Title: Adverse breast cancer treatment effects: the economic case for making rehabilitative programs standard of care

Concise title: Adverse breast cancer treatment effects

Manuscript category: Original Research

Authors: Kathryn H Schmitz[1], Tracey DiSipio[2], Louisa G Gordon[3], Sandra C Hayes[2]

Affiliations: 1. University of Pennsylvania, Perelman School of Medicine, Philadelphia, PA. 2. Queensland University of Technology, Institute of Health and Biomedical Innovation, School of Public Health and Social Work, Queensland, Brisbane, Australia. 3. Griffith University, Griffith Health Institute, Centre for Applied Health Economics, Logan, Queensland, Australia.

Corresponding Author:

Dr Tracey DiSipio

School of Public Health and Social Work

Faculty of Health

Queensland University of Technology

Victoria Park Road

KELVIN GROVE QLD 4059 AUSTRALIA

Ph: 617 3138 9674 Fax: 617 3138 3130 Email: t.disipio@qut.edu.au

Abstract

Purpose: The purpose of this work was to evaluate the patient-borne financial cost of common, adverse breast cancer treatment-associated effects, comparing cost across women with or without these side-effects. ***Methods:*** 287 Australian women diagnosed with early-stage breast cancer were prospectively followed starting at six months post-surgery for 12 months, with three-monthly assessment of detailed treatment-related side effects and their direct and indirect patient costs attributable to breast cancer. Bootstrapping statistics were used to analyze cost data and adjusted logistic regression was used to evaluate the association between costs and adverse events from breast cancer. Costs were inflated and converted from 2002 Australian to 2014 US dollars. ***Results:*** More than 90% of women experienced at least one adverse effect (i.e. post-surgical issue, reaction to radiotherapy, upper-body symptoms or reduced function, lymphedema, fatigue or weight gain). On average, women paid $5,636 (95%CI: $4,694, $6,577) in total costs. Women with any one of the following symptoms (fatigue, reduced upper-body function, upper-body symptoms) or women who report ≥4 adverse treatment-related effects, have 1.5 to nearly 4 times the odds of having higher healthcare costs than women who do not report these complaints ($p<0.05$). ***Conclusions:*** Women face substantial economic burden due to a range of treatment-related health problems, which may persist beyond the treatment period. Improving breast cancer care by incorporating prospective surveillance of treatment-related side effects, and strategies for prevention and treatment of concerns (e.g., exercise) has real potential for reducing patient-borne costs.

Keywords: breast cancer, economics, side effects, surveillance model, rehabilitation, survivorship care

Introduction

Approximately 200,000 women are diagnosed with breast cancer each year in the USA [1]. While the vast majority will survive their disease [1], adverse treatment effects are common, may persist beyond the treatment period, and contribute to the burden of cancer, including the economic burden [2,3]. Cancer rehabilitation and exercise interventions have been shown to prevent, attenuate or rehabilitate many of the physical and psychosocial side effects of breast cancer treatment [4-8]. Unfortunately, surveillance of treatment-related side effects is ad hoc, the majority of women are not offered a rehabilitative program after breast cancer [9], and women may even be unaware that interventions exist to assist with treatment-related side effects [10]. Instead, women are left with the impression that the presence of side effects is part of their 'new normal' [10].

Prospective surveillance and rehabilitation models are being promoted as best practice for breast cancer care [11,12]. Health promoting skills and behaviors, which incorporates education and regular assessment of common side effects, alongside exercise, reflect key components of these models given their role in early detection, prevention and alleviation of physical and psychosocial impairments. While the exercise rehabilitation programs for women with breast cancer have shown to be a cost-effective investment for health providers [11,13], cost from the patient-perspective needs to also be considered because invariably, the costs for these sorts of programs are borne by patients and their families.

The Pulling Through Study (PTS) collected data on the economic impact of breast cancer and its treatments in Australia and has previously reported that positive lymph nodes and younger age were associated with higher economic burden [14]. Women diagnosed with

breast cancer can face financial stress in three forms; 1) out-of-pocket expenses for medical care (co-payments, insurance) and non-medical expenses (parking, transportation); 2) loss of earnings; and 3) loss of household income of other family members due to caregiving needs. Australia has a publicly-funded universal healthcare scheme (Medicare) operated by the Australian Government. The aim is to provide universal access to healthcare to all Australian citizens at an affordable cost or at no cost, while allowing choice for individuals through substantial private sector involvement in delivery and financing. Healthcare funding through optional private health insurance and out-of-pocket payments by individuals collectively accounts for 30.3% of all healthcare funding in Australia [15]. Herein, these costs incurred by the patient, and not the healthcare system, are referred to as 'patient costs'. This area of inquiry, as well as direct and indirect healthcare expenditures for cancer, is an active one [16-18] and has recently been coined the 'financial toxicity' of cancer [19]. Patient costs are growing, with burden falling heaviest on those least able to afford these costs [20,21,18,22], potentially adding to health disparities across socio-demographic groups of breast cancer survivors. Understanding the economic burden of adverse effects of breast cancer is key to improving cancer care. Knowing the problem exists should be enough to change practice, but the potential to control healthcare costs, assist patients with return to gainful employment, and establish a more equitable supportive care infrastructure adds an important dimension that may assist in these efforts.

The purpose of this work was to evaluate the economic burden of common, adverse treatment effects, comparing burden across women with or without these outcomes, from the patient's perspective. While prior studies have examined the economic impact of single adverse treatment effects (e.g., lymphedema [23], chemotherapy-induced neutropenic

conditions [24], radiotherapy-induced skin toxicity [25]), we were unable to locate any prior studies that examine the economic burden of combined adverse effects of treatment. It would seem that this is an important perspective, given that that is the lived experience of the survivor. Our hypothesis was that women who experienced more adverse treatment effects over 18 months post-surgery would experience significantly greater economic burden of cancer than those who did not. We further sought to explore which specific adverse treatment effects were economically burdensome.

