexi-touch system, SPCD: Bio Compression 2004 Both groups applied pneumatic compression 1h/day for 12 weeks and worn 23hrs/day compression garment	Arm circumferences Local tissue water	For home maintenance, advanced pneumatic compression (APCD) provides better outcomes than standard pneumatic compression (SPCD).	0/5 4/10*
Gurdal (2012)[117]	Computer-generated numbers	CDT vs IPC + SLD N = 15 va 15 Both groups: 3x/wk for 6 weeks	Arm volume QOL	Both modalities are effective and tolerable. Greater improvement in the CDT group on QOL, but between group differences is not significant. IPC has the advantage of being performed at home.	1/5 5/10*
Haghighat (2010)[118]	Block randomization	CDT vs CDT + IPC N = 56 vs 56 Both groups: 5x/wk for 10-15 sessions; after fitted for compression garment and bandaging at night	Arm volume Subjective symptoms	CDT, with or without ICP, significantly reduces BCRL; however, CDT alone provided better results.	2/5 6/10*
Johansson (2013)[130]	Block randomization	Water-based exercise vs Control N = 15 vs 14 Water: 2-3x/wk for 8 weeks	Feasibility Lymphedema status Shoulder ROM	Water-based exercises are safe for BCRL and improved shoulder ROM.	4/5 7/10*
Kim (2010)[119]	No mention on the procedure	CDT + Resistance exercise vs CDT N = 20 vs 20 CDT: 5x/wk for 2 weeks; self-administered CDT for 6 weeks Resistance exercises for 8 weeks	Arm volume HRQOL	BCRL reduced and QOL improved in both groups; although more significantly in the CDT + resistance exercise.	0/5 4/10*

*PEDro score given in the database

Table 12. Details on included trials (2009-2015) (continued)

Study ID	Randomization	Intervention	Outcome	Conclusion	Quality
King (2012)[120]	Random number table	CDT (garment) vs CDT (bandages) N = 10 vs 11 Both groups : 5x/wk for 2 weeks	Arm volume Symptom Function	Both groups obtained an arm volume reduction, which was greater in the bandages group.	3/5
Lau (2009)[121]	Bebbington method	Low-level laser therapy (LLLT) vs No treatment N = 11 vs 10 LLLT: 3x/wk for 4 weeks	Arm volume Tissue resistance Disability	LLLT was effective in reducing BCRL and tissue hardness. Disability also improved.	2/5 6/10*
Lee (2009)[138]	Block randomization	Scapula exercise vs General exercise vs Control N = 16 vs 16 vs 18 Both groups : 1x/wk for 8 weeks	ROM Strength Pain Disability QOL Depression	Scapula exercise significantly improved pain, physical function, social function and QOL, and there was a trend toward significance in ROM. However, there was no between group significance.	3/5 6/10*
Letellier (2014)[131]	Block randomization	ALT + Exercises vs Exercises N = 13 vs 12 ALT : 1x/wk for 12 weeks Exercises : DVD performed daily	Feasibility Arm volume Grip strength Disability QOL	Feasible to conduct a larger RCT. ALT did not worsen BCRL and may serve as a safe alternative. Grip strength improved in both groups. Disability and pain only improved in the ALT group.	3/5 6/10*
Loudon (2014)[132]	Computer-generated random number system	Yoga vs Usual care wait-list N = 15 vs 13 Yoga: 1x/wk for 8 weeks + yoga DVD daily	Arm volume Tissue induration Sensation Pain / Fatigue / QOL	Yoga did not exacerbate BCRL and improved tissue induration and QOL.	3/5 6/10*
McClure (2010)[133]	Randomization matrix (sealed envelope)	Exercise + relaxation vs Usual care N = 16 vs 16 Exercise: 2x/wk for 5 weeks + daily at home; followed by 3 months daily at home	Arm volume ROM Mood QOL	Exercise and relaxation decrease BCRL, improve ROM, mood and QOL.	2/5 5/10*

*PEDro score given in the database

Table 12. Details on included trials (2009-2015) (continued)

Study ID	Randomization	Intervention	Outcome	Conclusion	Quality
Pekyavaş (2014)[122]	Random allocation software	CDT (bandage) vs CDT (bandage + kinesio Tape) vs CDT (kinesio tape, no bandage) N = 14 vs 13 vs 14 All groups: 5x/wk for 2 weeks, after fitted for compression garment	Arm volume QOL	All 3 groups obtained a significant arm volume reduction and improved QOL. Only the CDT + kinesio tape group had a decreasing effect during and at 4 weeks post-treatment.	3/5 6/10*
Ridner (2012)[123]	Permuted block	Truncal/chest/arm IPC vs Arm IPC N = 21 vs 21 Both groups: 30 days home self-care IPC	Physical and Psychological symptoms Function Circumferences	Symptoms significantly reduced in both groups. No change in arm circumferences in both groups. Both forms of IPC might be beneficial for BCRL.	2/5
Ridner (2013)[124]	Permuted block	MLD vs LLLT vs MLD + LLLT N = 15 vs 16 vs 15 3 groups: compression bandages after each treatment	Arm volume Physical and Psychological symptoms QOL	LLLT with bandages may offer time saving therapeutic option to MLD (20 minutes vs 40 minutes). The 3 groups obtained significant volume reduction, which could be accounted for by the compression bandaging.	1/5 5/10*
Schmitz (2010)[135]	Computer program	Weight lifting vs No exercise N = 72 vs 75 Weight: 2x/wk for 13 weeks supervised exercise, unsupervised from week 14 to 52.	Arm volume Anthropometric measures	Arm swelling is less likely to occur when progressive weight lifting is performed compared to no exercise.	3/5 8/10*
Smith (2014)[125]	Computer-generated	Acupuncture vs Usual care N = 9 vs 8 Acupuncture: 2x/wk for 4 weeks, then 1x/wk for 4 weeks Both groups: compression garment	Feasibility study Arm volume Symptoms	Acupuncture was an acceptable intervention and it stabilizes symptoms.	2/5

*PEDro score given in the database

Table 12. Details on included trials (2009-2015) (continued)

Study ID	Randomization	Intervention	Outcome	Conclusion	Quality
Smykla (2013)[126]	Computer-generated	Kinesiology tape (KT) vs quasi KT vs Bandages N = 20 vs 22 vs 23 3 groups: skin care, IPC, MLD; 3x/wk for 4 weeks	Arm volume	The 3 groups obtained a significant arm volume reduction, and it was greater in the bandages group. KT should not replace bandages.	2/5 6/10*
Tidhar (2010)[134]	Block sampling	ALT vs Self-management N = 16 vs 32 ALT: 1x/wk for 12 weeks	Arm volume QOL	ALT has immediate significant influence in reducing limb volume, but no long-term effects are noted, and it improved QOL.	3/5 7/10*
Uzkeser (2015)[127]	Alternate allocation based on admittance	CDT + ICP vs CDT N = 16 vs 15 Both groups: 5x/wk for 3 weeks	Arm volume Pain	Both group significantly reduced arm volume, with no significant between group difference. Pain: no between group differences, within group change significant.	2/5 5/10*

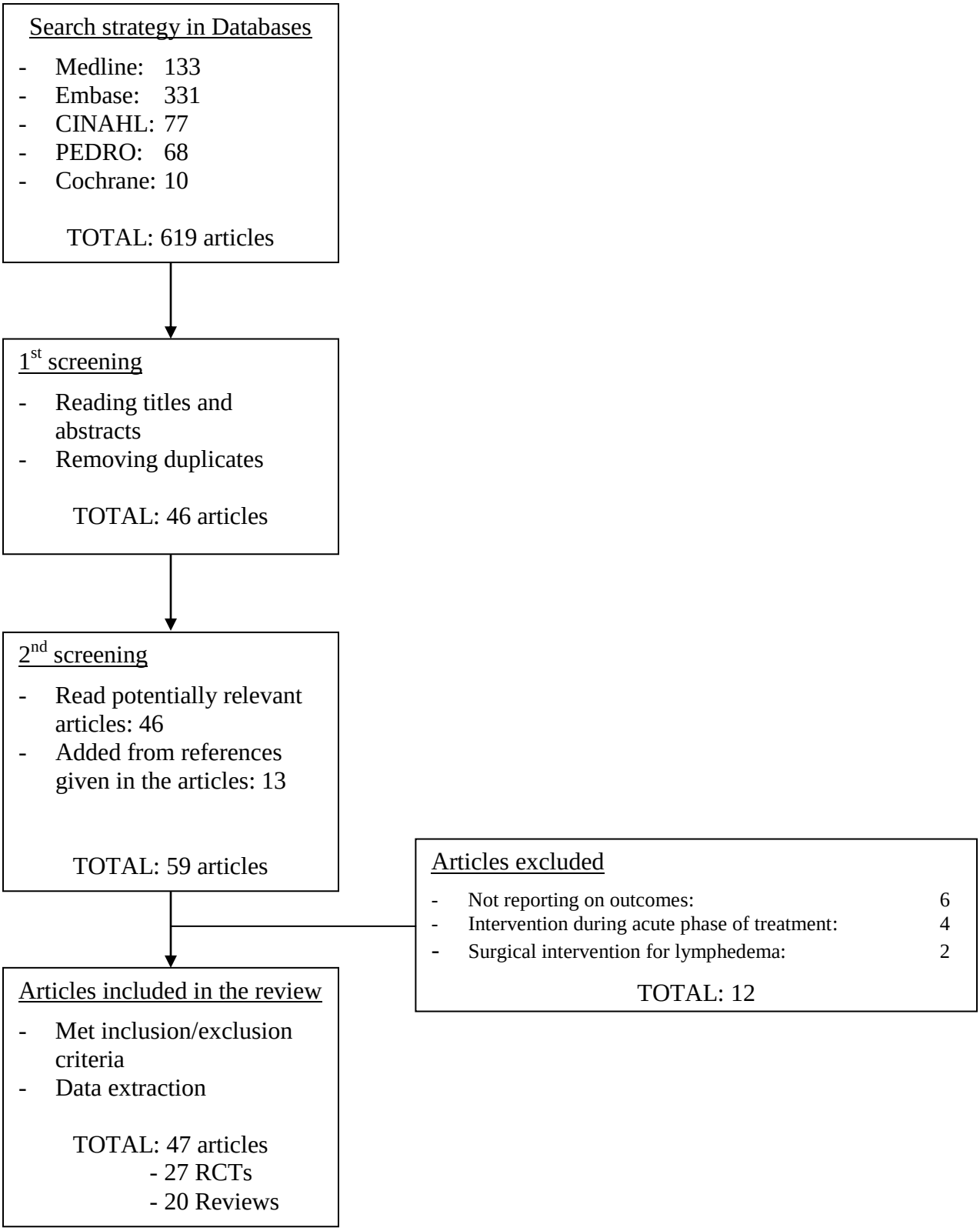
*PEDro score given in the database

Table 13. Details of excluded trials (2009-2015)

Study ID	Randomization	Intervention	Outcome	Reason for exclusion	Quality
Anderson (2012)[143]	No mention on the procedure	Comprehensive program vs Usual care N = 52 vs 52 Followed every 3 months for 18 months (N = 43 vs 39) Program: tailored exercise (2x/wk-3 months; 7-12 months encouraged to continue), lymphedema prevention, patient and diet education, and counselling Usual care: patient education	Physical function and HRQOL Arm volume	Intervention during acute phase (within 3 months post-surgery)	1/5 4/10*
do Amaral (2012)[144]	Computer generated sequence	Excercise + manual therapy vs Exercise N = 65 vs 66 Exercise: 3x/wk for 4 weeks Manual therapy: 2x/wk for 4 weeks	ROM Function	Intervention during acute phase (started 1 day post-surgery)	2/5 5/10*
Fernandez-Lao (2012)[140]	Coin flip	Myofascial massage vs Education N = 20 Myofascial: 40 minutes massage	Pressure pain threshold Saliva sample Attitude toward massage	Does not assess arm dysfunction	1/5 6/10*
Fernandez-Lao (2013)[141]	No randomization	Control vs Land vs Water exercise N = 34 vs 31 vs 33 Land: 3x/wk for 8 weeks Water: modified land exercise for 8 weeks	Body composition QOL	Does not assess arm dysfunction and not an RCT	0/5
Kilbreath (2012)[139]	Block randomization	Exercise program vs Control N = 81 vs 79 Exercise : 1x/wk for 8 weeks + home program	Arm symptoms ROM Strength Arm volume	The supervised exercise program did not reduce self-reported arm symptoms compared to written information. However, improvement in ROM was greater in the exercise group.	4/5 8/10*
Irwin (2015)[142]	No mention on the procedure	Exercise vs Usual care N = 61 vs 60	Arthralgia Pain Physical activity	Does not assess arm dysfunction (aromatase inhibitor-induced arthralgia)	0/5 6/10*
Torres Lacomba (2010)[145]	Computer generated sequence	Physiotherapy + Education vs Education N = 59 vs 57 Both groups: 3x/wk for 3 weeks	Arm volume	Intervention during acute phase (started 1 day post-surgery)	2/5 5/10*

* PEDro score given in the database

Figure 3. Flow chart (2009-2015)



Chapter 6: Integration of Manuscripts 2 and 3

Research questions of Manuscripts 2 and 3

Manuscript 2:

To estimate, for women post-acute treatment for breast cancer, the extent to which medication or physiotherapy techniques reduce pain, shoulder mobility and/or edema.

Manuscript 3:

To estimate the extent to which the content of the EORTC QLQ-C30 and EORTC QLQ-BR23 goes beyond functioning and include global feeling of well-being.

Integration of Manuscripts 2 and 3

The first two manuscripts summarized the literature in order to gain knowledge about arm impairment related to breast cancer treatment. Manuscript 2 identified systematically sequelae of breast cancer and the extent to which there are modalities to treat them.

Manuscript 3 moves to the "construct verification" part of the thesis and investigates whether or not two legacy questionnaires (EORTC QLQ-C30 and BR23) capture quality of life as they claim. In fact, we found, through a mapping exercise linking the items to the ICF Framework, that only the core questionnaire (QLQ-C30) goes beyond functioning and includes global feeling of well-being.

Chapter 7: Manuscript 3

Content verification of the EORTC QLQ-C30/EORTC QLQ-BR23 with the International Classification of Functioning, Disability and Health

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Content verification of the EORTC QLQ-C30/EORTC QLQ-BR23 with the International Classification of Functioning, Disability and Health

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Abstract
Purpose The aims of this study were to estimate the extent to which the content of the EORTC QLQ-C30 and EORTC QLQ-BR23 goes beyond functioning and include global feeling of well-being.
Methods Respectively, 21 and 13 healthcare professionals agreed to link the EORTC QLQ-C30 and EORTC QLQ-BR23 to the ICF. Mappers were asked to independently identify appropriate codes for the corresponding items of the EORTC QLQ-C30 and EORTC QLQ-BR23 following standardized linking rules and methodology. A Delphi technique was used in order to reach consensus. The threshold of agreement was 70 %. Rounds were stopped when the threshold was obtained or when it was clear that no consensus would be reached.
Results A total of 25 items out of 30 were endorsed for the EORTC QLQ-C30: 8 items were endorsed at the 4-digit level, 15 items at the 3-digit level, and 2 items reach the consensus that the items were not cover within the ICF. Only 2 items out of 23 did not reach consensus in the EORTC QLQ-BR23. Of the 21 items endorsed, 3 items were endorsed at the 5-digit level, 10 items at the 4-digit level, and 8 at the 3-digit level.
Conclusion This study demonstrates that the content of the EORTC QLQ-C30 goes beyond functioning and includes global feeling of well-being and that the content of the EORTC QLQ-BR23 is related to functioning. Furthermore, linking items to the ICF framework could be an additional method to validate the content of health-related questionnaires.

Keywords ICF · Mapping · Cancer · Breast cancer · QOL

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Introduction

Cancer is a disease affecting the women worldwide [1–3]. In Canada, in the last three decades, the number of diagnosed cancer has more than doubled, such that approximately 90,000 persons were newly diagnosed in 1985 compared to 191,300 persons in 2014 [4]. Moreover, cancer now surpasses cardiovascular disease as the leading cause of death, responsible for nearly 30 % of all deaths [4]. The risk of cancer increases with age and the population is aging [4]; coupled with improved survival, owing to advances in early diagnosis and treatment, the number of people living with the sequelae of cancer will increase.

The most common treatment for breast cancer is to remove the tumor burden by a breast-conserving surgery, followed by, in 84 % of the cases, radiation therapy

treatments [5]. Additionally, approximately 25 % of the women will receive chemotherapy [5]. All of these cures may lead to short- and/or long-term impairments of organ system function, pain, lymphedema, musculoskeletal disorders and/or psychosocial issues [6–11]. This could ultimately limit the patients in their participation in activities of daily living and/or in physical activities [6, 11], and represent a source of long-term disability [9–15].

A population-based study (NHANES) estimated the prevalence of participation restrictions and physical performance limitations in the general population, and also among recent (<5 years since diagnosis) and long-term (≥5 years) cancer survivors [6]. Their findings revealed that, respectively, cancer survivors were 1.5–1.8 (53 vs. 21 %) and 1.4–1.6 (31 vs. 13 %) times more likely to have physical performance limitations and participation restrictions than people with no history of cancer. This indicates that there is a need to address these components of the quality of life (QOL) in cancer survivors both in the short and long term [9, 16, 17].

QOL is a concept broader than just health and includes components of material comforts, health and personal safety, relationships, learning, creative expression, opportunity to help and encourage others, participation in public affairs, socializing, and leisure [18]. The World Health Organization (WHO) has defined QOL as "individuals' perception of their position in life in the context of the culture in which they live and in relation to their goals, expectations, standards and concerns." In the context of health research, QOL goes beyond a description of health status, but rather is a reflection of the way that people perceive and react to their health status and to other, non-medical aspects of their lives [19]. According to Petersen and colleagues (2008) [20], some studies have demonstrated that, after a diagnosis of cancer, QOL can paradoxically improve because the patient will reconsider their priorities and life goals, a phenomenon termed "response shift" [21]. On the other hand, it is also suggested that cancer survivors will show a poorer QOL compared to age-matched controls, mainly for the reason that cancer treatments may be an overwhelming burden [20, 22]. Therefore, there is an emerging emphasis on providing better long-term health care to these individuals and measuring the impact of this care. Cancer-specific QOL measures would be ideal for this purpose.

The European Organization Research and Treatment of Cancer (EORTC) have created one of the most widely used measures assessing QOL among people with cancer [23]. The EORTC QLQ-C30 questionnaire has additional modules that are available for addressing aspects of QOL of particular importance to people with specific cancers. The use of the main questionnaire with a specific module enhances the ability to detect clinically meaningful differences in QOL over time. For the purposes of this study, the interest is in the EORTC QLQ-C30 [23], and its specific module on breast cancer, the EORTC QLQ-BR23 [24].

The EORTC QLQ-C30 is a 30-item questionnaire divided into five functional scales (physical, role, cognitive, emotional, and social), three symptoms scales (fatigue, pain, and nausea and vomiting), six single-item questions, and a global health and QOL scale. High internal consistency, good inter-scale correlation and discriminative validity have been proven [23].

The EORTC QLQ-BR23 [24] questionnaire contains 23 items divided into two functional scales (body image and sexuality) and three symptom scales (arm symptoms, breast symptoms, and systemic therapy side effects). This supplementary module has been found to have a high internal consistency for four out of five scales and good known-group discriminative ability [24].

The psychometric properties of the two indices of interest are well established. Content validity, which is the extent to which items reflect the relevant and important aspects of the content it intends to represent, is an important feature in the development of items for a health index [25]. An additional requirement is that the content is specific enough to reflect the granularity of the construct being assessed. Given that the EORTC cancer-specific indices claim QOL as the construct of interest and have constructed the content to capture symptoms, function, and global QOL, it is of relevance to verify that this is indeed the content.