Materials and Methods

Study design and sample recruitment

The PTS was a prospective, population-based, cohort study designed to track and assess the physical and psychosocial recovery of women newly diagnosed with breast cancer. Recruitment and study design for the PTS have been described in detail elsewhere [26]. In brief, of the 511 women originally targeted for recruitment into the PTS, doctor consent (in accordance with local cancer registry protocols) was obtained for 82% of the sample. Of these, 287 women with characteristics representative of the wider breast cancer population consented to participate and were prospectively followed for 12 months from 6-months post-surgery (diagnosed in 2002; on average, women are treated within two to four weeks following diagnosis of breast cancer in Queensland (unpublished results)), with data collection procedures involving completion of a clinical assessment and/or a self-administered questionnaire every three months. Some of the women participated on a questionnaire-only basis; hence they lack objective assessments of lymphedema.

The study was approved by the university human research ethics committee and the local cancer registry before data collection.

Data Collection

Tumor characteristics were obtained from histopathology reports held by the Queensland Cancer Registry (e.g., histological grade, lymph node status, type of surgery) for the target sample (no other data collected on this group) and for all study participants. Study participants completed a mailed, self-administered questionnaire assessing demographic characteristics (e.g., age, children, education level, occupation, income, private health insurance), general health (e.g., co-morbidities, body mass index (BMI) (kg/m^2), weight, height, smoking status), type of adjuvant treatment received (e.g., chemotherapy, radiation, hormonal therapy), adverse treatment effects (e.g., post-surgical issues, skin/tissue reaction to radiotherapy, upper-body symptoms, weight gain, fatigue, upper-body function), and economic information.

Outcome variables:

The variable "*post-surgical issues*" includes a count of women who reported at least one of the following complications between diagnosis through to 18-months post-surgery: wound infection, other infection, seroma/hematoma, axillary web, cording. The variable "*skin/tissue reaction to radiation therapy*" was also created in the same manner. Two items (tingling and weakness) from the Disability of the Arm, Shoulder, and Hand scale (DASH) [27] and five items (pain, stiffness, range of motion, swelling and numbness) from the Functional Assessment of Cancer Therapy, Breast+4 (FACTB+4) [28] questionnaire were used to create the variable "*upper-body symptoms*". Women were considered to have a positive indication

for any of these upper-body symptoms when reporting “severe” to “extreme” on the DASH items or “quite a bit” to “very much” on the FACTB+4 items [29]. The proportion of women reporting at least one of these symptoms at each time-point was then calculated. Clinical assessments of *lymphedema* were performed by qualified Exercise Physiologists using bioimpedance spectroscopy (BIS) [30] and sum of arm circumferences (SOAC) [31]. A participant was classified as having lymphedema when the their L-DEX score was greater than 10 (BIS) or when the difference of their SOAC on the treated and untreated was >5cm. *Weight gain* was assessed by comparing measured values at 18-months post-surgery to self-reported weight six months prior to diagnosis. Where measured values at 18 months post-surgery were unavailable, measured values at 15 months (n=4) or 12 months (n=3) were used. Increases of >10% over these self-reported weights from six months prior to diagnosis were considered gains. The presence of *fatigue* was determined via the FACTB+4 item “I have a lack of energy” [28]. Again, those who reported “quite a bit” to “very much” were classified as having fatigue and positive indications were summed over time. *Upper-body function* was assessed by the DASH questionnaire [27], with scores >20 (scale: 0-100, with higher scores reflecting reduced function) defined as reduced upper-body function [32-34]. Participants were coded as “ever” having experienced a symptom over the 18-month study period if she answered ‘yes’ to the symptom at least once, and there was symptom information available for at least one data collection session for post-surgical issues and skin/tissue reaction to radiotherapy, or at least two data collection sessions for upper-body symptoms, lymphedema (SOAC or BIS), fatigue and upper-body function. The number of adverse treatment effects was then calculated (possible scores ranged between 0 to 7 adverse events).

Economic questions included health service expenditure specifically attributable to breast cancer using prompts (e.g., medical practitioner visits, physiotherapist visits, etc.), physical and social support programs undertaken, the use and cost of domestic services, family and other caregiving support, out-of-pocket expenses (e.g., wigs, customized bras, prosthetics, lymphedema sleeve, etc.), paid and unpaid work reductions and associated lost income [14]. The economic questions used for data collection can be found in our previously published work [14]. Women were asked to recall these expenses at regular intervals, with data collection points scheduled at 6, 9, 12, 15 and 18 months post-surgery. At the baseline assessment, women were asked to report costs incurred since their breast cancer diagnosis, while subsequent data collection questionnaires asked recall of costs in the previous three months. Data across the study period were then summed to obtain the outcome variables of direct, indirect, and total costs. The costs considered were from the perspective of the patient only; no health system data were collected.

Indirect costs included the value of lost income, unpaid help, and lost unpaid work. The average weekly earnings for women in Queensland were used to value lost income from paid employment [35]. Unpaid work is categorized into two broad types: production by households for their own consumption (e.g., a family member providing care for another family member), and volunteer, charity or community work provided free of charge to others outside the family. Although the distinctions between unpaid work and leisure are sometimes blurred and certainly debatable, unpaid work was defined here as those activities recognized by the study participants as time-committed and valued activities within their community that otherwise could be purchased from the market sector [36]. The quantities of unpaid work were valued with an hourly estimate using the ‘net opportunity

cost approach' [36]. This estimate was used to reflect the survivors' value of what they could have earned in wages (including employer benefits) had they spent the same amount of time in paid work as expended on unpaid work, after allowing for tax and any work-related costs.

Statistical analysis

Using SPSS version 19.0 (IBM Corp, Armonk, NY), descriptive analyses employed weighting procedures (1:1.3) to address oversampling of younger women. Direct costs included out-of-pocket expenditure on garments and aids, health services and paid home services. Indirect costs included the value of lost income, unpaid help and lost unpaid work. Descriptive statistics showing cost distributions (i.e., means, standard deviations, medians, minimums, maximums) and sums are presented. Cost data are summarised for direct, indirect, and total costs, and presented for participants with positive values (i.e., costs were greater than zero). Patient-level cost data are typically right-skewed and an acceptable approach to analysing these data is with non-parametric bootstrapping statistics. Bootstrapped means and 95% confidence intervals (95% CIs), using the bias-corrected-accelerated approach, were calculated from re-sampling the data 1000 times. This analysis used STATA SE Version 12. Costs were inflated and converted to 2014 US dollars using the CCEMG - EPPI-Centre Cost Converter (v.1.4 last update: 27 January 2014).

The group of interest were those women whose costs were above the median and in being able to characterize them. A dichotomous outcome variable was computed in order to distinguish factors which influenced costs spent above the median (lower cost versus higher cost). These two groups were compared using logistic regression models for direct, indirect,

and total cost, to generate odds ratios (ORs) and 95% CIs in order to identify correlates that influence these distinct groups, and to examine if the presence of adverse treatment effects influenced cost. Models were adjusted for age, income, BMI, cancer stage, and adjuvant therapies. Modelling was performed in SPSS version 19 (IBM Corp, Armonk, NY).

Results

Of the 511 women originally targeted for recruitment into the PTS, doctor consent was obtained for 82% of the sample. Of these, 287 women (69%) provided informed consent and baseline data (scheduled at six months post-surgery) and were followed prospectively for 12 months; 179 completed the 18 month follow-up with clinical data (Table 1). Study participants were representative of the target sample with respect to breast cancer characteristics (Grade 1: 26.7% versus 24.3%; Grade 2: 31.7% versus 35.7%; Grade 3: 30.7% versus 32.2%; Not available: 10.8% versus 7.8%, respectively) and treatments received (lumpectomy: 64.9% versus 62.2%, respectively). Response rates for the individual economic survey questions ranged from 85-99% across the five phases. The women were diverse with regard to education and occupation, with over one-third in the low education group and 23-30% within the lowest household income strata. The majority of the women had experienced stage I or II breast cancer, underwent axillary dissection, had positive lymph nodes, and underwent radiation therapy as part of their treatment. Current receipt of chemotherapy or radiotherapy diminished substantially over time; at the 12 and 18 months post-surgery assessment, only 4% and 1%, respectively reported current receipt of chemotherapy or radiotherapy.

Table 2 presents prevalence of symptoms up to 18 months post-surgery and Table 3 the direct, indirect, and total patient cost among women who experienced versus did not experience each adverse treatment effect queried in the PTS. On average, women paid $5,636 (95%CI: $4,694, $6,577) in total costs. Key findings include higher direct, indirect, and total costs among women who reported upper-body symptoms, and ≥4 persistent adverse effects of treatment, as well as higher total costs among women who reported fatigue and reduced upper-body function ($p<0.05$). No other characteristics examined, such as post-surgical issues, skin/tissue reaction to radiotherapy, lymphedema, weight gain and number of co-morbidities, showed differences in costs. Table 4 presents odds ratios from adjusted logistic regression models for each of the four outcomes for which statistically significant patient costs were noted. Key findings include that women who report upper-body symptoms have higher odds of having higher direct and total healthcare costs than women who do not report upper-body symptoms (2.6 and 2.1-fold increased odds, respectively). Similarly, women who report ≥4 persistent treatment-related adverse effects have 3.8 and 2.3 increased odds of having higher direct and total economic burden of breast cancer. Further, after adjustment for all other factors in the model, the odds of greater direct costs are higher among survivors who self-report fatigue and reduced upper-body function (1.8 and 1.9 fold increased odds, respectively).

Discussion

Breast cancer survivors who self-report upper-body symptoms, fatigue, or reduced upper-body function experience increased personal economic healthcare burden over 18 months of follow-up post-surgery. Further, women who report four or more of these common outcomes experience more than double the total healthcare costs (on average) and are at

3.8 fold increased odds of experiencing higher healthcare costs than women with three or fewer adverse treatment effects. There was also some evidence to suggest that indirect costs associated with these symptoms (which included the value of lost income, unpaid help, and lost unpaid work) was the driver behind the total cost increase observed when these symptoms were present. The current results lend support to exploring the potential cost-effectiveness of interventions that could prevent direct out-of-pocket expenses for patients of up to $2,000 USD per patient per year.

These findings build on prior work in this cohort which have detailed the frequency with which survivors experience adverse effects of cancer treatment (>50% over six years of follow-up)[37], as well as the economic burden faced by cancer survivors [14]. In contrast to previous findings by Shih et al [23] the current study did not observe greater economic burden among women with lymphedema compared with women without lymphedema. However, key differences in study design could explain discrepancies in findings. For example, the Shih et al study reported economic burden from the payer perspective (e.g., US Medicare), identified lymphedema cases via medical chart review and did not examine whether other persistent adverse effects of treatment influenced these higher costs. The current study presents economic burden from the patient perspective, identified lymphedema cases via clinical assessment, and presents adjusted analysis, taking into account other adverse effects. Irrespective of lymphedema status, it is noteworthy that the presence of moderate to severe upper-body symptoms, reduced upper-body function and fatigue contribute to substantially higher out-of-pocket patient expenses, and are reported by 40% of women following breast cancer. Importantly, there exists compelling evidence that show these same side effects are amenable to intervention, in particular exercise

[38,39,11]. Knowing the problem exists and having an effective treatment strategy are the first steps in changing practice. This current study places a cost on these treatment-related effects, and in doing so contributes to the evidence required to change practice.

There are few studies that have examined out-of-pocket costs for breast cancer survivors [16-18,25]. One prior study noted that about 20% of out-of-pocket costs among Canadian breast cancer survivors went toward treatment of complications and symptoms [16]. However, the authors noted that consultations with psychiatry, social work and occupational therapy are provided as part of hospital care and, thus, result in no out-of-pocket costs. This would be quite different in the USA. We found only one prior study that has specifically examined whether there are increased out-of-pocket costs associated with an adverse effect of treatment. Schnur et al [25] observed that women who experienced radiation-induced skin toxicity spent, on average, $132 more out-of-pocket than women without this common side effect (USA data, 2009/2010). Further, women with functional impairments due to this toxicity were particularly likely to spend more out-of-pocket.

Depending on socioeconomic position of the woman, out-of-pocket expenses related to breast cancer may represent a greater proportion of household income and contribute to disparities in the burden of cancer [18,22] and decreased quality of life [17]. Importantly, our findings represent a timely extension to those recently published which demonstrated that participation in breast cancer treatment, as well as adherence to treatment prescribed, was at least in part, economically motivated, with minority patients most vulnerable to privations and financial decline attributed to breast cancer [22]. It therefore seems likely that the ability to cope and respond to the presence of one or more treatment-related

adverse effects through participation in rehabilitative programs would be associated with an individual's economic position; yet these same adverse treatment effects would continue to influence one's ability to generate income in the first place.