The WHO's International Classification of Functioning, Disability and Health (ICF) provides a universal conceptual framework for describing functioning at the level of granularity deemed essential for this construct. Practitioners and researchers in the field of rehabilitation are making efforts toward the use of a universal conceptual framework and common language to inform both clinical practice and research [26–28]. In order to support claims of content validity, they have proposed the linkage of specific content to be assessed to the ICF [25].

The ICF is a bio-psycho-social model of functioning, disability, and health identifying relevant constructs with a standard coding system for each category with the construct [29]. All of the positive and negative components are, respectively, grouped under the umbrella term *"functioning"* and *"disability"* (Table 1) [29]. The ICF provides a hierarchical coding system where 1424 unique categories of health outcomes are classified. Within the ICF, four components are represented as follows: "b" signifying body function, "s" body structure, "d" activity and participation, and "e" environmental factors. Each letter is followed by a one- up to a five-digit code representing the level of granularity captured [29]. Granularity is also used to assess whether the items represent one or multiple constructs [25].

Table 1 Components of functioning and disability

Functioning	Disability
Body structure: anatomical component of a body (e.g., joint)	Impairment: problems in body function or structure (e.g., limited range of motion)
Body function: physiological component of a body (e.g., range of motion)	
Activity: execution of a task (e.g., walking)	Activity limitations: difficulties a person may have in executing activities
Participation: involvement of an individual in life situations from the perspective of society (e.g., working)	Participation restrictions: problems a person may experience in involvement in life situations

In order to offer clinicians and researchers with comprehensive but concise group of categories to describe the patient's global function considering a bio-psycho-social model, the ICF group has created Core Sets [15]. Brach et al. [12] developed the ICF Breast Cancer Core Set. It assesses each relevant domain and category within domain, and it provides a systematic framework covering the spectrum of breast cancer-related impairments, limitations in activity, and restrictions in participation.

The ICF framework has been mainly applied in rehabilitation; however, it is closely related to the medical model of health-related QOL proposed by Wilson and Cleary (W–C) [30]. The W–C links physiological variables to symptoms, functional status, general health perception, and overall QOL recognizing also the role of personal and environmental factors. Valderas and Alonso [31] have demonstrated that these two models can be used together: The ICF model provides codes for the first three levels of the W–C. Ferrans has shown that the items of the EORTC QLQ-C30 fit under the broad rubrics of W–C model [32].

The purpose of this study is to go a step further and contribute additional evidence for the content validity of the EORTC by estimating the extent to which the items of the EORTC QLQ-C30 and EORTC QLQ-BR23 reflect the specificity of functioning, disability, and health as set out by the ICF framework.

Methods

A structured ICF mapping protocol previously developed [33] was applied using two separate groups of mappers. One group ($n = 21$) mapped the EORTC QLQ-C30, and a second group ($n = 13$) mapped the EORTC QLQ-BR23. Briefly, the mapping protocol stipulates that multiple mappers independently choose the best ICF code for each item to be mapped using the linking rules established by Cieza et al. [34, 35]. A Delphi process is subsequently used to gain consensus on the most accurate code for each item.

All mappers received a training package prior to the mapping exercise, a presentation of the ICF framework, definitions, coding structure, and coding rules. Mappers were sent an electronic file for recording their codes and were asked to independently assign alphanumeric codes that they felt best corresponded to each of the items. The percentage of agreement was calculated for all suggested codes. Agreement greater than or equal to 70 % was selected a priori as the threshold needed for a code to be endorsed. If a code was endorsed at the higher level of granularity (e.g., 4-digit or 5-digit level), then the 3-digit root of that code was automatically endorsed. For items with less than 70 % agreement, mappers were sent an anonymous summary giving the suggested codes and percent of agreement. They were then asked to review the codes they had decided on. The process was repeated until 70 % agreement was reached, or it was determined that agreement would not be achieved. This is based on the consideration that rater agreement is an indicator of rater consistency and a well-accepted guideline for internal consistency is a value between 0.7 and 0.9 [36, p. 83]. In addition, with 13 raters, the probability that 9 would endorse an item (70 % endorsement) is unlikely to occur by chance alone ($p < 0.04$), using the normal approximation to the binomial distribution and assuming a probability of endorsement of ≤ 0.04, likely with many raters.

Content density (number of meaningful concepts/total number of items) [37] was calculated for both questionnaires. A content density value of 1 indicates that each item of an instrument contains only one meaningful concept. If the value is higher, it indicates that more concepts are contained within a single item. In addition, item efficiency per category was calculated (1/number of items to cover one ICF category) [38] with a value of 1 meaning no redundancy and hence optimal efficiency.

Results

The 21 professionals (doctors, nurse, physiotherapists, occupational therapists, kinesiologist, epidemiologists, and psychologist) who mapped the EORTC QLQ-C30 questionnaire all had experience with research and measurement and clinical experience with a variety of patient populations; 3 had specific expertise with cancer. The 13 professionals who mapped the EORTC QLQ-BR23 (physiotherapists, occupational therapist, kinesiologists, and clinical manager) had similar backgrounds; 3 had specific clinical or research experience in breast cancer. All mappers had on average 3.4 years (range 0–23 years) of

Table 2 Degree of endorsement to ICF content of the EORTC QLQ-C30 items

Sub-scale	Items (number)	4-digit level (% endorsed)	3-digit level (% endorsed)
PF	3. Do you have any trouble taking a short walk outside of the house?	d4500 (100)	d450 (100)
PF	2. Do you have any trouble taking a long walk?	d4501 (95)	d450 (100)
SI-AP	13. Have you lacked appetite?	b1302 (95)	b130 (95)
CF	20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	b1400 (86)	b140 (100)
NV	14. Have you felt nauseated?	b5350 (86)	b535 (90)
NV	15. Have you vomited?	b5106 (86)	b510 (90)
FA	10. Did you need to rest?	b4552 (70)	b455 (95)
EF	23. Did you feel irritable?	b1263 (70)	b126 (85)
RF	7. Were you limited in pursuing your hobbies or other leisure time activities?		d920 (100)
SI-SL	11. Have you had trouble sleeping?		b134 (100)
SI-CO	16. Have you been constipated?		b525 (100)
CF	25. Have you had difficulty remembering things?		b144 (100)
PF	1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?		d430 (95)
PA	9. Have you had pain?		b280 (95)
SI-DI	17. Have you had diarrhea?		b525 (95)
SI-DY	8. Were you short of breath?		b460 (85)
EF	21. Did you feel tense?		b152 (85)
RF	6. Were you limited in doing either your work or other daily activities?		d230 (80)
PA	19. Did pain interfere with your daily activities?		b280 (80)
			d230 (80)
SF	26. Has your physical condition or medical treatment interfered with your family life?		d760 (80)
FA	12. Have you felt weak?		b730 (75)
EF	24. Did you feel depressed?		b152 (75)
PF	4. Do you need to stay in bed or a chair during the day?		d415 (70)
QL	29. How would you rate your overall health during the past week?	Not covered (90)	
QL	30. How would you rate your overall quality of life during the past week?	Not covered (90)	
PF	5. Do you need help with eating, dressing, washing yourself or using the toilet?	Not endorsed	
FA	18. Were you tired?	Not endorsed	
EF	22. Did you worry?	Not endorsed	
SF	27. Has your physical condition or medical treatment interfered with your social activities?	Not endorsed	
SI-FI	28. Has your physical condition or medical treatment caused you financial difficulties?	Not endorsed	

Functioning Scales: Physical (PF), role (RF), cognitive (CF), emotional (EF), social (SF)

Symptom Scales: Fatigue (FA), pain (PA), nausea and vomiting (NV)

Single item (SI): Dyspnea (DY), insomnia (SL), appetite loss (AP), constipation (CO), diarrhea (DI), financial difficulties (FI)

Global health and QOL scale (QL)

experience using the ICF clinically and 3.9 years (range 0–11.5 years) of experience using the ICF in research.

Table 2 lists the items of the EORTC QLQ-C30 along with the results from the mapping exercise. Three rounds were needed to reach consensus at which time, and it was also clear that additional rounds would not yield further consensus. In all, 25 out of the 30 items were endorsed: Eight items were endorsed at the 4-digit level (range of agreement 70–100 %); 15 items at the 3-digit level (range of agreement 70–100 %); and, for two items, there was consensus (90 % agreement) that the items were not covered within the ICF. Figure 1 illustrates the content density and item efficiency. Content density has a value of 1.04 for endorsed items and 2.4 for non-endorsed items, meaning that more than one meaningful concept is represented per item. Item efficiency has 17 categories with a value of 1.0 and 3 with a value of 0.5, indicating that 3 ICF categories were redundant in measuring what they intent to measure.

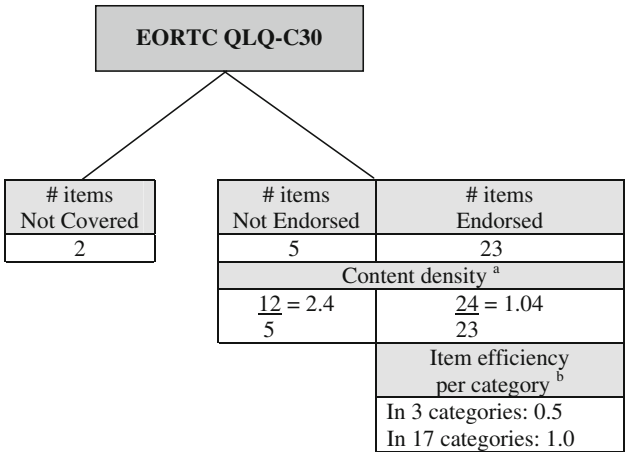

Fig. 1 Content density and item efficiency per category of the EORTC QLQ-C30. **a** Content density =# meaningful concepts/total # items; value of 1 = 1 meaningful concept. **b** Item efficiency per category = 1/number of items to cover one ICF category; value of 1 = higher item efficiency

The reason for the lack of endorsement for three items of the EORTC QLQ-C30 was that multiple constructs were included in the item. Item 5) "Do you need help with eating (d550, 60 %), dressing (d540, 55 %), washing yourself (d510, 55 %) or using the toilet (d530, 50 %)?" includes activities that are covered within the entire Chapter 5 of the Activity and Participation component of the ICF. Items 27 and 28 ask whether the physical condition (not covered) or medical treatment (e580, 25 %) interfered with the social activities (d920, 65 %) or caused financial difficulties (d870, 25 %, or e165, 50 %). On the other hand, for the two remaining items, mappers did not agreed on the meaning of the item. For item 18) "Were you tired?", the mappers could not agree as to whether the item refereed to energy level (b1300, 50 %), or fatigability (b4552, 55 %). Similarly, 22) "Did you worry?" mapped to two different codes: psychic stability (b1263, 50 %) and emotional function (b152, 50 %).

Table 3 presents the items of the EORTC QLQ-BR23 along with the results from the linking exercise. Of the 21 items endorsed, three items were endorsed at the highest level of granularity (5-digit) (range of agreement 77–92 %), 10 items at the 4-digit level (range of agreement 77–92 %), and eight at the 3-digit level (range of agreement 85–100 %). Figure 2 illustrates the content density and item efficiency. The content density is equal to 1 for both endorsed and not endorsed items, meaning that only one meaningful concept is represented per item. Item efficiency has 15 categories with a value of 1.0, 1 with a value of 0.5 and 1 with a value of 0.25, indicating that 2 categories were redundant in measuring what they intent to measure.

Only two items out of 23 of the EORTC QLQ-BR23 did not reach consensus after the third round. The main reason is that they were not able to find an appropriate code within the ICF framework. For item 5) "Did you feel ill or unwell?", mappers were considering this item as not being defined (nd, 46 %) or as emotional functions (b152, 38 %). For item 21) "Was the area of your affected breast swollen?", the structure of the breast and nipple (s6302, 69 %) was considered as well as the function of the lymphatic vessels (b4352, 54 %).

Table 4 and 5 present information comparing the content of the EORTC QLQ-C30 and EORTC QLQ-BR23 to the ICF Breast Cancer Core Set. Four components of the ICF framework are covered by 80 core set categories. The mapping exercise showed that the items of the EORTC QLQ-C30 and EORTC QLQ-BR23 linked to two components of the ICF: body function and activities and participation. Globally, of the 26 body function core set categories, the EORTC system (core and breast modules) captured 15 categories with 17 items; of the 22 activities and participation core set categories, 5 categories were captured with 5 items.

Discussion

EORTC QLQ-C30

The results of this linking exercise indicate that the majority of the content of the EORTC QLQ-C30 maps to the broad construct of functioning, with 15 of the 25 items mapping to impairment of body function, 7 mapping to activity limitations/participation restrictions, and 1 item mapping to both components. Only 2 items of the EORTC QLQ-C30 tapped content outside of functioning: 29) "How would you rate your overall health during the past week?" (perceived health) and 30) "How would you rate your overall QOL during the past week?" (global QOL). The work of Ferrans [32] concurs with this partitioning of content.

The content density and item efficiency, as illustrated in Fig. 1, point out that six items of the EORTC QLQ-C30 had more than one construct indicating the potential for different response interpretation across women and, within woman, over time. The item 19) "Did your pain (b280) interfere with your daily activities (d230)?" is the only one where the two constructs were endorsed. The mappers for the item 6) "Were you limited in doing either your work or other daily activities?" did not considered the work aspect part of the question in their rating. As for the mappers, this question might raise some concerns with the patient filling the questionnaire, as they might have issues with their work but not with their daily activities, or vice versa, and they

Table 3 Degree of endorsement to ICF content of the EORTC QLQ-BR23 items

Sub-scale	Item	4-digit level (% endorsed)	3-Digit level (% endorsed)
BRST	8. Did you have headaches?	b28010 (92)	b280 (92)
		b2801 (92)	
BRAS	17. Did you have any pain in your arm or shoulder?	b28014 (85)	b280 (100)
		b2801 (85)	
BRBS	20. Have you had any pain in the area of your affected breast?	b28011 (77)	b280 (100)
		b2801 (100)	
BRBI	11. Did you find it difficult to look at yourself naked?	b1801 (92)	b180 (92)
BRSEF	14. To what extent were you interested in sex?	b6400 (85)	b640 (92)
BRBI	9. Have you felt physically less attractive as a result of your disease or treatment?	b1801 (85)	b180 (85)
BRBI	10. Have you been feeling less feminine as a result of your disease or treatment?	b1801 (85)	b180 (85)
BRBI	12. Have you been dissatisfied with your body?	b1801 (85)	b180 (85)
BRAS	18. Did you have a swollen arm or hand?	b4352 (85)	b435 (85)
BRSEE	16. Answer this question only if you have been sexually active: To what extent was sex enjoyable for you?	b6403 (77)	b640 (100)
BRST	1. Did you have a dry mouth?	b5104 (77)	b510 (85)
BRST	7. Did you have hot flushes?	b6702 (77)	b670 (77)
BRSEF	15. To what extent were you sexually active? (with or without intercourse)	d7702 (77)	d770 (77)
SI-BRHL	5. Answer this question only if you had any hair loss: Were you upset by the lost of your hair?		b152 (100)
BRBS	22. Was the area of your affected breast oversensitive?		b270 (100)
BRST	2. Did food and drink taste different than usual?		b250 (92)
BRST	4. Have you lost any hair?		b850 (92)
BRST	3. Were your eyes painful, irritated or watery?		b220 (85)
BRFU	13. Were you worried about your health in the future?		b152 (85)
BRAS	19. Was it difficult to raise your arm or to move it sideways?		b710 (85)
BRBS	23. Have you had skin problems on or in the area of your affected breast (e.g., itchy, dry, flaky)?		b840 (85)
BRST	6. Did you feel ill or unwell?	Not defined	
BRBS	21. Was the area of your affected breast swollen?	Not endorsed	

Functioning Scales: Body image (BRBI), sexuality (BRSEF)

Single items: Sex enjoyable (BRSEE), future perspective (BRFU)

Symptom Scales: Arm symptoms (BRAS), breast symptoms (BRBS), systemic therapy side effects (BRST)

Single item: Upset by hair loss (BRHL)

might not answer the question properly. Same concerns with the item 5) "Do you need help with eating, dressing, washing yourself or using the toilet?", where each construct has an individual code. However, the mappers did not endorse any of the codes. As an example, after breast cancer treatment, some women have limited range of motion in their affected arm. They are able to eat, wash themselves, and use the toilet without any difficulty, but getting dressed is quite challenging. What would be their right answer: (1) Not at all or (3) Quite a bit? By asking each construct in an individual item, the appropriate respond could be obtained and linking to the ICF would be possible. In comparison, the ICF Breast Cancer Core Set proposed an item for each of these constructs, which would facilitate need-based treatment planning.

The three remaining items (26, 27, 28) asked about "Has your physical condition or medical treatment interfered with your family life/social activities or caused you financial difficulties?". Only the part asking for the interference with the family was endorsed by the mappers. As mentioned, having more than one construct in an item might lead to a misunderstanding of the question or answer inappropriately. A solution that can be proposed, to make sure that there is no ambiguity with the item and that it

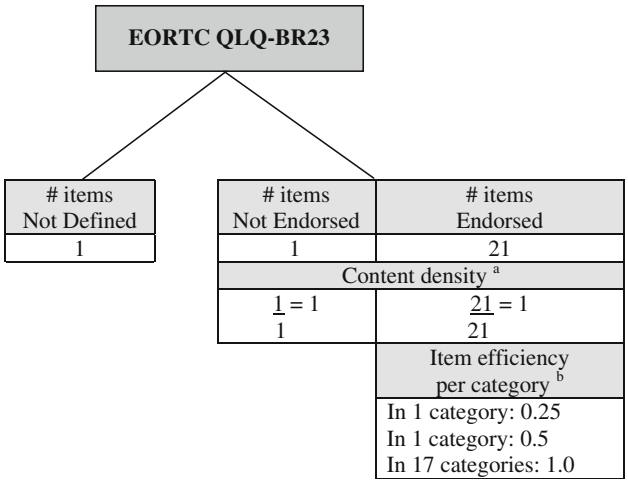

Fig. 2 Content density and item efficiency per category of the EORTC QLQ-BR23. **a** Content density = # meaningful concepts/total # items; value of 1 = 1 meaningful concept. **b** Item efficiency per category = 1/number of items to cover one ICF category; value of 1 = higher item efficiency

could be link to the ICF framework, would be, for example, to have the question separated by construct, where each aspect can be independently coded:

1. Has your physical condition interfered with/caused you difficulties with: (Not Covered)

    a. Your family life? (d760—Family relationships)
    b. Your social activities? (d9205—Socializing)
    c. Your financial situation? (e165—Assets)

2. Has your medical treatment interfered with/caused you difficulties with: (e5800—Health services)

    a. Your family life? (d760—Family relationships)
    b. Your social activities? (d9205—Socializing)
    c. Your financial situation? (e165—Assets)

It is known that financial difficulties due to the loss of an income are a strong predictor for a poorer QOL [22, 39]. In addition, there is a complex interaction between disability and the financial burden (e.g., increase expenses for medication and/or rehabilitation; reduced capacity to work), and therefore, an ideal item would be explicit as to the consequences of physical condition or medical treatment.

For two items, it was decided to stop the mapping exercise after the second round as it was clear that consensus would not be reached. For item 18) "Were you tired?", mappers considered two codes: b1300 (50 %) (Energy level), which is under the chapter of mental function, and b4552 (55 %) (Fatiguability), which is under the chapter of functions of the cardiovascular, hematological, immunological, and respiratory systems. The lack of consensus on this item points out challenges in eliciting information on a personally experienced, multidimensional, construct, such as fatigue. People may perceive "tired" as a physical sensation requiring a reduction in activities, or as a diminution in motivation and/or a mental fatigue [40].

In cancer, fatigue is often reported as a short- and/or long-term side effect of treatment and may fluctuate between mental and physical fatigue over the course of the disease and its treatment [40]. Of the three items within the Fatigue Subscale of the EORTC QLQ C-30, consensus was reached on two items: "Did you need to rest?" and "Have you felt weak?". These mapped to fatigability, reflecting physical fatigue. Because of this lack of specificity (mental versus physical fatigue), there was no consensus on "Were you tired?".

In devising or revising items, the ICF can guide the granularity and wording. For example, if the content is to reflect physical fatigue, perhaps wording compatible with the ICF code b4552 would be clearer (physical tiredness with respect to activity). If content related to mental fatigue was desired, wording from b1300 could act as a guide (mental function, vigor, and stamina). In future work, it would appear to be of value to develop content for both mental and physical fatigue as well as measured fatigability.

For item 22) "Did you worry?", mappers also considered two codes: b1263 (50 %) (psychic stability) and b152 (50 %) (emotional functions). This lack of consensus reflected a difference in opinion about whether the item was asking whether the person was in a state of worry "being worried" or experienced an event that made them worry and whether they are or are not considering themselves as a worried person. Clearly, this lack of consensus could serve as a flag for further investigation of this item, going back to patients for cognitive debriefing.

The observation that the content of the EORTC QLQ-C30 is largely related to functioning would make this measure an appropriate outcome for interventions targeting symptoms (e.g., different chemotherapeutic or radiation protocols or psycho-oncology), activities, and/or participation (e.g., cancer rehabilitation). As there were only two items that went beyond functioning (one each for perceived health and global QOL), this measure would not likely be responsive to interventions targeting purely QOL, such as through existential or meaning-making interventions [41, 42].

EORTC QLQ-BR23

As the EORTC QLQ-C30 is used as a core questionnaire and the EORTC QLQ-BR23 is a specific module, it could

Table 4 Body function: ICF Breast Cancer Core Set, EORTC QLQ-C30 and EORTC QLQ-BR23

ICF Breast Cancer Core Set	EORTC QLQ-C30	EORTC QLQ-BR23	ICF Category	Item(s)
b126			Temperament and personality functions	
	b1263		Psychic stability	23. Did you feel irritable?
b130			Energy and drive functions	
	b1302		Appetite	13. Have you lacked appetite?
b134	b134		Sleep functions	11. Have you had trouble sleeping?
	b1400		Sustaining attention	20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?
	b144		Memory functions	25. Have you had difficulty remembering things?
b152	b152	b152	Emotional functions	21. Did you feel tense?
				24. Did you feel depressed?
				5. Answer this question only if you had any hair loss: Were you upset by the lost of your hair?
				13.13. Were you worried about your health in the future?
b180			Experience of self and time functions	
b1801		b1801	Body image	9. Have you felt physically less attractive as a result of your disease or treatment?
				10. Have you been feeling less feminine as a result of your disease or treatment?
				11. Did you find it difficult to look at yourself naked?
				12. Have you been dissatisfied with your body?
		b220	Sensations associated with the eye and adjoining structures	3. Were your eyes painful, irritated or watery?
		b250	Taste function	2. Did food and drink taste different than usual?
b265			Touch function	
		b270	Sensory functions related to temperature and other stimuli	22. Was the area of your affected breast oversensitive?
b280	b280		Sensation of pain	9. Have you had pain?
				19. Did pain interfere with your daily activities? (with d230)
b2801			Pain in body part	
		b28010	Pain in head and neck	8. Did you have headaches?
		b28011	Pain in chest	22. Have you had any pain in the area of your affected breast?
		b28014	Pain in upper limb	17. Did you have pain in your arm or shoulder?
b435			Immunological system functions	
b4352		b4352	Functions of lymphatic vessels	18. Did you have a swollen arm or hand?
b4353			Functions of lymph nodes	
b455			Exercise tolerance functions	
	b4552		Fatiguability	10. Did you need to rest?
	b460		Sensation associated with cardiovascular and respiratory functions	8. Were you short of breath?
		b5104	Salivation	1. Did you have a dry mouth?
	b5106		Regurgitation and vomiting	15. Have you vomited?
	b525		Defecation functions	16. Have you been constipated?
				17. Have you had diarrhea?
b530			Weight maintenance functions	
	b5350		Sensation of nausea	14. Have you felt nauseated?
b640			Sexual functions	

Table 4 continued

ICF Breast Cancer Core Set	EORTC QLQ-C30	EORTC QLQ-BR23	ICF Category	Item(s)
		b6400	Functions of sexual arousal phase	14. To what extent were you interested in sex?
		b6403	Function of sexual resolution phase	16. Answer this question only if you have been sexually active: To what extent was sex enjoyable for you?
b650			Menstrual functions	
b660			Procreation functions	
b670			Sensation associated with genital and reproductive functions	
		b6702	Discomfort associated with menopause	7. Did you have hot flushes?
b710		b710	Mobility of joint functions	19. Was it difficult to raise your arm or to move it sideways?
b720			Mobility of bone functions (scapula, pelvis, carpal, tarsal)	
b730	b730		Muscle power functions	12. Have you felt weak?
b740			Muscle endurance functions	
b780			Sensations related to muscles and movement functions	
b810			Protective functions of the skin	
b820			Repair functions of the skin	
b840		b840	Sensation related to the skin	23. Have you had skin problems on or in the area of your affected breast (e.g., itchy, dry, flaky)?
		b850	Functions of hair	4. Have you lost any hair?

Code in italic: The 3-digit root is in the ICF Breast Cancer Core Set, and the mappers of the EORTC QLQ-C30 and EORTC QLQ-BR23 endorsed an ICF code with a higher granularity

be expected that the core questionnaire will endorsed a lower granularity and the specific module would be more precise. Twenty-one of 23 (91 %) EORTC QLQ-BR23 items were endorsed as mapping to the ICF framework: 20 of the items were at the impairment level and one at the activity and participation level. The content reflects largely side effects of treatment, and hence, this measure would be responsive to different protocols for adjuvant therapy, but not very responsive to rehabilitation interventions for breast cancer as only three items related to upper extremity ability. Therefore, the EORTC QLQ-BR23 should be recognized as an "impairment specific index" rather than a QOL measure.

Two items out of 23 were not endorsed. For item 6) "Did you feel ill or unwell?", mappers were debating between b152 (38 %) (Emotional functions) and not defined within the ICF framework (46 %). The confusion was probably around "feeling" that could map to b152 but "ill" or "unwell" is not characterize within the ICF.

The second item that was not endorsed is 21) "Was the area of your affected breast swollen?". One of the consequences of breast cancer, which some women may experience, is lymphedema. Lymphedema has been defined as a buildup of lymph fluid, and other elements (e.g., proteins), into the interstitial space of the affected region due to an imbalance between interstitial fluid production and transport capabilities [17]. This is caused by a mechanical impairment of lymph drainage induced by surgery, radiation therapy, and/or chemotherapy [11, 43–45]. Items 18 and 21 aim to capture this information by asking whether the patient has a swollen arm, hand, or breast. Item 18 has been endorsed after the third round with the code b4352, functions of lymphatics vessels, which is define as "functions related to vascular channels that transport lymph," under the immunological system function (b435). For item 21, it was decided to stop after the third round, even if it was close to reach consensus (69 % agreement), because it was capturing information regarding the structure of the breast and nipple (s6302) and not regarding the swelling in the affected breast.

Within the ICF framework, the direct classification of post-cancer-related lymphedema is not possible: only impairment to the lymphatic vessels/nodes functions (b4352/b4353) and structures (s4200/s4201) can be characterized. One of the problems with lymphedema is that it is often seen as an impairment rather than a disease. Therefore, even if the code b4352 has been endorsed, it might not be the optimal choice considering as the item does not address the real meaning of the code and the code does not really address the real issue of possible post-breast cancer swelling at any level.

When comparing the EORTC QLQ-C30 and EORTC QLQ-BR23 to the ICF Breast Cancer Core Set (see Table 3 and 4), it is of interest to note that the questionnaire items for pain in the EORTC QLQ-BR23 were at greater granularity than the ICF Core Set. On the

Table 5 Activities and participation: ICF Breast Cancer Core Set, EORTC QLQ-C30 and EORTC QLQ-BR23

ICF Breast Cancer Core Set	EORTC QLQ-C30	EORTC QLQ-BR23	ICF category	Item(s)
d177			Making decisions	
d230	d230		Carrying out daily routine	6. Were you limited in doing either your work or other daily activities?
d240			Handling stress and other psychological demands	
	d415		Maintaining a body position	4. Do you need to stay in bed or a chair during the day?
d430	d430		Lifting and carrying objects	1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?
d445			Hand and arm use	
	d4500		Walking short distances	3. Do you have any trouble taking a short walk outside the house?
	d4501		Walking long distances	2. Do you have any trouble taking a long walk?
d510			Washing oneself	
d520			Caring for body parts	
d540			Dressing	
d550			Eating	
d560			Drinking	
d570			Looking after one's health	
d620			Acquisition of goods and services	
d630			Preparing meals	
d640			Doing housework	
d650			Caring for household objects	
d660			Assisting others	
d720			Complex interpersonal interactions	
d750			Informal social relationships	
d760	d760		Family relationships	26. Has your physical condition or medical treatment interfered with your family life?
d770			Intimate relationships	
		d7702	Sexual relationships	15. To what extent were you sexually active (with or without intercourse)
d850			Remunerative employment	
d920	d920		Recreation and leisure	7. Were you limited in pursuing your hobbies or other leisure time activities?

Code in italic: The 3-digit root is in the ICF Breast Cancer Core Set, and the mappers of the EORTC QLQ-C30 and EORTC QLQ-BR23 endorsed an ICF code with a higher granularity

other hand, for many questionnaire items, the multiple constructs are reflected individually in the ICF Breast Cancer Core Set, which facilitate interpretation for both patients and clinicians. In addition, Brach et al. [12] concluded that their Breast Cancer Core Set was recommended for further validation. Glaessel et al. [46] did a content validity of this ICF Core Set, from the physiotherapists perspectives, and do proposed a more extensive Breast Cancer Core Set, which include higher granularity, as one example, for pain (head and neck, chest, back, upper limb and joints, and radiating pain in a dermatome).

Conclusion

The EORTC QLQ-C30 and EORTC QLQ-BR23 are two well-established questionnaires considered to measure of QOL among (breast) cancer patients. This study has shown that most items from two QOL indices can be linked to the ICF framework, meaning that the content reflects functioning, a key component of QOL, but not QOL per se. Only 2 of the 30 items of the EORTC QLQ-C30 went beyond functioning and included global feeling of well-being. Only 1 of the items (sexual activity) of the EORTC QLQ-BR23 related to content beyond symptoms (ICF

impairments) indicating that this measure would best be classified as an impairment inventory.

The advantage of the ICF is that it is very specific to functioning at a granularity that has been validated by experts and people with diverse disabilities. Thus, during the development process for a new measure, the ICF would be a good starting point to identify relevant content and optimal framing of items to avoid including more than one concept. With this approach, items related to range of motion of the shoulder and activities requiring arm movement would have been included. The ICF can also be used to identify items which may be redundant, reducing response burden.

For existing measures, linking to the ICF could be proposed as an additional method for content validation. Finally, the item-level analysis is useful for identifying whether a measure has content of sufficient specificity and granularity to be responsive to treatment approaches.

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Chapter 8: Integration of Manuscripts 3 and 4

Research questions of Manuscripts 3 and 4

Manuscript 3:

To estimate the extent to which the content of the EORTC QLQ-C30 and EORTC QLQ-BR23 goes beyond functioning and includes global feeling of well-being.

Manuscript 4:

To estimate the extent of agreement between health professionals' (ClinRO) and patients' (PRO) ratings on disabilities associated with breast cancer (impairments, activity limitations and participation restrictions).

Integration of Manuscripts 3 and 4

Both manuscripts fall under "construct verification". In Manuscript 3 a mapping exercise linked the items of the EORTC QLQ-C30 and EORTC QLQ-BR23 to the ICF framework, as the other legacy questionnaires used in this thesis were already mapped. It showed that only the EORTC QLQ-C30 goes beyond functioning and includes global feeling of well-being and that the content of the EORTC QLQ-BR23 is related to functioning only.

The work of Manuscript 3 was the prelude to Manuscript 4. As the five questionnaires were completed by the participants were mapped to the ICF framework, it was possible to compare these responses to the items of the ICF Breast Cancer Core Set completed by the health care professionals. The extent to which participants and health care professionals agreed on the presence and severity of the domains assessed was estimated.

Chapter 9: Manuscript 4

Assessment of Breast Cancer Disability: Agreement between Expert Assessment and Patient Reports

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Assessment of Breast Cancer Disability: Agreement between Expert Assessment and Patient Reports

Abstract

Objective: To estimate the extent of agreement between health professionals' (ClinRO) and patients' (PRO) ratings on disabilities associated with breast cancer (impairments, activity limitations and participation restrictions).

Methods: Health care professionals measured arm impairments, activity limitations and participation restrictions with the ICF Breast Cancer Core Set. Participants filled 5 outcomes measures targeting health aspects of QOL that were previously mapped to the ICF. Agreement between ClinRO and PRO was estimated with quadratic Kappa.

Results: 245 paired clinician and participant completed the outcomes measures. A total of 60 items mapped to 24 different ICF Breast Cancer Core Set codes, which provide 68 analyses for agreement. Impairment was better addressed with PROs (mostly poor and fair level of agreement); Activity limitations, both PROs and self-reported outcomes (SRO) (fair); Participation restrictions, PROs (fair).

Conclusion: Clinicians usually underestimate the symptoms and impairments of the patients, leading to a greater proportion of poor agreement. PRO's provide valuable information on impairments at the mental function level and pain. ClinRO's provide more valuable information on physically assessed impairments (edema). Activity limitations and participation restrictions, excluding reporting the difficulty aspect of various life situations, can be either SRO or observer-reported outcomes (ObsRO).

Introduction

Distressing disabilities are frequent following cancer treatment [1, 2]. These disabilities can be physical (e.g. pain, reduced range of motion, lymphedema) or psychological (e.g. body image, feminine role), and have an impact on all aspects of life and its quality at any time during the course of their illness or survival [2-6].Transient or permanent disability can occur throughout the cancer experience from diagnosis, treatment through to survivorship. Quality of life (QOL) is a global construct encompassing all aspects of life including those outside of health. QOL is defined by the World Health Organization (WHO) as the "individuals' perception of their position in life in the context of the culture in which they live and in relation to their goals, expectations, standards and concerns"[7]. In this context, a potentially life shortening and disability inducing health condition would impact on all of life experiences that make up QOL.

In most clinical settings, clinicians rate presence and severity of disabilities arising from oncological treatments, based on observation and clinical examination. Since 2009, the Food and Drug Administration (FDA) has been seeking to hear the patient's voice in order to support labelling claims of the medication [8]. This brought to the foreground the concept of using patient reported outcomes (PRO) in oncology clinical trials in combination with clinician reported outcomes (ClinRO).

ClinROs are those outcomes that can be measured through clinical examination implying an evaluation by an observer with some recognized professional training (e.g. clinician, psychologist) [9]. ClinROs are used for endpoints that can only be assessed with technology or expertise (e.g. level of platelets, lymphedema severity, pitting edema). On the other hand, PROs are those outcomes that can only be measured from the patient's perspective [9]. PROs are used to evaluate the patient's point of view on the impact of the disease and its treatment upon symptoms, function and other aspects of QOL [10]. Neither a clinician nor an observer can contribute to the interpretation of the patient's response.

The distinction between ClinRO and PRO is not as straight forward because some constructs can be reported on by the person accurately bypassing the need for clinical assessment. For example, physical function ability can be self-reported, and in most people will concur with a performance based assessment of physical function. Self-report outcomes (SRO) are not the same as PROs because the clinician or an observer can amend the interpretation of the person's response by observing the performance, but in the vast majority of instances the SRO is valid. When the observer is not expertly trained, the outcome being assessed is usually based on observed behaviour and is termed an Observer Reported Outcome (ObsRO). A special kind of observer is a proxy who, because of shared experience, can report on the outcome [11]. It

is important to make this distinction because what is being assessed and who is assessing it will impact on the accuracy of the information.

In the context of oncology, symptom burden can only be assessed by PROs [12-14]. Adverse events that are both symptomatic and can have exteriorized signs (nausea, itch), are best measured with both PRO and ClinRO [12-15]. In the context of functioning and disability, the literature reports that impairment at the mental function and pain levels are better addressed by PROs and clinicians are best at reporting on disabilities with exteriorized signs using a valid ClinRO [12-15]. Functional ability could be assessed either using SRO or ClinRO, but only if the aspect of functional ability being measured can be assessed directly through observation. Thus, limitation in walking up stairs can be self-reported or observed; difficulty in walking up stairs can only be reported on by the person and hence would be a PRO. Participations restrictions can be assessed by the person themselves or by a proxy observing behaviour (SRO or ObsRO); satisfaction with participation can only reported on by the person (PRO). The specific wording of each item to assess is critical in determining which source of information will be the most accurate.

The aim of this study was to estimate the extent of agreement between health professionals' (ClinRO) and patients' (PRO) ratings on disabilities associated with breast cancer (where these disabilities are impairments, activity limitations and participation restrictions) according to which "reporter" would be the most accurate for that disability. The hypothesis is that there will be lower agreement for disabilities that can only be measured by a PRO or only be measured by a ClinRO, and the highest agreement for disabilities that can be either self-reported or observed by others.

Methods

Study design and questionnaires

A secondary analysis of data set compiled to contribute to the validation the ICF Breast Cancer Core Set. Data were collected between 2004 and 2007 in 9 different sites. This will be the first analyses to validate the ICF Core Set elements assessed by health professionals against PROs. Participants in the study were women greater than 18 years of age with breast cancer as their main diagnosis. Excluded were women with an unhealed surgical incision. The project was approved by the Research Ethics Boards of each participating institution, and all participants gave informed consent.

In the field of rehabilitation, practitioners and researchers are making efforts towards the use of a universal conceptual framework and common language to inform both clinical practice and research [16-18]. In order

to offer clinicians and researchers with a comprehensive but concise group of categories with which to describe the person's global function considering a bio-psycho-social model, the International Classification of Functioning, Disability and Health (ICF) created Core Sets derived from the WHO ICF Framework [18-20], which assess relevant categories within each of four domains of the ICF Framework.

In this study, health care professionals assessed the presence and magnitude of impairments, activity limitations and participation restrictions, and the environmental factors using the categories listed in the comprehensive ICF Breast Cancer Core Set developed by Brach and colleagues (2004) [20]. The core set provides a systematic framework covering the spectrum of breast cancer-related functioning and disability. The four rubrics of the ICF framework are covered as followed by 80 categories: 26 items of body functions, 9 items of body structures, 22 items of activities and participation, and 23 items of environmental factors. Each code is then quantified on a five-level ordinal scale, ranking from: 0 (No impairment/difficulty) to 4 (Complete impairment/difficulty). In the eventuality that the item is not specified, not applicable or is a comorbid condition, the item is qualified respectively by 8, 9 or C. The environmental factors are quantified using the same ranking system, although using either barriers (negative) or facilitators (positive) qualifiers.

The participants reported on these disabilities with five generic or cancer-specific outcomes measures that were all previously mapped to the ICF framework [21-23] following a specific protocol [24, 25] and using a Delphi technique. Briefly, each construct of each item in the questionnaire is mapped to one specific code of the ICF framework. A code is endorsed when 70% or more of the raters agree. Consensus rounds are stopped when the threshold is obtained or when it is clear that no consensus among raters will be obtained.