The present study includes the unique, longitudinal collection of the personal economic and adverse treatment effect data within a relatively large, population-based cohort, over an 18-month follow-up period post-surgery. However, the nature of the data collection procedures prevents untangling the order in which events occurred (e.g., did the costs go up before, after, or concurrently with adverse effect onset). Consideration should also be given to the impact of other comorbid conditions, as well as the natural course of ageing in the relationship between patient costs incurred and adverse treatment symptoms. While there was an observed increase in patient costs incurred among women experiencing one or two comorbidities in this study, the relationship was not linear (or statistically significant). In addition, standard breast cancer care has changed since the period of data collection, with changes in treatment influencing the type and frequency of side effects experienced. Some changes may mean costs have been overestimated (e.g., sentinel node biopsy [SNB] prior to further axillary node dissection [AND] is now standard practice and SNB is associated with fewer treatment-related side effects compared with AND), while others (e.g., use of aromatase inhibitors is now standard practice, with this treatment influencing bone density and the need for bone density scans, with partial or full costs of scans borne by women) may mean costs have been underestimated. Also, while the self-report nature of the data collection involves the risk of recall bias (for side effects and economic burden) and high participant burden, this bias was minimised through the use of specific and targeted questions asked regularly (once every three months, with the exception of baseline

assessment which covered the previous 6 months), and this method of data collection has been shown to be highly efficient, as well as cheaper and more effective at covering a wide range of services relative to chart review (which is labour intensive) or claims data (which has poor scope)[40-44]. Further, approximately one-third of the sample had insufficient data to allow calculation of prevalence for every persistent adverse effect measured. Nonetheless, data within Table 1 support the similarity of those with complete and incomplete data.

Future studies are needed to assess interventions and associated costs that have potential to prevent and effectively manage treatment-related side effects, in particular fatigue, upper body symptoms, reduced function, as well as control healthcare and patient-borne costs, assist patients with return to gainful employment, and establish a more equitable supportive care infrastructure. Evidence supports exercise as an intervention associated with the prevention and attenuation of adverse effects of breast cancer treatment, improves function, health and quality of life during and following breast cancer treatment and may improve overall and disease-specific survival. It is now time to evaluate its cost-effectiveness. What remains to be determined is who would pay for these interventions. If the patient pays, the intervention will have to reduce costs for symptoms by more than the cost of the intervention. If the healthcare system pays, the patient will get “free” reductions in their own costs, while the healthcare system will see only increases in costs. Cost-effectiveness analyses are usually from the perspective of the healthcare system, not the patient. However, a reduction in the number of visits to physicians will decrease patients’ travel and time costs, and reduce costs paid by the healthcare system for the visit. While we acknowledge the lack of clarity regarding who would pay for the intervention, there is little

question that effective interventions to prevent and treat symptoms would hold value for survivors and those who care for them, beyond discussions of economics.

Acknowledgements

The authors wish to acknowledge the contributions of the women who participated in the Pulling Through Study. We would also like to acknowledge the National Breast Cancer Foundation (NBCF) for funding the Pulling Through Study, and the fellowship funding support provided by NBCF (SH, TD) and Cancer Council Queensland (SH).

Conflict of interest

Authors Schmitz, DiSipio, Gordon and Hayes declare that they have no conflict of interest.

References

1. American Cancer Society (2013) Cancer Facts & Figures 2013. American Cancer Society, Atlanta, GA

2. Curt G, Breitbart W, Cella D, Groopman J, Horning S, Itri L, Johnson D, Miaskowski C, Scherr S, Portenoy R, Vogelzang N (2000) Impact of cancer-related fatigue on the lives of patients: new findings from the fatigue coalition. The Oncologist 5:353-360

3. Hassett M, O'Malley A, Pakes J, Newhouse J, Earle C (2006) Frequency and cost of chemotherapy-related serious adverse effects in a population sample of women with breast cancer. J Natl Cancer I 98 (16):1108-1117

4. Ligibel J, Denlinger C (2013) New NCCN guidelines for survivorship care. Journal of the National Comprehensive Cancer Network 11:640-644

5. Rock C, Doyle C, Demark-Wahnefried W, Meyerhardt J, Courneya K, Schwartz A, Bandera E, Hamilton K, Grant B, McCullough M, Byers T, Gansler T (2012) Nutrition and physical activity guidelines for cancer survivors. CA-Cancer J Clin 62 (4):243-274

6. Schmitz K, Courneya K, Matthews C, Demark-Wahnefried W, Galvao D, Pinto B, Irwin M, Wolin K, Segal R, Lucia A, Schneider C, von Gruenigen V, Schwartz A, American College of Sports Medicine (2010) American College of Sports Medicine roundtable on exercise guidelines for cancer survivors. Med Sci Sport Exer 42:1409-1426

7. Silver J, Baima J (2013) Cancer prehabilitation: an opportunity to decrease treatment-related morbidity, increase cancer treatment options, and improve physical and psychological health outcomes. American Journal of Physical Medicine and Rehabilitation 92 (8):715-727

8. Silver J, Baima J, Mayer R (2013) Impairment-driven cancer rehabilitation: an essential component of quality care and survivorship. CA: A Cancer Journal for Clinicians 65 (5):295-317

9. Cheville A, Beck L, Petersen T, Marks R, Gamble G (2009) The detection and treatment of cancer-related functional problems in an outpatient setting. Support Care Cancer 17 (1):61-67. doi:10.1007/s00520-008-0461-x

10. Binkley J, Harris S, Levangie P, Pearl M, Guglielmino J, Kraus V, Rowden D (2012) Patient perspectives on breast cancer treatment side effects and the prospective surveillance model for physical rehabilitation for women with breast cancer. Cancer 118 (supplement 8):2207-2216

11. Stout NL, Binkley JM, Schmitz KH, Andrews K, Hayes SC, Campbell KL, McNeely ML, Soballe PW, Berger AM, Cheville AL, Fabian C, Gerber LH, Harris SR, Johansson K, Pusic AL, Prosnitz RG, Smith RA (2012) A prospective surveillance model for rehabilitation for women with breast cancer. Cancer 118 (8 Suppl):2191-2200. doi:10.1002/cncr.27476

12. Hayes S, Johanssen K, Alfano C, Schmitz K (2011) Exercise for breast cancer survivors: Bridging the gap. Translational Behavioral Medicine 1:539–544