- *Short Form Health Survey Medical Outcomes Study* (SF-36) [26]. SF-36 is a generic measure of perceived health status with a 36-item survey divided into eight health concepts: physical functioning, role limitations due to physical health problems, pain, general health perceptions, vitality, social functions, role limitations due to emotional problems, and mental health. Subscales scores range from 0 to 100, where a higher score indicates a better health status. Reliability, both test-retest and internal consistency has been demonstrated [27, 28]. Of the 36 items, nine mapped to body function, 11 to activities and participation, 10 were considered as function with no specific code, and 6 were considered as not being a function [21].
- *European Organization for Research and Treatment of Cancer QLQ-30* (EORTC QLQ-C30) [29]. This 30-item cancer-specific questionnaire looks at the construct of QOL among people with cancer. It includes five functional scales (physical, role, cognitive, emotional, and social), three symptoms scales (fatigue, pain, and nausea and vomiting), and a global health and QOL scale. Single items addressing issues reported by cancer patient are also asked. High internal consistency, good inter-

scale correlation and discriminative validity has been established [29]. Twenty-eight items are answered on a 4-point ordinal scale (1-not at all to 4-very much) and each scales' score is transformed on a 0 to 100 scale. For the functional scales, a higher score expresses a better level of functioning, whereas a higher score on the symptom-oriented scales and items illustrates a higher level of symptoms. Of the 30 items, 15 mapped to body functions, 7 to activities and participation, 2 were endorsed as not being covered within the ICF, and 5 were not endorsed [22].

- *European Organization for Research and Treatment of Cancer QLQ-BR-23* (EORTC QLQ-BR-23) [30]. Following the creation of the EORTC QLQ-C30, a modular measurement approach, specific to breast cancer, was developed comprising 23 items relating to body image, sexuality, arm symptoms, breast symptoms, and systemic therapy side effects. The scoring system is as described with the EORTC QLQ-30 and the module has high internal consistency for four out of five scales and good known-group discriminative ability. Of the 23 items, 20 mapped to body functions, 1 to activities and participation, and 2 did not reached consensus [22].
- *World Health Organization Disability Assessment Schedule II* (WHODAS II) [31]. This instrument was developed based on the ICF model in order to assess behavioral limitations and participation restrictions experienced by a person, independently from a medical diagnosis. The questionnaire completed by the participants is the self-administered 36-item version. This instrument captures the individual's functioning in the previous 30 days in six activities: understanding and communicating, getting around, self-care, getting along with people, life activities, and participation in society. The items are answered on a 5-point ordinal scale (1-none to 5-extreme/cannot do). The psychometric properties were tested in a breast cancer population; the measure as a high validity and reliability, and there is also a convergent validity with the SF-36 [32]. A total score is produced, as well as six subscale scores, ranging from 0 (best) to 100 (worst). Of the 36 items, 2 mapped to body functions, 31 mapped to activities and participation, 1 to both body functions and activities and participation, and 2 were considered as not applicable as they were impact question [23].
- *World Health Organization Quality of Life – Bref* (WHOQOL-Bref) [7, 33] was developed to profile QOL in the previous two weeks. Five of the 26 items were assessed here: 1) How would you rate your quality of life?, 2) How satisfied are you with your health?, 17) How satisfied are you with your ability to perform your daily activities?, 20) How satisfied are you with your personal relationships?, 23) How satisfied are you with the conditions of your living place? Of those five items, none was mapped to a specific ICF code: 2 were classified as "not a function", 2 as "satisfaction with function", and 1 as "satisfaction with environment" [21].

Statistical analysis

Apart from describing the cohort, analyses focused on estimating different agreement parameters on breast cancer disabilities (impairments, activity limitations and participation restrictions) between health professionals and patients according to the most accurate "reporter".

Four agreement parameters were calculated: agreement at the level of normal; crude agreement; expected agreement; and quadratic Kappa (κ_ω). Interpretation of Kappa is based on Landis and Kosh (1977) [34] : Kappa < 0 = no agreement, 0.00-0.20 = poor agreement, 0.21-0.40 = fair agreement, 0.41-0.60 = moderate agreement, 0.61-0.80 substantial agreement, 0.81-1.00 = almost perfect agreement. Most of the data are missing completely at random, as some sites did not collected information on some of the questionnaires. Analyses were performed without doing any imputation of the data.

PROs items were rescored to match the scoring of the ICF Breast Cancer Core Set, which had high values indicating a greater degree of impairment or limitation. Statistical analyses were conducted using the Statistical Analysis Systems (SAS) version 9.3 (SAS Institute Inc.).

Results

A total of 245 women and their health care professionals were involved. Health care professionals who completed the ICF Breast Cancer Core set were either physicians (84%) or psychologists (6%) (missing data: 10%). The participants' demographic and condition-specific information are reported in table 1. Women were on average 56.8 years old, 193 participants (79%) had breast cancer stage II or below, the majority (56%) had only one surgery, and the median time post-surgery was approximately 9 months, which is within the first two years post-treatment where most arm dysfunction symptoms occur.

A total of 80 categories in the ICF core set for breast cancer and 130 items from five generic and cancer-specific questionnaires were available for comparison in this study. A total of 24 ICF categories mapped to 60 questionnaire items providing 68 pairs for estimating agreement on disabilities. Tables 2 to 4 present, for each ICF Breast Cancer Core Set category for impairment, activity limitation, and participation restriction, the matching items from the questionnaires, as well as who would be the best source of information on that disability. As not everyone completed all questionnaires, the number of people with matching data is also presented (SF-36 n = 244; EORTC QLQ-C30 n = 71; EORTC QLQ-BR23 n = 218; WHODAS n = 198). Presented in these tables are: prevalence of the "normal" rating according to the ClinRO and PRO assessment; agreement on the normal or no disability rating; crude and expected agreement; and weighted Kappa (κ_ω) with 95% confidence intervals (CIs).

For ICF category b126 (Temperament and personality functions), the best reporter would be the person using a PRO, and the prevalence of the normal or no disability ICF category was 0.50. Four questionnaire items mapped to this single ICF category. The prevalence of the no disability rating across the four PRO items was from 0.05 to 0.41; concordance on the no disability ranged from 0.05 to 0.17; crude agreement ranged between 0.79 and 0.93; and expected agreement ranged between 0.77 and 0.93. κ_{ω} for the first pairing (with SF-36 item for calm and peaceful) was 0.08 (95% CI: 0.03-0.14); κ_{w} for the other 3 pairs were 0.07, 0.04, and 0.10, respectively. For each questionnaire item that mapped to an ICF code that was more precise than that of the ICF core set, the more precise code is indicated. For example, the SF-36 item "Feeling worn-out" mapped to b1300 Energy level, but the ICF core set category is b130 (Energy and drive function).

Some questionnaire items did not map to one ICF category with 70% consensus (indicated as non-mapped) because of multiple constructs or interpretation ambiguity [22], and so agreement was calculated between all ICF relevant categories. Thus, 60 questionnaire items yielded 68 paired comparisons.

The levels of agreement between ClinRO, PRO and SRO ranged from none to moderate (-0.28 to 0.52) and are summarized in table 5. Most items reflecting impairment are better addressed by a PRO and reached mostly a poor to fair level of agreement. Activity limitations are best addressed by both PRO and SRO, with mainly a fair level of agreement. As most of the items regarding participation restrictions are asking about the "difficulty" of doing something, PRO informed best, with mostly a fair level of agreement.

Discussion

The validation carried out here compared disability ratings between a clinician using the ICF Breast Cancer core set categories and what women with breast cancer reported using standardized generic and cancer-specific questionnaires. The fact that the agreement was low, achieving at best a moderate level (κ_{ω} 0.43 to 0.52), is because there is no gold standard for comparison. Questionnaires are best for identifying PROs, those items that only the person with the health concern can report on: pain, fatigue, psychological distress, as examples. As these, by definition cannot be interpreted by a clinician, the level of agreement was as expected, fair.

For disabilities that can be self-reported, such as limitations in mobility or activity, there should be better agreement between the clinician rating (here using the ICF) and the questionnaire items but this assumes that the questionnaire items are appropriately worded for limitation and not other qualifiers. For example, the observation that, for the ICF category b710, mobility of joints, the agreement was fair (κ_{ω} 0.34) owing

to the wording, the ICF category is likely closer to the truth with respect to range of motion, while the woman is reporting on her perception of the term "difficulty" which could imply effort or discomfort. The corresponding questionnaire item which refers to difficulty with moving the arm is not the same as limitation and can be interpreted differently by different people. Although agreement at the individual level was low, at the group level the prevalence of impairment was similar: 68% impaired using ClinRO and 71% impaired using PRO. Overall disabilities, the highest level of agreement was observed for activity limitations and participation restrictions (see table 5).

As the participants mostly had breast cancer stage II, or below, and had one surgery performed, it could be thought that women would be less likely to report arm dysfunction. However, women do experience symptoms. For example, 81% of them report experiencing pain in their arm or shoulder to a certain extent (mild: 33%, moderate: 33%, severe: 15%) even if the median time post-surgery is approximately 9 months (average 21 months). Therefore, regardless the stage of the disease, it is important to address impairment, activity limitations and participation restrictions at any time. Women can live for a long period of time with a dysfunction, as actually in this population the 5-year survival is 88% [35], and this can have an impact on their QOL.

In our study, the findings are similar to the literature regarding impairment [12, 13] and suggest that impairment at the mental, energy, sexual and pain level are best reported by the person, with the exception of interference of pain with daily activity that we consider as a SRO and sexual function that can be amended by the proxy. Furthermore, our results also suggest that clinicians tend to underestimate the person's impairments, with the exception of the function of the lymphatic vessels (participants underestimated their level of swelling) and pain, where both ClinRO and PRO provided similar "normal". On the other hand, we found that ClinRO would inform better on impairment regarding "medical" conditions such as lymphedema. Discrepancies are found between the best source of information for the ICF Breast Cancer Core Set and some of the items. When the difficulty/trouble in doing something is asked, this is a PRO. However, the definition provided by the ICF would, in some instances (e.g. sleep functions, exercises tolerance, joint mobility), benefit from being measured using a test of performance (PerfRO) [36] where the clinician can adequately assess the person.

Our study has several limitations. As this is a secondary analysis, the amount of information on the training and experience of the clinicians using the ICF was limited. The questionnaire items have some limitations in light of multiple constructs and potential for response shift. Not all people were administered questionnaires but the minimum sample size was 70, greater than the minimum suggested for agreement studies (n=30) [37].

It is known that arm dysfunction could occur at any time over the course of the disease or in the long-term [2, 4]. In our sample, women were on average 21 months post-surgery (median approximately 9 months), ranging from 0.1 month to 317 months (26.4 years) and were therefore at different stages of recovery or functioning. This could influence the level of agreement as their perception of themselves might have changed and they might have adapted over time – a phenomenon called response shift [38, 39]. Consequently, they might report having none or only mild impairment as they have modified their pattern and do not perform the task any more. However, when the clinician is asking about it, through a SRO or a PerfRO, she would see that there is an issue. Therefore, it would be interesting to see the level of agreement if women were followed several times over a long period of time.

The ICF Breast Cancer Core Set is not a measure, but rather is a systematic framework for reporting on functioning and disability after breast cancer. It indicates what to measure, not how to measure it. Glaessel (2011) [40] suggested a more expanded Core Set that would include more categories and a higher level of granularity. The mapping exercise revealed that some items had a higher granularity of what was proposed in the ICF Breast Cancer Core Set, indicated in table 2 to 4 by codes in brackets after each item, e.g. "did you have any pain in your arm or shoulder?" was mapped as "b28014 Pain in upper limb" [22]. However, it was analysed using its lower root "b2801 Pain in body part". Therefore, if a PRO mapped to the ICF is analysed with a ClinRO with the same level of granularity, it is likely that the level of agreement would have been better.

In conclusion, the ICF Breast Cancer Core Set is very specific regarding impairment, activity limitations and participation restrictions. The five generic and cancer-specific questionnaires that were used here do represent those disabilities. However, only 24 categories out of 80 (30%) are covered, indicating that the full spectrum of the Core Set is not covered. As expected, and similar to other findings in the literature, clinicians usually underestimate symptoms and impairments of the patients, leading to a poor agreement. Clinicians should rely on PROs when assessing mental function and pain level, and for physical function, they should use standardized tests or self-report questionnaires that ask limitation and not difficulty. In an ideal situation, activity limitations would be assessed by a SRO, an ObsRO and/or a PerfRO. Regarding participation restrictions, ObsRO should be considered. For future research, ClinRO would benefit from being revised by an expanded Breast Cancer Core Set, and the use of Patient Reported Outcomes Measurement Information System (PROMIS) should be considered for PRO.

Declaration of interest

The authors have no funding and conflicts of interest to disclose.

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Table 1. Descriptive statistics

Demographic (N = 245)	**Mean (SD) / Frequency (%) [range]**
Age (years)	56.8 (10.6) [29 – 86]
BMI (kg/m^2)	26.7 (4.5) [18 – 44]
Living situation:	
▪ Alone	59 (24%)
▪ With someone	182 (74%)
▪ Missing	4 (2%)
Occupation:	
▪ Working	94 (38%)
▪ Unemployed	54 (22%)
▪ Retired	97 (40%)
Condition specific	**Mean (SD) / Frequency (%) [range]**
Breast cancer stages:	
▪ Stage 0	8 (3%)
▪ Stage I	78 (32%)
▪ Stage IIA	71 (29%)
▪ Stage IIB	36 (15%)
▪ Stage IIIA	24 (10%)
▪ Stage IIIB	17 (7%)
▪ Stage IV	6 (2%)
▪ Missing	5 (2%)
Number of surgeries related to breast cancer:	
▪ 0	1 (0.4%)
▪ 1	137 (56%)
▪ 2	74 (30%)
▪ 3	22 (9%)
▪ 4 or more	7 (3%)
▪ Missing	4 (2%)
Number of hospitalization due to breast cancer (include rehab):	
▪ 0	2 (1%)
▪ 1	79 (32%)
▪ 2	96 (39%)
▪ 3	38 (16%)
▪ 4	9 (4%)
▪ 5 or more	14 (6%)
▪ Missing	7 (3%)
Time since last surgery (months)	21 (35) [0.1 – 317] 2.5^{th}: 1.4 25^{th}: 5.2 Median 8.9 75^{th}: 20.8 97.5^{th}: 107.6

Table 2. ICF Breast Cancer Core Set and corresponding mapped items for impairment (N = 245)

ICF Breast Cancer Core Set	Best source	Prevalence of ClinRO Normal	Item [questionnaire]	Reporter	Prevalence of PRO Normal	n	Concordance on Normal	Crude [Expected] agreement	κ_ω (95% CI)
b126 Temperament and personality functions *General mental functions of constitutional disposition of the individual to react in a particular way to situations, including the set of mental characteristics that makes the individual distinct from others.*	PRO	0.50	How much of the time during the past week have you felt calm and peaceful? [SF-36]	PRO	0.05	238	0.05	0.79 [0.77]	0.08 (0.03; 0.14)
			How much of the time during the past week have you felt downhearted and blue? [SF-36]	PRO	0.17	238	0.10	0.87 [0.86]	0.07 (0; 0.15)
			Did you feel irritable? [EORTC QLQ-C30]	PRO	0.41	70	0.17	0.93 [0.93]	0.04 (-0.20; 0.28)
			Did you worry? (b1263) (NON-MAPPED, also b152) [EORTC QLQ-C30]	PRO	0.21	70	0.11	0.91 [0.90]	0.10 (-0.10; 0.30)
b130 Energy and drive function *General mental functions of physiological and psychological mechanisms that cause the individual to move towards satisfying specific needs and general goals in a persistent manner.*	PRO	0.30	How much of the time during the past week did you feel worn-out? (b1300) [SF-36]	PRO	0.04	239	0.02	0.84 [0.82]	0.10 (0.03; 0.17)
			How much of the time during the past week did you feel tired? (b1300) [SF-36]	PRO	0.02	240	0.01	0.79 [0.77]	0.08 (0.03; 0.12)
			How much of the time during the past week did you feel full of pep? [SF-36]	PRO	0.02	235	0.02	0.79 [0.79]	0.07 (0.02; 0.13)
			How much of the time during the past week did you have a lot of energy? (b1300) [SF-36]	PRO	0.02	238	0.02	0.78 [0.78]	0.06 (0.03; 0.09)
			Were you tired? (b1300) (NON-MAPPED, also b455) [EORTC QLQ-C30]	PRO	0.11	70	0.04	0.91 [0.90]	0.05 (-0.15; 0.25)
b134 Sleep functions *General mental functions of periodic, reversible and selective physical and mental disengagement from one's immediate environment accompanied by characteristic physiological changes.*	PRO PerfRO	0.32	Have you had trouble sleeping? [EORTC QLQ-C30]	PRO	0.24	66	0.14	0.93 [0.87]	0.46 (0.29; 0.64)
b152 Emotional functions *Specific mental functions related to the feeling and affective components of the processes of the mind.*	PRO	0.35	How much of the time did you feel very nervous? [SF-36]	PRO	0.13	234	0.08	0.87 [0.85]	0.14 (0.05; 0.22)
			Did you feel tense? [EORTC QLQ-C30]	PRO	0.27	68	0.09	0.94 [0.93]	0.24 (0.01; 0.36)
			Did you feel depressed? [EORTC QLQ-30]	PRO	0.32	69	0.10	0.94 [0.92]	0.17 (-0.05; 0.38)
			Did you worry? (NON-MAPPED, also b126) [EORTC QLQ-C30]	PRO	0.21	69	0.06	0.93 [0.91]	0.19 (-0.02; 0.39)
			Did you feel ill or unwell? (NON-MAPPED) [EORTC QLQ-BR23]	PRO	0.26	209	0.13	0.92 [0.90]	0.19 (0.08; 0.30)
			Were you upset by the lost of your hair? [EORTC QLQ-BR23]	PRO	0.11	103	0.07	0.82 [0.83]	-0.03 (-0.15; 0.09)
			Were you worried about your health in the future? [EORTC QLQ-BR23]	PRO	0.06	213	0.03	0.87 [0.85]	0.14 (0.06; 0.21)
			How much have you been emotionally affected by your health condition? [WHODAS]	PRO	0.18	193	0.09	0.89 [0.87]	0.19 (0.08; 0.30)

Table 2. ICF Breast Cancer Core Set and corresponding mapped items for impairment (N = 245) (continued)

ICF Breast Cancer Core Set	Best source	Prevalence of ClinRO Normal	Item [questionnaire]	Reporter	Prevalence of PRO Normal	n	Concordance on Normal	Crude [Expected] agreement	κ_ω (95% CI)
b1801 Body image *Specific mental functions related to the representation and awareness of one's body.*	PRO	0.45	Have you been feeling less feminine as a result of your disease or treatment? [EORTC QLQ-BR23]	PRO	0.53	212	0.28	0.92 [0.89]	0.25 (0.12; 0.39)
			Have you felt physically less attractive as a result of your disease or treatment? [EORTC QLQ-BR23]	PRO	0.34	214	0.20	0.90 [0.87]	0.24 (0.11; 0.36)
			Did you find it difficult to look at yourself naked? [EORTC QLQ-BR23]	PRO	0.45	214	0.22	0.91 [0.89]	0.23 (0.10; 0.36)
			Have you been dissatisfied with your body? [EORTC QLQ-BR23]	PRO	0.32	214	0.16	0.90 [0.87]	0.22 (0.10; 0.34)
b280 Sensation of pain *Sensation of unpleasant feeling indicating potential or actual damage to some body structure.*	PRO	0.24	How much bodily pain have you had during the past 4 weeks? [SF-36]	PRO	0.20	228	0.09	0.94 [0.90]	0.38 (0.26; 0.49)
			How much did pain interfere with your normal work (including both work outside the home and housework)? [SF-36]	SRO	0.26	229	0.13	0.92 [0.87]	0.36 (0.25; 0.46)
			Have you had pain? [EORTC QLQ-C30]	PRO	0.27	65	0.12	0.95 [0.92]	0.28 (0.05; 0.41)
			Did pain interfere with your daily activities? (with d230) [EORTC QLQ-C30]	SRO	0.35	63	0.17	0.94 [0.92]	0.31 (0.05; 0.57)
b2801 Pain in body part *Sensation of unpleasant feeling indicating potential or actual damage to some body structure felt in a specific part, or parts, of the body.*	PRO	0.23	Did you have any pain in your arm or shoulder? (b28014) [EORTC QLQ-BR23]	PRO	0.18	203	0.08	0.93 [0.89]	0.32 (0.21; 0.43)
			Have you had any pain in the area of your affected breast? (b28011) [EORTC QLQ-BR23]	PRO	0.28	203	0.11	0.94 [0.91]	0.29 (0.16; 0.43)
b4352 Functions of lymphatics vessels *Functions related to vascular channels that transport lymph.*	ClinRO	0.34	Did you have a swollen arm or hand? [EORTC QLQ-BR23]	ClinRO	0.55	213	0.30	0.95 [0.90]	0.52 (0.41; 0.63)
			Was the area of your affected breast swollen? (NON-MAPPED) [EORTC QLQ-BR23]	ClinRO	0.49	209	0.21	0.93 [0.90]	0.22 (0.08; 0.35)
b455 Exercise tolerance functions *Functions related to respiratory and cardiovascular capacity as required for enduring physical exertion.*	PerfRO	0.58	Did you need to rest? (b4522) [EORTC QLQ-C30]	SRO	0.10	67	0.06	0.86 [0.85]	0.03 (-0.07; 0.14)
			Were you tired? (b4552) (NON-MAPPED, also b130) [EORTC QLQ-C30]	PRO	0.11	67	0.09	0.87 [0.85]	0.12 (-0.01; 0.25)
b640 Sexual functions *Mental and physical functions related to the sexual act, including the arousal, preparatory, orgasmic and resolution stages.*	PRO Proxy	0.25	To what extent were you interested in sex? (b6400) [EORTC QLQ-BR23]	PRO	0.04	142	0.09	0.86 [0.89]	-0.28 (-0.43; -0.13)
			To what extent was sex enjoyable for you? (b6403) [EORTC QLQ-BR23]	PRO	0.13	80	0.03	0.80 [0.84]	-0.24 (-0.39; -0.08)
b710 Mobility of joints functions *Functions of the range and ease of movement of a joint.*	PerfRO ClinRO	0.32	Was it difficult to raise your arm or to move it sideways? [EORTC QLQ-BR23]	PRO	0.29	200	0.17	0.92 [0.88]	0.34 (0.23; 0.46)
b840 Sensation related to the skin *Sensations related to the skin such as itching, burning sensation and tingling.*	SRO ObsRO	0.54	Have you had skin problems on or in the area of your affected breast (e.g., itchy, dry, flaky)? [EORTC QLQ-BR23]	SRO	0.41	209	0.23	0.90 [0.89]	0.07 (-0.04; 0.18)

κ_ω: Quadratic Kappa 95% CI: 95% Confidence interval

Table 3. ICF Breast Cancer Core Set and corresponding mapped items for activity limitations (N = 245)

ICF Breast Cancer Core Set	Best source	Prevalence of ClinRO Normal	Item [questionnaire]	Reporter	Prevalence of PRO Normal	n	Concordance on Normal	Crude [Expected] agreement	κ_ω (95% CI)
d230 Carrying out daily routine *Carrying out simple or complex and coordinated actions in order to plan, manage and complete the requirements of day-to-day procedures or duties, [...]*	SRO ObsRO	0.56	Were you limited in doing either your work or other daily activities? [EORTC QLQ-C30]	SRO	0.18	67	0.12	0.90 [0.86]	0.27 (0.08; 0.46)
			Did pain interfere with your daily activities? (with b280) [EORTC QLQ-C30]	SRO	0.35	67	0.19	0.93 [0.90]	0.27 (0.02; 0.53)
d430 Lifting and carrying objects *Raising up an object or taking something from one place to another, such as when lifting a cup or carrying a child from one room to another.*	SRO ObsRO PerfRO	0.25	Does your health limit you in lifting or carrying groceries? [SF-36]	SRO	0.19	234	0.11	0.92 [0.88]	0.39 (0.28; 0.50)
			Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or suitcase? [EORTC QLQ-C30]	PRO	0.13	68	0.06	0.91 [0.87]	0.31 (0.13; 0.48)
d510 Washing oneself *Washing and drying one's whole body, or body parts, using water and appropriate cleaning and drying materials or methods [...]*	SRO ObsRO PerfRO	0.84	Do you need help with eating, dressing, washing yourself or using the toilet? (NON-MAPPED, also d540, d550) [EORTC QLQ-C30]	SRO	0.93	69	0.86	0.99 [0.99]	0.46 (0.15; 0.77)
			How much difficulty did you have in washing your whole body? [WHODAS]	PRO	0.87	195	0.78	0.98 [0.97]	0.26 (0.10; 0.42)
d540 Dressing *Carrying out the coordinated actions and tasks of putting on and taking off clothes and footwear in sequence and in keeping with climatic and social conditions, [...]*	SRO ObsRO PerfRO	0.85	Do you need help with eating, dressing, washing yourself or using the toilet? (NON-MAPPED, also d510, d550) [EORTC QLQ-C30]	SRO	0.93	68	0.82	0.98 [0.98]	0.25 (-0.06; 0.56)
			How much difficulty did you have in getting dressed? [WHODAS]	PRO	0.87	192	0.79	0.98 [0.97]	0.21 (0.04; 0.37)
d550 Eating *Carrying out the coordinated tasks and actions of eating food that has been served, [...]*	SRO ObsRO PerfRO	0.92	Do you need help with eating, dressing, washing yourself or using the toilet? (NON-MAPPED, also d510, d540) [EORTC QLQ-C30]	SRO	0.93	69	0.91	0.99 [0.99]	-0.03 (-0.07; 0)
			How much difficulty did you have in eating? [WHODAS]	PRO	0.94	193	0.89	0.99 [0.99]	0 (-0.10; 0.09)
d640 Doing housework *Managing a household by cleaning the house, washing clothes, using household appliances, storing food and disposing of garbage, [...]*	SRO ObsRO PerfRO	0.30	Does your health limit you in moderate activities, such as moving a table, pushing a vacuum cleaner, bowling or playing golf? [SF-36]	SRO	0.22	231	0.11	0.93 [0.89]	0.38 (0.24; 0.51)
			How much difficulty did you have in doing most important household tasks well? (with d210, d220) [WHODAS]	PRO	0.38	190	0.14	0.94 [0.90]	0.45 (0.30; 0.60)
			How much difficulty did you have in getting all the household work done that you needed to do? (with d210, d220) [WHODAS]	PRO	0.26	191	0.11	0.93 [0.87]	0.44 (0.32; 0.57)
			How much difficulty did you have in getting your household work done as quickly as needed? (with d210, d220) [WHODAS]	PRO	0.15	189	0.06	0.92 [0.87]	0.43 (0.32; 0.54)

κ_ω: Quadratic Kappa
95% CI: 95% Confidence interval

Table 4. ICF Breast Cancer Core Set and corresponding mapped items for participation restrictions (N = 245)

ICF Breast Cancer Core Set	Best source	Prevalence of ClinRO Normal	Item [questionnaire]	Reporter	Prevalence of PRO Normal	n	Concordance on Normal	Crude [Expected] agreement	κ_ω (95% CI)
d720 Complex interpersonal interactions *Maintaining and managing interactions with other people, in a contextually and socially appropriate manner, [...]*	PRO ObsRO Proxy	0.67	How much difficulty did you have in making new friends? (with d7500) (d7200) [WHODAS]	PRO	0.54	188	0.44	0.92 [0.90]	0.21 (0.06; 0.37)
d750 Informal social relationship *Entering into relationships with others, such as casual relationships with people living in the same community or residence, or with co-workers, students, playmates or people with similar backgrounds or professions.*	PRO ObsRO Proxy	0.73	How much difficulty did you have in making new friends? (with d7200) (d7500) [WHODAS]	PRO	0.54	188	0.39	0.92 [0.90]	0.23 (0.06; 0.41)
			How much difficulty did you have in maintaining friendship? (d7500) [WHODAS]	PRO	0.80	189	0.61	0.96 [0.94]	0.35 (0.10; 0.60)
			How much difficulty did you have in getting along with people who are close to you? (with d760, d770) [WHODAS]	PRO	0.85	190	0.65	0.97 [0.95]	0.24 (0.10; 0.38)
d760 Family relationships *Creating and maintaining kinship relationships, such as with members of the nuclear family, extended family, foster and adopted family and step-relationships, more distant relationships such as second cousins, or legal guardians.*	PRO ObsRO Proxy	0.84	Has your condition or medical treatment interfered with your family life? [EORTC QLQ-C30]	PRO	0.37	69	0.28	0.91 [0.90]	0.18 (-0.05; 0.41)
			How much difficulty did you have in getting along with people who are close to you? (with d750, d770) [WHODAS]	PRO	0.85	194	0.75	0.97 [0.96]	0.30 (0.12; 0.49)
d770 Intimate relationships *Creating and maintaining close or romantic relationships between individuals, such as husband and wife, lovers or sexual partners.*	PRO ObsRO Proxy	0.48	To what extent were you sexually active (with or without intercourse)? (d7702) [EORTC QLQ-BR23]	PRO	0.05	162	0.19	0.87 [0.89]	-0.20 (-0.33; -0.08)
			How much difficulty did you have in sexual activities? (d7702) [WHODAS]	PRO	0.32	139	0.27	0.84 [0.77]	0.29 (0.17; 0.42)
			How much difficulty did you have in getting along with people who are close to you? (with d750, d760) [WHODAS]	PRO	0.85	151	0.51	0.94 [0.93]	0.18 (0.04; 0.32)
d850 Remunerative employment *Engaging in all aspects of work, as an occupation, trade, profession or other form of employment, for payment, as an employee, full or part time, or self-employed, such as seeking employment and getting a job, doing the required tasks of the job, attending work on time as required, supervising other workers or being supervised, and performing required tasks alone or in groups.*	PRO ObsRO	0.18	How much difficulty did you have in getting your work done as quickly as needed? [WHODAS]	PRO	0.10	47	0.21	0.88 [0.78]	0.43 (0.17; 0.68)
			How much difficulty did you have in getting done all the work that you needed to do? [WHODAS]	PRO	0.15	46	0.26	0.88 [0.81]	0.39 (0.11; 0.68)
			How much difficulty did you have in doing your day-to-day work/school tasks well? [WHODAS]	PRO	0.15	47	0.30	0.86 [0.78]	0.35 (0.06; 0.65)
			How much difficulty did you have in your day-to-day work/school? [WHODAS]	PRO	0.13	46	0.26	0.85 [0.77]	0.35 (0.06; 0.65)

Table 4. ICF Breast Cancer Core Set and corresponding mapped items for participation restrictions (N = 245) (continued)

ICF Breast Cancer Core Set	Best source	Prevalence of ClinRO Normal	Item [questionnaire]	Reporter	Prevalence of PRO Normal	n	Concordance on Normal	Crude [Expected] agreement	κ_ω (95% CI)
d920 Recreation and leisure *Engaging in any form of play, recreational or leisure activity, such as informal or organized play and sports, programmes of physical fitness, relaxation, amusement or diversion, going to art galleries, museums, cinemas or theatres; engaging in crafts or hobbies, reading for enjoyment, playing musical instruments; sightseeing, tourism and travelling for pleasure.*	PRO SRO ObsRO	0.47	To what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbours, or groups? (d9205) [SF-36]	PRO	0.34	235	0.26	0.90 [0.87]	0.22 (0.09; 0.35)
			Does your health limit you in vigourous activities, such as running, lifting heavy objects, participating in strenuous sports? (d9201) [SF-36]	SRO	0.06	235	0.04	0.83 [0.79]	0.16 (0.08; 0.24)
			Were you limited in pursuing your hobbies or other leisure time activities? [EORTC QLQ-C30]	SRO	0.18	67	0.10	0.91 [0.87]	0.32 (0.05; 0.58)
			Has your physical condition or medical treatment interfered with your social activities? (NON-MAPPED) [EORTC QLQ-C30]	PRO	0.32	68	0.16	0.91 [0.87]	0.32 (0.10; 0.54)
			How much difficulty did you have in doing things for relaxation or pleasure by yourself? [WHODAS]	PRO	0.30	192	0.51	0.87 [0.86]	0.04 (-0.11; 0.19)

κ_ω: Quadratic Kappa
95% CI: 95% Confidence interval
Formula for weighted Kappa, where ω_{ij} is the disagreement weight for the ij cells, p_{oij} is the proportions of observed judgments for the ij cells and p_{eij} is the proportion expected by chance for the ij cells:

$$\kappa_\omega = \frac{\sum \omega_{ij} p_{oij} - \sum \omega_{ij} p_{eij}}{1 - \sum \omega_{ij} p_{eij}}$$

Table 5. Spectrum of agreement on breast cancer disability between questionnaire information and expert evaluation using the categories of the ICF Breast Cancer Core Set

Disability best assessed by	# Items	Level of agreement (Kappa, range of agreement)			
		None [<0]	Poor [0.0-0.20]	Fair [0.21-0.40]	Moderate [0.41-0.60]
Impairment	**36**	**3**	**18**	**13**	**2**
PRO	30	3 (10%) [-0.28, -0.03]	16 (53%) [0.04, 0.19]	10 (33%) [0.22, 0.38]	1 (3%) [0.46]
SRO	4	0	2 (50%) [0.03, 0.07]	2 (50%) [0.31, 0.36]	0
ClinRO	2	0	0	1 (50%) [0.22]	1 (50%) [0.52]
Activity limitation	**14**	**1**	**1**	**8**	**4**
PRO	7	0	1 (14%) [0]	3 (43%) [0.21, 0.31]	3 (43%) [0.43, 0.45]
SRO	7	1 (14%) [-0.03]	0	5 (71%) [0.25, 0.39]	1 (14%) [0.46]
Participation restrictions	**18**	**1**	**4**	**12**	**1**
PRO	16	1 (6%) [-0.2]	3 (19%) [0.04, 0.18]	11 (69%) [0.21, 0.39]	1 (6%) [0.43]
SRO	2	0	1 (50%) [0.16]	1 (50%) [0.32]	0
TOTAL	**68**	**5**	**23**	**33**	**7**
PRO	**53**	4 (8%)	20 (38%)	24 (45%)	5 (9%)
SRO	**13**	1 (8%)	3 (23%)	8 (62%)	1 (8%)
ClinRO	**2**	0	0	1 (50%)	1 (50%)

Chapter 10: Integration of Manuscripts 4 and 5

Research questions of Manuscripts 4 and 5

Manuscript 4:

To estimate the extent of agreement between health professionals' (ClinRO) and patients' (PRO) ratings on disabilities associated with breast cancer (impairments, activity limitations and participation restrictions).

Manuscript 5:

To empirically test a bio-psycho-social conceptual model of HRQOL for breast cancer survivors.

Integration of Manuscripts 4 and 5

First, before integrating Manuscripts 4 and 5, it is important to mention that the work of Manuscript 3 was also the prelude of Manuscript 5. The codes provided by the mapping exercise allowed the items to be paired and served as a guide for the creation of the latent variables of Manuscript 5.

In Manuscript 4, items answered by participants and health care professionals were compared to see if there was an agreement between both. It was found that participants provided valuable information on impairments at the mental level function and pain; whereas clinicians provided more accurate information on physically assessed impairment.

In Manuscript 5, items are combined to create latent variables in order to test the Wilson-Cleary (W-C) model. The first two levels (biology and symptoms) include latent variables with both participants' and clinicians' answers; whereas the two following levels (function and general health perception) are filled exclusively with participants' answers. All rubrics of the W-C model were fulfilled; however, it was not possible to model up to overall quality of life as there was too much missing data.

Chapter 11: Manuscript 5

Foundations of quality of life in women with breast cancer: A structural equation modeling approach

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Foundations of quality of life in women with breast cancer: A structural equation modeling approach

Abstract

Objective: The effectiveness of early diagnosis and treatment has now made breast cancer a chronic disease where impairments, activity limitations and participation restrictions, well-known sequelae of (breast) cancer treatment, lead to poor health perception and sub-optimal quality of life (QOL). The Wilson-Cleary (W-C) model of health related QOL (HRQOL), which suggests causal links between biological and physiological factors, symptoms status, functional status, general health perceptions and overall QOL, has not been adequately tested in breast cancer. To improve understanding of how the sequelae of breast cancer and its treatment lay the foundation of QOL, the aim of this study was to empirically test a bio-psycho-social model of QOL for breast cancer survivors.

Methods: Women completed five outcomes measures (SF-36, EORTC QLQ C30 and -BR23, WHODAS, and WHOQOL), all of which have been previously mapped to the International Classification of Functioning, Disability and Health (ICF)); health care professionals completed the ICF Breast Cancer Core Set. Latent variables were created based on measures and individual items related to the same construct. All rubrics of the W-C model were fulfilled. A structural equation model (SEM) was fit using M*plus*.

Results: A total of 245 women (mean age 57) participated. A penultimate model, have an acceptable fit (CFI: 0.921; TLI: 0.899; RMSEA: 0.058; 0.062) and where 3 variables were endpoints. An ultimate model obtained a better fit (CFI: 0.937; TLI: 0.917; RMSEA: 0.052; 0.060), where Biology and Symptom are under the same rubric and where "perception" of self and of emotion are under General health perception rubric.

Conclusion: Pain had the strongest influence on all functioning variables and perception of self. Effort should be made to reduce the symptoms of pain early on in the continuum of care. The W-C model provided a good framework to inform breast cancer outcomes.

Introduction

One in every 9 women will develop breast cancer in their life time making this the leading cancer among women worldwide[1;2]. The outcome of a breast cancer diagnosis has changed over the past decades from duration of life to life's quality, and now it is seen as a chronic disease. The impact of breast cancer and its treatments are known to affect anatomical structures, physiological functions, activities normal for everyday life, and full participation in life's roles. These lead to a perception of poor health and are also the foundations for quality of life (QOL)[3;4].

QOL is an inclusive construct targeting all aspects of life, including those outside of health. The World Health Organization (WHO) as defined QOL as the "individuals' perception of their position in life in the context of the culture in which they live and in relation to their goals, expectations, standards and concerns"[5]. In the context of breast cancer, QOL is quite predominant, so why do we need yet another study?

One of the challenges faced in QOL research is the inconsistent and often incorrect use of terminology[6;7]. For example, health-related quality of life (HRQOL) and QOL are use quite often interchangeably in the literature. HRQOL has been defined as "a term referring to the health aspects of QOL, generally considered to reflect the impact of disease and treatment on disability and daily functioning; it has also been considered to reflect the impact of perceived health on an individual's ability to live a fulfilling life. However, most specifically HRQOL is a measure of the value assigned to duration of life as modified by impairments, functional states, perceptions and opportunities, as influenced by disease, injury, treatment and policy."[7] Therefore, HRQOL could be seen as construct formed by combining its components in an algorithmic fashion rather than as a primary construct easily spoken about whereas QOL is a more fundamental construct understood by all[8]. These terms refer to quite different concepts and must not be used interchangeably[7].

A limitation in understanding the functional foundations of QOL along the breast cancer continuum of care is that there is a variety of measurement approaches are used to identify areas of impairment making the interpretation of the results difficult to generalize

and to compare across studies[9]. An important way forward is to apply existing measurement models and two are in wide use: the International Classification of Functioning, Disability and Health (ICF) framework[10] and the Wilson-Cleary (W-C)[11] model. These can guide clinicians, researchers, and patients to identify what is important, to describe current state, to indicate appropriate measures, and ultimately to interpret these exteriorized signs of breast cancer impact in a broader perspective as foundations for QOL[9;10].