13. Gordon LG, Scuffham P, Battistutta D, Graves N, Tweeddale M, Newman B (2005) A cost-effectiveness analysis of two rehabilitation support services for women with breast cancer. Breast Cancer Res Tr 94 (2):123-133. doi:10.1007/s10549-005-5828-9

14. Gordon L, Scuffham P, Hayes S, Newman B (2007) Exploring the economic impact of breast cancers during the 18 months following diagnosis. Psycho-Oncol 16 (12):1130-1139

15. Private Health Insurance Administration Council (2013) Privately insured people with hospital treatment cover. Annual analysis by Sex, Age and State. PHIAC, Australian Capital Territory

16. Lauzier S, Levesque P, Mondor M, Drolet M, Coyle D, Brisson J, Masse B, Provencher L, Robidoux A, Maunsell E (2013) Out-of-pocket costs in the year after early breast cancer among Canadian women and spouses. J Natl Cancer I 105 (4):280-292

17. Meneses K, Azuero A, Hassey L, McNess P, Pisu M (2012) Does economic burden influence quality of life in breast cancer survivors? Gynecol Oncol 124 (3):437-443

18. Pisu M, Azuero A, Meneses K, Burkhardt J, McNess P (2011) Out-of-pocket cost comparison between Caucasian and minority breast cancer survivors in the Breast Cancer Education Intervention (BCEI). Breast Cancer Res Tr 127 (2):521-529

19. McDougall J, Ramsey S (2014) Financial toxicity: a growing concern among cancer patients in the United States. ISPOR Connections 20 (2)

20. Gordon L, Ferguson M, Chambers S, Dunn J (2009) Fuel, beds, meals and meds: out-of-pocket expenses for patients with cancer in rural Queensland. Cancer Forum 33 (3):202-208

21. Mujahid M, Janz N, Hawley S, Griggs J, Hamilton A, Graff J, Katz S (2011) Racial/ethnic differences in job loss for women with breast cancer. Journal of Cancer Survivorship 5 (1):102-111

22. Jagsi R, Pottow J, Griffith K, Bradley C, Hamilton A, Graff J, Katz S, Hawley S (2014) Long-term financial burden of breast cancer: experiences of a diverse cohort of survivors identified through population-based registries. J Clin Oncol. doi:10.1200/JCO.2013.53.0956

23. Shih Y, Xu Y, Cormier J, Giordano S, Ridner S, Buchholz T, Perkins G, Elting L (2009) Incidence, treatment costs, and complications of lymphedema after breast cancer among women of working age: a 2-year follow-up study. J Clin Oncol 27 (12):2007-2014

24. Calhoun E, Chang C, Welshman E, Fishman D, Lurain J, Bennett C (2001) Evaluating the total costs of chemotherapy-induced toxicity: results from a pilot study with ovarian cancer patients. Oncologist 6 (5):441-445

25. Schnur J, Graff Zivin J, Mattson D (2012) Acute skin toxicity-related, out-of-pocket expenses in patients with breasat cancer treated with external beam radiotherapy: a descriptive, exploratory study. Support Care Cancer 20:3105-3113

26. Hayes SC, Janda M, Cornish B, Battistutta D, Newman B (2008) Lymphoedema following breast cancer: incidence, risk factors and effect on upper body function. J Clin Oncol 26 (21):3536-3542

27. Beaton D, Katz J, Fossel A, Wright J, Tarasuk V, Bombardier C (2001) Measuring the whole or the parts? Validity, reliability, and responsiveness of the Disabilities of the Arm, Shoulder and Hand outcome measure in different regions of the upper extremity. Journal of Hand Therapy 14 (2):128-146

28. Cella D, Tulsky D, Gray G, Sarafian B, Linn E, Bonomi A, Silberman M, Yellen S, Winicour P, Brannon J (1993) The Functional Assessment of Cancer Therapy scale: Development and validation of the general measure. J Clin Oncol 11 (3):570-579

29. Hayes SC, Rye S, Battistutta D, Newman B (2010) Prevalence of upper-body symptoms following breast cancer and its relationship with upper-body function and lymphedema. Lymphology 43 (4):178-187

30. Ward L, Bunce I, Cornish B, Mirolo B, Thomas B, Jones L (1992) Multifrequency bioelectrical impedance augments the diagnosis and management of lymphedema in post-mastectomy patients. Eur J Clin Invest 22:751-754

31. Hayes SC, Janda M, Cornish B, Battistutta D, Newman B (2008) Lymphoedema secondary to breast cancer: how choice of measure influences diagnosis, prevalence and identifiable risk factors. Lymphology 41 (1):18-28

32. Smoot B, Wong J, Cooper B, Wanek L, Topp K, Byl N, Dodd M (2010) Upper extremity impairments in women with or without lymphedema following breast cancer treatment. Journal of Cancer Survivorship 4:167-178

33. Jeong H, Sim Y, Hwang K, Kim G (2011) Causes of shoulder pain in women with breast cancer-related lymphedema: a pilot study. Yonsei Medical Journal 52:661-667

34. Button J, Scott J, Taghizadeh R, Weiler-Mithoff E, Hart A (2010) Shoulder function following autologous latissimus dorsi breast reconstruction. A prospective three year observational study comparing quilting and non-quilting donor site techniques. Journal of Plastic, Reconstructive and Aesthetic Surgery 63:1505-1512

35. Australian Bureau of Statistics (2003) Average Weekly Earnings (Cat. No. 6302.0). Australian Bureau of Statistics, Canberra

36. Australian Bureau of Statistics (1997) Unpaid Work and the Australian Economy 1997. Australian Bureau of Statistics, Canberra

37. Schmitz K, Speck R, Rye S, DiSipio T, Hayes SC (2012) Prevalence of breast cancer treatment sequelae over six years of follow-up: The Pulling Through Study. Cancer 118 (8):S2217-2225

38. Speck R, Courneya KS, Masse L, Duval S, Schmitz K (2010) An update of controlled physical activity trials in cancer survivors: A systematic review and meta-analysis. Journal of Cancer Survivorship 4 (2):87-100

39. Hayes S, Spence R, Galvao D, Newton R (2009) Australian Association for Exercise and Sport Science position stand: Optimising cancer outcomes through exercise. J Sci Med Sport 12:428 - 434