Even though conceived of independently, the ICF and W-C models are both considered bio-psycho-social models and as such share common constructs[12] as shown in Figure 1. Under the W-C model, all of the constructs to the left of QOL would be considered to reflect HRQOL. Under the ICF model, all of the constructs excluding health perception and QOL reflect the positive construct of function or its negative opposite, disability.

The W-C model has five rubrics: biological and physiological variables, symptom status, functional status, general health perceptions, and overall QOL. In counterpart, the ICF model provides codes for the first three levels of the W-C model. The body structure and function of the ICF model will correspond to the biological and physiological variables and the symptom status of the Wilson-Cleary model. Coding of the ICF model for activity and participation can be integrated into the functional status of the W-C model. Last, the W-C model will talk about characteristics of the individual and the environment, whereas the ICF will consider those two items as being personal and environmental factors, which can influence all five rubrics[12]. Even if Figure 1 seems to indicate that the two models are linear, the components mutually affect each other.

The bio-psycho-social approach to understanding the effects of breast cancer has not been fully explored. The W-C model in particular has been tested in other medical conditions[6;13-20] and community-dwelling elderly[21], as well as in some cancers (Hodgkin's lymphoma, advanced cancer, and breast cancer)[22-24].

In breast cancer, our research team applied the W-C model in a very small study and as such does not provide an adequate evaluation[24]. The pilot study done by Dawes et al. (2008)[24] used the W-C model as their theoretical model to inform on the relationships

between impairments, activity limitations, participation restrictions and sub-optimal HRQOL in a breast cancer population. This study used path analysis, an extension of a multiple regression model[25], which allows for different influences on outcomes. The results of 50 women[24] indicated that pain was a key factor in the path to activity limitation, participation restriction, and sub-optimal HRQOL.

In advanced cancer, Rodriguez et al. (2013)[23] used measures that fit under the rubrics of the W-C model in stepwise multiple linear regression. They found that social support was the most important contributor to overall QOL, followed by general health perceptions, energy, social function, psychological function and physical function. The aim of this study was to identify whether different QOL measures were influenced by different constructs but the authors concluded that future studies should focus on structural equation modeling (SEM) to derive a more valid representation of this important and complex construct. SEM combines factor analysis, path analysis, and regression incorporating latent variables[25-27].

To improve understanding of how the sequelae of breast cancer and its treatment lay the foundation of QOL, the aim of this study was to empirically test a bio-psycho-social model of QOL for breast cancer survivors.

Methods

Source of data

The data for this analysis arise from the development of the ICF Breast Cancer Core Set. Prior steps to the development of an ICF Core Set involve: 1) Delphi survey[28], 2) systematic review[29], and 3) experts consensus[30]. The data collected here were for the validation of the Core Set. A total of 245 women were assessed once between 2004 and 2007 in nine different sites. In order to be included in the study, the participants had to have breast cancer as their main diagnosis, and be at least 18 years old. In addition, there was no specific time frame post-treatment to be involved in the study. The results of this study have not been published and we have been the first to report on the validation of

the ICF Breast Cancer Core Set[31]. The project was approved by the Research Ethics Boards of each participating institution, and all participants gave informed consent.

Overview of design

This cross-sectional analysis of data aimed to explore the structure and relationships among variables falling under the rubrics of the W-C model (personal characteristics, biology, symptoms, function, health perception, overall QOL, and characteristics of the environment) and operationalized using SEM. This advanced statistical methods was chosen as it is designed for testing a priori hypothesized relationships among multiple correlated variables[25-27]. One of the advantages of using SEM is the use of latent variables. This allows, by way of confirmatory factor analysis, the combination of measured correlated variables into latent (unobserved) constructs[26]. For constructs that are not directly measureable, the creation of latent variables reduces their measurement error.

Measures

Five legacy questionnaires [SF-36[32] (n=244), EORTC QLQ-C30[33] (n=71)/BR23[34] (n=218), WHODAS II[35] (n=198), and WHOQOL[36] (n=46)], completed by the participants, and the ICF Breast Cancer Core Set (n=245), filled by the health care professionals, formed the main dataset. These measures have all been linked previously to the ICF framework[37-39].

When the original study was designed, neither modeling QOL nor an SEM environment was in the analytical framework. Fortunately, the measures used reflected all the rubrics of the W-C model (Figure 2), including basic demographic and cancer-related information. Not all sites completed all questionnaires. In particular, only 29% of people completed the EORTC QLQ-C30 and 19% the WHOQOL; these measures were excluded from further analyses. Missing data on these questionnaires are considered ignorable as they were missing completely at random (MCAR). For other variables, missing data was minimal or less than 20% and the full information maximum likelihood (FIML) function within the SEM software (M*plus*) provided a solution[25;27].

To create latent variables, measures and individual items relating to the same construct were grouped and placed under the matching rubrics of the W-C model. SEM is optimally performed with continuous variables and it is preferable to keep all the items of a measure together[26], however, some constructs were better represented if items from measures were separated and placed under different latents.

For example, the three items of "Arm symptoms (BRAS)" scale of the EORTC QLQ-BR23[34] (Did you have any pain in your arm or shoulder?; Did you have a swollen arm or hand? Was it difficult to raise your arm or to move it sideways?) were respectively reconsidered under the latent variables "Pain", "Lymphatic system", and "Shoulder function". All measurement scales were rescored to have 0 to represent "worst level or complete impairment" and the highest score to the "best or no impairment". Functional scales of the EORTC QLQ-C30 (Physical, role, cognitive, emotional, social) already use this scale structure. However, the symptom scales (fatigue, pain, and nausea and vomiting) typically have a higher score indicating a poor level, more fatigue, as an example[33] and needed rescoring.

Statistical methods

The sample was characterized and distribution of measures was summarized using descriptive statistics. SEM was used to test the W-C theoretical model against the observed data. SEM encompasses factor analysis, path analysis and regression[25-27]. It has the ability to concurrently estimate a priori hypotheses concerning both direct and indirect relationships between and among constructs and variables within multiple alternative models[25].

SEM has both measurement and structural components[26]. Factor analysis was used for the measurement model to test the relationships between the observed variables and unobserved latents. Some latent variables could not be represented by the minimum of three observed variables[25] so either a single observed variable was used or the latent was removed from the analyses for theoretical reasons and/or model fit.

The structural model followed the sequences hypothesized by the W-C model. As a general strategy, correlations between the latent and observed variables within each W-C rubrics were allowed; e.g. biological variables were allowed to correlate with each other. Initially, only paths across adjacent rubrics were allowed; e.g. paths between biology and symptoms, and between symptoms and function. Only the paths that were significant and/or theoretically relevant were kept. Paths across a non-adjacent rubric were subsequently added, based on the modification indices, and were retained only if the model fit was improved.

Multivariate normality is an assumption of SEM and was tested prior to the analysis. As many construct-specific measures were not normally distributed, all models were estimated using robust maximum likelihood (MLM) estimation, which adjusts the standard error estimates and produce a more accurate Chi-square (χ^2) statistics[25]. Categorical variables were modeled as continuous variables as they all had more than four response levels[40].

Goodness of fit of the model was assessed using: Satorra-Bentler scaled χ^2, Comparative Fit Index (CFI), Tucker-Lewis Fit Index (TLI), Root Mean Square Error of Approximation (RMSEA), and the Standardized Root Mean Squared Residual (SRMR)[25;41]. For χ^2, a p-value greater than 0.05 indicate good fit. For CFI and TLI, values greater than 0.90 are indicative of reasonably good fit, greater than 0.95 are acceptable fit and 0.97 are good fit. Both measures fit relative to an independence model, however, a correction for model complexity is included with the TLI. RMSEA is a measure of global close fit where values less than 0.05 represent good fit and values up to 0.08 are considered reasonable. SRMR is a measure of badness of fit based on fitted residuals, values less than 0.05 represent good fit and values up to 0.10 are reasonable.

One of the limitation of SEM is the requirement of a large sample size, which will influence the model complexity[25], and often a minimum of 200 participants is recommended[25;27]. A "rule-of-thumb" suggests that 10 subjects per parameter estimated are needed for reliability. As the number of variables yielded more parameters than the sample size could support, irrelevant variables were thus eliminated (e.g. collinearity,

strong correlation with the outcome, or severely violating the assumption of normality). Statistical analyses were performed with SAS 9.4 software for data preparation and descriptive statistics, and M*plus* version 6.12 software was used for SEM.

Results

Table 1 presents the characteristics of the 245 participants. Seventy-nine percent of the participants were diagnosed at Stage I or II, indicating that the tumor was maximum 50mm in its greatest dimension with or without minimal lymph node invasion, or a tumor greater than 50mm with no lymph node involved[42]. All participants had at least one surgical procedure (42% had between 2 and 5 surgeries), and their breast cancer stage might suggest that surgery was combined with radiation therapy and/or chemotherapy (information not available regarding type of breast and/or axilla surgery, nor on subsequent treatments). Assessments were done at a median time of 9 months post-surgery, within the first two critical years where most of impairment, activity limitations and participations restrictions occur.

Figure 2 shows the initial hypothesized model with measures under all the rubrics of the W-C model. Apart from characteristics of the individual and the environment, there were 9 latent variables for biology, 7 for symptoms, 6 for function, and one each for general health perception and overall QOL. Fit of this initial model was poor as the sample size of 245 participants was inadequate. As the latent QOL was formed by items from questionnaires (EORTC QLQ-C30 and WHOQOL) that had too much missing data, the model was truncated at General Health Perception and did not cover the QOL rubric.

Table 2 Part A outlines the model progression for the W-C model ending at general health perception. The strict interpretation of the W-C model is a progression from biological factors (B) to symptoms (S) to functioning (F) to health perception (HP). The initial biology to symptoms progression of the penultimate model fitted with an acceptable to a good fit of the model; TLI greater than 0.90, CLI greater than 0.95, RMSEA and SRMR both below 0.05. In this and all subsequent models, Satorra-Bentler χ^2 were all below 0.05, except for the biology to function path of the ultimate model (Part

B, B to F, p-value = 0.09), suggesting a poor fit. This was offset by the sample size and low ratio of the χ^2 to its degrees of freedom (1.5). To improve our fit of the model, a path from biology to function had to be allowed. Even with the additional path, the penultimate model fit was below acceptable for TLI (0.899), and reasonable for CFI (0.921), RSMEA (0.058) and SRMR (0.062).

Table 3 provides the direct effects between the variables of the penultimate model. The "ON" statement represents the paths between the variables and the "WITH" statement illustrates the correlations. Let's recall that low score indicate complete impairment and high score indicate no impairment. For example, a change of 1 unit of the latent lymphatic, will improve by 22.2 units the symptoms of the latent pain, meaning that the better the lymphatic function is, less likely the patient will experienced pain. To note, the only variable that was not reversed is the breast cancer stage (BCSTAGE), indicating in this situation that a change of 1 unit in the cancer stage severity will decrease both the body image (BRBI) and physical function (PFI) by 2.8 and 3.1 units respectively.

Figure 3 depicts this model and shows that three constructs, 1) body image (BRBI, represented by an observed variable, 2) the latent variable representing emotion, and 3) the latent variable for general health perception (GHP) were endpoint constructs. This suggests that a different model design was needed to better represent these features of the data.

Table 2 Part B outlines the progression of analyses leading to the ultimate model. The first paths linked the biology variables with function, which provided a good fit for CFI (0.981), TLI (0.965), and RMSEA (0.043) and a reasonable fit for SRMR (0.063). We then introduced the correlations between biology and symptom (pain) with paths to function, which provided a good fit for CFI (0.957), RMSEA (0.0.054), and SRMR (0.051) and a reasonable fit for TLI (0.933). The number of iterations was reached when we were modeling to the rubric health perception. However, allowing a path from the latent pain to perception of self provided a model with a good fit for RMSEA (0.052) and a reasonable fit for CFI (0.0937), TLI (0.917) and SRMR (0.060).

Figure 4 depicts this ultimate model, where the end point variables from the penultimate model were reconsidered under the rubric general health perception. In addition, the latent pain was moved under biology and was correlated with both breast cancer stage and lymph variables.

Table 4 describes the cohort on the variables of ultimate model ordered from impairment (biology) through to general health. The number of participants who answered each item is provided along with the means of the observed and imputed data (FIML – accounting for missing data). All observed and imputed means are alike, except for Role emotional (ROLEM) (observed = 58.6, imputed = 57.9), suggesting that participants who did not answered might have their emotional role more likely to be less. In addition, Table 4 also provides the variables legend for the models.

Table 5 provides the direct effects between the variables of the ultimate model. The non-significant paths (dashed arrows, Figure 4) were kept in the model as they were theoretically relevant. However, as they are non-significant, their direct effects values should not be considered. For example, an improvement of 1 unit in lymph function, decrease the emotional role by 19 units, which is contradictory to theory that usually indicates a better emotional role when lymphedema is not present[43]. As expected, and similar to other findings[24], the latent pain is the variable that has the greatest influence in this model. An amelioration of 1 unit toward less pain is associated with an increase in all function variables (PFI = 14.4, SOCIAL = 8.4, ROLPH = 21.7, ROLEM = 21.7), and a greater perception of self (BRBI = 8.6).

Discussion

This study explored the foundation of QOL in a sample of breast cancer women post-cancer treatment, using the W-C model and operationalized with SEM. Overall, pain played the predominate role as it influenced all the physical, social, and role variables as well as perception of self. Pain had the strongest impact on the two role variables (b=21.7 ROLPH and b= 21.7 ROLEM), not surprising given the roles mainly related to challenges with work or other regular activities (see Table 5).

The causes of pain after breast cancer are multi-factorial[44] and include nerve and tissue damage from surgery, chemotherapy and radiotherapy. Pain can greatly affect physical and mental well-being, which ultimately will lead to a poorer QOL[44;45]. Patients tend to under report symptoms of pain and health care professionals will often neglect to ask about pain[45]. The results of this study support the importance of good communication between patients and health care professionals about treatment consequences that affect QOL and are potentially amenable to intervention.

In an earlier study on a smaller sample recruited clinically, Dawes et al. (2008)[24] also found that arm dysfunction was more strongly affected by pain than by lymphedema. Our model included paths from lymphatic function as they were theoretically relevant, but not statistically significant (in the penultimate model, lymphatic function had a strong influence on pain and body image supporting its relevance).

Lymphedema is a chronic condition caused by an imbalance between interstitial fluid production and transport capacity of the lymphatic system, and as a result the affected area (e.g. breast, arm) is swollen[46]. Lymphedema may lead to physical impairments (e.g. pain) and mental impairment (e.g. decreased self-confidence due to a distorted body image caused by the swollen limb) and have a significant negative impact on QOL[47].

This penultimate model provided a reasonable fit for almost all fit indices (CFI=0.921, RMSEA=0.058 and SRMR=0.062), except for TLI (0.899). As the observed variable "body image" (BRBI) and the latent variable "emotion" were endogenous variables, and the fit indices were only reasonable, we had to reconsider this model (Figure 3). The EORTC QLQ-BR23 body image measure (BRBI) is composed of the following items: "Have you felt physically less attractive as a result of your disease or treatment?; Have you been feeling less feminine as a result of your disease or your treatment?; Did you find it difficult to look at yourself naked?; and Have you been dissatisfied with your body?" Therefore, we considered that this measure would be more relevant by being reconsidered under "perception of self" rather than under symptoms, as those items reflect how the person's perceive herself image.

We also reconsidered the latent "emotion", which is composed of the following items and measures: EORCT QLQ-BR23 future perspective single item measure (BRFU – Were

you worried about your health in the future); SF-36 mental health measure (MHI –Have you been a very nervous person?; Have you felt so down in the dumps that nothing could cheer you up?; Have you felt calm and peaceful?; Have you felt downhearted and low?; Have you been a happy person?), WHODAS item D6.5 (RD6.5 – How much have you been emotionally affected by your health condition?) and ICF code b126 (Rbr126 – Temperament and personality functions). Here too, we considered that those items were better expressed as being perception of emotion rather than under symptoms, as it is reflecting how the person's emotionally perceive herself.

The reconfiguration of perception of self and perception of emotion under the rubric perception of health, and pain now under "impairment" (Figure 4) provided a simpler model with reasonable to good fit indices. We found that the W-C model held well from "impairment" to function and to health perception. Thus, our findings are illustrated in the redrawn W-C and ICF models in Figure 5. Our results suggest that ultimately, the foundations for QOL are a mix of perceptions of health, self and emotion. The EORTC QLQ-BR23 is a breast cancer specific questionnaire commonly used and it captures those three concepts. This questionnaire should thus be considered when researchers are interested in reporting on the patient's QOL.

The W-C model was used as the main framework to guide our hypothesized model. As health care professionals completed the ICF Breast Cancer Core Set and participants filled five legacy questionnaires all mapped to the ICF Framework, we consider that the W-C model was strongly influenced by the ICF model. Both have considerable conceptual and operational overlap, where the ICF codes for body function and body structure will inform the first two rubrics of the W-C model. In the redrawn model, we had to reconsider the first two rubrics into one, combining the biological variable (BCSTAGE) of the W-C model and the body function (impairment of lymphatic function and pain) of the ICF model, thus removing the symptom rubric.

There are several limitations to our approach. This study was not originally designed to conduct SEM analyses. The aim of the original study was to validate the ICF Breast Cancer Core Set. However, when dealing with SEM, a sample size around 200 participants only allows modeling simpler model. We had a lot of available items, but we

had to simplify the model in order to have a good fitting model. We kept what was relevant for us regarding impairment, activity limitations and participation restrictions. Therefore, another significant model could have emerged if conducting the analyses based on other disabilities.

In addition, the measurement strategy did not include any direct measures of arm impairment, such as arm circumferences measuring for arm lymphedema or range of motion addressing arm mobility issues. Having measured data on arm circumferences would probably had informed better the lymphatic function, as patients' reporting on signs and symptoms of lymphedema tend to be lower than when it is physically measured[48].

Because some data were MCAR on more that 75% of the sample, imputation was not possible to perform and we had to remove items from both the EORTC QLQ-C30 and the WHOQOL questionnaires. Those questionnaires were capturing relevant information regarding all five rubrics of the W-C and ultimately informing on overall QOL. Thus, we ended our model at general health perception rather than continuing on to overall QOL.

The W-C model, combined with the ICF model, had never been tested in breast cancer using SEM. We found that pain had the greatest influence on functioning and that the W-C model is a good framework informing on breast cancer outcomes. A better understanding of the components of HRQOL during the continuum of care is vital in the development of a more integrated and person-centered approach to enhance health management post-breast cancer treatments.

In this context, a potentially life shortening and disability inducing health condition would impact on all of life experiences that make up QOL. As impairment, activity limitation and participation restriction can affect the person at any time during the course of treatment and/or after, it is important that every stakeholder (e.g. physician, rehabilitation specialist) focus on reducing breast cancer impairments. In addition, as arm impairment also varies along the continuum of care, future research should consider the evolution of QOL and its components over time.

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Table 1. Descriptive statistics

Demographic (N = 245)	**Mean (SD) / Frequency (%) [range]**
Age (years)	56.8 (10.6) [29 – 86]
BMI (kg/m^2)	26.7 (4.5) [18 – 44]
Living situation:	
Alone	59 (24%)
With someone	182 (74%)
Missing	4 (2%)
Occupation:	
Working	94 (38%)
Unemployed	54 (22%)
Retired	97 (40%)
Condition specific	**Mean (SD) / Frequency (%) [range]**
Breast cancer stages*:	
Stage 0	8 (3%)
Stage I	78 (32%)
Stage IIA	71 (29%)
Stage IIB	36 (15%)
Stage IIIA	24 (10%)
Stage IIIB	17 (7%)
Stage IV	6 (2%)
Missing	5 (2%)
Time since last surgery (months)	21 (35) [0.1 – 317] 2.5^{th}: 1.4 25^{th}: 5.2 Median 8.9 75^{th}: 20.8 97.5^{th}: 107.6

*** Breast cancer stages definition**				
Stage 0	Tis	N0	M0	**Primary Tumor (T)**
Stage IA	T1	N0	M0	Tis: Carcinoma in situ
Stage IB	T0	N1mi	M0	T0: No evidence of primary tumor
	T1	N1mi	M0	T1: Tumor ≤ 20 mm in greatest dimension
Stage IIA	T0	N1	M0	T2: Tumor > 20 mm but ≤ 50 mm in greatest dimension
	T1	N1	M0	T3: Tumor > 50 mm in greatest dimension
	T2	N0	M0	T4: Tumor any size growing into the chest wall or the skin
Stage IIB	T2	N1	M0	**Regional Lymph Nodes (N)**
	T3	N0	M0	N0: No regional lymph node metastases
Stage IIIA	T0	N2	M0	N1: Cancer has spread to 1 to 3 axillary lymph nodes
	T1	N2	M0	N1mi: Micrometastases in 1 to 3 axillary lymph nodes
	T2	N2	M0	N2: Cancer has spread to 4 to 9 axillary lymph nodes, or enlarged internal mammary lymph nodes
	T3	N1	M0	
	T3	N2	M0	N3: Cancer has spread to > 10 axillary lymph nodes, with at least one area > 2mm, and/or clavicular lymph node involved and/or enlarged internal mammary lymph nodes
Stage IIIB	T4	N0	M0	
	T4	N1	M0	
	T4	N2	M0	**Distant Metastases (M)**
Stage IIIC	Any T	N3	M0	M0: No clinical or radiographic evidence of distant metastases
Stage IV	Any T	Any N	M1	M1: Cancer has spread to distant organs

Table 2. Model progression

Model	$\chi^{2,a}$	DF[b]	CFI[c]	TLI[d]	RMSEA[e]	SRMR[f]
Part A: Penultimate model						
Biology (B) to Symptom (S) to Function (F) to Health perception (HP)						
B to S	119.7	79	0.958	0.944	0.046	0.047
B to S to F	262.3	136	0.912	0.889	0.064	0.064
B to S to F, allowing path from B to F	249.6	135	0.920	0.898	0.059	0.063
B to S to F, allowing path from B to F, to HP	271.2	149	0.921	0.899	0.058	0.062
Part B: Ultimate model						
Biology (B) with Symptom (S) to Function (F) to Health perception (HP)						
B to F	29.0	20	0.981	0.965	0.043	0.063
B with S to F	85.7	50	0.957	0.933	0.054	0.051
B with S to F to HP, allowing path from S to HP	214.3	129	0.937	0.917	0.052	0.060

[a] χ^2 test of exact fit, using the Satorra-Bentler correction for non-normality. None of the models reach the desired *p* value of greater than 0.05, except for Part B B to F, p-value = 0.09.
[b] Degrees of freedom
[c] Comparative Fit Index
[d] Tucker-Lewis Fit Index
[e] Root Mean Square Error of Approximation
[f] Standardized Root Mean Squared Residual

Table 3. Direct effects between latent variables forming the W-C model, penultimate model.

Penultimate Model	Direct effect	SE	Standardized (STDYX)
Pain ON			
Breast cancer stage	1.367	1.014	0.086
Lymphatic	22.228	7.939	0.237
General health perception	0.377	0.102	0.340
Body image ON			
Breast cancer stage	-2.771	1.360	-0.127
Lymphatic	18.890	10.613	0.147
Social	0.398	0.090	0.307
Role emotional	0.092	0.048	0.133
Emotion ON			
Breast cancer stage	0.735	0.526	0.074
Lymphatic	5.239	3.385	0.089
Physical	0.080	0.036	0.130
Social	0.263	0.037	0.445
Role physical	-0.003	0.022	-0.010
Role emotional	0.105	0.020	0.331
General health perception	0.189	0.041	0.272
Physical ON			
Pain	0.585	0.069	0.574
Breast cancer stage	-3.134	0.861	-0.193
Social ON			
Pain	0.500	0.071	0.472
Role physical ON			
Pain	0.975	0.119	0.566
Role emotional ON			
Pain	0.937	0.141	0.472
General health perception ON			
Physical	0.139	0.066	0.157
Role physical	0.092	0.040	0.176
Role emotional	0.059	0.032	0.130
Breast cancer stage WITH			
Lymphatic	-0.048	0.025	-0.144
Body image WITH			
Emotion	103.856	21.450	0.242
Role emotion WITH			
Social	201.335	57.327	0.192
Rbr17 WITH			
Rbr18	0.189	0.045	0.195
Rbr19	0.258	0.052	0.262
Rbr19 WITH			
Rbr18	0.164	0.050	0.161

Table 4. Description of the cohort (Ultimate model) on the W-C rubrics: observed and imputed values

Variable	Indicator (re)scored Low (worst) to high (best)	N	Observed mean (SD)	Imputed mean	Legend for model
Latent					
Lymphatic function					Lymph
	b435 Immunological system function (ICF)	243	3.6 (1.0)	3.6	Rb435
	b4352 Function of lymph vessels (ICF)	242	3.1 (1.0)	3.1	Rb4352
	b4353 Function of lymph nodes (ICF)	242	3.2 (1.2)	3.2	Rb4353
	Swollen arm or hand (item 18 EORTC QLQ-BR23)	216	3.3 (1.0)	3.2	Rbr18
Pain					Pain
	Pain upper limb (item 17 EORTC QLQ-BR23)	217	2.5 (1.0)	2.5	Rbr17
	Pain breast (item 20 EORTC QLQ-BR23)	216	2.9 (0.9)	2.9	Rbr20
	Raise arm (item 19 EORTC QLQ-BR23)	215	2.8 (1.0)	2.7	Rbr19
	b2801 Pain in body part	233	3.0 (0.9)	3.0	Rb2801
Perception of Emotion					Emotion
	Mental health (SF-36)	241	64.1 (18.0)	64.1	MHI
	Worried about health (EORTC QLQ-BR23)	217	37.8 (31.0)	37.8	BRFU
	Emotionally affected (item D6.5 WHODAS)	195	2.8 (1.1)	2.5	RD6.5
	b126 Temperament and personality functions (ICF)	244	3.4 (0.8)	3.4	Rb126
Observed					
Breast cancer stage	Breast cancer stage (TNM)	240	2.3 (1.4)	2.7	BCSTAGE
Physical scale	Physical (SF-36)	243	65.9 (22.9)	65.9	PFI
Social scale	Social (SF-36)	243	74.3 (24.8)	74.4	SOCIAL
Physical role scale	Role physical (SF-36)	239	33.8 (38.4)	33.6	ROLPH
Emotional role scale	Role emotional (SF-36)	235	58.6 (44.1)	57.9	ROLEM
Health perception scale	General health perception (SF-36)	239	54.7 (20.3)	54.5	GHP
Perception of self	Body image (EORTC QLQ-BR23)	217	65.7 (31.0)	65.2	BRBI

Table 5. Direct effects between latent variables forming the W-C model, ultimate model.

Ultimate Model	Direct effect	SE	Standardized (STDYX)
Physical ON			
Breast cancer stage	-2.982	0.926	-0.183
Pain	14.410	1.956	0.510
Social ON			
Breast cancer stage	-1.713	1.052	-0.102
Pain	8.367	2.083	0.286
Role physical ON			
Breast cancer stage	-1.840	1.664	-0.068
Lymphatic	-9.502	9.701	-0.059
Pain	21.732	3.546	0.463
Role emotional ON			
Breast cancer stage	2.073	1.948	0.066
Lymphatic	-19.033	11.937	-0.102
Pain	21.686	4.179	0.400
General health perception ON			
Physical	0.227	0.055	0.259
Role physical	0.130	0.032	0.247
Role emotional	0.090	0.028	0.197
Perception of self ON			
Social	0.445	0.082	0.343
Pain	8.592	2.686	0.227
Perception of emotion ON			
Physical	0.141	0.034	0.235
Social	0.276	0.035	0.477
Role emotional	0.123	0.020	0.395
Breast cancer stage WITH			
Lymphatic	-0.047	0.025	-0.143
Pain	-0.007	0.083	-0.006
Lymphatic WITH			
Pain	0.058	0.021	0.301
Role physical WITH			
Physical	164.629	45.704	0.189
Social	234.598	52.777	0.261
Role emotional WITH			
Physical	151.907	52.429	0.151
Social	332.058	64.272	0.189
Role physical	334.859	95.198	0.261