40. Gordon L, Patrao T, Hawkes A (2012) Can colorectal cancer survivors recall their medications and doctor visits reliably? BMC Health Services Research 12:440

41. Lubeck D, Hubert H (2005) Self-report was a viable method for obtaining health care utilization data in community-dwelling seniors. J Clin Epidemiol 58:286-290

42. Pinto D, Robertson M, Hansen P, Abbott J (2011) Good agreement between questionnaire and administrative databases for health care use and costs in patients with osteoarthritis. BMC Medical Research Methodology 11:45

43. Reijneveld S, Stronks K (2001) The validity of self-reported use of health care across socioeconomic strata: a comparison of survey and registration data. International Journal of Epidemiology 30:1407-1414

44. van den Brink M, van den Hout W, Stiggelbout A, Putter H, van de Velde C, Kievit J (2005) Self-reports of health-care utilization: diary or questionnaire? International Journal of Technology Assessment in Health Care 21 (3):298-304

Table 1. Characteristics of the target and Pulling Through Study sample

Characteristic	**Pulling Through Study Participants**	
	All	**Cohort with complete data**
	n=287	**n=179**
Age years (mean (SD))	55.3 (10.0)[a]	54.2 (9.5)[a]
	n (%)[a]	**n (%)[a]**
Age (years)		
<50	94 (27.3)	64 (30.0)
50+	193 (72.7)	115 (70.0)
Children		
Yes	247 (86.1)	151 (84.2)
No	40 (13.9)	28 (15.8)
Education level		
Low	126 (45.2)	64 (36.9)
Moderate	41 (14.3)	24 (13.6)
High	118 (39.7)	90 (48.9)
Missing	2 (0.8)	1 (0.6)
Occupation Group		
Professional	103 (35.0)	72 (39.6)
White Collar	95 (33.1)	61 (34.2)
Blue Collar	11 (3.7)	5 (2.9)
Homemaker	34 (12.3)	19 (10.7)
Retired/student	19 (7.0)	11 (6.4)
Missing	25 (8.9)	11 (6.1)
Household income		
< A$26,000 p.a.	84 (30.4)	41 (23.8)
A$26,000 – 51,999 p.a.	73 (24.9)	51 (28.0)
>A$52,000 p.a.	94 (31.6)	71 (38.9)
Missing	36 (13.1)	16 (9.3)

Characteristic	Pulling Through Study Participants	
	All	Cohort with complete data
	n=287	n=179
Private Health Insurance		
No	84 (28.8)	36 (19.3)
Yes	202 (70.8)	143 (80.7)
Missing	1 (0.4)	0 (0.0)
Body Mass Index[b]		
Underweight (<18.5kg/m2)	9 (3.0)	7 (3.7)
Healthy weight (18.5-24.9 kg/m2)	114 (39.1)	79 (44.0)
Overweight (25.0-29.9 kg/m2)	80 (28.0)	48 (26.6)
Obese (30+ kg/m2)	56 (19.7)	37 (21.1)
Missing	28 (10.2)	8 (4.6)
Physical Activity[c]		
Sedentary	49 (16.8)	23 (12.5)
< 150 minutes per week	67 (23.3)	46 (25.6)
≥ 150 minutes per week	171 (59.8)	110 (61.9)
Current smoker		
Yes	30 (10.2)	12 (6.7)
No	255 (89.1)	165 (92.3)
Missing	2 (0.6)	2 (0.9)
Overall histological grade		
Grade 1	76 (26.7)	44 (24.7)
Grade 2	90 (31.7)	51 (28.7)
Grade 3	91 (30.7)	64 (35.0)
Not available	30 (10.8)	20 (11.6)

Characteristic	Pulling Through Study Participants	
	All	Cohort with complete data
	n=287	n=179
Cancer stage		
Stage 1	160 (56.6)	102 (58.2)
Stage 2	117 (39.8)	73 (39.5)
Stage 3+	8 (2.8)	3 (1.7)
Missing	2 (0.8)	1 (0.6)
Lymph node dissection		
Yes	249 (86.8)	154 (86.2)
Number removed, median (range)	12 (1, 47)	12 (1, 45)
Surgery type		
Mastectomy (Partial/Full)	102 (35.1)	63 (34.7)
Lumpectomy	185 (64.9)	116 (65.3)
Chemotherapy (% yes)		
At 6 months[d]	47 (15.9)	29 (15.6)
At 12 months[d]	6 (2.4)	4 (2.4)
At 18 months[d]	1 (0.3)	0 (0.0)
Ever[e]	122 (41.0)	80 (43.0)
Radiation (% yes)		
At 6 months[d]	31 (10.7)	26 (14.6)
At 12 months[d]	7 (2.5)	1 (0.6)
At 18 months[d]	1 (0.4)	1 (0.6)
Ever[e]	215 (75.0)	137 (76.5)
Hormone therapy (% yes)		
At 6 months[d]	95 (33.5)	60 (34.0)
At 12 months[d]	48 (31.3)	36 (19.8)
At 18 months[d]	93 (32.4)	59 (32.6)
Ever[e]	165 (57.9)	102 (57.3)

[a] Results have been appropriately weighted (<50 years, 1.0; ≥50 years, 1.3) for oversampling

Characteristic	Pulling Through Study Participants	
	All	Cohort with complete data
	n=287	n=179

of younger women.

[b] Body mass index calculated from self-reported height and weight at 6 months post-surgery, kg/m^2.

[c] Physical activity included total weekly moderate and vigorous activity.

[d] Data represents current treatment being received at time of questionnaire completion.

[e] Data represents ever receiving chemotherapy, radiation, or hormonal therapy since breast cancer diagnosis to 18 months post-surgery.

Table 2. Prevalence of symptoms up to 18 months post-surgery

Characteristics	**n**	**%**
Post-surgical issues[a]	156/287	54.4
Skin/tissue reaction to radiotherapy	196/287	68.3
Upper-body symptoms[b]	111/285	38.9
Lymphedema (SOAC)[c]	41/204	20.1
Lymphedema (BIS)[d]	62/202	30.7
Lymphedema (SOAC or BIS)	79/207	38.2
Weight gain of 10% or more[e]	45/186	24.2
Fatigue[f]	122/283	43.1
Reduced upper-body function[g]	102/274	37.2
Number of above adverse treatment effects[i]		
0	7	3.9
1	30	16.8
2	32	17.9
3	37	20.7
4	38	21.2
5	25	14.0
6	6	3.4
7	4	2.2
Number of above adverse treatment effects[i]		
0-3	106	59.2
4-7	73	40.8
Number of co-morbidities[i]		
0	148	51.6
1	54	18.8
2	38	13.2
3+	47	16.4

[a] Post-surgical issues include; wound infection, other infection, seroma/hematoma, axillary web, cording. Counts include women who reported at least one issue.

[b] Upper-body symptoms from DASH include tingling and weakness (rated severe to

Characteristics	n	%

extreme), and items from FACT –B+4 symptom specific concerns include pain, stiffness, range of motion, swelling, and numbness (rated quite a bit to very much). Counts include women who reported at least one symptom.

[c] Lymphedema measured via sum of arm circumferences (SOAC): lymphedema = when treated side was ≥5cm than untreated side.

[d] Lymphedema as measured via bioimpedance spectroscopy (BIS): lymphedema = when ratio is >3SD of normative values.

[e] Weight gain was assessed by comparing measured values at 18-months post-surgery to self-reported weight 6 months prior to diagnosis. Where measured values at 18-months post-surgery were unavailable, measured values at 15-months (n=4) or 12-months (n=3) was used. Increases of >10% over these self-reported weights from six months prior to diagnosis were considered gains.

[f] Fatigue 'I have a lack of energy' from FACT-B+4 Physical Well-being domain rated as quite a bit to very much.

[g] Upper-body function as assessed by the DASH (range 0 to 100): scores >20 categorized as reduced function.

[h] Number of adverse treatment effects includes; post-surgical issues, skin/tissue reaction to radiotherapy, upper-body symptoms, lymphedema (via sum of circumference or bioimpedance spectroscopy), weight gain, fatigue and upper-body function.

[i] Number of adverse treatment effects includes; post-surgical issues, skin/tissue reaction to radiotherapy, upper-body symptoms, lymphedema (via sum of circumference or bioimpedance spectroscopy), weight gain, fatigue and upper-body function. Only women with data available for all adverse treatment effects in each time point were included in this analysis.

Note: If a participant missed at least 4/5 observations for post-surgical issues and skin/tissue reaction to radiotherapy, or 3/5 observations for upper-body symptoms, lymphedema (via sum or circumference or bioimpedance spectroscopy), fatigue or upper-body function, she was classified as missing (if showed no evidence of the symptom at the other time-point(s)).

Table 3. Patient costs stratified by adverse treatment symptoms 6 to 18 months after diagnosis for breast cancer (Bootstrapped means, 95% CIs)

Characteristics	**Direct costs[a]**			**Indirect costs[b]**			**Total costs[c]**		
	n	**Mean $**	**95% CI $**	**n**	**Mean $**	**95% CI $**	**n**	**Mean $**	**95% CI $**
Total	252	2 269	1 824, 2 713	185	4 982	4 022, 5 942	265	5 636	4 694, 6 577
Post-surgical issues[d]									
Never	114	2 119	1 396, 2 842	79	4 087	2 818, 3 536	119	4 743	3 441, 6 045
Ever	138	2 392	1 843, 2 943	106	5 649	4 255, 7 044	146	6 363	4 985, 7 741
Skin/tissue reaction to radiotherapy									
Never	77	2 477	1 511, 3 444	54	4 105	2 275, 5 934	81	5 091	3 432, 6 751
Ever	175	2 177	1 711, 2 643	131	5 343	4 202, 6 486	184	5 875	4 754, 6 996
Upper-body symptoms[e]									
Never	148	1 816	1 286, 2 347	100	3 716	2 650, 4 782	156	4 105	3 127, 5 083
Ever	102	2 963*	2 208, 3 718	83	6 558*	4 729, 8 385	107	7 912**	6 133, 9 690
Lymphedema (SOAC)[f]									
Never	145	2 521	1 840, 3 202	110	5 120	3 856, 6 384	150	6 192	4 836, 7 549
Ever	38	2 546	1 549, 3 541	25	5 363	2 664, 8 062	40	5 770	3 136, 8 404
Lymphedema (BIS)[g]									
Never	122	2 207	1 579, 2 834	93	5 448	3 930, 6 967	127	6 111	4 618, 7 603
Ever	59	2 687	1 787, 3 587	42	5 034	3 289, 6 780	61	6 066	4 217, 7 914

Characteristics	Direct costs[a]			Indirect costs[b]			Total costs[c]		
	n	Mean $	95% CI $	n	Mean $	95% CI $	n	Mean $	95% CI $
Lymphedema (SOAC or BIS)									
Never	111	2 448	1 661, 3 235	85	5 157	3 716, 6 598	115	6 175	4 595, 7 754
Ever	75	2 574	1 805, 3 343	52	5 545	3 655, 7 283	78	6 121	4 388, 7 853
Weight gain of 10% or more[h]									
Never	125	2 806	2 110, 3 503	94	5 634	4 710, 7 097	130	6 773	4 276, 8 268
Ever	42	2 210	1 058, 3 362	31	4 867	2 850, 6 885	43	5 668	3 176, 8 159
Fatigue[i]									
Never	141	1 986	1 417, 2 555	92	4 182	3 049, 5 316	150	4 432	3 399, 5 464
Ever	107	2 717	1 995, 3 438	90	5 900	4 177, 7 623	111	7 402*	5 546, 9 259
Reduced upper-body function[j]									
Never	147	2 122	1 512, 2 733	98	4 255	3 134, 5 376	155	4 703	3 632, 5 774
Ever	94	2 620	1 964, 3 278	80	6 207	4 367, 8 047	98	7 580*	5 757, 9 405
Number of co-morbidities									
0	129	2 050	1 553, 2 547	86	4 455	3 134, 5 777	135	4 797	3 695, 5 900
1	43	3 251	1 537, 4 965	37	6 388	3 911, 8 865	49	7 677	4 730, 10 624
2	36	2 086	1 239, 2 933	28	6 039	2 922, 9 157	37	6 600	3 499, 9 701
3+	44	2 098	1 175, 3 021	34	3 912	2 141, 5 684	44	5 122	3 101, 7 142

Characteristics	Direct costs[a]			Indirect costs[b]			Total costs[c]		
	n	Mean $	95% CI $	n	Mean $	95% CI $	n	Mean $	95% CI $
Number of adverse treatment effects[k]									
0 - 3	153	1 699	1 206, 2 192	99	3 482	2 533, 4 431	161	3 756	2 955, 4 558
4 - 7	99	3 148*	2 406, 3 892	86	6 708**	4 958, 8 460	104	8 545**	6 592, 10 499

[a] Direct costs include: out-of-pocket expenditure on garments and aids, health services (co-payments, pharmaceuticals), paid home services; since breast cancer diagnosis to 18 months post-surgery.