Figure 1.Combination of the Wilson-Cleary and the ICF models

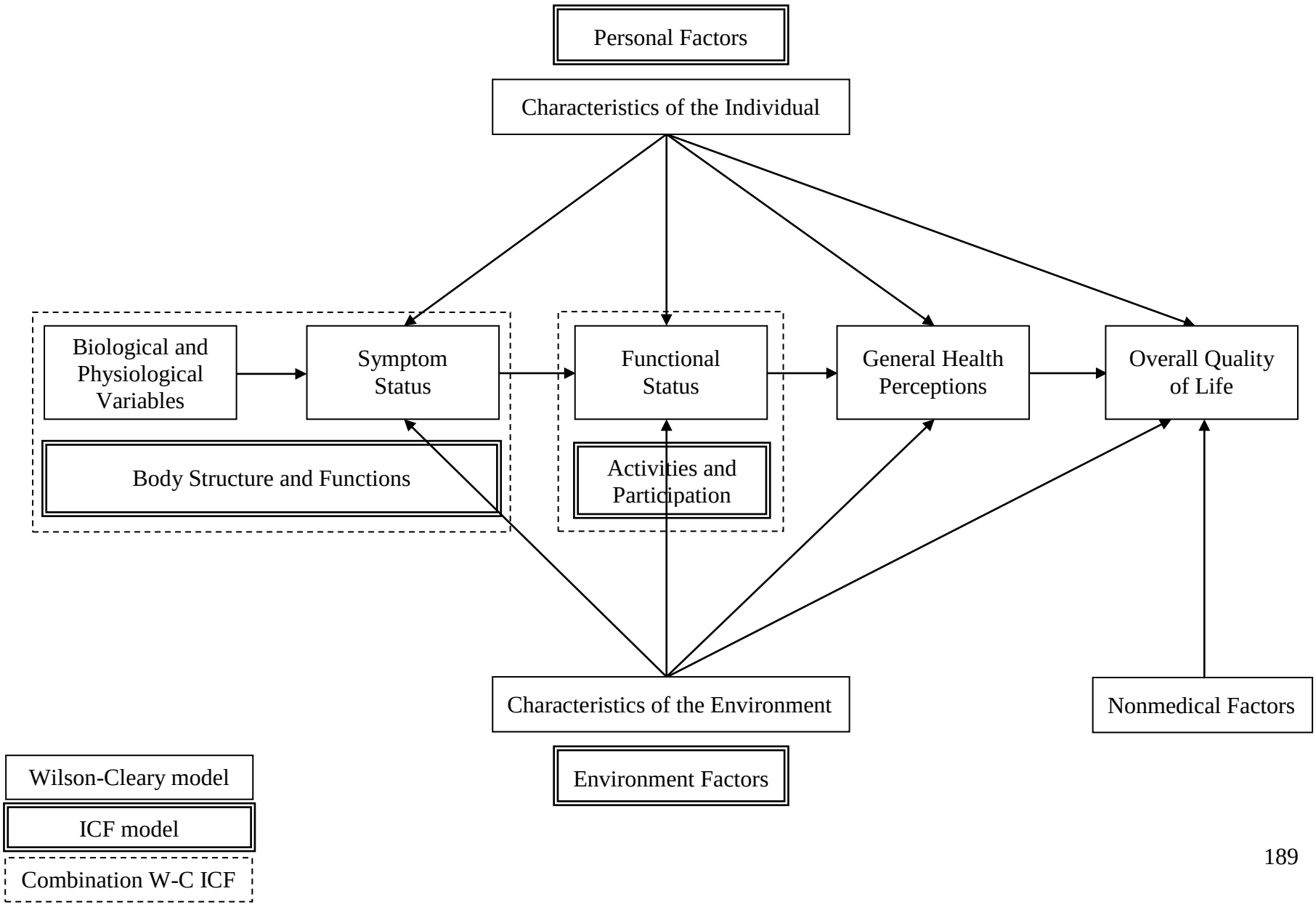


Figure 2. Hypothesized model

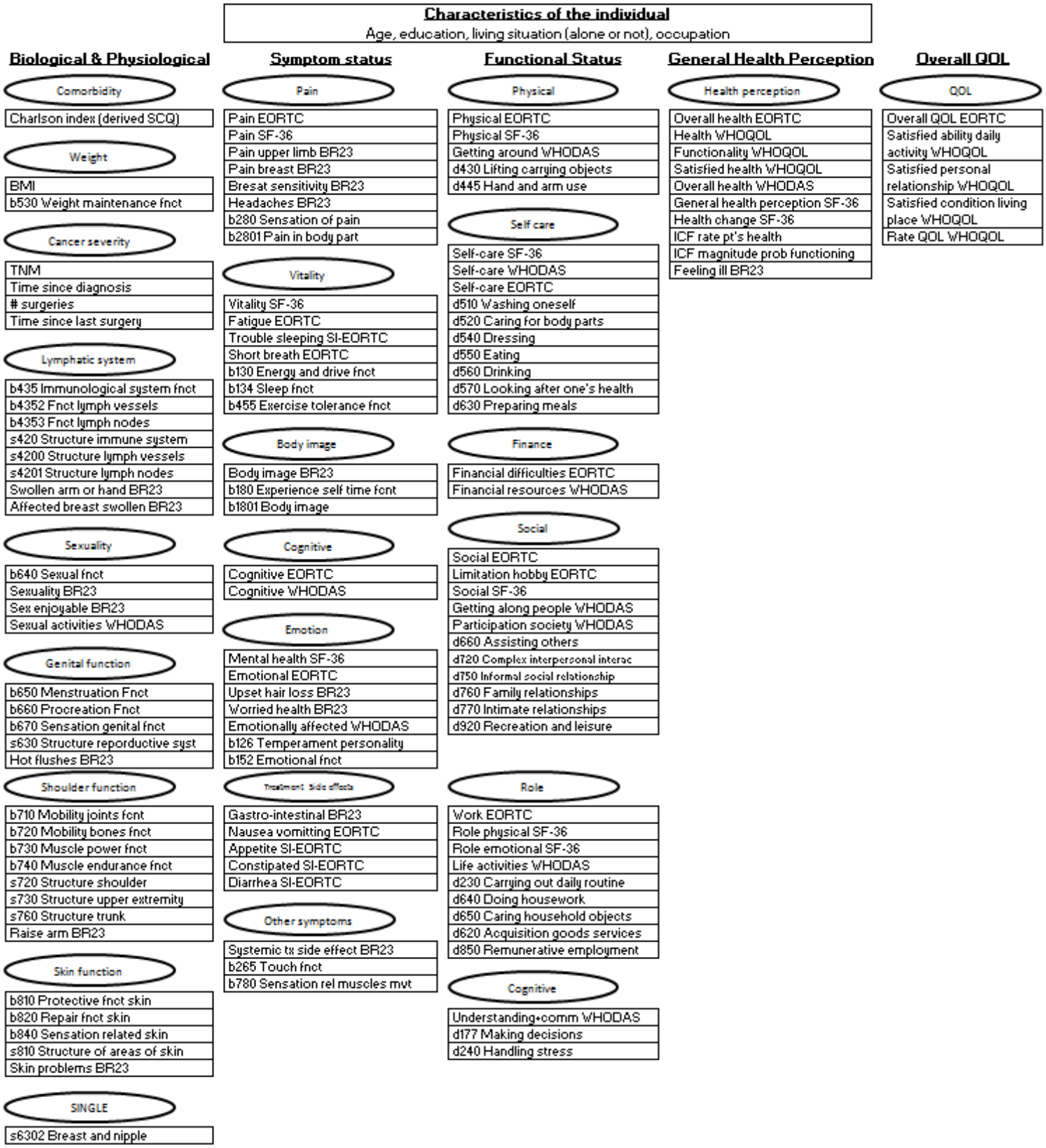


Figure 3. Penultimate model

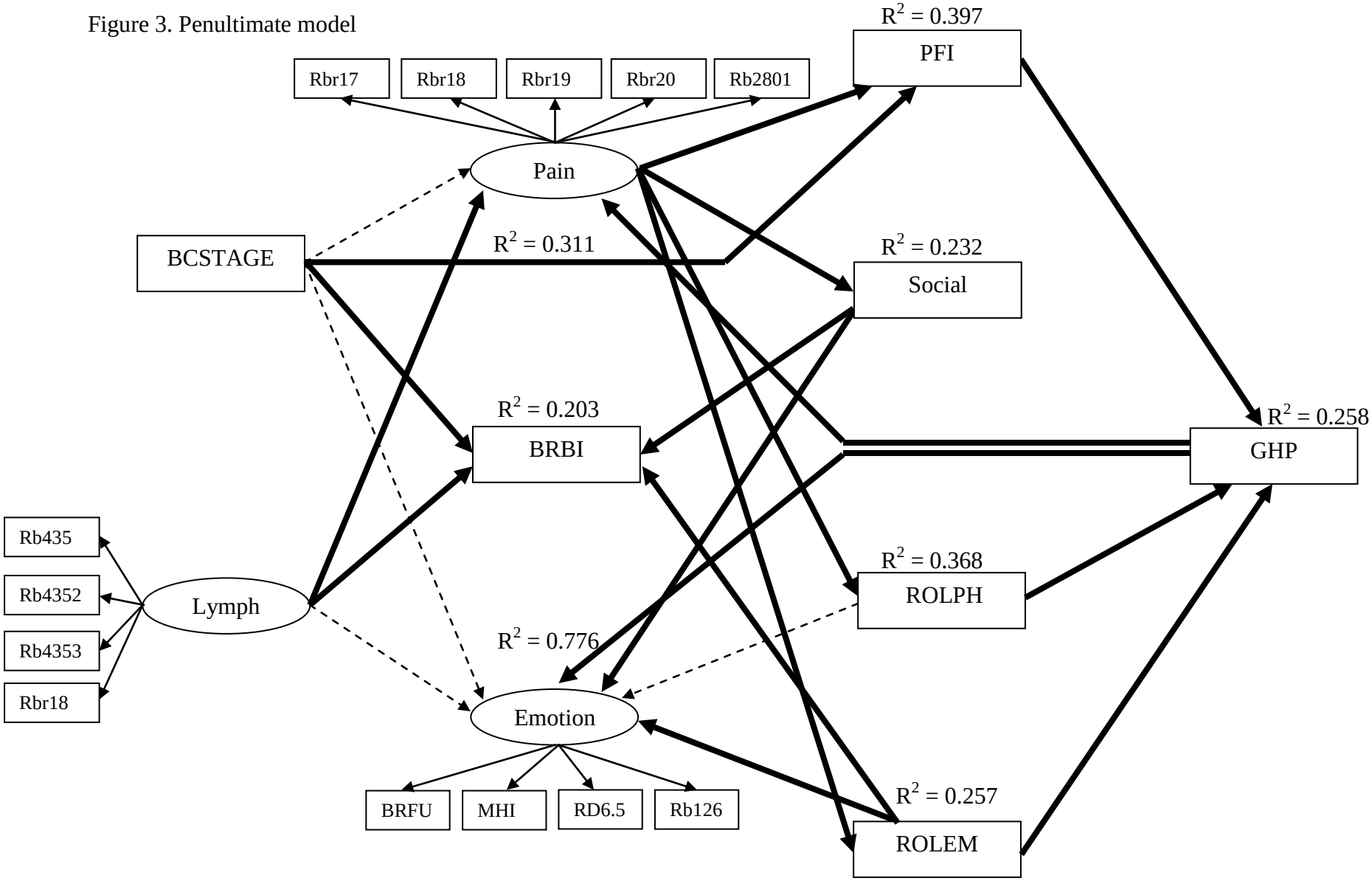


Figure 4. Ultimate model

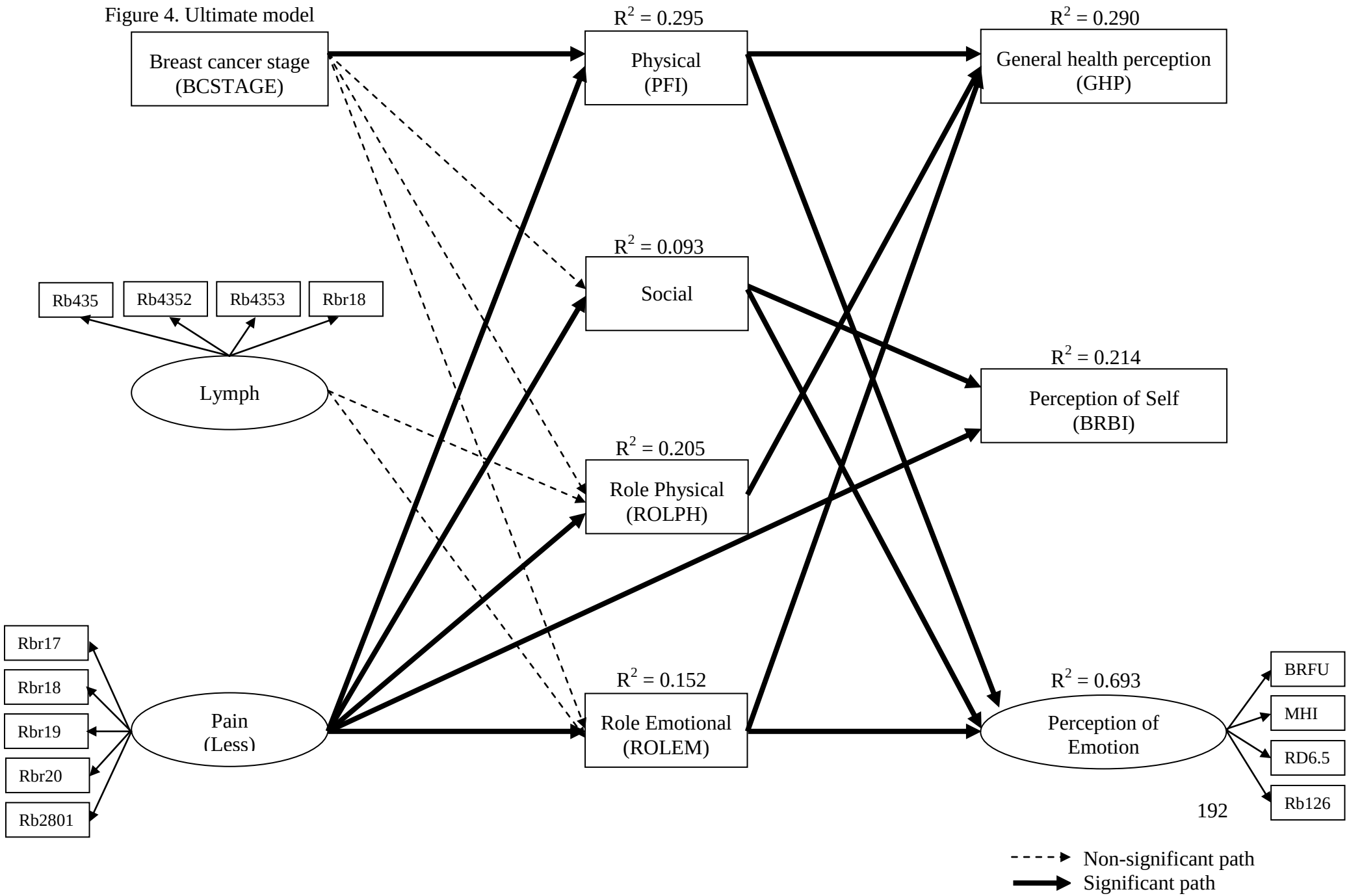
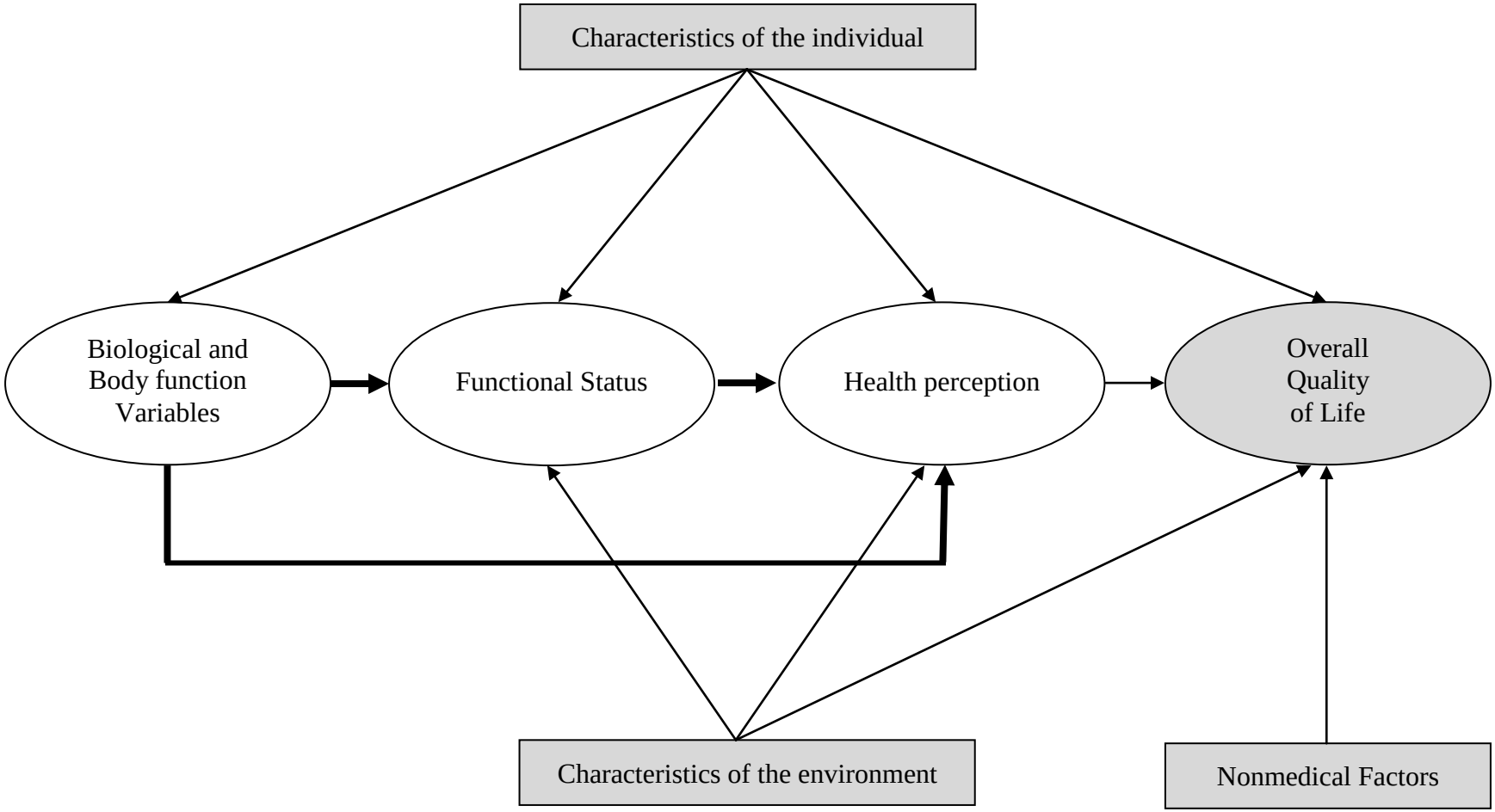


Figure 5. Redrawn Wilson-Cleary and ICF model of HRQOL for breast cancer



Chapter 12: Overall discussion and Conclusion

The overall aim of this thesis was to contribute evidence towards understanding the mechanisms and determinants underlying the components of arm dysfunction and their impact on quality of life (QOL) in women post-breast cancer treatment. This was achieved under three distinct components: i) construct investigation (Manuscript 1 and 2), ii) construct verification (Manuscript 3 and 4), iii) construct impact and determinants (Manuscript 5).

The specific objective for "construct investigation" was to summarize, in the context of rehabilitation, the scope and breadth of knowledge currently available regarding arm dysfunction after breast cancer. Manuscript 1 describes the pathophysiology of lymphedema, one of the most feared and debilitating sequelae related to breast cancer treatments[106]. Even though the lymphatic system has been studied for centuries, a complete understanding is just emerging with the advancement of new technologies. Lymphedema as a theoretical construct is defined; however, there no consensus operationalizing its theory into an entity. For example, many criteria are used: 10% relative increase in arm volume, 2 cm difference in one or more circumferential measurements, 200 ml difference[40;107;108]. In addition, most of the studies are performed either retrospectively or prospectively without involving pre-operation measurement, limiting the possibility of establishing the real incidence of lymphedema. Nevertheless, lymphedema is a chronic condition that needs to be taken in charge rapidly and effectively through rehabilitation interventions.

Manuscript 2 summarizes, in a narrative way, the therapies for arm dysfunction, targeting pain, shoulder mobility and/or edema using either pharmaceutical or physical modalities. As it was the post-acute phase of treatment that was the time frame searched, it occurred that the main emphasis was on lymphedema. The search was performed in two times: for the comprehensive PhD examination (July 2009), and updated literature (2009-2015).

A better approach would have been to conduct a systematic review involving at least two reviewers and summarizing evidence using a meta-analysis. For time management in order to fulfill this thesis requirement, it was decided to perform a narrative review

instead. Valuable information was obtained for physical modalities addressing arm dysfunction and only one study provided information on drugs having potential benefits on shoulder mobility.

The fact that the time frame was the post-acute phase of treatment eliminated a lot of studies on pain and shoulder mobility. A total of 44 randomized controlled trials (RCTs) and 30 reviews were reviewed and the evidence was not strong for creating specific guidelines. The strongest evidence was for physical activity, as exercise done progressively is a good start to prevent chronic diseases[79] and help improving arm dysfunction related to breast cancer treatments. In addition, early rehabilitation intervention is important to minimize the risks of developing arm dysfunction and/or to address them rapidly to reduce their burden.

The specific objective for "construct verification" was to estimate the extent to which the content of QOL measures are linked to the International Classification of Functioning, Disability and Health (ICF) framework (Manuscript 3) and to estimate the extent of agreement of those measures between clinician and patient reported arm dysfunction (Manuscript 4). For Manuscript 3, published in Quality of Life Research Journal, the content of two QOL measures (EORTC QLQ-C30/BR23) was linked to the ICF framework using a standardized mapping exercise. Mapping exercises help in validating content of a measure, by pointing out if there is a redundancy in the items. For three ICF codes (b152 Emotional functions: 4 items, b1801 Body image: 4 items, and b280 Sensation of pain: 2 items), even though the items asked different concepts, the mapping exercise suggest that there was redundancy in the items.

In addition, there were some gaps in the content of the EORTC measures. The Breast Cancer Core Set identifies what is important to measure in this population. The mapping exercises showed that there were gaps in content coverage. Problems with decision making and weight maintenance are in the Breast Cancer Core Set but not in the EORTC; also the Breast Cancer Core Set is very specific as to which basic activities of daily living are important to be assessed in breast cancer and identify 10 activities, but the EORTC addresses these using a single item grouping four activities together. However, the

EORTC has items that are not part of the core set, notably memory and attention. There is a suggestion in the literature to develop an expanded Core Set[109;110] as experience with new therapies identify different sequelae[111].

The mapping exercise performed in Manuscript 3, was the preliminary step for Manuscripts 4 and 5. These two last manuscripts are based on secondary analyses of data collected on 245 women and their health care professionals. The data were originally collected in order to validate the ICF Breast Cancer Core Set, for which the results have never been published. Participants completed five measures (SF-36, EORTC QLQ-C30/BR23, WHOQOL, and WHODAS) that were all previously mapped to the ICF framework or conducted for the purpose of this thesis, and clinicians filled the ICF Breast Cancer Core Set.

The aim of Manuscript 4, published in Disability and Rehabilitation Journal, was to compare the level of agreement between patient reported outcomes (PROs) and clinician reported outcomes (ClinRO). One of the first challenges encountered in this manuscript was the different terminology and how to differentiate between different outcomes: self-reported outcomes (SROs), PROs, ClinROs, observer reported outcomes (ObsRO), and performance reported outcomes (PerfRO). This is a topic fairly new in the literature and mostly information on PRO is available. However, as the distinction is not as straight forward between the different types of reported outcomes, the publication of this work will provide an opportunity to define and classify them more adequately.

As the response options of the items were categorical, the level of agreement was calculated based on quadratic Kappa ($\boldsymbol{\kappa}_{\omega}$) in order to account for disagreement that can occur between the patient's and clinician's ratings[112]. Thoughtful considerations had to be given to prepare the items for comparison. PROs items were revised and rescored, when appropriate, to match the scoring of the ICF Breast Cancer Core Set, where a low score indicates no impairment or limitation. The degree of agreement was poor for constructs that can only be rated by the patient (mental function and pain). Clinicians report more frequent occurrences of physical impairments but patients report a higher prevalence of activity limitations and participation restrictions. Overall the agreement was only fair

because clinicians rated constructs that only patient know about, and patients rated constructs that required expert assessment. A measurement battery that includes appropriate PROs and ClinROs, would solve the problem of poor agreement. A modification to the ICF core set could be to indicate which core set item should be PRO/SRO and which should be ClinRO.

Lessons learned

Building on the knowledge gained in Manuscripts 3 and 4, the specific objective for "construct impact and determinants" was to empirically test a bio-psycho-social conceptual model of health related QOL (HRQOL) for breast cancer survivors using a structural equation modeling (SEM) approach (Manuscript 5). This manuscript has been the most challenging part of this thesis. At first, if I would have been asked "Why are you doing SEM", I would have wrongly answered "Because Nancy (Dr. Mayo) told me so"! I knew from prior reading and other students in our group what an SEM model would look like, but I was nowhere close to know what it involved running one. I am not pretending mastering the topic, but I surely can argue the work that I have done!

The use of SEM allows simultaneous combination of observed and latent variables in order to estimate the relationships between and among constructs of QOL, in this instance. HRQOL and ultimately QOL are multi-level constructs made of observed and unobserved measures suggesting the use of SEM as it combines factor analysis, path analysis, and regression incorporating latent (unobserved) variables[94;95;113].

An early revelation was that my theoretically desired outcome was QOL but, because of specific features of the data on hand, this variable was not collected at all sites. While "designed-in" missing data makes this type of missingness "MCAR", missing completely at random and ignorable[86], the amount of missing data made imputation implausible. An early lesson learned was to adjust the model to have general health perception as the outcome, which is the outcome in the W-C model that completes the definition of HRQOL (biology, symptoms, function, general health perception).

The next challenge was to create the latent variables. This process was guided by the ICF codes obtained by the mapping exercise available for each questionnaire. Each individual item was sorted according to the rubrics of the Wilson-Cleary[89] (W-C) model and regrouped under similar latent constructs. Sometimes, an entire measurement sub-scale would fit under the W-C rubric, sometimes the items had to be separated as they captured quite different constructs. Once done, as learned in Manuscript 4, all response options were rescored, when applicable, so that a lower score would indicate "worst level or complete impairment".

Factor analysis is a key part of SEM. Because the initial hypothesized model was very complex, many attempts were made to make sensible factors. Finally, a decision was made to use the SF-36 subscales for physical (PFI), social (SOCIAL), role physical (ROLPH), and role emotional (ROLEM) as observed variables under the "function" rubric and this simplified the model and provided an acceptable-to-good statistical fit. In fact, due to the nature of the data, the model included only 3 latents and 7 observed variables (see Figure 3, p. 191).

The results indicated that three variables (2 observed and 1 latent) were endpoints as they did not associate with any other variables further along the hypothesized model. Even though the model had acceptable fit, the model was considered as penultimate. A new model was proposed with General Health Perception, Perception of Self, and Perception of Emotion as endpoints (see Figure 4, p. 192).

The ultimate model fits well with a rehabilitation orientation and points out how two important dysfunctions (pain and lymphedema) impact function and health perception, reducing HRQOL particularly when pain in present. It not possible to say that this is "THE" model for HRQOL post-breast cancer treatment; however it is the best model for these data. The results indicate that pain played an important role in this sample of women. The same conclusion was reached in an earlier study[9] done on a completely different sample, locally (Montreal), and much smaller.

Breast cancer is an emerging field of rehabilitation practice and research. This study contributes to understanding targets for intervention and where research may fill gaps in knowledge.

Strengths and limitations of the thesis

A strength of this thesis was the use of modern statistical methods, specifically SEM, to conceptualize HRQOL in breast cancer survivors. This allowed identifying that pain was a strong determinant of HRQOL.

Another strength was the use of an existing data set of a cohort of breast cancer survivors and their health care professionals. The analysis of data was an efficient and ethical way to maximize the knowledge obtained from previous work. However, one of the limitations doing this secondary analysis was that the data were not originally collected to conduct SEM analyses. The hypothesized model had to be simplified to fit the data and the available sample size.

Conclusion

This thesis comprises original work that, to my knowledge, has never been conducted before: 1) Content verification of the EORTC QLQ-C30/BR23 (Manuscript 3), 2) Identifying the best "reporter" on different types of reported outcomes and assess the level of agreement between the participants and their health care professionals (Manuscript 4), and 3) Using the W-C and ICF models with a SEM approach in breast cancer (Manuscript 5).

Through all the manuscripts, except Manuscript 3, arm dysfunction is the focus of enquiry. Women might experience arm dysfunction at any time during the continuum of care, which will greatly affect their life. From what was exposed in this thesis, there are huge implications for rehabilitation interventions, starting from assessing the women as early as pre-surgery and follow them over the years.

As there was support in the literature for exercise as an effective intervention for arm dysfunction, post-breast cancer, a rehabilitation program should be integrated into every

oncology service. Some women might never develop any dysfunction or might just ignore the mild symptoms if they do not greatly limit function. Those would require "minimum" attention in such program. On the other hand, women with already impaired function prior to surgery would probably benefit from (pre)rehabilitation as well as systematic follow-up.

Communication between the patient and their team of health care professionals is vital. Patients tend to underreport and clinicians tend to underestimate symptoms. Arm dysfunction may not be the focus of the medical team, but it needs to be systematically queried and assessed so that the appropriate evidence-based interventions can be applied. Rehabilitation is a key component of a person-centered approach to breast cancer.

The title of this thesis was "The impact of breast cancer and its treatment on arm dysfunction and quality of life". Breast cancer is a diagnostic that has rehabilitation professionals we have to face with our clientele. Arm dysfunction related to breast cancer treatment is what we are aiming at reducing. A lot of literature is available on the matter, particularly regarding lymphedema. What is missing is following the rehabilitation guidelines in every oncology services.

QOL is difficult to measure and putting a "value" to it is quite of a challenge. It is hard to put in a sense of a measure (through observed or latent variables), as every individual is unique and the questionnaire might not even capture information relevant to the person. A lot of researchers have the aim of targeting QOL in their research and the term is being abuse and commonly wrongly used as most of researchers will use available questionnaires that only investigate components of it, referring to the health aspects of QOL, such as functional states and impairments that the disease is involving, which by definition is HRQOL

With this thesis, I found that impairments, activity limitations and participation restrictions are foundations of QOL and inform HRQOL aspects, and this is only the tip of the iceberg as many other life aspects, such as psychological issues or work, which were not investigated here, might play a role and influence the overall aim of reaching QOL!

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