[b] Indirect costs include: value of lost income, unpaid help, lost unpaid work; since breast cancer diagnosis to 18 months post-surgery.

[c] Total costs include: direct and indirect costs; since breast cancer diagnosis to 18 months post-surgery.

[d] Post-surgical issues include; wound infection, other infection, seroma/hematoma, axillary web, cording. Counts include women who reported at least one issue.

[e] Upper-body symptoms from DASH include tingling and weakness (rated severe to extreme), and items from FACT –B+4 symptom specific concerns include pain, stiffness, range of motion, swelling, and numbness (rated quite a bit to very much). Counts include women who reported at least one symptom.

[f] Lymphedema measured via sum of arm circumferences (SOAC): lymphedema = when treated side was $\geq$5cm than untreated side.

[g] Lymphedema as measured via bioimpedance spectroscopy (BIS): lymphedema = when ratio is >3SD of normative values.

[h] Weight gain was assessed by comparing measured values at 18-months post-surgery to self-reported weight 6 months prior to diagnosis. Where measured values at 18-months post-surgery were unavailable, measured values at 15-months (n=4) or 12-months (n=3) was used. Increases of >10% over these self-reported weights from six months prior to diagnosis were considered gains.

[i] Fatigue 'I have a lack of energy' from FACT-B+4 Physical Well-being domain rated as quite a bit to very much.

[j] Upper-body function as assessed by the DASH (range 0 to 100): scores >20 categorized as reduced function.

[k] Number of adverse treatment effects includes; post-surgical issues, skin/tissue reaction to radiotherapy, upper-body symptoms, lymphedema (via sum of circumference or bioimpedance spectroscopy), weight gain, fatigue and upper-body function. Note: If a participant missed at least 4/5 observations for post-surgical issues and skin/tissue reaction to radiotherapy, or 3/5 observations for upper-body symptoms, lymphedema (via sum or circumference or bioimpedance spectroscopy), fatigue or upper-body function, she was classified as missing (if showed no evidence of the symptom at the other time-point(s)).

Characteristics	Direct costs[a]			Indirect costs[b]			Total costs[c]		
	n	Mean $	95% CI $	n	Mean $	95% CI $	n	Mean $	95% CI $
Notes: Statistically significant difference compared with the first group; * $p \leq 0.05$; ** $p \leq 0.001$.									

Table 4. Summary of adjusted results for the associations between patient costs (direct, indirect and total costs) and treatment symptoms over time (up to 18 months post-surgery)

Characteristics	Direct costs[a]			Indirect costs[b]			Total costs[c]		
	n	OR[d]	95% CI	n	OR[d]	95% CI	n	OR[d]	95% CI
Upper-body symptoms[e]									
Never	148	1.0	-	100	1.0	-	156	1.0	-
Ever	102	2.6*	1.4, 4.7	83	1.5	0.8, 3.0	107	2.1*	1.2, 3.7
Fatigue[f]									
Never	141	1.0	-	92	1.0	-	150	1.0	-
Ever	107	1.8*	1.0, 3.1	90	0.9	0.5, 1.8	111	1.5	0.9, 2.6
Reduced upper-body function[g]									
Never	147	1.0	-	98	1.0	-	155	1.0	-
Ever	94	1.9*	1.1, 3.5	80	1.4	0.7, 2.6	98	1.6	0.9, 2.8
Number of adverse treatment effects[h]									
0-3	153	1.0	-	99	1.0	-	161	1.0	-
4-7	99	3.8**	2.0, 7.1	86	1.7	0.9, 3.2	104	2.3*	1.3, 4.1

[a] Direct costs include: out-of-pocket expenditure on garments and aids, health services (co-payments, pharmaceuticals), paid home services; cost split at the median, higher cost $1193+; since breast cancer diagnosis to 18 months post-surgery.

[b] Indirect costs include: value of lost income, unpaid help, lost unpaid work; cost split at the median, higher cost $2682+; since breast cancer diagnosis to 18 months post-surgery.

[c] Total costs include: direct and indirect costs; cost split at the median, higher cost $2857+; since breast cancer diagnosis to 18 months post-surgery.

[d] Odds ratio of higher cost (versus lower cost); mutually adjusted for age (continuous), baseline income (<A$26,000 p.a., A$26,000-51,000 p.a., >A$52,000 p.a., missing), baseline BMI (body mass index calculated from self-reported height and weight, kg/m^2: underweight/healthy, overweight, obese, missing), cancer stage (I, II+), chemotherapy (no, yes), radiation (no, yes), hormonal therapy (no, yes); data represents ever receiving chemotherapy, radiation, or hormonal therapy over the study period up to 18 months post-surgery.

[e] Upper-body symptoms from DASH include tingling and weakness (rated severe to extreme), and items from FACT – B+4 symptom specific concerns include pain, stiffness, range of motion, swelling, and numbness (rated quite a bit to very much). Counts include women who reported at least one symptom.

[f] Fatigue measured as 'I have a lack of energy' from FACT-B+4 Physical well-being domain rated as quite a bit to very much.

[g] Upper-body function as assessed by the DASH (range 0 to 100): scores >20 categorized as reduced function.

[h] Number of adverse treatment effects includes: post-surgical issues, skin/tissue reaction to radiotherapy, upper-body symptoms, lymphedema (via sum of circumference or bioimpedance spectroscopy), weight gain, fatigue and upper-body function. Note: If a participant missed at least 4/5 observations for post-surgical issues and skin/tissue reaction to radiotherapy, or 3/5 observations for upper-body symptoms, lymphedema (via sum or circumference or bioimpedance spectroscopy), fatigue or upper-body function, she was classified as missing (if showed no evidence of the symptom at the other time-point(s)).

Notes: Statistically significant difference compared with the referent group; * $p \leq 0.05$; ** $p \leq 0.001$.